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A Model of Transient Internal Flow and Atomisation of Propellant/Ethanol Mixtures in Pressurised Metered Dose Inhalers (pMDI)

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Abstract
This paper reports the extension to binary propellant/excipient mixtures of the multiphase model of transient internal flow and atomisation in pressurised metered dose inhalers (pMDIs) of Gavtash et al. (2017a-b) for propellant-only flows. The work considers different accounts of the effect of less volatile ethanol on the saturated vapour pressure (SVP), viscosity and surface tension of HFA-based pMDI formulations. Representation of the SVP of HFA/ethanol mixtures by Raoult's law is compared with the empirical model developed by Gavtash et al. (2016) as well as different theoretical mixing rules for surface tension and viscosity. For initial ethanol contents ranging from 0 to 20% by mass, the temperature, pressure and spray velocity were predicted to be almost independent of ethanol concentration when using the empirical SVP model of Gavtash et al. (2016). The predicted aerosol droplet size increases with increasing concentration of ethanol. These model predictions compare favourably with phase Doppler anemometry (PDA) measurements of pMDI sprays. Exploration of model predictions with different mixing rules suggest that variations of the dynamic viscosity could result in 0.7 µm droplet size change, and different surface tension models yield around 1.5 µm droplet size change. The findings of this work challenge the view that the increase of droplet size is caused by the low volatility of excipients such as ethanol. Instead, attention is focused on composition-dependent viscosity and surface tension as potential...
controlling parameters with significant effect on the droplet size of HFA/ethanol sprays.

1 Introduction
Pressurised metered dose inhalers (pMDIs) for the treatment of diseases such as asthma and COPD are based on liquefied hydrofluoroalkane (HFA) propellants HFA134a and HFA227ea with the active pharmaceutical ingredient (API) in suspension or solution. Ethanol is commonly used to improve the physical/chemical stability of the API and as excipient in marketed solution pMDIs such as Airomir (UCB Pharma), Atrovent Duovent (Boehringer Ingelheim) and Beclojet (Chiesi Farmaceutici SpA) (Pilcer & Amighi, 2010). The presence of ethanol in the formulation is known to cause increases in the mean particle size and reduction the fine particle dose (Whitham & Eagle, 1994; Hickey 1996), which is attributed to changes in the thermophysical properties.

Ethanol is widely thought to cause a significant reduction of the vapour pressure of pMDI formulations. Vapour pressure is known, from early work by Polli et al. (1969) on suspension pMDIs with CFC propellant blends, to be closely linked to pMDI aerosol particle size. Temperature variation was used as the modulator of the vapour pressure and it was observed that increase in vapour pressure resulted in decrease of particle size. Clark (1991) confirmed this inverse relationship between vapour pressure and aerosol particle size for a range of CFC and HFA propellants. This trend was further substantiated for HFA-based propellants by Tzou (1998), Stefely et al. (2000), Smyth et al. (2002) and Smyth & Hickey (2002). To date, several studies have developed empirical correlations to predict initial droplet size of HFA/ethanol binary propellant mixtures, from residual droplet size measured by cascade impactors (Brambilla et al., 1999; Stein and Myrdal, 2004; Ivey et al., 2014). However, the requirement that the residual droplet size must be known limits the predictive capability of these correlations. Whilst the connections between vapour pressure and droplet size and between droplet size and ethanol content are well-established empirically, it is currently not possible to predict the aerosol droplet size produced by HFA/ethanol solution pMDIs from first principles.
This paper reports an extension of the internal flow and atomisation models described in Gavtash et al. (2017a-b) to predict pMDI spray velocity and droplet size for the practically important case of HFA/ethanol mixtures. The homogeneous frozen flow model (HFM) (Gavtash et al., 2017a) is used to determine the mass flow rate and velocity of the pMDI aerosol. The results of this model are linked to the linear sheet instability atomisation (LISA) model (Gavtash et al., 2017b) to predict aerosol droplet size. The numerical method is extended to account for the effect of ethanol concentration on the properties of pMDI aerosols. Two models of the effect of ethanol content on vapour pressure are implemented: Raoult’s law, which assumes a linear relationship between vapour pressure and molar concentration of ethanol, and the empirical expression developed by Gavtash et al. (2016), which captures the measured departures from Raoult’s law in HFA/ethanol mixtures. Predictions of transient aerosol velocity and drop size are compared with phase-Doppler anemometry (PDA) measurements reported previously by Myatt et al. (2015a-b). Furthermore, the outcome is presented of a parametric study to assess the potential effect of dynamic viscosity and surface tension of HFA/ethanol liquid mixture on the predicted droplet size, by using different mixing rules proposed in the literature.

2 Methods
2.1 Conceptual models and assumptions
The model concept of vapour-liquid flow inside pMDI actuators was originally proposed by Fletcher (1975) and Clark (1991) and is illustrated in Figure 1. The liquid phase in solution pMDIs consists of ethanol dissolved in HFA. As the spray event proceeds, evaporation occurs in the metering chamber and expansion chamber. The vapour propels the liquid out of the spray orifice and slip between the vapour and liquid phase is responsible for primary atomisation (see Figure 1a). An implementation of the model for transient propellant-only flows was described by Gavtash et al. (2017a). The following assumptions are involved in its extension to HFA/ethanol mixtures:

- Homogeneous liquid mixture (interpenetrating continua): HFA and ethanol are homogeneously mixed in liquid phase.
- Liquid mixture is an ideal solution, i.e. mixing the components does not produce any change in mixture volume and the enthalpy of mixing is zero.
• Ethanol is a non-evaporating species, so the vapour phase contains HFA vapour only. This justified, because the saturated vapour pressure of ethanol is about two orders of magnitude smaller than the saturated vapour pressure of pharmaceutical HFAs across the prevailing temperature range of 240–300 K.

• Saturated vapour pressure of HFA/ethanol mixtures is evaluated using (1) Raoult’s law and (2) Gavtash et al. (2016) empirical model.

• Viscosity and surface tension are functions of ethanol fraction (mass/molar based) and prevailing temperature (see section 2.2.2).

The homogeneous frozen flow model is used to evaluate the flow of two-phase mixture through the valve orifice and spray orifice. The frozen flow assumption is reasonable, since the residence time of the fluid in each orifice is very short (typically \(\approx 20-30 \, \mu s\)). Frozen flow implies that no evaporation takes place, but pre-existing vapour will expand as a result of isentropic expansion due to the pressure drop as the flow enters the orifice. Residence times in the metering and expansion chambers are around three orders of magnitude larger (typically \(\approx 20-30 \, ms\)) and, following Fletcher (1975), Clark (1991) and Gavtash et al. (2017a), the formulation will be assumed to be in thermodynamic equilibrium in these spaces.

The aerodynamic atomisation model developed by Gavtash et al. (2017b) is used to predict the size of the aerosol droplets produced at the spray orifice. Internal flow visualisation studies of pMDI spray events in transparent nozzles (Versteeg et al., 2006; Versteeg et al., 2017) suggested that a thin annular film on the surface of the spray orifice acts as the precursor liquid ligaments. Gavtash et al. (2017b) showed that the annular film can be approximated by a flat sheet to simplify the calculations. The Linear Instability Sheet Analysis (LISA) framework (Senecal et al., 1999) is used to estimate the growth of wave-induced instabilities at the vapour-liquid interface. The subsequent formation and break-up of unstable ligaments is responsible for sheet disintegration and subsequent formation of droplets (see Figure 1b).

