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REVIEW ARTICLE

Microneedles for drug delivery: trends and progress

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Abstract

In recent years, there has been a surge in the research and development of microneedles (MNs), 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 MNs have been researched in the literature and have several advantages compared with solid or hollow MNs, 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 MN research and shows the rapidly growing numbers of research papers and patent publications since the first invention of MNs (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.

Keywords

Autoregressive integrated moving average, microneedle, time series analysis

History

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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 (Davis et al., 2004; Escobar-Chávez et al., 2011). 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 (Guy, 1996). 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 and DNA (Benson & Namjoshi, 2008; Daugimont et al., 2010; Kalluri & Banga, 2011; Garland et al., 2012; Chandrasekhar et al., 2013; Katsumi et al., 2014), so that they can permeate through the skin.

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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 (MNs) 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) (Sullivan et al., 2008; Li et al., 2013). 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 (Sullivan et al., 2008). 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 (Prausnitz & Langer, 2008).

Transdermal delivery includes the applications of gels, creams, ointments and more recently TDP (Margetts & Sawyer, 2007; Behin et al., 2013; Nalesniak et al., 2013). One transdermally delivered drug that is commonly used is nicotine (Ravi et al., 2011), first developed in 1984 by Rose et al. (1984) to help smokers give up smoking. The drug was Food and Drug Administration (FDA) approved in 1991 and has been on the market since 1992 (Margetts & Sawyer, 2007).

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 (Sinha & Kaur, 2000; Garland et al., 2011; Han & Das, 2013; Ling & Chen, 2013). TDPs are applicable for molecules that are traditionally smaller than 500 Da (Benson, 2005). Methods that have been employed to solve the short comings of both TDPs and hypodermic injections are ultrasound (Yamashita et al., 1996; Han & Das, 2013; Nayak et al., in press), MNs, iontophoresis (Langkjær, et al., 1998), electroporation, chemical enhancers and others (Yamashita et al., 1996; Yang et al., 2011). These techniques can overcome the protective SC barrier as they allow the passage of large molecular compounds such as proteins and DNA (Benson & Namjoshi, 2008; Daugimont et al., 2010; Li et al., 2013; Zhang et al., 2014a,b). 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 (McAllister et al., 1998; Mitragotri, 2013; Pierre & Rossetti, 2014). The MNs are small enough in length to avoid touching nerve endings of a patient, thereby, causing little or no pain (Henry et al., 1998). Furthermore, MN technology has shown to be more advantageous in comparison to the other TDD techniques (Prausnitz et al., 2004), such as the ability to deliver large molecular molecules that are larger than 500 Da (Benson, 2005) 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 DD technologies (Wu et al., 2012; Chandrasekhar et al., 2013; Fazil et al., 2013; Kamboj et al., 2013; Tuan-Mahmood et al., 2013; Zhang et al., 2013; Ita, 2014; Nalwa, 2014; Wolff, 2014) and specific drug deliveries, such as insulin (Martanto et al., 2004; Zahn et al., 2005; Ito et al., 2006; Khanna et al., 2008; Taylor & Sahota, 2013; Bronger, 2014; Natayan, 2014). 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 (Giri Nandagopal et al., 2014; Jain et al., 2014). 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 for the development the MNs-based methods. 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 (e.g. ''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 analyze 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 (Pankratz, 1983). For the completeness of this article, we discuss other relevant issues as well as follows.

Why MNs?

