Microneedles for drug delivery: trends and progress

This item was submitted to Loughborough University's Institutional Repository by the/an author.


Additional Information:

- This article was published in the journal, Drug Delivery [© Informa] and the definitive version is available at: http://dx.doi.org/10.3109/10717544.2014.986309

Metadata Record: https://dspace.lboro.ac.uk/2134/16226

Version: Accepted for publication

Publisher: © Informa

Rights: This work is made available according to the conditions of the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) licence. Full details of this licence are available at: https://creativecommons.org/licenses/by-nc-nd/4.0/

Please cite the published version.
Microneedles for Drug Delivery: Trends and Progress

Karmen Cheung, Diganta B. Das

Department of Chemical Engineering, Loughborough University, Loughborough LE11 3TU, Leicestershire, UK

(*Corresponding author. Email: D.B.Das@lboro.ac.uk)

ABSTRACT

In recent years there has been a surge in the research and development of microneedles, a transdermal delivery system that combines the technology of transdermal patches and hypodermic needles. The needles are in the hundreds of micron length range and therefore allow relatively little or no pain. For example, biodegradable microneedles have been researched in the literature and have several advantages compared to solid or hollow microneedles, as they produce non-sharp waste and can be designed to allow rapid or slow release of drugs. However they also pose a disadvantage as successful insertion into the stratum corneum layer of the skin relies on sufficient mechanical strength of the biodegradable material. This review looks at the various technologies developed in microneedle research and shows the rapidly growing numbers of research papers and patent publications since the first invention of microneedles (using time series statistical analysis). This provides the research and industry communities a valuable synopsis of the trends and progress being made in this field.

KEY WORDS: Microneedle, time series analysis, autoregressive integrated moving average (ARIMA)

1. INTRODUCTION

Drug delivery (DD) has historically been pivotal in ensuring drugs can be administered in a manner that leads to therapeutic efficacy. Methods of DD, such as oral ingestion or hypodermic injections are considered to be the most common forms of drug administration [1, 2]. However, they possess several limitations, e.g., pain associated with hypodermic injections due to the long needles piercing nerve endings and absorption and metabolism issues associated with oral administration that lead to variability in bioavailability and also side effects from metabolites [3]. These disadvantages have led to the development of alternative DD methods. An encouraging alternative to the traditional methods is DD directly through the skin surface, i.e., transdermal drug delivery (TDD). Commercially available transdermal patches (TDP) now exist
which provide controlled release of medicines to patients in a minimally invasive manner. However, large molecules cannot passively permeate through the stratum corneum (SC), thereby, limiting the number of such transdermal drug products available to patients. Problems can also arise from the TDP’s peeling off due to the long periods for which they are required to be applied. Several approaches have been researched to overcome the problems with TDPs and allow delivery of compounds like proteins, DNA [4-9], so that they can permeate through the skin.

1.1 DD Routes

An overview of DD routes are described in this section briefly to provide some perspective on this important area of research, in particular, to provide an understanding of why there is a need to develop new technologies and where microneedles fit in to the picture. Numerous forms of DD routes are currently being used, which include, oral administration (gastric, colonic, enteric, etc.), hypodermic injections (e.g., intra-venous, intra-muscular, intra-cranial, sub-cutaneous injections, etc.), inhalation (pulmonary) and TDD (skin appendages) [10, 11]. Oral administration and hypodermic injections are the most common delivery methods with approximately 80% of drugs administered orally. However, several difficulties associated with oral dosage forms exist, e.g., pH changes within the body causing degradation to drugs, enzymatic activity, variable transit time, side effects and first pass metabolism [10]. The main disadvantages of using hypodermic injections is the resultant infection, pain caused during application, patient fear, anxiety and patient incompetence.

A good alternative that can overcome such problems is transdermal delivery of drugs (TDD), which can resolve issues such as by-passing first-pass metabolism (thus eliminating harmful metabolites whilst increasing bioavailability), and patient compliance. The method operates by transporting drug molecules from the surface of the skin into the body. It has been continuously developed ever since the first transdermal product was approved in 1979 in the United States to treat motion sickness [12]. Transdermal delivery includes the applications of gels, creams, ointments and more recently transdermal patches [13-15]. One transdermally delivered drug that is commonly used is nicotine [16], first developed in 1984 by Jarvik and Rose [17] to help smokers give up smoking. The drug was FDA approved in 1991 and has been on the market since 1992 [13].

However, there are disadvantages associated with TDPs, for example, the prevention of large molecules from bypassing the SC, the outermost layer of the skin, which is the rate-limiting barrier [18-21]. TDPs are applicable for molecules that are traditionally smaller than 500 Da [22]. Methods that have been employed to solve the short comings of both TDPs and hypodermic injections are ultrasound [20, 23, 24], MNs, iontophoresis [25], electroporation,
chemical enhancers, and others [23, 26]. These techniques can overcome the protective SC barrier as they allow the passage of large molecular compounds such as proteins and DNA [4, 5, 11, 27, 28]. MN technology in particular has grown over the past 15 years and can permit drugs to bypass the SC layer by the insertion of micron sized needles that create micro channels through the SC [29-31]. The MNs are small enough in length to avoid touching nerve endings of a patient, thereby, causing little or no pain [32]. Furthermore, MN technology has shown to be more advantageous in comparison to the other TDD techniques [33], such as the ability to deliver large molecular molecules that are larger than 500 Da [22] and the versatility in the application to allow solid or liquid formulations to be developed for disease specific applications.

