A fundamental study of the flow and droplet delivery from a pressurised metered dose inhaler (pMDI)

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A Fundamental Study of the Flow and Droplet Delivery from a Pressurised Metered Dose Inhaler (pMDI)

by

A. J. Davis

Submitted in partial fulfilment of the requirements for the award of Doctoral Thesis of Loughborough University

December 2008

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Abstract

The assessment of drug formulations delivered by the pressurised metered dose inhaler and used in the treatment of Asthma are assessed commercially using cascade impactors which are the preferred instruments for the assessment of particle size and respirable mass or fraction delivered by inhalation devices. The fundamental principle underpinning the design of cascade impactors is particle motion defined by Stokes theory. The analysis of impactor data raises a number of functional issues as calibration curves have long tails, which are not easily explained by a simplistic application of Stokes law. The atomisation process, propellant flashing, evaporation and aerodynamic properties of the residual drug particle determine the distribution of the drug particles within the lung and resultant therapeutic effect.

The research uses mathematical modelling and computational fluid dynamics (CFD) to evaluate the flow and inertial deposition in the USP throat and the plates of the ACI which is the most widely used cascade impactor. The CFD analysis shows the flow in the outlet section of the USP throat to be unstable for the basic design, when coupled to an outlet extension and when coupled to the ACI via the standard coupler and first jet stage. The modelling also provides insight as to why the calibration curves of the ACI have long tails and reveals a number of issues with the design of the ACI coupler and the fundamental design of impactor jet arrays as well as the position and functional response of upper impactor plates. Additional particle sizing methodologies were used to assess the lognormal characteristics of the atomised droplets and residual drug particles. The experimental data was compared to current atomisation model and modification recommended and a proposed alternative model with improved fit to the data.
Acknowledgments

I would like to thank my family and friends as without their sterling support during the early days of this project I would have not have had the resolve to see it through to a conclusion.

I would like to thank Graham and Henk for their comments, advice, discussion, and general help along the way. At times it has been difficult due to the confidentiality aspects regarding some of the work and the lack of a three way agreement between the parties involved. I would also like to thank the other staff and students of the department who have aided me from time to time.

I would like to thank 3M for the financial support provided during the initial stages of the research project and for giving me the freedom to pursue the research without the necessity for a dedicated industrial supervisor. The original creative and innovative ethos of 3M was undermined by the Six Sigma era introduced by McNerney. "We got a little tool happy (under McNerney)" said 3M research chief Larry Wendling, staff vice president, 3M Corp. Research labs. As a result of the large number of corporate changes during the course of the research there are few individual who have contributed but I would like to thank Rich Sadler for his efforts in the early days in ensuring the timely acquisition of equipment and materials. I would also like to thank the members of the analytical group for their support during some of the impactor testing. I would like to thank ID4 consultancy for the financial support during the final stages of the research.

Dr. David Greenleaf reviewed the thesis for 3M to evaluate confidentiality and intellectual property aspects and I would like to thank him for his constructive comments and Dr. Richard Toon for reviewing and constructive comments on the final draft.

i) 3M Shelves Six Sigma in R&D, J. Dodge, Design News, Reed Business Information, Dec 2007
Motivation

I joined the pharmaceutical industry as a process engineering to aid the development of a then new breath activated inhalation device (Autohaler™) that 3M Healthcare were developing for both in house and third party products. Having arrived with a background in polymer science, chemistry and process engineering I was initially responsible for the qualification of injection mould tooling and assembly equipment for the production of inhalation devices. At that time in the device development process there was not only a significant effort in the development of many products based around many different drug formulations but also on the horizon was a new era of formulation and delivery issues due to the phase out of the propellant systems that had been in use since the conception of the pressurised metered dose inhaler in 1956. The propellant systems had until this time used a class of propellants called Chlorofluorocarbons (CFC) but these were to be replaced by a family of propellants called Hyrdofluoroalkanes (HFA) that would have far lower impact on the environment.

After a few years in the process engineering role I was asked if I would take on a product development role because there were at that time many technical issues with the range of Autohaler™ devices currently under development. The issues centred on the matching of pharmaceutical performance between the Autohaler™ and the equivalent press and breathe products and also the pharmaceutical performance of matching CFC and HFA based products, for both Autohaler™ and press and breathe products.

I was very surprised to find that there were few if any design principles that could be readily applied with any degree of accuracy to the task in hand. Reference to the literature only revealed a bewildering array of claim and counter claim regarding the influence that various design variables would have on the pharmaceutical performance of inhalation devices. At first this was a surprising situation given that the pressured metered dose inhaler had been in use for at that time nearly 40 years. The solutions to product performance issues were solved by a combination of experience, educated...
guess work, combined with the judicial use of both design of experiments (DoE) and
the application of the Taguchi methodology. These methods still left many unanswered
questions but there was as is often the case in the commercial environment little time or
resource to pursue answers to some of the more puzzling questions.

Following a family tragedy I worked part-time and during this period I had time to
reflect on many of the problems encountered and also turned my thoughts to the
problem of how devices could be developed for the future. In the last 20 years the
dominance of the pressured metered dose inhaler as the primary choice for the delivery
of medicament to the lungs has come under pressure from a wide range of dry powder
devices and in recent years to a number of new technology devices for the delivery of
metered drug to the respiratory tract for both asthma and systemic use.

In 1999 whilst working on an unrelated problem that required the use of a high speed
video system (significantly faster than the one I was using at 3M) I came into contact
with Graham Hargrave of the Wolfson school of mechanical engineering at
Loughborough University. During one of our many discussions away from the problem
at hand I expressed my interest in solving some of these design problems and Graham
in turn discussed how he and some of his colleagues (including Henk Versteeg) had
worked with various pharmaceutical companies which were researching various issues
of inhaler design and spray measurement. I quickly formulated a project plan and
submitted it to 3M for approval and funding. In 2000 the project was approved and
after some delays due to various commercial pressures the project was started in earnest
in 2001/2.

Having been a life long asthmatic this project was always going to be a little more
vocational than might otherwise be expect. The illness has given me significant insight
into the problems of asthma treatment and problems that living with asthma can create.
Experience had taught me that in order to solve some of these issues a combination of
commercial pragmatism coupled with the rigor of the academic approach would be
required to gain the appropriate level of insight.
## Nomenclature

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Cross-sectional area (m²)</td>
</tr>
<tr>
<td>a</td>
<td>Subset of non homogenous equilibrium model (NEM)</td>
</tr>
<tr>
<td>b</td>
<td>Subset of non homogenous equilibrium model (NEM)</td>
</tr>
<tr>
<td>C</td>
<td>Specific heat (kJ kg⁻¹ K⁻¹)</td>
</tr>
<tr>
<td>Cc</td>
<td>Cunningham slip correction</td>
</tr>
<tr>
<td>Cd</td>
<td>Discharge coefficient</td>
</tr>
<tr>
<td>D</td>
<td>Diameter (mm)</td>
</tr>
<tr>
<td>d</td>
<td>Particle diameter or Subset of non homogenous equilibrium model (NEM)</td>
</tr>
<tr>
<td>e</td>
<td>Subset of non homogenous equilibrium model (NEM)</td>
</tr>
<tr>
<td>Ft</td>
<td>Thrust (N)</td>
</tr>
<tr>
<td>f</td>
<td>Friction factor</td>
</tr>
<tr>
<td>G</td>
<td>Mass flux (kg s⁻¹ m⁻²)</td>
</tr>
<tr>
<td>g</td>
<td>Gravity constant (m s⁻²)</td>
</tr>
<tr>
<td>ge</td>
<td>Defined in NEM two phase models</td>
</tr>
<tr>
<td>h</td>
<td>Enthalpy (kJ kg⁻¹)</td>
</tr>
<tr>
<td>K</td>
<td>Kelvin</td>
</tr>
<tr>
<td>k</td>
<td>Ratio of specific heats or evaporation rate constant</td>
</tr>
<tr>
<td>L</td>
<td>Short tube length (m)</td>
</tr>
<tr>
<td>l</td>
<td>Length of jet (m)</td>
</tr>
<tr>
<td>L/D</td>
<td>Ratio of short tube length to diameter</td>
</tr>
<tr>
<td>m*</td>
<td>Mass flow rate (kg s⁻¹)</td>
</tr>
<tr>
<td>mf</td>
<td>Mass fraction</td>
</tr>
<tr>
<td>mw</td>
<td>Molecular weight</td>
</tr>
<tr>
<td>N</td>
<td>Number count in cascade impactor plate calibration</td>
</tr>
<tr>
<td>P</td>
<td>Pressure (Pa) or Probability of particle deposition</td>
</tr>
<tr>
<td>Q</td>
<td>Volumetric flow rate (m³ s⁻¹)</td>
</tr>
<tr>
<td>R</td>
<td>Universal gas constant or Correlation coefficient</td>
</tr>
<tr>
<td>Re</td>
<td>Reynolds Number</td>
</tr>
<tr>
<td>r</td>
<td>Pressure ratio</td>
</tr>
<tr>
<td>SG</td>
<td>Specific Gravity</td>
</tr>
</tbody>
</table>
s  Entropy (kJ kg\(^{-1}\) K\(^{-1}\))
T  Temperature (K or °C)
t  Time (s)
u  Velocity (m s\(^{-1}\))
v  Specific volume (m\(^3\) kg\(^{-1}\))
v_f  Vapour fraction
w  Width or weight fraction (m)
q  Refrigerant quality

Greek letters
\(\alpha\)  Void fraction
\(\beta\)  Ratio of short tube diameters (downstream to upstream)
\(\gamma\)  Slip ratio
\(\eta\)  Dynamic viscosity (Pa s)
\(\rho\)  Density (kg m\(^{-3}\))
\(\sigma\)  Surface tension
\(\sigma_{GSD}\)  Geometric standard deviation
\(\psi\)  Thermal diffusion coefficient
\(\mu\)  Mean of lognormal distribution
\(\nu\)  Volume (m\(^3\))
\(\chi\)  Cross flow parameter
\(\Phi\)  Dissipation factor (spray momentum)
\(K_{1,2}\)  Constants in \(d_{50}\) equation
\(Y\)  Expansion factor

Subscripts
a  Ambient
cr  Critical
d  Drug
dn  Downstream
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Definition</th>
</tr>
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<tbody>
<tr>
<td>e</td>
<td>Expansion</td>
</tr>
<tr>
<td>f</td>
<td>Liquid</td>
</tr>
<tr>
<td>fg</td>
<td>Latent heat of vaporisation</td>
</tr>
<tr>
<td>g</td>
<td>Vapour, gas</td>
</tr>
<tr>
<td>p</td>
<td>Pressure</td>
</tr>
<tr>
<td>r</td>
<td>Residual</td>
</tr>
<tr>
<td>res</td>
<td>Residual</td>
</tr>
<tr>
<td>sat</td>
<td>Saturated</td>
</tr>
<tr>
<td>T</td>
<td>Total</td>
</tr>
<tr>
<td>tp</td>
<td>Two phase</td>
</tr>
<tr>
<td>up</td>
<td>Upstream</td>
</tr>
<tr>
<td>v</td>
<td>Volume</td>
</tr>
<tr>
<td>vc</td>
<td>Vena contracta</td>
</tr>
</tbody>
</table>

**Acronyms**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ACI</td>
<td>Andersen Cascade Impactor</td>
</tr>
<tr>
<td>API</td>
<td>Active Pharmaceutical Ingredient</td>
</tr>
<tr>
<td>APS</td>
<td>Aerodynamic Particle Size</td>
</tr>
<tr>
<td>BP</td>
<td>British Pharmacopoeia</td>
</tr>
<tr>
<td>CFC</td>
<td>Chlorofluorocarbon</td>
</tr>
<tr>
<td>CFD</td>
<td>Computational Fluid Dynamics</td>
</tr>
<tr>
<td>ECD</td>
<td>Effective Cut Diameter</td>
</tr>
<tr>
<td>EP</td>
<td>European Pharmacopoeia</td>
</tr>
<tr>
<td>FPD</td>
<td>Fine Particle Dose</td>
</tr>
<tr>
<td>GSD</td>
<td>Geometric Standard Deviation</td>
</tr>
<tr>
<td>HFA</td>
<td>Hydrofluoroalkane</td>
</tr>
<tr>
<td>PDA</td>
<td>Phase Doppler Anemometry</td>
</tr>
<tr>
<td>MMAD</td>
<td>Mass Median Aerodynamic Diameter</td>
</tr>
<tr>
<td>MMD</td>
<td>Mass Median Diameter</td>
</tr>
<tr>
<td>MOC</td>
<td>Micro Orifice Collector</td>
</tr>
<tr>
<td>USP</td>
<td>United States Pharmacopoeia</td>
</tr>
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Chapter 1 Introduction

1. Introduction

The main focus of this research project was to investigate the operation of the pressurised, metered dose inhaler (pMDI) used in the treatment of lung disorders such as asthma. Asthma is a condition in which the air passages of the lung become narrowed from time to time, making it difficult to breathe. The classic symptoms are chest tightness, cough and breathlessness with, commonly, an audible wheeze when air is forced through the narrowing air passages. These attacks are induced by many factors including, allergies, chest infections, stress, and air pollution. The word asthma comes from the Greek asthatikos, meaning 'breathe hard'.

Asthma is common, affecting about one in seven children and one in 25 adults (around 3.4 million people in Britain have the condition, including 1.5 million children). Research indicates that asthma is on the rise - one study indicated that three times as many children reported asthma attacks in the 1990s as in the previous decade.

An effective study of the drug delivery process is very complex because of the significant number of variables. The considerable breadth of subject knowledge needed to effectively understand and then to model the process of drug delivery only serves to complicate it further. Many of the research topics for which a deep understanding is required, are themselves areas of specific research. These include but are not limited to:

- Cavitation and Boiling
- Nucleation and Bubble growth
- Metastable thermodynamics
- Atomisation
- Vaporisation
- Evaporation
- Two phase flow
- Heat transfer
- Particle transport and Impaction
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The pressurised metered dose inhaler (pMDI) is small in size, convenient and easy to use. The apparently simple mode of operation, actuate and breathe, belie the very complex nature of the process. There are three basic functional classifications of inhaler types for asthma; they are relievers, which relieve the symptoms within minutes of being administered, preventers, which are taken regularly to reduce the underlying symptoms and combination products which are combinations of the other two and allow the patient to carry a single device.

The functional press and breathe pMDI contains three basic components:

- Formulation
- Container with a metering valve
- Actuator (drug delivery device)

The formulation contains the drug or active pharmaceutical ingredient (API). The API could be present in the form of a solution or a suspension. A solution is possible if the API is soluble in the propellant or can be solubilised by the use of a co-solvent or other solubilising excipient. The alternative and far more common formulation is that of the suspension. In the suspension formulation the micronised drug is present in the form of suspended solid particles in the respirable size range. The micronised particles can be produced by a number of processes including and not limited to, milling, high-energy impaction and spray drying.

Until very recently there were a large number of commercial products that still used CFC’s as the propellant system. These include propellants 11 (Trichlorofluoromethane), 12 (Dichlorodifluoromethane) and 114 (Dichlorotetrafluoroethane). Products developed since the mid nineties use HFA propellant, 134a (1,1,1,2 Tetrafluoroethane) and 227 (1,1,1,2,3,3,3 Heptafluoropropane) that have been shown to be more environmentally acceptable.
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On of the biggest challenges facing the manufacturer of inhaled therapies is the assessment of product performance. Whilst it is relatively easily to measure the simpler product performance criteria such as drug content and valve delivery, aspect such as the size and quantity of drug particles reaching the required site offer much more of a challenge. The table below serves to highlight the significant difference that can exist not only between identical products from different manufacturers but on the assessment of respirable masses and the numbers used to describe such particle sizes and particle size distributions.

Table 1-1 Cascade Impinger performance for 10 commercial Salbutamol products(J) by kind permission of the author

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<table>
<thead>
<tr>
<th>MDI</th>
<th>Mean amount of salbutamol recovered (µg) per 100 µg actuation (95% C.I.)</th>
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<tbody>
<tr>
<td>Manufacturer</td>
<td>Dose To In Particles In Particles</td>
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<tr>
<td></td>
<td>MSL1 &lt;5 µm In Particles &lt;3µm</td>
</tr>
<tr>
<td>CP</td>
<td>36.4 (34.0-38.8) 31.0 (27.1-34.9) 24.9 (19.4-30.4)</td>
</tr>
<tr>
<td>A&amp;H</td>
<td>30.0 (19.2-40.8) 24.6 (16.1-33.1) 19.1 (12.8-25.4)</td>
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<tr>
<td>K Pharm.</td>
<td>29.1 (18.5-39.7) 24.3 (16.2-32.4) 12.3 (12.8-24.8)</td>
</tr>
<tr>
<td>Generics</td>
<td>27.6 (17.4-37.8) 19.7 (17.7-21.7) 15.3 (13.5-17.1)</td>
</tr>
<tr>
<td>OPD - Kent</td>
<td>27.2 (18.3-35.6) 23.6 (16.1-31.1) 19.7 (13.3-26.1)</td>
</tr>
<tr>
<td>Baker Norton</td>
<td>25.8 (20.8-30.8) 22.7 (18.6-26.8) 12.0 (15.0-21.0)</td>
</tr>
<tr>
<td>Hillcross</td>
<td>25.0 (14.2-35.8) 21.1 (11.9-30.3) 16.7 (9.4-24.0)</td>
</tr>
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<td>APS</td>
<td>23.1 (20.3-25.9) 19.1 (16.4-21.8) 14.7 (12.0-17.4)</td>
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<tr>
<td>Cox</td>
<td>23.0 (16.0-30.0) 19.2 (13.8-24.6) 14.7 (11.0-18.4)</td>
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<tr>
<td>Berk</td>
<td>14.2 (10.7-17.7) 11.5 (9.2-13.8) 8.8 (7.1-10.5)</td>
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<table>
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<tr>
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<th>MMAD</th>
<th>GSD</th>
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<td>2.1(1.9-2.3)</td>
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<tr>
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<td>2.9</td>
<td>2.7(1.9-3.5)</td>
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<td>2.3(2.1-2.5)</td>
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<td>2.3</td>
<td>2.2(2.0-2.4)</td>
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<td>Berk</td>
<td>2.4</td>
<td>2.2(1.9-2.5)</td>
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The data for 10 identical (based on the label claim) commercial products (Table 1-1) clearly demonstrate the problem of relating pharmaceutical performance criteria with pharmacopoeia based measured assessment of particle size. The data in Table 1-1 show no clear link between the mass of respirable product, whether this is defined as dose to the measuring instrument or fractions less than specified inhalation size ranges (<5 µm or <3 µm) and the measured mean particle size parameter. The only sizing parameter defined in the British (BP) and European pharmacopoeia (EP)(2) is the MMAD (mass median aerodynamic diameter) which is a cumulative mass median and as such defines the particle size at which the measured mass can be split into two equal quantities one above and one below the median.

The use of cumulative mass median data is based on the assumption that the particle size distribution of the inhalation product is lognormal. The pharmacopoeia states that one should plot the cumulative mass data on log probability paper and from this the MMAD and GSD (geometric standard deviation) can be calculated. The geometric standard deviation is defined as

\[
\sigma_{\text{GSD}} = \sqrt[\log_{d_{84.13}}]{\frac{d_{84.13}}{d_{50}}} = \frac{d_{84.13}}{d_{50}} = \frac{d_{50}}{d_{15.87}}
\]

(1.1)

The pharmacopoeia(2) states that from the analysis of the solutions, calculate the mass of active substance deposited on each stage per discharge and the mass of active substance per discharge deposited in the induction port, mouthpiece adapter and when used, the pre- separator. Then starting at the final collection site (filter or micro orifice collector), derive a table of cumulative mass versus cut-off diameter or ECD (effective cut diameter) of the respective stage. Calculate by interpolation the mass of the active substance less than 5 µm. This is the Fine Particle Dose (FPD). The FPD is therefore a key parameter in defining the perceived pharmaceutical performance. It is often the
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case that pharmaceutical data are presented with the FPD being defined as less than 4.7-μm as this diameter coincides with a specific plate grouping from the commercial inertial impactors such as the Andersen cascade impactor (ACI).

The pharmacopoeia states that if necessary, and where appropriate (where there is a log-normal distribution), plot the cumulative fraction of active substance versus ECD diameter on log probability paper, and use this plot to determine values for the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) as appropriate. Appropriate computational methods may also be used. Although the clause where appropriate is used, no definition or test methodology is suggested.

The particle size distribution is a key parameter however a significant limitation in the process of determining a suitable functional parameter is the general lack of knowledge as to the basic nature of the distribution. It has long been regarded within the industry that the particle size of an inhalation product is of the lognormal type. The wording in the pharmacopoeia suggests that while this maybe the case it is by no means clear cut, hence the use of the term, where appropriate.

It has been suggested that a Rosin Rammler distribution is often a better fit to pharmaceutical based atomisation data (3-5). In an attempt to explain the lack of fit for impactor based data Thiel (6, 7) has proposed the use of numerical processing to determine the underlying lognormal from the non linear plots that are generally derived from cascade impactor data. Since the advent of the cascade impactor many authors have strived to define a method to accurately reconstruct the cascade data (8-14). Before this can be achieved however one must know the exact definition of the target distribution.

A key aspect to the problem of obtaining a full understanding of the particle size and the nature of distribution generated by the atomisation process is determining the most relevant particle characteristic. In inhalation it is the aerodynamic particle size, which is
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the diameter, normalised by density, which is the most important particle characteristic for the accurate determination of a particle's inertial deposition potential.

\[ D_{\text{aerodynamic}} = D_{\text{physical}} \times \sqrt{\frac{\text{SG}_{\text{particle}}}{\text{SG}_{\text{particle}}}} \] (1.2)

There are a wide range of instruments available to measure the size of particles within the size range generated by the atomisation of propellant systems. The choice of instrument used for the analysis is dependant on a number of choices as no one instrument can give all of the information required.

Table 1-2 A comparison of the various features that each of the particle sizing techniques considered has to offer

<table>
<thead>
<tr>
<th></th>
<th>Andersen Cascade Impactor (ACI)</th>
<th>Aerodynamic Particle Sizer (APS)</th>
<th>Phase Doppler Anemometer (PDA)</th>
<th>Laser Diffraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aerodynamic Diameter</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Active Ingredient</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>USP throat</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Potential</td>
</tr>
<tr>
<td>Spatial measurement</td>
<td>No</td>
<td>Potential</td>
<td>Yes</td>
<td>Partial</td>
</tr>
<tr>
<td>Temporal measurement</td>
<td>No</td>
<td>Potential</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Units tested per day</td>
<td>1-5</td>
<td>100's</td>
<td>100's</td>
<td>100's</td>
</tr>
<tr>
<td>Sample type</td>
<td>Full</td>
<td>Partial</td>
<td>Partial</td>
<td>Partial</td>
</tr>
</tbody>
</table>
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The cascade impactor is the preferred choice of the regulatory bodies and therefore the pharmaceutical industry because of the full analysis of the API. The remaining techniques find use in a variety of applications within various aspects of the industry because they offer the capability of providing answers to various design and testing aspects in a much shorter time and with less cost than cascade impactors, which because of the need to clean, dry, assemble, test and analyses each of the plates, requires a significant effort with respect to time. The other techniques can generate data in a much shorter time frame, generally in the order of a minute or less for repeated actuation/firing of a single unit.

While the PDA offers advantages in spatial and temporal measurement, it measures in a small spatial volume (< 1 mm³) and requires significant time and effort to map the spray generated by a pMDI and does not measure the aerodynamic diameter. Dunbar(4, 15) has demonstrated the benefits of using the PDA for the analysis of the spray emitted by the pMDI.

The laser diffraction instruments also offer fast data analysis of the pMDI spray but the measurement volume is limited to that occupied by the width of the instruments laser beam. There are a number of issues with respect to the correct instrument set up, these include but are not limited to the choice of optics and their alignment, diffraction theories (Fraunhofer, Mie), resolution, optical properties of the medium and data analysis algorithms(16).

If the designer of pMDI inhalation products is to be able to predict and model the drug delivery process then it is imperative that several key parameters regarding the delivery process are fully understood and that suitable data are available. The key parameters are the initial droplet size and velocity of the product as it exits the orifice of the delivery device. The droplets are essentially made up of the non-volatile residuals, drug and excipients such as surfactants and the relatively volatile liquid components such as residual subcooled propellant and moderately volatile excipients such as ethanol.

7
Therefore to successfully track a droplet from the exit to its point of impaction requires knowledge of the remaining constituents within the droplet and temperature of the droplet. The velocity of the droplet also requires an assessment of the exit momentum that includes the velocity of the flow field in which the droplets are being carried.

With the advancement in computer technology and computational software there has been a significant effort to model the deposition of particles in the mouth, throat, larynx and upper and lower respiratory tract(17-36). In most of these modelling scenarios especially those applicable to the upper airway the general assumption is made that the particle size is fixed (no evaporation) and significantly the particle velocity is generally assumed to be that of the local airflow. In reality these assumption cannot be applied because of the very dynamic nature of the inhalation drug delivery process.

Prior to the advent of computer based systems, data for the deposition of particles was obtained on simpler modelling assumption regarding the geometry together with the use of impaction criteria such as the Stokes number, or more specifically the square root of the Stokes number (proportional to aerodynamic diameter). The Stokes number does not provide an absolute solution to the impaction probability problem found in cascade impactors. It will be shown later that even the simplest form of impaction, that of round or rectangular jets onto perpendicular surfaces, results in a wide variation in the critical value of the Stokes number. This indicates that the Stokes number, whilst providing a good guide, does not produce absolute solutions because of the large number of geometric variables in the system.

In the mid sixties the Task Group on Lung Dynamics(37) defined a series of plots of deposition probability versus aerodynamic diameter for the nasal, pulmonary and tracheobronchial regions. The optimum deposition size for pulmonary deposition was in the region 2-3 μm aerodynamic diameter, with a further peak at the lower end of the sub micron region. In this particle size region the particles effectively behave like gas molecules and can become trapped in the alveolar re-circulatory regions as can larger
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particles that successfully penetrate that far into the lung and potentially can penetrate further on subsequent inhalation(18)

The nature of the turbulence in the oral cavity is another key aspect to understanding the deposition of the inhaler plume(38). The effect of turbulent flow on the impaction, interaction and transport of particles has been extensively studied(30, 31, 39-78) and is key to understanding deposition not only in the patient but also in the inertial based test methods.

It is widely regarded that the in vitro measurement of aerosol particles is important in the development of devices, formulations and quality control but offer only an imprecise estimates of potential in vivo lung deposition(79). It is therefore important that the inhalation product and device developer utilises all available tools and techniques in a logical way and does not become blinkered by the all too familiar and often limited pharmacopoeia based methods.

$\beta_2$ adrenoceptor agonists (relievers) such as salbutamol when administered by the inhalation route result in bronchodilation within minutes of the drug delivery. The therapeutic effect of the inhalation route is very efficient with the same therapeutic response being generated by the administration of 100 $\mu$g of inhaled drug as 4 mg by the oral route. The onset of the therapeutic effect is also significantly enhanced by inhalation compared to that of oral forms such as syrups. The inhalation effect takes only minutes whereas the orally administered syrup can take more than an hour to generate a similar level of bronchodilation. The inhalation route is therefore very attractive for the systemic delivery of drugs provided a suitable drug form and delivery can be achieved.

1.1 Formulation of the medicament

The greater part of the formulation is made up of the propellant system. In general the propellant constitutes between 70-99% by volume of the total. In most practical cases it is greater than 90%. The API is generally present in very low concentration, typically
between 50-200 μg per actuation, significantly less than 1% of the total. The propellants are liquefied gases and are preferred over compressed gases because of their ability to maintain a constant vapour pressure during the life time of the product and are not affected by the number of doses removed from the container.

Historically the propellants were of the CFC type with propellants 11, 12 and 114 being the preferred choice. Having 3 propellants with very different density, solubility and propellant pressures gave the formulator more choice than today where the ozone friendly HFA propellant 134a and 227 are used. Although the two HFA propellants offer density and solubility differences the propellant pressures are significantly closer than in the CFC’s, giving less flexibility with respect to propellant pressure and consequently the velocity of the spray.

The active drug or API needs to be delivered to the target area, in this case the lung in the most efficient way. As will be discussed later the particle size required for particle penetration to various parts of the lung has been reasonably well established such that the desired clinical effect can be achieved. The role of the product formulator is to ensure that the API is formulated such that it meets all of the requirements needed to satisfy the regulatory authority, with the primary focus on safety, efficacy and reliability for the shelf life of the product.

The API is either dissolved or suspended in the propellant. The simplest formulation is where the drug is soluble in the propellant and the formulation only contains the API and a propellant. In reality this is a very rare situation and the API generally needs to be dissolved in a co-solvent in order to produce a solution, therefore the simplest practical solution would contain three ingredients, API, propellant and co-solvent. The first step in the development process is to determine the solubility of the API in the propellants being considered as partial solubility of the API can lead to crystal growth and Ostwald ripening, which will result in a deterioration of the product performance due to the growth of the API particles in a suspension formulation.
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Formulations that contain drug in a suspended form will require the raw drug particles to be in the size range required for inhalation. The upper limit for inhalation is generally accepted as less than 10 μm and ideally the size should be less than this to allow for increase in size of the drug particles during the shelf life of the product due to factors such as agglomeration, crystallisation, Ostwald ripening. The most common method for reducing the size of the API is a fluid energy mill (microniser). The microniser uses large quantities of clean filter air to induce high-speed particle to particle collisions. It is the high-energy particle collisions that break up the drug into smaller particles. As the break up is purely mechanical, there is minimal risk of contamination of the drug. The use of large quantities of air help to ensure there is no thermal degradation of the drug and control of heat generated also minimises thermal effects and heat sensitive drugs can be micronised without degradation. However some drug materials do undergo polymorphic changes, these together with toxicology and degradation are outside the scope of this work.

One of the advantages of a solution formulation is the inherent homogeneity (the drug concentration is everywhere constant). In suspension formulations there is the risk of sedimentation or creaming, which is a function of the resolution of forces acting on the suspended particle. If gravity is the greater factor then sedimentation will result. In sedimentation the drug particles migrate to the bottom of the container. If buoyancy is the greater then creaming will occur and the particles will migrate to the surface. Brownian motion complicates the process for the movement of particles with diameters less than 0.5 μm as do processes such as flocculation.

The goal of the formulator is to minimise these effects by density matching the propellant density to that of the drug. However, this process is further complicated by the use of surfactants and the size of the drug particle. The settling velocity of the particle is proportional to density difference and the square of the diameter (based on Stokes law, to be discussed later).
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The patient is instructed to shake the device prior to administration. The key to a good suspension formulation is one that does not separate rapidly after shaking, if it does separate rapidly then there is the risk that the concentration of the formulation will not be homogeneous when the valve refills and the wrong dose level will be administered during the next actuation. Based on the design of the pMDI, the valve refills from the base of the container, if the formulation creams there is the risk of a low next dose and if it sinks there is the risk of a high dose. As a result time becomes a significant variable when testing pMDI’s for pharmaceutical performance.

Surfactants are widely used in the formulation of the pMDI. The term surfactant is used to describe a compound that forms an interaction with a surface. Hence the term surface-active agent is often used to describe such materials. One of the specific properties of surfactants is the specific nature of the polarity of the molecule. To be surface active it must have a polar or hydrophilic end and a non-polar or hydrophobic end. The surfactant aids the dispersion of the drug particles in the propellant by increasing the wetting of particles by propellant. Surfactant can also increase the solubilisation of the drug, the degree to which this is possible depends on the chemical structure of the surfactant, drug and propellant system. Surfactants are also beneficial for the mechanical function of the valve as the surface activity can lower friction. There are only a few surfactants approved for use in pMDI formulations. Sorbitan trioleate was used in CFC formulations but is not as compatible with the HFA propellants as oleic acid.

The surfactant molecules polar end is attracted to the drug particle leaving the hydrocarbon chain end as the outer layer thus increasing the compatibility with the propellant. The amount of surfactant needed will depend on the total surface area of the drug particles; any excess surfactant can form surfactant only droplets. Surfactant only droplets (Figure 1-1) are one of the main reasons the pharmaceutical industry prefers instrumentation that determines mass of the API.
1.2 Chemical, Physical and Mechanical Stability

It is important that the drug and excipients remain stable over the shelf life of the product. The general rule of thumb is that drug substances are more chemically stable in the solid form and that suspension products are therefore the preferred option, however, this needs to be established for every new product. The main source of potential catalysts for degradation comes from extractable materials from the rubber seals and other valve materials. It is normal practice to have an extraction process that removes as many of the extractable materials before the seals are used. It is however important that the extraction process does not detract from the mechanical stability of the seals.
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The mechanical stability of the pMDI is primarily concerned with the valve component and is discussed below. Whereas mechanic stability focuses on the valve, the formulation is the focus of physical stability. The main sources of instability are deposition of formulation onto the surfaces of the valve components or the container, diffusion, crystal growth and coagulation.

The final product is subject to years of stability testing, over a range of temperature, humidity and orientation conditions. Samples are removed at regular intervals for assessment of the physical, chemical and mechanical stability.

1.3 The metering valve

The quantity of drug delivered by the pMDI depends on the concentration of the API in the formulation and the metering volume of the valve. Commercially the volume of the valve will be in the range 25 to 100 μl. The valves are made from metal (stainless steel) or plastic and in some cases a combination of both. A key requirement of the valve function is the reproducibility of the volume delivery (metered) from actuation to actuation and from the start of the units life through to the last actuation, depending on its design.

The valve needs to function reliably for the specific life of the product, which is typically in the range 2-3 years and for the specified number of actuations, typically in the range 60-400. During the life of the product the moving parts of the valve should not stick and this is often achieved by the addition of a surfactant to the formulation or alternatively by pre-treating the metal surfaces with a lubricant. A more recent innovation is the use of a process that lowers the surface energy of the interfaces.
Figure 1-2 the various components used in the manufacture of one pMDI can closure systems (Reproduced by courtesy 3M Healthcare Ltd)

Friction plays an important role in the forces required to actuate the valve. It is important that the friction between the valve stem and the rubber seals does not undergo significant change during the life of the device. If the frictional force increases then the patient or the device (in the case of a breath actuated device) must apply more force to release the dose. This can pose a problem for both young and old or those with any form of infirmity. The typical pMDI device requires a force of approximately 25-35 N in order to depress the stem sufficiently for the metering valve to function and release the dose.

Changes can occur due to a variety of the physical time based changes in the rubber sealing materials. There are also a number of product specific changes that can occur, these can include, but not limited to, the deposition of drug particles onto the surface between the moving components, extraction of additives from the seal materials by the formulation and the time interval between actuations.

The time between actuations can be a significant variable depending on the type of pMDI product. In the use of relievers the patient is generally instructed to use the
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device as and when required (within the limits specified by the patient instruction leaflet or the practitioner) to relieve the symptoms of an asthma attack. This type of use can mean a device not being used for anything between a few days to a few months or longer if the device has been prescribed for a seasonal allergy problem. In the preventer and combination type products the patient is instructed to use the device at regular intervals.

The outer valve seal, can to valve seal and the valve crimp are designed to minimise leakage of the propellant system over a wide range of storage conditions.

Figure 1-3 Stages in the actuation and return of a metered dose inhaler valve

The metering volume dispensed by the device is a function of the dimensions of the valve components used in the construction. The basic valve design has a metering tank,
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ferrule, spring, stem and the rubber sealing components. The dimensions and hence the volume are also a function of the valve crimping process. The basic valve components can be seen in Figure 1-2. During assembly the valve components are crimped into the ferrule. In the manufacture of the aerosol unit the valve and ferrule unit is crimped on to the top of the can. The assembled components in the final configuration can be seen in Figure 1-4. The various stages of the metering process are shown in Figure 1-3.

1. In ‘a’ the device is at rest and in the in use orientation
2. In ‘b’ the device is starting to be actuated (compressed)
3. In ‘c’ the device has reached the point of firing (dose delivery)
4. In ‘d’ the device has been released and started to return to a
5. In ‘e’ the valve has started to refill
6. In ‘f’ the device has returned to ‘a’

The detailed sequence of events during device actuation/firing is as follows; assuming the device is at rest and in the correct orientation (valve down) the metering chamber is full of formulation. The metering valve has in effect two valves, one inlet and one outlet. The liquid part of the formulation is free to enter the valve through the open inlet (ideal situation). When a force is applied to the top of the unit the stem is compressed and starts to move upwards through the metering valve. After a short distance of travel the inner valve seals off and the volume of the metering chamber is now fixed and no material can leave or enter the metering chamber. As the stem continues to move into the valve the outlet opens (this outlet has a variety of names, the side pierce, stem orifice, or valve orifice to name but a few). Once this orifice is open the formulation (under saturated vapour pressure) is emitted from the device.

The rate at which the formulation is emitted by the device is a function of many variables as will be discussed later. It is critical that the force applied to actuate the device is not above a certain value or damage to the valve can result. The damage can be in the form of displacement of a seal, distortion of the valve components or permanent physical damage to the valve or its metering capability. Once the device has
fired and delivered the metered dose, the force is released and the spring in the valve pushes the stem back out of the device. As the stem moves outwards the outlet orifice is again sealed by the rubber outer seal and for a moment the valve is empty except for any vapour remaining from the previous actuation. As the stem continues to return to the at rest position the inner orifice passes through the inner seal and the metering valve is open once more to the contents of the aerosol can and the formulation can now pass into the metering chamber refilling it once more ready for the next dose to be delivered.

1.4 The Formulation Container

The formulation container (bottle, canister, can or closure) for the MDI is made from aluminium; however, glass, plastic and suitably coated materials also find limited use. Clear plastic or glass containers are useful for studies requiring visualisation of the formulation. The container has to be able to withstand the relatively high, saturated vapour pressures generated by the propellant. At room temperature the pressure will typically be in the region of 4-6 bar depending on the propellant, propellant mix and other co-solvents used. However at fairly modest temperature increases the vapour pressure rises very rapidly. Propellant 134a has a saturated vapour pressure of 570 kpa at 20°C, which rises to 1020 kpa at 40°C. The container has to be able to withstand continued cycle between temperatures. The temperature cycle of device is part of the stability protocol used in the development and regulatory submission for inhalation products. The seal between the container and the valve has to be capable of withstanding these high pressures as well as prevent the leakage of propellant out of the device. It also has the function of preventing the ingress of moisture into the formulation.

It is important that the container does not react with any constituent of the formulation. In certain cases it is necessary to coat the can with an epoxy or other suitable coating to prevent any such reactions taking place. The coating process can also reduce the mechanical deposition caused by the surface roughness of container. The coatings can also help to prevent deposition of the API onto the walls of the container. The use of an
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opaque container also serves other purposes such as preventing the patient from seeing
the formulation as well as prevent the transmission of light and ultra violet radiation
that can cause degradation of the API or any other component of the formulation.

1.5 The Actuator, Adaptor or Delivery Device

The terminology for this part of the inhalation device is based on derivations of its use.
The term adaptor is derived from the fact that the unit is designed to fit or ‘adapt’ to the
mouth or nose and hence the term adaptor is commonly used. The term actuator is
derived from the fact that one has to ‘actuate’ the valve in order to deliver the dose. The
primary function of the device is to aid the delivery of the drug to the patient and hence
delivery device is yet another common term.

Figure 1-4 section through a typical pMDI valve can and actuator (Reproduced by
courtesy 3M Healthcare Ltd)
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The actuator is generally moulded from plastic, the most commonly used materials being polypropylene and polyethylene.

There are a wide range of devices available for the inhalation delivery of the metered formulation to the patient. Although there is a wide range of designs, colours and sizes they all have a common design theme that has existed since the inception of the pMDI over fifty years ago.

The basic design is simple, as the actuator has to hold the container in the correct orientation, i.e. valve down and deliver the aerosol generated to the patient via the mouth. Given that the patient is assumed to be in a standing or sitting position and the relative orientation of the mouth, the actuator has to turn the flow through approximately 90 degrees to ensure the above criteria are met (Figure 1-4). The angle will be greater than 90 degrees for administration via the nasal route.

Figure 1-5 examples of the many and varied actuator designs currently in use (Reproduced by courtesy 3M Healthcare Ltd)
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The actuator is often regarded as just an extension of the valve and container but as will be discussed in greater detail later it forms a very important and integral part of the inhalation performance of the product.

The mouthpiece cover is often coloured different from the body of the actuator (Figure 1-5) to aid patient compliance, such that it is relatively obvious which part has to be removed prior to use. The cover is intended to prevent dirt, dust and other contaminants entering the depositing in and around the mouthpiece as these could be inhaled during use. The patient should always replace the cap when the device is not being used. This is particularly important if there were a ready supply of small particulates, fluff, dust etc. as would be found in the pocket or handbag of the user.

There are a number of aspects of the geometry and design of the actuator that affect the performance of the product. The most obvious aspect to the casual observer would be that the spray produced by the pMDI does not impact or impinge on the inside of the mouthpiece. That is the spray/plume needs to be central and the mouthpiece geometry such that deposition on the inner surfaces is minimised.

The airflow paths around the container need to be designed to minimise the pressure drop generated when the patient inhales. The smaller the air paths the greater will be the resistance to inhalation.

The stem of the valve has to form an interference fit with the plastic stem block to ensure that when actuated the formulation does not escape via this route causing a loss of dose to the patient and also prevent the stem from falling out of the actuator should the device be inverted.

The diameter of the orifice in the actuator has a number of influences on the pharmaceutical performance of the product. It is important that the dimensions of the orifice are tightly controlled during manufacture and are free from moulding defects.
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that can restrict the flow and is oriented such that the spray is centred in the mouthpiece.

The length of the orifice also has an influence but there are limits to the length that can be moulded if the orifice has a small diameter, due to the rigidity of the pin that forms the orifice during the moulding process.

The actuator is designed with a small chamber between the ledge onto which the aerosol stem is seated and the actuator orifice and this space together with a portion of the inside volume of the stem form an expansion chamber, into which the formulation will flow and flash, this forms a classic two orifice system.

1.6 Breath Actuated Inhalers

One of the major problems with inhalation therapy is ensuring patient compliance with respect to the correct use and accurate delivery of the emitted drug particles to the lung. One of the main failure modes for correct therapy administration is the inability of the patient to coordinate the two processes of breathing and actuating the device in the correct sequence. This failure mode can best be envisaged by considering two extremes. In the first the patient breathes too early and in the second too late. If the patient has completed the inhalation process before actuating the device then the drug will be deposited in the mouth and upper respiratory tract, any un-deposited drug will then be exhaled. In the second instance the patient actuates the device too early, in this case most of the drug will again be deposited in the mouth and upper respiratory tract, however any drug not deposited will be inhaled when the patient begins to breathe in.

One early solution to this problem was the use of a device called a spacer (section 1.7) a more recent innovation is a class of devices known as breath actuated inhalers. The breath actuated device works by removing the need for the patient to coordinate the press and breathing processes. The patient primes the device and then when ready places the device into the mouth and breathes in (depending on the device design it is also possible to breathe out through the device prior to breathing in).
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Breath actuated devices use a spring to apply the necessary force to depress the container so that the stem is pushed far enough into the valve to release the dose. The reason they do not fire when primed is based on the principle of stopping or blocking the motion of the container, until the patient breathes in. When the patient inhales a pressure drop is created across a flap or vane, once sufficient flow is achieved the vane or flap moves and releases the system that is stopping the motion of the canister and the dose is then delivered. The devices are designed such that the force required to release the blocking or holding mechanism is achieved when the flow rate is pre-designated range, which is normally between 15-50 litres per minute and ensures that the device activates early in the inhalation cycle. If the activation flow rate required to release the dose is too high or the patient is breathing in very slowly or a young/elderly patient is unable to generate sufficient flow rate, there will be a risk that the device will not release a dose. In such circumstances it should be possible to manually override the breath-actuated mode and revert to the basic press and breathe mode.

1.7 The use of Spacer Devices with pMDI’s

The spacer device derives its name from the fact that it increases the space between the mouthpiece of the actuator and the patient’s mouth. There are a very large number of spacers available commercially; they vary in design, size and shape. The very first press and breathe inhalers had very high levels of alcohol in the formulation and the mouthpiece length on these early units was considerably longer than those found on today’s inhalers. The purpose of the longer mouthpiece design is to increase the time available for evaporation of the volatile components, thereby improving the respirable portion of the inhaler spray. There are three basic reasons for the use of a spacer device and they are:

- To overcome problems with patient coordination
- Increase the time for droplet evaporation
- Increase the distance to the throat thereby reducing the velocity of the spray
Poor coordination, high drop velocity and increased drop sizes all increase the oropharyngeal deposition. The reduction of oropharyngeal deposition is beneficial in reducing side effects and increasing the quantity of medicament reaching the lung. Spacer design can be divided into three basic design types.

- Short tube spacers
- Medium volume spacers
- Large volume spacers

Short tube spacers are effectively an extension of the mouthpiece having similar internal widths and diameters. Medium volume spacers are generally of a one-piece design type, with a volume of a few hundred cubic centimetres. Large volume spacers are generally of a two-piece design, so they can be stored and carried more discreetly when not in use.

It is important that the spacer fit to the actuator correctly, without leaks around the interface and the actuator is correctly orientated so that the spray plume is centred in the spacer thus reducing the risk of impaction with the surface.

Some medium and large volume spacers have a valve built into the mouthpiece end of the spacer. The valve prevents the patient from breathing into the spacer. When the patient breathes out, the valve closes and redirects the exhaled air out of the spacer; thereby providing an escape route for the moist air exhaled by the patient. When the patient inhales the valve opens and allows the remaining suspended particles in the spacer to be inhaled by the patient. The design of the medium and large volume spacers is to accommodate the expanding plume emitted from the actuator.

The presence of electrostatic charge is one factor that is known to alter the performance of inhaler devices in general and specifically spacers in. The ideal spacer would be made from or coated with a conductive material.
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There are many problems encountered with the use of spacer devices, patients find them non discrete and bulky. Many asthmatics are self conscious when using their medication and having to assemble a large, rather conspicuous device is less than appealing.

1.8 Cavitation and Boiling

The terms cavitation and boiling are often used interchangeably to describe the formation of bubbles in a liquid. Though the basic mechanics of cavitation and boiling must clearly be similar, it is important to differentiate between the thermodynamic paths that precede the formation of vapour. There are differences in the practical manifestations of the two paths because, although it is fairly easy to cause uniform changes in pressure in a body of liquid, it is very difficult to uniformly change the temperature. Note that the critical values of the tension and superheat may be related when the magnitudes of these quantities are small (80).

A liquid at constant temperature could be subjected to a decreasing pressure, which falls below the saturated vapour pressure. The process of rupturing a liquid by decrease in pressure at roughly constant liquid temperature is termed cavitation.

A liquid at constant pressure may be subjected to a temperature, in excess of the normal saturation temperature, at this point at which point vapour is formed. The process of rupturing a liquid by increasing the temperature at roughly constant pressure is termed boiling.

1.9 Nucleation

In any practical experiment or application weaknesses can typically occur in two forms. The thermal motions within the liquid can form temporary, microscopic voids that can constitute the nuclei necessary for rupture and growth to macroscopic bubbles. This is termed homogeneous nucleation. In practical engineering situations it is much more common to find that the major weaknesses occur at the boundary between the liquid
and the solid wall of the container or between the liquid and small particles suspended in the liquid. When rupture occurs at such sites, it is termed heterogeneous nucleation (80)

The classical treatment using the kinetic theory of liquids is based on only the transient voids that happen to occur because of the thermal motions of the molecules. In any real system several other types of weakness are possible. It is possible that nucleation might occur at the junction of the liquid and a solid boundary. Kinetic theories have also been developed to cover such heterogeneous nucleation and allow evaluation of whether the chance that this will occur is larger or smaller than the chance of homogeneous nucleation. It is important to remember that heterogeneous nucleation could also occur on very small, sub-micron sized contaminant particles in the liquid. This is very significant from the pMDI perspective as most pMDI formulations are based on suspension formulations containing large numbers of such particles. It would be difficult to distinguish experimentally between the two types of nucleation.

1.10 Bubble Growth

The propellant systems used within the pMDI have boiling points well below ambient temperature. Therefore during use the propellant is stored under saturation condition. Any sudden reduction in pressure will initiate cavitation and the subsequent formation of vapour bubbles and once created these bubbles will continue to grow providing they are not limited by space, heat transfer or energy. The diameter of the bubbles will depend on the rate of growth, which can be determined, by the growth rate constant for the propellant system and time. The bubble growth rate is a critical aspect of flash atomisation.

1.11 Focus of the Present Research

The primary focus of the research was the factors that control the droplet size, residual particle size, particle size distribution, mass flow rate and the thrust of the spray. Secondary factors are the angle of the spray plume, evaporation of the droplets and the
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delivery/actuation time. These parameters control the overall efficiency in terms of the
delivery of the drug product. Another key aspect is the interaction of the above
parameters with the intended delivery target, whether to the patient (in vivo) or to some
laboratory particle sizing instrument (in vitro).

Particle size distributions are traditionally measured by means of impactors in the
pharmaceutical industry. In particular the Andersen Cascade Impactor (ACI) is a
widely-accepted instrument. More recently, the Aerodynamic Particle Sizer (APS) and
Phase-Doppler Anemometry (PDA) have begun to make inroads, but the characteristics
of these techniques are less well-known to the pharmaceutical community, so there is
considerable reservation about more widespread adoption of these techniques.

This research seeks to improve the understanding of the performance characteristics
and relative merits of these techniques through a programme of comparative testing and
data analysis. Additional investigations will be reported relating to the standard
measurement technique, which involves using the ACI in conjunction with the USP
throat as inlet port. The work assesses the merits of alternative inlet designs, which
eliminate some of the perceived disadvantages of the USP throat and enable more
meaningful interpretation of the results from the ACI and APS. The interactions of
particles with the USP throat and the various stages of the ACI depend on complex
interactions between particles and rapidly changing flow. Details of these interactions
are investigated using CFD. Finally, basic studies were carried out to document the
spray formation and atomisation processes as well as their interaction with the inlet port
region.
2. Literature Review

2.1 Cavitation, Nucleation and Bubble Growth

The transition from liquid to a two-phase mixture by flashing in pipes and nozzles usually takes place in several stages. Much of the literature focuses on systems in which in the initial stage the liquid is initially subcooled. In most studies liquid encounters a region of decreasing pressure, which may depend on acceleration and/or friction based on the geometry of the specific flow region. When the pressure decreases the liquid is brought to a saturated state. A further decrease in pressure causes the liquid to become superheated. As liquid superheat is obtained, bubble nucleation starts, slowly at first and then more rapidly as the superheat increases.

The nucleation rate is a strong function of the thermodynamic state of the superheated liquid, sometimes varying by orders of magnitude over very small temperature span (81). It is important to note the difference between literature for initially subcooled liquids and those situations as found in the pMDI where the liquid is already at the saturation point prior to the transition to the superheated state and any metastable state.

Shin and Jones (81) developed a distributed model for nucleation in the superheated zone upstream of the throat in nozzles during flashing with the following features:

2. Selection of a nucleating surface, which ties the stability criteria to an obtainable nucleation site density and cavity nucleation frequency in flashing flows.
3. Calculation of the departure size of nuclei in the nucleation zone.
4. Correlation of nucleation frequencies at a given site and the surface density of nucleation sites as determined from the existing data.
5. Determination of the maximum, energy-limited rate of nucleation.
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The nucleation model allows the throat superheat to be calculated within 2%. The nucleation site density was correlated from the data and found to vary approximately with the degree of superheat to the 4th power of the superheat. While the nucleation site density behaviour with superheat was quite similar to previous work, the actual magnitudes were very different due to their functionality with density. The resultant magnitudes of the bubble number densities in the case of flashing were found to be orders-of-magnitude larger than those computed for subcooled boiling.

Bubble sizes upstream of the throat were calculated to be in the range 1-100 mm and were not constant.

Gerum (82) studied the effects of superheat for several fluids including refrigerants, liquid gases, organic liquids and water in nucleate boiling and concluded that in heterogeneous nucleation theory the superheating of the liquid boundary layer in nucleate boiling describes not only the onset of nuclear boiling but also for the boiling crisis. The rate of superheat depends on the thermodynamic stability of the metastable liquid, which is influenced by the statistical fluctuations in the liquid and the nucleation at the solid surface. Because of the fact that the cavities acting as nuclei are too small for microscopic observation, the size and distribution function of the nuclei on the surface necessary for the determination of the probability of bubble formation cannot be detected by measuring techniques. The work of bubble formation reduced by the nuclei can be represented by a simple empirical function, whose coefficients are determined from boiling experiments. They were able to verify the use of heterogeneous nucleation theory to describe the superheating of the liquid studied.

In an accompanying work to that of Shin (81), Blinkov (83) developed a quasi-one-dimensional, five-equation, homogeneous, non-equilibrium model and utilized a microcomputer to calculate the behaviour of flowing, initially subcooled, flashing water systems. Equations for mixture and vapour mass conservation, mixture momentum conservation, liquid energy conservation and bubble transport were discretised and linearised semi-implicitly, and solved using a successive iteration Newton method.
Closure was obtained through simple constitutive equations for friction and spherical bubble growth, and a new nucleation model for wall nucleation in small nozzles combined with an existing model for bulk nucleation in large geometries to obtain the thermal non-equilibrium between phases. The model described was applied to choked nozzle flow with subcooled water inlets based on specified inlet conditions of pressure and temperature, and vanishing inlet void fraction and bubble number density. Good qualitative and quantitative agreement with the experiment confirms the adequacy of the nucleation models in determining both the initial size and number density of nuclei, and indicates that mechanical non-equilibrium between phases is not an important factor in these flows. It was shown that bulk nucleation becomes important as the volume-to-surface ratio of the geometry is increased.

Xu (84) conducted a series of transient critical flow experiments with convergent-divergent nozzle as the break geometry was conducted using a high-pressure steam-water test loop. Experimental results showed that with increased inlet subcooling, the critical mass flow rates are increased, however, the pressure undershoot and liquid superheat at incipient flashing are decreased.

A new wall surface cavity nucleation model was presented. Based on this theory, the conical contact angle at the meniscus of the nucleation cavity is 38° when saturated liquid initially discharges through the nozzles. With increased inlet stagnation subcooling, the conical contact angle at the meniscus is decreased while the curvature radius of the meniscus is increased. The predicted mass flow rates based on the new wall surface cavity nucleation model gave good agreement to published data.

In a study of homogeneous bubble nucleation in stretched fluids, bubble nucleation was studied from the viewpoint of understanding cavity formation within superheated liquids, computational methods were used to determine the work of forming cavities of various sizes within the superheated Lennard-Jones liquid at several negative pressures (85). The reversible work of forming cavities (defined as spherical regions devoid of any particle centres) of various sizes was determined for liquids under tension.
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at various temperatures. A critical cavity size was found to occur, beyond which the liquid would phase separate if not for the imposition of a volume constraint during the simulations. The radius of this critical cavity was found to decrease with an increase in the extent of penetration into the metastable region of the phase diagram, approaching a zero radius at the spinodal.

Unlike stable liquids, the presence of large cavities destabilizes metastable liquids, leading to further spontaneous growth of the cavity. The size of this critical cavity obtained at several temperatures also scaled with the ratio $\Delta \mu/\Delta \mu_{\text{spin}}$ (the ratio of chemical potential at that temperature to the chemical potential at the spinodal at that temperature) to be a natural parameter to correlate data dealing with the problem of bubble nucleation.

To determine the work of forming cavities beyond the critical cavity size, a volume constraint was imposed during the simulations. For at least negative pressure liquids, the work of cavity formation eventually displayed a maximum, decreasing for larger cavity radii. The dependence of the work of cavity formation and radius at the maximum on the temperature and pressure of the metastable liquid is qualitatively similar to that of a critical bubble. They were unsure as to whether cavity formation plays a dominant role in the mechanism of bubble nucleation. A bubble, which is characterized by a region of very low density, is similar to a cavity, a region completely empty of particle centres. Yet, the size of a bubble needed to contain even a few particles, such that the density of the bubble is near that of the corresponding vapour, is large. Thus, for highly superheated liquids, bubble nucleation may proceed via the formation of a small cavity that first serves to destabilize the liquid. As the cavity grows in size, particles may diffuse into the cavity, thereby forming a bubble. Afterward, bubble formation and growth would be driving the phase transition.

In a study aimed at predicting nucleate boiling heat flux values, Shin(86) the complex transport and coupled interface dynamics of nucleate boiling were simulated in three-dimensions using the Level Contour Reconstruction Method. The work was aimed at
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predicting nucleate boiling heat flux values more accurately on a real surface by including the effect of nucleation site density in the numerical model. This was achieved by changing the surface area for a single nucleate bubble corresponding to the wall temperature.

A numerical simulation of heat transfer during growth of single vapour bubbles in nucleate boiling was conducted by Genske (87). In the model presented the region around a single growing vapour bubble in nucleate boiling is subdivided into three parts: a small, ring-shaped zone between heating wall and bubble, called micro-region, the bubble itself, and its surrounding liquid, referred to as macro-region.

A special emphasis was placed on the micro-region as being the most important for heat transfer and a recently developed model put special emphasis on this region, and predicted heat transfer, bubble growth, and departure diameters of vapour bubbles for low to moderate heat fluxes fairly well.

In a study of bubble growth for both soft (slip) and rigid (no slip) bubbles was undertaken by Ivashnyov (88). Two mathematical models describing the thermal growth of a bubble in a stream of superheated liquid were developed. The models differed on whether shear stresses were preserved at the interface. A simple approximation for the dependence of Nusselt number on Jacob and Peclet numbers was developed on the ground of the self-similar solution. Comparison of numerical simulation results obtained using the suggested models with experimental data for a bubble rising in superheated water showed that until the bubble radius does not exceed critical size, determined by liquid superheats, the experimental data fits the model of the “rigid” interface. After the bubble radius reaches the critical size, the experimental points fit the curve provided by the model with a “soft” phase interface. The process of softening a vapour bubble for a phase interface in its growth is likely to take place.
A numerical procedure for spherical vapour bubble growth has been described by Lee(89) the complete process from the thermodynamic critical state over a wide range of pressure and superheat encountered in experimental work.

The disturbance necessary to compute vapour bubble growth from the critical size did not significantly affect subsequent bubble growth except for very low levels of superheat, provided that the disturbance is sufficiently small, and manifests itself as a change in the bubble growth delay time. The delay time converges to a constant as the magnitude of the disturbance decreases. The early stage of the growth was governed by surface tension and liquid inertia, and becomes of significance as either the initial liquid superheat or system pressure decreases. The bubble growth tends to become inertia controlled as either the liquid superheat increases or the system pressure decreases, or tends to become heat diffusion controlled as either the liquid superheat decreases or the system pressure increases.

In a study to measure the bubble size, velocity, void fraction and bubble concentration in flashing flows of propellant 12 behind a sudden contraction, Domnick(90) concluded that nucleation takes place in the re-circulation zone immediately behind the constriction, which is the location of the lowest static pressure. The mean flow field transports these bubbles downstream, during which they undergo further growth.

No additional nucleation was observed downstream of the re-circulation zone. A periodic, cloud type behaviour of the bubble formation was found which could be explained by the interaction between the bubble growth and the mean flow field. This interaction results in strong disturbances of the mean flow field, which manifests as an increase of the fluctuating bubble velocity by a factor of 3 compared to single-phase measurements in a region of 10 step heights behind the constriction. These fluctuations appeared more like a periodic change in the mean velocity rather than a higher turbulence level. The measured arithmetic mean bubble diameters rise from approx. 50-μm in the re-circulation region to about 70-80 μm 50 step heights downstream of the constriction.

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Elias(91) used a bubble transport equation, based on the theory of bubble nucleation and growth, in the analysis of two-phase flashing flows. Spontaneous nucleation at the flashing inception point and heterogeneous nucleation in the liquid bulk are used as boundary and initial conditions, respectively. Analytical solution of the transport equation yielded a constitutive relation for the net vapour generation rate along the tube, which is required for closure of a two-fluid set of conservation and balance equations. The model predictions, in terms of flow rates and void fraction distributions, compare favourably with measured data. A mechanistic representation of the thermodynamic and transport conditions at the flashing inception point is described.