TDPs have been delivering a variety of drugs since the early 1980's such as testosterone, nicotine, selegiline and clonidine (Prausnitz et al., 2004). Although there are several commercially available TDPs, they are limited by the SC, which includes overcoming the mass transfer resistance (Margetts & Sawyer, 2007). TDPs administer drugs *via* passive diffusion as illustrated in Figure 1(A) (Shah et al., 2011). 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 (Margetts & Sawyer, 2007). 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 short comings previously outlined. Indeed, it has been illustrated by Benson & Namjoshi (2008) and many other researchers (Li et al., 2011b; Shah et al., 2011; Liebl & Kloth, 2012) 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 (Osborne et al., 2013), 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 past 20 years. Since the independent invention of the hypodermic

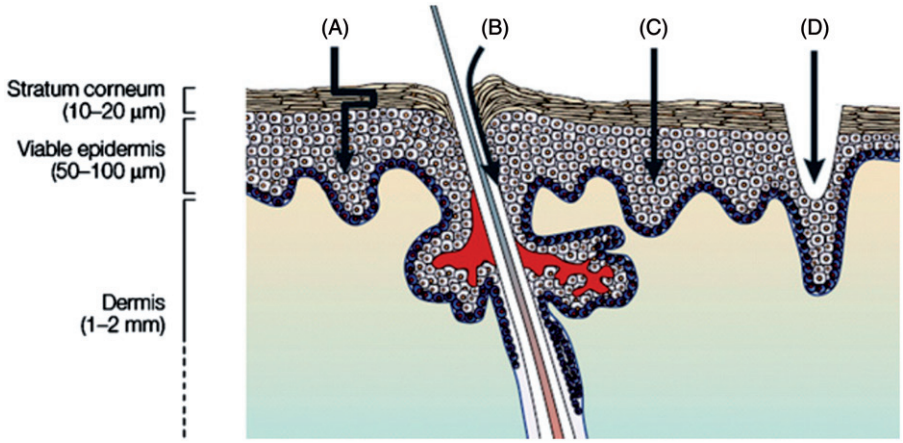

Figure 1. Cross section through human skin (A) intracellular, (B) hair follicles and sweat glands, (C) direct pathway through the SC and, (D) depicts the micron sized holes that can be created by MNs upon the skin (modified from Shah et al. (2011)).

needle in the mid 1850s (Krapp & Longe, 1998) by Wood & Pravaz, hypodermic needles (Lawrence, 2002), or syringes, have been the most common form to administer biotherapeutics (Sullivan et al., 2008). MN use has the advantage of simple patient administration of drugs with minimal invasiveness to the patients (Donnelly & Woolfson, 2014; Donnelly et al., 2014). The MNs would only permeate the SC and not the nerve receptors, consequently, the patients would feel little or no pain (Henry et al., 1998), though longer MNs 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 (Gratieri et al., 2013).

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 (Nordquist et al., 2007; Herwadkar & Banga, 2012; Kis et al., 2012; Singh et al., 2012; Edens et al., 2013; Koutsonanos et al., 2013; Ling & Chen, 2013; Cai et al., 2014; Gill et al., 2014). Vaccinations have the capacity to be delivered using MN patches, which require the patient to have no specialized training or the need for cold/refrigerated storage; this in turn can reduce the spread of diseases (Prausnitz et al., 2009; Edens et al., 2013). 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.

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 (Gray, 2005), 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 (Gray, 2008). The surface area of the skin constantly changes depending on age, weight loss and gain (Seidenari et al., 1994; Petrofsky et al., 2008), height and sex of a human being (Lee & Hwang, 2002). 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 (Gray, 2008; 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 (Shah et al., 2011). As evident in the figure, there are several pathways in which molecules can permeate through the skin, which can be categorized 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 (Benson, 2005). 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) (Benson, 2005).

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 (Kamboj et al., 2013). Therefore, analysis into skin thickness is important, as outlined in a study of skin thickness of Korean males and females conducted by Lee & Hwang (2002). 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 (Petrofsky et al., 2008). 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 (Kamboj et al., 2013) and MNs in specific.

Mechanical properties of skin

Understanding the mechanical properties of skin and detailed knowledge on various skin layers (Smalls et al., 2006) are important as the insertion of needles into the skin would alter the skins mechanical response to all skin layers (Roxhed et al., 2007). 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. (Cua et al., 1990; Karande et al., 2006; Smalls et al., 2006; Boettcher et al., 2013). It is a complex organ that continuously changes as we age (Cua et al., 1990). A property of skin that has been studied is the skin's ability to fold upon itself, such as wrinkling (Magnenat-Thalmann et al., 2002). Smalls et al. (2006) 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. (1990) 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 (Bohling et al., 2013).