There are numerous journal papers that have reviewed different types of drug delivery technologies [9, 34-41] and specific drug deliveries, such as insulin [42-48]. A number of review papers have also discussed specific technologies, e.g., various methods to fabricate MNs, or the devices that are currently being used or are likely to be used in clinical trials [49, 50]. Indeed one can safely assume that the most significant aspects of MNs research have been discussed in review or research papers. However, one issue that is obvious is that there is little attempt to quantify the trend in the progress of MN technology. In other words, it is not clear how slow or fast the rate of progress is the development the MNs based methods are. It is also not clear from the existing literature what method one could use to quantify the trends and, if the trend could be quantified reliably given that the MNs based research is still relatively new as compared to most other TDD methods. This review paper will look into assessing these gaps in the literature by using a time series analysis of the journal papers found in Scopus, using a time series analysis tool namely, ‘autoregressive integrated moving average (ARIMA) model’ (also known as univariate Box-Jenkins analysis) to look at the future trend patterns in the number of publications based on several key word searches. The information was gathered by conducting searches in the home page document search function only, as opposed to searching “microneedle” and then searching within the results the second key work (for example “solid”). Quantifying and predicting past and future trends are important to determine the market values of these products as there is a growing interest to produce MN’s to a commercial quality and scale. It is therefore important to view what is the current trend in literature, similar to how a start-up a business would require market research. We assume that the number of publications is the key indicator of how well the MN technology has developed and use the keywords “microneedle“, “solid microneedle“, “hollow microneedle“ and “dissolvable microneedle“ to determine the number of publications corresponding to each keywords (using Scopus). The program IBM SPSS Statistics version 21 was used to produce the time series analysis tool and analyse the data from Scopus. The ARIMA model was created by omitting 2014 data as it is
currently incomplete, therefore the analysis will give an indication of the trend till 2013 [51]. For the completeness of the paper, we discuss other relevant issues as well as follows.

1.2 Why microneedles?

TDPs have been delivering a variety of drugs since the early 1980’s such as testosterone, nicotine, Selegiline and Clonidine [33]. Although there are several commercially available TDPs, they are limited by the SC which includes overcoming the mass transfer resistance [13]. TDPs administer drugs via passive diffusion as illustrated in Figure 1a [52]. There are two mechanisms for the storage of drugs on TDPs. A drug is either stored in a reservoir or incorporated into the transdermal patch fabric, whereby it is transported across the skin via a concentration gradient [13]. Although these methods have shown to be applicable for a variety of drug formulations, they are still limited by the drug molecules that can permeate through the SC barrier. As mentioned earlier, MNs have been proposed as an alternative delivery method to TDPs and hypodermic syringes as they have shown to overcome the various shortcomings previously outlined. Indeed, it has been illustrated by Benson and Namjoshi [4] and many other researchers [52-54] that MN research is a promising field of research to be pursued more extensively as it can be used to overcome the skin’s natural defensive barrier, the SC in both adults and children. The rate of release of the drug depends upon the controlling membrane of the TDP [55] and therefore ensuring a consistent drug release profile can be uncertain.

MNs have been made possible to make due to the technological advances that have occurred in the last 20 years. Since the independent invention of the hypodermic needle in the mid 1850’s [56] by Wood and Pravaz, hypodermic needles [57], or syringes, have been the most common form to administer biotherapeutics [10]. MN use has the advantage of simple patient administration of drugs with minimal invasiveness to the patients [58, 59]. The MNs would only permeate the SC and not the nerve receptors, consequently, the patients would feel little or no pain [32], though longer microneedles can also be used where deeper delivery of the drug is desired. Therefore, the development of MNs is important as it has the potential to overcome numerous disadvantages posed by the traditional DD systems [60].

Current applications of MNs include the delivery of macromolecules such as vaccines, proteins and peptides including insulin for diabetics. One such example for vaccines delivery is reported by Edmonston-Zagreb for measles vaccination [21, 61-68]. Vaccinations have the capacity to be delivered using MN patches which require the patient to have no specialised training or the need for cold/refrigerated storage; this in turn can reduce the spread of diseases [63, 69]. Therefore, the successful delivery of patch biotherapeutics is a desirable drug administration method. Furthermore, there are initial challenges to overcome, such as the low permeability of skin which can limit the permeation of drugs. With MN, this challenge can be overcome.
1.3 Skin

We discuss skin and its properties briefly in this section because the skin barrier needs to be understood and overcome before MNs can be designed and applied successfully. Human skin is the largest organ in the human anatomy with an approximate surface area of 20,000 cm\(^2\) on an average human male, which spans the entire external surface of the body [70], in which its main function is to contain all the internal organs, protect them against foreign organisms and bacteria and act as a passive barrier. Some of the skin's other functions include the regulation of internal body temperature, insulation, resistance against foreign bacteria and to provide protection to the internal organs [71]. The surface area of the skin constantly changes depending on age, weight loss and gain, [72, 73] height and sex of a human being [74]. It is also a receptive organ to thermal heat and pain. The skin comprises of several layers of which the main layers consist of the epidermis, dermis and subcutaneous tissue [71], see Figure 1. The figure illustrates the SC, a non-living layer, which provides the first barrier to foreign bodies and DD. Below the SC layer is the epidermis containing living tissue with no blood vessels. Below this is where drugs are taken up by capillaries in the dermis layer [52]. As evident in the figure, there are several pathways in which molecules can permeate through the skin which can be categorised into two routes, the appendageal and transepidermal routes. The appendageal route includes the movement through hair follicles and sweat glands (Figure 1b) and offers a high permeability to ions and large polar molecules [22]. The surface area is considerably small, and therefore, the exploration of passing drugs using this form of route is considered of little importance. The transepidermal route is a direct pathway through the SC (Figure 1c). This can occur via an intracellular (Figure 1a) or transcellular route (Figure 1c) [22].