2.2 Mathematical formulation

2.2.1 Thermodynamic properties

The mass fraction of liquid ethanol in the liquid is denoted by \(Y_e\) and defined as follows:
\[ Y_e = \frac{m_{l,e}}{m_{l,H} + m_{l,e}} \]

\( m_l \) represents liquid mass and subscripts \( e \) and \( H \) represent two components of the mixture, ethanol and HFA, respectively. The mass fraction \( Y_H \) of HFA is given by:

\[ Y_H = 1 - Y_e \]

Since HFA is the only evaporating species, the mass fraction of vapour (quality) of the mixture \( x_m \) is equal to the ratio of the mass of HFA vapour, \( m_{g,H} \), and the total mass inside a chamber \( C \), denoted by \( m_{m,C} \):

\[ x_m = \frac{m_{g,H}}{m_{m,C}} = \frac{m_{g,H}}{m_{g,H} + m_{l,H} + m_{l,e}} \]

Linear mass-weighted averages of each species constituent are used to define the respective averages of extensive thermodynamic properties \( \Phi \) (specific enthalpy, specific volume) for the liquid phase \( \bar{\Phi}_l \) in equation 4, and for the entire fluid mixture \( \bar{\Phi}_m \) in equation 5. All mixture constituents' properties are evaluated using REFPROP V.7.0. (National Institute of Standards and Technology, Gaithersburg, MD, USA).

\[ \bar{\Phi}_l = Y_H \Phi_{l,H}(T) + Y_e \Phi_{l,e}(T) \]

\[ \bar{\Phi}_m = x_m \Phi_g(T) + (1 - x_m) \left[ Y_H \Phi_{l,H}(T) + Y_e \Phi_{l,e}(T) \right] \]

### 2.2.2 Transport properties: mixture viscosity and surface tension

Dynamic viscosity and surface tension of HFA/ethanol liquid mixture are two key transport properties in the LISA atomisation model (Senecal et al., 1999; Gavtash et al., 2017b), which affect the spray droplet size. At present, the estimation of these transport properties for HFA/ethanol binary mixture requires experimental data to quantify the interaction between HFA and ethanol molecules in the mixture (Reid et al., 1987; Perry et al., 1997). In absence of comprehensive data, four different mixing rules for composition-dependent viscosity and surface tension, based on mass and molar weighting of the constituent fractions are considered.

For mixture viscosity, the following linear mass-weighted mixing rule is widely implemented as the default model in commercial CFD codes such as Ansys-Fluent (2009) and Star-CCM+ (2015):
\[ \tilde{\mu}_i = Y_H \mu_{i,H}(T) + Y_e \mu_{i,e}(T) \]

Where \( \tilde{\mu}_i \) is the mixture dynamic viscosity and \( \mu \) is the dynamic viscosity of each constituent species.

Mole fraction weighting is also considered where the mole fraction of ethanol, \( X_e \), can be calculated from the corresponding ethanol mass fraction, \( Y_e \), using the following expression:

\[ X_e = \frac{M_H Y_e}{M_e (1 - Y_e) + M_H Y_e} \]  

and

\[ X_H = 1 - X_e \]

\( M_H \) and \( M_e \) are the molar masses of HFA and ethanol, respectively.

The average mixture viscosity using mole fraction weighted interpolation is represented by the following expression:

\[ \tilde{\mu}_i^n = X_H \mu_{i,H}^n(T) + X_e \mu_{i,e}^n(T) \]

Equation 8 has been used in the literature in conjunction with \( n = 1 \) and \( n = -1 \). Use of exponent value \( n = 1 \) generally yields the highest mixture viscosity value, whereas \( n = -1 \) gives the lowest value (Nielsen, 1978). The Arrhenius model (Reid et al. 1987; Perry et al. 1997) of mixture viscosity for ideal mixtures is also considered here:

\[ \ln \tilde{\mu}_i = X_H \ln \mu_{i,H}(T) + X_e \ln \mu_{i,e}(T) \]

The mixture surface tension, \( \tilde{\sigma}_i \), is routinely predicted in commercial CFD codes by means of linear mass-weighting mixing rule as shown by equation 10 (Ansys-Fluent, 2009; Star-CCM+ 2015):

\[ \tilde{\sigma}_i = Y_H \sigma_{i,H}(T) + Y_e \sigma_{i,e}(T) \]
In the present work, the mixture surface tension is also evaluated using molar fraction weighted interpolation by means of equation 11 in conjunction with the following three values of exponent $n = -1, 1$ and $-3$ (Reid et al. 1987):

$$\bar{\sigma}_i^n = X_H \sigma_{iH}^n(T) + X_e \sigma_{ie}^n(T)$$

Hadden (1966) suggests using $n = 1$ for hydrocarbon mixtures, but experiments indicated a closer match with $n = 1$ and $-3$ (Reid et al. 1987).

Figure S1 and S2 (see SI - section S.1 of this article) show the predicted viscosity and surface tension values of HFA134a/ethanol mixture, using the afore-mentioned mixing rules, as a function of ethanol concentration at different candidate temperatures. The viscosity and surface tension values of pure liquids are evaluated using REFPROP V.7.0. (National Institute of Standards and Technology, Gaithersburg, MD, USA).

### 2.2.3 Models for saturated vapour pressure of HFA/ethanol mixtures

Raoult's law states that the saturated vapour pressure $p_m$ of an HFA/ethanol mixture can be evaluated as a mole fraction weighted average of the saturated vapour pressures $p_e$ and $p_H$ of the constituents at the prevailing temperature $T$:

$$p_m(X_e, T) = [(1 - X_e)(p_H(T) - p_e(T)) + p_e(T)$$

This expression has been used in numerical models of HFA/ethanol mixtures by Ju et al. (2010). However, departures from Raoult’s law have been reported by Vervaet and Byron (1999), Smyth et al. (2002), Kleiner and Sadowski (2007) and Mason et al. (2014). Recently, Gavtash et al. (2016) developed an expression which captures measured deviations from Raoult’s law of the saturated vapour pressure of mixtures of HFA134a/ethanol and HFA227ea/ethanol:

$$p_m(X_e, T) = [(1 - X_e)(1 + f(X_e, T))(p_H(T) - p_e(T)) + p_e(T)$$

where $f(X_e, T)$ is the departure function having the following form:

$$f(X_e, T) = aX_e + bX_e^2 + cX_eT + dX_e^3 + eX_e^2T + fX_eT^2$$

Constants of equation 14 are summarised for HFA134a/ethanol and HFA227ea/ethanol mixtures in Table S1 (see SI - section S.2 of this article).
2.2.4 Multicomponent, multiphase mixture flow through orifices

The set of expressions required to calculate mass velocity of a homogeneous two-phase flow through orifices, under sub-critical/critical conditions is summarised in Table S2 (see section SI - S.3.1 of this article). These equations follow Fletcher (1975) and Clark (1991) and are comprehensively described in Gavtash et al. (2017a) for propellants-only flows. Use of these expressions for HFA/ethanol binary mixtures involves the application of the thermodynamic properties representations introduced in sections 2.2.1 and 2.2.3.