Increasing permeability of skin

The use of MN as a DD 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 (Dhamech et al., 2010; Gittard et al., 2010; Milewski et al., 2010; Singh et al., 2010). 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 (Lanke et al., 2009; Prausnitz et al., 2009; Subedi et al., 2010). It is important to look at skin thickness when investigating increasing permeability of skin, as increasing skin permeability is important for 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 (Prausnitz, 2004). 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 (Henry et al., 1998; Park et al., 2005; Singh & Banga, 2013).

There have been multiple papers outlining various methods conducted to analyze different techniques to increase the permeability of skin. They can be categorized into chemical- and physical-enhancing techniques, some of which include, thermal ablation, sonophoresis and electroporation (Guy, 1996; Sinha & Kaur, 2000; Mitragotri & Kost, 2004; Daugimont et al., 2010; Han & Das, 2013; Mitragotri, 2013). Sinha & Kaur (2000) 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. (2004) 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 1(D) 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 (Hilt & Peppas, 2005; Trommer & Neubert, 2006; Nava-Arzaluz et al., 2012). One such example is the use of sonophoresis with MNs. It is a technique that allows molecules to permeate through the barrier of the skin more readily as ultrasonic waves create micro-vibrations on the skin (Mitragotri & Kost, 2004). Monomeric insulin analogues were studied to investigate the rate of iontophoresis transport on mice skin (Langkjær et al., 1998). The study showed clinically relevant results for insulin regulation.

Several review papers have been published on different types of enhancement techniques (Al-Saidan, 2004; Benson, 2005; Arora et al., 2008; Tanner & Marks, 2008; Banga, 2009; Yadav et al., 2011; Milewski & Mitra, 2012; Mitragotri, 2012; Ukawala Ravikumar & Vasava, 2012; Nalesniak et al., 2013), which outline various uses of chemical enhancers like N-methyl-2-pyrrolidone, a pyrrolidone (Sinha & Kaur, 2000) 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 lists some examples of enhanced protein/peptide delivery systems across the skin and the outcome of the experiments.

Trends in MN DD 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 (Aggarwal et al., 2009; Bariya et al., 2012; Desale et al., 2012; Shikida, 2012). There are multiple MN designs that have been created over the past decade. They can be categorized into two types, solid or hollow MNs (Bariya et al., 2011). The materials that have been used to fabricate them range from metal (Choi et al., 2013), glass, silicon (Wei-Ze et al., 2010) and biodegradable polymers (polydimethylsiloxane) (Chu & Prausnitz, 2011; Bediz et al., 2013) and silk fibroin (Tsioris et al., 2012). More recently, the use of fish scales have also been investigated (Olatunji et al., 2014). Ideally, the materials used would be pharmacologically inert, non-toxic, compatible with pharmaceutical ingredients, etc. (Sinha & Kaur, 2000). Metals traditionally used for MN fabrication consist of stainless steel, nickel coated in gold, titanium, platinum and palladium (Martanto et al., 2004; Wang et al., 2006; Mansoor et al., 2013). Although numerous journal papers have been published on the use of silicon as a primary substituent of MN