With the varying skin surface areas there is also a dramatic difference in the skin thickness within the human body which is important in the absorption of therapeutics [37]. Therefore, analysis into skin thickness is important, as outlined in a study of skin thickness of Korean males and females conducted by Lee and Hwang [74]. In the study they found that the thickness of skin is vastly variable due to a number of factors. These include, the race, sex, and age of a person and also on different areas of the body. It has also been shown that aging and diabetes have an effect on skin thickness [72]. In particular it was found that subcutaneous fat thickness in different body regions was thinner in aging skin and in diabetic patients. A reduction in the skin thickness of the hand was also observed for diabetic patients. Therefore, consideration of skin thickness would need to be examined when choosing an active site for TDD in general [37] and MNs in specific.
1.3.1 Mechanical properties of skin

Understanding the mechanical properties of skin and detailed knowledge on various skin layers [76] are important as the insertion of needles into the skin would alter the skin’s mechanical response to all skin layers [77]. Knowledge of the properties of skin would help better understand the effect MNs have and therefore help determine what needs to be overcome when designing or inserting a MN. Skin is a viscoelastic material in which research has been conducted to ascertain what factors can influence skin properties. These include the site at which a material can be located, the age of the patient, the thickness of the skin, orientation, etc. [76, 78-80]. It is a complex organ that continuously changes as we age [79]. A property of skin that has been studied is the skin’s ability to fold upon itself, such as wrinkling [81]. Smalls et al. [76] investigated the body’s biomechanical skin properties which showed a significant difference in elasticity, stiffness and laxity for the right side in comparison to the left side of the body. This was possibly the result of 90% of subjects being right handed, which illustrated that an increase in muscle tone can also have an effect on the biomechanical skin properties. Cua et al. [79], concluded that the biomechanical properties of skin decreased with increasing age, which may be due to natural degeneration as we get older. SC thickness on human forearm, palm, cheek and lower leg were also studied to determine by using two non-invasive measuring techniques namely, confocal Raman spectroscopy and confocal laser scanning microscopy, to measure SC thickness which were then compared to the thickness in literature data. It was found that it was possible to accurately measure the SC thickness with both techniques [82].

1.3.2 Increasing Permeability of Skin

The use of MN as a drug delivery system is an important development as the potential to allow a wider scope of molecules to be transdermally delivered through the skin is greatly increased.
The amount of drug that is delivered can also be increased. However, an understanding of the permeability of skin would need to be established in order to determine how to increase drug content [69, 87, 88]. It is important to look at skin thickness when investigating increasing permeability of skin, as increasing skin permeability is important for transdermal drug delivery (TDD). The invention of the MN can overcome this factor as the needles bypass the SC layer, which is the rate dependent layer and can allow large molecular weight proteins to pass into the blood stream [89]. A well-known method to quantify the drug release through skin is the use of Franz diffusion cells, and therefore have been used in literature extensively to calculate the permeability of skin [32, 90, 91].

There have been multiple papers outlining various methods conducted to analyse different techniques to increase the permeability of skin. They can be categorised into chemical and physical enhancing techniques, some of which include, thermal ablation, sonophoresis and electroporation [3, 5, 19, 20, 30, 92]. Sinha and Kaur [19] stated that an individual enhancement technique cannot possess all the desired properties to facilitate the transport of drugs transdermally. However, the data published by Prausnitz et al. [33] illustrate that the use of MNs is a promising technique as it possessed many of the required properties for the delivery of drug therapeutics. Figure 1d depicts the micron sized holes that can be created by MNs upon the skin.

There are several physical methods that have been used in conjunction with MN technology to increase skin permeation [93-95]. One such example is the use of sonophoresis with MNs. It is a technique which allows molecules to permeate through the barrier of the skin more readily as ultrasonic waves create micro-vibrations on the skin [92]. Monomeric insulin analogues were studied to investigate the rate of iontophoresis transport on mice skin [25]. The study showed clinically relevant results for insulin regulation.

Several review papers have been published on different types of enhancement techniques [15, 22, 96-103] which outline various uses of chemical enhancers like N-methyl-2-pyrrolidone, a pyrrolidone [19] used in the application of insulin, ibuprofen and flurbiprofen. The applications of these techniques for increasing skin permeability would be useful when delivering drugs transdermally. Table 1 outlines some examples of enhanced protein/peptide delivery systems across the skin and the outcome of the experiments.

### 2. Trends in Microneedle (MN) Drug Delivery Method

MNs can be considered to be a micron scale hybrid between TDPs and hypodermic syringes, to overcome limitations that are associated with the individual application. They are small arrays of needles that are generally less than 1 mm in length [104-107]. There are multiple MN designs that have been created over the last decade. They can be categorised into two types,
solid or hollow MNs [108]. The materials that have been used to fabricate them range from metal [109], glass, silicon [110] and biodegradable polymers (polydimethylsiloxane) [111, 112] and silk fibroin [113]. More recently the use of fish scales have also been investigated [114]. Ideally the materials used would be pharmacologically inert, non-toxic, compatible with pharmaceutical ingredients, etc. [19]. Metals traditionally used for MN fabrication consist of stainless steel, nickel coated in gold, titanium, platinum, palladium [47, 115, 116]. Although numerous journal papers have been published on the use of silicon as a primary substituent of MN formulation, the material itself has yet to be FDA approved [90].

MNs provide a direct pathway for drugs to access the viable dermis, allowing for a painless DD that by-passes the SC [4]. They also differ in shape, ranging from square, circular, flat tipped, sharp tipped etc., [32, 90, 116-121]. There has been a lot of research conducted on MNs for the delivery and monitoring of various drugs such as glucose control for diabetics [61, 46, 122-125], Alzheimer’s disease [110], anti-cancer [126] and other conditions [127]. Vaccines have also been a prominent research field with numerous studies developed to allow dose sparing effects [63, 128, 129]. There have been multiple studies conducted to optimise the delivery of drugs using MNs with numerous methods to fabricate them.