The measured heat transfer data for the saturated flow boiling of R-134a in the narrow annular duct has been studied(92). They concluded that the saturated flow boiling heat transfer coefficient increases with a decrease in the gap size. The effects of the refrigerant mass flux and saturated temperature on the boiling heat transfer coefficient were small but cannot be neglected, flow visualization results from the study showed that the mean diameter of the bubbles departing from the heating surface decreases slightly with increasing refrigerant mass flux. At high heat flux many bubbles generated from the cavities in the heating surface tend to merge to form big bubbles. The mean bubble departure frequency increases with the increasing refrigerant mass flux and saturated temperature and with the decreasing duct size. The boiling heat transfer coefficient, mean bubble departure diameter, bubble departure frequency and active nucleation site density in the saturated flow boiling were correlated in terms of the relevant dimensionless groups.

Lie(93) also reported on investigations of the characteristics of the evaporation heat transfer for refrigerants R-134a and R-407C flowing in horizontal small tubes having the same inside diameter of 0.83 or 2.0 mm. In the study the effects of the refrigerant vapour quality, mass flux, saturation temperature and imposed heat flux on the measured evaporation heat transfer coefficient were examined in detail. The experimental data clearly show that both the R-134a and R-407C evaporation heat transfer coefficients increase almost linearly and significantly with the vapour quality.
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of the refrigerant, except at low mass flux and high heat flux. The evaporation heat transfer coefficients also increase substantially with the rises in the imposed heat flux, refrigerant mass flux and saturation temperature. At low R-134a mass flux and high imposed heat flux the evaporation heat transfer coefficient in the smaller tubes (0.83 mm diameter) may decline at increasing vapour quality when the quality is high, due to the partial dry out of the refrigerant flow in the smaller tubes at these conditions.

In a study to investigation the effect of non-condensable gas present in water, on flash evaporation in water(94) The effect on evaporation rates of air content in flashing water was investigated experimentally in a scaled-down open-channel flash evaporator. The ratio of the local liquid superheat to the equilibrium radius of bubbles was proposed as the correlating parameter for the flash-evaporation heat transfer Stanton Number, and a correlation was developed. The presence of air in the water was found to have an important influence on the process.

A new model for flashing flow based on wall nucleation has been proposed by Riznic(95). Model predictions were compared with experimental data. The bubble number density and volumetric flux transport equations are used. Thus it was possible to avoid the usual assumption of constant bubble number density. A vapour generation rate equation was derived. A correlation for the nucleation site density is adopted for application in the flashing flow scenario.

Following the nucleation process, the next key step is the generation of vapour in the superheated state that is induced by a sudden decrease in the pressure of the system. A study of the growth rate of vapour bubbles in superheated liquids is therefore a key step in the process of understanding and modelling flow in the actuator of the pMDI.

In the problem of heat transfer with boiling, the time history of bubble formation and growth in a superheated liquid is of great importance. Lord Rayleigh took the first step toward an understanding of the process of bubble growth (or collapse) when he formulated it as a problem in the hydrodynamics of an incompressible inviscid
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fluid (96). In simultaneous publications both Forster and Zuber (96) and Plesset and Zwick (97) came to similar conclusions on bubble growth.

Plesset and Zwick concluded that the growth of a vapour bubble in a superheated liquid is controlled by three factors: the inertia of the liquid, the surface tension, and the vapour pressure. As the bubble grows, evaporation takes place at the bubble boundary, and the temperature and vapour pressure in the bubble are thereby decreased. The heat inflow requirement of evaporation, however, depends on the rate of bubble growth, so that the dynamic problem is linked with a heat diffusion problem. They solved the heat diffusion problem. A solution for the radius of the vapour bubble as a function of time was obtained which is valid for sufficiently large radius. Their asymptotic solution covered the range of physical interest as the radius at which it becomes valid is near the lower limit of experimental observation. It shows the strong effect of heat diffusion on the rate of bubble growth. They found good agreement with experimental observations in superheated water.

Forster and Zuber formulated an equation set for the growth of a vapour bubble in a superheated liquid. They showed that two distinct time domains exist: one, of the order of $10^{-4}$ second, during which the effect of the hydrodynamic forces may be an important factor in the growth of the bubble, and another, during which this effect is unimportant. An equation was formulated for the latter. A solution of the problem, in closed form, valid for the entire interval of interest was presented and agreed well with experimental data for various superheats.

Scriven (98) presented both a consolidated mathematical statement of the problem together with an analysis of a single vapour bubble in an unlimited body of superheated liquid when growth is controlled solely by the transport of heat and matter for both pure and binary mixtures, which are applicable to the pMDI systems examined in the research.
2.2 Flashing and metastable flow of fluid systems

Thermodynamically flashing results from suddenly lowering the pressure on a liquid until the bubble point is reached. Further lowering of the pressure will leave the liquid superheated. Under adiabatic conditions the vapour formed can only obtain heat from the liquid. Flashing can also occur when a solution of gas in liquid is suddenly reduced below the bubble point.

Brown and York (99) made a significant early study of the flashing of liquid jets. Liquids forced from a high-pressure zone into a low-pressure zone often cross the equilibrium pressure for the liquid temperature and disintegrate into a spray by partial evolution of vapour, as flash boiling takes place. They reported on a study of the sprays formed by such a process and of the mechanism of spray formation. Sprays from water and Freon 11 jets were analysed for drop sizes, drop velocities, and spray patterns. The break-up mechanism was analysed and data presented to show some of the controlling factors.

A critical superheat was found, above which the jet of liquid is shattered by rapid bubble growth within it. The bubble-growth rate was correlated with the Weber number, and a critical value of the Weber number was found to be 12.5 for low-viscosity liquids. The mean drop size was also correlated with Weber number and degree of superheat.

The spray from rough orifices and sharp-edged orifices was compared with sprays produced from cold liquids by other techniques and was found to be comparable in all respects except temperature.

The flow of flashing liquids through orifices of different orifice diameters, length and surface roughness have shown significant flashing does not occur at temperatures just above saturation, but that a substantial increase above saturation must be provided. The temperature range between which no effect is observed on the jet and shattering occurring in the jet was very narrow (5°C). The mean temperature between these two
limits was termed the shattering temperature. The velocity of particles was calculated from double pulse photography (1 μs duration, 22 μs between exposures) down steam of the orifice.

2.3 Two Phase flow

Two phase flows through pipe and short orifice systems are of great industrial interest. Besides well-known applications in the nuclear and chemical industries, two-phase flow is also important in the development and design of modern aero engines. One of the key areas of research interest is centred on aspect of safety and the ability to model and predict the sudden release of pressurised liquids following the failure of vessels, pipes and valves.

The critical flow of a single-phase gas usually occurs when the speed of sound in the gas is reached (Mach number = 1) at the smallest cross-section. Even though the velocity is high, molecular relaxation phenomena are sufficiently rapid for the gas to be regarded as in thermodynamic equilibrium.

In two-phase critical flow the situation is more complex. Relaxation times for the formation of new interfaces (nucleation), heat, mass and momentum transfer, and the evolution of flow patterns are comparable with the time spent by the fluid in the "critical" region of rapid property change. Although it may be possible to define a mathematical condition of criticality at one location, an entire region (that may include parts of the upstream system) plays a role in determining how this condition is approached. Those readers who are familiar with the difficulties of making any two-phase gas-liquid flow situation "well-defined" will appreciate that we should perhaps not expect to be able to be too precise in our description of these phenomena.(100).

Wallis(100) published a review of critical two phase flow. The purpose of this paper was to give a critical overview of the various analytical approaches that have been taken to two-phase critical flow. Wallis emphasised the need present a general picture
of this field and view the various parts of it in perspective it has been necessary to avoid
detail, especially the repetition of long mathematical derivations. The reader who
wishes to investigate specific questions should be able to find the answer in the cited
literature.

Elias(101) conducted a review of two phase critical flow, with emphasis on the results
from system codes used to model the process. Ten different critical flow models
formulated and tested in the study against an extensive set of data from critical flow
experiments with water as the test fluid.

Sher(102) developed a spray model based on the spatial arrangement of bubbles that
expand in a two orifice system, the bubbles expand and explode on contact forming the
atomised droplets at or just beyond the outlet orifice. The assumed physical model for
the formation of spray by flashing appeared to be corroborated by the comparison
between the experimental results and the theoretical expression for the average drop
size, although the mathematical derivation is based on many simplifying assumptions,
neglecting the effect of interference of bubbles during their growth. The bubble growth
was not in thermodynamic equilibrium. Increasing the operating pressure in the spray
can causes the average drop size to become smaller. As the pressure was increased, the
average drop size is decreased but approach a lower limit. The distribution of droplet
sizes was found to be similar in all of the experiments. Nozzle diameter appeared to
have no appreciable influence on drop size provided there is ample opportunity for
generation of vapour nuclei.

A drop size model based on the geometry of expanding bubbles was developed(102) for
the mass median diameter \(d_{50}\) of the spray as

\[
d_{50} = \frac{K \sigma}{\rho_i} \left[ \frac{h_m^2 P^2 m w^2}{C_p \rho_i T^3 R^2 \psi^{1/2}} \right]^4 \exp(-2.5 \ln^2 \sigma_{GDP}) \exp(\frac{4}{K^2 \Delta P^4})
\]  

(2.1)
The homogeneous equilibrium model (HEM) of two-phase flow has been known for many years. The approach used in this model is to treat the two-phase mixture as a pseudo-fluid that can be described by the same equations as an equivalent single-phase flow. In the HEM the two phases are everywhere in equilibrium with equal velocities and temperatures.

The HEM is effective in predicting the critical mass flux, in long pipes where there is sufficient time for equilibrium to be achieved. Errors can be large (a factor of 5 or so on flow rate) for short pipes,(100), in which there is insufficient time for the vapour formation to proceed to equilibrium. A feature of the HEM is the discontinuity in fluid properties that occurs at the saturation line. As the HEM is based on the ideal case of complete interphase equilibrium, it is possible to derive a set of other models by making other limiting assumptions.

The complexity of two-phase flows is wide-ranging as can be judged by the vast number of models currently available to describe the flow, each depending on the various assumptions made during the respective derivation. Kim(103) presented a comparison of critical flow models for propellant based, two-phase flow, in which 3 basic classes were defined. Within these basic classes there are a number of further models.

1. Homogeneous equilibrium models (HEM)
   - Isenthalpic
   - Isentropic
   - Sajben

2. Homogeneous frozen models (HFM)
   - Wallis
   - Smith

3. Non-homogeneous equilibrium models (NEM)
   - Moody
   - Fauske
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Frozen flow
During the flow through short pipes or nozzles it is assumed that there is insufficient
time for any phase change to take place. Thus the quality or void fraction is kept
constant throughout the expansion.
When the fluid upstream of the nozzle is subcooled liquid, this model implies that no
vapour is formed during passage through the pipe or nozzle.

Sip flow models
Limiting assumptions can also be made about the relationship between the velocities of
the phases. If the void fraction is assumed to be known, based on a an equilibrium or
frozen flow model assumption, one can treat the velocity ratio as a variable and
determine for what value of this parameter the overall mass flow will be a maximum.
There are a number of other limiting assumptions that can be based on other models
that will predict higher critical flow rates than would be obtained with the simpler HEM
assumptions.

Tangren(104) studied the compressible effects in the two phase flow of gas water flow
through a de Laval nozzle. Apply the basic laws of continuity, momentum, energy and
ideal gas equations of state to a mixer, thus deriving an equation of state for the mixture
and an equation of motion for the mixture. The equations were then evaluated for the
special cases of, all gas state, all liquid state and intermediate states. The key
assumptions were:

1. The liquid is an incompressible fluid and the effects of the surface tension,
vapour pressure and viscosity are insignificant.
2. The gas is ideal with negligible viscosity, specific heat and is insoluble in the
liquid.
3. The mixture is homogeneous.
4. The flow is adiabatic and the temperature of the gas and liquid are identical.
5. The flow is laminar, one-dimensional and any expansion or compression of the
gas takes place such that inertial transients can be ignored.
6. The slow varying pressure change is transmitted through the mixture at definite critical/sonic velocity.

Good agreement between the predicted and experimental data was obtained (3-13%).

In a comparison of critical flow models(103) the following general form of the critical flow equation (Hsu and Graham), was used as the basis for categorising models:

$$G_{cr}^2 = \frac{-1}{\frac{\partial}{\partial P} \left[ \frac{q \gamma + (1-q)}{(1-q) \gamma_f + q \gamma_s} \right]}$$

In two-phase one component flow, there are three interfacial transports to consider. \( \partial y/\partial P \), the interfacial momentum transfer determines how fast each component accelerates. \( \partial v_g/\partial P \), the change in specific volume is determined by interfacial heat transfer and \( \partial x/\partial P \), the change in evaporation is estimated from interfacial mass transfer.

As stated previously the homogeneous equilibrium model is an extension of the single flow analysis in that the mixture is homogeneous in phase composition (any sample taken from the bulk would yield the same ratio of vapour to liquid), there is thermodynamic equilibrium between the vapour and liquid components and there is no relative motion (slip) between the vapour and liquid.

Isenthalpic HEM

The assumption of isenthalpic flow is used to solve for \( \partial x/\partial P \) using the thermodynamic relation. \( \bar{h} = h_f + x h_k \).
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\[ G_{cr}^2 = \frac{-1}{\frac{dv_f}{dP} - \left( \frac{v_f}{h_{fg}} \right) \frac{dh_f}{dP} + q \left[ \frac{dv_{fg}}{dP} - \left( \frac{v_{fg}}{h_{fg}} \right) \frac{dh_{fg}}{dP} \right]} \]  \hspace{1cm} (2.3)

Isentropic HEM
In the isentropic assumption the \( \partial q / \partial P \) term is derived from the thermodynamic relation \( \tilde{s} = s_f + x s_{fg} \).

\[ G_{cr}^2 = \frac{-1}{\frac{dv_f}{dP} - \left( \frac{v_f}{s_f} \right) \frac{ds_f}{dP} + q \left[ \frac{dv_{fg}}{dP} - \left( \frac{v_{fg}}{s_{fg}} \right) \frac{ds_{fg}}{dP} \right]} \]  \hspace{1cm} (2.4)

The Sajben HEM\(^{105}\)
The assumption of this model is based on adiabatic flow with friction. This is also referred to as the Fanno line assumption or Fanno flow (named after the engineer, Ginno Fanno). The model is applicable to flow processes, which are very fast compared to the heat transfer mechanism, as defined by a small Eckert number. The Eckert number is a dimensionless number used in flow calculations. It defines the ratio between kinetic energy and enthalpy and is defined as,

\[ Eck = \frac{U^2}{C_p \Delta T} \]  \hspace{1cm} (2.5)

The Sajben HEM is then defined as;
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\[ G_{cr} = \left[ \frac{h_f}{\nu_f} \left\{ \frac{d(h_f - h_g (\nu_f / \nu_g))}{dP} + (1 - q) \nu_f + q \nu_g \left[ \frac{d(h_g / \nu_g)}{dP} - 1 \right] \right\} \right]^{1/2} \] \quad (2.6)

Homogeneous frozen models

A second class of models, the homogeneous frozen models (HFMs), were developed for application where the flow is homogeneous but a restriction is imposed by a limitation on the interfacial mass transfer, due to insufficient time for vapour generation \((\partial x / \partial P = 0)\). The other assumption is that there is no slip between phases \((\gamma = 0)\).

The Wallis HFM

\[ G_{cr} = \left\{ -\left(q \frac{dv_g}{dP} + (1 - q) \frac{dv_f}{dP} \right)^{-1} \right\}^{1/2} \] \quad (2.7)

The Smith HFM was developed using a previously proposed pressure volume relationship for an isentropic process(104).

\[ G_{cr} = \left[ \frac{q C_{rg} + (1 - q) C_{rf}}{q C_{rg} + (1 - q) C_{rf} (\frac{P}{q v_g})} \right]^{1/2} \] \quad (2.8)

The non-homogeneous equilibrium models

The non-homogeneous equilibrium models (NEMs) are more complex than the HEMs or HFMs as they consider all three interfacial transportations without limitations. The interfacial slip velocity \((\gamma \neq 1)\), for which an expression must be derived in order to solve the equation.
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The Fauske NEM
The Fauske NEM defined the critical flow to occur at the point of maximum pressure gradient for a given flow rate and quality, thus \( x \) and \( G \) are fixed and \( P \) is then only a function of \( \gamma \). The term \( \frac{\partial x}{\partial P} \) was based on the isenthalpic assumption.

\[
G_{cr} = \left[ \frac{-g_e \gamma}{[(1-q+yq)x] \frac{dv_f}{dP} + (v_g (1+2\gamma q - 2q) + v_f (2\gamma - 2q - 2\gamma^2 + \gamma^2)) \frac{dq}{dP} + \gamma(1+q(\gamma - 2) - q\gamma (\gamma - 1)) \frac{dv_f}{dP}} \right]^{1/2}
\]  

(2.9)

The Moody NEM
The analysis by Moody was based on two-phase annular flow, with uniform velocity and equilibrium flow between the phases. The mass flux \( G \) was expressed as a function of \( P \) and \( \gamma \).

\[
G_{cr} = \left[ \frac{-2g_e (v_f + qv_g)}{a(ad + 2be)} \right]^{1/2}
\]  

(2.10)

Where

\[
a = \gamma v_f + q(v_g - \gamma v_f)
\]  

(2.11)

\[
b = \frac{1}{\gamma} + q \left( 1 - \frac{1}{\gamma} \right)
\]  

(2.12)
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\[ d = \left\{ \frac{1}{\gamma^2 s_{sf}} \frac{\partial s_{s}}{\partial P} - \frac{1}{s_{sf}} \frac{\partial s_{f}}{\partial P} \right\} + \chi \left\{ \frac{1}{\gamma^2 s_{sf}} \frac{\partial (s_{sf} \gamma^2)}{\partial P} - \frac{1}{s_{sf}} \frac{\partial s_{sf}}{\partial P} \right\} \]  
\[ (2.13) \]

\[ e = \left[ s_{sf} \frac{\partial}{\partial P} \left( \frac{\gamma v_f}{s_{sf}} \right) + \left( \frac{\gamma v_f}{s_{sf}} \right) \frac{\partial s_{s}}{\partial P} - \left( \frac{v_s}{s_{sf}} \right) \frac{\partial s_{f}}{\partial P} \right] + q \left[ s_{sf} \frac{\partial}{\partial P} \left( \frac{v_s}{s_{sf}} \right) - s_{sf} \frac{\partial}{\partial P} \left( \frac{v_f}{s_{sf}} \right) \right] \]
\[ (2.14) \]

There is an additional two phase flow model that can be added to the list of critical flow models defined by Kim(103). A non-equilibrium relaxation model for one-dimensional two-phase flow has been defined(106). In this model the relaxation time accounts for the non-equilibrium evaporation leading to metastable liquid conditions.

2.4 Atomisation and Spray formation

The atomisation of liquids is a complex process and has been the subject of much research since the first mathematical analysis of drop formations were carried out in the late 19th century by Lord Rayleigh(81). In his analysis Rayleigh studied the distortion of a cylinder, considering only the inertia and surface tension forces. He assumed a disturbance of the sine form and confined himself to linear analysis and defined a relationship between the cylinder and the resultant spherical drop diameter(107).

The complex process of atomisation can be split into three very broad categories based on the primary mechanism driving the droplet generation process and they are:

- Mechanical
- Effervescent
- Flash.

The mechanical mechanism of atomisation is the least efficient of the three mechanisms producing droplets that are generally an order of magnitude greater than those produced
Chapter 2 Literature

by the other two mechanisms when utilising the same fluid properties and drive pressure. The mechanical atomisation process is dependant of material properties, the geometry of the flow and the driving force. The atomisation proceeds through many distinct phases from the basic droplet formation, through first-wind, second-wind and full atomisation.

The Weber number (We) determines the transition to mechanical break-up, with values in the range 10 to 20 defining the critical range.

\[ We = \frac{\rho U_{rel} D}{\sigma} \]  \hspace{1cm} (2.15)

The diameter of the liquid is a key parameter in mechanical break-up as the jet relative velocity to the surrounding air only happens at the periphery of the liquid jet and the core of the jet is protected from the shear interaction. If the jet slows rapidly before the core region has broken up the velocity will be insufficient and large drops will ensure. To overcome this limitation the exit velocity and hence drive pressure must be relatively high compared to other atomisation mechanisms.

The complexity of atomisation has lead to many models each of which are generally correlations based on dimensionless or non-dimensionless groups depending on the degree of mathematical rigor applied in the analysis.

The effervescent atomisation technique is a relatively new technique that was developed as a natural progression from the relatively simple mechanical atomisation. In the search for improved atomisation from the simple plain orifice system workers developed various techniques to improve the efficiency by introducing a second fluid, usually a gas, to aid the basic mechanical atomisation process. These two fluid atomisers are now found in many commercial applications covering a range of industries. There are a number of distinct techniques including, air blast, pre-filming and the natural progression was to introduce the fluid more uniformly by effectively
Chapter 2 Literature

‘foaming’ the liquid fluid with the gaseous fluid. The effervescent techniques are more efficient atomisation methods (lower drive pressure for equivalent droplet size) than the basic two fluid techniques.

The flash atomisation technique applies to situations where the fluid is held generally under sub-cooled or saturated conditions. When the pressure of the fluid is suddenly decreased the liquid becomes superheated and the fluid cavitates with the formation of a gaseous bubbles. There are two types of flashing mechanisms, one where the gas or vapour is chemically the same as the liquid as in the case of propellant 134a used in during this research work and systems where a gaseous material such as carbon dioxide is dissolved under pressure into a liquid as can be found in many fizzy drinks processes. The first of these produces a one component two-phase flow whereas the latter produces a two component two-phase flow.

Flash atomisation is a thermodynamically driven process and as such there are a number of key material properties that have been used as the basis for predictive the drop size from the flash atomisation mechanism. Early studies of flash atomisation determined that the degree of superheat was critical in determining drop size and break up distance from the orifice. The degree of superheat is given by the temperature difference between the liquid reservoir temperature (stagnation temperature) and the fluid temperature at the equilibrium pressure in delivery region, downstream of the orifice. Under conditions of low superheat the effect of nucleation and bubble growth are limited and the atomisation process proceeds by the mechanical break up mechanism. For flashing based sprays a critical degree of superheat can be defined above which flashing is the dominant mechanism and below which mechanical break up dominates. In the region of critical superheat both mechanism play a significant role.

In flashing flows the point at which rapid nucleation and bubble growth occur can vary significantly with both fluid and degree superheat to the point where the onset of flashing occurs downstream of the exit orifice. The change in atomisation efficiency above the critical superheat can be very dramatic.
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As the degree of superheat increases the mechanical break up component decreases and bubbles can be observed in the liquid jet downstream of the orifice. The distance to where the bubbles form is defined as the idle time or nucleation period. Once formed the bubbles grow rapidly and result in the fluid filament shattering.

A two-phase flow can be generated under conditions of high superheat as nucleation and bubble growth can ensue upstream of the orifice exit plane or the orifice itself. If the geometry of the flow is such that an expansion to the flow path is encountered rapid nucleation and bubble growth can ensue and a well developed two-phase flow can develop upstream of the orifice section.

Another key variable is the Jakob number (Ja), which is also a parameter in many bubble growth calculation schemes.

\[
Ja = \frac{C_p \Delta T \rho_f}{h_{fr} \rho_g}
\]  

(2.16)

The effervescent and flash mechanism share many features in common and produce similar atomisation efficiencies. In effervescent atomisation a key variable is the air to liquid ration (ALR) that has many similarities with the void fraction in flash atomisation.

There have been a number of pMDI spray visualisation studies conducted to study aspects such as duration of the spray, shape, size, structure and velocity. In a study of the spray structure(108) four commercially available formulations were evaluated using high speed (200 frames/s). The actuators were shaken and actuated 3 times, 30 seconds apart, into still air and the spray images recorded. All four types gave similar plume shapes with the duration of the spray ranging between 65 and 95 ms. The average spray velocity was calculated as 13-17 m s\(^{-1}\) in the early stages but decreased over the next few frames to 3-7 m s\(^{-1}\). The plume was identified as having two distinct phases; the
Chapter 2 Literature

first a jet phase followed by a cloud phase after 10-15 ms. The plume was short lived and extended to a distance of 150 mm.

In a study of the flash boiling of heated water(ejected into heated air at ambient pressure (a relatively low level of gas co-flow was used). The air temperature ranged form 300 to 426°K, with an orifice diameter of 0.34mm and jet length 1.37 mm. The break regime just down stream of the orifice was studied using two types of illumination. The first used short duration back illumination of the emerging spray and the second used scattered light.

The drop size was measured using a laser light scattering technique at distances of 20, 40 and 60 mm from the spray exit. Droplet size was seen to decrease with distance from the orifice. The scattered light illumination technique showed spray patterns similar to those seen by other works using this technique. The short duration back illumination (20 ns) gave a very different set of images showing clearly that there was a more solid core at the centre of the plume which could not be interpreted from the light scattering images, which obscured this effect. Liquid mass flow was seen to decrease with increasing temperature and a dramatic mass flow transition occurred between 426 and 432K.

2.5 Flow through an orifice, short tubes and twin orifice systems

The flow through an orifice or short tube can be determined from the assumption of an incompressible, steady state, non-viscous flow with negligible friction losses. Under these conditions the Bernoulli equation can be reduced to conservation equation relating two points in the fluid flow.

\[ P_{up} + \frac{1}{2} \rho u_{up}^2 = P_{dn} + \frac{1}{2} \rho u_{dn}^2 \]  \hspace{1cm} (2.17)

Given that \( Q = AU \) and \( \beta = D_{dn} / D_{up} \) this can be rearranged to give
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\[ Q = C_d A_{dr} \sqrt{\frac{1}{1 - \beta^4}} \left( \frac{2(P_{up} - P_{dn})}{\rho_i} \right) \]  

(2.18)

When a gas passes through an orifice or short tube an expansion factor \( Y \) accounts for the adiabatic expansion of the gas

\[ Y = \sqrt{\frac{r^{2/k}}{k-1} \frac{k - 1}{1 - r^{(k-1)/k}} \frac{1 - \beta^4}{k - 1 - r - 1 - \beta^4 \rho_i^{2/k}}} \]  

(2.19)

The flow of an incompressible, laminar, viscous fluid flowing through a cylindrical pipe was determined independently in the 19\(^{th}\) century by G. Hagen and J-L Poiseuille and is referred to as the Hagen-Poiseuille equation.

\[ Q = \frac{\pi (D/2)^4 \Delta P}{8 \eta L} \]  

(2.20)

The orifice in the valve stem of the metering unit and the orifice in the actuator, control the flow of propellant in a pMDI device. The study of fluid flow through two orifices in series(110) has reported the relationship that exists for both liquid and saturated liquid flows in the two orifice configuration found in the pMDI.

The flow through the final orifice of a pMDI device is more complex than may at first appear due to the complex two phase processes occurring in flashing flows.
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In gas flow through an orifice there is a point where the gas velocity reaches sonic conditions. In air this occurs when the absolute pressure ratio is 0.528, where $P_{dn}$ is the downstream pressure and $P_{up}$ is the upstream pressure.

$$r_{cr} = \frac{P_{dn}}{P_{up}} = 0.528 \quad (2.21)$$

The critical pressure ($r_{cr}$) for a gas is defined as

$$r_{cr} = \left(\frac{2}{k+1}\right)^{\frac{k}{k-1}} \quad (2.22)$$

The sonic velocity in an isentropic gas is defined as

$$V_s = \left(\frac{P \cdot k}{\rho}\right)^{0.5} \quad (2.23)$$

Figure 2-1 Flow through an orifice, flow is constricted at vena contracta and recirculation of the fluid occurs in the stagnant areas behind the restriction (coloured grey)
Chapter 2 Literature

Once the sonic velocity for the fluid is reached the flow becomes choked. The parameter that becomes choked or limited is the velocity. If the upstream pressure is further increased there is no increase in the velocity through the orifice, however, an increase in mass flow rate will be observed, as the density of the fluid will increase with increasing pressure.

When the flow through an orifice is a one component, two-phase flow, the pressure, mass flow rate relationship is more complex. The complex nature of two-phase was discussed earlier.

The study of flow of refrigerant materials is important for many industries, as a consequence there are many studies reported in the literature(92, 93, 103, 111-124). The flow studies include visualisation of the flow, the influence of tube diameters, surface tension, flashing, met stability and heat transfer rates. The Study of two-phase flows in circular tubes covers a period of more than 40 years. The two-phase flow patterns observed in horizontal tubes are complicated asymmetry of the phase resulting from the influence of gravity and liquid shear. The generally accepted flow patterns are bubble, slug, stratified, wavy and annular(124). Various authors have produced two dimensional phase flow maps with gas and liquid velocities as the responses with contour lines showing the boundaries between the varies flow patterns listed above.

It is generally the case that certain material properties are not required when calculating the pressure drop for flow in pipes or tubes found in most practical applications. In the calculation of frictional flow in pipes the only physical parameter required for the fluid is the viscosity. In the calculation of entry losses in the flow through pipes the only physical parameter required is the fluid density.

The primary object of the drug delivery system designer is to achieve maximum lung penetration and this has created in recent years, due to the increased power of computers and more sophisticated software tools, a growth in the area of computer based modelling the of both the flow and deposition of particles and droplets as they
pass through the mouth, throat and upper respiratory tract and in some cases to back up the work with experimental data.(17, 20-25, 27, 29, 30, 34-36, 38, 125-140)

In the study of the pMDI the sonic velocity in a two-phase flow has been considered when calculating the exit velocity of the spray from the actuator orifice(5, 141). Both authors derive the same basic equation set, using different derivation routes. In another pMDI study the critical pressure ratio was used to calculate the velocity of the gas and liquid components(4).

Due to the wide range of industrial applications, two-phase flows have been the subject of a much research. Fletcher based his pMDI sonic flow studies on the two-phase work of Tangren(104). Clark extended this work and used the two-phase work of Wallis in his derivation of equations to describe the mass flow under choked conditions in the pMDI.

The most important feature of flashing liquid flows appears to be the non-equilibrium vapour generation process as the pressure drops. It manifests itself by the liquid’s failure to begin evaporation when saturation conditions are reached, leading to metastable conditions. As a result, the classical homogeneous equilibrium model, assuming equilibrium vapour generation, fails to reproduce not only qualitatively but also quantitatively measured distributions of the flow parameters(106).

Other studies of flashing and two phase flows, include the critical flashing flow through a relief line(142, 143), two-phase turbulent jet flow(144), non-equilibrium relaxation model for one dimensional flashing liquid flow(106), discharge characteristics of gas liquid flow(145), atomisation of liquids through a plain orifice(146), steady state multiple choked compressible flow for single, two phase flows(147), Prediction of single and two phase flow contraction through a short orifice(148), bubbly flow through an orifice or abrupt pipe constriction(149) and the Equal Velocity Unequal Temperature (EVUT) model(150).
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The flashing flow of a propellant behind a sudden constriction was used by Dunbar to explain the apparent pulsing of the spray produced by the flashing flow through the nozzle of a pMDI device.

2.6 Particle deposition

Particle inertial deposition in a tube with an abrupt contraction was studied experimentally and numerically at low pressure. Measurements were performed for particle deposition onto an orifice plate in a tube under low pressure and Reynolds number. The observed deposition-efficiency curve as a function of the Stokes number were different from those obtained under atmospheric conditions.

Cascade impactors are widely used in the characterisation studies of aerosol particles size. Although cascade impactors play a key role in this assessment there are practical limitations to the value of data generated under ideal laminar flow conditions to those found in practice where the flow field is often turbulent. It is therefore critical that turbulent deposition of aerosol particles is fully understood in order that the data from cascade impactors can be interpreted appropriately.

In a study of laminar dilute suspension flows of micron-particles were simulated in realistic double bifurcations with curved inlet tubes, using a commercial finite-volume code with user-enhanced code. The resulting airflow patterns as well as particle transport and wall depositions were analysed for different flow inlet conditions (uniform and parabolic velocity profiles), and geometric configurations. The curved inlet segments had a quite pronounced influence on airflow, particle motion and wall deposition in the downstream bifurcating airways. In contrast to straight double bifurcations, those with bent parent tubes also exhibit irregular variations in particle deposition. Under some flow conditions in sharply curved lung airways, relatively high, localized particle depositions may take place.
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In a study of the deposition of aerosol particles in a straight tube with a diameter of 0.5 cm sudden constriction (152) with hydraulic diameters between 0.22 and 0.25 cm with Reynolds numbers between 140 and 2800, it was concluded that deposition occurred after the constriction at a distance of 10 tube diameters. The deposition in this region increased with increasing flow rate, deposition also increased with particle size.

Particle deposition in a tube with an abrupt contraction has been studied numerically and the results compared with available experimental data (153). A two-dimensional fully developed flow field was obtained by solving the Navier-Stokes equations numerically using a computer program. Particles were deposited on the contraction due to inertial impaction and interception. The deposition efficiency was calculated by tracing particle trajectories in the flow field. Through parametric studies, a general correlation curve, giving the deposition efficiency as a function of modified Stokes number was obtained to characterize particle deposition in the abrupt contraction. The theoretical models were found to agree well with available experimental data and were successfully applied in predicting particle deposition.

In a study of deposition in a constricted tube designed to mimic part of the upper airway narrowing (stenoses) it was concluded that deposition could be described for all conditions using Reynolds number, Stokes number and Mach number (154).

Particle dispersion and deposition in a horizontal turbulent tube flow have been studied using a Turbulent Diffusion Model. Dispersion and deposition are modelled as the combined process of turbulent diffusion and gravitational settling. The particle diffusion is expressed in terms of the fluid diffusivity, taking into account the inertial effect. A one-dimensional solution to predict the two-dimensional deposition flux in a tube, and it is investigated how this depends on the particle diameter and the Froude number (66).
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2.7 Delivery from inhalation devices

In one of the earliest studies on the effects of formulation variables and actuator design on the particle size performance of the pMDI\((/55)\), the spray output from the device was characterised using a multistage cascade impactor. The variables studied included, vapour pressure (by varying propellant ratios and temperature), the concentration of drug in the formulation, particle size of the micronised drug, exit orifice diameter and surfactant concentration. The study used propellants 12 and 114 and the drug substance was dexamethasone sodium phosphate.

The work of Polli et al \((/50)\) appeared to give an excellent baseline for the system effects produced by the major system variables encountered in the design of the pMDI system.

The following conclusions were made:

Drug concentration at three levels produced a range of mass median diameters from 3.2 to 18 \(\mu m\). The increase in particle size was attributed to the following:

- Decreased efficiency of the spray orifice to break-up agglomerate.
- Decreased efficiency of the expansion chamber.
- Decreased ratio of propellant concentration to steroid concentration.

The level of surfactant was studied at two levels, 0% and 0.2% \(w/w\) with 1.43 mg/g of drug with the following results:

- 0% \(w/w\) surfactant with 1.43 mg/g drug gave a mass median diameter of 4.6 \(\mu m\)
- 0.2% \(w/w\) surfactant with 1.43 mg/g drug gave a mass median diameter of 3.2 \(\mu m\)

Conclusion: Increasing the surfactant level decreased the particle size of the residual drug emitted from the device.
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The spray orifice was studied at 3 levels, 0.46, 0.61 and 0.76 mm diameter using the 1.43 mg/g drug formulation with 0.2% w/w surfactant. The following results were obtained.

- 0.46 mm (0.018 in.) diameter orifice gave a mass median diameter of 3.2 μm.
- 0.61 mm (0.024 in.) diameter orifice gave a mass median diameter of 11.0 μm.
- 0.76 mm (0.03 in.) diameter orifice gave a mass median diameter of 11.0 μm.

Conclusion: Increasing the orifice diameter increased the particle size.

The temperature of the Propellant was studied at 3 levels, 24, 37 and 49°C using the standard formulation containing 1.43 mg/g drug with 0.2% w/w surfactant. The following results were obtained.

- Propellant temperature 24°C gave a mass median diameter of 3.2 μm.
- Propellant temperature 37°C gave a mass median diameter of 2.1 μm.
- Propellant temperature 49°C gave a mass median diameter of 1.8 μm.

Conclusion: An inverse relationship was observed between propellant temperature and aerosol particle size.

The propellant vapour pressure was studied at 3 levels using propellant 12; propellant 114 and a 20:80 mix of 12:114. The following results were obtained.

- Propellant 12 gave a mass median diameter of 1.3 μm.
- Propellant mix 80:20 gave a mass median diameter of 3.2 μm.
- Propellant 114 gave a mass median diameter of 11 μm.

Conclusion: An inverse relationship was observed between propellant pressure and aerosol particle size.
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The effects of drug particle size were studied at 3 levels, 1.4, 4.3 and 5.6 µm using the standard formulation containing 1.43-mg/g drug with 0.2% w/w surfactant. The following results were obtained.

- Drug particle size 5.6 µm gave a mass median diameter of 9.0 µm.
- Drug particle size 4.3 µm gave a mass median diameter of 6.0 µm.
- Drug particle size 1.4 µm gave a mass median diameter of 3.2 µm.

Conclusion: A direct relationship was observed between the raw drug particle size and the mass median diameter of the aerosol produced.

The effect of actuator design (one solution actuator and three mechanical break up actuators) on plume particle size using both light scatter particle size analysis and impactor analysis (Copley twin impinger and Delron DCI-6 six stage impactor) has been reported(156). The light scatter data was generated at various time delays into the spray delivery process. The data for mass median diameter obtained by light scattering showed an increase in particle size (4-9 µm) with increasing actuator diameter (0.2, 0.25, 0.3, 0.4 mm) for both active and placebo formulations.

The timed data exhibits a tendency for the particle size to decrease with time but also a short increase at the start of the time delay (<25 ms). The twin impinger data showed an increase in stage one deposition with increasing exit orifice diameter and the converse for stage two. There was no trend in the actuator deposition, however, the Riker actuator (0.25 mm exit orifice diameter) held up significantly more drug than the other three actuators (Valois design).

Data obtained from the multistage impactor showed the same ranking order as the twin stage impinger data; however, the multistage impactor data analysis will be discussed later. In a later report(157) the author outlined the limitation of the laser diffraction technique and emphasised the importance of understanding the instruments principle of
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measurement. It was also concluded that the particle size data from laser diffraction did not predict deposition efficiency of inhaled particles in the respiratory tract because of the large number of other variables at work in such a complex process. Ranucci(157) also indicated the importance of presenting particle size distribution data correctly when extracting single values to represent the particle size. The distribution relationship, lognormal, log-probability and Rosin Rammler should be correlated correctly to avoid interpretational errors.

Actuator deposition has been shown to be independent of the number of actuations, but does vary significantly (7-22%) from device to device(158).

The length of the actuator orifice has been shown to interact with the diameter when studying the fine particle dose (undefined) obtained from a pMDI(159). The length of the orifice was also shown to be more effective in increasing the normalised fine particle dose.

The actuator mouthpiece diameter has been shown to influence the deposition of larger particle in an oral pharyngeal-laryngeal airway cast(160). The study used a human oral cavity cast with a cadaver pharyngeal cast and air flows of 30, 60, 90 and 120 l/min were used to represent differing inspiratory flow rates. Three mono-dispersed particle sizes were used (2, 4 and 8 μm) and three actuator mouthpiece diameters (15, 20 and 27 mm).

The results showed that only a small percentage of the 2 μm particles deposited in the cast. There was significant deposition as the particle size increased with 90% deposition at 8 μm and high inspiratory flow rates. The authors concluded that a larger mouthpiece diameter gave lower deposition in the cast.

One aspect of the change from CFC to HFA based propellants is the significant water uptake of the HFA propellants. Increasing the water content of a 134a formulation
resulted in a higher MMAD(161). The study also indicated that increasing the valve delivery (metered volume) gave a less variable dose delivery.

The lack of solubility of traditional surfactants in HFA propellants means that a co-solvent is often used. The level of co-solvent may vary from a few percentage points to greater than 20%. Solutions form an ideal mixture if Raoult’s law is obeyed. When two materials are mixed together the resultant vapour pressure can be determined from the mole fraction of each material and their respective vapour pressure. There are two departures from the linear relationship; positive departure if the resultant vapour pressure is higher than predicted and negative departure is the resultant vapour pressure is lower than predicted. The influence of additives on the vapour pressure of 134a and 227 has been studied(161) and mixtures of 134a and 227 with ethanol(162).

Hallworth(163) has demonstrated the effect of formulation variables on the visual nature of the pMDI spray. The work clearly showed the basic nature of the pMDI spray to be that of a turbulent jet, the sputtering of the spray and the resultant large droplets produced by low vapour pressure propellant systems. The work also demonstrated how the image of the spray is altered by the addition of low volatility components such as ethanol and surfactant.

There have been several studies where the use of a video system has been used to evaluate the spray emitted from a pMDI(4, 5, 108, 163, 164). The video systems were either film based or a digital camera and the illumination methods for the spray vary from simple flash illumination to laser sheet. Some of the earlier work concluded that the duration of the spray was significantly less than 100 ms, but this could be due to the limitation of the illumination/camera system used or the specific set up of the lighting orientation and the angle of view with respect to the camera and the spray axis.

A study conducted to evaluate the ability to modulate the spray characteristics produced by a pMDI using formulation and actuator variables has been conducted(165, 166). The study showed the difference in atomisation potential between the two current HFA
propellants (134a and 227) with the higher vapour pressure propellant producing a smaller MMAD. The study also presented a relationship between the non-volatile content and the MMAD when referenced to a baseline non-volatile content and MMAD. The fine particle dose (plates 3 to filter, < 4.7 μm) decreased as the diameter of the exit orifice increased (0.25 to 0.42 mm), the corresponding MMAD also decreased but less significantly as did the associated GSD. The inclusion of non-volatile components such as glycerol or polyethylene glycol in HFA solution formulations for pressurised metered dose inhalers (pMDIs), greatly increases the particle size of the aerosol.

The characteristics of the plume can be further modulated by using non-volatile component together with the choice of propellant and the dimensions of the actuator, to give a chosen fine particle dose and particle diameter. This principle has been used to design solutions, which closely match the performance of chlorofluorocarbon based suspension formulations containing several different APIs as assessed for pharmaceutical equivalence using the Andersen Cascade impactor.

The change to HFA propellants has resulted in the need to develop alternative surfactant systems because the HFA propellants are more polar. Traditional surfactants can be used provided a suitable co-solvent can be found (162). The use of either approach is complicated by the existence of many competing patents and the fact that the science in the area is empirical and the use of predictive theoretical approaches are frustrated by the lack of an adequate database. Developments in this area must also take into account the need to avoid crystal growth and/or adhesion of micronised, suspended drug to internal surfaces(162).
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2.8 A Review of research specific to the pressurised metered dose inhaler

2.8.1 Fletcher (5)

The main focus of the work centred on the mathematical derivation and experimental verification of the various thermodynamic and fluid mechanics aspects of the flow through a twin orifice system.

Fletcher in his initial investigations used metered dose inhalers containing a typical CFC propellant mixture (50:25:25, propellants 12, 11 and 114 respectively) containing 1% w/w sorbitan trioleate ("span 85"). Initial investigations included visualisation of the spray process using a high speed (8000 fps) rotating prism camera and a 7 kW xenon arc lamp.

Three regions were studied;

- Expansion chamber and exit nozzle
- The region immediately downstream of the nozzle
- The whole spray

Atomisation was defined as occurring in two stages;

- Initial break-up in the expansion chamber
- Further break-up during passage through the nozzle.

From the image data the spray front velocity was calculated to be in the region of 30 m s\(^{-1}\) and constant over the first few centimetres of travel. Following the turbulent entrainment of air the spray velocity decayed to < 10 m s\(^{-1}\) at 100 mm. Large 100 μm drops were observed at the periphery of the spray and from the volume of the spray it was estimated that the spray was 90% entrained air and 10% propellant vapour.
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Fletcher then measured the temperature and pressure profiles as a function of time within the expansion chamber. The experimental work included the measurement of pressure (from dial gauges under continuous discharge conditions) and temperature on what was in practice a scaled up version (apart from orifice dimensions) of a typical generic actuator geometry in metal and plastic. The nature of the pressure measurement technique negated the measurement of transient conditions.

In order to simultaneously measure the velocity and particle size Fletcher evaluated several imaging techniques (Very high speed imaging, double image flash photography and holography) however due to various problems no significant progress was made.

One of the most important properties of a spray from a pharmaceutical point of view is the size distribution of the residual aerosol. In addition to being a measure of the efficiency of atomisation of the spray generator, it is this parameter that determines to a great extent, the part of the lungs on which the particles will be deposited. Particles, which are too fine, will, like smoke, be exhaled and those too large will impact on the upper regions of the respiratory tract.

Fletcher fired a number of shots into a sedimentation cylinder and allowing the resultant particles to sediment for 15 hours onto a series of glass slides then carried out an assessment of residual particle size and the particle size data was determined by measuring the particles on the glass slides, before correcting for the effect of droplet collapse (due to drying and surface tension) in order to obtain the actual droplet size.

The data was plotted on lognormal paper and the plots found to have slight curvature. Fletcher then proceeded to plot the data on Rosin Rammler paper and found the plots to approximate to a straight line. The mass median particle sizes were found to be 4.9 μm for a 0.25 mm orifice and 7.8 μm for a 0.58 mm orifice. However the data was confounded by the fact that the metered valves used were 25 and 50 μl respectively. The valve delivery volume of the metered dose pMDI has been shown to influence the drug deposition of the spray(167).
Fletcher then considered the theoretical aspects of axial velocity distribution within the spray and the flow of saturated liquid through a two-orifice nozzle.

The theoretical derivation of an expression to predict the axial and off-axis velocity of the spray was carried out. From the derivation predictions of the axial velocity of the gaseous component of a continuous spray generated by a liquefied gas propellant passing through a two-orifice system could be made. The expression was an approximate semi-empirical prediction. The model requires 3 factors:

1. The apparent origin of the spray
2. The angle of divergence
3. The degree of metastability

Fletcher concluded that the divergence angle of the spray was approximately equal to that of an air jet.

The model is difficult to use as numerical solutions for each of the factors are not easily determined and both 1 and 2 are depended on the method used to determine their value. Following recent advances in technology it is now possible to determine the velocities using techniques such as Particle Image Velocimetry (PIV) and Phase Doppler Particle Anemometry (PDPA or PDA).

The third parameter in the axial velocity prediction was for the degree of metastability. In order to calculate this parameter several thermodynamics equations need to be solved and Fletcher devotes much of his theory chapter to this end. He derived expressions for the mass flow rate of propellant through the upstream and downstream orifice, the mass flow rate through a twin orifice system and the temperature and thereby the quality of the propellant in the expansion chamber. The work was based on the assumption of mass limiting flow and expressions for the sonic based flow were also developed.
The experimental data was generated from continuous discharge experiments only.

Fletcher also proposed an empirical model for the mass median diameter (MMD) of the resultant spray based exclusively on the exit orifice diameter $D$. Fletcher defined an equation that predicted the mass median diameter (residual solute) for a solution-based formulation:

$$MMD = 1.6 \times 10^{-2} D$$ (2.24)

In light of the work carried out by Clark, this model would appear to have limitations, as the only variable is the exit orifice diameter. It may prove a suitable model for a given formulation but the constant would need redefining. The fact that Fletcher settled on such a simplistic model is surprising given his thermodynamic consideration of the flow problem through the twin orifice system.

Data was obtained on particle size and velocity using spark photography an early version of the modern PIV technique. There was also some attempt to use holographic techniques but due to the then state of the art (early 70’s) the results obtained were deemed to be unsatisfactory.

**2.8.2 Clark(141)**

Clark extended the mathematical derivation and modelling work of Fletcher. The work consisted of three main experimental areas:

1. Empirical experiments to determine critical factors in atomisation of pMDI’s
2. Continuous discharge
3. Metered discharge
The empirical spray studies, using the factor dispersion as the response (respirable percentage of the emitted dose, assessed by the metal inertial impaction device, type B, British Pharmacopoeia, 1988) was the main criterion for evaluation. The factors studied included:

1. Drug particle size
2. Surfactant concentration
3. Propellant vapour pressure
4. Solids content
5. Component geometry

Clark then proceeded to derive mass flow rate equations for both critical and sub critical flow regimes.

2.8.2.1 Sub critical flow

The flow model made the assumptions of isentropic behaviour, no heat or mass transfer between phases and the vapour phase acting as an ideal gas. The sub critical mass flow rate was derived from the one-dimensional Euler equation

\[
\frac{U^2}{2} = \int \frac{\rho_e dP}{\rho} \quad (2.25)
\]

\[
\frac{P}{\rho_g} = \text{Cons} \tan t \quad (2.26)
\]

\[
m_s = C_d \frac{\pi}{4} D_s^2 \rho U_s \quad (2.27)
\]
2.8.2.2 Critical flow

For mass discharge under critical conditions Clark used the sonic velocity in a two-phase method developed by Wallis.

\[ U_s = \left[ (\alpha \rho_f + (1-\alpha)\rho_l) \left( \frac{1-\alpha}{\rho_f U_f^2} + \frac{\alpha}{\rho_l U_l^2} \right) \right]^{-1} \tag{2.28} \]

Clark simplified the equation assuming that the velocity and sound and density of the liquid phase would be much higher than the vapour phase.

\[ U_s = \frac{U_f^2 \rho_f}{\rho_f \alpha (1-\alpha)} \tag{2.29} \]

Using the speed of sound in an isentropic vapour the sonic velocity equation can be rearranged

\[ U_s = \frac{kP}{\rho_l \alpha (1-\alpha)} \tag{2.30} \]

In terms of the mass fraction in the vapour phase or quality, as opposed to void fraction this may be written as
The above equations are reproduced from the Clark thesis. It should be noted however that the second sonic velocity equation is dimensionally incorrect. This can be corrected by squaring the first velocity term.

The third sonic velocity equation is again dimensionally incorrect and even when corrected; by again squaring the velocity term, it results in excessively high values for the velocity (exceeding the speed of sound in the vapour) as the void fraction increases. There is also a typographical error as the density should be for liquid and not the vapour.

The sonic velocity equation derived for quality rather than void fraction still contains void fraction and the density terms are inverted. The equation should read

\[ U_s = \sqrt{\frac{kPq}{\rho_s} \left[ 1 + \frac{1 - q}{q} \left( \frac{\rho_f}{\rho_s} \right) \right]} \quad (2.32) \]

From this data an equation to define the mass flow rate under sonic conditions was derived.

\[ m_s = C_d \frac{\pi}{4} D_s^2 \rho U_s \quad (2.33) \]

Where the spray orifice velocity is now the sonic or choked velocity defined above. As both the average density and choked velocity have to be evaluated in terms of the critical conditions thus
Chapter 2 Literature

\[ m_s = C_d \frac{\pi}{4} D_i^2 \left( \frac{k_{cr} P_{cr} \rho_{cr}}{q_{cr}} \right)^{1/2} \]  

(2.34)

Having assumed the vapour obeys the isentropic gas law and defining a critical pressure ratio \( cr \) the mass flow rate may be written in terms of the expansion chamber conditions

\[ m_s = C_d \frac{\pi}{4} D_i^2 \left( \frac{kP_e \rho_e}{q_e} r_e^{-1} \right)^{1/2} \]  

(2.35)

Having quantified the major factors, Clark then developed a computer-based model to predict the actuator conditions (temperature, pressure and exit thrust) during the delivery process. To achieve this goal Clark needed to solve several unknown constants within the flow and thermodynamic equations thus derived. However, very little information is given regarding the computer algorithm used, in addition several parameters needed to be solved by successive approximation.

The computer-based model was then extended to metered discharge, where a further series of equations needed to be solved.

2.8.2.3 Residual Particle Size analysis

Clark measured the residual particle size of the emitted spray from both continuous and metered discharge experiments. This was done using an early version of the aerodynamic particle sizer (APS) manufactured by TSI Inc. The technique uses the time taken for an accelerated particle to traverse a pair of parallel laser beams (a detailed description can be found in the appropriate chapter of this thesis).

Having obtained the residual particle size of the emitted dose Clark then used an equation to extrapolate the size backwards to determine the initial size of the particle at the time of exit from the actuator.
Chapter 2 Literature

\[ D_i = \frac{D_r}{\sqrt[3]{SG_{\text{drug}} \left( \frac{SG_{\text{drug}}}{SG_{\text{propellant}} w} \right)^3}} \]

(2.36)

Where \( w \) is the weight fraction of solute in the formulation and \( D_i \) and \( D_r \) are the initial and residual droplet diameters respectively and \( SG \) is the specific gravity of the drug and propellant. Dombrowski and Brown had previously defined a third root relationship for the solute concentration, in Fletcher(5)

Based on a review of the APS based particle size method developed by Clark, the following observations can be made.

1. The APS needed tuning to reduce false counts (cuts out the smaller end of the distribution).
2. Sampling technique not designed for larger droplets, therefore larger droplets never reach the APS (potentially cuts off the larger end of particle size distribution).
3. Long delay before sampling (settling rates for large droplets) and geometry of sampling volume.
4. Could not validate correlation between initial and final particle size (could not measure initial size, did however, support this with some laser diffraction based particle size data).
5. Uses a dimensionally incorrect, evaporation-based model to extrapolate back to initial particle size (although the error is small).
6. Did not make sufficient use of the metered valve data where the scatter of the particle size data increased significantly as did the apparent slope of the relationship (significant change in the value of the constant, 8.02) and model intercepts at 13 \( \mu \text{m} \) (infinite pressure and unity vapour mass fraction)
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One significant omission is the apparent lack of data regarding the particle size distribution, a parameter at least as important as the mean in trying to define particle sizes and their pharmaceutical deposition potential.

Clark states that the Geometric Standard Deviation (GSD) of the metered actuation is higher than in continuous discharge. This is to be expected given that there is a much wider range of conditions (values of pressure and quality) in metered actuation, whereas continuous discharge has a more defined and narrow range for both pressure and quality, which are both effectively under steady state conditions.

In the thesis appendix there is a section outlining some exploratory work carried out using the, relatively new at the time, technique of Phase Doppler Particle Analysis (PDPA). Dunbar (see below) considerably extended this area of work.

One of the most important outputs from Clark’s work was the generation of a mathematical model that could be used to predict the initial droplet size generated by a pMDI. The inputs to the equation are pressure and the mass fraction in the vapour phase (quality of the spray). It should be noted that the derivation of the influence of the vapour phase was based on the theory of effervescent atomisation (168-171) and is not based on flashing flow but on non-flashing pressurised gases to increase the atomisation efficiency of liquid systems.

The particle size model has limitations; the most notable being that it was developed from continuous discharge conditions only, where \( D_r \) is the residual drop diameter, \( q \) is the mass fraction in the vapour phase and \( P_{ec} \) is the expansion chamber pressure and \( P_a \) is the atmospheric pressure.

\[
D_r \xrightarrow{extrapolate} D_1 = \frac{8.02}{q^{0.46} \left[ \frac{P_{ec} - P_a}{P_a} \right]^{0.56}}
\]  
(2.37)

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The constant was defined by plotting the initial particle size (extrapolated from residual data) against the reciprocal of the denominator from the steady state atomisation experiments. When the equivalent data for metered dose atomisation was plotted the constant changed significantly and the scatter in the data increased considerably. Clark states in the metered data section that the drop size produced by the metering system is slightly coarser than in continuous whereas in the discussion section he reverses the statement. The data plot shows the metered data to be finer and Clark draws the conclusion that the GSD of the metered data was higher. This not surprising given that the equation uses both \( p \) and \( q \) and unless they maintain a dependant ratio during the metered delivery that maintains drop size at a fairly constant value then it follows that the particle size range must be wider. Given that Clark had the pressure profile in the expansion chamber and means to calculate the instantaneous value of \( q \) it is somewhat surprising he did not explore this further for metered applications.

When substituting values for \( q \) into the equation using values for \( p \) from the experimental peak pressure data. It can be shown that the numerical value of \( q \) covers a narrow range, and is close to the value for maximum choked flow predicted by the sonic flow equations used by Clark.

The shape and duration of the expansion chamber pressure profiles measured during metered atomisation do not match those predicted by the computer predictions. The pressure rise is too slow and the duration either too long or too short in many of the predicted profiles. Dunbar on the other predicted very fast pressure rise times, in excess of those found in experimental data.

The values calculated for the orifice discharge coefficient are typical of those expected for a plain circular inlet orifice, and the values are constant across the exit orifice range used. There is, however, a significant decrease in the orifice discharge coefficients determined for the valve orifice inlet. At small diameters there is agreement with those obtained for the spray orifice. Over the rest of the range studied the orifice discharge
coefficient decreases (the author has determined by visual observation (172) that it changes linearly with orifice diameter ($R^2 = 0.98$)). The orifice discharge coefficients were determined from mass flow rate experiments using a range of variables and plotting the theoretical flow rate against actual, the slope being the orifice discharge coefficient.

The significant change in the valve orifice discharge is not explained but the following observations are made

- Typical values for the Reynolds number for the orifice are in the region of 2000 and the discharge coefficient can change in this region (no calculation given).
- The flow impacts on the stem wall opposite the valve orifice (same for all orifice diameters)
- It cannot be taken as evidence of vaporisation in the orifice and violation of Pasque's criteria. Since, with constant wall thickness stems used in these experiments, $L/D$ decreases as $D$ increases and Pasque's criteria show that vaporisation is less likely, not more likely, as $L/D$ decreases.

Clark measured the exit thrust of the spray using a force transducer fitted with a 5 cm target on to which the spray impacted. The purpose of the thrust measurements was to determine the exit velocity from the momentum of the spray plume. The plotted data showed the thrust to decrease more rapidly than expected at distances more than 5 cm from the orifice. The one plot of peak thrust against distance shows the drop off occurring for all spray orifice diameters evaluated. It is noted that the presence of the target will result in divergence of the spray at an angle greater than that in an unconstrained plume, thereby causing the thrust to decrease more steeply than predicted.

Thrust measurements on a range of commercial products (CFC and HFA) has shown the extent to which both the peak thrust and spray duration can be altered by the exit orifice and the propellant system used (173).
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In the sections on continuous and metered discharge Clark uses the parameter variously designated as the discharge diameter, discharge diameter ratio, discharge orifice ratio and orifice discharge diameter ratio. The argument for this approach is to correct for the low valve orifice discharge coefficients (as discussed above). The reasons being that firstly in a continuous equilibrium discharge system the expansion chamber conditions would be expected to be the same for a given ratio regardless of the absolute diameters. Secondly the ratio of the discharge diameters has the property that it tends to zero when the valve orifice is large and the spray orifice is present and infinity when the spray orifice is large and only the valve orifice is present.

A summary of the conclusions drawn by Clark during the preliminary studies are listed in Table 2-1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Effect on dispersion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orifice diameter</td>
<td>Inversely proportional to orifice diameter</td>
</tr>
<tr>
<td>Propellant vapour pressure</td>
<td>Proportional to Square root of pressure</td>
</tr>
<tr>
<td>Surfactant concentration</td>
<td>Inversely proportional to concentration</td>
</tr>
<tr>
<td>Suspended solids</td>
<td>Inversely proportional to log of solids</td>
</tr>
<tr>
<td>Suspended solids size</td>
<td>Proportional to size</td>
</tr>
</tbody>
</table>

It should be noted that the measurement of dispersion were only evaluated in the screening studies conducted in factors influencing metered dose inhaler performance (chapter 4 of the thesis) and therefore none of the above conclusions can be drawn from the main body of the thesis (continuous and metered delivery). The conclusion regarding the suspended solids cannot be drawn from the data presented. The only data on suspended solids shows dispersion to be inversely proportional to the solids concentration. The only data presented for it being inversely proportional to the log of solids concentration is the data from Meakin and Stroud presented in his literature review.
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The Dispersion is stated to be Proportional to Square root of pressure. The limited data presented shows a more linear relationship as does the continuous atomisation data for particle size (dispersion is shown to be proportional to particle size for suspensions) as Clark draws straight lines through the data presented.