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

Protein/peptide	Delivery method	Main outcome	References
Bovine serum albumin	Polymeric microneedles	All drug released in six hours for *in vitro* permeation studies	Kochhar et al., 2012
Bovine serum albumin	Microneedles, ultrasound	BSA permeability of 1 μm/s is achieved with a 1.5-mm height microneedle and 15 W ultrasound output	Han & Das, 2013
Bovine insulin and bovine serum albumin	Microneedles coupled with iontophoresis	MN design containing 361 MNs/cm^2 of drug permeation in six hours on neonatal porcine skin *in vitro*	Garland et al., 2012
Botulinum toxin A	Stainless steel microneedles	Efficient diffusion through the dermis	Torrisi et al., 2013
Hepatitis B surface antigen	Elastic liposomes	Systemic and mucosal antibody response elicited in mice	Benson & Namjoshi, 2008
Hepatitis B virus DNA vaccine	Jet propulsion (Powderject)	Application to healthy human volunteers resulted in both humoral- and cell-mediated immune responses	Benson & Namjoshi, 2008
Insulin	Insulin-loaded dissolvable microneedle made of starch and gelatin	Dissolved in five minutes in rats to relative pharmacological availability and relative bioavailability of 92%	Ling & Chen, 2013
Influenza subunit vaccine	Microneedles delivery	Application to intramuscular injection in guinea pigs. Hemagglutinin concentrations as high as 20 mg/ml	Kommareddy et al., 2013
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 tilters	Edens et al., 2013

formulation, the material itself has yet to be FDA approved (Park et al., 2005).

MNs provide a direct pathway for drugs to access the viable dermis, allowing for a painless DD that by-passes the SC (Benson & Namjoshi, 2008). They also differ in shape, ranging from square, circular, flat tipped, sharp tipped, etc. (Henry et al., 1998; Park et al., 2005; Gupta et al., 2009; Swain et al., 2011; Kommareddy et al., 2013; Mansoor et al., 2013; Torrisi et al., 2013; Pierre & Rossetti, 2014). There has been a lot of research conducted on MNs for the delivery and monitoring of various drugs such as glucose control for diabetics (Ito et al., 2006; Nordquist et al., 2007; Ainslie & Desai, 2008; El-Laboudi et al., 2013; Taylor & Sahota, 2013; Ita, 2014), Alzheimer's disease (Wei-Ze et al., 2010), anti-cancer (Fang et al., 2008) and other conditions (Ezan, 2013). Vaccines have also been a prominent research field with numerous studies developed to allow dose sparing effects (Edens et al., 2013; Norman et al., 2014; van der Maaden et al., 2014). There have been multiple studies conducted to optimize the delivery of drugs using MNs with numerous methods to fabricate them.

Park et al. (2005) 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. (2009) 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 (Gupta et al., 2009).

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 (Indermun et al., 2014). 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 (Cheung et al., 2014; Nayak et al., 2014) or by channeling the drug through the channels of a hollow MN (Prausnitz, 2004). Multiple MN designs have been fabricated that facilitate the piercing of the SC allowing the permeation of drugs (Wei-Ze et al., 2010).

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 MN 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

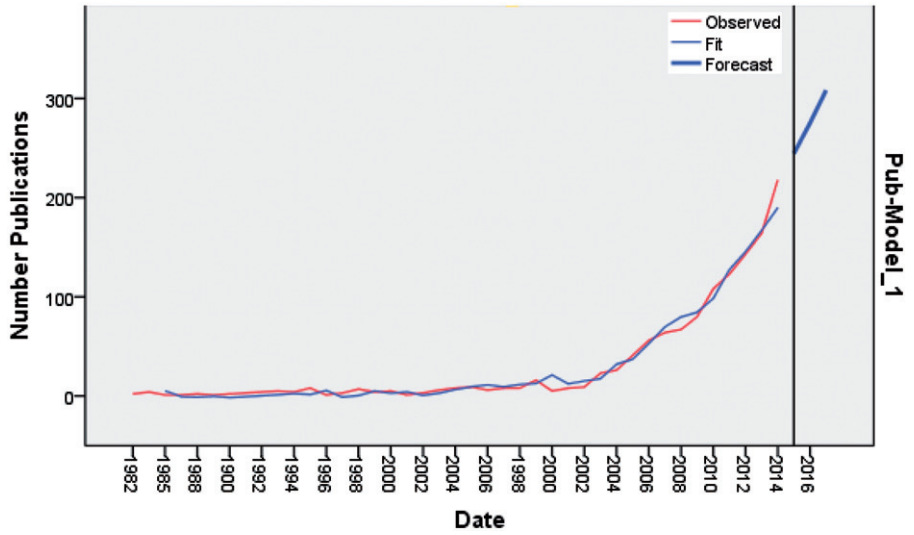

Figure 2. Forecasted, fitted and observed results on the trend of publications on microneedles using the keyword ''microneedle''.