### Table 1 Examples of enhanced protein/peptide delivery to and across the skin

<table>
<thead>
<tr>
<th>Protein/Peptide</th>
<th>Delivery Method</th>
<th>Main Outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine serum albumin</td>
<td>Polymeric microneedles</td>
<td>All drug released in 6 hours for in vitro permeation studies</td>
<td>[130]</td>
</tr>
<tr>
<td>Bovine serum albumin</td>
<td>Microneedles, ultrasound</td>
<td>BSA permeability of 1 µm/s is achieved with a 1.5 mm height microneedle and 15 W ultrasound output</td>
<td>[20]</td>
</tr>
<tr>
<td>Bovine insulin and bovine serum albumin</td>
<td>Microneedles coupled with iontophoresis</td>
<td>MN design containing 361 MNs/cm² of drug permeation in 6 hours on neonatal porcine skin in vitro</td>
<td>[6]</td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>Stainless steel microneedles</td>
<td>Efficient diffusion through the dermis</td>
<td>[118]</td>
</tr>
<tr>
<td>Hepatitis B Surface Antigen</td>
<td>Elastic liposomes</td>
<td>Systemic and mucosal antibody response elicited in mice</td>
<td>[4]</td>
</tr>
<tr>
<td>Hepatitis B Virus DNA Vaccine</td>
<td>Jet propulsion (Powderject)</td>
<td>Application to healthy human volunteers resulted in both humoral and cell-mediated immune responses</td>
<td>[4]</td>
</tr>
<tr>
<td>Insulin</td>
<td>Insulin loaded dissolvable microneedle made of starch and gelatin</td>
<td>Dissolved in 5 minutes in rats to relative pharmacological availability and relative bioavailability of 92%</td>
<td>[21]</td>
</tr>
<tr>
<td>Influenza subunit vaccine</td>
<td>Microneedles Delivery</td>
<td>Application to intramuscular injection in guinea pigs. Hemagglutinin concentrations as high as 20.</td>
<td>[117]</td>
</tr>
</tbody>
</table>
Measles Microneedles Delivery | Measles was able to be coated and dried onto MN. Vaccine delivery into rats was comparable to using hypodermic needles which gave similar antibody titers | [63]

Park et al. [90] used biodegradable polymer MNs with sharp tips, to overcome problems associated with safety and disposal. They found that the use of biodegradable MNs increased skin permeability by three fold which increase the delivery of drugs transdermally. Gupta et al. [119] used hollow MNs for bolus delivery of lispro insulin in comparison to catheter infusion. They found that MNs inserted 1 mm into human skin showed rapid insulin absorption with no pain observed from the volunteers in comparison to catheter infusion [131].

A method to fabricate MNs is important, as desirable attributes would be to have a simplistic fabrication method that is low cost and reproducible. This would be advantageous when mass producing MNs for industrial application [132]. However, the delivery of drugs using MNs can be conducted in four different ways. These can be known as “poke and patch”, “coat and poke”, formulating the API (active pharmaceutical ingredient) with a biodegradable polymeric MN [133, 134] or by channelling the drug through the channels of a hollow MN [89]. Multiple MN designs have been fabricated that facilitate the piercing of the SC allowing the permeation of drugs [110].

The rate of the development in MN research has increased significantly since the first papers have been published. A time series analysis forecast based on ARIMA model has been applied to the 1228 papers that have been found using the database Scopus with the search term “microneedle”. ARIMA is used to extrapolate future trends in data based on previous data sets. The forecast is shown in Figure 2. Trends will also be determined for specific microneedle types in the forthcoming sections in the paper.

A “single series” of ARIMA forecast is based only on the past values of the variables being forecasted, the variables in this case are the number of journal publications (NOJP). It tells us how an observation on the NOJP is statistically related to past observation on the same variable. All forecasts are extrapolations and therefore produce projections based on past patterns or relationships into the future. The model is used for short term forecasting in this paper which relies upon the data collected from recent pasts as opposed to distant past.

Figure 2 represents the time series analysis in graphical form. The observed and fitted data show a good match which give the confidence that the ARIMA model is reliable in predicting the trend. The trend shows that there are some fluctuations in the number of publications in various years. However, overall, there is a considerable increase in the number of MN publications in
the past 10 years. The ARIMA fit shows a good prediction of the trend (beyond 2015) when the total number of future MN publications are forecasted. The figure shows the yearly observations of the number of publications published since 1982-2013 (1228 total publications) and forecasted to 2016. The predicted NOJP for 2016 are shown to be approximately 300 which is a significant increase from the 218 papers found in Scopus for year 2013.

Figure 2. Forecasted, fitted and observed results on the trend of publications on microneedles using the keyword "microneedle"

### 2.1 Hollow MNs

Hollow MNs are traditionally used to allow liquid formulations through the SC and act like micron scale syringes. They have an added advantage as they can permit the administration of a larger drug dose compared to solid MNs [4]. They have also been shown to allow an increase in drug infusion rate due the fact that pressure can be applied across the length of the MN with administration. Ahmad et al. [135] have shown the in-situ assembly of hollow liquid filled polymeric microneedles for drug delivery. Hollow metal MN arrays have been fabricated to allow the continuous administration of drugs. Micromachining methods have been used to make machine moulds from polyethylene terephthalate using UV lasers [77, 136, 137]. However, hollow MNs are still considered to be mechanically weaker involving complicated manufacturing processes and more complex to use than solid MNs as solid MNs are considered to be more robust [1]. There have been other advancements in recent research to allow manufacture of any height, pitch and lumen-lumen spacing of the MNs [116, 138]. Griss and Stemme [137] fabricated out-of-plane hollow MNs to overcome the short comings of blockages caused by hollow MNs. The design consists of an opening on the shaft of the MN as opposed to the tip for the delivery of drugs using a microfluidic liquid transfer. These were made by a deep reactive-ion etching (DRIE) method.
Roxhed et al. [77] developed a method of fabricating MNs that combines a controlled flow of drugs using out of plane MNs. Nordquist et al. [61] conducted a study using hollow MNs fabricated from metal which improved the Griss and Stemme design. MNs of length 400 µm and pitch 500 µm were produced.