Given that Clark has shown in the continuous atomisation chapter that droplet size is inversely proportional to vapour pressure. Then it is surprising to find it presented later in the chapter, when combined with the product of q to have square root term (q is also shown to have a square root term).

2.8.3 Dunbar(4)
The most recent comprehensive research in the area of pMDI atomisation is that of Dunbar(4). Dunbar reported on both the experimental and theoretical aspects of the spray delivered by a pMDI. The experimental work focused on the measurement of particles sized by a Phase Doppler Particle Anemometer (PDPA or PDA). The theoretical aspects focused on developing models for both actuator flow and the pMDI spray.
The work of Dunbar was in three main chapters:

> Experimental work using PDPA analysis of the spray both temporally and spatially
> A theoretical model of actuator flow (computer based flow model)
> A theoretical model of pMDI spray (CFD based analysis)

The experimental work was based around the spatial and temporal analysis of the spray emitted from the actuator using the PDA technique.

The following parameters were determined from the PDPA data:
The number of variables in the experimental work was rather limited in comparison to Clark, being restricted to 3 formulations, 134a placebo and a mixture of P11 and P12 (ratio 28:72 wt/wt) with and without drug (0.133% wt/wt propellant). The drug formulation also contained a surfactant (10% wt/wt drug). The drug-based formulation was a commercial CFC based product.

The PDPA spatial analysis was determined at one point (0.09s into the spray), which coincides with the most pressure stable part of the delivery.

Spray cone angles were determined by photographic methods with means of between 10.8 to 10.9 degrees being quoted for all formulations.

In his work on modelling actuator flow, Dunbar bases most of his work on that of Clark, including the data for the orifice discharge coefficients, for both valve orifice and actuator orifice.

In measurements of the duration of the spray Dunbar reports significant differences in the delivery times of the P11: P12 formulation with and without drug. The drug based formulation having an increased delivery time on average 35% greater than for the placebo.
The data outputs presented by his actuator flow model do not, in the case of outputs that are easily measured such as the pressure rise time, match the experimental data for such parameters in Clark.

Dunbar reports that the only previously reported model that fitted his near orifice data was that of Clark. Although the number of models evaluated was limited. The model is given as:

\[ D_{0.5} := \frac{8.02 \cdot \sqrt{\frac{q^{0.56} \left( p_{ec} - p_a \right)^{0.46}}{p_a}}} \]  \hspace{1cm} (2.38)

Where \( D_{0.5} \) is volume mean diameter, \( q \) is the vapour mass fraction and \( p \) is the pressure (subscript \( ec \) = expansion chamber and \( a \) = atmospheric)

This is an interesting finding given that the model appears to be incorrectly defined in Clark due to a potential typographical error. The plots used to calculate the constant (Clark) have the power terms reversed (compare with Eqn. 2.37).

Dunbar, in his next development, presented data on his theoretical model for the pMDI spray. The model was based on CFD (Computational Fluid Dynamics) modelling.

The model used a separated discrete droplet model (DDM) in which the continuous gas phase and liquid phase interact via source terms (momentum, heat and mass). The turbulent dispersion of droplets in the gas phase in accomplished by using a stochastic model utilising the local eddy interaction. The spray was introduced into the flow domain via a single injection cell. The sizes of the particles introduced into the flow domain were determined from the predicted actuator flow model exit conditions and the initial drop size equation (Clark). Due to the rather large number of droplets produced by real sprays, droplet parcels (same velocity, size, temperature, position and time)
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were used to represent the droplets and the calculations used a statistical, Monte Carlo simulation technique to determine the whole spray properties.

2.9 Cascade impactors and Impaction theory

Impaction instruments are used to assess the inertial properties of particles by categorising their aerodynamic diameter, which is, the diameter of a unity density sphere having the same settling velocity. Aerodynamic diameter accounts for both density and shape factor.

The basic design of impaction devices has been studied both theoretically and experimentally, in numerous published works. The theoretical work is focuses mainly on single jet designs with either round or rectangular jets, whereas the experimental work focuses on the multi-jet commercial instruments. In commercial instruments there is a need to quantify the efficiency and ECD characteristics of the stage, inter and intra stage wall losses, particle bounce, re-entrainment, blow off and mensuration.

Marple et al(174-176) conducted a comprehensive experimental and mathematical modelling of single impactor jets. The flow field in a series of round and rectangular single jets was studied using a 2D numerical solution of the Navier-Stokes equations to compute the flow velocity vectors. Particle trajectories were computed using an nth order Runge-Kutta integration over small incremental time steps. This technique gives the position of the particle at the end of each time increment. The process is repeated and the path of the particle tracked until it either makes contact with a wall or exits the flow domain. The work was further developed by Rader(177) who evaluated the use of finer grids on particle trajectories and the effects of ultra-Stokesian drag. He concluded that finer grids resulted in sharper curves and higher ECDs and the use of the ultra-Stokesian drag coefficient produced a slight upward shift in the impactor efficiency curve.

Details of mensuration studies can be found in Svensson et al(178) Roberts and Romay(179) and mensuration on performance Stein et al(180, 181) details of particle
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size calibration methods can be found in Mercer et al (182, 183), Rao and Whitby (184, 185), Mitchell et al (16, 186, 187) Vaughan (188) and Marple et al (189). Another aspect that requires consideration is that of accuracy and calibration of the particle detecting equipment used in the procedure (187). While the mensuration technique is applicable to establishing and maintaining system suitability only testing against standard particle sizes provides a true calibration.

Limitations in the design of the USP throat with respect to deposition patterns have been shown (190) as well as the effect of flow rate (191) and the actual ECD size range has been debated for some time.

In recent years attempts have been made to assess the particle size by replacing the USP inlet throat with alternative designs like a glass bowl (192) or designs intended to mimic the human upper airway (193).

The use of a medium volume glass bowl type inlet resulted in the MMAD decreasing when compared to the USP throat (192) which is contrary to the results obtained here and can be explained because the glass bowl inlet technique fails to maintain time ordered sampling of the spray throughout the delivery process. The correct sampling regime is essential when using any sampling based instrument like the APS. The glass bowl technique over samples the fine particles that float around in the large void of the bowl and fails to accurately sample the statistically albeit lower in number larger particles resulting in a decrease in the mean size when compared to data generated using the USP or tube design inlets.

2.9.1 Streamlines and particle motion

Inertial impactors function by making use of specific characteristics of curvilinear particle motion. The fluid flow passes through a jet and the output directed against an impaction surface. The proximity of the impaction surface deflects the fluid flow and the flow is forced to turn and travel adjacent to the impaction surface.
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A visualisation of the fluid flow can be obtained by plotting the streamlines. Streamlines are computed from the magnitude fluid flow velocity vectors. The most important aspect of the streamline with respect to the functionality of an impactor is the rate at which the streamline changes direction as it approaches the impaction surface (Figure 2-2). It is a particle's inertia that determines how closely the particle will follow the streamline. As the inertia increases there is a greater probability that the particle will impact rather than follow the fluid flow. The calculated streamlines for a single jet, based on the dimensions of a jet from plate 3 of the ACI, using the average inlet velocity, are shown below.

![Streamlines in jet 3 of the ACI at 28.3 l/min showing angle of contact with impaction plate, S is the jet to plate distance, W is the jet width and T is the jet length.](image)

Figure 2-2 streamlines in jet 3 of the ACI at 28.3 l/min showing angle of contact with impaction plate (S is the jet to plate distance, W is the jet width and T is the jet length).

2.9.2 The Stokes Number

A particle can be defined by a characteristic relaxation time \( \tau_p \) and the flow system characterised by a relaxation time \( \tau_f \).
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\[ \tau_p = \frac{\rho_p d_p^2 C_c}{18 \eta} \]  
(2.39)

\[ \tau_f = \frac{w_j}{2u} \]  
(2.40)

The ratio of the two relaxation times defines the dimensionless Stokes Number.

\[ Stk = \frac{\tau_p}{\tau_f} = \frac{\rho_p d_p^2 C_c u}{9\eta w_j} \]  
(2.41)

\( \rho_p \) is the density of the particle, \( d_p \) is the particle diameter, \( C_c \) is the Cunningham slip correction, \( w_j \) is the width of the jet, \( u \) is the average flow velocity, and \( \eta \) is the viscosity of the fluid.

2.9.3 The probability of impaction

The probability that a particle will impact is determined by the magnitude of the Stokes Number or more precisely by the \( \sqrt{Stk} \), which is proportional to the aerodynamic diameter. Collection efficiency curves are usually plotted against aerodynamic diameter or \( \sqrt{Stk} \). The value \( \sqrt{Stk_{50}} \) is determined at the 50% collection efficiency. Unfortunately there is no uniquely definable Stokes number for an impactor design.

Mercer and Stafford(183) derived streamlines based on simple geometric assumptions that expanded on the work of Ranz and Wong(194). Mercer also conducted a series of experimental studies that showed the plate to jet width ratio was critical in determining \( \sqrt{Stk_{50}} \) and the slope of the efficiency curve was a function of S/W. Marple(174) showed experimentally and theoretically that the square root of the Stokes Number approaches 0.5 for a round jet impactor and 0.75 for a rectangular jet impactor. It was shown that the Stokes Number is a function of several geometrical parameters and
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included the ratio of jet to impaction plate distance \((S)\) to the jet width \((W)\), the length of the jet \((T)\) to the jet width \((W)\) and the Reynolds Number. The optimum values are given in the Table 2-2.

Table 2-2 Impactor design guidelines for round and rectangular jets

<table>
<thead>
<tr>
<th>Jet Type</th>
<th>S/W</th>
<th>T/W</th>
<th>Reynolds Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Round</td>
<td>0.5</td>
<td>1</td>
<td>3000</td>
</tr>
<tr>
<td>Rectangular</td>
<td>1</td>
<td>1</td>
<td>3000</td>
</tr>
</tbody>
</table>

Marple\(^{189}\) issued the guidelines (Table 2-2) for round jet impactors, \(S/W > 1\) and Reynolds Number \(500 < Re < 3000\). The Reynolds Number \((Re)\) is defined as

\[
Re = \frac{\rho jwu}{\eta} \quad \text{Round Jet} \tag{2.42}
\]

\[
Re = \frac{\rho j2wu}{\eta} \quad \text{Rectangular Jet} \tag{2.43}
\]

Figure 2-3 comparison of rectangular and round jets (taken from John\(^{190}\))
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John(195) derived a simple, accurate ECD for both round and rectangular jet impactor designs and showed theoretically (with some assumptions) that $\sqrt{StK_{50}}$ was 0.5 and 0.75 for round and rectangular jets respectively (Figure 2-3).

2.9.4 Other factors controlling impactor efficiency

Apart from the determination of ECDs and efficiency curves there are a number of other important aspects that determine the overall performance of multi-stage cascade impactors. Deviation from ideal performance can be due to addition factors such as, particle bounce, and re-entrainment, blow off and wall losses. Particle bounce occurs when a particle with sufficient inertia to deposit on the impaction surface recoils from the surface and re-enters the fluid flow.

There are a variety of factors that can lead to this type of behaviour, including excess velocity(183), the compliance of the particle, droplet or surface, adhesive nature of the surfaces and energy dissipation(196). There are many studies where the surface of the impaction substrate has been coated with a thin layer of grease(188), grease in a solvent (186), oil, petroleum jelly (184), silicone oil, buffer solution (197), silicone oil (183, 198), silicone spray (199). The impaction surface has also been evaluated and collection surfaces used include stainless steel, glass, liquid, glass fibre and filter paper. When the deposits build up on the impaction surface and a process known as ‘Blow off’ can occur, this is when the particles are loosely bound to previous deposits and the force of the impaction fluid jet and or the incoming particles is sufficient to dislodge the already deposited particles. This problem is can also be related to factors such as the number of doses per test and the concentration of particles in the aerosol.

In the perfect cascade impactor all of the aerosol would be deposited on the impaction plates. Wall losses account for the balance of material and these losses are due to the poor design of the flow paths through the impactor. Vaughan (188) conducted visualisation studies using phosphor powder that fluoresced under ultra violet
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illumination and identified several areas within the ACI where wall losses occurred. He concluded that most deposition occurred in areas where the airflow either converged or changed direction. The losses on jet stage 0 were concentrated in the centre of the stage when the cone inlet was used and were in three distinct regions below each inlet when the pre-impactor was used. There was considerable deposition around the periphery of stage 0 that was reduced in the Mk II, when a hole in the centre of the upper impaction plates was introduced. However, the introduction of the hole altered the flow pattern and produced deposition in the dead space underneath stage 0.

Turbulent flow is another aspect that has been shown to influence the sharpness and ECD is the onset of turbulence, Marple(174) recommended that the best optimum conditions for impactor operation were with a Reynolds number of 3000. It should be noted however that no turbulence models were used during Marples work. May(200) concluded that higher Reynolds Number produced well-defined haloes around the central impaction spot and thus reduced the sharpness of the cut off.

A similar conclusion was reach by Berner(201) who studied the affect of jet to plate distance and Reynolds Number on the size and shape of secondary deposits around the central impaction zone. Berner concluded that reducing the distance between the jet and the plate increased the secondary deposition. The space between the central impaction zone and the secondary (halo) deposits was almost completely free of particles and that the particles in the central impaction zone were larger than those in the halo deposit. This effect was attributed to the fact that the boundary layer near the impaction surface becomes turbulent. Gomez-Moreno et al(52) concluded that as the jet to plate distance increases the stabilising effect of the impaction plate on the jet is diminished and that increasing the plate to jet distance was analogous to increasing the Reynolds Number. In a review of the performance of many cascade impactors it was highlighted that the performance of some stages deteriorated as the Reynolds Number of the stage increased.
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The influence of gravity on impactor performance has been studied by inverting the impactor and a shift in efficiency curves reported (200). The ECD was lower when gravity acted in the direction of flow. Gravity had a more pronounced effect when particle diameters were larger and the flow velocity was low. It was concluded that gravity would have little influence on particles less than 5 um. In a computational study it was shown that the ECD was shifted to the left by inclusion of the gravity term for Reynolds Numbers in the range 10 to 3000 (202, 203).

In an experimental study it was concluded that the effect of cross flow in multi-jet impactor designs would be minimised if certain design criteria were met. Fang et al (198) derived an empirical equation based on the experimental work of Rouf (204), which in turn were based on heat transfer experiments. The equation contains a cross-flow parameter

\[
\frac{x}{D} = 1.06[\chi]^0.27
\] (2.44)

where \(x\) is the deflection distance relative to the jet centre line, \(D\) is the jet diameter. The cross flow parameter \(\chi\) is defined as

\[
\chi = \left[ \frac{1}{mD} \right]^S
\] (2.45)

where \(m\) is the ratio of jet to cross flow mass flux and \(S\) is the jet to plate distance, and the periphery of the flow is defined as

\[
\chi = \left[ \frac{D_sN}{4D_c} \right]
\] (2.46)
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where $N$ is the number of jets and $D_s$ is the diameter of the jet cluster.

Fang(198) in concluding recommended the use of a cross flow parameter less than 1.2.

2.10 Review of the literature

2.10.1 Interpretation of particle size and distribution

The correct interpretation of pharmaceutical particle size data is a fundamental step in understanding and thereby improving drug delivery. A good example of how variation in data interpretation can lead to the incorrect assessment of experimental data can be found in Polli(155) which is a widely used reference for the effects that system variables such as drug loading, pressure and exit orifice have on the performance of a pMDI.

Polli reported that the exit orifice size was influential in the resultant particle size determination and the effect could be dramatic in terms of the MMAD with reported data showing a shift from $3.2 \mu m$ to $11 \mu m$ and a more dramatic shift in MMAD for a change in the formulation drug concentration, with the MMAD ranging from $3.2 \mu m$ up to $18 \mu m$. These shifts are far greater than that seen in the current work and raise an obvious question as to why this should be. The most obvious difference is the type of propellant system used, whereas the current work uses an HFA propellant; Polli used a mixture of CFC propellants and this technique was also used by Clark(141).

The main formulation system used by Polli containing 20% propellant 12 and 80% propellant 114. This mixture produces a formulation with a very low vapour pressure (31 psig, reported) which is not only low in comparison to the HFA systems used in here but is low when compared to most of the older commercial CFC formulations. The 20/80 CFC mixtures (12/114) formed the lowest pressure point in the derivation of the Clark atomisation model and CFC propellant mixtures of similar vapour pressure were shown to produce large droplets at the spray front(163) and probably forms the basis of the visually interpreted and cascade impactor measured ballistic fraction(6, 7).
Analysis of Polli experimental work shows a not uncommon error when analysing cumulative based MMAD data. The error can be relatively simply explained by analysis of the type of data interpretation used to assess the effects of system variables. The flaw in the analysis is to assume all material deposited in the inlet/throat section is larger than that deposited on the first impactor stage. In the analysis of the MMAD response Polli appears to have used the cumulative mass with the assumption that all material deposited in the throat section is larger than the cut off for the first impactor stage and the cumulative plots do not therefore go to 100%. The mass in the throat is taken as part of the total cumulative mass but without a size assignment. Therefore the total drug deposited on the impactor stages is less than 100% and this shifts the interpreted 50% point, given a false MMAD value as can be seen in Figure 2-4. In Figure 2-4 a change of only a few percentage points in throat deposition (from 47 to 50%) shift the MMAD from 4 μm to 16 μm.

The most notable shift in MMAD seen by Polli was for the drug concentration. In the reported data an order of magnitude shift in the formulation drug concentration has no effect on MMAD (3.2 μm to 3.2 μm) but a subsequent doubling of the drug concentration shifts the MMAD from 3.2 μm to 18 μm, a value, it should be noted, that is greater than that of the largest impaction plate (16 μm) present in the cascade impactor used in the Polli study.

It is therefore proposed that the large shifts seen by Polli are as a result of the analysis techniques used rather than for the variables reported and further emphasises the importance placed on data analysis methods and the problems that can arise from not using a statically based assessment of the particle size mean and distribution generated by the pMDI (Figure 2-4).
Figure 2-4 the effect of including throat deposition in total cumulative mass, with the addition of only an extra 3% of particle deposition in the throat section shifts the MMAD from 4 to 16 μm.

One of the major limitations to modelling the particle size generated by the pMDI is the method used to assess both size and distribution. The correct interpretation of particle size data is the biggest challenge facing both the pharmaceutical and device developers.

2.10.2 Modelling the flow through a pMDI

2.10.2.1 Isentropic flow

The speed of sound in the vapour phase is a fundamental parameter in determining the velocity in a choked two phase flow scenario. The isentropic flow assumption is used in the development of the basic homogeneous two phase flow model. In an isentropic flow, the relationship for the vapour pressure (P), density (ρ) and the adiabatic index or ratio of specific heats (γ) can be defined as a constant(141)
Chapter 2 Literature

\[ \frac{P}{\rho^k} = \text{Constant} \quad (2.2) \]

And the speed of sound in an isentropic gas is defined as

\[ u_{\text{sound}} = \sqrt{\frac{Pk}{\rho}} \quad (2.3) \]

The data for the speed of sound in the propellant vapour was taken from the propellant manufacturers data(205) and the pressure, density and ratio of specific heats required for the computation of the speed of sound in an isentropic gas from propellant manufacturers data(206).

The results comparing the manufacturer’s data with the isentropic law are shown in Figure 2-5 and indicate there is a significant difference not only in the value but in the temperature response with the measured values peaking at just under 147 m s\(^{-1}\) whereas the isentropic based value shows an approximate linear increase with temperature.

![Figure 2-5 Speed of sound in 134a propellant vapour based on manufacturers data and computed from the isentropic law](image-url)
Chapter 2 Literature

The speed of sound in an isentropic vapour was used by Clark in the derivation of the mass flow equation that incorporated a simplified version of the speed of sound in a two phase flow derived from classical theory (100, 207). The equation for the speed of sound in an isentropic vapour incorrectly determines the speed of sound for propellant 134a when compared to the supplier's data (205) which shows very little change in the speed of sound over the range covered by the experimental data. Based on this data interpretation the isentropic assumption is not valid.

2.10.2.2 Homogeneous flow

The homogeneous flow assumes that the vapour and liquid phases are uniformly dispersed within the two phase flow domain and is a fundamental assumption used in previous pMDI actuator two phase flow models.

The flow in the expansion chamber and exit orifice region has been studied previously (5, 208) and shows the distribution to be non homogeneous. Data presented in A.V High speed spray image analysis and A.VI Temporal analysis of the spray plume for the axial and transverse spray plume shows the distribution within the plume to be non-homogeneous. The validity of the homogeneous assumption and flow models based upon the assumption must therefore be doubted.

2.10.2.3 Two phase flow model assumptions

The literature review reveals a wide array of models have been used to account for varying aspects to the two phase flow models such as slip, vapour generation, homogeneity etc. It must be recognised that in most published work on propellant based systems has been conducted under idealised conditions where variables such as pressure, temperature, vapour state and flow rate are under controlled conditions and yet there still remains no consensus on two phase flow models and given the transient non idealised flow conditions that exist during the flow in a pMDI an exact solution remains unresolved.
2.10.2.3.1 No slip between phases

The assumption of no slip between the gas and liquid phases during two phase flow would appear to be invalid as published data for the flow of 134a through narrow tubes shows there not only is slip present but it also varies depending on the type of two phase dispersion present, including but not limited to dispersed, bubbly, slug, churn, annular and annular mist and that a wide range of velocity components exist between the two phases (209-211).

It can be concluded that the assumption of no slip between phases would be inappropriate in the modelling of actuator flow.

2.10.2.3.2 Frozen flow

Dunbar has proposed a mechanism for bubble growth within the orifice flow of an MDI (4, 212). The bubble growth rates and vapour generation rates for 134a propellant can be considered to be very high, based on the rapid volume expansion measured in stem and expansion chamber during the start of the metered delivery cycle and the measured vapour pressure recorded within the metering valve during propellant delivery (141).

In previous work it has been postulated that the flow through the exit orifice develops an annular liquid layer and such a flow regime would also support the non-homogeneous assumption (208) however the length of the orifice used in this study was longer than that found in commercial actuators.

It can be concluded that the frozen flow assumption would be inappropriate in the modelling of actuator flow.

2.10.2.3.3 Bubble growth and the rate of flashing

Bubble growth rate is critical in determining whether the saturated vapour conditions can be maintained in the valve during the delivery process. Experimental results for metal valves show this could be the case but in plastic valves it will need to be validated before the assumption can be made with any degree of reliability.
Chapter 2 Literature

The instantaneous flashing of propellant 134a is not well defined. In the flow of superheated liquids from small orifice designs it has been that there is an idle time, usually of the order of a few milliseconds, that can exist prior to explosive expansion taking place\(^\text{(99, 213, 214)}\). The accurate prediction of the early metastable thermodynamics present in the delivery system are not easily solved and could account for the large differences in pressure rises within the expansion volume of the MDI. In the Clark model the pressure rises much slower than would be indicated by the experimental data whereas the instantaneous flashing approach utilised by Dunbar significantly oversimplifies this complex early stage of the delivery process.

It can be concluded that bubble growth rate and flashing are important and supports the assumption made above that the frozen assumption is not valid.

2.10.2.3.4 Metastability

Metastability is the ability of a non-equilibrium state to persist for some period of time. In the case of the flow through the MDI delivery system the state can exist when rapid changes take place such as those observed at the start of the metered delivery process when the rapid flashing of the propellant takes place and thermodynamic equilibrium for the saturated state momentarily fails to apply. The use of the term metastable has often been used in flow modelling of MDI's to account for errors in model prediction rather than limitation induced by the basic model assumptions. Metastability can be expected to play a significant role in the modelling process but its effects could be masked by other factors.

2.10.2.4 Air purging and the potential flow phase of the delivery process

During the very early phase of the delivery process it is assumed that the expansion and stem volume are full of air under ambient conditions. When the valve orifice is open to the metered volume the formulation expands rapidly towards the exit orifice. In doing so there are three possible scenarios;
Chapter 2 Literature

- The air is purged out of the system ahead of and by the advancing propellant
- The air is entrained and mixed with the advancing two phase propellant
- The majority of the air is purged ahead of the advancing two phase flow but some will be entrained by the flashing flow front.

Given the asymmetrical flow path in the stem and actuator volume a large portion of the air can be expected to have been purged by the advancing propellant front.

2.10.3 Atomisation models for the pMDI

The flash atomisation model of Sher(102) is difficult to use as it requires knowledge of bubble growth and the geometric standard deviation and is based on the assumption of ideal gas behaviour. A predictive model requiring the GSD and bubble growth parameters is not ideal for the practising aerosol developer.

The drop size model of Fletcher(5) predicts the mass median diameter to be proportional to the exit orifice diameter (for solution formulations) however published data for solution formulations(192) would indicate a dependence on the orifice diameter it would not appear proportional.

The model of Clark(141) is difficult to use because of the dependence on the quality of the flow through the expansion chamber of the device. The quality (mass fraction in the vapour phase) is a parameter not easily determined and will vary during the deliver process. There is however supporting work for the model as Dunbar(4) reported a good correlation, using phase Doppler anemometry, between droplet sizes, measured for both CFC and HFA based formulations and the predictive equation of Clark but confusion over the correct exponents to be used in the correlation equation (3.8.3).

Dunbar used the value of 8.02 for K whereas in Clark it is stated that this value is applicable only to the continuous atomisation mechanism whereas Dunbar used only metered actuation. When Clark evaluated the metered dose process the value for K was
Chapter 2 Literature

reported to be 1.82 and the correlation coefficient quoted by Clark had also decreased showing far less reliability in the method used to derive the equation.

A further aspect regarding Dunbar’s correlation with the equation is the significant difference in the void fractions calculated in their respective works. Dunbar has the derived void fraction at very high values, generally greater than 99% whereas Clark does not specify any void fractions but it can be interpreted from his two-phase flow work that the void fraction would be somewhere in the region that would give a minimum two phase velocity through the exit orifice and the void fractions in the Clark derivation would be in the region of 27 to 63 % and this range of values is in agreement with the orifice velocity range predicted by his homogeneous two phase flow model.

Had Dunbar had used the metering value of 1.82 for constant in his work then the results would not have given such a good agreement to those generated by Clark, as the droplet size would change by a factor of approximately 4.

During the first half of the delivery process the Dunbar actuator flow model predicted expansion chamber qualities to be less than 0.02 and only exceed 0.01 towards the end of the delivery cycle. Based on Dunbar’s predicted expansion pressures the correlation to Clark should be poor. If it is assumed that Dunbar used his actuator flow model predictions for exit quality rather than expansion quality then the correlation to Clark improves. There is however a number of technical limitations with the Dunbar actuator flow model that need to be highlighted before a full judgement can be made and these are:

- The predicted exit void fraction (>0.992) is excessive for an adiabatic flow based flow model
- The average residence time (<5μs) in the exit orifice is several orders of magnitude too short for the required degree of flashing to occur given the velocity predicted and the length of the exit orifice.
Chapter 2 Literature

- The exit velocity predicted (225 m s$^{-1}$) is well in excess of the speed of sound in propellant 134a (approximately 145 m s$^{-1}$)
- The predicted output of the model fails to transition smoothly between sonic and subsonic flow
- Assumption of instantaneous flashing and the attainment of full saturated vapour pressure irrespective of the orifice or expansion volumes used
- The predicted expansion pressure profile does not match those obtained from the experimental route

The predicted outputs from Dunbar's flow model data have been recalculated by the current author and show the difference between using the expansion volume and final exit condition in the model (Table 2-3).

<table>
<thead>
<tr>
<th>Flow Period</th>
<th>Quality in expansion Volume</th>
<th>Quality at exit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Start</td>
<td>51 μm</td>
<td>4.5 μm</td>
</tr>
<tr>
<td>0.05s</td>
<td>42 μm</td>
<td>4.7 μm</td>
</tr>
<tr>
<td>0.1s</td>
<td>34 μm</td>
<td>5.1 μm</td>
</tr>
<tr>
<td>0.15s</td>
<td>26 μm</td>
<td>6.0 μm</td>
</tr>
</tbody>
</table>

Only 5 of the 10 flash correlation factors presented in a recent review of flash atomisation(215) have a pressure term as a variable and where pressure is used it is in association with one or more thermodynamic system variables and all of the correlation factors are based on a form of internal energy function except the Weber based factors. Which further supports the assumption presented here that what Clark actually measured was an indirect measure of the internal energy function namely the resultant vapour pressure produced by the proportional mixing of two propellant systems?
2.11 Conclusions

The correct interpretation of cascade impactor data is fundamental to understanding the products therapeutic effects and the principles covering the design of delivery technology however much of the published pharmaceutical data results in conflicting opinions as to the basic nature of the distribution produced by the pMDI. A study to understand the functional performance of the cascade impactor is required.

The inlet designs of the cascade impactor will affect how the plate data is interpreted as demonstrated by the Polli data analysis.

An understanding of the atomisation potential of the pMDI requires a study of both the formulation and the critical device parameters such as the diameter of the exit orifice.

Current flow models for the pMDI have limitations either in the complex difficult to measure parameters like quality of the flow or the dependence on limited assumptions regarding the nature of the two phase flow. It is clear that the thermodynamic properties other than pressure play a significant role in determining the size and distribution of the spray.
Chapter 3 Objectives

3. Objective of the research

The primary objective of the research was to develop an understanding of the factors that control the particle size and particle distribution of the spray emitted from a pMDI and how this data is interpreted commercially. It was important that the objective was achieved using methods and techniques acceptable to the pharmaceutical industry and where appropriate develop and understanding of why the standard regulatory defined pharmaceutical methods such as the inertial impactor may not be appropriate in achieving the objective.

The primary particle characteristic used in assessing respirable potential of the dose emitted by a pMDI is the aerodynamic diameter which was studied using both the pharmaceutically acceptable ACI technique and the less acceptable but significantly enhanced aerodynamically capability of the APS technique.

Mathematical modelling of the predicted deposition for a range of inhalation based distributions was conducted using a model constructed using literature values for calibration data applicable to the ACI and to assess the deviation from ideal performance of Andersen cascade impactor thus produced. A CFD model of the airflow through the impaction stages of the most widely used commercial multistage cascade impactor (Andersen non viable eight stage cascade impactor) was developed and the data compared to the aerodynamic data measured by the aerodynamic particle sizer (APS).

It is recognised within the pharmaceutical industry that the design of inlet samplers and the impact they have on the interpretation of particle size is not well understood. To facilitate the correct particle sampling of the emitted dose produced by the pMDI a suitable alternative design for an inlet sampler was developed using the techniques of high speed laser sheet imaging to evaluate plume geometry and computational fluid dynamics (CFD) to understand and then improve the design of an inlet to be used as the sampler interface to the APS to facilitate an improved understanding of the particle size characteristics produced by the pMDI. High-speed digital, laser sheet illuminated video
Chapter 3 Objectives

images was digitally analysed to produce data to assess the fundamental nature of the plume exiting the delivery device.

The currently accepted mechanistic principles driving the atomisation process were evaluated. The currently accepted theories centre on the primary factors being the vapour pressure and the fraction of gas (void fraction or mass fraction in the vapour phase) present in the two phase mixture. To facilitate this aspect a set of experimental studies together with a detailed review of the literature regarding theories and validity of assumptions previously applied to the modelling of two phase flow through inhalers and flash atomisation was undertaken.

The critical review of the literature has indicated that current flow models used to predict the flow through an inhalation delivery system are limited by some of the fundamental assumptions made regarding the thermodynamics and two phase flow used at the core of these models. In practice there is an almost infinite set of solutions that can be generated and to overcome these limitations only the extreme limits of flashing and quality were considered. The potential for developing a suitable two-phase flow model was evaluated. The current flow models were evaluated and critically reviewed.

Force based measurement systems were developed to measure both the effect of variables temperature and pressure and to assess the potential effect that momentum transfer from the spray plume to the test airflow has on throat/inlet geometry.
Chapter 4 Cascade impactor

4. Cascade Impactor

The cascade impactor is the pharmaceutical regulatory bodies preferred instrument for the assessment of new inhalation products and the performance monitoring of licensed inhalation therapies.

Experimental methods and results from the following investigations covering a range of theoretical and experimental performance related aspects of the ACI are reported in this chapter:

➢ Generate baseline ACI data for a solution and a suspension formulation
➢ Outline the functional use of the ACI, calibration methods, components and configurations
➢ Conduct a droplet deposition study to assess the deposition pattern on the first impaction plate
➢ Develop a mathematical model to predict the performance of the ACI based on realistic plate calibration data
➢ Use the mathematical model to assess the ACI response to mono-modal and multi-modal distributions
➢ Conduct a mathematical based study to assess bimodal tendency reported in the literature for the ACI
➢ Assess the practical limitations for combinations of MMAD and GSD and the truncation of distributions by the USP inlet throat
➢ Evaluate the limitations of the lognormal with respect to the lower level applicable for the correlation coefficient
➢ Assess the bounce potential of a suspension based particles at the functionally critical respirable diameter of 4.7 μm
Chapter 4 Cascade impactor

4.1 Cascade Impactor Data for Suspension and Solution formulations

4.1.1 Introduction
The objective of the initial ACI work was to generate a baseline for impactor data for both solution and suspension formulations. The solution formulations used here will be the base formulation to be used in the droplet generations studies. The suspension formulation is used to demonstrate the non lognormal behaviour generally reported for suspension formulations(7). The size and distribution of a solution formulation is a function of the atomisation process whereas the suspension formulation depends not only on the basic atomisation but also on the size of the discrete drug particles generated by the micronisation of the raw drug material and any processes that alter the nature of the association between the discrete drug particles once in the formulation.

4.1.2 Methods for ACI testing
The ACI tests were performed using a standard volumetric flow rate (28.3 l min-1). During each assessment the test units were actuated ten times with a 30 second interval with a shake period prior to each actuation. The ACI was disassembled and the drug deposited on each component analysed(216). Five replicates from each design were tested and the average presented (thanks to L. Marriott and staff of the Analytical Group, 3M Healthcare Ltd, who carried out the analysis). The data presented are therefore the average of 5 test each of 10 actuations.

Andersen cascade impactor testing was conducted using the commercial HFA products QVAR™ (solution) and Airomir™ (suspension).
The suspension formulation was tested using actuators with exit orifice diameters of 0.22, 0.28 and 0.34 mm. The solution formulation was tested using orifice diameters of 0.25, 0.30 and 0.34 mm diameters (the variation in orifice diameters results from the two studies being conducted at different times using different batches of actuators). The upper exit orifice diameter was determined by the point at which the ballistic fraction (USP throat deposition) accounted for approximately half the total drug recovered from the ACI.
The data were analysed and presented using a custom written 3M proprietary software package, the theoretical principles and mathematical processes used in the development of the software can be found in Thiel (6, 7).

4.1.3 Results and discussion

4.1.3.1 Analysis of cascade impactor data – suspension formulation

Using the data analysis method proposed by Thiel (6, 7) it can be concluded that the cascade impactor data for suspension formulation are not, from an ideal perspective, accurately described by the lognormal distribution (Figure 4-1 to Figure 4-3). The distributions have a characteristic S shape rather than the expected straight line expected for the log probability plot.

The suspension formulation shows a deviation from the expected linear correlation. It should be noted that there is no real evidence in the literature to verify that any suspension formulation should conform to a specific distribution because of the complex nature and system variables found in the suspension formulation. The drug was produced by a micronisation technique and should the process produce a lognormal distribution there are many other factors that can alter the size of the particles once in the suspension formulation environment. The level of suspending agent would be expected to influence particle size. Ostwald ripening would also alter the natural particle distribution because of the difference in surface energy levels resulting from the micronisation process and because any solubility of the drug in either the propellant or co-solvent would result in a preferential shift in material from the small sub micron particles to the larger particles (217-219).

The transfer of material from small to large particles and due to the Kelvin effect is primarily a diffusion driven process and is therefore a function of time. It can therefore be expected that particle size and distribution for a suspension formulation will change as a function of time. This type of time-based shift in product performance will have an
impact on the shelf life of the product, given that the product has to maintain a specification (particle size and distribution) within a window based on the data generated at the start of life and the product stability database.

The non-linear regression process (Figure 4-4 to Figure 4-6) results in a significant change in both MMAD and GSD of the data. The MMAD shifts upwards from approximately 2 to 2.5 μm and the GSD decreases from approximately 1.9 to 1.5. Reference to the data plot show that there are 8 data points from the cascade impactor (cumulative mass data from 7 plates plus the filter). Of the 8 data points plotted 4 represent less than 10 percent of the total mass and are at the extremes of the distribution. The correlation coefficient \((r^2)\) used to determine the goodness of fit functions by determining the minimum error terms to the best-fit straight line and the resultant correlation coefficient can be misinterpreted\((172)\).

Data points at the extremities of the linear plot have the greater influence on the calculated error term. The points in the central region have a smaller influence and a point at the centre would have little influence, as it would be possible to rotate the straight line about this point, will little or no effect on the magnitude of the error term for that point.

### 4.1.3.2 Analysis of cascade impactor data – solution formulation

The solution formulations deviated from the lognormal but the deviation was not as visually significant as that found in the suspension formulations (Figure 4-7 to Figure 4-8). The suspension and solution formulation the same propellant systems (propellant 134a) with the suspension formulation having a higher level of the ethanol co-solvent (15% w/w). The distribution of the solution formulation will be governed solely by the atomisation process whereas the suspension formulation may have lognormal droplet distribution whilst the residual particle will be based on the distribution of the particulates within the droplets.
Chapter 4 Cascade impactor

It should be noted that the ACI deposition profile for the much finer solution formulation is centred on plate 4-6 with much greater deposition in the filter whereas the suspension formulation was centred on plates 3-5. The mean particle size is less than half that of the suspension formulation and highlights the advantages of a solution formulation where the particle size is controlled by the atomisation process and not as in the case of the suspension by micronised drug particles and formulation parameters such as surfactant level. In the solution data the upper four ACI plates contain less deposition than the filter.

The GSD of the solution formulation is greater than those determined for the suspension formulation and this could indicate that the atomisation process produces larger droplets than could be predicted by the suspension data. The GSD is a relatively difficult measure to visualise because it is the slope of lognormal distribution centred at the MMAD. In a solution formulation the GSD of the initially atomised droplets will have the same GSD as that of the residual droplet after the co-solvent and residual propellant have evaporated because all the droplets decrease in size by the same ratio\(^{(192)}\). GSD is therefore not easily interpreted when considering a range of particle size without reference to the MMAD; this is not the same when one compares it to the standard deviation of a Gaussian distribution, where the standard deviation would decrease with a reduction in droplet size.

If the data were re-plotted without the upper three plates the MMAD and GSD are both reduced. The drug deposition detected on plates 0 and 1 of the ACI is not that different between the two formulation types, which given the much smaller MMAD of the solution formulation is unexpected and gives further support to the claims that the upper stages of the ACI do not perform functionally as claimed by the manufacture (the functional performance of the upper plates will be discussed later in chapter 4 and the airflow modelled in the chapter 6).
Chapter 4 Cascade impactor

4.1.3.3 Spray orifice diameter

The spray orifice diameter had no apparent effect on the median particle size (MMAD) determined from the ACI data (Table 4-1). The orifice diameter did however, as expected increase the deposition in the induction port of the ACI, as defined by the ballistic fraction (Figure 4-4 to Figure 4-6, Figure 4-10 and Figure 4-12).

A wider range of formulation and actuator variables will be evaluated in chapter 5 where the assessment of particle size will be determined by an instrument designed to measures aerodynamic diameter to a significantly higher aerodynamic resolution than attainable using the ACI.

Table 4-1 Summary of lognormal fits for the ACI data (Figure 4-1 - Figure 4-12) including the non linear regression analysis method proposed by Thiel*

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Orifice (mm)</th>
<th>MMAD</th>
<th>GSD</th>
<th>Correlation coefficient</th>
<th>MMAD*</th>
<th>GSD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution</td>
<td>0.25</td>
<td>1.16</td>
<td>2.26</td>
<td>0.978</td>
<td>1.20</td>
<td>1.92</td>
</tr>
<tr>
<td>Solution</td>
<td>0.30</td>
<td>1.21</td>
<td>2.24</td>
<td>0.971</td>
<td>1.21</td>
<td>1.86</td>
</tr>
<tr>
<td>Solution</td>
<td>0.34</td>
<td>1.18</td>
<td>2.25</td>
<td>0.977</td>
<td>1.24</td>
<td>1.94</td>
</tr>
<tr>
<td>Suspension</td>
<td>0.22</td>
<td>1.97</td>
<td>1.91</td>
<td>0.965</td>
<td>2.50</td>
<td>1.46</td>
</tr>
<tr>
<td>Suspension</td>
<td>0.28</td>
<td>1.95</td>
<td>1.97</td>
<td>0.965</td>
<td>2.47</td>
<td>1.48</td>
</tr>
<tr>
<td>Suspension</td>
<td>0.34</td>
<td>1.99</td>
<td>2.03</td>
<td>0.964</td>
<td>2.58</td>
<td>1.52</td>
</tr>
</tbody>
</table>
Chapter 4 Cascade impactor

Figure 4-1 Log probability plot for suspension formulation with 0.22 mm exit orifice

Figure 4-2 Log probability plot for suspension formulation with 0.28 mm exit orifice
Chapter 4 Cascade impactor

Figure 4-3 Log probability plot for suspension formulation with 0.34 mm exit orifice

The dashed line is from log probability estimates of MMAD = 1.9662 and GSD = 2.0365; r² for this fit to the lognormal curve is: 0.712306

The solid curve is the final fit to the lognormal curve with CORRECTED MMAD 2.502 and GSD 1.163; r² for the CORRECTED fit is: 0.97147

"Non-biological" Fraction of Dose: 0.756

Figure 4-4 Log normal distribution(7) for an 0.22 mm exit orifice
Chapter 4 Cascade impactor

Log-Normal Distribution

The dashed line is from log probability estimates of MMAD = 1.952 and GSD = 1.071. r² for this fit to the lognormal curve is: 0.989032

The solid curve is the final fit to the lognormal curve with CORRECTED MMAD 2.475 and GSD 1.464 r² for the CORRECTED fit is: 0.985343

"Non-ballistic" Fraction of Dose: 0.595

Experimental

Calculated

Figure 4-5 Log normal distribution(7) for an 0.28 mm exit orifice

Log-Normal Distribution

The dashed line is from log probability estimates of MMAD = 1.996 and GSD = 2.026. r² for this fit to the lognormal curve is: 0.689431

The solid curve is the final fit to the lognormal curve with CORRECTED MMAD 2.579 and GSD 1.526 r² for the CORRECTED fit is: 0.955733

"Non-ballistic" Fraction of Dose: 0.469

Experimental

Calculated

Figure 4-6 Log normal distribution(7) for an 0.34 mm exit orifice
Chapter 4 Cascade impactor

Figure 4-7 Log probability plot for solution formulation with 0.25 mm exit orifice

Figure 4-8 Log probability plot for solution formulation with 0.30 mm exit orifice
Chapter 4 Cascade impactor

Figure 4-9 Log probability plot for solution formulation with 0.34 mm exit orifice (solution)

Log-Normal Distribution

The dashed line is from log probability estimates of MMAD = 1.166 and GSD = 2.262. r² for this fit to the lognormal curve is: 0.88964

The solid curve is the final fit to the lognormal curve with CORRECTED MMAD = 1.200 and GSD = 1.819.

r² for the CORRECTED fit is: 0.944597

"Non-ballistic" Fraction of Dose: 0.693

Figure 4-10 Log normal distribution(7) for 0.22 mm exit orifice (solution)
Chapter 4 Cascade impactor

Log-Normal Distribution

The dashed line is from log probability estimates of MMAD = 1.238 and GSD = 2.238. r² for this fit to the lognormal curve is: 0.9890493

The solid curve is the final fit to the lognormal curve with CORRECTED MMAD = 1.210 and GSD = 1.869
r² for the CORRECTED fit is: 0.964956
"Non-ballistic" Fraction of Dose: 0.675

Figure 4-11 Lognormal distribution(7) for 0.28 mm exit orifice (solution)

Log-Normal Distribution

The dashed line is from log probability estimates of MMAD = 1.184 and GSD = 2.251. r² for this fit to the lognormal curve is: 0.910092

The solid curve is the final fit to the lognormal curve with CORRECTED MMAD = 1.238 and GSD = 1.839
r² for the CORRECTED fit is: 0.937718
"Non-ballistic" Fraction of Dose: 0.635

Figure 4-12 Lognormal distribution(7) for 0.34 mm exit orifice (solution)
4.2 Modelling drug deposition in the Andersen Cascade Impactor

4.2.1 Introduction
In the preliminary investigation studies (4.1) it was shown that the data from ACI testing, when classically processed, did not result in an ideal fit to that expected of a lognormal distribution. The lack of fit to a lognormal distribution as shown in section 4.1 is not unusual and most inhalation products show some deviation from the lognormal and in a few cases the departure determined is significant (7) and raises questions regarding the fundamental understanding of the inhalation properties being measured and the assumptions there in.

The objective of the work undertaken here is to mathematically model the deposition characteristics of the ACI in an attempt to resolve the observed differences in both mean and distribution data produced by the standard ACI testing of pMDI's when compared to other particle size techniques such as the APS and PDA.

4.2.2 The Andersen cascade impactor
The ACI was chosen for the study because it is the most widely reported cascade impactor used in the assessment of inhaled pharmaceutical products and is due in part to its heritage, the number of impactor stages (perceived resolution), its relative flexibility in the range of calibrated flow rates that can be accommodated and as a result it can be regarded as the industry standard method for the assessment of the inertial impaction properties of inhaled therapies.

In the assessment of pMDI's the instrument is normally operated at 28.3 l min⁻¹ but can also be used to assess DPI's at flow rates of 60 or 90 l min⁻¹ when configured appropriately. When used for the assessment of DPI's, a pre-separator unit, designed to trap larger particles (197) before they can enter the sizing stages of the instrument can
Chapter 4 Cascade impactor

be fitted between the induction/inlet port and the first impactor stage. The stage layouts, cut sizes and flow rates of the Mark II ACI are shown in Table 4-2.

Table 4-2 Flow rate and stage layouts for the ACI

<table>
<thead>
<tr>
<th>Stage layout</th>
<th>Stage No.</th>
<th>Cut-point (um)</th>
<th>Hole in</th>
<th>Stage</th>
<th>Cut-point (um)</th>
<th>Hole in</th>
<th>Stage No.</th>
<th>Cut-point (um)</th>
<th>Hole in</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>impactor plate</td>
<td>No. 1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0</td>
<td>9</td>
<td>Yes</td>
<td>-1</td>
<td>8.6</td>
<td>Yes</td>
<td>-2</td>
<td>8</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5.8</td>
<td>Yes</td>
<td>-0</td>
<td>6.5</td>
<td>Yes</td>
<td>-1</td>
<td>6.5</td>
<td>Yes</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>4.7</td>
<td>No</td>
<td>1</td>
<td>4.4</td>
<td>Yes</td>
<td>-0</td>
<td>5.2</td>
<td>Yes</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
<td>3.3</td>
<td>No</td>
<td>2</td>
<td>3.3</td>
<td>No</td>
<td>1</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<tr>
<td>5</td>
<td>4</td>
<td>2.1</td>
<td>No</td>
<td>3</td>
<td>2</td>
<td>No</td>
<td>2</td>
<td>2.6</td>
<td>No</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>1.1</td>
<td>No</td>
<td>4</td>
<td>1.1</td>
<td>No</td>
<td>3</td>
<td>1.7</td>
<td>No</td>
</tr>
<tr>
<td>7</td>
<td>6</td>
<td>0.7</td>
<td>No</td>
<td>5</td>
<td>0.54</td>
<td>No</td>
<td>4</td>
<td>1.0</td>
<td>No</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>0.4</td>
<td>No</td>
<td>6</td>
<td>0.25</td>
<td>No</td>
<td>5</td>
<td>0.43</td>
<td>No</td>
</tr>
</tbody>
</table>

Over the years there have been many revisions to the basic design of the ACI, one glass and two metal throats and a design modification to reduce wall losses in the upper stages in which the number and size of jets were changed and the flow path altered in the upper impaction plates (188). Stages 1 to 5 are common to all flow configurations but the ECDs are shifted downward as the flow rate increases. Stage 1 has ECDs of 5.8, 4.4 and 3.5 μm at flow rates of 28.3, 60 and 90 l/min respectively. A hole in the centre of the impaction plate was added to reduce the wall losses in the upper stages (188).

4.2.3 The components of the ACI

The ACI consists of two main functional components; the inlet throat with coupler section and the cascade impaction stack consisting of 8 impaction stages (stages 0-7) and a final filter stage. The influence of the inlet stage with respect to airflow etc. has been studied in the CFD chapter and with respect to atomisation in chapter 7.

4.2.4 Calibration of impactors and the basics of stage efficiency modelling

Calibration of cascade impactors is one of the biggest challenges facing the pharmaceutical industry because there are no simple calibration methods available. The ACI user has to choose between the simpler mensuration technique, which require the
accurate measurement and statistical analysis of the jet diameter or the more expensive and time-consuming process of challenging each impactor plate with a range of calibrated mono-dispersed particles and the subsequent generation of an impactor efficiency curve for each stage.

A full system calibration would include an assessment of all deposits, including wall losses. A spectroscopic or visualisation technique is normally used in this type of calibration procedures to accurately determine the quantity of calibration material both on the impaction plate and other particle deposition sites. Another technique that is widely used is the counting of mono-dispersed particles before and after the impaction stage. By using a range of particle sizes either side of the impactor ECD an impactor efficiency plot can be constructed. The collection efficiency $E$ for each stage can be calculated from:

$$E = 100(1 - N_1 / N_2)$$  \hspace{1cm} (4.1)

where $N_1$ is the number count with the impaction plate and $N_2$ is the count without the impaction plate.

The ideal impactor efficiency curve will be a step function where $E$ equals 1 just above the ECD and 0 just below the ECD. In practice the deposition efficiency curve for a real impactor approximates to a sigmoidal and the Geometric Standard Deviation (GSD) can define the particle size range of the impactor stage.

$$GSD = \sqrt[\frac{d_{84.1}}{d_{15.9}}}$$  \hspace{1cm} (4.2)

Where $d_{15.9}$ and $d_{84.1}$ are the diameters corresponding to the efficiency values at 15.9% and 84.1% respectively.
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The probability of a particle impacting can be determined from the Stokes number for that particle. The Stokes number is defined as

\[ P_{\text{dep}} = \text{StkNo.} = \frac{C_c \rho d^2 u}{18 \eta D} \]  \hspace{1cm} (4.3)

Where \( D \) is a characteristic diameter associated with the flow path. When the flow out of the jet is symmetric about the central axis the characteristic diameter becomes half the jet width (\( w/2 \)) and the Stokes number for a cascade impactor becomes

\[ P_{\text{dep}} = \text{StkNo.} = \frac{C_c \rho d^2 u}{9 \eta w} \]  \hspace{1cm} (4.4)

In the ideal design the Stokes number associated with ECD of each impactor stage would be a constant; however in practice there are a number of other system variables that influence the overall flow characteristics. The probability of impaction is a function of the Stokes number

\[ P_{\text{dep}} = f(\text{StkNo}) \]  \hspace{1cm} (4.5)

The probability of impaction is also a function of the particle position within the jet width and the probability of deposition becomes

\[ P_{\text{dep}} = f(\text{StkNo}, \frac{x}{w}) \]  \hspace{1cm} (4.6)

It can now be seen that in a practical impactor a sharp ideal ECD can not be defined due to the inclusion of the distribution parameter (\( x/w \)).

The classical mathematical derivation assumes a constant uniform inlet velocity (\( u \)) within the impactor jet whereas in practice the entry effects for a Newtonian fluid will
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result in a developing velocity profile across the jet width and the velocity profile will be a function of the Reynolds number (Re), the jet width (w) and length (l). Equation 4.6 can now be modified to include the variation of velocity about the mean value

\[ P_{dp} = f(StkNo, \frac{x}{w}, \frac{l}{w}, Re) \]  \hspace{1cm} (4.7)

In cascade impactors with multiple jet arrays per impaction stage a further variation in the probability of deposition will occur due to non uniform pressure drop at the exit of each jet as the pressure at the jet outlet is a function of the jets position within the narrow outlet flow path resulting in a positional dependant jet velocity.

Based on the nominal impactor design criteria, the square root of the critical Stokes number can be computed from the quoted ECD for each stage. The computed data in Table 4-3 includes the percentage deviation from three values, the average of the ACI, the ideal value of 0.47 and the mathematical derivation value of 0.5(195)

Table 4-3 Stokes impaction numbers for the ACI with percentage deviations from three reference values

<table>
<thead>
<tr>
<th>Stk No</th>
<th>Stk(^{1.5})</th>
<th>0.47</th>
<th>0.5</th>
<th>ACI average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate 0</td>
<td>0.19</td>
<td>0.44</td>
<td>-6.7</td>
<td>-12.3</td>
</tr>
<tr>
<td>Plate 1</td>
<td>0.20</td>
<td>0.45</td>
<td>-5.3</td>
<td>-11.0</td>
</tr>
<tr>
<td>Plate 2</td>
<td>0.28</td>
<td>0.53</td>
<td>12.9</td>
<td>6.1</td>
</tr>
<tr>
<td>Plate 3</td>
<td>0.30</td>
<td>0.54</td>
<td>15.6</td>
<td>8.7</td>
</tr>
<tr>
<td>Plate 4</td>
<td>0.30</td>
<td>0.54</td>
<td>15.9</td>
<td>8.9</td>
</tr>
<tr>
<td>Plate 5</td>
<td>0.33</td>
<td>0.57</td>
<td>22.1</td>
<td>14.8</td>
</tr>
<tr>
<td>Plate 6</td>
<td>0.36</td>
<td>0.60</td>
<td>27.9</td>
<td>20.2</td>
</tr>
<tr>
<td>Plate 7</td>
<td>0.27</td>
<td>0.52</td>
<td>10.4</td>
<td>3.8</td>
</tr>
</tbody>
</table>
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4.3 Distribution of impacted deposits on upper plate of the ACI

The validity of using the deposition data obtained from the upper plates was discussed previously (4.1.3.2). The purpose of the work in this section is to investigate the distribution of droplet impaction on the upper plate of the ACI that could further the understanding of the cascade impactor data.

A previous fluid flow based review of the basic design and layout of the plate jet array had led to the conclusion that the flow velocity through impactor jets would be position dependent due to the non symmetrical flow paths present between the jet exit and the surface of the impaction plate (220). If a differential pressure based velocity variation predicted by the design review could be verified experimentally then the validity of the assumptions in equation 4.7 would be established and the use of a non analytical based modelling solution for predicting particle deposition would be valid.

The distribution of droplet impaction was assessed using a 134a/ethanol formulation. The residual ethanol was sufficient to give indication on an ethanol sensitive paper placed on the surface of the impaction plate.

A 134a propellant formulation containing 25% w/w ethanol was cold transferred into aluminium cans and then a Spraymiser™ 50µl valve was crimped to the can using a bench mounted Pamasol crimper.

Ethanol sensitive paper (Hewlett Packard, P/N 5080-8735) was cut to shape and glued, sensitive side up, to the upper surface of the first impaction plate (Plate 0).

The ACI was assembled, the aerosol primed to waste and five actuations of the formulation were dispensed into the apparatus at a flow rate of 28.3 l min⁻¹.

Three flow conditions were assessed as follows:

1. The ACI fitted with a standard USP inlet throat and a standard plate 0.
2. The ACI fitted with a 25 mm diameter straight vertical inlet, 300 mm in length and a standard plate 0.
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3. The ACI fitted with a standard USP inlet throat and a plate 0 with no central hole.

Following each test the paper was removed and a new sample placed on plate 0 and the test repeated under the appropriate conditions.

4.3.1 Results of the upper plate deposition study

The results show very distinctive deposition patterns on the impaction plate and are associated with the ring position. In the configuration where the standard USP throat was used with no hole through the centre of the first impaction plate (Figure 4-13a) the deposition pattern for the outer ring is well defined and spherical with a heavier deposition than for the other jet rings. The deposition pattern gets progressively lighter as you move from outer ring to inner ring. The shape of the deposition pattern becomes more elongated and slit like in appearance for the inner 3 rings.

In the standard ACI configuration (Figure 4-13b) the deposition produced by flow through the inner ring of impactor jets is much darker than those produced by the other 3 rings and the deposition pattern is distorted with a crescent shaped pattern with a heavier deposition on the inner side with the deposition becoming lighter towards the outer edge. The deposition pattern below the outer ring of jets is symmetrical but lighter than the inner ring deposition. As you move from the outer ring the deposition becomes lighter and distorted with the deposition pattern becoming more slit like.

The deposition patterns for the straight inlet throat (Figure 4-13c) are very similar to those of the standard USP inlet throat, however, the deposition patterns are darker indicating an increased quantity of deposition.
Figure 4-13 Deposition patterns from plate 0, a) with no central hole, b) standard USP inlet and c) straight inlet throat with no bend.

4.3.2 Discussion of the upper plate deposition study

The comparison of the deposition patterns produced by the standard USP inlet throat (Figure 4-13b) with that of a no bend inlet throat section (Figure 4-13c) demonstrates that the deposition pattern produced is not a function of the inlet flow and the airflow disturbance resulting from the 90 degree change of flow direction does not have an effect on particle distribution. The resulting deposition from the straight through inlet
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throat is as expected higher due to the lower inertial impaction in the bend section allowing a greater number of larger droplets to reach the first impaction stage. The actuation of the device into the straight throat inlet (no bend) required the device to be primed in the normal orientation before insertion into the throat. After actuation the valve was retained in the fired position momentarily until the device had been removed prior to releasing the valve. The device was then primed in the normal orientation.

The crescent shaped pattern to the deposition below the inner ring of jets (Figure 4-13b and Figure 4-13c) can be explained by reference to a 2D CFD study for this configuration (197). The CFD analysis clearly showed the velocity contours through the inner jets did not flow symmetrically as would be expected for an ideal impactor design but were curved towards the hole in the centre of the impaction plate.

The distortion from the ideal circular deposition in all but the outer ring supports the assumption that performance of each jet ring will be different not only in ECD value due to velocity variations but also in the shape of the probability of deposition efficiency curve. The overall performance of any of the impactor stages will be the summation of these various departures from the ideal and result in a performance significantly different than predicted by the ideal Stokes only based assumptions.

The inner three rings have slot like deposition patterns (Figure 4-13a) that get lighter as you move towards the inner indicating a decrease in jet velocity or reduced sampling efficiency, which can be attributed to an increase in the pressure drop across each jet ring moving radially inwards across the plate from outer to inner most jet ring. This is caused by the cross flow in the jet outlet region when there is only one exit flow point around the outer edge of the impaction plate. The increasing pressure drop across the outer ring results in a concomitant increase in velocity and increased particle deposition below it.

The deposition pattern in the configuration where the central hole was removed from the design supports the above assumption. The outer ring retains a symmetrical
deposition pattern with some elliptical tendency and could result from the impingement of the airflow from adjacent rings. The outer ring is only restricted on the inner side of the jet and is therefore more symmetrical.

The change in shape from ideal circular deposition to slot shaped deposeations is due to the impingement of the airflow with adjacent jet rings. The inner ring also produced a slot shaped deposition pattern which at first would appear abnormal for this ring as there is no jet ring on the inner side. The flow out of the inner jet ring is however constrained by the flow into the central region of the impaction plate of the adjacent inner jets forming a stagnant low flow central region that hinders the outflow from the inner jet ring on that side.

The fact that ethanol can be detected on the surface of the first impaction plate also serves to prove the incomplete evaporation assumption. The ethanol paper is sensitive to the presence of liquid ethanol only and the detection of ethanol demonstrates the incomplete evaporation when ethanol is used at higher levels, however, caution in the interpretation needs also consider that the fact that increased ethanol level decreases the atomisation efficiency and as such increases the size range thus increasing the likelihood of detection at the first stage. The cascading nature and implied time shift between stage sampling could lead to distortion of the data from the underlying distribution. Any distortion would be the result of the test method and if present would render interpreted particle size data invalid from a real world delivery to the lung scenario.