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.

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 (Benson & Namjoshi, 2008). 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. (2009) have shown the *in situ* assembly of hollow liquid filled polymeric MNs for DD. 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 (Griss & Stemme, 2003; Davis et al., 2005; Roxhed et al., 2007). 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 (Escobar-Chávez et al., 2011). There have been other advancements in recent research to allow manufacture of any height, pitch and lumen-lumen spacing of the MNs (Lee & Jung, 2012; Mansoor et al., 2013). Griss & Stemme (2003) 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 method.

Roxhed et al. (2007) developed a method of fabricating MNs that combines a controlled flow of drugs using out of plane MNs. Nordquist et al. (2007) 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 MNs 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.

Solid MNs

Solid MNs are more robust than hollow MNs and have a stronger mechanical strength (Escobar-Chávez et al., 2011). MNs can produce micro pores in skin, which bypasses the SC layer, and allow drugs to permeate to the viable epidermis (Wei-Ze et al., 2010). There have been a number of methods and materials used to fabricate solid MNs (Jain et al., 2011; Khan et al., 2014), some of which are represented in Table 2.

The first reported case of solid MNs in literature was in the study of gene therapy (Hashmi et al., 1995). However, Henry et al. (1998) 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 four 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. (2014) prepared coated MNs utilizing a process named ''electrohydrodynamic atomization'' to produce pharmaceutical coatings on a single MN

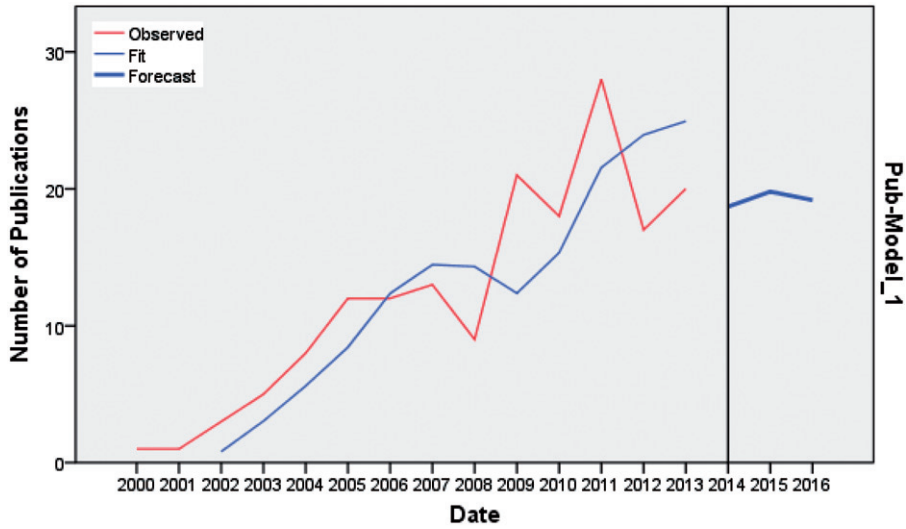

Figure 3. Forecasted, fitted and observed results on the trend of publications on hollow microneedle using the keyword ''hollow microneedle''.

patch for the purpose of applying personalized medicine. Martanto et al. (2004) 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 × 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. (2005) 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 (Park et al., 2005). The material was considered to be a safer alternative as it is mechanically strong and relatively inexpensive.