ARIMA model has been applied to the 167 journal papers that have been found in the journal data base Scopus with the search term “hollow microneedle” (Figure 3). It is obvious that the fitted and the observed data do not match well which is due to the small number of publications per year. This suggests that while the total numbers of publications relating to hollow microneedles are increasing, the trend (e.g., the number of publications in different years) cannot be reliably predicted. Nevertheless, the ARIMA model has been applied to predict the future trend in the journal papers. It shows that the number of publications on hollow MNs would decline, which seems to support a hypothesis that research groups are potentially leading away from hollow MNs use due to the complications in manufacture and their brittle nature.

Figure 3 Forecasted, fitted and observed results on the trend of publications on hollow microneedle using the keyword “hollow microneedle”

2.2 Solid MNs

Solid MNs are more robust than hollow MNs and have a stronger mechanical strength [1]. MNs can produce micro pores in skin, which bypasses the SC layer, and allow drugs to permeate to the viable epidermis [110]. There have been a number of methods and materials used to fabricate solid MNs [139] [140], some of which are represented in Table 2.

The first reported case of solid MNs in literature was in the study of gene therapy [141]. However, Henry et al. [32] was the first to demonstrate the feasibility of delivering drugs
transdermally. They designed conical shaped MNs, 150 µm in length and <1 µm tip diameter (Figure 4A). This allowed easy piercing of the MN into skin and produced a 4 order of magnitude increase in skin permeability. In this study, a deep reactive ion etching microfabrication technique was used. Although the fabrication method yielded reproducible fabrication of MNs, the insertion of MNs into human cadaver skin left a small proportion of the needles bent at the tip 5-10 µm. Khan et al. [140] prepared coated MNs utilising a process named ‘electrohydrodynamic atomisation (EHDA)’ to produce pharmaceutical coatings on a single MN patch for the purpose of applying personalised medicine. Martanto et al. [142] fabricated solid metal MNs by cutting metal sheets with an infrared laser. The MNs were then manually bent into the 90° angle. The MNs were in an array containing 105 MNs, 1000 µm in length and a cross section at base of 50 µm x 200 µm. The MN was tapered to a sharp tip (angle 20°) (Illustrated in Figure 4B). This method of fabrication was shown to be laborious and used a number of strong acids which could pose problems when disposing of such chemicals. The application of this MN into hairless rats also required an external high velocity applicator to successfully insert the MN into the skin. Although the MNs used to elucidate the transdermal delivery of insulin produced successful data in reducing glucose levels by up to 80%, the fabrication method would not be considered a simple process.

The fabrication of biodegradable and biocompatible polymers was proposed by Park et al. [90] to address the issues associated with cost effective fabrication materials and problems associated with MN fabrication materials, such as metal, a sharp hazardous waste, and silicon which has yet to be FDA approved [90]. The material was considered to be a safer alternative as it is mechanically strong and relatively inexpensive.

As shown in Table 2, silicon has been widely researched when developing MNs. Polydimethylsiloxane was used by Chu and Prausnitz [111] to show the material combined the mechanical strength that metal MNs can provide and the useful properties of silicon drug based arrow head (Figure 6). They showed that the production of a blunt metal shaft with a detachable
drug encapsulated arrow head on the end could provide drug to the viable epidermis within seconds to porcine and human cadaver skin.

There have been several types of polymer MNs that have been created to overcome the non-biocompatible and non-biodegradable properties of metal and silicon MNs [90, 143-145]. The biodegradable MNs were fabricated using a lithographic approach. Dissolving MNs were fabricated by Ito et al. [46] in which insulin was mixed at room temperature to dextrin and deionised water and dried in a desiccator after thread was attached. Three different mixtures of insulin were made and tested on rats which illustrated the uses of dissolving MNs to successfully deliver the drug precutaneously. Table 2 illustrates a general overview of the transdermal MN methods used to administer drugs and vaccines. For example, the table shows that dissolving insulin based MNs were made with starch and gelatin [21] for a 5 minute dissolution time when inserted into the skin. It was shown that 600 μm height and 300 μm base MN retained pharmalogical activity in the starch/gelatin matrix.

ARIMA model has been applied to the 112 journal papers that have been found using the journal data base Scopus with the search term “solid microneedle”. Although the trend has declined in the observed data for 2013-2014, the results show that there would be an increase in the amount of solid MN papers in the future.