4.4 Methodology for a Computer based model for predicting ACI deposition

Previous ACI data had shown the distribution of particle sizes from both solution and suspension formulations were not well described by the lognormal distribution. Analysis of the design and flow characteristics of the throat of the ACI failed to account
for the non-linearity; however, the particle deposition based study of the upper impactor plates did indicate non ideal airflow patterns and deposition patterns respectively.

Design issues in the ECD designs and overlap between stages could explain the non-linearity. Analysis of the function of the 50% ECD shows that although a unique value of diameter can be assigned to the ECD, this value relates only to an experimentally determined nominal design that deviates significantly from the ideal.

In the ideal impactor the ECD would be representative of the particle depositions present on each stage, in reality the more the ECD deviates from the ideal the more complex the analysis of the deposition becomes and increases significantly in regions where the stage efficiency curves of adjacent stages overlap. In such cases the ideal ECD based analysis would not actually represent the mass distribution present on a plate.

It is proposed that the actual range of particle sizes deposited on a specific plate will be a function of the deposition efficiency curve (calibration curve) and any potential errors by definition will cascade from one plate to the next. Failure to retain particles at the site of impaction will result in those particles impacting on a plate lower down the stack on a plate with a lower diameter range. Due to the complex issue of particle bounce the most efficient deposition is that for liquid droplets onto uncoated plates. The coating of plates with oils etc. is used to increase the collection efficiency of solid particulates by reducing the potential for bounce (221-225).

The preceding data raises important questions regarding the functional performance of the ACI. In section 4.4 a model of ACI deposition will be developed based on numerical description of calibration curves for each ACI stage from literature data; this enables the analysis of discretised distributions of particle size – using discretised distributions means that they are not limited to specific functional forms but could potentially be any distribution and any size; in section 4.5 the analysis will be carried out for artificial lognormal distributions with mono-modal, bi- and tri-modal.
Chapter 4 Cascade impactor characteristics to highlight potential problems with the ACI response. In section 4.6-4.9 lognormal distributions that are more representative of real pharmaceutical aerosols are analysed to highlight a range of problematic issues relating to the interpretation of ACI data.

4.4.1 ACI calibration curves

The potential solution to the problem was therefore to define a mathematical model for the probability of deposition for each of the impactor stages. In order to achieve this objective an accurate probability of deposition curve is required for each plate. Many calibration curves are available for the plates of the ACI including the original manufacturer’s data (Figure 4-15).

Based on a review of the calibration methods it was decided that for plates 2 to 6 of the ACI the calibration data from Rao and Whitby(185) would be the most suitable set available because the data was obtained under the correct flow conditions. Importantly the calibration curves of Rao and Whitby were considered complete as they extended all the way to the limits of efficiency (0 and 100%) and a range of materials were assessed in detail providing more fundamental information on limitation of impaction characteristics with respect to collection efficiencies due to the nature of the particle. As the data of Rao and Whitby was obtained on the Mk I ACI the upper stage calibrations cannot be used, because the design has subsequently changed for stages 0 and 1. For the remaining impactor stages the best compromise between the data of Vaughan(188) (figure 8.3) and Mitchell et al(186) was chosen based on completeness of the data sets presented.

The efficiency curve defined for each plate needs to be accurate and more importantly account for the curvature of the calibration data points in the key regions of 0-20% and 80-100% deposition efficiency. Initially a series of polynomials and sigmoidal functions were used but although the correlation coefficients appeared to give a sufficient fit to the calibration data, visual examination of the fitted curves showed
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deficiencies in curvature and shape in the key regions of deposition efficiency curve (Figure 4-14).

![Impactor Plate Particle Collection Efficiency Curve](image)

Figure 4-14 Typical shape of a non ideal impactor stage deposition efficiency curve with significant curvature in the key regions outside the data region used to compute GSD (16.4 to 84.6%)

![Calibration curves for the ACI](image)

Figure 4-15 Calibration curves for the ACI(188)

### 4.4.2 Modelling the probability of deposition for each impactor plate

The shape of the impactor efficiency curves are often treated, in the data inversion approach, as being sigmoidal in shape(226). The literature based calibration data sets
were evaluated against sigmoidal curves, both symmetric and asymmetric as well as cumulative lognormal and other related curves. The best fit in terms of both general shape, curvature in the extremities of the data set and fit to the calibration data was found to be an exponentially modified normal distribution (EMG) equation of the general form.

\[ P_{dep} = \frac{a}{2} \left[ 1 + \Gamma \left( \frac{x - b}{\sqrt{2c}} \right) - \left( \frac{d}{d} + \Gamma \left( \frac{x - b - \frac{c}{\sqrt{2d}}}{} \right) \right) \exp \left( \frac{c^2}{2d^2} + \frac{b - x}{d} \right) \right] \]  (4.8)

Where \( x \) is the diameter of the particle

<table>
<thead>
<tr>
<th>Stage</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.003</td>
<td>7.333</td>
<td>1.188</td>
<td>2.014</td>
</tr>
<tr>
<td>1</td>
<td>1.001</td>
<td>4.558</td>
<td>0.676</td>
<td>1.473</td>
</tr>
<tr>
<td>2</td>
<td>1.003</td>
<td>4.354</td>
<td>1.057</td>
<td>2.204</td>
</tr>
<tr>
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<td>4</td>
<td>1.000</td>
<td>2.003</td>
<td>0.128</td>
<td>0.400</td>
</tr>
<tr>
<td>5</td>
<td>1.000</td>
<td>1.166</td>
<td>0.104</td>
<td>0.073</td>
</tr>
<tr>
<td>6</td>
<td>1.000</td>
<td>0.607</td>
<td>0.053</td>
<td>0.074</td>
</tr>
<tr>
<td>7</td>
<td>1.000</td>
<td>0.361</td>
<td>0.075</td>
<td>0.077</td>
</tr>
</tbody>
</table>

In order to avoid the potential for excessive computation and unrealistic finite probabilities due to tails in the shape of the deposition probability solution the following boundary limits were placed on the computed deposition probability solution.

If \( P_{dep} \leq 0.001 \) then \( P_{dep} = 0 \)

If \( P_{dep} \geq 0.999 \) then \( P_{dep} = 1 \)
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4.4.3 Results and discussion for the plate probability deposition curves

The mathematically modelled probability curves are shown in Figure 4-16 and compare well with the published curves in Figure 4-15. The crossover point between plates 1 and 2 is slightly offset.

It should be noted that there is an absence of good calibration data covering a range of particle type and where there are data they often do not include the extremities of the plate efficiency. It is not clear if this is due to technical difficulties or that it is not deemed an important aspect because the general focus is on the mid point efficiency for the stage and how close it is to confirming the design or pharmaceutically quoted value. In the relatively new NGI impactor the calibration data from the development consortium only published data for the main portion of the curves (5-10% up to 90-95%) (227).

Figure 4-16 Impactor efficiency curves generated for each stage of the ACI using equation 4.8.
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![Diagram showing efficiency vs. aerodynamic diameter](image)

Figure 4-17 Comparison of model fits to the calibration data for plate 3 of the ACI

Table 4-5 Computed GSD’s for each of the modelled stage impactor efficiency functions

<table>
<thead>
<tr>
<th>Plate</th>
<th>GSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate 0</td>
<td>1.25</td>
</tr>
<tr>
<td>Plate 1</td>
<td>1.27</td>
</tr>
<tr>
<td>Plate 2</td>
<td>1.4</td>
</tr>
<tr>
<td>Plate 3</td>
<td>1.21</td>
</tr>
<tr>
<td>Plate 4</td>
<td>1.16</td>
</tr>
<tr>
<td>Plate 5</td>
<td>1.12</td>
</tr>
<tr>
<td>Plate 6</td>
<td>1.13</td>
</tr>
<tr>
<td>Plate 7</td>
<td>1.26</td>
</tr>
</tbody>
</table>

The GSD data for each efficiency curve (Table 4-5) numerically demonstrates the lack of consistency in the design of individual plates. As the GSD data represents the slope of the major portion of the efficiency curve it makes clear two important aspects, one there is a noteworthy difference between the GSD values for the main respirable size determining plates (plates 3-6) where the GSD is <1.22 and the upper plates (plates 0-2) where the GSD is >1.24. Plate 2 has the highest GSD and accounts for the significant crossover with plate 1. The manufacturer’s calibration data in Figure 4-15 is based on
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the original designs for plates 0 and 1. The shift and overlap between plates 1 and 2 is probably a result of the design change that occurred between the Mk I and Mk II ACI designs when the jet diameters and jet layout were changed and central holes in the plate 0 and 1 were introduced(188).

From a technical perspective the use of GSD values is only applicable to the cumulative lognormal distribution however as previously stated the exponentially modified normal equation has been used. The GSD data has been presented here because historically it has been used to assess and compare impactor efficiency curves and the data in Figure 4-17 plots the lognormal, sigmoid and the exponentially modified normal and all have similar responses over the range for which the GSD is calculated (plus and minus one standard deviation). Where they deviate from one another is in the regions either below 20% or above 80%.

A computer based methodology was developed based on the following functional steps

1. Generate distribution (random number based)
2. Curve fit the lognormal distribution and verify MMAD and GSD
3. Assign a probability (between 0 and 1) to each particle
4. Calculate the probability of deposition on the first stage
5. Store deposited particles in the stage array
6. Store remainder of distribution for presentation to the next stage
7. Assign a probability (between 0 and 1) to each remaining particle
8. Calculate the probability of deposition on the next stage
9. Store deposited particle in stages array
10. Store remainder of distribution for presentation to the next stage
11. Repeat steps 7 to 10 until all stages have been evaluated
12. Compute filter deposition
13. End
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The probability \((P)\) of an individual particle with a diameter \((d)\), impacting or passing a plate is determined by a logical comparison between the particle's probability and that determined from equation 4.8. If the probability of impaction for that diameter is greater it is retained and if it is lower it passes to the next stage where the process is repeated.

\[
\text{If } P_d < P_{\text{dep},d} \text{ then particle is stored in stages particle array}
\]

\[
\text{If } P_d \geq P_{\text{dep},d} \text{ then particle stored in aerosol array for presentation to next stage}
\]

At the end of the computation process there is an array for each stage plus the filter, with each array containing the number of particles for each diameter. The diameter resolution was 0.01 \(\mu\)m and therefore to store particle diameter from 0.01 \(\mu\)m to 20 \(\mu\)m requires a 2000 element array.

The characteristic long tail produced by a lognormal distribution imposes a constraint on the number of lognormal particles generated to describe the specific MMAD and GSD. In the lognormal distribution the tail can be long but the number of particles small, they do however, due to their diameter, contain a significant mass and therefore need to be accurately represented in the model. To ensure the results were independent of particle number a particle count of \(1 \times 10^8\) was selected.

4.4.4 Validation of the model

The model was subjected to several validation processes to evaluate both the validity of the plate retention on a plate by plate basis and importantly from the pharmaceutical perspective the total material balance.

The first validation step involved removing specific plates from the computation and checking the deposition change on the next plate in the cascade.
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The second validation step involved checking that no particles outside the calibration range for a specific impaction plate were outside the range defined by the calibration curve for that plate.

The third validation step involved collecting all the predicted deposition data from each plate summing the data together and recalculating the cumulative size distribution and then finally checking the summed cumulative distribution against the input distribution for each run. The predicted collected and summed values gave perfect agreement with the starting distribution thus validating the material balance and the calculation algorithms.

4.5 Mono-modal and multi-modal distributions

The computational methodology outlined above was then used to assess the variation in plate deposition when narrow lognormal distributed mono-modal samples were input. This demonstrates that particles of very narrow size distribution are not retained on a single ACI stage, but deposited across a number of different plates within the impactor stack. Three mono-modal distributions were selected each with an MMAD centred on one of the ideal ECD for three consecutive plates within the ACI stack. The three ACI plates chosen for the study were plate 2 with a ECD of 4.7 μm, plates 3 with a ECD of 3.3 μm and Plate 4 with a ECD of 2.1 μm. The GSD’s of the mono-modal samples were 1.06.

4.5.1 Results and Discussion for mono-modal distributions

The computational results clearly show how widely the particles from each distribution are spread within the impactor. The 4.7 μm mono-disperse aerosol is spread across four plates, the 3.3 μm aerosol over five plates and the 2.1 μm aerosol over four plates (Figure 4-18). The relative mass fractions are given in the Table 4-6.
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Table 4-6 Fractional mass plate depositions for three mono-modal distributions

<table>
<thead>
<tr>
<th></th>
<th>2.1μm</th>
<th>3.3μm</th>
<th>4.7μm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate 1</td>
<td>0.000</td>
<td>0.005</td>
<td>0.175</td>
</tr>
<tr>
<td>Plate 2</td>
<td>0.014</td>
<td>0.050</td>
<td>0.245</td>
</tr>
<tr>
<td>Plate 3</td>
<td>0.001</td>
<td>0.182</td>
<td>0.474</td>
</tr>
<tr>
<td>Plate 4</td>
<td>0.252</td>
<td>0.741</td>
<td>0.106</td>
</tr>
<tr>
<td>Plate 5</td>
<td>0.733</td>
<td>0.023</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Figure 4-18 Plate distributions for the three mono-modal aerosols

The pharmacopoeia(2) based analysis of the plate deposition data makes the basic assumption that the ECDs are ideal and then applies the undersize assumption in the calculation of MMAD and GSD. Plate 3 for example has a ECD of 3.3 μm and therefore based on the efficiency curve retains material above this diameter. The pharmacopoeia however assumes that what is deposited on plate 3 is between the ECD for plate 3 (3.3 μm) and plate 2 (4.7 μm). In the calculation(2) of MMAD and GSD the mass of plate 3 is plotted against 4.7 μm and hence the term undersize is used however
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this is not the true upper limit of the deposition on plate 3 because the upper limit of 4.7-μm is based on the incorrect assumption that the ECD is ideal and in reality the upper limit of the particles deposited on plate 3 will be greater than 4.7 μm.

Applying the pharmacopoeia analogy to any of the mono-modal distributions would result in any of the mono-modal sample being split between the two plates either side of the samples MMAD. The mono-modal sample with MMAD of 3.3 μm would be split approximately 50:50 between plates 3 and 4. The approximation is due to lack of symmetry in the lognormal even for distributions with lower GSD’s. The ideal 50:50 split would be obtained only if a normally distributed sample were used.

4.5.2 Results and discussion for a tri-modal distribution

When the distributions from three mono-modal samples are combined (with similar mass for each distribution) to form a single tri-modal aerosol, the deposition modelling repeated and the results plotted using the pharmacopoeia methodology a significant and surprising result is obtained from the lognormal plot of the predicted deposition (Figure 4.19). The plot and statistical analysis indicate that the aerosol is of a lognormal distribution ($r^2 > 0.99$) with a GSD of 1.58 and MMAD 2.93

The fact that a tri-modal aerosol can give rise to a lognormal solution raises questions regarding the interpretation of particle size and distribution data generated by the ACI irrespective of the apparent fit to the lognormal assumption. The very narrow mono-modal and tri-modal distributions are just extreme examples where things can go wrong with relatively little practical importance; it is anyhow not realistic to expect the ACI to be able to determine the tri-modal distribution; ACI acts as a sieve and cannot be expected to capture details of distributions that are happening in between different sieve trays (only more trays/stages would resolve these aspects).
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Figure 4-19 Log probability plot for tri-modal aerosol

The original three mono-sized distributions have GSD smaller than each of the plates and they do not overlap; the filtering process in the ACI (even the assumed ideal ECD filtering) can never capture details of the input distribution with size differences smaller than the ECD point distance between the plates: i.e. if you make the three mono-modal distributions progressively smoother by increasing their GSD the ACI would initially not notice anything until the distributions were so wide that some material was retained on higher or lower plates.

4.6 Computational modelling of aerosol distributions

A total of four lognormal sample distributions were computed and each checked for conformance to a lognormal distribution and the MMAD and GSD of each determined. The distributions were chosen to represent different particle sizes covering the range MMAD normally found in commercial inhalation products. The smallest with an MMAD of 1.45 (sample 1) represents the lower end of the product spectrum (typical solution based formulation) and that with an MMAD of 5.0 (sample 4) represents a product on the borderline for acceptable inhalation characteristics (acceptable respirable...
particle size). The other two aerosols with MMAD’s of 2 and 3 μm were chosen to represent the range covered by good quality commercial suspension products. The GSD was selected to increase with increasing MMAD. The four sample distributions were then input to the computer program and the deposition on each plate calculated.

4.6.1 Results and discussion for typical lognormal distributions

The depositions from each plate were analysed using the standard pharmaceutical method of plotting cumulative percentage against the predefined ECDs(2). The process was repeated for each of four samples and the data tabulated. The standard analysis showed all distributions to be lognormal as can be interpreted from the ACI correction values in Table 4-7.

Table 4-7 Data for generated distributions and the corresponding results from the ACI simulation using computed calibration data and *Corrected(7)

<table>
<thead>
<tr>
<th>Sample1</th>
<th>Sample2</th>
<th>Sample3</th>
<th>Sample4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMAD</td>
<td>GSD</td>
<td>MMAD</td>
<td>GSD</td>
</tr>
<tr>
<td>Input</td>
<td>1.45</td>
<td>1.3</td>
<td>2.0</td>
</tr>
<tr>
<td>ACI</td>
<td>1.4</td>
<td>1.39</td>
<td>1.98</td>
</tr>
<tr>
<td>ACI *</td>
<td>1.33</td>
<td>1.21</td>
<td>1.81</td>
</tr>
</tbody>
</table>

The cumulative distribution data from each plate of the modelled data was analysed separately and tabulated below. The simulated ACI data under predicts the MMAD with the degree of under prediction increasing with increasing MMAD. The nonlinear correction method of Thiel consistently increases the under-correction for MMAD with all results showing a decrease in MMAD compared to the predicted ACI values on which the correction is based.

The consistent under prediction is surprising given the undersize assumption made for the plate groupings that was previously highlighted in section 4.5.1. To investigate this further the MMAD of the size distribution computed to be retained on each plate was
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compared with the values designated in the pharmacopoeia plot based method in Table 4-8.

Table 4-8 Comparison of the MMAD determined for each plate against the values stated in the pharmacopoeia for each of the lognormal distributions analysed

<table>
<thead>
<tr>
<th>ECD</th>
<th>Sample 1</th>
<th>Sample 2</th>
<th>Sample 3</th>
<th>Sample 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMAD</td>
<td>1.45</td>
<td>2.0</td>
<td>3.0</td>
<td>5.0</td>
</tr>
<tr>
<td>GSD</td>
<td>1.3</td>
<td>1.4</td>
<td>1.5</td>
<td>2.0</td>
</tr>
<tr>
<td>Plate 0</td>
<td>9.0</td>
<td>-</td>
<td>5.57</td>
<td>7.90</td>
</tr>
<tr>
<td>Plate 1</td>
<td>5.6</td>
<td>3.19</td>
<td>4.64</td>
<td>5.63</td>
</tr>
<tr>
<td>Plate 2</td>
<td>4.7</td>
<td>2.36</td>
<td>3.55</td>
<td>4.59</td>
</tr>
<tr>
<td>Plate 3</td>
<td>3.3</td>
<td>3.00</td>
<td>3.64</td>
<td>4.15</td>
</tr>
<tr>
<td>Plate 4</td>
<td>2.1</td>
<td>2.33</td>
<td>2.65</td>
<td>2.98</td>
</tr>
<tr>
<td>Plate 5</td>
<td>1.1</td>
<td>1.50</td>
<td>1.76</td>
<td>1.96</td>
</tr>
<tr>
<td>Plate 6</td>
<td>0.7</td>
<td>1.02</td>
<td>1.03</td>
<td>1.04</td>
</tr>
<tr>
<td>Plate 7</td>
<td>0.4</td>
<td>0.75</td>
<td>0.73</td>
<td>0.73</td>
</tr>
<tr>
<td>Filter</td>
<td>-</td>
<td>0.61</td>
<td>0.59</td>
<td>0.57</td>
</tr>
</tbody>
</table>

The MMAD for plate 0 of sample 1 could not be calculated as there was insufficient data (too few particles) due to the narrow particle size distribution (GSD 1.3). In sample 1 the MMAD is relatively small and very little material is deposited on the upper plates. The design overlap between plate 1 and 2 ensures that most of the larger particles are collected on plate 2 and the fact that only the lower end of plate 2’s deposition efficiency is being used can be judged by the cumulative analysis performed on this plate. The MMAD (2.36 μm) is significantly below the designated cut diameter for this plate and significantly lower than for the value of the next plate (5.6 μm) in the cascade series against which this mass will be plotted in the standard percent undersize analysis.

The cumulative particle size data for each plate was analysed for fit to a lognormal distribution and to a first approximation the data is lognormal (correlation coefficient, >0.99) however visual examination of the individual plate data shows that while some of the plate depositions approached a cumulative lognormal most were not because the plate deposition is a complex interaction function of the collection efficiency of the plates and the distorted input distribution reaching it (Figure 4-20).
Figure 4-20 Relative mass distributions on Plate 5 of the ACI for the four lognormal distributions

The results clearly indicate that the mass median value of a plate deposition can vary significantly from the designated ECD and the ECD value is a function of the distribution being tested. The effect is clearly demonstrated in Figure 4-20 where the relative distributions for each of the four lognormal samples from plate 5 are compared. It can be seen that not only are the MMAD's different (Table 4-8) but also the shape of the deposited mass distribution shows significant variation and none are lognormal a fact most notable in sample 4. The pharmacopoeia based analysis results show inconsistency in both MMAD and GSD when compared to the parameters of the input aerosol used to model the deposition.

The modelling results highlight some interesting aspects in the analysis methods used to assess the pharmaceutical performance of inhalation products. It demonstrates that the cascade impactor has an inherent capacity to see all broadly distributed aerosols as approximately lognormal. This is most likely due to a combination of irregularly spaced ECDs, non ideal efficiency curves and non ideal overlapping efficiency curves. The effect is perfectly illustrated by the tri-modal distribution that on conventional
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analysis looks to be a perfect lognormal distribution because the data is effectively spread across many plates.

The results of the modelling clearly show the significant error that can result from assuming the fixed ECD values for the plates when analysing the data using the percent undersize methodology recommended in the pharmacopoeia. The results show how dependent the ECD values are on the distribution of the aerosol being tested and the need to account for this if the results are to approximate to the true aerosol parameters and allow comparison of cascade size data with that generated from other instrumental techniques.

From the design standpoint the 50% cumulative mass on a plate will be a function of the distribution being tested. The problem can best be explained by reference to a specific example. Consider in the first instance an impactor with a single plate. If the particle size distribution being tested has an upper particle size equal to the ECD of the impactor plate, only particles of the lower part of the impactor plates collection range will be collected and the cumulative mass on the plate will be well below the ECD, if this process is then applied to a multiple plate impactor system, then the values against which the particle size distribution will be plotted and the particle size of the sample subsequently used in calculations will be incorrect. This is best demonstrated by a comparison of the actual particle size values from the modelling using plate 1 data.

In the standard percent undersize pharmacopoeia based method the data from plate 1 is plotted against the ECD of the plate above (plate 0) which as a designated value of 9.0-μm whereas the model analysis shows the actual means to be 3.19, 4.64, 5.63 and 6.85 μm respectively. Plotting these points will significantly distort the resulting cumulative lognormal analysis because data at the extreme of the regression analysis have the biggest impact on the correlation coefficient and the calculated MMAD and GSD will be distorted by their inclusion. It would be prudent to eliminate from the analysis data for plates where low masses are collected to avoid such distortions.
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4.7 Analysis of the bi-modal tendency in ACI data

There are a number of instances in the literature where the data interpretation of ACI data has led to the conclusion that the aerosol distribution being tested has a bi-modal distribution (229, 230). The objective of this study is to show how this bi-modal indication may be attributable to design flaws and methods used in data interpretation of ACI based tests.

4.7.1 Experimental

The experimental data is a re-interpretation of the data previously used for the analysis of plate depositions in the preceding section. In this analysis we are only interested in the interpretation of mass distributions seen in the ACI data. The analysis conducted here therefore is similar to that used in the presentation of ACI data where only the mass of drug per plate is known.

4.7.2 Results of the bi-modal anomaly

The data from the 4 sample lognormal distributions (section 4.6) is plotted as the mass per plate (Figure 4-21). The mass on each plate is calculated from the summation of all particles deposited on the plate (equation 4.9) and is based on the particle size range, number, density and volume of the deposition.

\[
Mass = \rho \sum_{i=d_{min}}^{d_{max}} \eta_i \frac{4}{3} \pi \left(\frac{d_i}{2}\right)^3
\]  

(4.9)

Where \(d\) is particle diameter and \(\rho\) is particle density.

The mass data is plotted as the mass deposited per plate versus plate number to match the literature based format (229, 230) where the data is plotted as either mass or percentage mass.
Figure 4-21 Percentage mass deposited per ACI plate for the 4 mono-modal lognormal distributions

4.7.3 Discussion of the bi-modal anomaly

The modelled deposition data from the four mono-modal lognormal input distributions (Figure 4-21) clearly demonstrates how easily an incorrect conclusion regarding the modality of the ACI data can be drawn. The data for both lognormal samples 3 and 4 appear to have a second peak in the plate data above plate 2.

The input data in all cases is known to be mono-modal and it can therefore be concluded that the appearance of the second peak is an artefact of the test and does not result from the aerosol input to the system. The appearance of the second peak is associated with the significant overlap and departure from idealistic plate efficiency curves. The overlap in efficiencies results in an unequal distribution of mass in the upper plates with a noticeable overlap between plate 2 and those preceding it in the ACI stack with the result that as either the MMAD or GSD increases the proportion of larger particle size and increases the bi-modal appearance of the data as can be judge as you move from sample 1 through to sample 4.
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The effect seen here is independent of any other particle/droplet size factors such as droplet evaporation rate. If the evaporation rate of a formulation is low then it is possible that due to the cascading time sequence present in the ACI the appearance of the bi-modal effect may be enhanced because of the increased longevity of larger droplets further distorting the deposition pattern due to increased deposition on the upper plates.

The basic problem is the overlap that exists between the upper plates and the fundamental design issue this raises. Once the issue is recognised it is possible for the data analysts to be aware of the limitations of the test method and to provide a suitable caveat to any data interpretation.

The mass of the deposition on plate 0 for all the samples modelled were in practice lower than the values seen in the actual ACI data (section 4.1). This could be due to the characteristics of the specific calibration curve used in the model development. It could also be due to other factors such as evaporation rate and the time dependant effect of incomplete evaporation of droplets or momentum that is transferred from the pMDI spray which raises the velocity of the particles reaching the first impactor stage.

4.8 Potential limitations to the MMAD and GSD determined from USP throat

4.8.1 Introduction

The data generated from ACI testing is intended to give information on the respirable performance of the product. The GSD parameter is used to determine the upper and lower limits of the particle size, however the GSD is not, when compared to the more familiar standard deviation, an easy parameter to utilise regarding the outer limits of the distribution. The standard deviation can be used to assess the range of the distribution without reference to a central tendency measures such the mean, median etc. The GSD can only be used to assess the distribution range when the associated geometric mean is also known. The data in table 4.3 shows the GSD for the ACI plate efficiencies demonstrates very similar GSD values for all the plate efficiencies. Plates 0
and 7 have almost identical GSD's but whereas plate 7 has a total deposition range of <0.6 \mu m, plate 0 has a deposition range >13 \mu m. The accurate determination of both MMAD and GSD is critical in determining the true particle size distribution. The design of the USP throat and the resultant inertial based deposition potentially truncates the input distribution and distorts the resultant analysis.

The objective therefore is to define the range of both MMAD and GSD outside of which the determined values could be considered to be in error.

4.8.2 Methodology

The lognormal probability distribution function is defined(7) by

$$f(x, \mu, \sigma) = \frac{1}{\sigma \sqrt{2\pi}} \exp\left\{ -\frac{\left[\ln(x) - \mu\right]^2}{2\sigma^2}\right\}$$

Where $x$ is the particle diameter, $\mu$ and $\sigma$ are the natural logarithms of the mean particle diameter and its standard deviation respectively and the upper and lower 3\sigma confidence intervals are defined as

$$Lower = \frac{\mu}{\sigma^3}$$  \hspace{1cm} (4.11)

$$Upper = \mu \sigma^3$$  \hspace{1cm} (4.12)

4.8.3 Results and discussion

The ECD efficiency of the USP inlet will have a significant influence on the range of particles reaching the impactor stages and the resultant value of MMAD and GSD determined from ACI analysis.

There is limited literature data for the efficiency of the USP inlet and not all data is determined for a flow rate of 28.3 l min$^{-1}$. In previous modelling the ECD efficiency
was assumed to be 20 μm (188) and for a flow rate of 60 l min\(^{-1}\) as 12 μm (231) and would equate to 17.5 μm at 28.3 l min\(^{-1}\) (16). Stokes based calculations, assuming a critical Stokes value applicable to that of a round impactor jet (0.47), gives a value closer to 28 μm.

The data in Figure 4-22 is a contour plot for a matrix of MMAD (1-6 μm) and GSD (1-3 μm) values and defines the boundary where the throat efficiency begins to impact on the computed values due to truncation of the lognormal distribution. The white zone indicates combinations of MMAD and GSD for which the lognormal distribution is truncated assuming a 20μm ECD for the USP throat (20 μm is a literature based value and there is no detailed data on the overall efficiency or shape of the efficiency curve). In the analysis an ideal efficiency has been assumed.

Figure 4-22 Contour plots of MMAD against GSD with upper distribution contour limits of 10 and 20 μm for throat ECD.
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The relatively high exit thrust of the spray emitted from a pMDI (141) will raise the total flow velocity and therefore increase the particle Stokes number and decrease the effective ECD.

Any aerosol with an upper range that exceeds the ECD of the inlet section will result in a truncated distribution reaching the plates of the ACI and any calculations based on the truncated data will be in error as no assessment or correction of the lost data can be made.

The data presented in Figure 4-22 indicates that much of the published aerosol data (7) is somewhat unreliable as many of the analysed products have combination of MMAD and GSD that fall outside the boundary limit defined by the 20 µm contour. For products based on pMDI’s with high vapour pressure formulations and larger exit orifices the increased spray momentum may well lower the ECD of the inlet significantly and may well approach or fall below the 10 µm contour.

It is not possible to use the deposition level in the throat as an indicator of ECD because the throat deposition is a function of many deposition mechanisms. Apart from the simple inertial mechanism it is well known that other deposition modes based on electrostatics, additional spray induced momentum, geometrical constraints and turbulence exist to further complicate the analysis of total throat deposition however the throat deposition will increase due to momentum transfer from the spray plume and if the throat deposition ECD approaches 10 µm then 20% of the upper distribution in Figure 4-23 will be lost and the resultant MMAD and GSD will be reduced to 2.9 and 2.2 respectively as shown in Figure 4-24.
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Figure 4-23 the number, mass and cumulative mass for an aerosol with an MMAD of 4 and GSD of 2.

![Aerodynamic Diameter (μm)](Image)

Figure 4-24 Log probability plot of a lognormal distribution truncated at 10 μm. The input distribution had an MMAD = 4 and a GSD = 2.5 (figure 4.21), the truncated distribution appears lognormal with an MMAD of 2.9 and a GSD of 2.2
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The GSD values determined for narrowly distributed mono-modal input samples (Table 4-9) shows clearly the limitations of the ACI with respect to accurate determination of the true GSD when the input materials have narrow GSD's (1.05) the increased diffusion of particles across numerous plates results in values ranged from 1.22 to 1.38.

Table 4-9 GSD data determined from the ACI modelling of the mono-modal distributions

<table>
<thead>
<tr>
<th>Mono-modal MMAD</th>
<th>2.1 µm</th>
<th>3.3 µm</th>
<th>4.7 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSD input</td>
<td>1.05</td>
<td>1.05</td>
<td>1.05</td>
</tr>
<tr>
<td>GSD measured</td>
<td>1.31</td>
<td>1.38</td>
<td>1.22</td>
</tr>
</tbody>
</table>

Is it worth noting that the potential particle filtering that happens in the USP throat tends to flatter coarser particle size distributions by moving their MMAD significantly downwards compared with finer particle size distributions which are unaffected and the ACI analysis reports a GSD that is higher than the actual GSD for very narrow mono-modal size distributions which is a desirable attribute for targeted delivery.

4.9 Limitations of the lognormal assumption

4.9.1 Introduction

Although the pharmacopoeia states where appropriate the MMAD and GSD should be determined there is no guidance as to what is appropriate with the result that the lognormal distribution is nearly always assumed in published data and MMAD and GSD values are regularly determined and quoted. In the nonlinear regression for a better fit to the lognormal(7) the MMAD and GSD are computed even in cases where the correlation coefficient ($r^2$) is unacceptably low and the assumption of a lognormal distribution is clearly inappropriate.
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The objective of this study is to demonstrate the lack of sensitivity in the cumulative lognormal probability plot methodology and how inappropriate the cumulative lognormal assumption can be in the analysis of aerosol distributions.

4.9.2. Experimental

In the data analysis method used here the ECDs of the ACI are assumed to be ideal as defined in the pharmacopoeia. The input distributions considered here were as broad as possible and defined as follows:

1. Constant particle number at each diameter within the ACI range
2. Constant mass at each diameter within the ACI range

The particle size range used in the study was 0-10 μm; the upper limit of 10 μm is due to the percent under size calculation which results in the material deposited on plate 0 not being used in the log probability analysis.

4.9.3. Results

![Log probability (probit) plot for input sample aerosol sample of constant mass distribution (uniform mass at each aerosol particle diameter)](image)

Figure 4-25 log probability (probit) plot for input sample aerosol sample of constant mass distribution (uniform mass at each aerosol particle diameter)
Figure 4-26 log probability plot for an input aerosol sample with a constant number distribution

4.9.4 Discussion

It is very significant that both probability plots (Figure 4-25 and Figure 4-26) appear to fit the lognormal distribution reasonably well given that neither of the input distributions are even close to lognormal. It is even more significant when the results are compared to the fit characteristics published for a wide range of inhalation products(7). The correlation coefficient for the constant number distribution is greater than all but two of the 22 inhalation products assessed and the constant mass greater than 17 of the 22 products.

The fact that these non lognormal distributions give very good correlations should sound a cautionary note to all in the inhalation field. Before making an assumption about the distribution one should obtain data from other test methods such as APS, Laser diffraction, PDA to better assess the true nature of the distribution before drawing conclusions about the nature of the distribution.

The validity of the correlation is significant when considering the determination of both the MMAD and GSD for the inhalation product. In the analysis of cascade impactor
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data it is important to determine the significance of outer data points which are based on low levels of probability. The outer data points can have a significant effect on the regression line and the subsequently determined MMAD and GSD(228).

4.10 Suspension formulation stability and impactor plate bounce

4.10.1 Introduction
In section 4.1. the ACI data for a suspension formulation showed no change in the MMAD as a function of the actuator exit orifice diameter. The time dependant stability of suspension formulations was also discussed. The significance of impactor plate bounce was also raised in the discussion and the impact this could have on the interpretation of particle size data. In order to answer some of these questions an additional study was added with the objective of further evaluate the significance of these critical aspects.

4.10.2 Method
A suspension formulation that was known to undergo a slight shift in the MMAD on storage at 40°C was tested using a range of exit orifice diameters. The shift in particle size was due to a degree of particle agglomeration. The agglomerates formed were not permanent and could be broken up by low level ultrasonic agitation. If the agitation was carried for a sufficient period the particle size of the aged formulation once again approach that of the starting material.

The actuators used were standard Autohaler™ actuators with exit orifice diameters of 0.22, 0.28 and 0.4 mm.

The units were tested using the standard APS coupled to the 3306 impactor unit fitted with a standard USP inlet throat operating at a flow rate of 28.3 l min⁻¹.

For a comparison of particle bounce a placebo formulation containing a blue dye to aid visual inspection was used. The blue dye aerosol used the same components as the suspension formulation (can, valve, propellant) but the dye was dissolved in ethanol.
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(8% w/w propellant) before being cold transferred to the propellant to give a 100 μg per actuation solution aerosol. The blue dye aerosol was tested using the 0.4 mm exit orifice diameter actuator detailed above.

4.10.3 Results and discussion

The particle size data in Table 4-10 show two important facts, one that the measured particle size is independent of the orifice size used in the testing and the other that difference between the aged and un-aged suspension formulation is consistent and reproducible.

It can be concluded that the exit orifice size does not significantly alter the particle size of a suspension even where the increase in size is due to low level particle agglomeration.

Table 4-10 MMAD for aged and un-aged suspension formulation using 3 exit orifice diameters.

<table>
<thead>
<tr>
<th>Exit orifice diameter</th>
<th>MMAD (initial)</th>
<th>MMAD (stored @ 40C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.22mm</td>
<td>2.87μm</td>
<td>3.12μm</td>
</tr>
<tr>
<td>0.28mm</td>
<td>2.87μm</td>
<td>3.13μm</td>
</tr>
<tr>
<td>0.40mm</td>
<td>2.86μm</td>
<td>3.13μm</td>
</tr>
</tbody>
</table>

The surface of the impaction plate of the APS 3306 impactor unit was visually inspected after testing with the 0.4mm diameter exit orifice for the aged, un-aged suspension formulation and blue dye solution aerosol formulation.

The deposition pattern found on the impaction plate for the blue dye aerosol showed the expected deposition pattern. The deposition pattern was elliptical not round and of a similar diameter to the impactor jet. The deposition pattern for the suspension formulation was visually the same for both the aged and un-aged units. The deposition pattern was elliptical and much larger than the impactor jet and there was additional
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material deposited outside the impaction zone indicating a significant level of particle bounce. The deposition outside the normal impaction zone forms a ‘Y’ shape deposition pattern in Figure 4-27.

Figure 4-27 Impaction deposition pattern for suspension formulation

Although the suspension formulation contains less ethanol than the solution formulation the particle size is larger due to the size of the suspended drug particles. The MMAD of the solution formulation is approximately 1 μm whereas the
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suspensions averages out at 3 μm and therefore contains a greater proportion of particles above the ECD of the 3306 impaction stage (4.7 μm). The large deposition seen in Figure 4-27 required only 4 actuations of the aerosol whereas the deposition in Figure 4-28 required 15 actuations of the solution formulation. The blue dye was used to give sufficient contrast to enhance the visual deposition of the solution formulation because of the fineness of the deposition from the solution formulation.

The results presented here show that particle bounce was independent of the formulation, valve and actuator and was a function of the particle characteristics. The ACI data for the formulation is shown in A.X ACI data for a formulation showing bounce in the APS.

4.11 Conclusions

- Lognormal plots of the mass deposited in ACI for suspension and solution formulations show varying degrees of departure from the ideal lognormal response.

- The MMAD interpreted from ACI deposition data for both suspension and solution formulations did not show any dependence on exit orifice diameter whereas the throat deposition (ballistic fraction) did increase with increasing orifice diameter.

- Computational modelling of the ACI stage deposition has shown the stage deposition is a function of the input distribution.

- Important differences were seen between the MMAD and GSD of the input material and the MMAD and GSD data interpreted from the computer based prediction.

- The fixed pharmacopoeia based ECD analysis methodology has the potential to significantly distort the log probability plot because the mean of the material
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deposited on plates can be considerably different from those defined in the pharmacopoeia. In the 4 samples analysed the MMAD of the material on plate 1 was 3.19, 4.64, 5.63 and 6.85 μm yet when analysed by the pharmacopoeia method the masses associated with these MMAD’s would be plotted against the fixed value of 9 μm.

- The upper plates of the ACI contain mass data with very unreliable size characteristics and these are primarily due to combination of poor design, overlapping stage performances and momentum effects.

- When the quantity of drug deposition on an ACI plate is low it can be used as an indication that the mean particle size on the plate will be significantly different from the designated mean for the plate. It can therefore be used as a justification for the removal of the plate data from any calculations made to determine the MMAD and GSD because the sizing accuracy of these deposits is limited and tends to distort the true lognormal trend.

- The GSD value determined from ACI data is limited at the upper end of the range by the dynamic range of the ACI and at the lower end by non ideal ECDs, overlapping plate efficiencies and plate spacing.

- The non linear correction methodology proposed by Thiel was found to be unreliable in correcting the ACI data and tended to further reduce the MMAD below that determined by the ACI and further from the true MMAD of the input material.

- When evaluated with a tri-modal distribution the computed ACI data using the standard pharmaceutical methodology tends to the mono-modal lognormal because of the particle diffusion induced by the non ideal cut characteristics, overlapping efficiencies and because the tri-modal distribution maximises the spread of data via the spacing of the individual mono-modal peaks.
The ACI modelling has shown how data from the ACI can be interpreted as being bi-modal whereas in reality this is purely an anomaly created by the shape and spacing of the stage efficiencies. The bi-modal nature to the data interpretation will be increased by any momentum induced deposition on the upper plates and incomplete droplet evaporation.

Any ACI based particle distribution analysis where the combination of MMAD and GSD that predict upper particle limits above the 20 μm boundary must be viewed with caution and any data obtained from pMDI’s with large exit orifice diameters then the upper limit for the distribution should be reduced to the range defined by the 10 μm to 20 μm contour of figure 4.20.

The reasonable fit to a lognormal has been show to apply for constant mass and constant number input distributions. The characteristics of these input distributions do not resemble those of a lognormal distribution and this fact coupled with the tendency for all distributions tested in the ACI model tend to a lognormal and it can be concluded that a significant justification would be required to ascertain the lognormal assumption and the use of calculated MMAD and GSD if the cumulative lognormal correlation is less than 0.95.

The data points at the extreme of the cumulative lognormal plot have a greater potential to influence the determination of the aerosols MMAD and GSD and to decrease the correlation coefficient.

Particle deposition studies in the upper stage of the ACI have shown variations in the level of deposition and non symmetrical deposition patterns for the inner 3 rings. The variations in deposition make evident the design flaws in the jet plate design where there is potential for impingement of airflows in the inner rings producing elongated depositions and distortion of the streamlines from the inner ring towards the hole in the impaction plate. The increased deposition
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pattern seen under the inner jet ring could indicate deposition due to non ideal flow mechanisms such as an increased deposition due to momentum. Any momentum based effect will also induce a non linear distortion due to the out of phase arrival of particles at the first stage of the ACI due to the phase separation of pressure wave and particle based time of flight through the throat section.

- Any determination of a MMAD and GSD should be supported by another measurement technology to independently prove the validity of the lognormal assumption.

4.12 Questions that require further investigation

- What is the true distribution shape of solution and suspension formulations?
- What is the filtering process in the USP throat?
- Would an alternative throat design aid the process of defining understanding?
- What is the initial droplet size and distribution?
- Are there non-ideal flow design issues with the plate design and layout in the ACI and can they be quantified?

In an attempt to answer the questions raised above a series of additional set of experimental tools and techniques together with additional computer modelling techniques were required. These include the APS for aerodynamic diameter, PDA for droplet analysis close to the exit orifice, CFD for flow analysis of the ACI and USP throat and computational modelling for droplet evaporation, initial droplet size and correlation to the Clark atomisation model.
Chapter 5 Measurement of particle size distributions using APS and PDA

5. Measurement of Particle Size Distributions using APS and PDA

5.1 Introduction and Objectives

For the results to be acceptable to the inhalation pharmaceutical community the particle size data must be from sources that are acceptable to and understood by the industry. Currently the measurement method of choice for the study of product inhalation performance and deposition patterns is the cascade impactor. Techniques such as APS, PDA and laser diffraction have been widely applied to the study of sprays (15, 157, 214, 232-238), but the pharmaceutical industry will always view these instruments with some degree of scepticism as cascade impactor data is the foundation for inhalation product knowledge, product development, regulatory submission data as well as product and process understanding. A rigorous study using identical inhaler devices and formulations enables a comparison between particle size distributions measured using the ACI, APS and PDA techniques. Furthermore, a careful analysis of the results can yield important clues relating to the atomisation processes.

It was shown in the preliminary impactor studies (section 4.1) that the particle size distribution of a solution or a suspension formulation exhibited departures from a lognormal distribution when analysed by the ACI using the method defined in the pharmacopoeia guidelines. Whilst this is not a surprise for a suspension formulation, it is for a solution product where the size distribution is very much a function of the atomisation process and previous workers have shown fits to either lognormal or Rosin Rammler type distributions (4-7) and the regulatory guidelines indicate the use of a lognormal based analysis unless otherwise justified (2).

The question is now raised as to whether the ACI output can actually give useful indications of the effects of changes in the device and formulation variables. Moreover, the USP throat was known to distort the particle size distribution by filtering out substantial quantities of the larger particles and the ECD for the USP throat has not
been quantified however a ECD of 20 μm was assumed by Vaughan (188) This makes it more difficult to link ACI particle size distributions to the atomisation mechanism. In order to address these issues particle size distributions were measured using an Aerodynamic Particle Sizer (APS) and a limited study was carried out using Phase-Doppler Anemometry (PDA). To investigate this issue particle size distributions were measured with the APS using (i) a USP throat and (ii) an enlarged inlet designed to avoid direct impaction of the larger particle size fraction (20 μm and above) if present in the pMDI aerosols.

The use of non volatile co-solvent and other additives have been shown to modulate the spray characteristics and influence the size of the resultant residual droplets (165, 166, 239, 240). The size of the residual droplet and the influence of ethanol level on throat deposition have also been shown (190, 192, 241) The study presented here will focus on propellant 134a with ethanol as a co-solvent. The selection of this system is based on the principles of limiting the pressure variation in the formulation whilst also giving greater control on the non flashing component of the formulation.

The inclusion of ethanol into the formulation does not reduce the vapour pressure of the mixture as rapidly as predicted by Raoult’s law (162) of an ideal solution is dependant on the mole fraction of the components. In mixtures of propellant 134a and ethanol there is a significant and positive departure from the law (162) The plot shows the vapour pressure against percent weight for weight ethanol in 134a. The plot shows that the vapour pressure does not change significantly between 8 and 30 % w/w ethanol (Figure 5-1).
Chapter 5 Measurement of particle size distributions using APS and PDA

![Vapour Pressure (gauge) 134a and Ethanol](image)

Figure 5-1 Saturated vapour pressure for mixtures of propellant 134a and ethanol (taken from EP550031, Hoechst AG now Solvay)

The inclusion of ethanol also serves a second function. In previous studies it has been assumed that a very high degree of flashing occurs in the expansion chamber of the actuator during drug delivery(4). The inclusion of a relatively non-volatile liquid component places a definable lower limit on the void fraction that can be generated during the passage of the formulation as it flows through the actuator because this component is always in the liquid form and does not contribute to the vapour volume.

Experimental methods and results from the following investigations are reported in this chapter:

- Effect of device (section 5.3): particle size distributions measured with APS for actuators with diameter 0.22 mm and 0.5 mm in conjunction with the USP throat (standard ACI inlet port)
Chapter 5 Measurement of particle size distributions using APS and PDA

- **Effect of inlet port** (section 5.4): Particle size distributions measured with APS for actuators with diameter 0.22 mm and 0.5 mm in conjunction with a large inlet port designed to minimise direct impaction of large particles.

- **Effect of presence of inlet port/direct measurement of initial aerosol** (section 5.5): Particle/drop size distributions directly downstream from the actuator at a distance of 70 mm using PDA.

- **Effect of formulation** (section 5.8): Particle size distributions measured with APS for formulations with ethanol co-solvent content varying between 8% and 48% w/w for actuators with diameter 0.22 mm and 0.5 mm in conjunction with the USP throat and large inlet.

- **Effect of formulation** (section 5.9): Distributions measured with APS for suspension formulation for actuators with diameter 0.22 mm and 0.5 mm in conjunction with the USP throat and large inlet.

### 5.1.1 The use of Particle sizing parameters

The primary measure for the mean particle size will be MMAD and the distribution parameter, GSD. Whilst these two parameters are favoured by the pharmaceutical industry they are not robust measurements in sampled aerosol techniques. In sampling based measurement techniques like the APS a few large particle can skew the data significantly because of the mass based cumulative calculation. Due to this limitation the particle size was also calculated using more conventional and widely used particle size parameters that are based on the calculation of an arithmetic mean weighted by a factor such as number, surface or volume. One of the most widely used parameters in the study of sprays is the Sauter mean diameter ($D_{32}$). There are a series of mean based diameters that can be used in the characterisation of particle sizes, number ($D_{10}$), surface ($D_{20}$) and volume ($D_{30}$) are a few and are derived from the general form;
Chapter 5 Measurement of particle size distributions using APS and PDA

\[
\bar{D}_{mn} = \left( \frac{\sum_{i=1}^{T} D_i^m}{\sum_{i=1}^{T} D_i^n} \right)^{\frac{1}{m-n}}
\]  

(5.1)

For \(D_{10}\) \(m = 1\) and \(n = 0\), for \(D_{30}\) \(m = 3\) and \(n = 0\) and for \(D_{32}\) \(m = 3\) and \(n = 2\).

The GSD is a measure of the spread in a lognormal distribution and is the slope of the best fit line between the plus and minus one standard deviation points. Due to the scaling factor on the droplet volume calculation for the evaporation process the GSD for the residual particles, will be the same as that for the droplets prior to the evaporation process (192). The GSD will not change between droplet formation immediately after the atomisation process has ceased and the final fully evaporated residual.

The use of number based mean diameters can have little meaning when assessing pMDI atomisation because the large number of small particles present, biases the mean to the low end of the distribution, effectively nullifying the influence of any large particles on the calculated mean. To take this bias into account the volume mean diameter (\(D_{30}\)) will also be calculated in parallel to the MMAD data because the dose of drug received is in terms of its mass or volume, if density is constant, a better indication of the mean size that is weighted by the relative contribution to the drug dose represented by each particle.

5.1.2 Effect of Formulation

The selection of a propellant system is crucial in obtaining a better understanding of the processes involved in the atomisation during actuation of the pMDI. Clark (141) studied the effect of formulation on the resulting particle size distribution by combining different mixtures of two propellants, assuming that there is a correlation between propellant vapour pressure and atomisation.
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5.2 Droplet evaporation in the USP throat and new inlet sampler

5.2.1 Introduction

The rate of droplet evaporation will have a substantial impact on the probability of larger droplets having sufficient longevity for inertial impaction to be a significant factor in USP throat deposition and the potential generation of secondary droplets.

In the new inlet sampler designed to overcome the inertial aspects of the pMDI delivery the longevity of droplets is important because although the length of the inlet provides significant evaporation time, gravitational settling adds to the analysis of the result.

The objective here is to review dimensional and flow velocity data to assess the deposition probability of larger droplets using the droplet evaporation model of Stein (242).

5.2.2 Size of droplets in the inertial impaction zone of the USP throat

We can estimate the range of air velocity within the inlet section as being between 1 and 3.2 m s⁻¹ (excluding the near wall region) with an average velocity of 1.66 m s⁻¹ based on an inlet flow of 28.3 l min⁻¹ and a diameter of 19 mm in the inertial impaction region.

The critical distances from the exit orifice to the back of the throat (Figure 6-1) can be determined as follows:

USP throat inlet to back wall (97 mm+9.5 mm) = 106.5 mm
Exit orifice to mouthpiece = 30 mm
Distance droplets measured at (from orifice) = 50 mm
Distance to travel (106.5 mm+30 mm-50 mm) = 86.5 mm
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The computed transit times to traverse the distance from measurement point to impaction zone on posterior wall of mitre bend in the USP throat are

- Maximum time (86.5 mm at 1 m s⁻¹) = 86.5 ms
- Minimum time (86.5 mm at 3.2 m s⁻¹) = 27.0 ms
- Average time (86.5 mm at 1.66 m s⁻¹) = 52.1 ms

Using the ethanol evaporation model (243) and the average traverse time assuming the minimum impaction size is 15 μm it can be computed that the largest ethanol droplet that can traverse the 86.5 mm and still be 15 μm or less is 20.1 μm and therefore the probability of a 150 μm (typical of the diameter seen in the high speed imaging in 5.7) evaporating sufficiently before the inertial impaction zone is zero. In contrast a 150 μm diameter droplet of the more volatile 134a would have only evaporated down to 145-μm in 52 ms clearly demonstrating the limitation these large droplets pose in the assessment of USP based cascade impaction data, whatever their liquid content.

### 5.2.3 Adaptation of the classical evaporation theory

The classical film theory for droplet evaporation yields the D²-law in which the square of the droplet diameter (d²) is inversely proportional to the time (t). An application of the classical theory to droplets of propellant 134a and ethanol yielded good approximations to the D²-law (242) were determined as

\[ t = k_{\text{ethanol}} d_{\text{ethanol}}^n \]  \hspace{1cm} (5.2)

\[ t = k_{134a} d_{134a}^n \]  \hspace{1cm} (5.3)

Where k is the evaporation rate constant.

The classical theory relates to a one component system and needs adapting for application to a two component system. The D²-law was modified assuming the droplet is homogeneous and therefore not diffusion limited. The mass flux of each component
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out of the surface film will be proportional to the volumetric fraction in the surface film and 5.2 and 5.3 can be modified to solve for the volumetric change as a function of a time interval for each of the components.

\[
v_{\text{loss, ethanol}} = \frac{1}{6\pi} \left[ \frac{t_1}{k_{\text{ethanol}}} \right]^n - \left[ \frac{t_2}{k_{\text{ethanol}}} \right]^n \frac{v_{\text{ethanol}}}{v_{\text{droplet}}} \Delta t
\]

(5.4)

\[
v_{\text{loss, 134a}} = \frac{1}{6\pi} \left[ \frac{t_1}{k_{\text{134a}}} \right]^n - \left[ \frac{t_2}{k_{\text{134a}}} \right]^n \frac{v_{\text{134a}}}{v_{\text{droplet}}} \Delta t
\]

(5.5)

Where in the classical analysis \(n=2\), but here the exact values determined by Stein(242) were applied to equations 5.4 and 5.5.

For initial droplet diameters of 20 \(\mu\text{m}\) (approximates to the 50% efficiency point of the USP throat) and 32 \(\mu\text{m}\) (upper efficiency limit for the USP throat) the results were solved numerically and the resultant droplet diameter for various combinations of ethanol and propellant 134a plotted assuming adiabatic flashing prior to final droplet formation.
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Figure 5-2 variation in droplet evaporation for a 20 μm diameter droplet ranging from 100% propellant 134a to 100% ethanol

Figure 5-3 variation in droplet evaporation for a 32 μm diameter droplet ranging from 100% propellant 134a to 100% ethanol
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5.2.4 Discussion

In practice the velocity of the plume could reduce the droplet transit time and therefore under these conditions larger droplets will reach the impaction area, the posterior wall of the mitre bend. Larger drops also have the potential to deposit in the entry region of the USP throat given the turbulent nature of this region adding to the complex deposition patterns\(^{(190)}\).

Droplets of pure 134a up to diameters of approximately 50 \(\mu\)m can be expected to evaporate sufficiently prior to reaching the inertial impaction region (mitre bend) of the USP throat. The inclusion of ethanol significantly increases the evaporation time and limits the droplet diameter change during the transition period between leaving the exit orifice of the delivery system and reaching the mitre bend (Figure 5-2 and Figure 5-3).

The rate of evaporation of pharmaceutical droplets is complex due to the significant number of potential unknown variables within the system. The velocity of the droplets is largely unknown due to factors such as momentum transfer from the plume and changes rapidly with distance from the orifice. Larger droplets can be expected to have a lower initial velocity but due to momentum will maintain the velocity over longer distances (stopping distance). In a study comparing the relative influence of atomisation and evaporation on pMDI efficiency\(^{(243)}\) and the relationship between droplet lifetime and drug delivery efficiency\(^{(242)}\) a relationship between droplet diameter and residence time was determined for both pure propellant 134a and pure ethanol. It was acknowledged in the derivation that many of the variables are interrelated. The evaporation rate for 134a was an order of magnitude greater than that of ethanol and therefore it would be expected that low ethanol formulations would show a different response to those with higher ethanol content.

Based on these factors it would be safe to assume that little or no evaporation could take place for larger droplets given the expected throat transit time.
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A study of the evaporation of propellant 12 droplets delivered by a pMDI using PDA analysis compared the experimental droplet distribution to that predicted by the classical theory and concluded that smaller droplets evaporated faster than larger droplets when measured at three distances downstream of the mouthpiece causing a shift in the distribution when compared to the theory (244). Application of this observation would add to the complexity of determining a particle size distribution.

5.3 Preliminary study of residual particle size and distribution with APS for solution formulations

5.3.1 Method
The objective is to collect size and distribution data from a range of exit orifice diameters found in commercial actuator designs. Using the standard 3320 APS fitted with the 3306 aerosol inlet sampler and using the standard USP throat and a flow rate of 28.3 l min⁻¹. The QVAR™ solution formulation containing 134a and ethanol 8% w/w and 100 µg per dose API were inserted into Autohaler™ actuators moulded with exit orifice diameter of 0.22 mm and 0.5 mm (representing the range cover by most commercial actuators). The testing consisted of 5 assembled devices; each device was fired to waste 5 times prior to testing. One actuation per device was fired into the USP inlet throat. The data from each actuation was combined to form one data set per test combination. The data was plotted as cumulative mass and fitted to a cumulative lognormal curve using Tablecurve2D® software. Details of the mask generation method together with calibration of the APS can be found in A.IV Calibration of the APS and mask generation

5.3.2 Results and discussion
The data (discrete points) is presented in the form of cumulative mass fraction (y-axis) and a linear scale of residual aerodynamic diameter (x-axis). The best fit cumulative lognormal curve (continuous line) is also displayed.

The data for the solution formulation, generated using identical flow rate and inlet geometry to that used in the ACI testing yields a distribution that conforms more
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closely to a lognormal distribution (Figure 5-4 and Figure 5-5) than the ACI generated
data (section 4.1).

![Figure 5-4 Cumulative mass fraction plot for 0.22 mm orifice measured in the APS using ACI inlet throat (residual particle diameter is in μm).](image)

The APS generated data for the lower end of the commercial actuator exit orifice range (0.22mm) demonstrates a good fit to the lognormal curve (Figure 5-4). The larger exit orifice (0.5 mm) does show some deviation away from the lognormal (Figure 5-5), in the lower and upper particle size ranges but fits well throughout the main size range which is contrary to the ACI data which deviates more in the central size range.
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The data presented by the APS instrument provides significantly more information regarding the shape of the particle size distribution due to the increased resolution compared to that of the ACI technique.

The APS based particle size data shows a decrease in the MMAD (0.88 and 0.98 μm) when compared to the equivalent ACI data set (1.15 and 1.18 μm).

The data for the two different analyses raises fundamental questions: is the change in size and shape of the distribution due to

- An interaction with the USP inlet throat due to differences in the instrumental flow paths
- The fundamental differences in the particle analysis technique

In order to resolve these questions the problem needs to broken down into component solutions the first of which is to assess the influence of the USP inlet throat by replacing it with a larger inlet throat.
5.4 Study of residual particle size distributions using APS measurements and a larger inlet port

5.4.1 Introduction
The APS and ACI based data for similar delivery systems showed a difference in both the MMAD and distribution characteristics of the emitted aerosol. The objective here is to establish the influence that the standard USP throat could have on the determination of MMAD and distribution parameters. The standard USP inlet has an inlet section that tapers to a diameter of 19 mm in this study a 100 mm diameter inlet is proposed. The distance from the mouthpiece to the bend increases slightly whereas the width increases significantly. In order to eliminate the convergent characteristics of the inlet section of the standard USP throat an alternate much wider inlet design was chosen.

5.4.2 Method
Using a custom made inlet section consisting of short pipe 150 mm in length having a 90-degree bend with a radius of 100 mm and a diameter of 100 mm. The inlet was fitted with a blanking plate modified in the centre to take the same inlet coupler used in the USP throat and the outlet was fitted with a blanking plate modified at the centre to take a pipe with the dimensions of the lower section of the USP throat so that it had the same coupling arrangement to the 3306 impactor unit as the USP throat.