2.2.5 Fluid state inside metering chamber and expansion chamber

The metering chamber and expansion chamber are assumed to be at thermodynamic equilibrium. Thermodynamic properties of the multicomponent two-phase mixture are functions of the prevailing temperature and species mass fraction in the liquid phase. Equations 15 and 16 are used to evaluate average specific volume and specific enthalpy of the two-phase mixture:

\[
\bar{\nu}_m = \frac{m_{m,C}}{V_{ol_C}} = x_m \nu_g(T) + (1 - x_m)[Y_H \nu_{l,H}(T) + Y_e \nu_{l,e}(T)]
\]

\[
\bar{h}_m = \frac{H_{m,C}}{m_{m,C}} = x_m h_g(T) + (1 - x_m)[Y_H h_{l,H}(T) + Y_e h_{l,e}(T)]
\]

Where subscript \( C \) refers to chamber. \( \nu \) and \( h \) are specific volume and specific enthalpy, respectively. \( m_{m,C} \) is the total mass of the multicomponent, two-phase mixture of chamber \( C \) and \( V_{ol_C} \) is the chamber volume. The mixture quality \( x_m \) can be eliminated from equations 15 and 16, which yields:

\[
\frac{\bar{\nu}_m - Y_H \nu_{l,H}(T) + (Y_H - 1) \nu_{l,e}(T)}{\nu_g(T) - Y_H \nu_{l,H}(T) + (Y_H - 1) \nu_{l,e}(T)} = \frac{\bar{h}_m - Y_H h_{l,H}(T) + (Y_H - 1) h_{l,e}(T)}{h_g(T) - Y_H h_{l,H}(T) + (Y_H - 1) h_{l,e}(T)} = 0
\]

Equation 17 is a nonlinear equation with temperature \( T \) and HFA mass fraction \( Y_H \) of the liquid phase as the unknowns. As evaporation takes place and HFA mass transfers from the liquid to the vapour phase, the liquid becomes progressively more enriched with ethanol. Equation 17 can be solved using an iterative approach based around a Newton-Raphson root finding routine to find the mixture temperature \( T \). The HFA mass fraction \( Y_H \) of the liquid phase is found from the mass balance of the formulation constituents: i.e. from the total mass of formulation in the chamber \( C \), the
mixture quality $x_m$ and the condition that ethanol is not present in the vapour phase.

The solution procedure is as follows:

1. Initial guess of $Y_H^*$, (in practice the last calculated value is used).
2. Solve equation 17 for $T$ using a Newton-Raphson root finding routine.
3. Calculate $x_m$ from equation 15 (or 16) using calculated $T$ from Step 2, and guessed $Y_H^*$ value from Step 1.
4. Evaluate mixture constituents' masses ($m_g$, $m_{l,H}$ and $m_{l,\ell}$) based on species specific volume at $T$.
5. Calculate new value of $Y_H^*$ from equations 1 and 2.
6. Iterate Steps 1-5 until the following criterion is satisfied:

$$\left| Y_H - Y_H^* \right| \leq \varepsilon$$

where $\varepsilon$ is set to 0.001.

Using the quasi-steady assumption (Gavtash et al., 2017a), the instantaneous multicomponent mixture mass $m_{m,c}$ and enthalpy $H_{m,c}$ in a chamber at time $t$ is determined by applying mass and energy conservation given by equations 19 and 20 to the chamber.

$$m_{m,c}(t) = m_{m,c}(0) + \int_{\tau=0}^{\tau=t} \dot{m}_{m,c,in}(\tau)d\tau - \int_{\tau=0}^{\tau=t} \dot{m}_{m,c,out}(\tau)d\tau$$

$$H_{m,c}(t) = H_{m,c}(0) + \text{Vol}_c[p_{m}(0) - p_m(t)] + \int_{\tau=0}^{\tau=t} \dot{h}_{m,c,in}(\tau)d\tau - \int_{\tau=0}^{\tau=t} \dot{h}_{m,c,out}(\tau)d\tau$$

$m_{m,c}(0)$ and $H_{m,c}(0)$ are initial mass and enthalpy of the multicomponent mixture inside a chamber and subscripts $\text{in}/\text{out}$ denotes inflow and outflow of mass and enthalpy. For the sake of simplicity, the Euler forward differencing numerical algorithm was chosen to solve equations 19 and 20.

### 2.2.6 Multicomponent atomisation

As described in section 2.1 and schematically shown in Figure 1b, the atomisation model assumes an annular liquid film inside the spray orifice, which is approximated as a flat sheet. Therefore, the linear sheet instability atomisation (LISA) framework developed by Senecal et al. (1999) can be used to estimate the droplet size. The
details of the model and justification of flat sheet approximation were set out in Gavtash et al. (2017b). The expressions are modified to incorporate the effect of ethanol content on mixture properties by using the expression described in section 2.2.1 and 2.2.2 for the transport properties and thermodynamic properties. The relevant expressions are summarised in Tables S3 and S4 (see SI - section S.3.2 of this article), where the theory of flat sheet disintegration is also briefly described.

2.2.7 Near-orifice spray acceleration and droplet flashing

As discussed in Gavtash et al. (2017a), in choked conditions, the pressure at the spray orifice exit is higher than the downstream atmospheric pressure. This imbalance of pressure results in rapid spray acceleration in the near-orifice region. Furthermore, according to Gavtash et al. (2017b) the calculated temperature of the propellant at the spray orifice exit suggests that the emerging droplet is superheated. Therefore, the superheated propellant fraction will flash off in the near-orifice region, which results in reduction of size, mass and HFA content of the droplets. Near orifice velocity and droplet size can be calculated using the expressions of Table S5 (see SI - section S.3.3 of this article).

2.3 Model validation approach

The spray velocity and droplet size predicted by the numerical models were compared with phase Doppler anemometry (PDA) measurements from Myatt et al. (2015a-b) for HFA134a/ethanol mixture formulations, using Bespak 630 series actuator. The PDA data was acquired at a distance \( z = 15 \) mm from the spray orifice and were ensemble averaged over 10 ms time bins. The relevant actuator/test parameters for each PDA study are summarised in Table S6 (see SI - section S.4 of this article).

As described by Gavtash et al. (2017a) direct comparison of model velocity predictions against PDA data requires knowledge of the axial decay rate of spray velocity and droplet size. This is essential to extrapolate the data at the PDA measurement location back to the near-orifice region where the results of the flow model and atomisation model are valid. This axial trend was accounted for by developing empirical correlations which were implemented to extrapolate PDA measurements to the near-orifice region. The details of the analysis and the final correlations are presented in section SI (see SI - section S.5 of this article).
3 Results and discussion

3.1 Chambers pressure and temperature

After the pMDI is actuated, the HFA/ethanol mixture in the metering chamber is exposed to ambient pressure. Propellant starts to evaporate and propels the fluid through the valve orifice into the expansion chamber and, hence, out of the actuator through the spray orifice. The pressure and temperature in the metering chamber experience a monotonic decrease with time (see SI - Figure S4 and S5; section S.6 of this article). Figures 2 and 3 show comparisons of the predicted temporal distributions of pressure and temperature of the fluid in the expansion chamber for four different initial ethanol concentrations $Y_{e,0} = 0, 5, 10$ and $20\%$ by mass. Two representations of the saturated vapour pressure are considered: (a) Raoult's law, and (b) the empirical SVP model of Gavtash et al., (2016).