Figure 5 Forecasted, fitted and observed result on the trend of publications on solid microneedle using the keyword "solid microneedles"
Figure 6 Images of an arrow head microneedle [111]
<table>
<thead>
<tr>
<th>Methods</th>
<th>Materials</th>
<th>Dimensions (µm)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Separable dissolving Arrow Heads</td>
<td>(polydimethylsiloxane (PDMS) Sylgard 184,), Metal shaft, Water soluble excipients-PVP, sucrose, PLGA</td>
<td>600 µm-long PVP/PVA arrowhead capped onto a metal shaft with an exposed length of 600 µm and a 100 µm overlap.</td>
<td>● Rapid (1-5 seconds) /painless drug/ vaccines delivery, PDMS: Inert/Non-toxic/ Non flammable Rapid (1-5 seconds) /painless drug/ vaccines delivery, convenient/safe/potential self-administration, can allow controlled release of active ingredient ● Advantage over coated needles-elimination of bio-hazardous waste, allow self-administration ● Does not require extended patch wearing even for long duration of drug releases. ● PDMS: Inert ● PDMS: Non-toxic ● PDMS: Non flammable</td>
<td>● Difficult insertion into skin as requires wider needle geometry (non-blunt shaft) ● Non reusable ● fibrotic reaction</td>
<td>[111, 146]</td>
</tr>
<tr>
<td>Dissolving</td>
<td>Mixture Insulin, water, dextrin</td>
<td>basal diameter: 3.24±0.16 and 0.55±0.03 mm</td>
<td>● Bio-compatible</td>
<td>● Produce bio hazardous sharp waste ● Large tipped</td>
<td>[46]</td>
</tr>
<tr>
<td>Pyramidal dissolving Polymer</td>
<td>polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP) ● A = Pyramidal MN ● B = Extended pyramidal MNs ● C = Pedestal MNs</td>
<td>base width x base depth x needle height: A: 300 µm x 300 µm x 600 µm. B: 300 µm x300 µm x 900 µm. C: 340 µm x 340 µm x 900 µm) 10x10 array</td>
<td>● Ability to increase drug capacity and localise to the MN tip ● Allowed a deeper insertion ● Higher increase of drug to be dissolved</td>
<td>● Produce bio hazardous sharp waste</td>
<td>[147]</td>
</tr>
<tr>
<td>Deep reactive Ion etching</td>
<td>Chromium, Silicon wafers</td>
<td>120 µm length, &lt;1 µm tip diameter</td>
<td>● Mechanically strong</td>
<td>● Reusability questionably ● Top 5- 10 µm of MN damaged for a few samples</td>
<td>[32]</td>
</tr>
<tr>
<td>Dissolving, Fabricated by a</td>
<td>Maltose</td>
<td>1200 µm length 60 µm tip diameter</td>
<td>● Requires no moulds, therefore no sharp waste</td>
<td>● Complicated process</td>
<td>[148]</td>
</tr>
<tr>
<td>Drawing technique to create a sharp tip</td>
<td>Cutting metal using infrared laser, manually bending the MN structure, electropolished</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>------------------------------------------------------------------------------------</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metal</td>
<td>1000 µm length, 50 µm x 200 µm cross section at base, tapered to a sharp tip (angle 20°), 106 array</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• A short MN insertion time was better than a longer insertion time to facilitate drug permeation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Insertion of large array was difficult by hand without external device</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Strong acids used</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Silicon master mould to make PDMS inverse mould</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Sugar glass MN:</td>
</tr>
<tr>
<td>• Trehalose/mannitol (50:50 w/w)</td>
</tr>
<tr>
<td>• Trehalose dehydrate/sucrose (75:25 w/w)</td>
</tr>
<tr>
<td>• Trehalose/sucrose (75:25 w/w)</td>
</tr>
<tr>
<td>• Trehalose/sucrose (50:50 w/w)</td>
</tr>
<tr>
<td>• 2% (w/w) methylene blue</td>
</tr>
<tr>
<td>• 200 µm base 20 µm tip 300 µm height</td>
</tr>
<tr>
<td>• Fast dissolution of drug into skin</td>
</tr>
<tr>
<td>• Use of simple sugars to create biodegradable MNs</td>
</tr>
<tr>
<td>• MN patch needles to be left on the skin for potentially over 20 minutes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stainless steel MN produced by chemical etching</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Stainless steel</td>
</tr>
<tr>
<td>• 750 µm height 200 µm x 50 µm at the base. Single row of 5 MNs</td>
</tr>
<tr>
<td>• Dose of Measles vaccine is small, therefore the dimensions of the MN are sufficient to allow coating and delivery of the vaccine</td>
</tr>
<tr>
<td>• Needles long enough for rat dorsal thickness (700 µm-1000 µm) penetration</td>
</tr>
<tr>
<td>• Cost effective manufacturing</td>
</tr>
<tr>
<td>• Produce bio hazardous sharp waste</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dissolving MN</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Starch/gelatin (1:1 ratio)</td>
</tr>
<tr>
<td>• PDMS mould</td>
</tr>
<tr>
<td>• 600 µm height 300 µm base 5 µm tip</td>
</tr>
<tr>
<td>• Rapid dissolution of 5 minutes was achieved</td>
</tr>
<tr>
<td>• Pharmacological activity retain in the starch/gelatin</td>
</tr>
<tr>
<td>• Time to reach minimum plasma glucose level slightly longer for MN than for subcutaneous injection of insulin</td>
</tr>
</tbody>
</table>

[47][149][63][21]
It has been reported in the literature that breakage of MNs is considered to be minimal as long as the insertion of the MNs is gentle. It was also stated that metal MNs are more robust than other materials used to manufacture MNs and that biodegradable needles are safer [4].

Although the use of silicon as a primary material in some MN fabrication methods is favoured, it is hindered by the fact that the material is currently not approved by the Food and Drug Administration (FDA) [90]. Research has been conducted on the use of large sharp MNs but little has been carried out on the effect of short blunt MNs on increasing the permeability of skin. What little research has been conducted shows increasing permeability to longer sharper MNs. This shows that there is a potential for developing a new MN which is blunt and short in length.

Solid MNs have been shown in the literature to have a typical length of 150 µm-350 µm. However, studies into the fabrication of super short MNs with a length of 70-80 µm were conducted by Wei-Ze et al. who have shown that super-short MNs are capable of successfully delivering galanthamine (GAL), a drug used for Alzheimer’s. The study compared the use of sharp super-short MNs against blunt super-short MNs and longer sharp needles of 1500 µm as shown in Figure 7. The super short MNs were made using wet etching of silicon using acupuncture needles backed onto the minipore of a basement. The study found that as more pressure was applied to insert the MNs, the permeation of the drug increased [110]. There is currently little literature regarding the feasibility of blunt short MNs against sharp long MNs. Based on the findings of Wei-Ze et al. there could potentially be a gap in the literature to pursue further the implications of using the is method of DD on various drugs and see the effect the MN has on skin permeability. This shows a promising fabrication method for the delivery of drugs transdermally. Table 3 shows the main parameters of super short MNs in the study conducted by [110]. However, considering the various fabrication methods, there seems to be a need for a simpler robust technique that requires minimal cost, as the process is economically viable and relatively robust.