Standard 50μl metered valve QVAR™ aerosol units using identical Autohaler™ actuators with the exception of orifice diameters of 0.22 mm and 0.5 mm were used. Five devices, one actuation per device with the data combined to form one data set per test combination.

5.4.3 Results and discussion
The data generated using the larger inlet throat reveals some interesting results regarding both the particle size and distribution measured.

The distribution of the spray produced by the 0.22 mm exit orifice (Figure 5-6) now shows a lack of fit in the upper region of the characteristic S shaped cumulative data.
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The MMAD particle size has decreased slightly from 0.98 µm to 0.96 µm but from a practical perspective they are comparable.

The change in the 0.5 mm exit orifice data (Figure 5-7) is more noteworthy with a shift in the MMAD up to 1.09 µm from 0.98 µm and an increase in the number of particles in the 2-4 µm range. This is surprising given that the USP throat is understood to only capture particles >20 µm and indicates the potential significance of droplet evaporation.

The change in particle size distribution and particularly the MMAD has a significant impact on whether the APS fitted with the standard USP throat would be a suitable system to assess particle size data in an atomisation study. The above data along with the fact that the formulation used here produces the lowest MMAD generated by any commercial pMDI system. This suggests that an alternative inlet configuration may be preferable for atomisation studies.

![Figure 5-6 Cumulative mass fraction plot for 0.22 mm orifice measured in the APS using alternate large diameter throat (residual particle diameter is in µm).](image-url)
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![Figure 5-7 Cumulative mass fraction plot for 0.5 mm orifice measured in the APS using alternate bend throat (residual particle diameter is in μm).](image)

5.5 Droplet size data using PDA measurements

5.5.1 Method

The initial droplet size downstream of the actuator orifice is measured using Phase Doppler Anemometry (PDA) in this study.

The aerosol formulation and actuators used in this work were the same as those in section 5.3.1. The previous results had shown the larger orifice to have the wider range of particle sizes, a higher MMAD (Figure 5-5) and a greater deviation from the lognormal it was therefore determined that the 0.5 mm diameter exit orifice was necessary for this stage of the experimental studies.

The droplet size was measured along the central axis 70mm downstream of the exit orifice using a Dantec 1D PDA system. The data was collected and processed using SIZEware™ software. The raw data file was then processed for individual particle data using custom routines and the data exported to Tablecurve2D® software for plotting.
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against a cumulative lognormal distribution as used previously for comparison purposes.

5.5.2 Results and discussion

The mean droplet diameter was determined to be approximately 7 μm when plotted as cumulative volume based on the PDA diameter measurements. The PDA determines volume based diameters and does not therefore generate MMAD data and therefore no simple direct numerical comparison can be made between the data in Figure 5-8 and that in Figure 5-4 to Figure 5-7 other than and rather significantly the data from both techniques approximates to a lognormal distribution. The GSD for the data in Figure 5-8 is 1.98. If an assumption about the ratio of ethanol and propellant present in the droplet is made then it is possible to extrapolate to the residual particle diameter (the relationship between residual diameter data obtained from the APS and the initial droplet size will be explored in chapter 7).

The approximation to a lognormal distribution for a solution based formulation is a significant factor when comparing the ACI and APS data from two fundamentally different instruments and tends to support the APS data for the assumption of a true lognormal distribution.

The data generated here will be used later to validate the extrapolation process used to determine the initial drop size from residual particle size data in chapter 7.
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![Cumulative mass fraction plot](image)

Figure 5-8 Cumulative mass fraction plot for 0.5 mm orifice with 8% w/w ethanol measured using a Phase Doppler Anemometer (PDA) into still air at a distance of 70 mm from the orifice.

5.6 Droplet formation and residual particle size

5.6.1 Method

The previous studies have highlighted the limitation of the ACI and the USP throat for studying the residual particle size generated by the pMDI. The following study will use the APS as the aerodynamic particle size measuring device and the APS will be fitted with both the standard USP inlet throat as used in the ACI and the NGI cascade impactor devices and an alternate custom designed inlet section, referenced as the “tube” from this point. The principles used in the design of the tube inlet section can be found in A.VIII New inlet section design for the APS and CFD analysis. The design was generated by combining observations and measurements made using spray visualisation studies, standard ACI testing, modelling of the ACI (Chapter 4) and the CFD studies (to be reported in Chapter 6).

The purpose of the study reported in this section is to investigate in more detail the effect on pMDI aerosol particle size and distribution due to variations of the ethanol concentration for two actuator orifice diameters and two different inlet configurations. The aerosols were both standard and modified QVAR™ units fitted with 50 µl
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Spraymiser™ valves. A pre-weighed batch of aerosols was chilled to -56°C overnight. The units were removed from the chiller and the valve was immediately removed from the aerosol using a custom designed tool and the contents placed into clean, dry, pre-chilled aluminium cans. A predetermined quantity of ethanol/drug solution for each formulation was added to the can and immediately a new 25 µl valve crimped to the can some units were also fitted with 50 µl valves, with the option to study valve size as a variable. The volume of the expansion zone for the actuator system used was 114 µl. The drug content was maintained at 100 µg per actuation but the ethanol level was 8, 14.5, 25.1, 33.4 and 47.8% w/w. A set of plastic actuators with exit orifice diameters of 0.22 mm and 0.5 mm were cleaned and dried. The exit orifice examined under magnification for moulding defects, those will any sign of defects were removed from the study. The aerosol units were primed and allowed to stabilise, valve down, for 7 days prior to testing.

The units were tested with an inlet airflow rate of 28.3 l/min using either;

- The APS fitted with the standard USP throat and a small extension tube (100mm) at the outlet end.
- The new ‘tube’ design (design principles can be found in A.VIII New inlet section design for the APS and CFD analysis)

The units were test fired and a single test shot from 5 separate units. The data from the 5 shots were pooled for analysis. The same APS data mask was used for all the data sets (the data mask is intended to correct data from the 3320 version of the APS to that produced by the redesigned 3321 version). Testing 5 shots from a single device was considered but it was deemed necessary to include as much device variability as possible into delivery from the pMDI’s and pooling the data from 5 separate units minimises variation due to valve, drug and ethanol content.

In order to aid the comparative analysis of the particle size and nature of the particle distribution and characteristic the dynamic range evaluated by the APS was limited to

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that of the ACI (<9 μm because the data on plate 0 of the ACI is not utilised in the standard pharmaceutical method for ACI analysis). Using this approach overcomes two potential limitations of the APS. Firstly it removes any potential for the incorrect sizing of phantom particles (245) and overcomes the sampling limitations and distortions induced by a few larger particles (>10 μm) and secondly it makes the direct comparison of data comparable because both instruments are assessed using the dynamic range for particle size.

Discrete particle sizing techniques can be subject to sampling errors particularly where wide ranges of particle sizes are found, as is the case with the lognormal distribution where only a relatively small number of large particle/droplets exist. The APS samples only a small portion of the incoming flow (0.2 % of the spray), which equates to 1 in 500 particle counts. If the large particles are only present in a ratio of 1 in 500 or less then the resultant data will be biased to the those particles with a greater probability. In the APS the further dilution of the iso-kinetic sample reduces the probability still further. Assessing the potential for any loss of sample is critical in obtaining a full understanding of the underlying atomisation process.

5.6.2 Results and discussion
Cumulative particle size distribution data are given in Figure 5-9 to Figure 5-16 for two orifice diameters, two ethanol levels and two inlet designs. The resulting MMAD and GSD values are reported below in Table 5-1 and Table 5-2. The distributions shown in Figure 5-9 - Figure 5-12 show no lack of fit to the upper portion of the lognormal particle size range indicating a good fit to the lognormal approximation. The data for an 0.5 mm exit orifice (Figure 5-9 to Figure 5-12) show very little difference in either the MMAD or distribution characteristics which given the significant difference in the level of propellant is unexpected (141). When the same combination of formulation and exit orifice is tested using the tube inlet design rather than the USP throat as the inlet there is a difference in both the MMAD and the upper end of the distribution range and the MMAD data (Table 5-1)
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Figure 5-9 Cumulative mass fraction data for 8% w/w ethanol tested with a 0.5 mm diameter exit orifice using the standard aluminium USP throat

Figure 5-10 Cumulative mass fraction data for 48% w/w ethanol tested with a 0.5 mm diameter exit orifice using the standard aluminium USP throat
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Figure 5-11 Cumulative mass fraction data for 8% w/w ethanol tested with a 0.5 mm diameter exit orifice using the tube throat design

Figure 5-12 Cumulative mass fraction data for 48% w/w ethanol tested with a 0.5 mm diameter exit orifice using the tube throat design
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Figure 5-13 Cumulative mass fraction data for 8% w/w ethanol tested with a 0.22 mm diameter exit orifice using the standard aluminium USP throat

Figure 5-14 Cumulative mass fraction data for 48% and w/w ethanol tested with a 0.22 mm diameter exit orifice using the standard aluminium USP throat
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Figure 5-15 Cumulative mass fraction data for 8% w/w ethanol tested with a 0.22 mm exit orifice using the tube throat design

Figure 5-16 Cumulative mass fraction data for 48% w/w ethanol tested with a 0.22 mm exit orifice using the tube throat design
Chapter 5 Measurement of particle size distributions using APS and PDA

Table 5-1 Summary of MMAD for orifice diameter, inlet sampler and ethanol level

<table>
<thead>
<tr>
<th>Orifice Diameter</th>
<th>Sampler inlet</th>
<th>8% Ethanol</th>
<th>48% Ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5mm USP</td>
<td>0.98 µm</td>
<td>1.11 µm</td>
<td></td>
</tr>
<tr>
<td>0.5mm Tube</td>
<td>1.03 µm</td>
<td>1.49 µm</td>
<td></td>
</tr>
<tr>
<td>0.22mm USP</td>
<td>0.88 µm</td>
<td>1.20 µm</td>
<td></td>
</tr>
<tr>
<td>0.22mm Tube</td>
<td>0.86 µm</td>
<td>2.29 µm</td>
<td></td>
</tr>
</tbody>
</table>

Table 5-2 Summary of GSD for diameter, inlet sampler and ethanol level

<table>
<thead>
<tr>
<th>Orifice Diameter</th>
<th>Sampler inlet</th>
<th>8% Ethanol</th>
<th>48% Ethanol</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5mm USP</td>
<td>1.46</td>
<td>1.48</td>
<td></td>
</tr>
<tr>
<td>0.5mm Tube</td>
<td>1.49</td>
<td>1.77</td>
<td></td>
</tr>
<tr>
<td>0.22mm USP</td>
<td>1.39</td>
<td>1.53</td>
<td></td>
</tr>
<tr>
<td>0.22mm Tube</td>
<td>1.43</td>
<td>2.41</td>
<td></td>
</tr>
</tbody>
</table>

The particle size is expected to increase with increasing ethanol content. The data in Figure 5-9 and Figure 5-10 suggests that the USP throat limits the breadth of the particle size distribution reaching the APS for the sprays produced by the larger orifice: the MMAD is 0.98 µm for 8% ethanol and only increases to 1.11 µm for 48% ethanol formulation. In the all data relating to cases where the USP inlet was used, no particles greater than 4 µm (any combination of orifice diameter and ethanol) were found, which, given the ACI deposition data in section 4.1 and the expected ECD of the USP throat is surprising. This could also account for the lower GSD’s seen with the USP inlet based APS data.

In contrast the data in Figure 5-11 and Figure 5-12 relating to tests carried out with the tube inlet design shows an upward shift in both the MMAD and GSD the difference is small in the low ethanol formulation but noteworthy in the high ethanol formulation. As the input systems and particle measurement systems are the same the difference is therefore a result of the inlet design and is a significant aspect in measuring and therefore understanding the atomisation processes. It would appear likely that
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Impaction of these larger droplets onto the surface of the USP throat generates smaller secondary droplets that increases the number of droplets at the smaller end of the distribution that is significantly out of proportion for the ethanol level being assessed. These data for the USP throat clearly highlight the limitation on particle size assessment when assessing formulations that produce large droplets.

The effect of orifice diameter on MMAD is clearly defined for the tube inlet compared to the USP and the same applies to the values for GSD and indicates much broader distributions are being generated. The effect of orifice diameter on the MMAD is interesting because at the low ethanol level the MMAD increases with increasing diameter whereas in the high ethanol level the opposite effect is seen. This could indicate a change in the primary mechanism of atomisation or that the droplets in the upper size range from the larger orifice are so large they do not reach the detector in the tube due to gravitational settling. The data in Figure 5-16 shows the particle diameter data is not asymptotic (indicating a truncation of the distribution and a limitation of the dynamic range used) from the MMAD and GSD the upper 95% confidence limit is 13-μm and the 99% limit 32 μm. These values indicate initial droplet sizes of >100 μm and >300 μm respectively (141).

High resolution images close to the exit orifice will be used to assess the break-up mechanism and assess the true upper limit to the droplet diameters produced by high ethanol content 134a formulations.

5.7 High speed digital imaging of the spray

In the previous section it was postulated that the reduction in detection efficacy of the APS was due to the production of larger droplets that from both a statistical and practical perspective would not reach the particle size detector. In the lognormal distribution large droplets are fewer in number and therefore statistically are more likely to be under-sampled. Moreover, due to the effect of gravity large droplets will settle rapidly and will therefore not reach the inlet to the APS resulting in a loss of the
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larger particle size end of the distribution and a false determination of both the mean and distribution parameters.

The objective is to use high speed digital imaging to ascertain whether these larger droplets do in practice exist.

5.7.1 Methodology for large droplet detection

The emitted spray was imaged 50 mm downstream of the exit orifice using a Photron™ Ultima™ high speed digital camera. Illumination was provided by an Oxford lasers 30-W copper vapour laser utilising diffuse back screen illumination via a fibre optic feed. The camera was set to record at 10000 fps using an image resolution of 512*512 pixels.

The video images were post processed using Mathcad® software incorporating the image analysis software extension.

5.7.2 Results and discussion

The images from the entire metered actuation of both 8% and 48% ethanol in 134a formulations were analysed.

![Image](image.png)

Figure 5-17 Section of a 512*512 image showing the droplets produced by an 8% ethanol in 134a formulation
Figure 5-18 Section of a 512*512 image showing the droplets produced by a 48% ethanol in 134a formulation

The image from an 8% ethanol formulation (Figure 5-17) is typical of that seen during the metered actuation. The size of the droplets appears to be consistent during the delivery cycle with droplet diameters up to 20-30 μm. It is not possible to see or size the smaller droplets due to the field of view and the pixel resolution which results in a single pixel size of approximately 5 μm. When viewed as an animation the large number of very small droplets appears like a fog moving across the image and look as if to move in waves across the field of view. A wave like appearance to the flow has been reported previously (208).

The image from a 48% ethanol formulation (Figure 5-18) is typical of those seen during the early phase of the delivery process and confirms the presence of droplets too large to reach the detector of the APS. The image shown was chosen because it conveys several important pieces of information. There are three large droplets in the focal plane but several other larger droplets can be detected as faint out of focus objects. There are also a large number of smaller droplets present in the 20 μm to 50 μm diameter range. The large droplet in the upper right-hand area appears to be either about to separate into two droplets or conversely two large droplets are coalescing and a small ligament extending from the lower left edge of the droplet.
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The lack of circular symmetry of the larger droplets is probably due to the recoil process often seen following droplet formation. However, due to the high velocity of the droplets and the narrow field of view the droplets only appear on a single frame and it was therefore not possible to observe the phenomena in greater detail.

The disproportionate number of larger droplets (for a lognormal distribution) and the lack of droplets in the intermediate range of 50 μm to 100 μm could indicate the presence of a second break-up mechanism. Given the reported exit velocities determined in the two phase flow study then in the case of high ethanol contents (lower degree of flashing potential) then both flash and aerodynamic shear mechanisms are possible as well as secondary droplet scatter following impingement and subsequent pooling of cooled liquid onto surfaces such as the inner mouthpiece wall and actuator exit cone area as physical examination of the devices after testing showed there to be drug deposits in these regions.

The second atomisation mechanism could also be due to the non-homogeneous distribution in the two phase flow entering the exit orifice and this mechanism would be further enhanced by temperature variations lowering the systems flashing potential. Previous atomisation studies, using mixtures of propellants to lower the formulation pressure, have reported irregular droplet formation(141, 163) often described as ‘sputtering’ and has been used to quantify the point at which the propellant mixture ratio is no longer suitable for atomisation. It is likely that the phenomena responsible for ‘sputtering’ occur at mixture ratios near this point but the effect becomes progressively masked by the increasing flashing mechanism. The ‘sputtering’ may be the first visual observation of the lack of flashing potential as the degree of superheat for the formulation decreases.

The presence of large droplets supports the earlier conjecture (see section 5.6.2) that formulations containing higher levels of ethanol, can potentially generate a secondary droplet fraction on impact with the USP throat. Based on the video evidence the volume/mass of these larger particles would significantly reduce the detection levels.
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seen by the APS and potentially distort the mean and distribution parameters by increasing the number of residual particles in the micron and submicron range. A CFD study to be reported in Chapter 6 will investigate further the range of droplet sizes that are expected to impact in the USP throat.

With respect to the potential droplet diameters shown Figure 5-18, given the potential droplet diameter range, it would be expected that nearly all of the droplets would deposit in the USP throat unless the droplet evaporation rate is sufficiently high for the droplets in the >50 μm range to have time to evaporate to <20 μm prior to reaching the inertial deposition site in the USP throat.

5.8 Effect of ethanol on droplet diameter

5.8.1 Normalised mass balance

The normalised mass balance data (Figure 5-19) is used to assess the amount of material deposited in the actuator and inlet section without the need to chemically assay. The loss of particles in the inlet section (USP or tube design) is an important parameter when analysing aerosol data. The standard analytical approach is to chemically assay the deposition in the inlet for API. This process is time consuming and labour intensive so an alternative approach of normalising the loss was implemented.

The drug content in each formulation is constant and therefore the same residual volume should be detected for each formulation. The volume of material detected by the APS has been normalised to the base level of 8% ethanol (reference) data to obtain a relative measure of the mass reduction due to drug deposition on the actuator surfaces and the inlet (USP or tube design).

5.8.2 Method

The data detected by the APS is a sample taken from the spray and the volume/mass of the spray has been shown to correlate well to the ACI when a suitable data mask is
used (245) and extension tubes are used between the USP inlet and the APS to improve evaporation (246) when ethanol levels are high.

The mass of material detected by the APS was referenced to the level of the lowest ethanol formulation (8% w/w) for each inlet design using the following method:

\[
\text{Mass} = \rho \sum_{i=d_{\text{min}}}^{d_{\text{max}}} n_i \frac{4}{3} \pi \left( \frac{d_i}{2} \right)^3
\]

\[
\text{Normalised} = \frac{\text{Mass} = \rho \sum_{i=d_{\text{min}}}^{d_{\text{max}}} n_i \frac{4}{3} \pi \left( \frac{d_i}{2} \right)^3}{\text{Mass}_{\text{ref}} = \rho \sum_{i=d_{\text{min}}}^{d_{\text{max}}} n_i \frac{4}{3} \pi \left( \frac{d_i}{2} \right)^3}
\]

Where \(d\) is particle diameter, \(n\) is the number count and \(\rho\) is particle density.

5.8.3 Results and discussion

The data presented in Figure 5-19 clearly shows there to be an increasing loss of mass (or volume assuming constant density of the residual droplets) due to inlet deposition as the particle size increases with increasing ethanol content. The loss as expected from a design perspective is greater in the USP throat than in the tube design (tube design consistently detected more counts compared to the USP inlet however each design is normalised to its own base ethanol level).
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![Figure 5-19 Normalised mass balances for USP and tube inlets](image)

The significant loss of data raises a doubt as to the true particle size at 48% w/w ethanol as up to 80% of the material is unaccounted for. The exception is the 0.22 mm orifice in the tube and could be an indication of a change in the break up mechanism due to impaction and secondary droplet production. The 220 μm exit orifice diameter imposes a physical upper limit on droplet diameter.

The increased losses as a function of ethanol level are due to a combination of increased deposition with drop size (inertial and gravitational deposition) and potential statistical sampling error because of the very large droplets in the tube design (greater than the dynamic range of the APS) and also because of gravitational settling in the tube design for droplets greater than 20 μm. In a like for like comparison, there is always a greater number of larger droplets (4-20 μm) in the tube design compared to the USP and this demonstrates the USP throats limitation when conducting fundamental particle-sizing experiments and highlights the potential loss of data that should pass through the USP throat at the test flow rate assuming the objective is to measure actual particle size.
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The limitations of the USP throat design raises questions regarding the validity of cascade impactor data when using such \textit{in vitro} techniques to assess product performance for other than quality assurance purposes. In QA testing the USP throat is 'consistent' as is the plate deposition. The USP design does however impose limitations for all other types of testing such as device design and true particle size assessment. It is critical that the geometry in to which the pMDI is actuated is as close, in terms of shape, volume, surface etc., to the human inhalation route and this should also include other key factors such as the surface nature of the geometry and the velocity of the air flow being used to determine said performance in order to avoid significant product assessment errors being made.

5.8.4 Assessment of Particle size (Median vs Mean)

The assessment of particle size and distribution is a fundamental requirement in the assessment of inhalation therapy. The effect of ethanol level on the particle size is assessed using both the pharmaceutical convention of median and the particle size assessment of the mean which is common in many other industries. Whereas the median is simply the mid point when data is arranged orderly from low to high and in the case of inhalation this is by mass. In contrast the weighted mean (equation 5.3) is less sensitive to outliers and can be weighted according to number of parameters such as surface area, volume or mass. In this analysis the full dynamic measurement range of the APS was utilised (0.5-20 μm).

5.8.5 Results and discussion

The affect of ethanol on the MMAD is presented in Figure 5-20 and Figure 5-22 for exit orifice diameter of 0.22 mm and 0.5 mm respectively. Both orifice diameter show similar trends with the MMAD increasing with ethanol content for the tube design and remaining also independent of ethanol level in the USP throat with a slight increase in MMAD with ethanol for the 0.22 mm orifice whereas the response in the 0.5 mm orifice is almost independent of the ethanol content and remains constant at approximately 1 μm.
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Figure 5-20 MMAD for a 0.22mm diameter exit orifice

The GSD determined for the same ethanol content range and the 0.22mm orifice (Figure 5-21) demonstrates the importance of assessing particle size distribution and clearly shows an increased spread in the particle size distribution, as a function of ethanol content and the concomitant reduction in the enthalpy for a flash based atomisation process assumption, when assessed with the tube design. It is clear from the USP based data that the functional design of the USP throat is such that it is unable to quantify a change in such a critical response because the GSD remains effectively constant across the entire ethanol range.
Figure 5-21 GSD for a 0.22 mm diameter exit orifice

When the exit orifice diameter is increased to 0.5 mm it is still possible to elucidate an increase in GSD with ethanol in the tube inlet whereas the USP throat based data shows no change in GSD as a function of ethanol content and potentially a decrease above 25% ethanol. The plateau in both MMAD and GSD indicates the USP throat limits the range of particle/droplet diameters that penetrate to the particle sizing region. It has previously been shown that the quantity of USP throat deposition tends to plateau and even decrease as a function of the exit momentum generated by increasing exit orifice diameters. It is therefore likely that impaction and partial break up of the larger droplets leads to a plateau in the particle size range. The chaotic nature of this type of break up gives results that are effectively independent of both ethanol and the basic atomisation process and results from an interaction between the system being assessed and the system being used to conduct the assessment.
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Figure 5-22 MMAD for a 0.5mm diameter exit orifice

Figure 5-23 GSD for a 0.5 mm diameter exit orifice
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Figure 5-24 $D_{10}$ particle size data for USP

Figure 5-25 $D_{30}$ particle size data for USP
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When the APS data set for ethanol content and exit orifice diameter is processed using the weighted mean particle size technique it is possible to detect an increase in particle size with increasing ethanol content across the entire ethanol range and for both exit orifice diameters. The $D_{10}$ and $D_{30}$ data for the USP show a crossover response, which is indicative of an interactive response. As would be expected the volume-weighted parameter showing a higher mean across the range of ethanol values compared to the $D_{10}$. A similar trend is seen in the tube data with the values for the $D_{30}$ (Figure 5-27) being higher than the corresponding value for the USP throat due to the increased capacity for larger particles detection but is not as significant as seen in the MMAD data because of the change in diameter weighting. The tube based data does not exhibit the crossover response rather a convergence at the higher ethanol level. The tube data indicates a degree of curvature with the curvature more pronounced in the $D_{30}$ data where the increased number of larger particles begins to have an influence on the volume weighted mean.

A comparison of the MMAD and the more computational $D_{10}$ and $D_{30}$ for the same data sets show how important the particle size analysis technique is when trying to assess the output from pMDI’s and the variations induced by formulation and actuator designs. The response of the MMAD was effectively independent of ethanol level whereas the $D_{10}$ and $D_{30}$ determination did show a linear increase with ethanol content. It is important to note that MMAD is a median and $D_{10}$ and $D_{30}$ are means. In sampling techniques like those used in the APS and where distributions are not normal the median can be influenced by the presence or absence of particles that may actually represent a large portion of the mass or volume.
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Figure 5-26 D$_{10}$ particle size data for tube design

Figure 5-27 D$_{30}$ particle size data for tube design
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5.9 A study of residual particle size and distribution with the APS for suspension formulation assessment

The previous studies for the size and distribution of sprays emitted by the pMDI have focused on the solution formulation. The solution formulation is the ideal model because the concentration of the drug is in theory uniform in all the droplets produced. In the suspension formulation the situation is more complex because the drug is present in discrete particles suspended in the formulation. The process is further complicated by the addition of suspending agents to stabilise the discrete particles by limiting processes that cause particles to coalesce.

The presence of non-active formulation additives such as surfactants is one of the main reasons why sizing techniques like the APS are not favoured by the pharmaceutical regulators because it can not distinguish between a drug particle and a residual surfactant or other particulate in the formulation.

The objective for the work presented here is to assess the particle distribution characteristics generated by a suspension formulation and to assess the nature of the particle size distribution.

5.9.1 Method

The objective is to collect size and distribution data from a range of exit orifice diameters found in commercial actuator designs. Using the standard 3320 APS fitted with the 3306 aerosol inlet sampler and using either the standard USP throat or the tube inlet and a flow rate of 28.3 l min⁻¹. The Airomir™ suspension formulation containing 134a and ethanol 14.7% w/w and salbutamol sulphate as the API were inserted into Autohaler™ actuators moulded with exit orifice diameter of 0.22mm and 0.5mm. The testing consisted of 5 assembled devices; each device was fired to waste 5 times prior to testing. One actuation per device was fired into the USP inlet throat. The data from each actuation was combined to form one data set per test combination. The data was plotted as cumulative mass and fitted to a cumulative lognormal curve using Tablecurve2D® software.
5.9.2 Results and discussion

The data for the suspension formulation, generated using identical flow rate and inlet geometry to that used in the ACI testing yields a distribution that appears to conform more closely to the lognormal distribution (Figure 5-28 and Figure 5-29) than the ACI generated data (section 4.1).

The deviation in the lognormal fit in the tail region below 1.2 μm (Figure 5-28 to Figure 5-31) it most probably due the result of the aforementioned surfactant droplets. When a placebo only aerosol is fired into the APS under the same set of test conditions a small but significant number of small particles are detected and highlights why the APS technique is not favoured from a pharmaceutical perspective however the contribution of these particles to the total mass is small. The fit to the lognormal would be further enhanced if the tail of the distribution included genuine suspended drug particles only.

The fit to the lognormal distribution is improved, both visually and when assessed by the correlation coefficient, when the tube inlet design is used (Figure 5-30 and Figure 5-31) however there is an increase and a shape change to the distribution in the sub 1.5-μm range. There is also a significant shift in the total mass of particles in the <2 μm range. In the USP data for the 0.22 mm exit orifice 45% of the mass falls within this range whereas in the equivalent tube inlet data the mass is <20%. A similar difference is seen in the larger exit orifice.

It can also be seen that the proportion of small droplets, characterised by the departure from the lognormal fit at the lower end of the distribution, is higher in the USP data set than see in the tube (departure from the lognormal occurs at 10% mass in tube inlet and 20% in USP inlet) and could indicate a shift due to a loss at the upper size range or an increase in the lower distribution due to inertial impaction fragments. The GSD values for the USP throat based data are higher than the tube design and the MMAD is lower (Table 5-3).
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The influence of the exit orifice is surprising given the nature of the formulation as it would not be expected that the fundamental size of the discrete particles could be altered. The most likely explanation for the effect is the influence of the exit orifice on the fundamental atomisation process. The solution formulation based studies did show the fundamental size changes with exit orifice diameter and therefore as the fundamental drop size changes so does the ratio of suspended drug particles to the number of droplets and thereby altering the statistical probability of more than one discrete particle occupying a droplet.

Figure 5-28 Cumulative mass fraction plot of a suspension formulation tested using a 0.22mm exit orifice and the USP throat.
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Figure 5-29 Cumulative mass fraction plot of a suspension formulation tested using a 0.5mm exit orifice and the USP throat.

Figure 5-30 Cumulative mass fraction plot of a suspension formulation tested using a 0.22mm exit orifice and the tube design inlet.
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Figure 5-31 Cumulative mass fraction plot of a suspension formulation tested using a 0.5mm exit orifice and the tube design inlet.

Table 5-3 MMAD and GSD data for suspension formulation

<table>
<thead>
<tr>
<th>EXIT ORIFICE</th>
<th>INLET DESIGN</th>
<th>MMAD</th>
<th>GSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.22mm</td>
<td>USP</td>
<td>2.12</td>
<td>1.73</td>
</tr>
<tr>
<td>0.5mm</td>
<td>USP</td>
<td>2.25</td>
<td>1.87</td>
</tr>
<tr>
<td>0.22mm</td>
<td>Tube</td>
<td>2.84</td>
<td>1.60</td>
</tr>
<tr>
<td>0.5mm</td>
<td>Tube</td>
<td>3.18</td>
<td>1.63</td>
</tr>
</tbody>
</table>
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5.10 Conclusions

➢ The particle size data from the APS exhibit a better fit to the lognormal distribution than the equivalent ACI data for the same formulations and delivery system.

➢ The data obtained from PDA measurements demonstrated a good fit to the lognormal distribution and supports the data generated by the APS not only in the distribution but also the relationship between drop diameter and residual diameter.

➢ Use of the USP throat distorts the distribution data by truncating the data above 20 μm and conversely increases the fraction of data in the micron to submicron range.

➢ The USP throat places upper constraints on the GSD that can be determined from the deposition data.

➢ The USP throat inertial based deposition will truncate and limit the size range of residual particles entering the particle sizing region.

➢ The USP throat is not suitable for studying and quantifying the atomisation process however that does not imply that the USP throat does not give consistent deposition data but it can alter the interpretation of the distribution produced by the pMDI.

➢ Droplets generated by the pMDI delivery system which are greater than 25 μm in diameter will in general have insufficient time to evaporate prior to reaching the inertial deposition region of the USP throat.
Chapter 5 Measurement of particle size distributions using APS and PDA

➢ The impaction of large droplets in the USP throat could result in the generation of smaller satellite droplets from the subsequent liquid break up and thereby increase the distribution parameter.

➢ The use of a larger diameter inlet throat with similar flow length to the USP throat indicated more of a deviation from the lognormal at the higher end of the distribution range for all exit orifice diameters and an upward shift was observed in the MMAD for larger exit orifice diameters.

➢ Particle size parameters based on the more computationally defined parameters based around various types of mean particle size such as the \( D_{10} \) and \( D_{30} \) produce a more reliable assessments of the atomisation process than the median based methods like MMAD when using discrete particle sampling techniques like the APS.

➢ There appears to be a disproportionate gap in the droplet range between 50 µm and 100 µm for higher ethanol formulations and could indicate that more than one break-up mechanism applies when these larger droplets are present in the plume.

➢ The combination of upper droplet diameter range and spray velocity produced by large exit orifice diameters and high ethanol content indicate that some droplets fall within the Weber break-up scheme.

➢ The experimental results for the higher ethanol content formulations highlights the significant problems associated with the methods used to measure the very wide range of droplet sizes found in these systems and the dynamic range that the instrumentation technique must be able to measure to ensure accurate results. The loss of larger droplet data has been estimated using the loss of volumetric material detected by the APS. The lack of suitable dynamic range and or sampling errors applies to other instrumentation such as laser light.
Chapter 5 Measurement of particle size distributions using APS and PDA scattering, PDA, ACI and imaging techniques and no single instrument can be relied upon to give all the necessary data. The full analysis can only be obtained by the use of complimentary analysis techniques. The addition of suitable modelling techniques and the use of CFD further enhance the aerosol scientist’s toolbox.

➢ The work here has shown the importance of error/loss analysis in determining the true nature of the droplet range generated by a pMDI.

5.11 Summary

Computer modelling of the ACI indicated that the output from the analysis of ACI data should approach the lognormal even when the input distribution was not lognormal. Subsequent analysis of the residual particle size by the APS fitted with either the standard USP throat or the tube inlet design showed the distribution to approach the lognormal and the lognormal distribution was supported by a further instrumental technique (PDA). The data also showed clear differences in both the size and distribution with different inlets.

The design of the inlet plays a important part in the determination of the particle size but there is little published data on the performance of the USP throat and the use of a flow analysis technique like CFD may further aid the understanding.

The CFD technique may also help to explain why the impaction characteristics for the upper plates of the ACI are far from ideal by providing insight into the complex flow patterns highlighted by the deposition study for plate 0.

The analysis of the residual particle size and the theoretical extrapolation to the initial droplet size may aid the understanding as would a correlation of the ethanol formulations with an atomisation model for the pMDI.
5.12 Questions generated by the analysis of the data in chapter 5

- What are the inertial characteristics of the USP throat?
- What effect does momentum of the spray have on deposition?
- Why is APS data better represented by the lognormal?
- Why does ACI not show a lognormal response when techniques such as the APS, PDA and computational modelling do?
Chapter 6 Computational Fluid Dynamics

6. Computational Fluid Dynamics

6.1 Introduction

The importance of flow processes in the understanding and the characterisation of particles for inhalation therapy were shown in chapters 4 and 5. Many of the aspects covered by the research involve flow based problems, in one form or another, whether it is in device design, two phase flow, sampling for atomisation or the generation and interpretation of cascade impactor data.

The primary objective of this chapter is to provide a number of modelled flow solutions that are to be used to explain and support data from the preceding chapter and to evaluate many of the flow issues associated with:

- Flow in various stages of the cascade impactor (inlet and impactor plates)
- The interpretation and use of data obtained from commercial cascade impactors
- Development of the velocity profile in impactor jets
- The flow through the new design of inlet spray sampler
- Flow through commercial actuators

Computational fluid dynamics (CFD) provides a set of computational based modelling methodologies for studying fluid flow and particle trajectories which due to their complexity are not readily studied via the experimental techniques route or the outputs are very dependent on specific aspects such as particle properties as is the case with cascade impactor plate deposition studies.

6.1.1 The cascade impactor

The interpretation of cascade impactor data forms the basis for assessing the particle size and distribution of inhaled therapies (chapter 1, 3 and 4). In practice there are many impactor designs used to assess these critical performance measures, however the comparison of data from different designs can be difficult due to significant geometric variations and test flow rates. The first significant difference in impactor designs is the
inlet section, often called the throat or induction port. It is often assumed that the design of the inlet section is to mimic the human oropharyngeal region. Comparison of the many commercial designs would, however, indicate they are more concerned with the ease of manufacture and coupling the inhaler device (which produces a horizontal aerosol plume) to the impactor (which has a vertical inlet passage) by turning the inlet airflow through 90 degrees.

Based on the results generated in the ACI and APS studies and the data collated from the literature it was concluded that the design of the inlet section would have a significant influence on the particle deposition and subsequent particle size distribution that passed through the inlet section. It was also anticipated that any numerical Stokes based ECD analysis would be insufficient to understand or predicting deposition in the throat.

The primary objective is to characterise the basic flow distribution of air through both the inlet section and impactor stages when the data for drug deposition does not always fit the lognormal assumption. CFD through the computation of streamlines and particle tracking is the perfect tool to meet these objectives and to quantify the departure from the ideal; Stoke’s based solutions (section 4.2). CFD analysis will also be used to assess the design of an inlet sampler (A.VIII New inlet section design for the APS and CFD analysis) used in chapter 5 as an alternative to the USP throat.

In the work presented here a number of simple assumptions regarding the actuator and the inlet flow were made in order to simplify the problem and in some cases to limit the computational complexity.

The construction of all the 3D flow domains were based on actual dimensions measured on commercial instruments. Data for jet dimensions and plate spacing was taken from the literature\(^{188, 189}\). The measured dimensions used in the construction of the flow domains were also checked against manufacturers drawings\(^{247}\) and as such many of the critical dimensions can not be reproduced here. It can however be stated that all
measurement made were in good agreement with manufacturers drawings. Some of the fine design detail associated with radii were omitted or simplified in order to minimise meshing issues associated with such fine detail.

The work presented here is to assist the interpretation of the data obtained in chapters 4 and 5. Very little information was available regarding boundary conditions within the stages of the cascade impactor other than the overall mass flow rate. Given these limitations the study should not be regarded as a definitive study but is fit for the purpose of understanding the complex flow issue within the USP throat and ACI.

6.1.2 Methodology used for Model Construction

Once the physical dimensions and geometry simplification processes have been completed a solid model of the flow domain can be constructed. After the solid model phase has been completed the inlet and outlet boundaries can be defined.

The next stage is to define the meshing scheme to be used and the number and distribution of finite volumes needed to obtain a satisfactory flow solution. The choice of meshing scheme can influence the solution due to numerical diffusion, setup time and computational overhead(248). The numerical diffusion errors can be minimised by using hexahedral meshes aligned with the flow direction however complex geometries preclude the use of structured hexahedral meshes. The creation of structured or block-structured grids (consisting of quadrilateral or hexahedral elements) for such problems can be extremely time-consuming if not impossible. Therefore, setup time for complex geometries is the major motivation for using unstructured grids employing triangular or tetrahedral cells.

The complexity of the flow domains studied within the ACI vary significantly with the inlet section, from geometrical perspective, being relatively simple, consisting of simple tube geometry with a 90 degree bend and a few tapered sections at the inlet and outlet. The upper plates of the cascade impactor are slightly more complex due to the number of flows paths, in the lower plates the flow is further complicated by the
Chapter 6 Computational Fluid Dynamics

significant increase in the number of flow paths and the very rapid changes in both pressure and velocity. The relatively simple flow domains in the throat section lend themselves to the use of structured hexahedral meshes\(^{(191)}\) whereas the more complex re-entrant nature of the flow domain in the cascade impactor plates required the use of unstructured tetrahedral meshes.

Although only the USP throat has been considered during the research the flow through another standard pharmacopoeia inlet (TSI) has been included in A.1X Modelling airflow through commercial actuators for comparison.

6.1.3 Computational basics for the models

The following computational parameters and assumptions were used for all solutions except where indicated.

- Fluent® 6.3.26 and TGrid™ 4.0.16 (Ansys® Inc.)
- The 3D double precision, implicit, pressure based solver
- Pressure, velocity coupling using the SIMPLE algorithm
- Standard discretisation used for pressure
- First order upwind for momentum discretisation with hexahedral meshes
- Second order upwind for momentum discretisation with tetrahedral meshes
- Default under relaxation values
- Convergence tolerance 0.001
- Laminar steady state incompressible flow
- Velocity inlets normal to the boundary

6.2 Modelling flow in the basic USP inlet throat

The characteristics of the flow through the delivery system and into and through the ACI throat are critical in determining the potential nature and degree of drug deposition within the cascade impactor. The initial objectives of this study were therefore to characterise
Chapter 6 Computational Fluid Dynamics

- Inertial based impaction characteristics of the USP throat
- Directional effects induced by fundamental actuator design changes

6.2.1 Model construction of the USP throat

Modelling the flow in the ACI throat was initially complicated by the fact that two inlet section designs were identified. The throat section supplied with the APS instrument had a single taper at the inlet. A 3D model of the flow domain was constructed and meshed using Gambit® (Ansys® Inc.) and the data in Figure 6-1.

The current pharmacopoeia based design has two tapered sections at the inlet(2). Although the design change has a potential impact on pharmaceutical testing it was not considered significant given the small dimensional changes involved and for all testing in chapter 4 and 5 the double tapered inlet USP throat had been used.

The mouthpiece section from a commercial HFA (Proventil®, HFA) press and breath actuator (tubular section mouthpiece, 21 mm internal diameter) was added to the inlet section to represent a more realistic input boundary condition. The use of this commercial actuator geometry minimised other mouthpiece geometric effects because the internal diameter closely matches that of the non taper section of the standard USP throat.

The mouthpiece design of this actuator was used because it is both symmetrical and wider than most commercial designs (Figure 6-2). Nearly all commercial actuators have mouthpiece sections that are both non-symmetrical and smaller in cross sectional area, both of these factors can induce more flow variation and deposition on the inner surface of the mouthpiece due to the proximity of the surface and this would add to the complexity of the analysis.
Figure 6-1 Schematic of the USP inlet/throat section used in the ACI showing critical dimensions(2)

Figure 6-2 Photograph showing the basic direction of the inlet airflow for three commercial actuators and the variation in the angle of the mouthpiece relative to the inlet. Inserts show significant variation in the respective mouthpiece cross sectional profile a) press & breathe inhaler QVAR™, b) press and breath inhaler (3M), c) breath-actuated inhaler Autohaler™
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The basic USP throat (internal) section is shown below (Figure 6-3); note the two tapers at the inlet and one taper at the outlet.

![Figure 6-3](image)

Figure 6-3 Basic USP throat design with actuator mouthpiece showing a typical hexahedral mesh aligned with the basic flow direction.

![Figure 6-4](image)

Figure 6-4 Solid model of the ACI throat with a round actuator mouthpiece placed centrally at the inlet and a short parallel extension at the outlet.
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6.2.2 Methodology for the basic USP throat section

For flow studies in the basic USP throat a range of hexahedral meshing schemes were assessed ranging from 5k to 121k elements. Reference to the literature (191) for throat modelling data indicated that high mesh counts would not be necessary. In order to validate this assumption a grid independence study was conducted using meshes with 5k, 10k, 34k, 72k and 121k elements.

The mesh was generated with hexahedral/wedge elements applying a Cooper scheme meshed using the flow inlet, mouthpiece outlet and flow outlets as the source faces.

<table>
<thead>
<tr>
<th>Solver</th>
<th>Fluent 6</th>
<th>Inlet Boundary</th>
<th>Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>5k-121k</td>
<td>Outlet Boundary</td>
<td>Pressure</td>
</tr>
<tr>
<td>Grid</td>
<td>Hexahedral, T-Grid</td>
<td>Discretisation</td>
<td>1st Order Upwind</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>Laminar</td>
</tr>
<tr>
<td>Boundary</td>
<td>Vin = -1.37 m/s</td>
<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>

Having defined the mesh a solution for the given set of boundary conditions is computed. In this case the inlet velocity was set, based on the cross sectional area of the inlet section, to give the volumetric flow rate defined in the pharmacopoeia (ACI flow rate for pMDI testing is defined as 28.3 l min⁻¹). A uniform velocity profile normal to the inlet was defined as the inlet boundary condition (this idealisation of the inlet flow will be revisited in section 6.4 where more complex inlet distributions are considered).

6.2.3 Results and discussion for flow in the basic USP throat

The mouthpiece section is 30mm long and allows some development of a parabolic velocity profile characteristic of steady state Newtonian fluid flow.

The hexahedral mesh defined for the throat was aligned with the direction of primary fluid flow and because the problem can be considered a simple duct flow a first order upwind discretisation scheme should have been adequate (248) however during the
computational process a reversed flow in faces on the pressure outlet boundary was reported due to the formation of a recirculation zone in the outlet taper after a few iterations. Although a convergent solution to a constant mass flow rate was achieved the validity of the solution must be viewed with a degree of caution. It has previously been reported that flow in the lower section of the ACI throat is complex and is typical of the flow found in a mitre bend (191) and the results here support that conclusion.

The grid independence study (Table 6-2) indicated that a hexahedral mesh size of 72k cells or greater would provide a solution of sufficient accuracy.

Table 6-2 Grid independence study for basic ACI throat design

<table>
<thead>
<tr>
<th>Mesh elements</th>
<th>Mass Flow Rate (kg/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5k</td>
<td>5.69*10^-4</td>
</tr>
<tr>
<td>10k</td>
<td>5.12*10^-4</td>
</tr>
<tr>
<td>34k</td>
<td>5.15*10^-4</td>
</tr>
<tr>
<td>72k</td>
<td>5.09*10^-4</td>
</tr>
<tr>
<td>121k</td>
<td>5.08*10^-4</td>
</tr>
</tbody>
</table>

Based on calculated and published Reynolds number data for the flow in the throat and jet plates of the ACI a laminar flow solution was assumed. The maximum Reynolds number computed for the throat section at 28.3 l min^-1 is in the region of 2000, which is generally considered to be below the onset of turbulent flow. The onset of turbulent flow would generally be considered to occur in the region 2000-4000. The Reynolds number for all the impactor plate jets of the ACI is well below the onset of turbulent flow with all the plate jets having Reynolds numbers less than 800 (188, 189).

The contours of velocity magnitude along the central plane (z=0) were observed every few iterations during the convergence process and revealed that even at the predefined convergence criteria 1*10^-3 the velocity profile was still undergo slight changes in the bend and downstream regions and as the primary objective was to model impaction
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characteristics of the USP throat and the influence of inlet flow directional effects on impaction characteristics this was not considered adequate. In all grids the convergence to constant mass occurred at $>1 \times 10^{-5}$. Based on the objectives for this section of the work the most important, from a particle trajectory perspective, are the velocity vectors and distribution as these are used to compute the streamlines and the inertia based particle paths and particle deposition.

During the solution computation the velocity increased in the bend region and a recirculation zone developed on the anterior wall of the downstream section of the bend and the high velocity region curved around the recirculation zone and made contact with the posterior wall adjacent to the recirculation zone. When the scaled residuals reached $1 \times 10^{-3}$ the velocity profile was as shown in Figure 6-5 and from this point the velocity contours remained constant with very small changes to the contours of the velocity magnitude.

![Figure 6-5 Contours of velocity magnitude along the centre (z=0) of the ACI throat computed using a first order scheme and a 72k hexahedral mesh.](image)

Figure 6-5 Contours of velocity magnitude along the centre (z=0) of the ACI throat computed using a first order scheme and a 72k hexahedral mesh.
A second order scheme was evaluated to assess whether the first order scheme coupled with the flow aligned mesh was influencing the solution. The first and second order schemes produced somewhat different flow structures in the bend and lower section of the ACI with the first order scheme producing a flow where the maximum velocity was close to the posterior wall (opposite the inlet) and remained close to the wall down as far as the outlet taper section and beyond (Figure 6-5). From the inlet to the bend entry region the first and second order schemes produced very similar results but differed significantly in the recirculation zone in the outside corner of the bend and the inner recirculation zone just after the inner corner of the bend. Beyond the bend the second order scheme produced a flow that moved away from the rear wall towards the centre of the tapered outlet. It was noted that the residuals reached a plateau then oscillated (the continuity and y-velocity remained just above the convergence criteria whilst the x and z-velocity achieved the criteria). This was due to the unstable flow in the region downstream of the bend and specifically as a function of the size of the recirculation region at the outflow boundary. The streamline plots in Figure 6-7 and Figure 6-8.
demonstrate the similarity of the flows up to the bend but significant differences after the bend. The second order scheme producing a flow in the region between the bend and the outlet that is characterised by spiralling type and gives a strong indication of the unstable flow previously reported for this flow region (191).

Figure 6-7 Streamlines plots for the first order solution in the USP throat.

Figure 6-8 Streamlines plots for the second order solution in the USP throat.

Because the flow in the exit region of the USP throat is unstable it was assumed that short outlet section and divergent exit taper were the cause of the instability. Specific
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aspects where this flow solution would be critical in determining an accurate solution is the isokinetic sampling of the APS, where the inlet of the sampler tube is located centrally in the tapered outlet section of the USP throat and the flow in the ACI coupler and the approach to the first jet stage.

Based on velocity gradients and the complex flow patterns seen downstream of the bend of the USP throat the hexahedral meshing scheme may not be suitable given the complex re-circulation seen in the outlet region. It is also concluded that an outlet extension like those recommended for the APS and an alternate unstructured grid was required to overcome the re-circulatory problems in the tapered outlet.

6.3 Modelling flow in the USP throat when connected to the APS or ACI

6.3.1 Introduction

It has previously been determined that the flow characteristics in the USP throat would be very dependent on the outlet geometry and boundary conditions. The objective is to model the flow in the USP throat when connected to the two particle sizing instrument used in the determination of particle size distributions.

6.3.2 Model construction of the USP throat with an outlet extension

The previous work has shown the position of the APS isokinetic inlet sampler tube to be located in a position where the collection efficiency may not be ideal due to wide velocity distributions and the flow characteristics.

The USP throat was extended with a straight tube of circular cross-section with a length of a 100 mm and a diameter of 25.4 mm, that would be coupled between the USP throat outlet and the inlet to the 3306 sampler attached to the APS.

The model was constructed using Gambit® (Ansys® Inc.) solid modeller and meshed using an unstructured tetrahedral mesh of 156k elements. The mesh was generated
using TGrid™ with an interval size of 1.8. A grid independence study was not considered necessary given the smaller interval size used for the mesh generation.

Table 6-3 Variables and settings used in the CFD modelling of the USP throat with outlet extension

<table>
<thead>
<tr>
<th>Solver</th>
<th>Inlet Boundary</th>
<th>Outlet Boundary</th>
<th>Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>Fluent 6</td>
<td>Tetrahedral, T-Grid</td>
<td>Outflow</td>
</tr>
<tr>
<td>Grid</td>
<td>Inlet Boundary</td>
<td>Discretisation</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>Laminar</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>Default</td>
</tr>
<tr>
<td>Boundary</td>
<td>Vin = -1.37 m/s</td>
<td>Underrelaxation</td>
<td></td>
</tr>
</tbody>
</table>

6.3.3 Results and discussion

The addition of a 100mm extension to the outlet of the USP throat failed to impart stability to the flow after the mitre bend and the default convergence criteria were only achieved for the x and z-velocity but not continuity and y-velocity due to the instability of the flow in the outlet region (Figure 6-9). The convergence was judged by the visual stability of the streamlines (and particle inertial trajectory characteristics) through the critical inertial impaction region. During the solution computation the iteration process was periodically interrupted and streamlines and velocity contours plotted. During the initial stages of the computation the flow in the outlet taper and extension zones appeared stable but as the flow in the mitre bend approach stability the flow in the lower regions became unstable. The recirculation zone on the anterior wall of the outlet taper was still evident (which induced the reversed flow at outflow faces reported for both the first and second order hexahedral USP throat flow models).

The addition of the extension fails to produce a stable flow at the sampling entrance to the APS isokinetic sampler. The flow model indicates that the APS fitted with the 3306 impactor inlet will potentially not uniformly sample the aerosol plume with or without an extension.
6.3.4 Model flow in the USP throat when attached to the ACI coupler and first jet stage

The flow models of the USP throat with and without extension had shown the flow in the outlet region to be unsteady. In both of the previous model scenarios the output was either a pressure outlet or a simple outflow. The objective of this section is to establish the flow characteristics when the design geometry of the ACI inlet coupler and first jet stage are added to the outlet of the basic USP throat design.

6.3.5 Model construction of the USP throat with ACI coupler and first jet stage

The model was constructed using Gambit® (Ansys® Inc.) solid modeller (Figure 6-10) and meshed using an unstructured tetrahedral mesh of 218k elements. The mesh was constructed as follows: meshing the wall faces of the 96 jets, the tapered face of the coupler and the upper face of the jet stage using a scheme triangular pave scheme with an interval size of 1 and then volume meshed using an interval size of 2. A finer mesh for the coupler and jet stage was used to give an adequate number of cells in each of the
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96 jets and the inlet taper to each jet. The coupler and jet stage contain approximately 110K elements (Figure 6-11).

Table 6-4 Variables and settings used in the CFD modelling of the USP throat with ACI coupler and first jet plate

<table>
<thead>
<tr>
<th>Solver</th>
<th>Fluent 6</th>
<th>Inlet Boundary</th>
<th>Velocity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>218k</td>
<td>Outlet Boundary</td>
<td>Outflow</td>
</tr>
<tr>
<td>Grid</td>
<td>Tetrahedral, T-Grid</td>
<td>Discretisation</td>
<td>2nd Order Upwind</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
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<td>Turbulence model</td>
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</tr>
<tr>
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<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>

Figure 6-10 Solid model of USP throat ACI coupler and first jet stage
6.3.6 Results and discussion

The residuals plot showed the initial computations to be stable and a smoothly converging solution was indicated (Figure 6-12). The residuals began to plateau after about 100 iterations by which time the velocity contours for the flow in the bend were still changing but approaching a stable value and the flow through the jet stage appeared to be both stable and symmetrical (Figure 6-13b). Further iterations produced no change in the residuals but the velocity contours in the bend approached stability while the flow in the lower section between the outlet taper of the USP throat and the inlet to the jet stage became unsteady. Beyond 300 iterations no change in the velocity contours through the mitre bend were observed but the flow in the lower coupler region continued to fluctuate. The maximum velocity being maintained along the posterior wall and the recirculation region adjacent to the outlet taper of the USP throat continued to fluctuate in size and position (Figure 6-14).

The computation was repeated using very low values of under relaxation (0.15 for pressure and continuity) and the solution monitored for 2500 iterations with no change in the outcome to the final solution of cyclic flow in the bend and unstable flow between the bend and the jet stage, primarily in the region of the outlet taper. The solution did approach the desired convergence criteria after approximately 100 iterations but then began to diverge before stabilising above the convergence criteria.
During the early part of the computational solution the flow through the coupler region resembles that of an impactor jet stage (Figure 6-13b) with symmetrical re-circulatory regions. The 96 holes in the jet plate acts like a baffle and stabilises the flow by raising the pressure in the coupler. The area of the 96 jets equals the outlet area of the USP throat and the 96 discharge coefficients for the plane orifice flow increase the pressure in the coupler compared to the open ended outflow used in Figure 6-5 to Figure 6-9.
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Figure 6-13 Contours of velocity magnitude in USP throat with ACI coupler and first jet stage a) stable flow in mitre bend and unsteady flow between bend and jet stage b) flow developing in mitre bend balanced flow between bend and jet stage.

Figure 6-14 Re-circulation zones in outlet taper that induce unstable flow in the coupler region

In an attempt to solve the problem several other combinations of pressure velocity coupling and discretisation were tried including SIMPLEC and second order pressure scheme without suitable convergence being achieved.
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A k-e turbulence model was also evaluated based on the default k-e settings and the specification method being hydraulic diameter with various levels of turbulence intensity. The solution did fluctuate about the convergence criteria but the instability was still present in the lower section of the USP throat.

It could now be concluded that the flow in the outlet region of the USP throat is unsteady and an ideal stable solution not achievable. This in itself is an important conclusion and could go some towards explaining deposition in the upper plates of the ACI. As the main criteria for the work was to define the inertial impaction characteristics of the USP throat it was decided that an alternative convergence criteria was needed. The normal convergence criteria are for the entire flow domain. In the case of inertial impaction the criteria is for the velocity magnitude in the region of the bend and not the full domain. As the convergence problem was associated with the outlet region it was determined that a test of the velocity magnitude was required. Assessing the velocity contour variation in a 3D flow is complex but as the objective is the inertial impaction it was decided that an assessment of the impaction criteria would be the most suitable assessment method.

The method was relatively simple to implement. The flow domain was initialised and a data file saved to disc after every tenth iteration and all previous defaults used. The solution was computed for 400 iterations producing 40 data files.

Each data file was loaded sequentially and the deposition efficiency for 20 μm aerodynamic diameter particles released from a plane 55mm from the centre of the mitre bend. The value of 20 μm was based on previous non CFD modelling work(188). The impaction efficiency was then plotted against iterations and shown in Figure 6-15.
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Figure 6-15 Probability of deposition for 20 \( \mu m \) diameter particles in the bend of the USP throat as a function of the iteration process.

Figure 6-16 Residuals plot for USP throat, coupler and first jet stage (data files used in figure 6-15)
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A comparison of the data in Figure 6-15 compared to the iteration plot in Figure 6-16 shows that although the residuals appear to plateau after only 50 iterations the flow in the mitre bend continues to develop until approximately 150 iterations beyond which the flow velocity can be judged to cycle over a period of 60 iterations. The midpoint of the cycle gives a probability of approximately 0.5 and is close to the expected value for the ECD. Whilst this solution is not ideal it is considered adequate and fit for purpose if the frequency of the flow field variation is not required.

6.4 Temporal analysis of the flow in the USP throat

6.4.1 Introduction

The flow in the USP throat was previously shown to be unsteady but with an apparent periodic frequency component and the objective is to establish the frequency of the variation.

6.4.2 Methodology

The following parameters were used to compute the solution;

<table>
<thead>
<tr>
<th>Solver</th>
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<th>Velocity</th>
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<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>Laminar</td>
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<tr>
<td>Boundary</td>
<td>Vin = -1.37 m/s</td>
<td>Underrelaxation</td>
<td>0.9 for P and cont</td>
</tr>
</tbody>
</table>

In transient computations it is important that the characteristic time of transit of a fluid element across a control volume does not exceed the time step. An initial time step of 1.5ms was determined from the requirement to keep the dimensionless Courant number <1 based on the average cell velocity and the average cell dimension in the coupler region.
6.4.3 Results and discussion

The convergence criteria ($1 \times 10^{-4}$) was met in all time steps requiring approximately 30 iterations at the start of the solution decreasing to 8-10 iterations per time step during the cyclic flow stage. The convergence plot for the last few time steps is shown in Figure 6-17. The significant extra computational overhead required by the unsteady solution can be judged by the number of iterations required in Figure 6-17 compared to those for the equivalent steady state solution in Figure 6-16.

![Figure 6-17 convergence characteristics during the final few time steps](image)

The distribution of velocity magnitude through the bend region is complex and time dependent. A plot of the peak velocity determined for each time interval is shown in Figure 6-17 where the repeat period for the temporal variation is 105-115 ms giving a frequency of approximately 9 Hz to the flow variation. The variation in the peak velocity is not symmetrical with a sharp transition in the valley of each cycle and a plateau in the region of the peak velocity and further highlights the complex nature of the flow variation within the critical inertial impaction region.
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The cyclic inertial impaction characteristics will have significance if the spray plume delivery is of a similar duration (Figure 6-18). In most inhalation devices the duration of the spray plume is typically in the region 90-250 ms and therefore can potentially alter the impaction characteristics between successive actuations of the device. The mass flow rate out of the inhalation device is non linear and the duration of the maximum mass flow will change the impaction characteristics determined between the peak and trough of the cyclic velocity variation.

Figure 6-18 Variation in the peak velocity as a function of time during the computed solution.

6.5 The effect of input flow direction to the bend flow in the USP throat

6.5.1 Introduction

The previous flow model assumed that the input flow was normal to the inlet boundary. In all commercial actuator designs the airflow into the device is not in the same plane as the flow out of the mouthpiece. The vast majority of designs conform to the general configurations seen in Figure 6-2. In most press & breathe (P&B) type actuators the flow generally transitions through an angle somewhere between 70 and 90 degrees
relative to the vertical inlet axis. The two P&B actuators in Figure 6-2a and Figure 6-2b turn the flow 90 degrees or 75 degrees, respectively. The breath actuated device in Figure 6-2c turns the air in the opposite direction and through an angle of 105 degrees (a CFD flow analysis for models of the two P&B actuator designs can be found in A.IX Modelling airflow through commercial actuators).

The data presented in Figure 6-5 to Figure 6-9 and Figure 6-13 assumes that the inlet velocity was uniform and normal to the boundary (x-velocity constant) with no velocity component in the y or z-coordinate. As discussed above the inlet velocity at the start of the mouthpiece section will depend on the flow between the aerosol and the actuator wall and the flow conditions around the stem socket region etc. The previous analysis treated the USP throat as an ideal impactor with flow velocity normal to the inlet boundary. In real use the input flow direction will change as a function of the commercial actuator design being tested.