The predictions in Figure 2a show a strong dependence of predicted pressure on initial ethanol content if the vapour pressure is evaluated with Raoult’s law. The predicted peak pressure in expansion chamber reduces from 5.5 to 3.5 bar as the initial ethanol content increases from $Y_{e,0} = 0\%$ to $Y_{e,0} = 20\%$ by mass. The results based on the Gavtash et al. (2016) SVP model in Figure 2b, on the other hand, predict a small effect of ethanol concentration: minor differences occur only as the initial ethanol content changes from $Y_{e,0} = 0\%$ to $Y_{e,0} = 5\%$.

Figure 3a-b show the corresponding predictions of expansion chamber temperature. These also depend more strongly on ethanol concentration when Raoult’s law is used to predict saturated vapour pressure. The final temperature in Figure 3a varies from 247K to 260K, respectively. The Gavtash et al. (2016) SVP model returns temperature traces with differences smaller than 4 K for different ethanol concentrations. The reasons behind the differences between the predicted fluid states in the actuator are explored in more detail in the Supplementary Information. The paths connecting fluid pressure, ethanol mole fraction and temperature as the metered spray event progresses are illustrated in Figure S6 and S7 (see SI - section S.6 of this article) for predictions with Raoult’s law and the Gavtash et al. (2016) SVP model.
3.2 Velocity and droplet size

Comparisons of the predicted velocity and droplet size with PDA data of Myatt et al. (2015 a-b) are presented in Figures 4 and 5 for initial ethanol concentrations $Y_{e,0} = 5$ and 20% w/w. Predictions for $Y_{e,0} = 10\%$ w/w can be found in Figure S8 (see SI – section S.7 of this article). PDA data extrapolated to the near-orifice region (NO; dashed lines) are compared with model predictions generated with Raoult’s law and the Gavtash et al. (2016) SVP model. The mixture viscosity and surface tension were evaluated using equations 6 and 10, respectively (i.e. linear mass fraction weighted).

Figure 4a-b show that the temporal trends of the spray velocity, including the timing of the extrema corresponding to different stages of the actuation event, are reasonably well captured by the multicomponent flow model for the first 200 ms of the actuation event. This portion of the predicted traces, shown as a solid line, corresponds to the time interval $\tau_{95\%}$ during which 95% of the original metering chamber mass $m_{m,c}$ is emitted through the spray orifice: i.e. $\sum_{t=0}^{t=\tau_{95\%}} m_{SO}(t)/m_{m,c} = 0.95$. Model calculations predict an abrupt end to the spray event around 250 ms for all of the formulations. This behaviour is associated with the adiabatic assumption made in this model, which causes cooling of the mixture as HFA evaporates and rapidly reduces the pressure of the mixture to atmospheric pressure. The PDA data, on the other hand, shows a more gradual velocity decay. Gavtash et al. (2017a) attributed this behaviour to slow evaporation of formulation remnants inside the actuator body emitting spray in the form of intermittent “puffs”. It is expected that heat transfer between the formulation and the actuator walls plays a role at this stage. Representation of the final stages of the actuation event, which emit the last 5% of the formulation mass was outside the scope of the present work. These parts of the prediction traces are shown as dashed lines indicating reduced confidence.

Table 1 compares event-averages from the start of the spray event up to $t = \tau_{95\%}$ of the predicted velocity traces with extrapolated PDA data. The differences are generally small when the empirical SVP model of Gavtash et al. (2016) is used. The maximum deviation of 3% occurs at $Y_{e,0} = 10\%$. On the other hand, predictions based on Raoult’s law show progressively larger deviation from measured data as ethanol concentration increases. Raoult’s law predicts a reduction of the saturated vapour
pressure with increasing ethanol content. This yields lower expansion chamber pressures, so less energy is available for spray generation and acceleration. Measurements reported in Gavtash et al. (2016) showed a strong positive deviation from Raoult’s law for HFA/ethanol mixtures. Hence, the available energy does not reduce significantly as the ethanol content increases to 20% w/w, maintaining high levels of spray velocity.

The predicted temporal trends of droplet size are compared with measured $D_{10}$ and $D_{32}$ in Figure 5a-b (see also Figure S.8b). The initial peak and subsequent gradual decrease in droplet size are well captured by the model. A closer look at the PDA data in Figures 5a and 5b reveals that the droplet size $D_{10}$ increases with ethanol concentration during the first 200 ms, whereas $D_{32}$ does not change significantly. Comparison of Figures 4 and 5 shows that the inverse relationship between velocity and droplet size, which is present in the measured data, is adequately captured by model predictions. This confirms the previous findings of Baeckstroem and Nilsson (1988) and Harnor et al. (1993) for CFC formulations, as well as those of Clark (1991) and Wigley et al. (2002) for HFA formulation. It should be noted that the LISA model predicts a “characteristic droplet size”. In the literature, the predictions of this model are usually compared with measured SMD ($D_{32}$) values (Senecal et al., 1999; Schmidt et al., 1999; Shim et al., 2008). However, it is not clear whether this practice necessarily applies to pMDIs, which produce sprays with much smaller droplet size than typical industrial airblast or air-assist atomisers. This work shows that the atomisation model predictions of droplet size are closer to the measured trends of $D_{10}$.

Table 2 presents event-averages up to $t = \tau_{95\%}$ of the predicted temporal traces and PDA data for $D_{10}$ and $D_{32}$. Raoult’s law predicts a 75% increase in the event-averaged droplet size as ethanol content increases to 20% by mass. Such a strong increase is not detectable in the measured data. The trend in the event-averaged values of $D_{10}$ is best captured when the empirical model of Gavtash et al. (2016) is used to compute the saturated vapour pressure.

The assumed mechanism of primary atomisation is aerodynamic, so fluid kinetic energy in the spray orifice is the energy source for atomisation. The vapour pressure in the expansion chamber is the driving force for acceleration of the flow in the spray
orifice. Accurate representation of the effect of composition on saturated vapour pressure clearly plays a key role in the prediction of aerosol velocity and, hence, droplet size of pMDI formulations containing less volatile excipients, such as ethanol.

### 3.3 Effect of viscosity and surface tension

The measured event-averaged spray velocity was almost independent of ethanol content (Table 1), but the droplet size was found to increase with increasing ethanol concentration (Table 2). Therefore, the changes in pMDI aerosol droplet size should be attributable to the effects on atomisation of variations other than the vapour pressure of the formulation. Two key transport properties that are known to affect aerodynamic atomisation are the dynamic viscosity and surface tension. Experimental data for the viscosity and surface tension of pharmaceutically-relevant HFA/ethanol mixtures is not available to the knowledge of the present authors. In absence of these, this section theoretically examines the possibility that the presence of ethanol can cause sufficiently large variations of mixture viscosity and surface tension to affect the aerosol droplet size. An order-of-magnitude estimate of the effect on atomisation of typical changes of these transport properties is attempted by comparing the results of the atomisation model for the various mixing rules presented in section 2.2.2.