Figure 7 Super-short microneedles used in this study, SEM images of A: a single sharp tipped super-short microneedle, B: a single flat tipped super-short microneedle and C: an angled view of a flat tipped super-short microneedle array [110]
ARIMA model has been applied to the 16 journal papers that have been published in the journal data base Scopus with the search term “dissolvable microneedle”.

Figure 8 Forecasted, fitted and observed result on the trend of publications on dissolvable microneedle using the keywords "dissolvable microneedle"

There is little data on the publication of dissolvable MNs. However there is a growing trend in the use of dissolvable MNs, which is apparent due to the benefits of incorporating active drug directly to the manufacture of MNs. Although the ARIMA forecast in Figure 8 seems to fit this trend due to the lack of observations the forecast would not be a useful estimate of the mean as there would essentially only be one observation per mean. Therefore this forecast would not be an ideal assumption of the predicted NOJP for 2016.
<table>
<thead>
<tr>
<th>Method</th>
<th>Materials</th>
<th>Dimensions (µm)</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
</table>
| Sharp tipped Super Short microneedles | Microneedle: Silicon with 30% potassium hydroxide  
Patch:  
- Backing: polyethylene  
- Adhesive: polyisobutylene | 75              | - Strong material which does not break with insertion forces exceeding 8 N  
- Reusable                                                                                       | - Permeability of drug is lower compared to flat tipped microneedle  
- Skin folding shown upon insertion of needle compared to flat tipped microneedle                  |
| Flat tipped Super Short microneedles | Microneedle: Silicon with 30% potassium hydroxide  
Patch:  
- Backing: polyethylene  
- Adhesive: polyisobutylene | 80              | - Increase permeability in skin compared to sharp tipped microneedle  
- Decreases skin barrier function  
- No skin folding shown upon insertion of needle compared to sharp tipped microneedle  
- Strong material which does not break with insertion forces exceeding 8 N  
- Reusable                                                                                       | N/A                                                                                               |
3. MNs Patents

MNs have become more prominent within the last decade. The use of MNs as a method for the transdermal delivery of drugs has become a more appealing technique as it overcomes many disadvantages such as discomfort and pain that can be caused by hypodermic needles or the non-bioavailability that oral dosage forms provide. Therefore it is important to look at patents that have been filed within the last decade to correlate the trends of MNs [150-152]. Table 4 shows a summary of patents that have been taken out on materials to fabricate MNs. Table 5 illustrates some example patents on the methods of MN fabrication. Table 6 shows patents on chemicals used for MN transdermal delivery system. Figure 9 illustrates the number of patents taken for various MN designs. It can be seen that there is a considerable amount of MN patents taken out on hollow MNs. This may be due to the fact that hollow MNs have the advantage of delivering a higher dosage in comparison to other methods [108].

![Figure 9 Division of patents filed based on type of MNs](image)

Transdermal delivery of drugs is a continually growing field with an abundant of journal papers being published each year on MN technology and an increasing number of patents filed. Therefore an increase in development for more commercially viable MN products would need to be conducted.
<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Date of Filing</th>
<th>Applicant</th>
<th>Key Invention</th>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 2010042050</td>
<td>16th April 2007</td>
<td>Nemaura Pharma Ltd, USA</td>
<td>Applicator for microneedles</td>
<td>USA, European, Japan, China, India</td>
<td>[153]</td>
</tr>
<tr>
<td>WO 2011016230</td>
<td>4th Aug 2010</td>
<td>Medrx Co., Ltd., Japan</td>
<td>Provided is a microneedle device which protects microneedles, has an easily portable shape, is free from such problems as breakage of fine needles in the step of puncturing the skin with the microneedles, and ensures appropriate skin puncture to administer a drug.</td>
<td>Japan</td>
<td>[154]</td>
</tr>
<tr>
<td>WO 2011084951, US 20110172645</td>
<td>4th Jan 2011, 8th Jan 2010</td>
<td>Ratio, Inc., USA</td>
<td>Microneedle configured to facilitate delivery of the drug to the subject. The microneedle includes a tip portion and is moveable from an inactive position to an activated position</td>
<td>USA</td>
<td>[155]</td>
</tr>
<tr>
<td>WO 2011014514</td>
<td>27th Jul 2010</td>
<td>3M Innovative Properties Company, USA</td>
<td>The present disclosure relates to apparatus, assemblies, combinations, and methods for infusing fluids by hollow microneedles.</td>
<td>USA</td>
<td>[156]</td>
</tr>
<tr>
<td>WO 2013096026</td>
<td>12th Dec 2012</td>
<td>3M Innovative Properties Company, USA</td>
<td>Assembly of a microneedle adhesive patch. The assembly can include a backing, and an adhesive and a matrix coupled to the backing</td>
<td>USA</td>
<td>[158]</td>
</tr>
<tr>
<td>WO 2013066262</td>
<td>2nd Nov 2011</td>
<td>Singapore</td>
<td>Invention relates to plastic microneedle strips that are used in TDD for increasing the DD rate through the skin</td>
<td>Spain</td>
<td>[159]</td>
</tr>
<tr>
<td>Patent Number</td>
<td>Date of Filing</td>
<td>Applicant</td>
<td>Key Invention</td>
<td>Country</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------</td>
<td>----------------</td>
<td>-----------</td>
<td>---------------</td>
<td>---------</td>
<td>-----------</td>
</tr>
<tr>
<td>EP 2289843</td>
<td>31st Aug 2009</td>
<td>University College Cork-National University of Ireland, Cork, Ireland.</td>
<td>The invention relates to a method of fabricating a microneedle device of the type comprising an array of microneedles on a flexible polymer support layer.</td>
<td>European</td>
<td>[160]</td>
</tr>
<tr>
<td>JP 2011083387</td>
<td>14th Oct 2009</td>
<td>Kyushu Institute of Technology, Japan; Nichiban Co., Ltd.</td>
<td>Manufactured by (1) performing Bosch process to a Si wafer to form a Si microneedle having a tapered tip and a columnar part with the same diameter or a decreasing diameter in the longitudinal direction, etching the tip with an etching solution and/or a reactive radical.</td>
<td>Japan</td>
<td>[161]</td>
</tr>
<tr>
<td>CN 102000020</td>
<td>17th Nov 2010</td>
<td>Beijing Pharmaceutical Research Institute, Henan Lingrui Pharmaceutical Co., Ltd., People Republic of China; Beijing Lingrui Hi-tech Co., Ltd.</td>
<td>The title polymer (molecular weight: 1000-10000,000) is selected from poly(p-dioxanone) or p-dioxanone containing copolymer (containing p-dioxanone 10-100 wt.%), such as poly(p-dioxanone-lactide), poly(p-dioxanone-glycolide), etc.</td>
<td>China</td>
<td>[162]</td>
</tr>
<tr>
<td>CN 103263727</td>
<td>22nd May 2013</td>
<td>Tsinghua University, People Republic of China.</td>
<td>A metallic microneedle array, including: substrate; and a metal sheet fixed on the surface of the substrate.</td>
<td>China</td>
<td>[163]</td>
</tr>
<tr>
<td>US 20130030374 A1</td>
<td>11 Oct 2012</td>
<td>Toppan Printing Co., Ltd.</td>
<td>Microneedle including forming a plurality of first linear grooves on a substrate in parallel to one another along a first direction using grinding and forming a plurality of second linear grooves on the substrate in parallel to one another in a second direction intersecting the first direction using grinding.</td>
<td>USA</td>
<td>[164]</td>
</tr>
<tr>
<td>CN 103181887</td>
<td>30 Dec 2011</td>
<td>Shanghai No.7 People's Hospital, People Republic of China.</td>
<td>The invention relates to triamcinolone acetonide biodegradable maltose microneedle array which contains (1) triamcinolone acetonide or its pharmaceutically acceptable salt and (2) maltose or its hydrate, wherein the length of microneedle is 800-1500 μm, the diam. of the microneedle is 100-300 μm and array d. is 9-100 needles/cm².</td>
<td>China</td>
<td>[165]</td>
</tr>
</tbody>
</table>
Table 6 Patents on chemicals used for microneedle transdermal delivery system