The objective of the analysis presented here is to model the flow under two sets of conditions that represent the typical flow direction of commercial delivery systems using assumed inlet velocity profiles.

6.5.2 Methodology

Two flow scenarios were produced by vectoring the velocity at the inlet velocity using either an equal \(-x\) and \(-y\)-component or an equal \(-x\) and \(y\)-component. The velocity components were set such that the mass flow rate was the same as that used in the previous in line inlet analysis (Figure 6-13). Using this approach yields solutions that in general terms represent the extremes of directional airflow input.

The generalised inputs are used because each actuator design presents specific flow characteristics due to factors such as can dimensions, clearance between actuator and can and the general shape and position of the stem block region where the aerosol in inserted. All other flow domain inputs are as given in the previous section.
6.5.3 Results and discussion

The flow domain mesh and convergence criteria are identical to those used in section 6.3.

Close examination of the contours (Figure 6-19) show that the flow through the mouthpiece now mirrors the general flow behaviour found in the bend of the USP throat. The flow is forced more to one side due to the momentum effects produced by the sudden change in flow direction. The highest velocity is along the lower surface of the mouthpiece region with a corresponding increase in the recirculation region between the upper mouthpiece region and the tapered inlet of the throat (low velocity region).

![Figure 6-19 Contours of velocity magnitude with an inlet flow transition in a conventional actuator design (air flow turns through 90 degrees within the actuator, with the air inlet at the top of actuator around the periphery of the can).](image)

There are a total of five re-circulation regions of flow within the USP throat section (characterised by areas of low velocity) one in the lower section outlet taper, the inner
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bend and outer bend. These change significantly with flow direction whereas the ones at the mouthpiece exit change significantly with the direction of the inlet flow (Figure 6-19 and Figure 6-20). There are two large re-circulatory regions within the coupler due to the rapid divergence at the entrance to the coupler.

![Velocity Contours](image)

Figure 6-20 Velocity contours with a simulated flow transition in a reversed flow actuator design like that found in the Autohaler™ device (inlet flow from below the actuator, opposite direction to that in figure 6.11).

When the inlet air enters through the base of the actuator and is turned through 90 degrees in the opposite direction to the standard flow as is the case found in the Autohaler™ device the contours now show the reverse effect seen in Figure 6-19. The maximum velocity through the mouthpiece is now at the top of the mouthpiece (Figure 6-20). The velocity contours predicted for the bend region are significantly distorted from those computed for the flow downward into the actuator. The flow into the coupler region is more symmetrical than predicted for the downward actuator flow.

The change in flow characteristics for both the mitre bend region and the coupler could have a significant impact on the inertial deposition determined in each region. The
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magnitude of the difference is very much due to the characteristic shape of the bend and the induced velocity and re-circulatory regions that result from the mitre bend and the approaching velocity profile. In practice this is a very sharp, knife edge bend with no radius and is far removed from the shape of the human throat.

6.6 Particle tracking in CFD

6.6.1 Introduction
The CFD software presents the capability to perform, Lagrangian particle tracking within the continuous phase. Two types of analysis are possible, coupled and uncoupled. In the analysis of flow through the USP throat section only uncoupled analysis has been used because it is assumed that the concentration of particles in the pMDI spray is low and therefore does not interact or alter the basic fluid flow.

The objective is to characterise a device independent baseline deposition pattern for the USP throat without introducing device dependant variables such as propellant system, orifice size, valve volume etc. or to add flow complexity such as specific mouthpiece geometries. The flow is assumed to be laminar as the Reynolds number is below 2000, which is the threshold for the transition from laminar to turbulent flow.

6.6.2 Methodology for particle tracking
In the particle tracking studies the particles are assumed to be spherical and selected to have unit density (1000 kg m$^{-3}$), so that the particles’ aerodynamic diameter is identical to the physical diameter. The use of unity density avoids the need to convert particle diameters between aerodynamic and physical diameters. The particles are released from points on a plane parallel to the inlet flow. The plane selected was either 65 mm in the x-coordinate (for throat deposition) or 120 mm in the y-coordinate (for first jet plate deposition).
The wall boundary was set to the ideal condition of trapping particles that impact on the wall to match the criteria recommended by the pharmacopoeia (2). Where it is stated that in cases where particle retention is poor, then surfaces should be coated to prevent particle bounce. The ideal impactor should retain all particles that contact a surface otherwise the analysis of the data becomes, as will be discussed later, very complex.

The particle tracking scheme utilised the automated tracking scheme with the trapezoidal method for the higher order scheme and implicit for the lower order scheme. The drag law selected for particle tracking was the Stokes-Cunningham drag law. The Cunningham correction values were calculated using an appropriate method for the particle diameters (248).

In the assumption used here the particle motion is dictated only by the size of the particle, particle drag, gravity, viscosity of the fluid, local fluid vectors (no local turbulence intensity as laminar assumption used) of the continuous phase and contact with the wall.

The modelled solutions were for the flow scenarios determined in the previous section for the USP throat fitted with a 100mm outlet extension (APS configuration) and USP throat fitted to the ACI coupler and the exit of the jets in the first jet stage as the outlet boundary (ACI configuration).

Particle size inputs from 8 to 30 μm were considered as suitable for the construction of an inertial based inlet efficiency curve.

A flow rate of 28.3 l min⁻¹ was used for all particle deposition studies except for one study conducted at 60 l min⁻¹ (alternate ACI flow rate used for DPI’s).
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Table 6-6 Details of the particle tracking scheme.

<table>
<thead>
<tr>
<th>Option</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drag law</td>
<td>Stokes-Cunningham</td>
</tr>
<tr>
<td>Step length factor</td>
<td>5</td>
</tr>
<tr>
<td>Maximum number of steps</td>
<td>400-1200</td>
</tr>
<tr>
<td>Maximum refinements</td>
<td>20</td>
</tr>
<tr>
<td>Higher order scheme</td>
<td>Trapezoidal</td>
</tr>
<tr>
<td>Lower order scheme</td>
<td>Implicit</td>
</tr>
<tr>
<td>Initial particle velocity (m/s)</td>
<td>0</td>
</tr>
<tr>
<td>Diameter distribution</td>
<td>Uniform</td>
</tr>
</tbody>
</table>

6.6.3 Results and discussion

The computed flow solution showed, as previously discussed, flow in the coupler whilst in the bend region the flow was significantly more stable but did fluctuate by a few percent about a mean value. The variation is not significant and the presented analysis is based on the central tendency previously observed.

![Graph](image)

Figure 6-21 Inlet efficiency of the USP fitted with 100mm extension (APS) and coupler plus first jet stage (ACI)
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The data for the different configuration is shown in Figure 6-21 for an inlet flow normal to the inlet boundary and Figure 6-22 for the flow induced by the extremes of inlet flow due to the fundamental actuator inlet airflow design.

The efficiency curves for the USP throat and the APS extended throat configurations (Figure 6-21) show very similar ECD values of 19 and 20 $\mu$m respectively. The 20 $\mu$m value agrees well with the value assumed by Vaughan (188) for numerical modelling but is slightly higher than the flow rate corrected ($60 \text{ l min}^{-1}$ to $28.3 \text{ l min}^{-1}$) value of Olson (231).

The direction of airflow flow through the actuator has a significant affect on the inertial throat deposition. Flow in through the top of the actuator lowers the deposition probability ($P=0.5$, 50% efficiency) to 16 $\mu$m whereas the flow through the base of the actuator raises the 50% efficiency to 22 $\mu$m.

![Figure 6-22 Inlet efficiency of the USP throat fitted with ACI coupler and first jet stage (ACI configuration) with two basic actuator flow inlets, inlet from the top of the actuator (Figure 6-19) and from bottom of the actuator (Figure 6-20)]
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Figure 6-23 Flow of 20 μm diameter particles into the USP throat coupled to a 100mm extension outlet (APS)

The particle tracking through the USP throat with the 100mm extension clearly shows the potential problems of obtaining a representative sample of the aerosol due to the complex flow characteristics following the flow through the USP bend. Tracking 20 μm particles (Figure 6-23) shows how the particle flow is distributed after contact with the posterior wall of the bend. Those particles not trapped by inertial impaction flow downward adjacent to the posterior wall whilst the remainder of the flow splits and flows around the wall of the down tube and merge approximately 2 diameters downstream of the bend on the anterior wall.

From the external views (Figure 6-23) the outflow appears full of particles but this is an illusion created by the flow structure. When viewed from the outlet (Figure 6-24) the particles flow as a sheath close to the wall of the down tube. In Figure 6-24 the flow of the particle core can be seen necking as it enters the bend. The particles are coloured by location with the core particles being red and yellow and the sheath particles are shades of blue and green. The core of particles are exposed at the inertial impaction site because the nearly all the particles in the upper part of the sheath either impact or re-
circulate in the upper corner of the mitre joint. The exposure of the core can be seen clearly in the three views presented in Figure 6-23.

![Figure 6-24 Flow of 20 µm diameter particles into the USP throat coupled to a 100 mm extension outlet (APS) showing particles that pass through the mitre bend are confined to the periphery of the flow](image)

The formation of the sheath in the outlet tube has significant consequences for the effective sampling of the APS instrument when fitted with the 3306 impactor unit. The aerosol sampling tube is located in the centre of the outflow and will therefore not sample larger particles that pass through the USP throat. The resultant particle size analysis will be truncated and underestimate the particle mean and distribution parameters.

The problem is not just confined to the larger particles because the 3306 APS sampler is designed to take an isokinetic sample from the base of the USP throat. The velocity contours indicate that the velocity is higher along the posterior wall and lower in central region when the isokinetic sampler of the APS is located. The location of the sampler in
the throat questions the validity of the isokinetic assumption and implies an underestimate of the large particles.

Figure 6-25 Streamlines generated from a line (x=-0.009 mm to 0.009 mm at z=0, y=-0.030) below the centre of the bend showing complex flow between the mitre bend and the jet stage and the impactor effect presented by the central region of the first jet stage.

The streamline traces in Figure 6-25 illustrate the complex flow in the down tube and the streamlines do not curve towards the first stage jets until just above the centre of the jet plate. In the Mk I ACI design the jets extended across the plate whereas in the Mk II there are no centrally located jets and the approach to the jet acts like an impactor stage. Although the shape of the coupler gives the impression of aiding the divergence of the flow the shape only serves to create additional re-circulation regions within the coupler.

Larger particles that penetrate the throat therefore have the potential to impact on the central region of the first jet stage. Even when larger particles negotiate this region they then have to turn through approximately 90 degrees to enter one of the 96 jets further increasing the risk of deposition on the jet entry or side wall as observed experimentally by Vaughan (188).

Deposition on the first jet stage increases the wall loss (188) and increases the effective ECD of the USP throat. The efficiency of the jet stage is shown in Figure 6-26 together.
with the previously determined USP throat curve and the resultant combined efficiency curve where the effective ECD drops to 16 μm.

Figure 6-26 CFD based efficiency curves for USP throat, first jet plate and combined efficiency.

The deposition predicted by the CFD particle tracking does not take account of the incidence angle. The walls of the flow domain are set to ‘trap’ any particle that makes contact. In practice particles with a decreasing angle of incident at the wall will have an increasing tendency to bounce. In computed solutions therefore the deposition will be higher than expected in the down tube of the USP throat and in the jets of the first stage. Visual analysis of the particle tracks through the jet stage indicate that a significant portion of the particles that pass through the central impaction region of the jet stage enter the jet ring region with the angle of incident to the wall sufficiently low for there to be a high probability of particle bounce occurring. It can therefore be assumed that the curves in Figure 6-26 significantly overestimate the degree of deposition. However practical use of the ACI indicates that deposition on the jet stage does occur particularly when the pre-impactor unit (commonly used for DPI devices) is not used.
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The data in Table 6-7 shows the percentage of the delivered dose that was recovered from the first jet plate during the ACI testing in section 4.1. Deposition seen in the solution formulation is higher than for the suspension formulation which given the significantly smaller particle size is at first surprising but is most likely due to the fact that all solution droplets contacting the first jet plate will leave some residue whereas the solid particles within the suspension formulation will leave all (adhesion) or nothing (bounce) following impaction.

Table 6-7 Jet plate deposition data for the formulations used in ACI studies (section 4.1)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Jet Plate deposition (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution</td>
<td>0.9</td>
</tr>
<tr>
<td>Suspension</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Figure 6-27 Fraction of particles exiting each of the four rings of impactor jets in the first jet plate.
The distribution of particles exiting the jet region of the first impactor plate would be expected to remain constant but the modelled data shows the distribution changes as a function of the particle diameter (Figure 6-27). While the performance of the inner two rings remains independent of the particle diameter the performance of the outer two rings changes significantly once the particle diameter exceeds 16 μm. Above 16 μm the number of particles exiting the outer ring drops to zero at 25 μm the third ring becomes the primary flow path with up to 70% of particles predicted at 28 μm.

The distribution of particle diameters results from the design of the coupler stage and the resultant impactor like flow toward the centre of the jet stage (Figure 6-25). The average velocity through the coupler drops from 1.4 m s⁻¹ in the lower region of the USP throat to less than 1 m s⁻¹ as the flow approaches the centre of the jet plate. As a result the gravitation component in the particle path computations becomes significant (Figure 6-28). The settling velocity is given by

\[ u = \frac{(\rho_p - \rho_f)C_d d^2 g}{18\eta} \]  \hspace{1cm} (6.1)

The settling velocity of a 20 μm diameter particle with a density of 1000 kg m⁻³ is 0.012 m s⁻¹ and is therefore significant in relation to the average flow velocity when computing the relatively long curvilinear particle paths in the coupler region.

In Figure 6-29 the inertial impaction characteristics of the USP throat are compared at flow rates of 28.3 l min⁻¹ and 60 l min⁻¹.

The deposition predicted at 60 l min⁻¹ shows a reduction in the ECD to 14 μm compared to 20 μm predicted at 28.3 l min⁻¹ and agrees well with the impactor stage ECD correction equation for flow at known reference (187).

\[ d_{50} = d_{50\text{ref}} \left[ \frac{Q_{\text{ref}}}{Q} \right]^{-0.5} \]  \hspace{1cm} (6.2)
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Figure 6-28 Influence of gravity component on the efficiency of the first jet plate

Figure 6-29 USP throat depositions at flow rates of 28.3 l min\(^{-1}\) and 60 l min\(^{-1}\)
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The computation assumes a fixed diameter for the particle however the rate at which the initial droplets are converted to the final or residual size will have a bearing on the deposition pattern in the throat and potentially on detection rates in the APS if residual droplets are still greater than 20 μm by the time they reach the back of the USP throat.

In practice the momentum of the spray may well raise the inlet velocity to beyond the threshold for transition to turbulent flow (Reynolds Number >4000) and the plume from the pMDI will also be turbulent adding to the turbulent component. Studies on deposition in the USP throat have shown deposition to be greater in the inlet section (190) than at the back of the throat as would be predicted by Stokes based, laminar approach. It should be remembered throat deposition is a function of several mechanisms in practice the throat deposition will consist of inertial, plume induced dynamics and electrostatic deposition (249-251). Electrostatic charge has been shown to peak for particles in the 1-3 μm diameter range (250).

The combination of inlet region deposition (190) and inertial deposition has significant implications for the interpretation of particle size data as without a method to separate the deposition modes into their source components it is impossible to accurately size and determine a distribution parameter for the spray. The combination of these effects increases the uncertainty when making the comparison of data generated by different impactor methods given the part that geometrical variables and flow rate will have on the deposition. The existence of two deposition modes also helps to explain an often seen phenomenon whereby the throat deposition decreases with increasing flow rate (191). If the deposition was by inertia only it would increase with flow rate. Particle bounce further complicates the issue; even coated surfaces are not guaranteed to retain all particles. It has been shown that when particle inertia increases solely from an increase in the flow rate then particle retention can decrease due to particle bounce (183).
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Based on the typical predicted droplet size range for pMDI's it can be concluded that a large portion of throat/induction port deposition will be due to mechanisms other than inertial deposition and throat/induction port deposition will include a large number of smaller particles that would not otherwise deposit in this region and this factor was considered during the design of a more suitable sampler inlet used in the pMDI droplet studies.

There are many other aspects of the spray system that need to be utilised in order to fully characterise deposition but insufficient data is currently available. In the current analysis no droplet evaporation models have been used, impact with the wall has assumed total entrapment, there are no secondary break-up models invoked and the momentum induced by the pMDI spray has not been modelled.

6.7 Computational Fluid Dynamics Modelling of the ACI

6.7.1 Introduction

Having studied the flow in the inlet section of the ACI the objective of the work presented here is to study many of the perceived design flaws(188) in the basic impactor plate design using CFD modelling. The aim is to quantify the departure from ideal impactor performance found beyond the inlet section and to examine the validity of the assumptions used in the computational ACI model, such as (i) the nature of the flow through the upper stages where holes are present in the impactor plate, (ii) the implication of jet layout in the lower plates and (iii) the development of the velocity profile within jet holes and the resulting departure from the Stokes based impactor stage performance as outlined in chapter 4.

One limitation from the modelling perspective is the large number of jets found in the impactor jet plates of the ACI, in the upper plates there are 96 jets per plate and 400 per plate in the lower plates (plate 2 downward, in the 28.3 l min⁻¹ configuration) excluding plate 7 which has 201 jets. In the upper plates the 96 jets are arranged in four concentric rings with the 24 radial rows each of four jets. The design symmetry allows the section to be divided into 24 equal segments each of 15 degrees.
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The coupler which was modelled in the previous section is located on the top of the ACI stack (Figure 6-30) and acts as the interface onto which the throat is connected.

![Diagram of ACI stack with flow paths through impactor plates](image)

Figure 6-30 Schematic showing flow paths through ACI stack. Note the additional flow paths through the impaction plates of stages 0 and 1.

6.7.2 Modelling the flow through impactor Plates 0 and 1

The distribution and velocity of air flow through the jet array of the impactor is fundamental in determining the overall impactor efficiency characteristics. The objective of this section is to evaluate the flow characteristics found in plates 0 and 1 of
the ACI and how these flow characteristics alter the shape of stage ECD from the ideal due to any non ideal flow characteristics.

The flow through the throat and coupler was shown to be unstable and an ideal convergent solution could not be determined. Based on this fact the design of each stage will be viewed in isolation to ensure that any modelling issues related to a stage are not cascaded to the next stage design therefore each stage will be treated as a stand alone design. The input boundaries will therefore be set to achieve the correct mass flow rate for the section as the objective is to understand the basic flow characteristics and any departures from the ideal. The objective being to assess the departures from uniform distribution of flows and pressures for jet holes at different radius and the exploration of possible implications of these departures.

6.7.2.1 Methodology used to model flow through Plates 0 and 1

Due to symmetrical layout of the jets in plate 0 and plate 1, 24 identical segments can be defined resulting in a plane of symmetry defined every 15 degrees. One of the resultant segment sections is shown below. In plate 0 the inlet flow is through a single boundary but the outlet flow is split between the flow passing through the centre of the first impaction plate and that which passes around the outside edge of the plate and through the inter stage flow path (Figure 6-31). In plate 1 there are two inlet flow boundaries (the two outlet flow boundaries from plate 0). A schematic for the flow is plate 1 is shown in Figure 6-32.
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Figure 6-31 Jet plate 0 and first impaction plate. Flow into plenum above jet plate assumed uniform. The two outflows are through the hole in the centre of the impaction plate and around the outer edge of impaction plate into the plenum of next stage.

Figure 6-32 Complex flow in stage 1 as the flow into plenum above jet plate is from two sources and the outflow is through two exits (one through a hole in the centre of the impaction plate and one around the outer edge of the impaction plate).
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The modelling of the flow through jet plate 1 is slightly more complex than for plate 0 as the boundary conditions now consist of two inlet flow paths and two outlet flows. There are several potential solutions to solve this boundary problem. One would be to use a velocity inlet and an outflow but this would require a waiting for the two outflows. The method adopted here was to assume a pressure inlet and pressure outlets. As no boundary conditions are known it was assumed that the outlet boundary pressures would be similar as they both exit into the large plenum above the next stage. A best guess of the pressure drop was determined from standard orifice calculations and then adding a pressure factor for the outlet flow between the jet plate and the impact plate. The computed mass flow was then compared to the expected mass flow and the pressure adjusted until the defined mass flow was obtained. The basic assumption made here is that the pressure at the outlets is equal.

Table 6-8 Variables and settings used in the CFD modelling of the ACI stage 0

<table>
<thead>
<tr>
<th>Solver</th>
<th>Fluent 6</th>
<th>Inlet Boundary</th>
<th>Pressure</th>
</tr>
</thead>
<tbody>
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<tr>
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<td>Discretisation</td>
<td>2nd Order Upwind</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>Laminar</td>
</tr>
<tr>
<td>Boundary</td>
<td>Pin=0, Pout=-4.5 Pa</td>
<td>Underrelaxation</td>
<td>Default</td>
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</tbody>
</table>

Table 6-9 Variables and settings used in the CFD modelling of the ACI stage 1

<table>
<thead>
<tr>
<th>Solver</th>
<th>Fluent 6</th>
<th>Inlet Boundary</th>
<th>Pressure (* 2 )</th>
</tr>
</thead>
<tbody>
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<td>Pressure (* 2)</td>
</tr>
<tr>
<td>Grid</td>
<td>Tetrahedral, T-Grid</td>
<td>Discretisation</td>
<td>2nd Order Upwind</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>Laminar</td>
</tr>
<tr>
<td>Boundary</td>
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<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>

6.7.2.2 Mesh Generation and Refinement

The generation of a suitable tetrahedral mesh is more complicated in plate 1 due to the number of inlet and outlet flow paths and the added complexity of the tapered inlets to
the jets. In plates 2 to 7 of the ACI the jets have sharp edged inlets rather than tapered inlets. Previous modelling work of the ACI upper plates has simplified the modelling process by omitted the tapered jet inlets (197). The discharge coefficient for a taper inlet will be higher than in the sharp edged jet.

The solid model was generated in Gambit® and the mesh generated using TGrid™. The volume was meshed using and interval spacing of 0.8 giving an initial mesh of 37k elements.

6.7.2.3 Grid Adaption

There are two critical aspects to the meshing and these are the number of elements in the main body of the flow domain and the number of elements in the jet region required to ensure a stable, grid independent solution. It is therefore necessary to adapt and refine the tetrahedral mesh in areas of high pressure or velocity change. These critical areas were determined by generating a relatively coarse tetrahedral mesh and then refining the mesh in the critical flow regions.

The CFD software provides several grid adaption methods. In the development of the grid, the iso-value technique was used. An initial convergent flow solution was computed and the case and data files saved to disc.

The grid was then adapted using the iso value method with static pressure as the adaption variable using pressure ranges determined from visual inspection of the computed contours. The method resulted in a mesh refinement primarily at the entrance to the jet regions. The saved case and data file reloaded and the process repeated with an appropriate pressure range as the adaption criteria to refine the grid region between the jet outlet region and the flow region above the impaction plate. The increased mesh density in the jet region can be compared to the basic mesh density in Figure 6-33 for plate 0 and Figure 6-34 for plate 1. The resulting meshes for plate's 0 and 1 had 60k and 66k unstructured tetrahedral elements respectively.
6.7.2.4 Stability and Convergence Study

The initial solution convergence was achieved after 61 iterations. A review of the initial data showed as expected a large variation in the velocity vectors in the x and y-planes, with the primary component being in the negative y-plane. Based on these observations
a series of solutions were generated with various values of the y-velocity patched into the flow domain prior to the commencement of the iterative process. The patching of velocity vectors improved both the stability and convergence time for a suitable solution. Initial velocity vectors were 0, -0.5, -1, -1.5, -2 and -2.5 m s\(^{-1}\) with the iteration counts 61, 48, 28, 33, 45, 52 respectively. Based on the results of the study a patched y-velocity of -1 m s\(^{-1}\) was used in the final solution for plate 0.

The process was repeated for plate 1 however in this case it was observed that during the initial phase the solution was less stable than in plate 0 and was probably due to a combination of the re-entrant nature of the flow paths (the added complexity of two inlet and two outlet flow paths) and the larger changes in both velocity and pressure in the region of the jet array. For a comparable number of elements the number of iterations was 102.

Initial y-velocity vectors of were 0, -1, -2, -3 and -4 m s\(^{-1}\) with the iteration counts 102, 69, 58, 72, and 79 respectively. Based on the results of the study a patched y-velocity of -2 m s\(^{-1}\) was used in the final solution for plate 1.

### 6.7.2.6 Results and discussion for plates 0 and 1

The modelling of the flow through the upper jet plates shows the flow is not evenly distributed across the array of jets. The inlet pressure distribution is substantially uniform, but the pressure differential at the jet exit plane is non uniform due to the cross-flow in the exit space. This generates a radial pressure gradient along the jet hole outlets towards the two flow outlets from the stage (central hole in impactor plate or around outside of the impactor plate) (Figure 6-35). The flow toward the hole in the impactor plate is through a convergent section, whilst that to the inter stage flow path is divergent. Previous modelling work\((197)\) has also highlighted this problem albeit to a lesser degree due to the acknowledged limitation of the 2D model used in that study. The 3D model allows the interaction of the separated flows as they emerging from the jets and how the flow of the inner jets splits to flow around the outer jets. The results of the modelling work highlight the benefits of using 3D modelling to solve complex flow
problems. The downside to 3D modelling is the increased mesh complexity and the increase in computer processing time required. The volumetric flow is split by the differential outlet pressures (Figure 6-35) with the major portion of the flow being around the outside of the impaction plate.

The velocity contours for jet plate 0 (Figure 6-36) show the velocity to be higher in the inner and outer jets and that the outlet flow from the inner jet is asymmetrical and directed towards the hole in the impaction plate and results in streamlines that are not directed downwards normal to the impaction surface as shown in theoretical derivations of impactor streamlines(174-176, 195) and this has serious implication for the function of this jet in the designed impaction mode and could be one factor accounting for the long tails seen in the impaction efficiency calibration curve data for the first few plates of the ACI(185, 186, 188). This problem is exacerbated in plate 0 by the fact that due to inertial effects a larger proportion of the particulate material passes through the inner two rings of the jet plate thereby putting a greater emphasis on the accurate function of the inner jet arrays(188, 220) and will be explored further in section 6.8.

The pressure and velocity contours for plate 1 are shown in Figure 6-37 and Figure 6-38 respectively and the velocity and pressure distribution is similar to that seen in plate 0 with the velocity higher through the outer two jets.
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Figure 6-35 Pressure drop in stage 0 at standard flow rate.

Figure 6-36 Velocity contours in stage 0 showing higher velocity in both the inner and outer jet. Inner jet shows non ideal flow characteristics
Figure 6-37 Pressure profile in stage 1 with uniform pressure in plenum above jets and unequal pressure drops across jets with a greater pressure drop across the inner and outer jets compared to inner pair of jets.

Figure 6-38 Velocity contours in stage 1 indicating higher velocity in both inner and outer jets. Flow at outlet of inner jet curved towards central hole in impaction plate.

The streamline traces (Figure 6-39) demonstrate how the flow splitting from the plate 0 outlets is critical in determining how the particles that penetrate through stage 0 are presented to the jet array of plate 1.
6.7.3 Impactor Plate Flow Modelling in Plates 2 to 7

As stated previously the distribution and velocity of air flow through the jet array of the impactor is fundamental in determining how the particles are presented to the following stage is critical due to the fundamental principle that errors tend to cascade down the impactor stack. Any failure of a plate to perform within its design window results in oversized material being presented to the next stage.

The objective of this section is to evaluate the non ideal flow characteristics found in plates 2 to 7 and how the actual flow characteristics alter the impactor ECDs from the ideal as predicted by the Stokes equation.

The flow problem is more complicated in lower plates by the layout of the jet array. In plates 0 and 1 the jets are arranged in symmetrical pattern whereas in the lower plates the jet array layout does not facilitate this approach, there is however one radial section where all 11 rings of jets are centrally aligned. In the upper two plates 24 identical segments could be defined each at 15 degrees. In the lower plates the segments have to
be increased to 18 degrees to ensure an integer number of jets in each segment. When this segment size is used there are 20 jets per segment but each segment is slightly different from the next because of the array layout. When defining these segments it is necessary to adjust the position of a couple of jets that were intersected by the symmetry wall either into or out of the segment but maintaining the radial position to maintain the 20 jets per segment requirement to maintain the correct total mass flow through the flow domain and it assumed that these minor positional changes do not have a significant influence on the overall mass flow balance. The solution to the jet layout problem is not ideal but as the only other option was to model the entire plate but technically was not feasible. The segment chosen for the modelling is unique because it is the only segment that can be defined having a row of holes down the centre line with one hole from each of the 11 rings of jets. It gives the most complete view of the radial variation and specifically velocity variation through the jets as a function of plate position.

The flow paths for plates 3 to 6 are identical in all respects except the dimensions of the jets. Plate 7 is unique in having only 20 jets but it has a very similar jet layout to those found in plates 2 to 6 but with the even numbered jet rings removed and the number of jets in the inner two rings reduced by 50%.

As the lower plates have very similar layouts it was concluded that only one needed modelling in detail. Based on personal experience of analysing suspension formulations plate 3 is generally the plate containing the most drug deposition and the jet layout of plate 3 has previously been studied (220).
Figure 6-40 Plate 3 flow domain showing jet layout with inlet (red) and outlet (blue)

Table 6-10 Variables and settings used in the CFD modelling of the ACI stage 3

<table>
<thead>
<tr>
<th>Solver</th>
<th>Fluent 6</th>
<th>Inlet Boundary</th>
<th>Pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cells</td>
<td>194127</td>
<td>Outlet Boundary</td>
<td>Pressure</td>
</tr>
<tr>
<td>Grid</td>
<td>Tetrahedral, T-Grid</td>
<td>Discretisation</td>
<td>2nd Order Upwind</td>
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<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>Laminar</td>
</tr>
<tr>
<td>Boundary</td>
<td>Pin=0,Pout=-28 Pa</td>
<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>

6.7.3.1 Mesh Generation and Refinement

The generation of a suitable mesh is more complicated than for plates 0 and 1 due to increased number of jets and the irregular spacing. In plate 3 the total volume of the 20 jets represents less than 0.5% of the total flow domain and it is therefore necessary to adapt or refine the tetrahedral mesh in these critical areas.

There are two important aspects to the meshing and they are the number of element in the main body of the flow domain and the number of elements in the jet region required to ensure a stable solution.
6.7.3.2 Grid Adaption

The same process as used for plate 0 and 1 was applied. In this case a basic unstructured tetrahedral model was generated utilising an interval size of 0.7 resulting in a 72k element model. An initial convergent flow solution with appropriate boundary conditions was computed using the data in Table 6-10 and the case and data files saved to disc.
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The grid was then adapted using the iso value method with static pressure and velocity adaption as described previously. The grid adaption techniques yielded grid refinement results that are difficult to evaluate. The grid check within Fluent® was implemented to check for potential problems. A detailed review of the flow within the domain was conducted and the data from each adaption process considered together with the data from the initial grid. From the visual analysis it was clear, as expected, that the flow balance through the jet array was critical in determining the resultant flow and critical pressure drop in the exit channel between the jet array and the impaction plate. Based on this data and the need to ensure the grid structure in each jet was the same, to ensure no grid dependent flow variations were induced by the grid structure, the following grid generation methodology was used.

The walls of the 20 jet were meshed separately each with 160 triangular face elements. Then the unstructured tetrahedral mesh was generated. Grid adaption based on the iso-value technique was then used to refine only the grid in the region between the jet array and the impaction plate using appropriate values for the static pressure.

The resulting mesh for plate 3 had 195k unstructured tetrahedral elements with more than 70k of these elements were within the jet array or close proximity to the entry and exit regions. Sections of the refined mesh are shown in Figure 6-41 and Figure 6-42.

6.7.3.3 Grid Independence Study

The primary parameter for determining the relative jet velocities is the pressure profile in the flow between the jet array plate and the impaction plate. The grid independence study used this parameter as the determining factor.

Four meshed models were produced, with 22k, 60k, 195k and 570k elements, with the later two having grid refinement as outlined above. Convergent solutions for each model were computed using identical boundary conditions (inlet to outlet pressure drop -28 Pa).

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The parameter chosen as the metric was the pressure drop across the impaction plate as this was determined from the fit for purpose perspective give that the flow across the impactor plate surface is the critical factor in determining the relative velocity in each jet. The metric was also chosen because published experimental data (220) was available for a subsection of the pressure drop. The radial pressure was experimentally measured as 4.2 Pa and the corresponding region in the final solution was 4.5 Pa. It should be noted that the experimental data was obtained from the viable version of the impactor and the pharmaceutical version is the non-viable configuration however the jet to plate distance should be within the manufacturer’s tolerance. The results indicated the solution was fit for purpose.

The pressure was then evaluated for each of the grids to determine at what level of mesh refinement a suitable grid independent solution was reached. The pressure drop results were 3.5, 6.2, 6.8 and 6.8 Pa respectively and it was concluded that 195k elements were sufficient to produce a grid independent solution.

Table 6-11 Grid independence study for ACI throat

<table>
<thead>
<tr>
<th>Mesh size</th>
<th>Critical Pressure drop (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>22K</td>
<td>3.5</td>
</tr>
<tr>
<td>60K</td>
<td>6.2</td>
</tr>
<tr>
<td>196K</td>
<td>6.8</td>
</tr>
<tr>
<td>570k</td>
<td>6.8</td>
</tr>
</tbody>
</table>

6.7.3.4 Stability and Convergence for plate 3

The stable solution convergence plot for plate 3 is shown for a convergence tolerance of $1 \times 10^{-3}$. The x and y-velocity residuals were the controlling factors as this is plane in which the flow transitions from the jets and exits across face of the impaction plate.
6.7.3.5 Results and discussion for Plate 3 Modelling

From plate 3 onwards the airflow between stages is via the inter stage flow path only as there are no holes in the centre of the impaction plates beyond plate 1. The airflow is turned through 180 degrees as it passes around the outer edge of the impaction plate (Figure 6-44) before entering the plenum above the next jet stage.

Figure 6-44 Streamlines and 15 um particle tracks (the streamlines are indicated by the arrowed lines) in inter stage flow section of the ACI demonstrating how the higher inertia particles migrate to the outside of the flow. The effect has most significance when considering the flow and distribution in the upper plates of the ACI.
The flow into the plenum of plate 3 is through a narrow annular slit that runs around the periphery of the plenum. Due to the depth of the plenum and the directional nature of the inlet flow the flow is directed across the plenum under the impaction plate of the stage above resulting in the flow converging towards the centre thus creating a re-circulatory flow. The re-circulatory flow interacts with the incoming flow and influences the flow direction with respect to the jet layout. The velocity variation can be clearly seen in the velocity contour plot (Figure 6-46). The pressure drop, across the top of the impaction plate where the flow exits below the jet stage, creating the velocity variation can be seen in the pressure contour plot (Figure 6-45).

Figure 6-45 Pressure contours in plate 3 note large relative pressure drop across the impaction plate surface and re-circulation zone due to direction of flow into plenum.
Figure 6-46 Velocity contours for flow in plate 3 with re-circulation zone and increase jet velocity as you move from inner most jet to outer most jet.

Particle tracks in this flow show how the particles can be separated by inertia resulting in larger particles migrating to the outside of the flow resulting in a particle size gradient within the flow as it enters the plenum of the next stage as shown schematically in Figure 6-47. The flow with the larger concentration of larger diameter particles (Figure 6-44) is directed primarily towards the outer jet rings and the air with the finer particle size material is directed primarily towards the inner jet rings (Figure 6-47). This would not be a problem if the flow velocity through each ring of jets were identical. The flow analysis clearly shows that this is not the case and the velocity of the air progressively increases with radius from inner ring to outer ring.

Figure 6-47 Re-circulation flow in plate 3 with potential particle size separation process induced by flow in inter stage connecting flow path (see Figure 6-44). Particle paths coloured by entry position through inter stage flow path.
6.8 Modelling of the flow velocity profile within the jets of plate 3 of the ACI

The impaction efficiency ECD and shape of the impaction efficiency curve of an ACI impactor stage is based on the particle impaction characteristics defined by the Stokes equation and the classical mathematical derivation of impactor efficiency assumes a single uniform input velocity(195).

The objective of the modelling presented here is to demonstrate how, due to jet design factors, a significant deviation from ideal exists in real cascade impactor designs and that these deviations have a significant influence on the instruments real performance.

The development of a parabolic velocity profile for a Newtonian fluid flowing in a channel is a well defined function of the Reynolds number and empirical equations exist that define the channel entry length necessary for fully developed laminar flow to develop(18, 183).

The empirical equation approach is rather limited because it only defines the entry length required for fully developed flow it does not predict the velocity variation at a given distance from the entry. The output from the CFD modelling will be used to demonstrate and validate the development of the non ideal velocity profiles seen in the ACI plate 0,1 and 3 (but is also applicable to in all scenarios where the jet length, diameter and Reynolds number are known) modelling work and the existing empirical equation used to validate the CFD results.

6.8.1 Methodology for model construction in jet flow analysis

The model consists of simple jet (tube) geometry with the diameter of the jets present in plate 3 of the ACI (0.711mm). The length of the tube was defined as 5 mm and was a design compromise based on the empirical entry length requirement to give sufficient length to fully characterise the development of the velocity profile in plate 3 and over the range of jet velocities found in the ACI. A structured hexahedral meshing scheme
was used with refinement in the near wall region to fully capture the rapid change in the velocity profile in the near wall region.

The grid was refined towards the wall of the jet as shown in Figure 6-48. The outlet was defined as a simple outflow. Based on the previous grid independence study for plate 3 it was concluded that as this mesh had a sufficient element density given the relatively simple flow path. The inlet was set as uniform velocity acting normal to the inlet plane. Three separate studies were conducted with Reynolds numbers of 40, 400 and 4000.

Figure 6-48 Mesh used for modelling velocity profiles. Cross section shows detail of mesh refinement close to the wall
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Table 6-12 Variables and settings used in the CFD modelling of a stage jet velocity profile

<table>
<thead>
<tr>
<th>Solver</th>
<th>Fluent 6</th>
<th>Inlet Boundary</th>
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<td>Default</td>
</tr>
</tbody>
</table>

6.8.2 Results and discussion for the flow velocity profile in impactor jets

The range of Reynolds numbers for jet flow within the ACI range from 40 to 800 and fall well within the range studied. The inlet throat Reynolds numbers range 2000 to 6000. The upper range of 4000 was defined by the transition to turbulent impactor deposition (201) where secondary deposition occurs and to demonstrate how critical the Reynolds number is in determining the ideal impactor characteristics. No turbulence model was used for the higher Reynolds number study because in stable, smooth walled, steady state flow, turbulence is not generally seen until the upper limit of the Reynolds number range for the transition from laminar to turbulent flow and the length scales of the jet are small.

The range of Reynolds numbers was chosen to cover not only the full range of values found in both the Mk I and Mk II ACI designs, where the Reynolds numbers range from 63 to 782 at 28.3 l min⁻¹, but extended up to the transition from laminar to turbulent flow which corresponds to the region where the flow velocity profile approaches the maximum with respect to the theoretical derivation of the ECD efficiency based on Stokes theory. Although the analysis here is based on the diameter of plate 3, the rapid development of velocity profiles is critical to most of the jet plates found within the ACI device, especially the upper impaction plates (plates 0 to 6).

As the velocity range covered by the CFD modelling covers two orders of magnitude the velocity data was normalised to the maximum central velocity determined at a distance of 1.5 mm from the inlet.
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The modelling of air flow for ACI plates 0, 1 and 3 indicated that the velocity was much higher down the centre of the jet than in the regions near the wall; however this work used a limited cell count due to the overall complexity of the plate models given the number of jets and flow paths modelled. The results presented here quantify the velocity profile seen in these earlier models. The models were created with additional jet length so the development of the velocity profile could be accurately modelled and compared to the widely used empirical equation (18, 183). This process also served to aid the validation of the CFD modelling work by providing comparative data.

In inviscid, plug, or “top hat” flow velocity profile is essentially uniform except where the fluid approaches the boundary wall of the jet. Inviscid flow will occur when a fluid flows from a reservoir into a pipe or tube. The viscous flow develops first at the wall where the no-slip condition requires the fluid to stick to the wall and the inviscid core will transition to viscous flow and the rate of the development will depend on several variables and is often expressed in terms of pipe length or the number of pipe diameters the flow must travel into the pipe before viscous, full parabolic profile is fully developed. The empirical equation for the entry length necessary to achieve fully developed viscous flow in a pipe or tube has be defined as

$$L = \frac{0.06 \nu \rho D^2}{\eta}$$

(6.3)

The velocity $v$ of the flow, the diameter $D$ and two fluid properties, density $\rho$ and viscosity $\eta$, define the distance $L$ to the point at which fully developed viscous flow is achieved. The empirical equation has limited use in impactor jet design because of the relatively short jet lengths and gives no measure of the change in velocity profile with distance.

A key aspect in controlling the performance of cascade impactor jet design is the air velocity profile that develops during passage through the jet. The ideal velocity profile, giving minimum variation, is where the velocity profile is uniform and can be
approximated by a single velocity value as used in the Stokes equation where the 
impaction parameter is directly proportional to the velocity. It is therefore evident that 
the more variation there is in the velocity component within the jet the more variation 
there will be in the impaction probability of the particles being carried in the fluid 
stream. A uniform fluid velocity is required to give the narrowest ECD curve for the 
impactor stage.

The Reynolds number for the fluid flow in a jet on stage 3 is 141 (188) and the predicted 
velocity profiles are shown in Figure 6-49 to Figure 6-51. A comparison of the exit 
velocity profiles in plate 3 for different Reynolds numbers is shown in Figure 6-52.

In Figure 6-49 where the Reynolds number is high (Re=4000) the effect of the length of 
the jet on the outlet flow distribution is insignificant because the velocity of the core 
remains almost constant across most of the jet width and represents a good impactor jet 
design. In contrast, Figure 6-51 shows that at low Reynolds numbers (Re=40) the 
effect of jet length on outlet flow distribution is small, but in this case at the other end 
of the scale as all jet lengths give non ideal velocity profiles as all but the very shortest 
jet lengths approach fully developed parabolic flow profiles.

The data generated for a Reynolds number of 40 shows good agreement with the 
empirical equation. The equation predicts a fully developed flow at a distance of 1.7-
mm and the data in Figure 6-51 shows that at any jet length over 1.5 mm the flow 
profile approaches parabolic. A plot of the CFD velocity data at a distance of 5 mm fits 
well ($r^2 = 0.9994$) to a parabolic curve (Figure 6-53).

The empirical equation only defines the point where fully developed flow is deemed to 
be reached and this is the main limitation with that approach. With the CFD modelling 
it is possible to study the development of the velocity profile at lengths less than those 
predicted empirically and therefore provide a better estimate of the jet velocity profile 
development.
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Figure 6-49 Velocity profiles at different distance along a jet with the diameter of ACI plate 3 showing lack of viscous flow development at a Reynolds number of 4000.

The results for the jet velocity profile suggest that the impactor ECD curves of the ACI is likely to be more distorted from the ideal than would be predicted from a simple application of the Stokes number. In application of the Stokes number (6.4) the velocity is assumed to be constant but in the case of plate 3 in the ACI the velocity profile is parabolic where the centreline velocity is twice the average velocity. Therefore the Stokes equation needs to modify to account for this variation as discussed in chapter 4.

\[ S_{ik} = \frac{\rho_{pf}d_f^2C_u u}{9\eta w_j} \]  \hspace{1cm} (6.4)

The velocity can now be defined (6.5) as a function for the velocity range, in the case of the upper plates in the ACI a parabolic function can be used.

\[ S_{ik} = \frac{\rho_{pf}d_f^2C_u f(r/d, Re, l/d)}{9\eta w_j} \]  \hspace{1cm} (6.5)
Figure 6-50 Velocity profiles at different distance along a jet with the diameter of AC1 plate 3 showing an increase in the development of viscous flow at a Reynolds number of 400.

Figure 6-51 Velocity profiles at different distance along a jet with the diameter of AC1 plate 3 showing fully development to full viscous flow at a Reynolds number of 40.
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Figure 6-52 Comparison of velocity profiles at the outlet (1.3 mm) of a jet in the ACI plate 3 for a range of Reynolds numbers showing the development from the ideal "top hat" profile to the fully developed parabolic velocity profile.

Figure 6-53 Parabolic fit (line) of the velocity data (points) at 5 mm from the inlet in a jet of diameter 0.711 mm (ACI plate 3) indicating a fully developed laminar flow for Re=40.
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6.9 Conclusions

- Flow in the outlet section of the USP throat is unsteady and in both the APS (extension tube) and ACI (coupler and first stage) configurations. The flow is induced by the tapered outlet section and re-circulation on the anterior wall. The introduction of the symmetrical 96 jet first stage fails to stabilise the flow in the outlet.

- The flow through the coupler region is unsteady and temporal CFD analysis shows a periodic nature to the instability. The frequency has a periodicity of 110 ms and the velocity variation and particle deposition is not symmetrical.

- The flow through the divergently tapered coupler does not alter the basic flow and the taper section induces no divergence in the core flow. The flow does not diverge until just above the first jet plate.

- The flow in the outlet section of the extension splits and recombines on the anterior wall and larger particles migrate to form a sheath resulting in a very low probability of these larger particles being sampled by the iso-kinetic probe used in the 3306 impactor unit of the APS.

- The directional nature of the flow through the actuator alters the fundamental flow through the inertial impaction zone of the USP throat and will therefore shift the Stokes based impaction characteristics with the ECD moving several microns up (22.5 μm) or down (16 μm) from the nominal inertial impaction value (20 μm) produced when the input is normal to the inlet.

- The central region of the first impactor stage acts like an inertial impactor and has a ECD slightly higher than the USP throat however the losses of the two combined lower the input ECD to 18 μm. A large proportion of the predicted deposition on the first jet plate occurs on the side walls of the jets and the is an
increased probability this material will bounce through to the impactor stage below due to the low angle of incidence with the jet wall.

- The design of the USP throat coupler region does not facilitate the smooth transition of the flow between the throat section and the first impactor plate. As a result the flow diverges very rapidly above the plate surface and is the turn through 90 degrees at the entry to the impactor jet array. This non ideal design is probably the reason the taper inlets were introduced in the Mk II design to overcome deposition in the jet entry region that results from the poor flow design.

- The effect of gravity contributes a significant proportion of the losses in the coupler to first impactor plate due to the impactor type flow path introduced by the redesign from Mk I to MK II versions and the change in both the flow direction and velocity.

- The distribution of material entering the four jet rings varies as a function of the particle size. The quantity of material passing through the inner two rings is effectively independent of the particle diameter whereas the outer two rings demonstrating a significant dependence of particle diameter with the outer ring dominating at lower particle diameters and the third ring at diameters over 20-\(\mu\)m with the flow of particles in the outer ring dropping to zero at diameters greater than 25 \(\mu\)m.

- The comparison of the modelled flow through the USP and TSI inlets demonstrates the significant variation in flow structure and results in very different Stokes based impaction characteristic that make comparison of the data generated by different throat designs very subjective.

- The flow through the jets of plate 0 and 1 is not balanced resulting in a higher velocity through the inner and outer rings and a lower velocity through the inner
two rings. The streamlines through the inner jet rings of plates 0 and 1 highlight a design failure as particles can miss the impaction plate and pass straight through the central hole in the impaction plate and deposit on plates lower down the stack. The fact that these particle do not deposit results in the widening of the stage efficiency further from the ideal. Should these particles be on the larger end of the size range they could well have sufficient momentum at subsequent impaction stages to bounce and result in their deposition becoming unpredictable.

- The flow downstream of the mitre bend in the USP throat is not balanced with respect to the distribution seen at the first plate and means the directional nature of the plume will induce different distributions at the first stage which will based on the above be subject to further variation due to the non uniform jet velocity seen at each jet ring.

- The velocities through the jets of plate 3 are not uniform but increase progressively from the inner to the outer jet array. The result of this design flaw is to widen the stage efficiency curve increasing the departure from the ideal impactor characteristics and increasing uncertainty in the resulting impaction data.

- The design of the flow through the inter-stage flow region coupled with the recirculatory nature of the flow in the plenum above the jet array has the potential to distribute particles non-uniformly to the jet array and widen the efficiency curve.

- The profile of the air velocity through the each of impactor stages in the ACI is not ideal because a significant flow development can take place and the flow can approach the fully developed parabolic velocity profile. The development of a velocity profile increases the velocity range within the jet and increases the
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departure from the ideal with a resultant increase in the efficiency curve and further increase the departure from the ideal inertial impactor response.

- The design of a new inlet sampler has been designed and flow modelled to overcome many of the deficiencies identified in the USP throat and should aid the understanding and interpretation of the atomisation process.

- The modelling of the airflow through two commercial actuators has demonstrated that the change of airflow direction in this design type induces a pressure differential across the emerging spray plume in the mouthpiece region (between the top and bottom) and the results in the downward deflection of the spray plume often reported in this type of design. High speed laser sheet video imaging has shown the flow in the Autohaler™ design type (reverse inlet flow direction) to be horizontal or slightly inclined in the upward direction and it is therefore proposed that the inlet flow is fundamental in determining the directional nature of the plume from the mouthpiece.

- The work conducted here does not imply that the USP throat or the ACI are not reproducible instruments but the interpretation of data generated should be studied in detail to extract as much information as possible before making judgements on particle size and distribution particularly where there is nonlinearity in the data.
Chapter 7 Actuator flow and droplet formation

7. Actuator flow and droplet formation

7.1 Introduction and objectives

It is apparent from the computational flow modelling of the USP throat, the atomisation studies with the APS and the ACI modelling that both the transient propellant pressure and nature of the flow exiting the actuator requires a fundamental development in understanding if effective predictions for atomisation and spray momentum are to be developed with suitable accuracy. The propellant pressure and the mass flow directly influence the thrust generated by the spray plume and the impact that the thrust will play in raising the momentum and turbulence in both the USP throat and other impactor inlets. The mass flow rate and the nature of fluid flow (quality, metastability, phase slip, temperature, and homogeneity) will control exit velocity and subsequent atomisation processes.

Reference to the current state of the art regarding the modelling of flow through the pMDI is far from ideal with many of the predicted outputs from the models showing significant deviation from those determined from experimental data. A fundamental requirement to understanding the flow and subsequent atomisation processes will depend on identifying and addressing the true nature of the two phase flow through the device and the resultant plume velocity.

The objectives for the work presented here are to quantify the effect of spray force on throat momentum, compute initial droplet data by extrapolating residual particle size data using assumptions for flashing and heat transfer and compute the actuator flow conditions at the start of the delivery process and compare predictions to those of the Clark atomisation model.
7.2 Expansion chamber pressure measurement

7.2.1 Introduction and objectives

The delivery pressure in the expansion chamber has been shown to be a fundamental variable in the modelling of the particle size emitted by the pMDI (4, 141).

The objective of the work presented here is to develop a suitable method and data collection methodology for the transient pressure response generated during metered operation of the pMDI.

7.2.2 Method – Pressure measurement

In order to successfully measure the pressure during the rapid delivery from metered dose inhalers it was important to have a transducer small enough to fit unobtrusively in the critical expansion chamber region of the actuator.

To achieve this objective and given the constraints of size and location, it was decided to design and manufacture a custom transducer based around the core sensor of a commercial transducer. A transducer with a suitable pressure range (piezo differential pressure, 0-200 psi, RS components) and the basic transducer geometry was modified as follows:

The threaded connection end of the transducer was machined away and the current sensing volume reduced further by the removal of material close to the sensing area of the transducer to reduce the dead volume to a minimum. A stainless steel tube (outside diameter 0.5 mm and internal diameter 0.38 mm) was cut to length (20mm) and then carefully bonded to the transducer body, close to the sensing element.

The transducer was connected to a 9-volt, dc stabilised power supply and the output from the transducer, in the mV range, was connected to a commercial computer interface board having a variable, software selectable, high gain amplifier. (See A.I Pressure transducer for details of response time and calibration).
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The signal was recorded using a custom written data acquisition software utility with the recording trigger (pressure level) being set via the custom software. The output from the acquisition software was in the form of a print file that could be imported directly into a Microsoft® Excel® spreadsheet or Mathcad® for further processing and analysis.

![Diagram of expansion chamber with pressure transducer and orifice](image)

Figure 7-1 Location of pressure transducer in relation to exit orifice

After careful consideration it was determined that the most suitable location for the transducer was in the wall of the expansion chamber directly opposite the orifice entrance (Figure 7-1). A suitable diameter hole was drilled into the actuator and the resultant hole was then reamed with a taper tool until the stainless steel tube formed an interference fit into the actuator.

### 7.2.3 Experimental method

The aerosols used were commercial placebos (QVAR™) using a 50μl Sprymiser™ metering valve. Three sets of moulded actuators were used with actuator exit orifice diameters of 0.3, 0.4 and 0.5 mm (valve orifice diameter 0.5 mm). The units were primed with 5 shots and stored valve down at ambient laboratory conditions.
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(approximately 17C) for 24 hours prior to testing. During testing the unit was fired 5 times and the resulting profiles averaged to give one pressure time profile.

7.2.4 Results and discussion for the preliminary pressure profile study

In the experimental study the pressure rise time (time taken to reach 90% of the peak value) is typically 10-20 ms and the peak pressure is reached in 20-35 ms as shown in Figure 7-2. The pressure profiles for all 3 orifice diameters show the same initial trend but then diverge due to the size of the exit orifice and the resultant mass flow of propellant out of the expansion chamber with the result that the smaller exit orifice takes longer to reach a peak value and to discharge the same volume of propellant/formulation. The result is that all three systems show different peak pressures for the same propellant system and boundary conditions with the exception of the exit orifice diameter. This is an important aspect as it demonstrates metastability due to limitations in nucleation and bubble growth rates.

Once the peak pressure is reached there is no plateau, only a steady decay of pressure. As the pressure decays in the expansion chamber the pressure signal can be seen to undulate and could indicate a region of instability within the expansion chamber region. Once the pressure has decayed by approximately 50% the pressure signal becomes stable as the pressure decays back to zero.

The rate of pressure decay being a function of system variables in this case the exit orifice diameter. Other system variables that will influence the shape and duration of the pressure profile are those that control expansion and flow such as valve orifice diameter, metering chamber volume and expansion chamber volume. The pressure of the propellant is very much a function of the environmental temperature and the storage and testing temperature can significantly alter the pressure.

The total duration of the pressure pulse is easily defined however the overall shape of the pressure pulse is irregular with half life pulse widths of 110, 160 and 290 ms.
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![Pressure profile](image)

Figure 7-2 Experimental pressure profiles for 3 exit orifice diameters

### 7.3 Spray force measurement

#### 7.3.1 Introduction and objectives
Measurement of the thrust produced by the spray provides a measure of the flow characteristics of the pMDI and allows comparison between several key actuator design parameter both from the actuator design standpoint as well as the formulation. The relative momentum of the spray is believed to be significantly greater than that of the basic airflow rate used in standard testing using cascade impactors and the objective was to assess the dynamic range for spray force and momentum for a range of exit orifice diameters and propellant temperature.

Thrust measurements presented here were conducted in unconstrained flow condition. The thrust produced by the pMDI is the product of mass flow rate \( (m^*) \) and velocity \( (u) \) and momentum can be computed by integrating the mass flow rate in 7.1 over the duration of pulse.
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\[ F_r = m' u \]  \hspace{1cm} (7.1)

7.3.2 Method – Spray force measurement

The spray force measurement rig consists of a force transducer, an impaction plate (target) an electronic interface and a PC utilising customised data logging software.

The force transducer (model 31 tension/compression load cell, RDP electronics) was connected to the electronic interface (S7DC strain gauge transducer amplifier, RDP electronics) and a stabilised voltage power supply unit. The output of the transducer amplifier was connected to a PC fitted with a 12 bit analogue to digital data acquisition card. The system was driven by a custom set of software codes. The transducer target was constructed from a 10cm diameter, 1.5 mm thick, ridged card to minimise weight (Figure 7-3). The card was bonded to a screw insert supplied with the transducer. Several types of construction for the target were evaluated with the ridged card providing the best compromise of stiffness and weight (details of calibration can be found in A.II Calibration of the force transducer and assessment of sound component on spray force measurement).

![Figure 7-3 Layout and orientation of the spray force rig](image)

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The design of the spray force rig is similar to that utilised by both Clark (141) and Gabrio (173). The force measurement rig consists of the following:

- Force transducer (250 g full scale, model 31)
- Strain gauge stabilised power supply and amplifier
- Target (10 cm diameter)
- Data logging system (Analogue to Digital interface card and PC)
- Data logging software (custom written)
- Analysis software (custom written)
- A switched electronic low pass filter (20 Hz)

7.3.3 Preliminary Results and discussion for spray force

The initial plots of spray force versus time were in good agreement to those obtained by both Clark (141) and Gabrio et al (173). The evaluation of the initial data showed there to be a high frequency component to the spray force signal (Figure 7-4).

The frequency and amplitude in the current data spray force data appeared to be higher than that previously reported data (141, 173) and it was initially assumed this high frequency signal was a function of the fluid flow and indicated the exit flow was subject to rapid variations in the propellant flow rate through the exit orifice.

The frequency of the signal in appears to be of a higher frequency than that reported by earlier studies (141, 173) where the higher frequency component appears to have more of a regular sinusoidal nature and the author has determined the frequency to be approximately 140 Hz. The variation in signal amplitude of the current data was also higher than previously reported.

During the initial setup process several false recordings were obtained because the recording system triggered before the device had been actuated. It was determined that
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the recording system was being initiated by the sound produced during the interval between arming the data acquisition system and actuating the device. It was subsequently determined that environmental background noises were sufficient to trigger the recording system highlighting the sensitivity of the thrust measurement system to the environment.

![Unfiltered and Filtered Thrust Signal](image)

Figure 7-4 Unfiltered and electronically filtered spray force measurements

7.3.4 Investigation into the high frequency component of the spray force signal

7.3.4.1 Introduction

The initial data and previously reported data have all shown a higher frequency component in the force data. The objective was therefore to identify a potential source of the higher frequency component and determine if it was part of the spray force and an indication of flow conditions and if not then it was important to define the true peak force.

Initial studies indicated that high frequency component to the spray force was too symmetrical to be part of the basic two phase flow and the higher frequency component
may emanate from the sound waves generated during the spray release because when a metered dose actuator is fired it generates a characteristic ‘hissing’ sound and the sensitivity required to detect the low force combined with the size of the transducer target may result in the transducer acting as a dual sensor.

7.3.4.2 Method

The actuator and aerosol were as used above for spray force measurement. The sound recording system was a small electret microphone and the recording system was an ADC200 digital oscilloscope (Pico Technology) connected to a PC via the standard parallel interface.

The microphone was placed directly below the expansion chamber and out of the path of the spray plume and the recording was triggered by the voltage level from the microphone and the sensitivity adjusted to start of the spray recording process.

7.3.4.3 Results and discussion

The signal form the microphone is shown in Figure 7-5. The signal is very similar in terms of duration and amplitude variation as the ‘noise’ signal in Figure 7-4 with the peak variation occurring approximately 50ms after the start of the actuation and then decaying as the force decayed. The frequency of the signal recorded by the microphone is very much higher than the signal recoded by the force transducer.

The current spray force transducer system was designed for maximum sensitivity. To achieve this aim the target was constructed from a thin but rigid card material to reduce the moving mass of the force sensing unit of the transducer and to allow for a larger target (10 cm diameter) compared to the 4.5 cm square and 5 cm round targets(141, 173) In the previously published work a metal disc was used for the sensing element of the force transducer.
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Figure 7-5 Output signal from microphone placed below the expansion chamber (out of the spray path)

It appears that the transducer sensitivity to measure the very low forces (5-150 mN) generated by the spray emitted by a pMDI is sensitive enough to act as a microphone. The transducer with large light weight target (10 cm diameter) acts as a microphone. The force trace recorded by the data acquisition system is a modulated signal of both spray force any temporal spray force variation and the sound produced by the delivery process.