Results of this comparison are presented in Figure 6a-b for initial ethanol mass fraction $Y_{e,0} = 20\%$. This condition was considered here, because different mixing rules yield the widest range of viscosity and surface tension values at the highest initial ethanol concentration. Figure 6a considers the effect of viscosity on droplet size: four different mixing rules for dynamic viscosity (i.e. equations 6, 8 with $n = \pm 1$ and equation 9) are applied in conjunction with mass-weighted averaging to predict the surface tension of the mixture (equation 10). In Figure 6b the surface tension is predicted with four different mixing rules (equation 10 and equation 11 with $n = \pm 1$ and $-3$) together with mass-weighted averaging to compute the mixture viscosity (equation 6). The empirical model of Gavtash et al. (2016) is used to compute the saturated vapour pressure of the mixture in all cases. The magnitude of the predicted droplet sizes compares reasonably well with the PDA measurements for all
mixing rules. As noted earlier, it is not clear for pMDI sprays whether the predictions of the atomisation model should be compared with $D_{10}$ or $D_{32}$, so no attempt is made at present to comment on the superiority of any of the mixing rules.

Inspection of the results in Figures 6a-b shows that the predicted droplet size changes by around 0.7 $\mu$m size by using different mixing rules for viscosity, and by 1.5 $\mu$m when different surface tension models are used. The temporal variations of viscosity and surface tension inside the expansion chamber that occur as the actuation event progresses are illustrated in Figure S9a-b (see SI - section S.7 of this article). Differences of around 40% of dynamic viscosity and 20% of surface tension are predicted when different mixing rules are applied. Figure 6a-b suggests that these variations result in almost 12% and 21% variation in the predicted maximum droplet size, respectively.

Viscosity and surface tension are, of course, well-known properties that influence the droplet size in aerodynamic type industrial atomisers (Lefebvre, 1989). Smyth (2003) has suggested that addition of ethanol to HFA-based pMDI formulations alters the mixture viscosity and surface tension and noted that this could potentially change atomisation quality of pMDIs. Villermaux (2007) shows that viscous effects can cause reduction of droplet size if ligaments are stretched sufficiently rapidly along their length. The experiments in the present work suggest the opposite trend: an increase of the droplet size $D_{10}$ as the ethanol content - and hence, viscosity - increases. The conceptual model of Senecal’s LISA model used in the present work involves the formation of circumferential ligaments. These ligaments are assumed to develop circumferential instability without stretching. The droplet sizes predicted by the model increase with viscosity, in line with the experimental results. Further work is clearly needed to determine the exact sequence of events responsible for primary atomisation in pMDIs. However, the findings of this study confirm that variations of viscosity and surface tension with plausible magnitude can produce significant changes of the droplet size of HFA/ethanol sprays.

4 Concluding remarks

Most of the published pMDI literature suggests that atomisation quality is mainly controlled by the saturated vapour pressure of the formulation. Moreover, it is
asserted that droplet size increases when less volatile excipients such as ethanol are added to the formulation, because ethanol reduces the saturated vapour pressure. The models of flow and atomisation of HFA/ethanol mixtures by a pMDI, presented in this paper, suggest that the assumed connection between ethanol content and saturated vapour pressure needs to be re-examined.

Measurements have shown that saturated vapour pressure is only weakly dependent on ethanol. When the internal flow and atomisation models are run in conjunction with an empirical correlation based on these measurements of saturated vapour pressure of HFA/ethanol mixtures, they predict that the spray velocity is substantially unaffected by ethanol concentration. This prediction agrees with PDA velocity data for pMDI sprays in the near-orifice region.

The droplet size predicted by the atomisation model and the measured $D_{10}$ values of pMDI aerosols were found to increase as ethanol concentration increased. This is unexpected if the aerosol droplet size is only controlled by saturated vapour pressure of the pMDI formulation. An exploration of different mixing rules for dynamic viscosity and surface tension models indicated that typical variations of these transport properties as a function of ethanol content could be responsible for significant variations of the droplet size. This finding is in line with recent work by Myatt et al. (2015b) and stresses the need for further work to characterise the thermophysical and transport properties of pMDI formulations.

5 Acknowledgement

The authors gratefully acknowledge financial support for this research by Chiesi Farmaceutici SpA.

6 References


Gavtash, B., Versteeg, H.K., Hargrave, G., Myatt, B., Lewis, D., Church, T. and Brambilla, G. (2017a). Transient flashing propellant models to predict internal flow characteristics, spray velocity, and aerosol droplet size of a pMDI. Aerosol Science and Technology, **51** (5): 564–575


Ivey, J.W., Lewis, D., Church, T., Finlay, W.H. and Vehring, R. (2014). A correlation equation for the mass median aerodynamic diameter of the aerosol emitted by


Figure 1. Schematic of mixture flow and atomisation models
(a) Mixture constituents and mixture formulation flow state inside metering valve
(b) Mixture formulation flow inside the spray orifice, perturbed liquid sheet and droplet formation using LISA mechanism

Figure 2 Temporal evolution of formulation pressure inside pMDI expansion chamber for two different models of saturated vapour pressure of HFA/ethanol mixtures
(a) Raoult’s law
(b) Gavtash et al. (2016) empirical model

Figure 3 Temporal evolution of formulation temperature inside pMDI expansion chamber for two different models of saturated vapour pressure of HFA/ethanol mixtures
(a) Raoult’s law
(b) Gavtash et al. (2016) empirical model

Figure 4 Comparison of predictions and extrapolated PDA data of spray velocity in near-orifice region for initial ethanol concentration $Y_{e,0}=5\%$ and $20\%$ w/w
(a) $Y_{e,0}=5\%$
(b) $Y_{e,0}=20\%$

Figure 5 Comparison of predictions and measured PDA data of spray droplet size in near-orifice region for initial ethanol concentration $Y_{e,0}=5\%$ and $20\%$ w/w
(a) $Y_{e,0}=5\%$
(b) $Y_{e,0}=20\%$

Figure 6 Predicted HFA134/ethanol droplet size using different viscosity/surface tension mixture model representations, for $Y_{e,0} =20\%$ ethanol mass fraction
(a) Comparison of mixing rules for dynamic viscosity (surface tension predicted with Equation 10)
(b) Comparison of mixing rules for surface tension (dynamic viscosity predicted with Equation 6)

Table 1 Event-averaged aerosol velocity for HFA/ethanol mixtures over duration of 95% mass emission

Table 2 Event-averaged aerosol droplet size for HFA/ethanol mixtures over duration of 95% mass emission
A Model of Transient Internal Flow and Atomisation of Propellant/Ethanol Mixtures in Pressurised Metered Dose Inhalers (pMDI)

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<table>
<thead>
<tr>
<th>Ethanol content (w/w %)</th>
<th>PDA at 15 mm (Extrapolated to 10 mm)</th>
<th>Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Raoult’s law</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SVP model</td>
</tr>
<tr>
<td>5</td>
<td>63.99</td>
<td>60.73</td>
</tr>
<tr>
<td>10</td>
<td>63.84</td>
<td>55.17</td>
</tr>
<tr>
<td>20</td>
<td>67.89</td>
<td>42.44</td>
</tr>
</tbody>
</table>

Table 1 Event-averaged aerosol velocity for HFA/ethanol mixtures over duration of 95% mass emission