<table>
<thead>
<tr>
<th>Patent Number</th>
<th>Date of Filing</th>
<th>Applicant</th>
<th>Key Invention</th>
<th>Country</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>GB2472778A</td>
<td>17th Aug 2009</td>
<td>PANGAEA LAB LTD</td>
<td>Microneedle Roller.</td>
<td>Great Britain</td>
<td>[166]</td>
</tr>
<tr>
<td>WO 2011026144 or S 20110052694</td>
<td>31st Aug 2009</td>
<td>AllTranz Inc., USA</td>
<td>DD system for pharma active ingredients (e.g., cannabidiol and prodrugs of cannabidiol.)</td>
<td>USA</td>
<td>[167]</td>
</tr>
<tr>
<td>US 20130171722</td>
<td>3rd Jan 2012</td>
<td>City University of Hong Kong, Hong Kong</td>
<td>Injection of a substance into a subject including elongate non-hollow micro-nanoneedles for delivering bioactive substance including drug and gene molecules such as plasmid DNA, siRNA, miRNA, shRNA,</td>
<td>USA</td>
<td>[170]</td>
</tr>
</tbody>
</table>
4. Conclusion

Oral administration and hypodermic syringes are the most commonly used delivery methods in today’s society. However, they pose several disadvantages such as painful side effects of using hypodermic syringes or the problem associated with oral administration such as drug bioequivalence [3]. TDPs pose numerous advantages as an alternative method as they provide controlled release of medicine to the patient in a minimally invasive manner. However, they cannot permeate large molecules to pass the SC (the top layer of skin), thereby limiting the medical application to patients. MNs have been proposed to overcome this limitation and provide the transdermal delivery of large molecular weight proteins such as shown by Benson and Namjoshi [4]. Various MN designs and fabrication methods have been explored in the literature ranging from the fabrication of, hollow, solid, desolvable, sharp and short MNs. MNs can be made from polymers, metals, glass and silk. There is a gap in the literature that has not been explored – the commercial viability of MNs – for an industrially viable product to be manufactured on an industrial scale. Various techniques discussed in this literature review have shown laborious techniques and involve the use of non FDA approved excipients such as silicon. There is a growing trend in the amount of publications surrounding MN technology. With the increase in the use of MN for commercial scale products, the upward trend in number of publications is unlikely to change in the next decade, due to continuous advances in technology.

The use of time series analysis allows the extrapolation of trends in data to predict the number of journal papers published. This can occur provided the number of data sets (observations) is sufficient to produce a good estimate. In the case of microneedles, solid and hollow, this was possible. However this was not sufficient for dissolvable microneedles.

5. Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

6. Funding

This work was partly supported by Loughborough University, UK and EPSRC, UK.
7. References


[34] H. M. Wolff, “Future of transdermal drug delivery systems (TDDS),” American


[58] R. F. Donnelly and A. D. Woolfson, “Patient safety and beyond: What should we expect
from microneedle arrays in the transdermal delivery arena?,” *Therapeutic Delivery*, vol. 5, no. 6, pp. 653-662, 2014.


[80] B. Boettcher, K. J. Stahlhofer, V. Mattle, V. Seeber, C. Brezinka and L. Wildt,


X. Chen and W. Zhang, “Method and apparatus for delivery of bioactive molecules to
cells”. Hong Kong Patent US 20130171722, 4 July 2013.