The frequency and amplitude of the sound signal could provide a suitable method for investigating and characterising the atomisation process further as this additional data may provide further insight into the processes involved in the two phase flow based spray generation mechanism.

In the analysis of the force produced by HFA based sprays[173), the peak force values were used in the comparison, based on the sound amplitude component this analysis could be somewhat in error given the large component that can result from the sound part of the signal when measuring the spray force close to the spray origin (see A.II
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Calibration of the force transducer and assessment of sound component on spray force measurement).

The rapidly varying contribution can be minimised by filtering the signal (either electronically or via software) to remove the higher frequency component. In the case considered here it was decided to utilise the inbuilt filter within the transducer amplifier unit. The basic amplifier had a bandwidth of 250 Hz which is reduced to 20 Hz with the input filter switch selected. Alternatively the distance to the target can be increased, however, it maybe necessary to increase the diameter of the target due to the divergence of the spray plume to minimise momentum losses at the periphery of the spray resulting from eddy formation and roll off from the periphery of the plume.

It should be noted that even if the high frequency component were part of the flow process it is symmetrical about the main spray force signal and therefore a filtered signal would still produce a true average for the spray force provided that minimal data is lost during the filtering process.

The plots shown above in Figure 7-4 are for the unfiltered signal from the spray force transducer and a repeat test from the same test configuration with an electronic filter switched on in the amplifier control. In order to preserve the signal detail these signals are not averaged and demonstrate the slight shot to shot variation produced by the pMDI (details of the frequency response and magnitude of the sound component with distance can be found in A.II Calibration of the force transducer and assessment of sound component on spray force measurement).

The size, shape and mass of the thrust rig target together with the frequency response of the force transducer will limit the frequency range of the sound signal that can be recorded. If the sound signal were to be studied it would be necessary to record the signal at frequencies higher than used in the initial study in order to ensure the capture of the full frequency spectrum. It may also be necessary to use a high quality
microphone to reduce distortion of the current signal and to capture the higher frequency components.

7.4 Effect of distance on spray force

The objective of the initial thrust measurement experiments will focus on confirming the conservation of spray momentum by measuring the spray force at distances up to 20 cm from the exit orifice or twice the typical distance from the impaction zone of the USP throat to the mouthpiece of the device. It has previously been observed that the metered flow from a pMDI will generate an induced airflow. It is possible that variations in the flow path design will alter the thrust value recorded by flow. All measurements of flow in this study were carried out with the mouthpiece and restrictive airflow sections removed to minimise any drag forces acting on the spray plume.

7.4.1 Methodology for spray force distance

The electronically filtered spray force was measured at distances of 0, 50, 100, 150, 200 mm from the exit of the orifice. The units were primed and stored at ambient conditions for 24 hours prior to testing. One priming shot was fired to waste to ensure the valve was refilled with formulation. The unit was held at a predefined mark on the test table and aligned with the centre of the 10 cm transducer target. The data acquisition system was armed and the unit actuated. The trigger level for data recording was set for a force greater than 4 mN and once this force was achieved the recording process was activated for a set period and the data saved to disc. The process was repeated 3 times for each distance and the data for the 3 tests averaged.

The testing was conducted at 20°C using QVAR™ placebo and an actuator with a 0.34 mm diameter exit orifice.

7.4.2 Results and discussion for spray force distance

The spray force profile and duration were found to remain at a consistent level over the range of distances covered in the study and thus confirm the theory of conservation of
spray momentum (Figure 7-6). The consistency in the temporal nature of the signal confirms observation that there is little mixing in the axial direction.

Visualisation studies show that eddies at the periphery of the spray will result in some momentum loss at the longer distances and the divergence of the turbulent jet will result in the periphery of the spray missing the target at distances over 400 mm based on the measured spray half angle (7.1°) for an MDI/5). High speed video images showed the angle for the actuators used in this study to be larger than 7.1° and oriented above the horizontal plane defined by the exit orifice (see A.V High speed spray image analysis).

Clark reported a sharp drop in the peak thrust measurement, when using a range of orifice diameters, at distances greater than 100 mm. The result is surprising given the acknowledged divergence angle of the spray and the size of the target used (50 mm) but could be explained by the fact that the use of unfiltered peak force values will decrease with distance (see A.II Calibration of the force transducer and assessment of sound component on spray force measurement) if there is a sound component superimposed on the actual force signal whereas, as shown below, the underlying force signal does not decay over such distances.

One source of error at the longer distances is the alignment between the exit orifice axis and the centre of the target as a couple of degrees error at longer distances will result in some of the plume missing the edge of the force transducers target and producing a lower than expected force. Spray plume divergence angles measured for a range of exit orifice diameters showed the plume to be non-symmetrical. The angle measured close to the plume (50mm) was wider than the angle at 110mm. The plumes were either horizontal or oriented upward relative to the orifice plane. The actuator mouthpiece limited the divergence of the plume which was significantly wider when the mouthpiece was removed (the spray plume images and spray angle data can be found in A.V High speed spray image analysis).
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Figure 7-6 Spray force (electronically filtered signal) at distances of 0, 5, 10, 15 and 20cm from the exit orifice

7.5. Effect of temperature on spray force and expansion chamber pressure

7.5.1 Introduction

In order to achieve effective modelling of MDI delivery in the future the model will have to be able to account for factors other than dimensional aspects of the delivery system but will also need to factor in changes in thermodynamics properties due to changes in propellant type and or mixture and environmental aspects such as temperature variation. The fact that propellant pressure increases significantly with temperature is of significance when considering environmental factors during patient use. Temperature strongly affects the vapour pressure of the propellant in the MDI metering chamber and will therefore have a major effect on the resulting spray characteristics.

7.5.2 Method for measuring the effect of propellant temperature

The spray force and pressure measuring techniques were as previously outlined. The actuators and aerosols were as used in the initial spray force measurement study. The
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aerosol units were primed and stored valve down for 24 hours at the chosen temperature (0, 20, 35 or 50°C) prior to testing. The aerosol was removed from storage, placed into an actuator (orifice diameter 0.22, 0.34 and 0.5 mm) and the testing performed. To ensure minimal thermal changes within the metering valve the unit was immediately, following the testing for a single actuation, removed from the actuator and placed back into the appropriate storage condition and remained there for 10 minutes prior to commencement of the next actuation. The data from each actuation was saved to disc for 3 repetitions from each design point were then averaged and plotted.

7.5.3 Results and discussion for temperature and exit orifice diameter

It had been postulated that pressure along with mass fraction in the vapour phase are the controlling factors in determining the atomisation potential of the pMDI (141). The results show the peak pressure reached in the expansion chamber is as expected always lower than predicted by the prevailing propellant saturated conditions at the time of actuation and the departure from the saturated pressure becomes significantly more pronounced as the initial propellant temperature increases. Figure 7-7 shows the measured peak expansion chamber pressure to be effectively linear over the range of temperature in the study whereas the saturated vapour pressure over the same range shows more of an exponential response and indicate an increase in the degree of metastability with temperature.

The peak spray force (Figure 7-8) also demonstrates a linear response over the same temperature range. The linear regression of the spray force data shows the force will decay to zero at the propellants boiling point (-26°C) and serves to validate the assumptions made regarding the spray force method and the electronic filtering technique used during the data gathering. It provides additional evidence for the assumed accuracy of the technique. The peak pressure in the expansion chamber was shown to be a linear function of temperature but does not intercept the temperature axis at the boiling point. In Figure 7-9 the peak pressure is shown to be a function of the exit orifice diameter and temperature.
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At 0°C the difference between the saturated vapour pressure and the expansion chamber pressure is less than 10% whereas at 50°C the difference is nearly 40% and is due to the significant difference in the temperature dependent vapour generation rates which can be computed from the Jakob number (3.16) which is a subset of the bubble growth rate (96, 97) as the temperature of the propellant increases a greater volume of liquid is required to flash to fill a given void.

As the temperature of the propellant increases a significantly greater volume of liquid is required to flash to fill the void (expansion volume) in the two orifice system with the result that the bulk temperature in the void must fall producing a concomitant fall in the maximum vapour pressure attainable in the void or an increase in the degree of metastability. The peak pressure values (Figure 7-9) would tend to indicate an increase in metastability with increasing exit orifice diameter due to the increasing mass flow at the exit.
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Figure 7-8 Peak Spray force over a range of propellant temperatures

Figure 7-9 Peak expansion chamber pressure for three exit orifice diameters
Experimental results for a propellant 134a formulation with similar levels of ethanol to those used here show an initial and rapid temperature drop in the expansion chamber of 12-13°C during the start up phase of the metered delivery process (252). The influence of temperature is critical in determining the product's true performance when used under a wide range of environmental conditions and not just the standard ambient testing conditions specified in the pharmacopoeia as the spray force has been shown to correlate with throat deposition in the USP throat and a biological throat (173) up to 80 mN where the deposition peaks before decaying with further spray force.

The decrease in throat deposition above a spray force of 80 mN is probably due to secondary scatter from the surface of the USP throat. The spray force is the product of velocity and mass flow rate and under choked two phase flow condition the only way to increase the spray force is to increase the mass flow by increasing the area of the exit orifice and as shown in chapter 5 increasing the exit orifice increases the droplet size and distribution and therefore inertial deposition should continue to increase and supports the assumptions made in chapter 5.
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The increase in orifice diameter and the accompanying increase in droplet size could provide an alternative theory for the decrease in throat deposition with increasing spray force. The increase in drop size and distribution results in a decrease in smaller particles and the smaller particles are more likely to deposit by other mechanisms such as turbulence and electrostatics. The decrease in smaller droplets with increasing spray force would therefore potentially reduce deposition by mechanisms other than inertia.

Contour plots of the experimental expansion chamber pressure are shown in Figure 7-11, Figure 7-13 and Figure 7-15 as functions of the exit orifice diameter, temperature and time and show the rapid changes with valve/formulation temperature and the effect on flow rate as demonstrated by the variation in total flow time. The changes in flow time are more clearly defined in Figure 7-12, Figure 7-14 and Figure 7-16 where the effect of temperature on spray force and exit orifice diameter is the shown. The superimposed higher frequency component to spray force signal that was effectively filtered out at 20°C increases with increasing temperature indicating a more audible spray.

There is no apparent correlation between the peak pressure and the peak spray force. The peak spray force increases with increasing area of the exit orifice due to the increased mass flow rate that the increasing flow cross sectional area permits with the peak force showing an effective linear response with exit orifice diameter (Figure 7-10).

The filtering of the spray force signal allows the observation of a characteristic seen in all the spray force data presented in Figure 7-12, Figure 7-14 and Figure 7-16. In the determination of expansion pressure the rise to peak pressure is smooth and rapid. The spray force shows an initial rapid increase up to >50% of the peak value and then either plateaus or decreases by a few milliNewtons before increasing to the peak spray force. The duration of the transient change is between 5 and 30 ms. The transition is more evident with both decreasing temperature and exit orifice diameter. The transition in the
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Spray force is evidence of the transitions in the two phase flow in the two orifice system.

The time take for the spray force to reach a maximum is generally longer than the time taken to reach maximum expansion chamber pressure.

When the stem of the valve is depressed sufficiently for the side pierce hole in the stem to pass into the metering chamber, the metered fluid content, under saturated vapour conditions, is forced by the prevailing saturated vapour pressure to flow through the valve orifice and into the stem. As the pressure in the metering valve falls, cavitation occurs and the propellant vapour bubbles generated expand providing the necessary pressure to maintain the flow. By definition this flow will be two phase from the instant the vapour bubbles start to form and will be choked until the pressure in the stem and expansion chamber rises sufficiently for the pressure drop across the valve orifice to fall below the prevailing critical pressure for choked flow. The rise in pressure will be a function of the rate of flashing in the stem, the metastable state, the volume for expansion and the rate of flow of air and then vapour out of the system through the actuator exit orifice.

During the rapid expansion of the propellant system following actuation of the metering valve the air contained within the actuator and valve stem places a dynamic limitation on both the expansion volume available and the volumetric flow because the flow of air out of the system is limited by the prevailing choked flow conditions once the pressure in the expansion chamber reaches the critical pressure value. Based on the measured pressure profiles the critical pressure for choked flow is reached within a few milliseconds from the time of propellant release. Once the critical pressure is reached and the exit flow of the purged air becomes limited and the residual air volume now reduces the effective volume of the expansion system. This will result in the expansion chamber pressure rising more rapidly than predicted by a model based solely on the initial volume of the expansion volume, due to the trapped volume of air.
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Figure 7-11 Response surface model of the expansion chamber pressure contour for a 0.5 mm diameter exit orifice

Figure 7-12 Average spray force measured for a 0.5 mm diameter exit orifice
Figure 7-13 Response surface model of the expansion chamber pressure contour for a 0.34 mm diameter exit orifice

Figure 7-14 Spray force measured for a 0.34 mm diameter exit orifice
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Figure 7-15 Response surface model of the expansion chamber pressure profiles for a 0.22 mm diameter exit orifice

Figure 7-16 Spray force measured for a 0.22 mm diameter exit orifice
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Previous actuator flow models have failed to take account of two crucial aspects associated with metered flow and they are the bubble growth rates in the metering chamber of the valve which is necessary to ensure an accurate calculation of the pressure on the supply side of the valve orifice and the flashing rate in the void in the two orifice system which is required to accurately determine the pressure on the demand side of the valve orifice.

Pressure and the nature of the two phase flow (critical or sub critical) are crucial in determining the flow through a two orifice system. Previous actuator flow models have assumed homogeneous two phase flow whereas the temporal video analysis (see A.VI Temporal analysis of the spray plume) indicate a non homogenous based flow model would be required. The time intervals between changes in flow states through the valve and exit orifice are of the order of a few milliseconds and very accurate modelling predictions would be required to calculate the correct mass flow rates during such short time intervals given the complex nature of the flashing processes, two phase flows and volumes present.

If the correct pressures and material states are not accurate the ability of the model to correctly reproduce the correct conditions during this critical supply and demand phase of the metered delivery will be erroneous. The temporal force/thrust data highlight this crucial period as the spray force plateaus or drops momentarily during this crucial supply and demand phase (the plateau can only be detected in the filtered force data).

The flashing induced temperature fall within the expansion volume during the start up phase is fundamental in determining the quality of the flow during the initial flow phase. The flow model of Clark predicted a rapid temperature drop during the initial delivery phase of 30°C then a rapid rise back up to towards the bulk propellant temperature, however the supporting experimental results showed a drop of only 3-4°C followed by a short plateau; there was no increase in temperature only a steady decrease during the rest of the delivery cycle. The difference between the predicted and
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measured values is most likely due to the experimental set up and the thermocouple used.

The model of Dunbar, although assuming a high degree of flashing during the early phase of the delivery, predicted very little temperature change during this critical start up phase and did not predict large temperature changes in the expansion volume until the end of the metering process.

Changes in temperature give an additional set of data to assess the early phase changes in the expansion volume. Several thermocouples were evaluated but none gave acceptable combinations of physical robustness, relative size of the measurement volume and thermocouple head, response time and potential nucleation effects, consequently the measurement was not pursued. Previous attempts to measure expansion chamber temperature have also encountered this problem (141) where the 90% response time to a sudden temperature change was determined as 35-40 ms, which is longer than the critical transition periods at the start of the delivery process. Given the critical nature of the metastable effects this is not acceptable. Accurate temperature measurement coupled with that of pressure and force may provide further insight into why previous computational models (4, 5, 141) fail to give accurate predictions of critical characteristics of the MDI such as exit spray velocity, pressure peak and profile, dynamic temperature and the duration of the drug delivery process as well as providing information to be used in understanding the atomisation process or processes in the MDI and potential upper limits for momentum transfer effects in the USP throat.

7.6 Modelling the system atomisation process

The characteristics and complexity of atomisation processes during drug delivery from the pMDI can be judged by the number of published theories proposing different primary atomisation processes, with some favouring an aerodynamic shear process (141, 253) as the primary mechanism and others favouring the flash atomisation process (4, 5).
212, 254) as the primary mechanism. Of these there is a distinction made between flashing upstream of the orifice and flashing downstream of the orifice.

To date there are very few models available for predicting the atomisation and droplet size or residual particles size of the emitted dose delivered by the actuation of a pMDI device. Fletcher (5) produced a simple model for residual droplet size based on the orifice dimensions and a CFC based formulation. Clark (141) produced a drop size model based on the parameters of expansion chamber pressure and quality assuming an aerodynamic air blast shear type atomisation mechanism using CFC propellant systems. It has been stated that the Clark model has been shown to give agreement with an HFA (134a) formulation when the particle droplet size was measured downstream of the exit orifice by the use of the PDA technique (4, 15). However, these are isolated findings and the size and distribution of respirable particles produced by the pMDI atomisation process cannot in general be predicted with any degree of confidence.

The objective of this section is to consider the influence of formulation and orifice diameter on the particle size produced by the pMDI and to compare the measured particle sizes with predictions from Clark’s model which is based on the pressure and quality of the delivery.

7.6.1 Relationship between Residual and Initial Particle Size

Comparison of particle size distributions from identical devices and formulations, but measured by the three different techniques, ACI, APS and PDA, highlight their relative merits and enable an assessment of their respective contributions to our understanding of the actual particle size distribution generated by a pMDI aerosol. Before proceeding with this it is necessary to examine in more detail the relationship between the particle size distribution generated by the pMDI and those measured by each instrument.

Figure 7-17 considers the reduction in particle size as aerosol particles evaporate following the initial atomisation for different potential inhalation aerosols. A pure propellant droplet would produce no residual particle because all propellant would flash
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and or evaporate. In practice, a placebo aerosol would leave a residual particle of finite size due to impurities and surfactants if present (surfactant is often used to aid valve lubrication and included in placebo formulations). In a solution formulation the size of the residual particle will be determined by the initial droplet size and the concentration of the solute. In suspension formulations the residual size is independent of the drop size and is dependent only on the size of the suspended particle or particles.

Figure 7-17 Formation of the residual particle size from different starting formulations.

The particle sizing principle employed in the ACI and APS studies is that of measuring the residual particle size after evaporation of all the propellant. The PDA collects pointwise aerosol particle size data at a short distance downstream from the actuator nozzle, where substantial quantities of volatile material have not yet had the chance to evaporate. Thus, the size distribution indicated by the PDA is likely to be fairly close to the distribution of particles/droplets that is produced by the pMDI atomisation process.
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For the solution formulations used in this work, the evaporation of the remaining ethanol and sub-cooled propellant leaves a residual particle comprising of just the solute part of the formulation. Knowing the volume of the solute and the density it is possible to relate the residual particle size to the initial droplet size based on composition and geometrical considerations. The technique was used Fletcher(5) to estimate the D_{32} for the data generated by Polli where the data was calculated from the mean and distribution data and the cube root of the solute concentration. The basic drop size calculation (equation 7.2) was also used by Clark (141) to extrapolate from residual to initial droplet size data in the derivation of an atomisation model for the pMDI. Clark proposed to calculate the initial drop diameter \( d_{\text{drop}} \) from the residual particle size \( d_{\text{res}} \) when the mass fraction of drug \( mf_{\text{drug}} \), specific gravity of the drug \( SG_{\text{drug}} \) and specific gravity of the propellant \( SG_I \) are known diameter by means equation 7.2.

\[
d_{\text{drop}} = \frac{d_{\text{res}}}{\sqrt{SG_{\text{drug}}} \left( \frac{SG_{\text{drug}}}{SG_I mf_{\text{drug}}} \right)^{1/3}}
\]

Validation of the one third root law was evaluated over a range of solute levels and the details of methods and results can be found in the A.III Effect of solute concentration on residual particle size.

In the simplest formulation consisting only of propellant and dissolved drug the solution would still require an assessment of the proportion of propellant that has been converted to vapour prior to the formation of the final droplet. In many works this flashing fraction is ignored. In the formulations used here there is a second non volatile liquid, ethanol, which also has to be accounted for in the droplet extrapolation.

Equation 7.2 has been further developed here to include the addition of a second volatile component \( mf_{\text{eth}} \) and the fraction of propellant flashing \( mf_{\text{vapour}} \) prior to atomisation occurring.
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\[ d_{\text{drop}} = \frac{d_{\text{res}}}{\sqrt{SG_{\text{drug}}}} \left[ \left( SG_f (mf_f - mf_{\text{vapour}}) \right) + (SG_{\text{eth}} mf_{\text{eth}}) + (SG_{\text{drug}} mf_{\text{drug}}) \right]^{1/3} \]  

Equation 7.2 can now account for the ethanol content in the formulation and the mass fraction of propellant that has been converted to vapour prior to droplet formation. The loss of liquid component to vapour phase will consist of that lost to the bubble growth process in the metering chamber, the flashing that occurs in the stem and expansion chamber and the flashing component from the atomisation process just downstream of the exit orifice. Taking these effects into account in calculations of the initial particle size from the residual particle size requires an estimate of the quantity of propellant that has flashed prior to atomisation taking place. These processes will be driven by the instantaneous degree of superheat plus any additional heat transfer during the delivery process, which are difficult to determine a priori.

7.6.2 Clark’s atomisation model

Clark (147) proposed a model for the prediction of initial aerosol drop size as a function of the pressure and vapour quality within the expansion chamber. The model was derived from APS based data and therefore to enable particle size comparison to the model requires residual particle size data. The form of the model was as follows:

\[ D_i = \frac{C}{q^{m} \left[ \frac{P_c - P_a}{P_a} \right]^n} \]  

The value of the constant \( C = 8.02 \) is recommended for continuous atomisation and \( C = 1.82 \) for metered atomisation. The model was defined with some ambiguity by Clark because in the text the two exponents (\( m \) and \( n \)) are defined in one order whereas in the plots to determine the constant 8.02 for continuous atomisation and 1.82 for metered atomisation the value of the exponents were reversed. In the computations presented in this work this ambiguity was resolved by considering all four possible combinations of constants and exponents.
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1. \( C = 8.02 \, m = 0.46, \, n = 0.56 \) 
2. \( C = 8.02 \, m = 0.56, \, n = 0.46 \) 
3. \( C = 1.82 \, m = 0.46, \, n = 0.56 \) 
4. \( C = 1.82 \, m = 0.56, \, n = 0.46 \) 

The objective of the work presented here is to extrapolate the residual particle size data obtained from the APS to the initial droplet diameter using assumptions about the degree of flashing and the some degree of heat transfer. The experimental drop diameters will be compared to the prediction of the Clark atomisation model using experimentally determined peak expansion chamber pressure and predictions for the minimum and maximum quality of the spray.

7.6.4 Extrapolation of residual particle to droplet diameter

The APS data obtained using the tube inlet design was extrapolated using the droplet equation (7.3) with the following scenarios being implemented:

- No flashing assumption
- Adiabatic flashing assumption
- Adiabatic flashing assumption with limited heat transfer

The no flashing assumption makes possible the comparison with published data (141, 192) where no assessment of propellant losses due to flashing has been made when extrapolating from residual to original droplet size.

The adiabatic assumption is based on the enthalpy, specific heat capacity and the latent heat of vaporisation of the propellant (205) to determine the fraction of propellant flashing using previously defined methods (4) and the residual droplets are at the boiling point.
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The adiabatic flashing plus limited heat transfer assumption is based on two levels of flashing (based on the quality of the flow) and assumes that there is sufficient heat transfer from the metal valve components to compensate for the heat lost due to the flashing, beyond that determined for purely adiabatic conditions, occurring prior to the exit orifice. The mass, specific heat capacity and thermal diffusivity of the metal boundary components are sufficient to provide this level of enthalpy provided the valve is not subject to a rapid sequence of actuations. Following an actuation the thermal equilibrium will be rapidly established in the valve, internally due to the incoming refill material being at the bulk (room temperature) temperature and externally because the valve is sitting in the bulk formulation and the thickness of the metal valve components separating the metering chamber from the bulk formulation. The length of stem that extends beyond the valve will only reach equilibrium through heat conducted from the surrounding air and the tip of the stem from heat conduction from the actuator stem block in which it sits. The time interval between shots is critical as rapid firing has been shown to alter droplet diameter (244) and this is probably due to the reduction in heat transfer and further supports the third assumption.

7.6.5 Results and discussion for extrapolation to droplets

Table 7-1 Prediction of droplet diameters (μm) for various flashing scenarios using a 0.22mm diameter exit orifice

<table>
<thead>
<tr>
<th>%Ethanol</th>
<th>Residual diameter (μm)</th>
<th>No Flashing</th>
<th>Adiabatic Flashing</th>
<th>Adiabatic + q=0.02</th>
<th>Adiabatic + q=0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.86</td>
<td>8.68</td>
<td>7.79</td>
<td>7.74</td>
<td>7.56</td>
</tr>
<tr>
<td>15</td>
<td>0.87</td>
<td>8.87</td>
<td>8.07</td>
<td>8.03</td>
<td>7.87</td>
</tr>
<tr>
<td>25</td>
<td>1.06</td>
<td>11.01</td>
<td>10.19</td>
<td>10.15</td>
<td>9.99</td>
</tr>
<tr>
<td>33</td>
<td>1.32</td>
<td>13.89</td>
<td>13.01</td>
<td>12.98</td>
<td>12.81</td>
</tr>
<tr>
<td>48</td>
<td>2.16</td>
<td>23.32</td>
<td>22.28</td>
<td>22.23</td>
<td>22.04</td>
</tr>
</tbody>
</table>
Table 7-2 Prediction of droplet diameters (µm) for various flashing scenarios using a 0.5mm diameter exit orifice

<table>
<thead>
<tr>
<th>%Ethanol</th>
<th>Residual diameter (µm)</th>
<th>No Flashing</th>
<th>Adiabatic Flashing</th>
<th>Adiabatic + q=0.02</th>
<th>Adiabatic + q=0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>1.03</td>
<td>10.40</td>
<td>9.33</td>
<td>9.28</td>
<td>9.06</td>
</tr>
<tr>
<td>15</td>
<td>1.03</td>
<td>10.51</td>
<td>9.55</td>
<td>9.51</td>
<td>9.32</td>
</tr>
<tr>
<td>25</td>
<td>1.16</td>
<td>12.05</td>
<td>11.15</td>
<td>11.11</td>
<td>10.94</td>
</tr>
<tr>
<td>33</td>
<td>1.22</td>
<td>12.84</td>
<td>12.03</td>
<td>12.00</td>
<td>11.84</td>
</tr>
<tr>
<td>48</td>
<td>1.75</td>
<td>18.90</td>
<td>18.05</td>
<td>18.01</td>
<td>17.85</td>
</tr>
</tbody>
</table>

When extrapolating from residual aerodynamic particle diameters it is often the preferred route to base the extrapolation on the bulk formulation(141, 192) as this requires no assumptions of or knowledge about the atomisation, flashing or actuator flow processes. The results presented here for the no flashing assumption agree well with those published for a similar propellant system(192). The additional computations based on flashing and heat transfer show how the predicted droplet diameter will decrease with increasing degree of flashing and with increasing heat transfer during the transient metered delivery process (Table 7-1 and Table 7-2).

The adiabatic flashing assumption reduces the predicted initial drop diameter by up to 10% compared to the no flash assumption for the low ethanol level but at higher ethanol levels the difference between no flashing and adiabatic flashing becomes less significant due to the large volume of the non volatile liquid phase.

The analysis of the droplet size and distribution downstream of the exit orifice using PDA showed the median diameter to be 7 µm and the extrapolated diameter based on the APS data and the same combination of formulation and actuator predicts a diameter of 7.7 µm assuming adiabatic flashing (equation 7.3) and 8.67 µm based on the no
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flashing assumption (equation 7.2). The extrapolation based on the adiabatic flashing assumption is nearer to the experimentally determined diameter and the addition of some additional heat transfer during the delivery process would reduce the difference between the PDA and extrapolated APS. The difference could also be due to detection of larger droplets.

The problem of detecting large droplets is not limited just to the APS instrument used here. The PDA system utilises a small measuring volume and a single point in space making detection of rare events somewhat limited. Laser diffraction instruments struggle with the dynamic range and the beam steer due to dense sprays mean the low angle scatter data is confounded. Cascade impactor inlets do not facilitate a resolution of the droplet sizes deposited in the inlet section and can also result in large droplets breaking up and giving a false data interpretation further down the stack.

7.6.6 Minimum and maximum void fraction

7.6.6.1 Introduction and objective

The Clark atomisation model has input variables of expansion chamber pressure and the quality of the spray. The ratio of vapour to liquid in the expansion chamber can be expressed as either the void fraction, a critical factor in determining the velocity in homogeneous two phase flow, which is the ratio of the vapour phase volume to total volume or the quality of the spray which is the ratio of the mass of vapour to the total mass in the expansion chamber. The void fraction or quality is not easily measured and must be estimated on the basis of the assumption for the propellant flashing process between metering chamber and expansion chamber. Provided the density of the liquid and vapour phase is known then the two terms can be interchanged.

To date there are very few models available for predicting the atomisation and droplet size or residual particles size of the emitted dose delivered by the actuation of a pMDI device (see section 7.6). It has been stated that the Clark model has been shown to give
agreement with an HFA (134a) formulation when the particle droplet size was measured downstream of the exit orifice by the use of the PDA technique(4, 15).

The purpose of the study reported in this section is to investigate in detail the correlation between extrapolated droplet size data and the calculated values for defined initial expansion chamber conditions (pressure and quality) against the Clark atomisation model.

7.6.6.2 Method for determining minimum and maximum void fraction

It has been well documented that the nucleation and bubble growth necessary for the flash atomisation mechanism is a function of the degree of superheat(81, 99, 213, 255-260). The boiling point of propellant 134a is approximately -26°C and if the metering chamber is at 20°C then the difference is 46 degrees of superheat however the bubble growth process in the metering valve and the flashing that occurs between the valve orifice and the exit orifice will lower the average temperature of the propellant and hence the degree of superheat due to latent heat of vaporisation.

Under adiabatic conditions the quantity of propellant that will flash can be determined from the thermodynamic reference data(205, 206), however if heat transfer between the walls of the delivery system (valve and stem) can take place the mass fraction that can flash will increase and an adjustment to the equation for predicting initial drop size will be necessary.

Due to the critical nature of determining the void fraction and the central part the ratio of vapour to liquid plays in the determination of choked flow(80) a 25 µl metering valve was chosen, such a choice was desired to place a definable limit on the void fraction range that could practically exist based on the geometrical constraints imposed by the total volumes of the flow domain defined by the volume sum of the valve, stem and actuator sump.
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An analysis of all the model variables and assumption that can be made regarding, nucleating, flashing, metastability, two phase flow, air purging, temperature, vapour density, heat transfer etc. would be vast. It was therefore concluded that the best approach would be to consider the two most extreme scenarios as all other modelled scenarios would fall within these limits.

![Figure 7-18 Schematic of metering valve with orifice and an expansion volume with orifice.](image)

Two scenario are consider that define the extreme of flashing and these are:
1. Maximum void fraction
   The valve opens and the propellant mixture flows through the valve orifice and flashing is homogeneous, instant and adiabatic and the process continues until the expansion volume is full based on the specific volume of saturated propellant liquid and vapour and applying the measured vapour pressure (maximum metastability) assuming no material passes out of the expansion volume until the expansion volume is full.
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2. Minimum void fraction
The valve opens and the propellant mixture adiabatic flashing is suppressed until the expansion and metering valve volume is full of a homogeneous two phase mixture. The basic assumption used here is that the valve and expansion volume become one and is based on the assumption that at the start of the delivery process the pressure in the valve can not be less than in the expansion volume.

Scenario 1 can be solved numerically by incremental flow of aliquots of propellant mixture into the expansion volume and the volume and mass of vapour generated calculated as well as the volume and mass of liquid propellant and ethanol until the expansion volume is full.

Scenario 2 can be solved numerically by flashing aliquots of propellant until the expansion volume is full.

The air present at the start is assumed to be purged from the expansion volume during vapour expansion. If a proportion of air is included it will raise the void fraction but lower the critical parameter of vapour mass fraction (q). Due to the asymmetrical, tubular shape of the flow path a large portion of the air can be expected to be purged ahead of the expanding two phase homogeneous propellant flow.

A third scenario could be used to verify the absolute minimum void fraction attainable. If the liquid content of the valve at the start of delivery process, is transferred instantaneously into the metering volume, then this would define the maximum liquid fraction in the expansion volume and the minimum void fraction.

The volume of the stem and expansion chamber was 114 μl and the maximum void fraction can be determined, assuming an infinite flashing volume expansion, as
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\[
\alpha_{\text{min}} = \frac{V_T - V_f}{V_T}
\]  

(7.9)

And \( V_T \) is the total expansion volume and \( V_T - V_g \) is the total volume of liquid present.

There is however a small volume of propellant liquid flashing to vapour that needs to be accounted for as follows

\[
\alpha_{\text{min}} = \frac{V_T - V_f - V_{f \rightarrow g}}{V_T}
\]  

(7.10)

Where \( V_{f \rightarrow g} \) is the volume of liquid propellant vaporised to fill the remainder of the void.

The ethanol levels of 8 to 48% w/w propellant also place limits on the void fraction by increasing the quantity of the residual non flashing liquid phase in the expansion volume. The ethanol content also plays a critical role in determining the level of adiabatic flashing that can take place due to the specific heat capacity of ethanol being almost twice that of the propellant.
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![Flow chart for the steps in computing the maximum void fraction in the expansion volume](image)

**7.6.6.3 Results and discussion**

The minimum void fraction was computed by assuming a minimum flashing rate where the volumes of the valve and delivery system are coupled. The 25 µl valve in this study coupled to the actuator design gives a minimum void fraction of 0.834 but the quality depends on the ethanol content of the formulation.

The quality is classically defined as the mass fraction in the vapour phase. Here the same approach is used and the non volatile ethanol content (within the pressures and time frames considered for flashing) only forms part of the liquid phase volume.
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Table 7-3 The minimum void fraction and quality in chosen actuator system fitted with 25 μl metering valve

<table>
<thead>
<tr>
<th>% Ethanol</th>
<th>Void Fraction</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.83</td>
<td>0.11</td>
</tr>
<tr>
<td>15</td>
<td>0.83</td>
<td>0.11</td>
</tr>
<tr>
<td>25</td>
<td>0.83</td>
<td>0.12</td>
</tr>
<tr>
<td>33</td>
<td>0.83</td>
<td>0.12</td>
</tr>
<tr>
<td>48</td>
<td>0.83</td>
<td>0.13</td>
</tr>
</tbody>
</table>

Table 7-4 maximum void fraction and quality in chosen actuator system assuming adiabatic instantaneous flashing with 25 μl valve

<table>
<thead>
<tr>
<th>% Ethanol</th>
<th>Void Fraction</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>0.94</td>
<td>0.38</td>
</tr>
<tr>
<td>15</td>
<td>0.92</td>
<td>0.33</td>
</tr>
<tr>
<td>25</td>
<td>0.89</td>
<td>0.26</td>
</tr>
<tr>
<td>33</td>
<td>0.86</td>
<td>0.21</td>
</tr>
<tr>
<td>48</td>
<td>0.79</td>
<td>0.15</td>
</tr>
</tbody>
</table>

7.6.7 Correlation with the Clark atomisation model

The predicted droplet data was compared to the atomisation model of Clark (141) and the modelling and experimental data of Dunbar (4).

The quality values are taken from Table 7-3 and Table 7-4 for predicted minimum and maximum qualities respectively. The peak expansion pressure values are taken from experimental values determined in section 7.5 for combinations of actuator and formulation. The predicted droplet diameters were computed using equation 7.5-7.8 and tabulated (Table 7-5 and Table 7-6).
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Table 7-5 Predicted droplet diameter (µm) for the minimum computed quality for a 0.22 mm exit orifice using the experimental peak pressure for computation

<table>
<thead>
<tr>
<th>QUALITY</th>
<th>0.11</th>
<th>0.11</th>
<th>0.12</th>
<th>0.13</th>
<th>0.13</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pe (max)</td>
<td>4.4</td>
<td>4.25</td>
<td>4.1</td>
<td>3.9</td>
<td>3.48</td>
</tr>
<tr>
<td>Equation 7.5</td>
<td>11.16</td>
<td>11.44</td>
<td>11.29</td>
<td>11.29</td>
<td>12.33</td>
</tr>
<tr>
<td>Equation 7.6</td>
<td>15.72</td>
<td>16.05</td>
<td>15.62</td>
<td>15.41</td>
<td>16.55</td>
</tr>
<tr>
<td>Equation 7.7</td>
<td>2.53</td>
<td>2.59</td>
<td>2.56</td>
<td>2.56</td>
<td>2.80</td>
</tr>
<tr>
<td>Equation 7.8</td>
<td>3.57</td>
<td>3.55</td>
<td>3.55</td>
<td>3.50</td>
<td>3.76</td>
</tr>
</tbody>
</table>

Table 7-6 Predicted droplet diameter (µm) for the maximum computed quality for a 0.22 mm exit orifice using the experimental peak pressure for computation

<table>
<thead>
<tr>
<th>QUALITY</th>
<th>0.38</th>
<th>0.33</th>
<th>0.26</th>
<th>0.21</th>
<th>0.15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pe (max)</td>
<td>4.4</td>
<td>4.25</td>
<td>4.1</td>
<td>3.9</td>
<td>3.48</td>
</tr>
<tr>
<td>Equation 7.5</td>
<td>6.31</td>
<td>6.9</td>
<td>7.91</td>
<td>9.06</td>
<td>11.54</td>
</tr>
<tr>
<td>Equation 7.6</td>
<td>7.85</td>
<td>8.68</td>
<td>10.13</td>
<td>11.78</td>
<td>15.28</td>
</tr>
<tr>
<td>Equation 7.7</td>
<td>1.43</td>
<td>1.56</td>
<td>1.79</td>
<td>2.06</td>
<td>2.62</td>
</tr>
<tr>
<td>Equation 7.8</td>
<td>1.78</td>
<td>1.97</td>
<td>2.3</td>
<td>2.67</td>
<td>3.47</td>
</tr>
</tbody>
</table>

Figure 7-20 Predicted drop size with the assumptions of no flashing, adiabatic flashing and adiabatic flashing with heat transfer
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Figure 7-21 Comparison of experimental based droplet prediction and those predicted by equations 7.5 and 7.6 assuming maximum flashing (high quality flow)

Figure 7-22 Comparison of experimental droplet predictions over the limits of flashing in the actuator and valve system used and the predictions using forms of the Clark equation
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7.6.8 Discussion of droplet extrapolation and correlation to the Clark model

In previous work on modelling of the pMDI system the initial droplet size has been estimated from the base formulation. In the work presented here an attempt has been made to compare the effects of the flash atomisation process together with an estimate of the droplet size post adiabatic flashing whilst also accounting for potential heat transfer effects that can occur during the passage of the formulation from the valve to the exit orifice. The assumption is that due to the degree of superheat present the flashing process will be very rapid and complete only a few diameters downstream of the exit orifice and has been confirmed experimentally (213).

The valves used in this study are of an all metal construction type and the mass of stainless steel present is more than an order of magnitude greater than the mass of formulation and therefore has the potential to provide additional heat to the flashing flow process as demonstrated by the rapid drop in the stem and valve temperature after only a single actuation of the valve.

As expected the greater the degree of flashing the smaller is the predicted initial droplet diameter although the change is less significant beyond the limit of the adiabatic flashing because the diameter is based on volumetric loss of propellant during the flashing process and a significant level of heat transfer is required to have a significant effect on the flashing potential of the rapidly cooled liquid propellant remaining after adiabatic flashing has ceased.

The heat transfer effect is limited to the effect on droplet diameter extrapolations only and not to any effect that the increasing heat transfer would have on the flashing potential of the formulation downstream of the orifice and the potential decrease in particle size that additional superheat would provide. It can therefore be concluded the effect of the different flashing/heat transfer assumptions on droplet diameter is fairly small beyond that defined by the adiabatic limit.
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The predicted droplet diameters for the 0.22mm diameter exit orifice with higher ethanol levels are lower than expected and are probably due to the errors in the sampling efficiency of the APS with respect to very large droplets, the inlet sampling efficiency limits of the APS and gravitational deposition of droplets >40 μm.

High speed digital imaging using a pulsed laser diffuse back illumination imaging technique showed the droplets produced by the high ethanol level have a range of diameter much wider than seen with the low ethanol content (section 5.7).

The predicted minimum and maximum void fractions (quality) show a range of 0.83 (q=0.11) to 0.94 (q=0.38) for low ethanol contents and 0.83 (q=0.13) to 0.79 (q=0.15) for the highest ethanol content. The minimum values of quality are much higher than those quoted by Clark but it should be noted that the valve volume used here was 25μl but the stem and actuator volumes were similar. The small valve volume imposes greater limitations on the quantity of liquid that can be present in the expansion volume during the start up phase of the metered delivery.

The lower levels of void fraction predicted here is less than could exist in real systems because the low value can only be created by suppressing the flashing process beyond the practical limit, below that of any metastability effect, giving the highest possible liquid content in the expansion chamber. In contrast the higher quality is achieved by having the flashing process proceed at the theoretical maximum rate. The higher quality flow values are much higher than those predicted by Clark for metered dose delivery where the upper limit was approximately 0.06 using a 50 μl valve and 0.08 using a 100 μl valve with pure 134a propellant. The vast majority of the Clark data was obtained with quality values less than 0.05.

The predictions using the metered form of the Clark equation (constant=1.82) are far too low ranging as they do between 1.5 and 3.5 μm, however the slope of 1.82 for metered atomisation model does not pass through zero but has an intercept on the drop diameter axis at approximately 13 μm (determined by the author). The form of the
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equation however dictates that it should approach the constant C (equation 7.4) for q=1 and infinite pressure.

It can be conclude that the metered version of the Clark model is incorrect as demonstrated by the shape of Clark’s correlation plot. It can also be concluded that the error is in the determination of the quality component of the metered atomisation as the pressure in the expansion chamber was measured and highlights the problem associated with expansion chamber conditions. The error in quality is most likely due to either an inclusion of excess air in the expansion chamber calculation due to the significant density difference between the propellant vapour and air or assumptions regarding the metastable state.

Practical application of either metered version of the Clark equation (7.7 and 7.8 variants) must be questioned on the basis that application of the equations yields values well below those determined here from either the APS and PDA or literature data for similar combinations of exit orifice and formulation to those used here (192).

The extrapolated drop size diameter predicted here of 7.7 µm and based on APS measurements for the 8% ethanol in 134a propellant tested with an 0.5 mm exit orifice agrees well with the PDA measured droplet diameter of 6.98 µm (section 5.5).

Functionally the Clark model is weighted heavily on the difficult to determine quality term whereas the pressure range is only limited by the propellant system used and the temperature. The design of the formulation and valve size used in this work limits the pressure range by the judicious use of ethanol as the co-solvent as demonstrated by the data in Figure 7-22 where the use of minimum theoretical quality values shows no response in predicted droplet size with increasing ethanol.

The Clark continuous atomisation model does have a similar response to that predicted by experimental drop size data when the determined values for void fraction/quality are high as shown by data in Figure 7-22. Clark’s APS data should overestimate the mean due to the acknowledged problem regarding the detection of residual diameters below
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1 µm in the older APS model used. The difference could however be explained by the sampling technique employed. Although Clark used a large vessel for capturing the spray it may not have achieved a uniform sample without consideration of factors such as gravitational settling of the large particles/droplets and over sampling the smaller ones.

The fit to the experimental data can be improved significantly by setting the exponents \( n \) and \( m \) to 1 and setting the constant \( C \) to 10.

\[
D_i = \frac{C}{q \left[ \frac{P_t - P_a}{P_a} \right]} \tag{7.11}
\]

Based on the experimental data, the modification over predicts the droplet diameter, however, we know from the high speed video that there are large droplets not captured in the APS analysis.

The Clark atomisation model was based on a theory of aerodynamic shear and ligament break up and not flash atomisation although the flashing potential of the mixture of propellant used in the study would also have given a good correlation. The Clark model does not give an adequate response unless the degree of flashing is close to the limits imposed by the system (scenario 1). It could therefore be argued that the maximum flashing does not actually need to take place in the expansion chamber and that the full flashing takes place downstream of the exit orifice until the adiabatic flashing limit is reached. In order to support the flash atomisation theory the adiabatic droplet size predictions were plotted against the mass fraction of the propellant that could flash adiabatically and shown in Figure 7-23.

The correlation was for an of 0.22 mm diameter exit orifice data set and the correlation was based on equation 7.12

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\[ D_i = a + \frac{b}{m_{\text{flash}}^2} \]  

(7.12)

Where \( a = 0.104 \) (asymptote for infinite flashing) and \( b = 5.75 \) (rate constant for 134a)

The aerodynamic shear approach requires knowledge of the quality of the spray whereas the mass fraction flashing only requires a simple thermodynamic calculation to estimate the potential droplet size.

Figure 7-23 Correlation between the extrapolated droplet diameter and the mass of propellant that can flash adiabatically for each of the formulations.

In the flash atomisation process the contribution the exit orifice diameter plays in the atomisation process is probably limited to how it influences the simultaneous processes of heat transfer, enthalpy dissipation, vapour distribution and mass transfer, rather than any specific geometrical effect and could potentially be used to adjust the flashing mass fraction calculation used in equation 7.12
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7.7 Momentum transfer in the ACI

7.7.1 Introduction

It is well documented that the peak velocity of the spray emitted by a pMDI has been determined as being between 40 and 110 m s\(^{-1}\) and these velocities are significantly higher than the air inlet velocity used in cascade impactor testing. The momentum added by the spray plume is believed to be significant and the objective is to assess the effect on the flow at the inlet to the first impactor jet plate (Plate 0).

The measurement of the thrust from a pMDI has been reported previously\((141, 173)\) and the thrust produced is a product of the mass flow rate \(m^{*}_{\text{spray}}\) and the velocity \(u_{\text{spray}}\)

\[
F_{\text{spray}} = m^{*}_{\text{spray}} \times u_{\text{spray}} \quad (7.13)
\]

The force of the air flowing through the impactor is given by

\[
F_{\text{air}} = m^{*}_{\text{air}} \times u_{\text{air}} \quad (7.14)
\]

The spray reaching the first impactor plate (P0) should have decayed to the design velocity assuming all spray momentum has been dissipated in the USP throat and the dissipation factor \((\Phi)\) defined as

\[
\Phi = \frac{u_{\text{air}}}{u_{\text{spray, P0}}} \quad (7.15)
\]

If the dissipation factor is less than 1 then the velocity at first impactor stage will be greater than the designated design value by \(1-\Phi\)
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\[ F_{\text{spray, } p_0} = (m_{\text{spray}} \cdot u_{\text{air}}) \cdot (1 - \Phi) \]  

(7.16)

And the total force at the first impactor stage will be

\[ F_{\text{spray, } 0} = |(m_{\text{spray}} \cdot u_{\text{air}})| \cdot (1 - \Phi) + (m_{\text{air}} \cdot u_{\text{air}}) \]  

(7.17)

The measured spray force at the first impactor stage can be determined experimentally and numerically integrated over the delivery time (t) of the spray.

\[ F_{\text{spray, at } p_0} = \sum_{t=0}^{t=d} m_{\text{spray}} \cdot u \, dt \]  

(7.18)

And dividing by the integral of 7.17 minus the force of the airflow, assuming \( \Phi = 1 \), will give the average velocity increase.

7.7.2 Experimental

The force transducer system (7.3.2) was positioned directly below and central to the outlet face of the USP inlet/throat at a distance defined by the position of the first impactor jet plate(247).

An aluminium aerosol can containing a 134a/ethanol placebo mixture and fitted with a 50 \( \mu \)l metering valve (QVARTM) was used throughout. Identical actuator designs with exit orifice diameters of 0.34 and 0.5 mm were used in the testing.

Inlet airflow to the USP inlet/throat of 28.3 l min\(^{-1}\) was used throughout testing and the actuator coupled to the inlet section by a custom moulded adaptor.
Once the airflow was turned on and set to the correct flow the force reading was checked and then the recording system was reset to zero before the aerosol was placed into custom moulded adaptor and actuated.

7.7.3 Results

The force-time signal for the two orifice diameters are shown below. Due to the low level of the force signal generated the gain of the acquisition system needed to be set to the maximum amplification available. The high gain increased the settling time of the input amplifier and therefore the number of data points was limited by the short duration of the flow. The data presented below is from three consecutive actuations of the aerosol.

![Graph](image)

Figure 7-24 Force at plate 0 developed from a 0.34 mm diameter exit orifice in the ACI at a flow rate of 28.3 l min⁻¹

There is consistency between the replicates from each run with respect to duration and there appears to be a consistency in the time varying component of the thrust signal (Figure 7-24 and Figure 7-25) but as stated above the data acquisition rate was limited by the signal amplification required.
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The spray force signal goes to zero between 10 and 30 ms and corresponds with the flow transition plateau seen in the basic spray force test when the spray force was filtered. When the device is activated the air in the throat is compressed by the force of the emerging spray and the drop at the first impactor plate could be due to the transient flow effect. A transient effect has been detected in the measurements taken by a PDA system in a similar time frame(236).

The computations are tabulated below (Table 7-7) and show the relative magnitude of the flows and the effective average velocity increase.

![Graph showing force vs time](image)

Figure 7-25 Force at plate 0 developed from a 0.5 mm diameter exit orifice in the ACI at a flow rate of 28.3 l min⁻¹
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Table 7-7 Calculations for exit orifice diameter of 0.34 mm and 0.5 mm

<table>
<thead>
<tr>
<th>Exit orifice diameter (mm)</th>
<th>0.34</th>
<th>0.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>(I) Integral for airflow (x10^3)</td>
<td>0.203</td>
<td>0.129</td>
</tr>
<tr>
<td>(II) Integral for spray (x10^3)</td>
<td>0.098</td>
<td>0.098</td>
</tr>
<tr>
<td>(III) Integral at Plate 0 (x10^5)</td>
<td>0.476</td>
<td>0.471</td>
</tr>
<tr>
<td>Ratio (III)/(I+II)</td>
<td>1.58</td>
<td>2.07</td>
</tr>
<tr>
<td>Effective increase in velocity</td>
<td>58%</td>
<td>107%</td>
</tr>
</tbody>
</table>

7.7.4 Discussion

The results show how the velocity at the first stage of the impactor can be greatly increased and the increase is a function of the exit orifice diameter used in the actuator (Table 7-7). The increase in velocity will significantly change the ECD of the first stage which at the standard flow rate has a ECD of 9 μm however this will decrease to 7.1-μm for the 0.34 mm diameter exit orifice and 6.3 μm for a 0.5 mm exit orifice given the average velocity increase predicted (Table 7-7).

The additional momentum will further complicate the flow in ACI coupler region and the increased effect this focused flow has on the path of least resistance, the inner ring of jets. The overloading of the inner ring was evident in Figure 4-13 where the deposition at the inner ring is out of proportion to that predicted by a simple flow analysis and the CFD analysis showed why the performance of plate 0 can be distorted by the non ideal impaction fluid flow through jets close to the central hole in the impactor plate.

The increased inertia for large particles approaching the flow divergence region just above plate 0 jet rings will further increase the wall losses to the top surface of the plate 0 jet ring first shown by Vaughan and emphasize the need to assay the jet plate 0 for deposition (wall loss).
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There is a secondary problem associated with an increased velocity of particles as although the reduction in ECD should increase deposition on the stage the shift in the deposition efficiency tends only to increase the deposition of particles at the smaller end of the deposition probability curve. Those at the top end of the efficiency curve are now statistically more likely to bounce\(^{183, 196}\) and thereby further distort the analysis.

Whilst the increased momentum at plate 0 demonstrates that not all the spray momentum is dissipated in the throat section a large portion of the momentum is dissipated and much of the momentum will cause increased deposition in the throat due to the effective ECD of the throat being reduced below the ideal, steady state, laminar inlet flow value of 17-20 μm (28.3 l min\(^{-1}\)) determined in chapter 6.

The impactor data for solution and suspension inhalation products (section 4.1) showed a significant departure from the lognormal in terms of either the correlation to a probability lognormal plot or significant deviation to the expected MMAD or GSD. The earlier computer modelling confirmed that even where the input aerosol was not lognormal the impactor based data analysis would tend to approach the lognormal.

The increased momentum biased deposition on upper plates, can distort the material distribution as well as contribute to the less well understood problem of bounce which is a potential problem that occurs with increasing velocity.

The effectiveness of plate coatings, as discussed in the literature review, can be difficult to assess due to factors that are complex to define and include the nature of the particle with respect to density, hardness, adhesive properties of the surface, adhesive properties of the coating, compliance, angle of contact, coefficient of restitution, particle shape, particle agglomeration and drug loading to name a few.

The drug loading is an important aspect because even where the surface coating is good at reducing bounce the surface will soon become coated in a thin layer of impacted
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particles and once this has taken place other factors such as re-entrainment can become the dominant factor in the deposition dynamics.

The avoidance of bounce is a critical issue as bounce results in particles depositing on plates further down the impaction stack producing false size data with an underestimate of aerosol mean particle size and a distortion of distribution parameters such as the GSD.

It has been well documented that particle bounce can increase with increasing particle velocity and therefore any factors that increase velocity will induce potentially mutually exclusive effects.

It has long been established that the calibration of cascade impactors is key to their successful use and one of the primary aspects is the control of the volumetric air flow through the impactor. The volumetric flow directly controls the velocity of air through the impactor jets and is a key parameter in the determination of the Stokes Number which in turn determines the performance of the impaction system.

Factors that change the volumetric flow rate such as calibration of the volumetric flow meters and dimensional integrity of the jets can be controlled through calibration procedures. There are other factors that have not received much attention from users of cascade impactors with metered dose inhalers over the years and one of these is the potential influence that the momentum of the spray could have on the air velocity.

Experimental data indicate that the peak momentum of the spray, over a range of exit orifice diameters and propellant temperatures, is up to two orders of magnitude greater than that of the test air flow (section 7.5).

At the instant the actuator begins to deliver the spray the velocity in the first stage will rise rapidly due to the incompressibility of the air column, however due to the finite time required for the first particles to traverse the length of the throat the initial particles
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will not arrive at the first stage at this time and the sizing and delivery process will be phase separated.

Under non dynamic test conditions it takes the inlet air approximately 150 ms to travel between the actuator mouthpiece and the inlet to the first stage (assuming a distance of 250 mm and an inlet flow rate of 28.3 l min\(^{-1}\)). This time will shorten as the momentum transfer increases.

The out of phase relationship between the induced flow rate increase and the particles could result in a non linear relationship due to the phase lag resulting from the distance the particles have to travel and give rise to the distorted sizing of the distribution seen in section 4.1.

The Stokes Number maybe affected by the viscosity change resulting from the addition of propellant vapour to the air flow as the propellant contribution is significant and increases with increasing valve volume and exit orifice diameter.

7.8 Conclusions

➢ The rapid pressure rise seen at the start of the metered delivery will rapidly exceed the critical pressure ratio as the air/vapour present in the expansion volume are rapidly compressed and reduce the theoretical expansion volume available for flashing and the flow of the vapour out of the metering volume will be choked earlier than otherwise predicted.

➢ The time taken for the expansion pressure to reach a maximum (rise time to 90% maximum) is typically less than 20 ms. The rapid rise coupled with a small exit orifice where the peak expansion pressure approaches the saturated vapour pressure would indicate that the metastability effects may not be significant when adiabatic flashing is the main flashing process.
The spray force data shows the momentum of the spray to be at least an order of magnitude greater than that of the air used in standard ACI testing of the pMDI and could potentially have significant implications in the interpretation of ACI based particle size analysis due to momentum transfer increasing the velocity at the first impactor stage.

The spray force method provides an alternative to actuator flow modelling for determining the effects of system variables (exit orifice diameter, propellant pressure, temperature etc.) on the spray delivery process without the need for complex modelling.

The variation seen in the spray force signal appears symmetrical about the mean whereas the variation in the laser light plane illumination method is non-symmetrical with irregular high and low frequency components.

Due to the high sensitivity needed and the proximity of the transducer to measure the low spray force the sound of the spray emanating from the delivery process is modulated with the spray force signal making the true spray force measurement difficult to assess.

Suitable electronic filtering of the spray force signal permits the underlying force signal to be seen in greater detail and reveals for the first time potential evidence for the early choked two phase flow.

Spray force measurements recorded at distances up to 200 mm confirm the conservation of momentum and also indicate a lack of temporal mixing. The spray force duration and profile remained constant over longer distances than previously reported and most likely result from the improved transducer design and the removal of the modulated sound signal.
Use of the Clark atomisation model did not result in a good correlation to the experimental atomisation data generated in these studies however a slight modification to the value of the constant and exponents did produce an improved fit.

The range of experimental droplet diameters measured in these studies falls well outside those measured by Clark in his derivation of the model and the accuracy of the predictions should be judged accordingly. The particle size data measured here will be lower than measured by Clark due to improvements in detector design of the APS instrument used in these studies.

The Clark model does not work for metered atomisation because in practice it can only predict droplet diameters greater than 13 μm which, based on the work generated here, is too high for 134a based formulations. The most likely source of the lack of accuracy of the Clark model is the incorrect computation of the quality term for the metered atomisation process because the pressure values were determined experimentally and highlights the significant challenges if accurate flow models with the correct determination of terms for variables such as quality are to be forthcoming.

The use of the adiabatic flashing assumption and heat transfer in the extrapolation of residual particle size to the initial drop size reduces the predicted droplet size and gives good agreement with experimental data measured using the PDA technique.

For the first time a method has been proposed and experimentally proven to demonstrate that momentum transferred from the spray is sufficient to increase the inertial deposition in the throat and at the entrance to plate 0.

The momentum transferred from the spray to the airflow will raise the ECD for stage 0 and potentially distort the distribution of material in the ACI.
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- The momentum transfer is unique to the pMDI as the momentum in the testing of DPI’s is provided only by the test airflow, unless the DPI is gas or propulsion assisted.
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8. Discussion and Conclusions

8.1 Discussion

One of the biggest challenges facing the developer of inhalation therapy is the correct determination of particle size and specifically the respirable fraction of mass that theoretically penetrates into the critical areas of the lung. The critical size determined to meet this criteria is that less than 5 μm although recently it has been proposed that <3 μm is a more critical size for defining inhalation performance (261). The pharmacopoeia (EP and USP) states “Starting at the final collection site (filter or MOC), derive a table of cumulative mass versus ECD diameter of the respective. Calculate by interpolation the mass of the active substance less than 5 μm. This is the Fine Particle Dose (FPD)”. There are however no instructions as to how this interpolation should be conducted and it is common practice for those using cascade impactors to quote the mass less than 4.7-μm because this is a defined ECD diameter of a specific plate of the ACI and therefore all plates below this can be grouped to define the respirable mass.

The use of 4.7 μm plate based grouping is ambiguous because the computational modelling shows the deposition range to exceed those ideal ECDs defined in the pharmacopoeia and varies as a function of the input distribution.

The pharmacopoeia then goes on to say “If necessary, and where appropriate (e.g., where there is a log-normal distribution), plot the cumulative fraction of active substance versus ECD diameter on log probability paper, and use this plot to determine values for the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) as appropriate. Appropriate computational methods may also be used”. The use of the term appropriate would imply that a lognormal distribution is not expected and probably reflects the general nature of data submitted for regulatory approval or published in scientific journals.

The computational based modelling of the ACI deposition profile confirmed that the determination should approach that of a lognormal distribution even when the input
Chapter 8 Discussion and Conclusions

distribution was not lognormal. It was also shown that multimodal input distributions (bi and tri-modal) could also result in a lognormal conclusion being determined from the determination. In addition it was shown that input distributions that were not lognormal, being either of a constant mass or constant number for each diameter and coupled with the assumption of ideal impactor efficiency also resulted in outputs that approach the lognormal. The fit of data to the lognormal assumption indicated a better fit to the lognormal than seen in many of the published data sets for pharmaceutical based determinations from the pMDI’s.