<table>
<thead>
<tr>
<th>Ethanol content (w/w %)</th>
<th>PDA (Myatt et al. 2015 a)</th>
<th>Predictions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Raoult’s law</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SVP model</td>
</tr>
<tr>
<td>5</td>
<td>2.73</td>
<td>4.27</td>
</tr>
<tr>
<td>10</td>
<td>2.74</td>
<td>5.16</td>
</tr>
<tr>
<td>20</td>
<td>3.34</td>
<td>8.19</td>
</tr>
</tbody>
</table>

Table 2 Event-averaged aerosol droplet size for HFA/ethanol mixtures over duration of 95% mass emission
Figure 1. Schematic of mixture flow and atomisation models (a) Mixture constituents and mixture formulation flow state inside metering valve

158x144mm (96 x 96 DPI)
Figure 1. Schematic of mixture flow and atomisation models (b) Mixture formulation flow inside the spray orifice, perturbed liquid sheet and droplet formation using LISA mechanism

149x143mm (96 x 96 DPI)
Figure 2 Temporal evolution of formulation pressure inside pMDI expansion chamber for two different models of saturated vapour pressure of HFA/ethanol mixtures (a) Raoult’s law

123x100mm (96 x 96 DPI)
Figure 2 Temporal evolution of formulation pressure inside pMDI expansion chamber for two different models of saturated vapour pressure of HFA/ethanol mixtures (b) Gavtash et al. (2016) empirical model
Figure 3 Temporal evolution of formulation temperature inside pMDI expansion chamber for two different models of saturated vapour pressure of HFA/ethanol mixtures (a) Raoult’s law

128x94mm (96 x 96 DPI)
Figure 3 Temporal evolution of formulation temperature inside pMDI expansion chamber for two different models of saturated vapour pressure of HFA/ethanol mixtures (b) Gavtash et al. (2016) empirical model
Figure 4 Comparison of predictions and extrapolated PDA data of spray velocity in near-orifice region for initial ethanol concentration $Y_{(e,0)} = 5\%$ and 20\% w/w (a) $Y_{(e,0)} = 5\%$

149x123mm (96 x 96 DPI)
Figure 4 Comparison of predictions and extrapolated PDA data of spray velocity in near-orifice region for initial ethanol concentration $Y_{(e,0)} = 5\%$ and $20\%$ w/w (b) $Y_{(e,0)} = 20\%$

146x126mm (96 x 96 DPI)
Figure 5 Comparison of predictions and measured PDA data of spray droplet size in near-orifice region for initial ethanol concentration $Y_{(e,0)} = 5\%$ and 20\% w/w (a) $Y_{(e,0)} = 5\%$

145x124mm (96 x 96 DPI)
Figure 5 Comparison of predictions and measured PDA data of spray droplet size in near-orifice region for initial ethanol concentration $Y_{(e,0)} = 5\%$ and $20\%$ w/w (b) $Y_{(e,0)} = 20\%$

157x129mm (96 x 96 DPI)
Figure 6 Predicted HFA134/ethanol droplet size using different viscosity/surface tension mixture model representations, for $Y_{(e,0)} = 20\%$ ethanol mass fraction (a) Comparison of mixing rules for dynamic viscosity (surface tension predicted with Equation 10)

153x125mm (96 x 96 DPI)
Figure 6 Predicted HFA134/ethanol droplet size using different viscosity/surface tension mixture model representations, for $Y_{e,0} = 20\%$ ethanol mass fraction (b) Comparison of mixing rules for surface tension (dynamic viscosity predicted with Equation 6)

152x120mm (96 x 96 DPI)
SUPPLEMENTARY INFORMATION

A Model of Transient Internal Flow and Atomisation of Propellant/Ethanol Mixtures in Pressurised Metered Dose Inhalers (pMDI)

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S.1 Comparison of surface tension/viscosity values using different models

Figure S1. HFA134a/ethanol mixture dynamic viscosity as a function of ethanol partial fraction, using different mixing rules

(a) T=250 K
(b) T=275 K
(c) T=295 K

Figure S2. HFA134a/ethanol mixture surface tension as a function of ethanol partial fraction, using different mixing rules

(a) T=250 K
(b) T=275 K
(c) T=295 K
The values are predicted using the mixing rules described in section 2.3.2. The values are predicted at 250 K, 275 K and 295 K which are the lowest, intermediate and highest temperature values used in our modelling, respectively.

### S.2 Constants for saturated vapour pressure departure function

Constants for equation 14 of Gavtash et al., (2016) empirical vapour pressure model:

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>$a$</th>
<th>$b$</th>
<th>$c$</th>
<th>$d$</th>
<th>$e$</th>
<th>$f$</th>
</tr>
</thead>
<tbody>
<tr>
<td>HFA134a</td>
<td>-57.73</td>
<td>4.325</td>
<td>0.4202</td>
<td>0.01125</td>
<td>-0.005239</td>
<td>-0.000759</td>
</tr>
<tr>
<td>HFA227ea</td>
<td>0.613</td>
<td>-6.784</td>
<td>0.0171</td>
<td>-2.666</td>
<td>0.03957</td>
<td>$-7.149 \times 10^{-5}$</td>
</tr>
</tbody>
</table>

Table S1. Saturated vapour pressure polynomial departure function coefficients for mixtures of HFA/ethanol
S.3 Tables of mathematical expressions

S.3.1 Multicomponent, multiphase mixture flow through orifices

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mathematical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Mass-velocity</td>
<td>( G_{m,t} = C_d \left( \frac{p_{m,0}}{v_{m,0}^2 \rho_{g,0}} \left( \frac{1 - x_{m,0}}{x_{m,0}} \right) \left( \frac{v_{1,0}}{v_{g,0}} \right) \frac{2 \eta^2}{\gamma} \right)^{\frac{1}{2}} \left( \frac{1 - x_{m,0}}{x_{m,0}} \right) \left( \frac{v_{1,0}}{v_{g,0}} \right) \left( 1 - \frac{\eta}{\gamma} \right) \left( 1 - \frac{1 - \eta}{\gamma} \right) \right)^{\frac{1}{2}} )</td>
</tr>
<tr>
<td>2 Subcritical pressure ratio</td>
<td>( \eta = \frac{p_{t,m}}{p_{0,m}} )</td>
</tr>
<tr>
<td>3 Critical pressure ratio (Fletcher, 1975)</td>
<td>( \left( \frac{1}{\eta_c} - 1 \right) + X_c \frac{\gamma}{\gamma - 1} \left( \frac{1 - \eta}{\eta_c} - 1 \right) = \frac{\gamma X_c}{2} \left( \frac{1}{X_c} + 1 \right)^2 )</td>
</tr>
</tbody>
</table>

where:

\( \frac{1}{X_c} = \left( \frac{1 - x_{m,0}}{x_{0,m}} \right) \left( \frac{w_{1,0}}{v_{g,0}} \right) \left( \frac{1}{\eta_c} \right) \)

Table S2. Homogenous Frozen Model (HFM) expressions required to predict mass-velocity through valve and spray orifices of pMDI (Clark 1991; Gavtash et al., 2017a)

In the expressions of Table S2, subscript \( t \) and \( 0 \) represents conditions at the orifice throat (i.e. narrowest cross-section) and in the supply reservoir, respectively. Subscript \( m \) represents the properties of the multicomponent, two-phase mixture and subscript \( c \) represents the critical condition (choked flow). The quality \( x_{m,0} \) of the mixture in the upstream reservoir that feeds the orifice is calculated from the instantaneous mixture composition using equation 3. The average specific volume of liquid phase, \( \bar{v}_{1,0} \), can be calculated with equation 4. Finally, \( v_{g,0} \), the specific volume of the HFA vapour phase, is evaluated from the local pressure and temperature.

S.3.2 Multicomponent atomisation

The theory of disintegration and breakup of flat liquid sheets involves a dispersion equation for the evolution of initially small disturbances. Solutions to the dispersion equation recognise two wave-generation regimes, namely short waves and long...
waves. These are distinguished on the basis of the gas-phase cut-off Weber number, $We_{g,h}$, using the liquid half sheet thickness of $h/2$, as the characteristic length (Senecal et al., 1999). If $We_{g,h} \geq 27/16$, then short waves are generated, otherwise the long wave is the dominant regime. For convenience of the readers, we summarise the key mathematical expressions used to calculate the droplet size, in Table S3 and S4.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mathematical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Cut-off Weber number (-)</td>
<td>$We_{g,h} = \frac{\rho_g V^2 h}{2\sigma_l}$</td>
</tr>
<tr>
<td>2 Sheet thickness (m)</td>
<td>$h = \frac{D_{so}}{2} (1 - \sqrt{\alpha})$</td>
</tr>
<tr>
<td>3 Void fraction (-)</td>
<td>$\alpha = \frac{1}{1 + \left(\frac{1 - \chi_m}{\chi_m}\right) \left(\frac{v_l}{v_g}\right)}$</td>
</tr>
</tbody>
</table>

Table S3. Expressions required to estimate cut-off Weber number to identify the dominant wave regime (Senecal et al., 1999; Gavtash et al., 2017b)
<table>
<thead>
<tr>
<th>Variable</th>
<th>Mathematical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Droplet size (m)</td>
<td>(D_{d,SO} = 1.88d_{tg}(1 + 30h)^{1/6})</td>
</tr>
<tr>
<td>2 Ohnesorge number (-)</td>
<td>(Oh = \sqrt{\frac{\bar{v}_l\mu^3}{\bar{\sigma}<em>t d</em>{tg}}})</td>
</tr>
<tr>
<td>3 Ligament diameter (m)</td>
<td>(d_{tg} = \frac{2\pi C_{tg}}{K_s})</td>
</tr>
<tr>
<td>4 Wave number (1/m)</td>
<td>(K_s = \frac{d \left(-2\bar{v}_l k^2 + \sqrt{4\bar{v}_l^2 k^4 + \Gamma V^2 k^2 - \bar{\sigma}_l k^3} \right)}{d k} = 0)</td>
</tr>
<tr>
<td>5 Ligament diameter (m)</td>
<td>(d_{tg} = \frac{4h}{K_s})</td>
</tr>
<tr>
<td>6 Wave number (1/m)</td>
<td>(K_s = \frac{\rho_g V^2}{2\bar{\sigma}_l})</td>
</tr>
</tbody>
</table>

**Short wave regime \((We_{gh} \geq 27/16)\)**

\(d_{tg} = \frac{2\pi C_{tg}}{K_s}\)

where: \(C_{tg} = 0.5\) \(\text{(Hutcheson et al., 2008; Ghose et al., 2014)}\)

**Long wave regime \((We_{gh} < 27/16)\)**

\(d_{tg} = \frac{4h}{K_s}\)

\(K_s = \frac{\rho_g V^2}{2\bar{\sigma}_l}\)

Table S4. Expressions required to predict droplet size of multicomponent two-phase mixture of HFA/ethanol, using LISA framework \(\text{(Senecal et al., 1999; Gavtash et al., 2017b)}\)

In the expressions summarised in Table S3, \(V\) is the average two-phase velocity and \(\rho_g\) is the density of HFA vapour. \(\alpha\) is the void fraction for a homogenous two-phase flow and \(D_{SO}\) is the spray orifice diameter which is schematically shown in Figure 1 (b).

In the expressions of Table S4, \(D_{d,SO}\) is the droplet size at spray orifice where \(d_{tg}\) is the diameter of the unstable ligament which is fragmented to final droplets (Figure 1 (b)). \(\Gamma\) is the density ratio between the HFA vapour and multicomponent liquid phase i.e. \(\rho_g/\bar{\rho}_l\) in which \(\bar{\rho}_l = 1/\bar{v}_l\) and \(\bar{v}_l\) can be calculated using equation 4. \(\bar{\mu}_l\) is the mixture dynamic viscosity which is calculated using equations 6, 8 and 9. \(\bar{\sigma}_l\) is the mixture surface tension and is estimated using equation 10 and 11. Finally, \(\bar{v}_l(= \bar{\mu}_l/\bar{\rho}_l)\) is the mixture kinematic viscosity, \(k\) is the disturbance wave number and \(K_s\) is the wave number corresponding to the disturbance with maximum growth rate.
S.3.3 Near-orifice spray acceleration and droplet flashing

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mathematical expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Near-orifice velocity</td>
<td>$V_{NO} = \frac{p_{SO} - p_{amb}}{G_{t,m}} + V_{SO}$</td>
</tr>
<tr>
<td></td>
<td>where $V_{SO} = G_{t,m} \bar{v}_{t,m}$</td>
</tr>
<tr>
<td>2 Near-orifice droplet</td>
<td>$D_{d,NO} = D_{d,SO} \sqrt{\frac{(1 - \Delta x_{NO}) \bar{v}<em>{l(sat,amb)}}{\bar{v}</em>{l,SO}}}$</td>
</tr>
<tr>
<td>size</td>
<td>where $\Delta x_{NO} = \frac{\bar{h}<em>{l,SO} - \bar{h}</em>{l,sat,amb}}{(\bar{h}<em>{l} - \bar{h}</em>{g})_{sat,amb}}$</td>
</tr>
</tbody>
</table>

Table S5. Expressions required to calculate near-orifice spray velocity and droplet (Clark 1991; Gavtash et al., 2017a & b)

In the expression of Table S5, subscripts “NO” and “SO” denote near-orifice and spray orifice exit regions, respectively and subscript $\text{sat, amb}$ denotes saturation state at ambient pressure.

S.4 Actuator and test case parameters

The details of the actuator geometric properties and modelling parameters are summarised in Table S6:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{Vol_{mc}}$</td>
<td>50 µl</td>
<td>$D_{vo}$</td>
<td>0.7 mm</td>
</tr>
<tr>
<td>$V_{Vol_{ec}}$</td>
<td>50 µl</td>
<td>$D_{so}$</td>
<td>0.3 mm</td>
</tr>
<tr>
<td>$C_{d,vo}$</td>
<td>0.6</td>
<td>$C_{d,so}$</td>
<td>0.7</td>
</tr>
<tr>
<td>$T_{amb}$</td>
<td>295 K</td>
<td>Propellant</td>
<td>HFA134a</td>
</tr>
</tbody>
</table>

Table S6 Geometric and modelling parameters of the case of Myatt et al. (2015 a,b)

S.5 Details of model validation

The PDA measurements (Myatt et al. 2015 a-b) considered here for model validation are acquires at 15 mm away from the spray orifice. As described by Gavtash et al., (2017a) this measurement point is located in the far-field spray region ($z/D_{so} = 50$), where spray flashing is completed and the spray velocity undergoes
axial velocity degradation. Therefore it is essential to have knowledge of the spray velocity decay rate with respect to axial distance to extrapolate PDA results to the near-orifice position corresponding to model prediction. Figure S1 (a) shows the axial spray velocity on the nominal spray orifice axis of a Bespak 630 series actuator for different HFA134a/ethanol mixture compositions. Measurement locations are between 5 and 100 mm from the spray orifice.