The stage calibrations used in the computational model were based on oil droplet calibration studies which could be expected to give deposition characteristics that approach the ideal response for inertial impaction properties. As the nature of the impaction particle changes with respect to factors such as surface properties, rigidity etc. the dispersion of particles increases with a corresponding decrease in accuracy of the deposition. In general terms these processes will decrease the MMAD and increase the GSD.

Based on the above observations the aerodynamic diameter from a range of formulations and exit orifice diameter were measured using the APS to verify the shape of the distribution produced by the systems. The APS data showed the distributions to approach the lognormal. The testing of a suspension formulation using the APS also showed the distribution to approach the lognormal.

There are as discussed advantages and disadvantages with all the particle sizing methods available for the analysis of inhalation distributions and to obtain a second opinion the droplets of the solution formulation were analysed downstream of the exit orifice using a Phase Doppler Anemometer (PDA). The data from the PDA analysis also showed a lognormal distribution. The data measured by the PDA is a volume based diameter not aerodynamic diameter but in a solution formulation the droplet distribution will be the same as the distribution of the residual diameters because the volume scaling factor is a constant, the one third root law for the solute. Therefore two
methods indicated lognormal distributions whilst cascade impactor showed a deviation from the lognormal.

The predictive modelling of the deposition within the ACI, based on numerical models for the true stage performance, showed the true size of the drug deposition on the upper plates fell well below the diameter designated for those stages as defined by both the pharmacopoeia and the instrument manufacturer. Based on those results the validity of using plate deposition data where the deposited mass is small must be called in to question when calculating MMAD and GSD data as the data on these plates skew the analysis (172, 228) and result in an increase in the GSD.

The results from the computation modelling of the ACI indicated that the ACI would underestimate the MMAD and overestimate the GSD when challenged with a known lognormal distribution. When the ACI data was corrected by the nonlinear method proposed by Thiel the MMAD was shifted further from the true value and the GSD was under corrected for low GSD’s and overcorrected for higher GSD’s.

The computational modelling of Mono-modal distributions showed the ACI would overestimate the GSD of the input distribution and the modelling showed the deposition on the upper stages to be a function of the input distribution and probably results from a combination of poor impactor stage design and overlapping stage performance. The actual MMAD predicted for a stage was appreciably different and lower than the diameter the data would be correlated against in the conventional lognormal probability plot.

The distribution of particle size was higher for the ACI than the APS (or PDA when corrected for evaporation). The APS data could be expected to be lower based on the loss of data less than 0.5 μm (due to lower detection limit). The use of multiple instrumental techniques to measure particle size and distribution demonstrated the importance of not relying on one instrumental technique to make critical assumptions regarding key descriptive parameters. The use of more than one particle size parameter
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also demonstrated how trends could be more clearly defined as the MMAD showed little response to increasing ethanol content in the formulation whereas the $D_{10}$ and $D_{30}$ parameters which are based on the numerical computation of a mean and are particularly important when computing data from sampling instruments like the APS where a few large particles can significantly alter a parameter like the MMAD.

The solution and suspension formulations used in these studies are based on the first commercial formulations to use HFA propellants and the cascade impactor data determined are generally better fits to the lognormal than those generally reported in the literature for inhalation products.

The validity of the cumulative lognormal technique was assessed with distributions that were either of constant number or constant mass function for all diameters covered by the dynamic range of the ACI. The lognormal plot showed that these distributions produced fits on a cumulative lognormal probability plot better than those determined for a significant number of published inhalation products and therefore poses the question at what level of correlation coefficient should be deemed appropriate for a lognormal plot before the data value determined for MMAD and GSD are inappropriate. Based on the model predictions generated for these non lognormal distributions and coupled with the fact that most distributions even those that are multimodal should approximate to the lognormal, the acceptable correlation coefficient should therefore be greater than 0.95 to be considered lognormal.

The influence of the USP throat was evaluated for a range of formulation and exit orifice diameters and it was observed that the data obtained from the APS showed no significant change in either the mean or distribution as a function of formulation or orifice diameter. The same combination of formulation and exit orifice were then evaluated using a custom designed throat inlet where it was shown the mean and distribution increased with increasing ethanol content and exit orifice diameter thus demonstrating the limitations of the USP throat in determining the true distribution characteristics.
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Due to inertial deposition in USP throat the size of data reaching the cascade impactor plates is restricted and this limits the dynamic range of the ACI. Therefore lognormal distributions with tails longer than the ECD of the USP throat will have their distribution truncated. The computation model showed that even a truncated lognormal distribution will appear lognormal in the ACI and the MMAD and GSD for the truncated distribution will be incorrect with the MMAD being reduced and the GSD increased. Any combination of MMAD and GSD that predicts the distribution extends beyond 20 μm should be viewed with a degree of scepticism and a contour plot was developed to indicate combinations of MMAD and GSD as a function of throat ECD that would produce particle distribution data that should be considered unreliable.

The computer modelling also showed the possibility of interpreting lognormal data as a bi-modal distribution and is due to the functional response of the upper stages and the overlapping of the stage efficiency curves.

Analysis of the APS data when fitted with a USP throat showed there to be no particles greater than 3 μm using low ethanol formulations, increasing to 4 μm with the highest ethanol content and given the deposition pattern in the equivalent ACI data was surprising as drug was detected on all upper plates of the ACI and the first impactor jet plate. It can therefore be concluded that the deposition seen on the upper plates of the ACI is not a true reflection of the input particle size distribution and occurs due to the long tails at the lower end of the efficiency curves capturing particles smaller than the defined ECD. The assumption was supported by the computational modelling of the ACI which demonstrated that the deposition varied as a function of the input distribution and the average of the median diameter of the deposits on the upper plates was well below the ECD.

Measurements of the force delivered by the pMDI's were tested over a range of temperature and orifice diameters and the results indicate that the momentum of the airflow could be raised significantly as there was up to two orders of magnitude
difference between the momentum of the airflow and that produced by the spray. It is therefore probable that droplets will traverse the distance from the exit orifice to the inertial impaction site much faster than predicted by the airflow alone. As the velocity is raised by the momentum transfer the cut off efficiency curve for the mitre bend decreases, however the momentum transfer is limited by the incompressibility of the air column and the dual tapered inlet to the USP throat as demonstrated by the lack of momentum transfer measured at the outlet of the USP throat.

Based on an extrapolation of the residual aerodynamic diameter the largest diameter droplets passing through the USP throat, based on the upper portion of the efficiency curve, would be between 30 and 40 μm. Given the efficiency of the USP throat a droplet with an initial diameter >50 μm must undergo significant evaporation prior to reaching the mitre bend. A 50 μm diameter droplet from the high ethanol formulation requires more than 200 ms to evaporate down to 20 μm diameter. Assuming the droplet is travelling at the average instrument airflow velocity it has between 62.5 ms and 125 ms depending on the particle trajectory with the shortest transition time alone the centre line and up to twice that if travelling close to the wall. Given the expected exit velocity of the pMDI spray (>50 m s\(^{-1}\)) and the momentum transferred from the spray plume then theoretically there is insufficient time for such droplet to evaporate down to a diameter small enough to pass through the USP throat.

One possible explanation for the droplets having an increased evaporation time could be due to the inability of the sprays’ plume to penetrate the column of air in the USP throat because measurements of the spray force at the exit of the USP throat show approximately 90% of the spray based momentum has been dissipated. It would explain the previously observed deposition pattern in the USP throat where a significant fraction of the deposition was in the inlet region adjacent to the mouthpiece exit and not in the bend region\(/(90)\). The dual taper inlet design of the USP throat would impede the expansion of the spray plume and further exacerbate the problem.
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The droplet evaporation rate coupled with the momentum transfer dynamically changes the inertial characteristics for the USP throat and to further the understanding of droplet evaporation a dual component evaporation model was developed assuming adiabatic flashing of the propellant during droplet formation. The APS based experimental when fitted with the USP throat confirmed that no particles greater than 4 \( \mu m \) were detected from the high ethanol formulations. In the low ethanol formulations the upper particle size was limited to the range 2-3 \( \mu m \). The significant limitation to the upper range detected by the APS raises serious questions regarding the deposition distribution on the upper plates of the ACI. Based on the formulation and potential residual droplet diameters these upper limits for particle diameter confirm the upper inertial impaction range in the USP throat.

The flow path between the mitre bend and the first impactor jet plate is longer than that between the inlet and the mitre bend increasing the evaporation time available prior to the start of the particle sizing process. It is clear from the dual component evaporation model that there is insufficient time for droplets at the upper end of the USP efficiency curve to fully evaporate prior to reaching the first impactor stage. It is therefore inevitable that much of the deposition seen on the early stages of the ACI from mid to high ethanol formulations is due to incomplete evaporation and the resultant particle distribution distorted with the result that the particle size data determined is unique to the test method and may not bear any resemblance to the true \textit{in vivo} performance of the product.

It can be concluded that whilst the ACI data is reproducible and fit for purpose with respect to quality control the relationship to the true inhalation performance will remain contentious until a suitable fit for purpose test method or correlation technique is developed.

ACI based data is not suitable for understanding the true particle size and distribution characteristics or the atomisation process due to limitations imposed by the USP and aforementioned evaporation limitations. In order to overcome these limitations a
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custom designed inlet throat or tube was used. The data from the new inlet showed the upper residual particles from low ethanol formulations to be 3 μm and up to 15 μm for the higher ethanol formulations, corresponding to initial droplet diameter of approximately 30 to 150 μm respectively. The upper limit for the predicted initial droplet diameter agrees well with the droplet diameters determined from high speed video analysis.

The data reported by the APS instrument when fitted with the USP throat indicated the maximum particle size to be no greater than 4 μm and was supported by the PDA data which allowing for evaporation of ethanol and residual propellant indicated a similar value. Given that the cascade impactor data showed deposition on the upper plate where the ECD is significantly greater than 4 μm and therefore raises the question of the comparative accuracy of the ACI and the APS methods. Particularly as the ACI data for the solution formulation was higher than the APS albeit by only 0.2 μm, however the lower detection limit for the APS is 0.5 μm. The ACI cascade data indicates that approximately 10% of the mass is less than 0.4 μm, based on the mass in the filter. As the MMAD is based on cumulative mass and knowing the APS is ‘missing’ approximately 10% of the mass the MMAD for the APS data can be corrected for this loss. Once this is done comparable MMAD values are determined from the two instruments.

CFD modelling of the USP throat, USP throat plus a 100 mm extension and the USP throat with the ACI coupler and first jet stage, all showed similar results with respect to suitable convergent solution indicating that the flow in the outlet section of the USP throat is unstable and therefore not conducive to imparting ideal flow characteristics at the entrance to the first jet stage. Animations of the velocity contours during the convergence process showed the flow to eventually become unsteady with a period tendency. Using an unsteady time dependent CFD solution the periodic frequency was determined as 9 Hz. Within the peak to peak period of 110ms the effective ECD efficiency for a 20 μm diameter particle varied between 0.47 and 0.53 in the mitre bend region of the USP throat.
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The periodic nature to the impaction characteristics has significant implications where the duration of the spray approaches the frequency of the flow as the timing of the actuation will have significant influence over the level of deposition and the potential for reliable and reproducible data from single shot analysis is limited by the non ideal periodic nature of the flow.

The design of the ACI coupler does not facilitate the divergence of the flow as it exits the USP throat and the redesign of the first jet stage (from Mk I to Mk II) where the layout of the jets was altered results in the flow from the throat approaching the central region of the jet plate as if it were an impactor plate. The flow has to diverge rapidly just above the jet plate and the sudden change in direction can facilitate particle deposition on the central region of the jet plate. The rapid change in direction results in the airflow having just turned through 90 degrees, having to turn back through 90 degrees to enter the jets of the first stage. This sudden change in the direction of the airflow results in the potential deposition of particles not just on the central region of the jet plate but also the jet entry regions of the first jet plate.

Theoretically deposition is undesirable on the jet stage as it would be classed as wall loss. Data that is not recovered lowers the material balance which is a key pharmaceutical parameter. Chemical assay from the ACI testing showed a significant level of drug on the first jet stage (0.5 to 1% of that entering the ACI, beyond the USP throat). Interestingly the higher deposition was detected in the solution formulation which had the lower MMAD and a greater limit to the upper particle diameters. One possible explanation is that the impaction of liquid droplets would leave drug residue behind; whereas a droplet with a single suspension particle will result in either all or none of the drug in that particle being deposited.

The directional effect of the airflow through different inhalation delivery devices was evaluated by taking simplified inlet boundary versions representing the extremes of device input airflow with the airflow entering either through the top or the bottom of
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the device when orientated for laboratory testing or patient use. The direction of the inlet airflow changed not only the flow through the delivery device but also through the mitre bend of the USP throat and beyond. The particle tracking analysis showed a shift of several microns either side of the idealised input airflow.

CFD based particle tracking in the USP throat with an extension as used for the APS raises questions regarding the isokinetic sampling capabilities of the APS when fitted with the 3306 impactor sampler. The particle tracking indicated a tendency for the larger particles to migrate to the outer regions of the USP throat and the extension tube producing a sheath of particles the trajectory of which results in them not passing close to the inlet of the isokinetic sampler. Any momentum effect could also cause sampling issues due to the increased flow velocity taking the average velocity in the throat above the sampling rate designed for the isokinetic sampler which is based on the standard airflow.

The CFD modelling of the first and second impactor stages showed the non ideal inertial impaction characteristics of the inner ring with the flow out of the inner ring angled towards the central hole in the impactor plate. The non ideal angled impaction can result in particles that should be retained on the impaction plate subsequently bouncing through the impaction stage to the stage below. In the case of the first stage (stage 0) the process will be repeated at the second stage (stage 1) because particles passing through the inner impactor plate jets are presented to the inner two rings of the next stage with the result that particles that should have deposited on plate 0 can eventually reach plate 2. If particles that should have deposited on plate 0 reach plate 2 they will have sufficient impaction energy, due to the increasing flow velocity, to make their deposition characteristics unreliable due to particle bounce and these particles could therefore deposit on any of the subsequent impactor plates or eventually the filter.

A particle deposition study showed the nature of the deposits on the first stage to vary with the jet ring position and the shape of the deposits were not circular thus demonstrating a departure from ideal impaction. The size and shape of the deposits
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confirmed the assumption that the efficiency curves are much wider than Stokes based theory would predict. The broadening of the efficiency curve is due to pressure drop variation on the impactor plate side of the jet, impingement of airflows between jets, the development of parabolic velocity profiles especially in the upper plates where the Reynolds number are low, the position of the holes in the centre of the upper two impaction plates and the distribution of the airflow approaching the first stage.

The CFD modelling showed the velocity difference between the inner two and outer two jet rings of the upper two stages to be significant which will broaden the impaction characteristics of the stage. The modelling also demonstrated a significant development of the velocity profile within each of the jets which results in a wider range of particle velocities and therefore a further broadening of the impaction characteristics. The difference in the average velocity between the inner and outer rings was due to the pressure differential induced by the different outlet flow paths. The significance of the outlet flow path was further highlighted by the CFD modelling of stage 3 where there is only one outlet flow path that passes below all eleven jet rings resulting in a significant pressure drop and a corresponding velocity variation in the jets with the maximum velocity found in the outer jets and the minimum in the inner jets with a resultant widening of the stage efficiency curve.

The CFD modelling was also used to verify the parabolic velocity profile developed by the flow of a Newtonian fluid through short tubes. The development of a parabolic flow further decreases the efficiency of an impactor stage due to the wider distribution of the air velocity. Guidelines for the design of cascade impactor stages have recommended a range of 500-3000 for the Reynolds number but this fact appears to cause some confusion as in a recent publication the range of 500-3000 was attributed to the need to maintain a turbulent flow and nothing could be further from the truth.

The analysis of true particle size and distribution characteristics are restricted by the design of the USP throat with its unsteady outlet flow, dual tapered inlet region and mitre bend all contributing to unsuitable deposition patterns. To overcome these
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limitations an inlet was designed to facilitate the capture of all particles within the
dynamic range of the APS instrument.

The sampler was designed to overcome potential limitations of the USP throat by
increasing the range of aerodynamic diameters capable of reaching the detector and a
CFD analysis carried out to assess the flow and particle transfer characteristics. The
new inlet was designed to provide sufficient expansion space and plume penetration
distance and to permit significant evaporation of the droplets whilst maintaining the
time based sampling capabilities necessary for sampling instruments like the APS. The
use of large volume expansion devices distort the particle size distribution by limiting
the sampling probability of larger droplets while simultaneously over-sampling the
large fraction of fine particles that float around in the large volume due to low
gravitational settling characteristics and air currents circulating within the large volume.
The CFD demonstrated that particles as large as 20 μm (the upper detection limit of the
APS) could reach the instrument.

Measurement of the expansion chamber pressure showed the pressure to rise somewhat
between the assumptions of Dunbar and Clark and the pressure never achieves a steady
state. Add to this the complexities nucleation and initial bubble growth and any
metastable thermodynamic effect and it is easy to appreciate the significant complexity
in modelling the flow. Include the knowledge that those who study the two phase flow
of propellants flowing under controlled conditions invoke different models for two
phase flow, slip and bubble or void distributions. It is therefore difficult to assess the
pMDI atomisation model of Clark especially as Clark himself failed to get an adequate
fit to the metered version of the model where the absolute minimum size predicted
should approximate to 13 μm. In the development of the model the pressure was known
and the quality computed and it is this computation that must be in error and highlights
the complexity in determining the void fraction or quality during the delivery phase of
the pMDI.
Chapter 8 Discussion and Conclusions

The atomisation data was correlated to the Clark model using four potential variants of the model and it was shown that the assumption of minimal void fraction showed no correlation with the measured data but using the assumption of maximum void fraction a reasonable acceptable correlation could be achieved using the continuous atomisation version of the model. The metered version as discussed in chapter 7 was not suitable and potential reasons were explored there. The Clark model was modified to give an improved correlation with the experimental data by increasing the constant \( C \) from 8.02 to 10 and removing the exponent from both the pressure and quality terms giving

\[
D_i = \frac{C}{q \left( \frac{P_e - P_a}{P_a} \right)}
\]

The experimental data and the response of the model would tend to suggest that quality is a significant factor and that some degree of correlation may indeed exist.

A correlation to the experimental data was improved further by correlating the adiabatic flashing fraction of propellant with extrapolated droplet diameter.

\[
D_i = a + \frac{b}{mf_{\text{flash}}}^2
\]

Although a good correlation could be obtained from the Clark model it does require the assumption of maximum flashing within the expansion chamber. The agreement with the Clark model by Dunbar assumed complete flashing within the exit orifice. However the practical evidence contradicts these theories, as complete adiabatic flashing would result in little or no divergence of the emerging spray. Under complete adiabatic flashing the temperature of the liquid approaches the boiling point and the saturated
vapour pressure drops to atmospheric. The Dunbar model also relied on the existence of an unproven bubble growth recirculation region within the exit orifice.

The modelling of the delivery from the metered dose inhaler is complicated by the small volumes involved, the short non steady state duration and a lack of detailed knowledge relating to the transient thermodynamic properties.

The correlation of the atomisation data to that predicted by the Clark model is reasonable at the low ethanol level but deviates significantly at the higher ethanol level. Given that it is now accepted that the higher ethanol data is an underestimate due to the non detection of large droplets, then the model does not predict with any degree of accuracy. The shape of the response is however in the same direction as the experimental data; whereas the data for the minimum quality prediction is flat, indicating no response to the changing ethanol levels. The Clark model does not contain a distribution factor, which is a limitation to any practical application of a model with this kind of deficiency. At best a models of this form provides only an approximation to a central tendency, but in many applications maybe all that is required.

The novel approach taken here involved designing the system (formulation and expansion volume) to limit the potential range of void fraction or quality. Based on these limitations it was simple to calculate the two extremes for quality at the start of the atomisation process, one where the assumption is minimum flashing which is relatively easy to compute and the maximum flashing (no idle time, or bubble growth requirements) assuming only adiabatic flashing occurs. The use of a non volatile co-solvent reduces the error limitations by imposing a known non flashing component into the void.

The high speed video images indicated a dearth of droplets in the 50 to 100 μm range and could indicate that in formulations where flash atomisation is inhibited a second atomisation mechanism could become prominent, as the APS data still indicates a large
Chapter 8 Discussion and Conclusions

proportion of small particles. The second mode which generates the larger droplets could be present in all formulations but becomes more prominent as the flashing based process declines. This could explain the spluttering effect observed in low vapour pressure formulations where the degree of flashing and non homogenous flow become more significant factors.

Computational modelling of the ACI confirmed that plate deposition should conform to a lognormal distribution even where the input distribution is not lognormal. It was further shown that bi and tri-modal input distributions approximated to the lognormal distribution and the deposition profile is a function of the input distribution.

The ACI has a propensity to indicate a bi-modal distribution when the data is analysed on a mass per plate basis due to the spacing and overlapping nature of the ECD of the upper plates with the bi-modal tendency increasing with increasing MMAD and to a lesser extent GSD.

Attempts to correct the modelled distributions using the non linear method of Thiel further decreased the MMAD below the value defined by the known input distributions.

For a conclusion of a lognormal distribution assumption to be valid the correlation coefficient for the lognormal plot needs to be >0.95

Any determination of a lognormal distribution should be supported by at least one other particle sizing methodology to validate the assumption.

The plate depositions at either end of the cumulative mass plot, principally at the upper end, exert greater influence on the assumptions made regarding the correlation. However caution is necessary as these depositions can be influenced by a significant number of other factors and should be disregarded if the underlying cause is not understood or validated by another sizing method.
8.2 Conclusions

Computer based modelling has shown that the average diameter of the deposits on the upper plates is not only a function of the input distribution but is significantly lower than the pharmacopoeia based ECD for any of the plates.

A number of factors have been identified that contribute to the non ideal deposition on the upper plates including non ideal probability curves and overlapping stage performance. Droplet evaporation computations have shown that larger droplets passing through the mitre bend of the USP throat have insufficient time to fully evaporate prior to reaching the first stage and the resultant deposits skew the distribution on the upper plates and contribute to the wall losses on the first impactor stage.

CFD analysis has exposed several design flaws in the upper stages of the ACI with respect to jet layout, the position and diameter of the holes in the centre of the impactor plates, velocity variation, development of a parabolic velocity profile at the jet exit and directional flow through the inter-stage flow path, all of which contribute to the broadening of the deposition efficiency curves.

CFD modelling has verified the non ideal flow characteristics in the USP throat where an unsteady flow analysis has established a periodic variation in the ECD of the throat and a major periodic flow in the coupler region where the periodic frequency was determined as 9Hz. This could significantly influence the determination of throat deposition when a lower number of test actuations are required and the duration of the spray plume is less than 200ms. The unsteady flow also contributes to the deposition pattern on the first impactor plate.

A CFD study confirmed the ECD of the USP throat varies as a function of the directional nature of the airflow through the actuator. Spray visualisation studies demonstrated an upward directional nature to the plume that increased with increasing exit orifice diameter when tested using an Autohaler™ delivery device. This raises
doubts over the theory that the downward direction of the plume is due to recirculation in the exit orifice as the flow through the Autohaler™ device prior to the exit orifice is identical to that found in conventional press and breathe devices.

CFD analysis has shown that the flow is asymmetrical in the lower section of the standard USP inlet throat and the particle sampling by the isokinetic sampler tube in the APS is not positioned to sample uniformly from spray, so this results in lower mass sampling. The magnitude of the problem can be reduced by the addition of extension tubes to the section between the end of the inlet throat and the inlet of the 3306 sampler unit. The addition of the extensions provides more time for the flow and more importantly the particles being carried, to establish a more uniform distribution before reaching the sampler inlet.

Measurement of the spray force at the exit of the USP throat indicates significant momentum transfer to the airflow increasing the average velocity at the first impactor stage, further increasing the deposition. Spray force measurement of the plume have revealed that previously published peak spray force measurement are overestimated because there is a sound component modulated onto the spray force signal. Distance based studies confirmed the conservation of momentum whilst demonstrating a decrease in the sound component.

The spray electronically filtered spray force signal showed for the first time a critical transition in the flow 10-20ms after actuation which varies as a function of exit orifice diameter and temperature. Measurements of the spray force at the exit of the USP throat confirmed the transition.

APS and PDA based data show the particle size of the spray from the solution formulation to be lognormally distributed and the corresponding distribution for the suspension formulation approximates to lognormal. The USP throat truncates the droplet distribution due to incomplete evaporation and limits any fundamental
Chapter 8 Discussion and Conclusions

understanding that can be concluded regarding an inhaler spray size distribution and respirable performance.

Using extreme limits for the degree of adiabatic flashing, within the dimensional constraints used, showed the Clark atomisation model did not fit the experimental data when the quality of the spray was low, but did improve when the maximum quality was used. An improved fit between the experimental data and the model was establish by increasing the value of the constant and setting the exponent terms for the quality and pressure to unity.

A further improvement to the experimental data was determined by implementing a model based on the maximum adiabatic flashing that could occur in each of the formulations.

It can therefore be concluded that the objectives set at the start of the research have been met.
9. Recommendations for further work

The development of computational models for other cascade impactors and impingers including the NGI and Marple Miller Impinger.

Enhancements to the computational modelling approach through the development of models for particle bounce and droplet evaporation.

Improvements to the design of the USP throat to eliminate the unstable flow characteristics.

Improvements to the design and layout of the upper jet stages, impactor plates and inter-stage flow paths of the ACI.

CFD modelling of the full stage designs and flow paths of the ACI to validate the use of symmetry boundaries.

CFD modelling of each stage of the ACI and the NGI to establish whether the NGI should replace the ACI as the primary impactor for pharmaceutical analysis.

The development of suitable two phase flow models for the transient flow process stages in the metered delivery of the pMDI.

Development of a suitable multi component evaporation model to account for variation in droplet temperature and velocity factors.
Appendix

A.1 Pressure transducer

The manufacturer (Honeywell) of the sensing unit used in the construction of the custom made pressure transducer quotes a response time of 1ms for the transducer in the as supplied configuration. The custom construction utilised most of the original transducer including the pressure sensor, housing and electrical connectors. The custom construction shortened the existing pressure coupling region reducing the volume of the inlet and then added volume in the form of a small bore stainless steel tube.

No pressure calibrator available that could apply an instantaneous calibrated pressure pulse of the required magnitude. The balloon burst technique utilised by Clark was considered but due to the limited pressure range was not considered a suitable transducer test. The response time of the transducer was evaluated using a modified actuator and placebo aerosol. The exit orifice of the actuator was blocked with epoxy resin. The pressure transducer was inserted into a hole drilled into the side wall of the expansion chamber and connected to the analogue to digital converter board (ADC). The aerosol (QVARTM placebo) was actuated and the pressure in the expansion chamber was recorded by the PC/ADC and plotted using an Excel® spreadsheet.

The response time, assessed as the time to reach 90% of maximum input, was determined as less than 9ms and the response time to 50% was less than 3ms. The response time includes the expansion of the propellant up to saturated equilibrium and therefore the true response time of the transducer can be considered as being significantly less than 9ms given the bubble growth rate and vapour expansion expected for the propellant system.
Appendix

Figure 0-1 Figure pressure rise for custom pressure transducer

A.II Calibration of the force transducer and assessment of sound component on spray force measurement

The spray force signal contained a higher frequency component that had been determined as the sound of the spray delivery process being modulated onto the spray force signal. The composite signal made the determination of true force difficult due to the magnitude of the sound component. A similar high frequency component had been seen in previous published spray force data.

The high frequency component was lower than the value of 740Hz quoted in the manufacturer’s data sheet for the type 31 force transducers natural/ringing frequency.

The higher frequency component, presented in the experimental section, was removed from the spray force signal in real time using the 20Hz filter of the force transducer amplifier unit (S7DC, RDP Electronics Ltd).
Appendix

Due to the conservation of momentum the spray force signal does not decay with distance to the transducer whereas the sound component did as shown below.

Figure 0-2 Figure Spray force measured at 10mm without filtering (QVAR™ placebo and 0.28mm diameter exit orifice)

Figure 0-3 Spray force measured at 100mm without filtering (QVAR™ placebo and 0.28mm diameter exit orifice)
Appendix

Figure 0-4 Spray force measured at 200mm without filtering (QVAR™ placebo and 0.28mm diameter exit orifice)

The results from the unfiltered plots show how the duration and magnitude (steady component) of the spray force remain independent of the distance to the transducer whereas the high frequency component decays. At a distance of 10mm the high frequency component has a peak to peak value of 35mN and at 200mm the value has decayed to 10mN. The peak of the underlying spray force is only 30mN and therefore measuring the spray force close to the exit orifice without filtering significantly alters the determination of true spray force.

A.II.1 Calibration and set up of force transducer

The force transducer was calibrated by rotating the transducer through 90 degrees with the target uppermost and using a set of calibrated weights (1, 2, 5 and 10 grams) to check the linearity and set the full scale output to the ADC.

The output of the amplifier was trimmed to zero and the required weight added. The gain was adjusted to set the required full scale output to the PC/ADC. After calibration the transducer was rotated back into the spray force measuring orientation and the output set to zero.
Appendix

A.III Effect of solute concentration on residual particle size

The effect of the solute concentration on the residual particle size diameter was studied to validate the one third solute law and to assess the low detection limit of the APS.

A series of aerosols were prepared using different concentrations of solute. The solute was dissolved in a specified quantity of ethanol and aliquots the resultant solution was cold transferred into 10ml aluminium cans containing 134a propellant. A 50μl Spraymiser™ valve was then crimped onto the can. The units were allowed to stabilise, valve down for 7 days prior to testing.

The process was repeated for each level of solute solution (Table 0-1)

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Solute Concentration %</th>
</tr>
</thead>
<tbody>
<tr>
<td>i</td>
<td>0.0004</td>
</tr>
<tr>
<td>ii</td>
<td>0.0008</td>
</tr>
<tr>
<td>iii</td>
<td>0.0016</td>
</tr>
<tr>
<td>iv</td>
<td>0.0024</td>
</tr>
<tr>
<td>v</td>
<td>0.0032</td>
</tr>
<tr>
<td>vi</td>
<td>0.004</td>
</tr>
<tr>
<td>vii</td>
<td>0.0048</td>
</tr>
<tr>
<td>viii</td>
<td>0.0056</td>
</tr>
<tr>
<td>ix</td>
<td>0.008</td>
</tr>
<tr>
<td>x</td>
<td>0.016</td>
</tr>
<tr>
<td>xi</td>
<td>0.024</td>
</tr>
</tbody>
</table>
Appendix

Figure 0-5 Figure Plot of solute concentration against residual particle diameter

Figure 0-6 Plot of solute concentration against residual particle diameter with model fit, 95% confidence interval and residuals for the experimental data
Appendix

Figure 0-7 Plot of solute concentration against residual particle diameter with model fit, 95% confidence interval and residuals showing better fit with lower concentrate formulations removed

The data confirms the one third solute law used in the prediction of droplet size from the residual diameter measured by the APS and also highlighted the lower detection limit of the APS at the lower solute concentration levels. A second cause for the departure from the ideal one third root law is the level of impurities present in the starting materials. The propellant and ethanol used in the study were pharmaceutical grade however even these grades have low levels of impurities that become significant as the concentration of the solute approaches zero. Second sources of particulates are those due to material fragments from the valve and can. Materials extracted from the valve seal also increase the level of impurities.

A.IV Calibration of the APS and mask generation

The re-circulation of very small particles within the optical measuring cell of the 3320 APS can result in incorrect particle size characterisation due to the instrument characterising small particle as being much larger. It is possible to remove these false particles by applying a data mask to the basic instrument data set when the instrument is operated in the correlated mode. In this mode the aerodynamic particle size for each particle recorded is logged together with the corresponding side scatter light intensity
Appendix

data. By application of a suitable mask it is possible to remove the false particles from the analysis before computing the spray particle size characteristics. The mask removes all particle size data where the intensity of the light scattered by the particle is either too low or too high for that specific particle diameter.

A mask was developed from the aerodynamic particle size and corresponding side scatter data produced by the injection of particles of accurately determined particle size characteristics. A range of BCR (Community Bureau of Reference) polydispersed, glass micro-spheres, metrology standards, traceable to NPL and BCR standards, were used to produce a suitable mask covering the particle size range of the aerosols to be used in the study. The standards are supplied with particle size distribution certificate with data obtained from several laboratories using two sizing methods (Coulter counter and Andreason pipette).

Two delivery techniques were used to evaluate the BCR standards;

- Dispersion of the BCR standard into a pMDI placebo aerosol.
- Air powered injection of the BCR standard into the APS.

Two BCR standards were used in the study (1-10\(\mu\)m and 3-30\(\mu\)m). The BCR standards were also used to evaluate other important aspect in the APS calibration process. The specification for the APS quotes a sampling efficiency of 100% for small particles, decreasing to 90% for particles at the upper sizing limit of 20 \(\mu\)m. From the calibrated particle size data a sampling efficiency curve can be determined from the difference between the measured particle size distributions to those recorded by the APS.

The calibration standards were also selected because of their compatibility with constituents of the formulations, the lack of very small particle diameters and relatively high density, parameters that help to reduce the risk of small particles re-circulation.
Appendix

The standards are also spherical and thus the scattered light intensity in the detection cell would give a good correlation with particle diameter.

The data from the APS is available as a matrix of particle size versus side scatter intensity. The APS data was stored in a standard spreadsheet format and was linked to the master calibration mask.

The inlet airflow to the APS is through an USP inlet throat. The nature of the airflow and how it interfaces with the spray plume will have significant impact on the particle size measurement if the deposition within the ACI throat is not based solely on aerodynamic impaction.

The graphs below show how the use of the mask shifts the particle size distribution by removing false particles from the analysis.

Four suspension formulations were used to evaluate the sensitivity of the APS. They utilise the same base formulation with the exception of the ethanol level and the particle size distribution of the raw drug used in the formulation.

Varying the number of times the drug was passed through the micronising process induced the difference in particle size of the raw drug (Table 0-2). The two levels of ethanol were 13 and 17 percent by weight of propellant.

The assessment of the data mask was carried out using the four suspension formulations (Table 0-3). The suspension formulations were varied in the raw drug particle size and ethanol level. The details for which are given in the table below.

The pMDI units were tested using the APS with USP inlet throat in the 3306. All testes were conducted with inlet airflow of 28.3 l min⁻¹.
Appendix

Figure 0-8 Cumulative volume distributions for the 4 formulations without data mask

Figure 0-9 Cumulative volume distributions for the 4 formulations with data mask
Appendix

Table 0-2 Table Particle size data for suspension formulation (as supplied)

<table>
<thead>
<tr>
<th>Number</th>
<th>Coarse (one pass)</th>
<th>Fine (three passes)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% &lt; 1.5 μm</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>% &lt; 3.0 μm</td>
<td>72</td>
<td>96</td>
</tr>
<tr>
<td>% &lt; 5.0 μm</td>
<td>93</td>
<td>100</td>
</tr>
<tr>
<td>% &lt; 10 μm</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

Table 0-3 Suspension formulation variables

<table>
<thead>
<tr>
<th>FORMULATION</th>
<th>ETHANOL</th>
<th>DRUG</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>13</td>
<td>Fine</td>
</tr>
<tr>
<td>b</td>
<td>17</td>
<td>Fine</td>
</tr>
<tr>
<td>c</td>
<td>13</td>
<td>Coarse</td>
</tr>
<tr>
<td>d</td>
<td>17</td>
<td>Coarse</td>
</tr>
</tbody>
</table>

The results demonstrate several key aspects to the interpretation of APS based data. The detection of false particles can significantly shift the MMAD determined from the analysis. The effect is significant in the formulations where the coarse drug was used. Prior to the mask the MMAD of the formulations are >10 μm (Figure 0-8) whereas application of the data mask the MMAD are <5 μm (Figure 0-9). The data also demonstrates the sensitivity of the APS to formulation variables such as ethanol level. The mask data also shows the presence of larger particles in the emitted spray up to the dynamic limit of the APS that are close to the ECD of the USP throat and give the lack of evaporation time prior to reaching the mitre bend of the throat and many of these should theoretically have been deposited in the USP inlet throat and indicates the tendency for particulates to bounce through the throat section and into the ACI stack.

Based on the particle size of the drug put into the formulations the shift in MMAD also demonstrates the possibility of particle growth, agglomeration or multiple droplet occupancy.
Appendix

A.V High speed spray image analysis
High-speed digital images were used to assess various aspects of the plume produced by the pMDI; among these were duration, maximum diameter, length, divergence angle, velocity and the spray density (intensity of reflected light).
The high-speed camera utilised for this work was the Kodak 4540 and a synchronised pulsed copper vapour laser provided the illumination. The frame rate used was 9000 fps (pixel resolution 256 * 128) corresponding to a dimension of 160mm * 80mm.

High-speed video data is very informative from the perspective of visual interpretation, however, visual information cannot easily be conveyed and a numerical interpretation method was developed to overcome this limitation.

A.V.I Laser sheet imaging
Laser sheet images were obtained from a range of actuator geometry.
In simplest terms the intensity of the scattered light is related to the number and size of the particles within the laser beam. The viewing angle of the camera is at 90 degrees to the plane of the illumination. In viewing the emitted light at a 90 degree angle it is possible to make the assumption that very little light received by the imaging chip in the camera will be from either diffracted or refracted light but is almost entirely reflected light from formulation droplets. The light in such an orientation has a relatively simple relationship to the diameter of the reflecting surface, assuming spherical droplets. If the assumption of uniform mean diameter and particle size distribution is applied then the reflected light, which assumes the mean particle diameter and particle size distribution does not change significantly during the duration of the spray, will be proportional to the mass flow. Based on published work this assumption is well founded except at the tail end of the spray duration period.

The images produced are very informative; however, reliable spatial and temporal information can only be determined from specific software analysis of the image.
Appendix

sequences produced. Whilst an image of the spray may give valuable information regarding plume distance as a function of time, apparent spray angle, turbulent characteristics such as vortex shedding, etc.

The spray image was processed using the digital image analysis toolkit for Mathcad® a mathematical analysis software package to enhance the periphery of the spray plume. The periphery of a turbulent jet is difficult to define due to the Gaussian nature of the distribution.

The spray axis analysis revealed several interesting characteristics to the spray plume. The enhanced image analysis showed the plume angle and direction to vary with the size of the exit orifice tested and also depended on the proximity of the mouthpiece. Previous spray image work on pMDI plumes have quoted specific divergence angle for the plume whereas the data here shows significant variation. The first significant point of interest is the spray does not diverge with a constant angle (Table 0-4). The direction of the spray is generally upward (Figure 0-11 to A-14) rather than horizontal or downward as previously reported and supports the assumptions made in the CFD modelling of the USP regarding the directional nature of the flow and the potential influence on the level of drug deposition as a function of actuator geometry.

Table 0-4 Spray plume divergence angles and maximum width of the spray at two distances from the orifice

<table>
<thead>
<tr>
<th>ORIFICE DIAMETER</th>
<th>LOWER ANGLE</th>
<th>UPPER ANGLE</th>
<th>LOWER ANGLE</th>
<th>UPPER ANGLE</th>
<th>MAXIMUM WIDTH</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>@50mm</td>
<td>@50mm</td>
<td>@110mm</td>
<td>@110mm</td>
<td></td>
</tr>
<tr>
<td>0.22mm</td>
<td>11</td>
<td>12</td>
<td>6</td>
<td>7.5</td>
<td>45mm</td>
</tr>
<tr>
<td>0.34mm</td>
<td>9</td>
<td>11</td>
<td>6</td>
<td>12</td>
<td>47.5mm</td>
</tr>
<tr>
<td>0.5mm</td>
<td>10</td>
<td>14</td>
<td>6</td>
<td>12</td>
<td>50mm</td>
</tr>
<tr>
<td>0.34mm(no M/P)</td>
<td>11</td>
<td>15</td>
<td>7</td>
<td>18</td>
<td>56mm</td>
</tr>
</tbody>
</table>
Figure 0-10 image sequence showing the typical development of the spray plume. a) 10ms after the actuation, b) 50 frames after a, c) 100 frames after a and d) 200 frames after a.
Figure 0-11 Plume shape for the 0.34 mm diameter exit orifice plus digitally enhanced processed image showing true boundary regions.

Figure 0-12 Plume shape for the 0.22 mm diameter exit orifice plus digitally enhanced processed image showing true boundary regions.
Appendix

Figure 0-13 Plume shape for the 0.5 mm diameter exit orifice plus digitally enhanced processed image showing true boundary regions.

Figure 0-14 Plume shape for the 0.34 mm diameter exit orifice with the mouthpiece section removed, plus digitally enhanced processed image showing true boundary regions.
Appendix

The actuators used in the study were Autohaler™ devices which have an unusual airflow arrangement when compared to conventional inhalation actuators. The airflow enters through the base of the actuator and the airflow turns through 90 degrees before exiting the mouthpiece. The effect of this directional effect was studied in the CFD analysis of the USP throat.

The larger the exit orifice diameter the greater is the upward direction of the plume. When the mouthpiece of the actuator was removed the spray direction was more central and the width of the plume increased (Figure 0-14).

The diameter of the new inlet sampler was 65mm and was based on the dimensions of spray plume determined here. The maximum observable penetration of the plume into still air was <300mm.

A.VI Temporal analysis of the spray plume

In the measurement of the spray force a temporal variation was observed in the spray force signal. The analysis indicated that the variation was that of the pressure waves generated by the sound of the spray delivery process. The temporal variation of the spray was analysed by digital processing of the high speed video images.

The first requirement was to determine the optimum frame rate at which the data should be collected for the analysis of spray characteristics to give the correct interpretation of aspects such as the pulsing nature of the spray.

The data analysis used the average light intensity in an 80*1 vertical pixel matrix, approximately 40 mm downstream of the mouthpiece exit (the region just beyond the central cone of maximum light scatter intensity).

The ordinate is the average light intensity in the matrix and the abscissa the frame number. Previous work(4, 15, 15) has shown that the spray emitted from the orifice of a
pMDI is not a continuous flow but does, when viewed at high speed, pulsate at a defined frequency, which was reported as 700 Hz. It was important to establish the ideal recording speed that would facilitate the analysis of key features without the need to record excessive quantities of data. Aliasing is used to describe the situation where a distortion or artefact of the original signal results from incorrect sampling of the original signal. Aliasing can be avoided by sampling at the critical sampling frequency, often referred to as the Nyquist or Nyquist-Shannon sampling theorem. The theorem states that in order to reconstruct a signal the sampling must be at a higher frequency higher than the bandwidth of the sampled signal. It is generally accepted that aliasing will not occur if the sampling frequency is at least twice the frequency being sampled. As the critical frequency of the spray has previously been reported as 700 Hz then the sampling rate needs to be at least 1400 Hz. It was therefore decided to capture the data at 9000fps as this is more than an order of magnitude greater than the expected frequency of the flow. The digital images were processed using the algorithm shown in Figure 0-15 and the data plotted in Figure 0-16.

Figure 0-15 Computational algorithm for digital spray images
The data shows there to be no significant high frequency component to the spray. The maximum frequency seen is not at 700 Hz and the variation seen does not have the frequency component attributed to the sound in the spray force measurement.

All plots show a relatively fast rise to a maximum intensity followed by either a short plateau, at or close to the maximum value or a gradual decrease onto which is superimposed what appears to be a random series of pulses. The pulses tend to be more significant towards the end of the actuation cycle. These pulses were subjected to further analysis using fast Fourier transform analysis to evaluate the frequency components within the data.

A.VI.1 Transverse temporal analysis of the spray plume

The same optical set up was also used to generate data for sections through the spray, transverse to the delivery axis. In this process the relative orientation of the laser sheet and camera to the spray are rotated by 90 degrees, so the laser cuts the spray and the camera view is towards the mouthpiece.
Appendix

The analysis showed the formation of a few larger droplets at the start of the actuation and these can be seen in Figure 0-17.

The data in Figure 0-18 shows the instantaneous and time-averaged transverse section through the spray, 35 mm from the mouthpiece exit. The digitally enhanced instantaneous images show the spatial variation in the spray and the time-averaged image shows the Gaussian nature of the plume. The temporal and spatial variation support the assumption of non-homogeneous flow.

Figure 0-17 Images showing the development of the spray plume in a transverse section through the plume at a distance of 100 mm from the mouthpiece. The frame spacing is 20 frames between each image.
Figure 0-18 Digitally enhanced images of the spray plume showing a transverse section through the plume at a distance of 35 mm from the mouthpiece. A is 50ms after actuation, B is 60ms after actuation, C is 70ms after actuation, D is the numerical average of a 20ms period.
Appendix

A.VII CFD modelling of flow in the Twin stage impinger throat (TSI)

A.VII.I Introduction

The nature of the flow and inertial deposition of flow through the inlet section of an impactor is essential in determining the correct assessment of particle size and distribution. In order to highlight this factor the flow through another pharmacopoeia based method is modelled for comparison with the flow through the USP throat and to demonstrate the difference between commercial throats with the objective of highlighting the complexity involved in understanding inertial based induction port/throat impaction.

The twin stage impinger (TSI) is commonly used in the release testing of UK based pMDI products because it offers greater speed and simplicity over the more labour intensive ACI test. The popularity of the TSI has decreased in recent years due to the technical limitations(262) now accepted by the industry. The test divides the particle into two fractions hence the term twin stage. This approach is acceptable for quality testing although it has been shown that just assessing two fractions of the emitted spray can give very misleading results(262).

There are a considerable number of geometrical differences between the throat sections of the TSI and the USP. The TSI has a complex series of interconnected profiles with the outlet diameter being smaller than the inlet. By comparison the USP throat is a very simplistic tube with a sharp bend.

A.VII.II Methods for TSI modelling

The glass inlet throat section of the TSI is shown with the mesh used for the flow analysis. To maintain a common inlet scenario the same mouthpiece profile used in the USP work was also used for the TSI inlet. The TSI throat has a large bulbous central section, which has a complex geometry and therefore an unstructured tetrahedral mesh is required.
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Table 0-5 Variables and settings used in the CFD modelling of the TSI throat

<table>
<thead>
<tr>
<th>SOLVER</th>
<th>FLUENT 6</th>
<th>INLET BOUNDARY</th>
<th>VELOCITY</th>
</tr>
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<tbody>
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<td>Grid</td>
<td>Tetrahedral, T-Grid</td>
<td>Discretisation</td>
<td>2nd Order Upwind</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>k-e, 10% intensity</td>
</tr>
<tr>
<td>Boundary</td>
<td>Vin = 2.88 m/s</td>
<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>

The meshed model is shown below. The inlet section (mouthpiece inlet) is to the right hand side and the outlet section is vertically downwards and the tapered outlet section fits into the next section of the TSI glassware. The volumetric flow rate for the TSI is 60 l/min which results in a much higher inlet velocity compared to the ACI.

The Reynolds number for the outlet of the TSI is >4000 and a basic k-e turbulence model was invoked for the model.

Figure 0-19 Meshed model of the TSI throat section with circular mouthpiece at the inlet.

The very complex flow patterns within the TSI throat can be seen in the streamline traces (Figure 0-20) and velocity contour (Figure 0-21) shown below. The large round bulbous section between two tubular, inlet and outlet sections induces complex flow
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patterns and the streamlines and velocity contours indicate that particles in the upper region of the bulbous throat could remain for some time due to complex re-circulatory flow patterns before passing on through the outlet section. The increased retention time could influence the droplet size given the increased residence time giving greater time for propellant and volatile excipient evaporation to take place.

Figure 0-20 Regularly spaced streamlines on the central plane (z=0) show complex flow structure present in TSI inlet throat; note the large re-circulation region at the top of the spherical section.

Figure 0-21 Velocity contours for flow in TSI inlet throat
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The inertial based impaction characteristics of the TSI throat will be very dependant on the specific alignment of the incoming flow because of the curvature of the impaction surface and the proximity of the large recirculation zone.

The higher flow rate and slightly shorter distance to the back of the throat significantly reduce the residence time of droplets and the time for evaporation of sub-cooled propellant and other volatile excipients. The time for a 20 μm diameter particle travelling along a central path line to reach the back of the throat takes 49ms compared to 94ms for the USP throat giving greater time for evaporation to occur, however when the USP throat is used at 60 l min⁻¹ the transit times are comparable.

The directional effects of the actuator inlet flow direction are likely to be more pronounced in the TSI throat given the shorter inlet length and the more extensive re-circulatory region.

A.VIII New inlet section design for the APS and CFD analysis

A.VIII.1 Introduction

The objective of the work presented here is to assess the flow characteristics of the new inlet sampler for the APS and used in chapter 6 and the principles used in the design. In order to achieve these objectives it was necessary to start by defining all the potential modes of deposition that can occur in the throat sections of inertial impactors. It is generally assumed that most throat deposition is based on inertial deposition and the analysis of throat deposition has been termed as having a ballistic fraction(6) and the analysis of cascade impactor data by Polli(155) mistakenly assumed that all deposition in the throat section was greater than the ECD of the first impactor stage.

A detailed review of throat deposition studies reveals there are deposition mechanisms other than those based solely on inertial properties. It has been shown that the inlet section can change the interpretation of particle size and deposition(187, 191-193, 263,
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264), the deposition can be due to turbulence(190), electrostatics(1, 249-251), surface coating(191) and the data from the previous USP throat modelling has shown how both the inlet flow direction can alter the flow distribution in the inertial sizing region of the throat section. The deposition in the throat section is therefore the summation of these various mechanisms minus that fraction that is lost due to particle bounce and secondary break up. The design of the inlet section needs account for the various deposition modes if the true nature of the atomisation process is to be accurately reported for both mean particle size and distribution.

Based on the CFD modelling of the USP throat, particle tracking, high speed video and data reported in the literature it was considered necessary to redesign the inlet section of APS to increase the sampling efficiency to ensure adequate sampling of all particle sizes generated by the pMDI spray. Clark(141) in his particle sizing work used a large holding chamber into which the aerosol was actuated; a delay of 10 seconds was used before the APS sampling was started. Due to the directional nature of the pMDI plume it was not felt that this approach would ensure adequate sampling across all sample sizes because

- Large droplets could settle before sampling commenced (gravitational).
- The trajectory of large particles was not optimised for efficient collection in the APS inlet section.
- Time order is not maintained in large volumes (proportional sampling).

Clark(141) also reported problems in the sizing of small particles (<1μm) a problem that has been significantly reduced in the later 3320 model used in this study. The lower size limit of the APS detection system now approaches the inherent problem imposed by the wavelength of light (diameters less than 0.5μm).
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A.VIII.II Methodology used in the design of the new inlet sampler

The spray visualisation work was used to establish the effective plume length (distance at which the spray had effectively stopped) and diameter of the spray plume. The new design also needs to accommodate the need to allow adequate evaporation of the larger droplets before they reach the particle-sizing region of the APS.

The atomisation experimental plan included using ethanol levels up to 50% w/w. If the atomisation of formulations with these levels of non volatile component are to be characterised then the inlet design would need to account for not only the size of the droplets but also the much longer evaporation time expected from such an increase based on simple assumption of the evaporation rate as a function of droplet diameter.

To determine a suitable inlet length that would provide sufficient time for evaporation to take place a series of experiments with a 50% w/w ethanol aerosol fitted with a large (0.5 mm) exit orifice actuator were conducted using an ethanol sensitive paper set up. The ethanol sensitive paper turns blue on contact with ethanol droplets. The unit was fired at ever increasing distances from the ethanol sensitive paper until droplet could no longer be detected.
There were many factors that needed to be considered in order to define the requirements needed in the design process for an inlet suitable for studying the atomisation process. Figure 6.48 shows the regions of the ACI throat that were considered in the design process and the reasons are as follow:

a) The region immediately downstream of the actuator mouthpiece has been shown to trap a large quantity of the spray (190).

b) The inlet section after the tapered inlet is only 19mm in diameter and this is much smaller than the visualisation studies show for the plume diameter.

c) Is the region where most inertial deposition takes place (191).

d) Is the length available for evaporation to take place prior to inertial sizing in region c.
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e) The length available for the evaporation down to the final residual size prior to the measurement of aerodynamic diameter in the APS or the first impactor stage of the ACI.

The proposed inlet design was then evaluated using CFD to characterise the flow and more importantly the particle trajectories along the inlet section.

Initial work assumed that the maximum particle diameter, after evaporation and traversing several hundred millimetres through the sampler inlet section, would be no more than 20 μm. Any residual particles or droplets bigger than this would be outside the dynamic range of the APS and would not be detected and therefore the design limit was determined by the upper limit of the detectable range.

A solid model was generated and meshed using an unstructured tetrahedral mesh. An uncoupled Lagrangian particle-tracking scheme (Stokes-Cunningham) was implemented to assess the particle trajectory of particles with the upper design limit diameter (20 μm).

Based on the visualisation studies it was assumed that the particles/plume would travel more than 200-300mm due to the exit momentum of the spray, however this was into still air whereas in the test method there would be airflow of approximately 1.4 m s\(^{-1}\) through the actuator and this would extend the distance travelled by the plume. It was also assumed that the confined space would not unduly slow the spray.

Table 0-6 Variables and settings used in the CFD modelling of the new inlet section for the atomisation study

<table>
<thead>
<tr>
<th>SOLVER</th>
<th>FLUENT 6</th>
<th>INLET BOUNDARY</th>
<th>VELOCITY INLET</th>
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<td>2nd Order Upwind</td>
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<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
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<td>Fluid</td>
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<td>Turbulence model</td>
<td>Laminar</td>
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<tr>
<td>Boundary</td>
<td>Vin 1.36 m/s</td>
<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>
Appendix

The diameter of the inlet section is critical for two reasons, it needed to be wide enough to minimise contact with the periphery of the plume and narrow enough to prevent material at the periphery of the plume from floating around for excessive lengths of time and the time based order in the spray is lost (over sampling of small particles occurs because they have a greater opportunity to be captured by the APS whereas the larger droplets/particles impact immediately or sediment rapidly due to gravitation.

Based on plume dimensional data obtained from the imaging work in sections A6 and A7, a dimension of 65mm was selected as a compromise to meet the design requirements of a and b. The width of the inlet region needed to be wide enough to prevent turbulent deposition(190) of the spray plume (requirement a).

The length of the inlet section (requirements c, d and e) was determined by a combination of the ethanol detection test and the penetration distance of the plumes into still air (based on high speed results). This distance for ethanol detection was in the range 400-450mm and the penetration of the plume particles was in the range 200-300mm. Based on this information the inlet section was set at 450 mm. The transition from horizontal to vertical was accomplished using a curved section and the diameter of the pipe adjusted to give a smooth transition into the 3306 APS unit (25mm diameter).

The incline of the new inlet section was designed to minimise gravitational settling of larger diameter components of the spray. The perfect solution for this would be to have the inlet section vertical but there were practical limitation imposed by the existing height of the workbench, the APS plus 3306 sampler, the height of the operator and safety issues. There is also the additional problem that pMDI’s need to be in the correct orientation to permit the valve to refill correctly after firing.

Based on these assumptions and the CFD flow modelling and particle tracking it was expected that particles/droplets at the design limit of 20 μm would reach the bend at the base of the sampler and travel downward to the APS isokinetic sampler tube. In figure 6.49 the particle tracks for 20 μm are traced from the point at which the forward momentum of the spray ceases and only the test airflow now acts in the flow direction
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and gravitation now becomes a significant component of the forces acting on the particle/droplet. The streamline plot in Figure 0-23 shows how the airflow diverges rapidly downstream of the mouthpiece and the velocity contour plot demonstrates how rapidly the airflow velocity decreases.

Figure 0-23 Sampler inlet (connection to APS not shown) showing flow streamlines from the inlet (top), air velocity contours (middle) and particle tracking for 20 μm aerodynamic diameter particles showing gravitational settling.

A.IX Modelling airflow through commercial actuators

The objective is to demonstrate the distribution of airflow through conventional commercial actuators to support the assumptions made in the CFD chapter. The data will also be used to give an alternative explanation for the directional nature seen in plumes emitted from pMDIs'\(^{(4, 212, 265)}\). These previous studies attributed the
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downward directional nature to an unlikely bubble growth mechanism in the actuator orifice.

A.IX.I Methodology for model construction

Two solid models of commercial actuators were produced using the Gambit® software and meshed using an unstructured tetrahedral scheme (TGrid™). Both actuators were modelled with the canister in the fired (fully depressed/down) position. The airflow was modelled at the rate used in standard pMDI pharmaceutical testing (28.3 l min⁻¹).

The two press and breathe designs (Figure 6-2) were chosen because they represent very different designs with one having a basic rounded corner rectangular mouthpiece that has many similarities with most commercial designs and could be considered as a generic design, the other has a larger round mouthpiece section (used in the USP throat modelling studies) giving the potential for a different flow structure in the mouthpiece region.

Table 0-7 Variables and settings used in the CFD modelling of the rectangular (generic) actuator design

<table>
<thead>
<tr>
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<td>Equations solved</td>
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<td>Boundary</td>
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Table 0-8 Variables and settings used in the CFD modelling of the round actuator design

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<th>SOLVER</th>
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<th>INLET BOUNDARY</th>
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<td>2nd Order Upwind</td>
</tr>
<tr>
<td>Equations solved</td>
<td>U, V, W, P</td>
<td>Solution algorithm</td>
<td>SIMPLE</td>
</tr>
<tr>
<td>Fluid</td>
<td>Air</td>
<td>Turbulence model</td>
<td>k-e 10%</td>
</tr>
<tr>
<td>Boundary</td>
<td>Vin = 8m/s</td>
<td>Underrelaxation</td>
<td>Default</td>
</tr>
</tbody>
</table>
Appendix

The results from both designs show very similar trends with respect to the airflow through the mouthpiece section. The sudden change in flow direction induces a non-symmetrical flow through the mouthpiece section with an increase in the velocity along the base of the mouthpiece. Figure 0-24 highlights the complex flow around the orifice stem block and the spacing of centre line streamlines in Figure 0-25. Both designs show a re-circulatory region in the top of the mouthpiece.

The Bernoulli theorem predicts that an increase in velocity will be accompanied by a decrease in pressure. The decrease in pressure will induce a differential pressure to act on the spray plume close to its source (exit orifice) and potentially induce a direction change in the spray axis due to the non-symmetrical pressure profile. In the conventional actuator design scenario this will be in a downward direction, the direction induced by the differential pressure gradient.

The degree to which the spray is deflected with be a function of the airflow rate and the flow rate of the spray. It is therefore possible for the direction of the spray to alter not only as a function of design parameters such as the orifice diameter and length, airflow rate, valve volume but also change during the course of a single spray delivery cycle due to the time dependant change in mass flow from the orifice.

In the designs used in the spray visualisation studies the actuator type used there works in a fundamentally difference mode of operation to that found in almost all other actuators used in the delivery of inhaled therapies. In this design layout the airflow enters at the base of the actuator and then turns to exit the mouthpiece thereby changing the fundamental direction of the airflow by 180 degrees and induces the low pressure region at the top of the mouthpiece resulting in a shift in the direction of the spray axis in the upward direction. The theory presented here gives an alternative solution to the directional nature of the plume emitted from a pMDI to that previously proposed(4)

It should be noted that as with all computational based systems the output is only as good as the boundary conditions permit. Only flow through the actuator was modelled
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here and is therefore a function of the outflow boundary which has insufficient length for an ideal solution. The problem results from the re-circulatory flow in the upper region of the mouthpiece and induces an inflow at outflow at the outlet boundary due to insufficient outflow length. The mouthpiece in Figure 0-25 was used in the USP throat modelling where the outlet flow remains horizontal and demonstrates the significance of the outlet boundary geometry and position.

In the cases studied here however the overriding flow principles for momentum based flow field distortion in the flow around a pipe bend will always be valid even though the fine details from design to design may change the outcome and the general principle will always hold true as seen in the CFD modelling of the USP throat with various inlet and outlet boundaries.

Figure 0-24 Rectangular mouthpiece actuator design (‘generic’) showing the non symmetrical flow in the mouthpiece.
Figure 0-25 Round mouthpiece design actuator showing the same generic flow pattern associated with airflow change at a 90 degree bend (streamlines not shown in body of actuator to improve clarity)

A.X ACI data for a formulation showing bounce in the APS impactor stage
References


References


References


References


References


References


References


References


References


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References


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