Considerable decay in plume velocity over a distance of 100 mm from the spray orifice is observed, as a result of significant plume-air momentum transfer. According to Gavtash et al., (2017a) the velocity decay can be described by quasi-steady jet/plume relationships (Abramovich, 1976), using expression S1:

\[
\frac{V_{ct}}{V_{ref}} = \frac{A}{(z - z_s)/D_{SO}}
\]

S1

Where \(V_{ct}\) and \(V_{ref}\) are plume centreline and reference velocity respectively. \(A\) is the model constant, \(z\) is the distance to the spray orifice and \(z_s\) is the distance from the spray orifice exit to the effective jet/plume source location. The nonlinear least squares method using the Levenberg-Marquardt algorithm was implemented in Matlab (Mathworks, Natick, MA, USA) to determine the best-fit model constants \(V_{ref}\), \(A\) and \(z_s\) in equation S1 from axial distributions of plume centreline velocity in the PDA data sets of Myatt et al. (2015a-b). The constant of equation S1 for each formulation composition is summarised in Table S7.
Judging by the closeness of values of the constants in Table S7, it is conclusive that the centreline velocity is almost independent of the ethanol composition. By neglecting differences between axial traces, an average trace is representative of all formulations, as shown with solid line in Figure S1 (b). The constants of such average line are presented in the last row of Table S7. The average deviation of the data from the best fit is 2.90 % with a maximum deviation of 7.27% at axial position of 65 mm from spray orifice exit.

In the current validation activity, the near-orifice location of 10 mm from the spray orifice exit plane was chosen for comparison between PDA data and numerical results. This is the closest distance to the spray orifice where velocity values can be measured by PDA with high accuracy, as determined by Myatt et al. (2015a-b). Closer to the spray orifice, the PDA measurements showed considerable data dropout, which is indicative of dense spray effects, reducing the reliability of the measured values in this region. It should also be noted that the analysis of the data showed that there did not appear to be much correlation between velocity and drop size. In this case, extrapolation is not applicable to droplet trends. Hence the raw droplet data will be used as it is for comparison/trend verification.

### S.6 Metering chamber pressure and temperature

Figures S4 and S5 a comparison of the temporal distributions of pressure and temperature in the metering chamber, using alternative saturated vapour pressure models for initial ethanol concentration from $Y_{e,0} = 0\%$ to $Y_{e,0} = 20\%$ by mass. It can be

<table>
<thead>
<tr>
<th>Composition</th>
<th>$A$</th>
<th>$V_{ref}$</th>
<th>$z_s$</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$Y_{e,0} = 5%$</td>
<td>56.9</td>
<td>57.79</td>
<td>9.38</td>
<td>0.99</td>
</tr>
<tr>
<td>$Y_{e,0} = 10%$</td>
<td>56.95</td>
<td>58.52</td>
<td>10.52</td>
<td>0.99</td>
</tr>
<tr>
<td>$Y_{e,0} = 20%$</td>
<td>60.19</td>
<td>60.98</td>
<td>11.29</td>
<td>0.99</td>
</tr>
<tr>
<td>Average line</td>
<td>57.21</td>
<td>60.43</td>
<td>10.39</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Table S7. Constants in equation S1 for different ethanol compositions and average line in mixture formulation
seen that the dependence of pressure/temperature to ethanol content in the formulation is minimal when empirical vapour pressure model of Gavtash et al., (2016) was used. Such dependence becomes significant when Raoult’s law represents vapour pressure of the mixture.

Figure S4. Temporal evolution of formulation pressure inside pMDI metering chamber

Figure S5. Temporal evolution of formulation temperature inside pMDI metering chamber

Reasons for the difference in the predicted final states of the formulation inside the chambers are explored in more details by examining the saturated vapour pressure values as functions of ethanol mole fraction and temperature which are shown in Figure S5 and S6 (see SI - section S.6 of this article). In both figures, the surface colour provides an indication of the local saturated vapour pressure over the temperature and ethanol fraction range of support of the correlation. Four coloured lines (black, green, red and blue) indicate how the $p_m - T_m - Y_e$ conditions of the
HFA134a/ethanol mixtures with initial ethanol concentrations 0, 5, 10 and 20% w/w were predicted to vary inside the metering chamber during an actuation event. The colours are those used in the diagrams with pressure-time and temperature-time traces (Figures S4 and S5) for corresponding initial ethanol mass fractions. The initial and final states are indicated by means of black dashed lines.

The saturated vapour pressure and temperature in the metering chamber continually decrease until the atmospheric pressure condition is reached. For the Gavtash et al., (2016) empirical correlation of saturated vapour pressure, the final temperature is lowest for pure HFA134a, whereas, for the remaining ethanol concentrations, the final temperatures are slightly higher, but there is little difference between them. According to S7, Raoult’s law predicts final temperatures of 250 K, 253 K and 260 K for $Y_{e,0} = 5\%$, 10% and 20% formulation, respectively, so the final temperatures predicted with Raoult’s law are quite different. These differences between the final temperatures depend on the details of the shape of the $p_m - T_m - Y_e$ surface in the vicinity of atmospheric pressure.

Figure S6. Three-dimensional representation of saturated vapour pressure of HFA134a/ethanol mixtures as a function of ethanol mole fraction and temperature calculated using empirical SVP correlation (Gavtash et al, 2016)
S.7 Velocity and droplet size

Figure S8 shows a comparison of predicted near-orifice (NO) velocity and droplet size with PDA measurements of Myatt et al. (2015 a-b) for ethanol concentration of 10% by mass.
S.8 Time dependent evolution of mixture transport properties

Figure S9 (a-b) (see SI - section S.7 of this article), shows predictions of temporal evolution of mixture viscosity and surface tension for the formulation composition of $y_{e,0} = 20\%$, inside the expansion chamber. For corresponding mixing rule employed, please refer to section 2.3.2 of the article.

![Figure S9](image_url)

(a) Dynamic viscosity  
(b) Surface tension

Figure S9. Predicted HFA134/ethanol transport properties using different model representations for $y_{e,0}$=20% ethanol mass fraction

The temporal trends of droplet size of all ethanol-containing formulations are similar, the highest ethanol concentration ($y_{e,0} = 20\%$) was chosen to illustrate the largest effect of the different mixing rules. According to Figure S9 (a), it can be seen that equation 8 with $n = 1$ and $n = -1$ predicts the highest and lowest viscosity values, respectively, whereas the Arrhenius model and equation 6 predicts intermediate viscosity values. Figure S9 (b) shows that implementation of equation 11 with values $n$ to 1, -1 and -3, systematically reduces the surface tension values. The linear mass weighting rule (equation 10) exhibit values very close to equation 11, i.e. molar-weighted averaging in conjunction with $n = -1$. 