As listed in Table 2, silicon has been widely researched when developing MNs. Polydimethylsiloxane was used by Chu & Prausnitz (2011) to show the material combined the mechanical strength that metal MNs (Figure 5) 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 (Park et al., 2005; Hong et al., 2013; Lee et al., 2013; Nayak & Das, 2013). The biodegradable MNs were fabricated using a lithographic approach. Dissolving MNs were fabricated by Ito et al. (2006) in which insulin was mixed at room temperature to dextrin and deionized 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 (Ling & Chen, 2013) for a five-minute dissolution time when inserted into the skin. It was shown that 600 μm height and 300 μm base MN retained pharmacological 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.

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 (Benson & Namjoshi, 2008).

Although the use of silicon as a primary material in some MN fabrication methods is favored, it is hindered by the fact that the material is currently not approved by the FDA (Park et al., 2005). 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, 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

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Table 2. Methods of fabricating solid MNs.

Methods	Materials	Dimensions (μm)	Advantages	Disadvantages	References
Separable dissolving arrow heads	• (Polydimethylsiloxane (PDMS) Sylgard 184,), • Metal shaft • Water-soluble excipients – PVP, sucrose • PLGA	600 μm-long PVP/PVA arrowhead capped onto a metal shaft with an exposed length of 600 μm and a 100 μm overlap.	• Rapid (1–5 s)/painless drug/vaccines delivery • PDMS: inert/non-toxic/non flammable Rapid (1–5 s)/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	• Difficult insertion into skin as requires wider needle geometry (non-blunt shaft) • Non reusable • Fibrotic reaction	Chu & Prausnitz, 2011; Backovic et al., 2007
Dissolving	• Mixture insulin, water, dextrin	Basal diameter: 3.24 ± 0.16 and 0.55 ± 0.03 mm	• Bio-compatible	• Produce bio hazardous sharp waste • Large tipped	Ito et al., 2006
Pyramidal dissolving polymer	• Polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP) • A = pyramidal MN • B = extended pyramidal MNs • C = pedestal MNs	Base width × base depth × needle height: A: 300 μm× 300 μm× 600 μm. B: 300 μm× 300 μm× 900 μm. C: 340 μm× 340 μm× 900 μm) 10 × 10 array	• Ability to increase drug capacity and localize to the MN tip • Allowed a deeper insertion • Higher increase of drug to be dissolved	• Produce bio hazardous sharp waste	Chu et al., 2010
Deep reactive ion etching	• Chromium • Silicon wafers	120 μm length, < 1 μm tip diameter	• Mechanically strong	• Reusability questionably • Top 5–10 μm of MN damaged for a few samples	Henry et al., 1998
Dissolving. fabricated by a drawing technique to create a sharp tip	• Maltose	1200 μm length 60 μm tip diameter	• Requires no moulds, therefore no sharp waste	• Complicated process	Lee et al., 2011
Cutting metal using infrared laser, manually bending the MN structure, electropolished	• Metal	1000 μm length, 50 μm× 200 μm cross section at base, tapered to a sharp tip (angle 20°), 106 array	• A short MN insertion time was better than a longer insertion time to facilitate drug permeation	• Insertion of large array was difficult by hand without external device • Strong acids used	Martanto et al., 2004

(*continued*)

Table 2. Continued

Methods	Materials	Dimensions (μm)	Advantages	Disadvantages	References
Silicon master mould to make PDMS inverse mould	• Sugar glass MN: • Trehalose/mannitol (50:50 w/w) • Trehalose dehydrate/sucrose (75:25w/w) • Trehalose/sucrose (75:25 w/w) • Trehalose/sucrose (50:50 w/w) • 2% (w.w) methylene blue	200 μm base 20 μm tip 300 μm height	• Fast dissolution of drug into skin • Use of simple sugars to create biodegradable MNs	• MN patch needles to be left on the skin for potentially over 20 min	Martin et al., 2012
Stainless steel MN produced by chemical etching	• Stainless steel	750 μm height 200 μm × 50 μm at the base. Single row of five MNs	• Dose of measles vaccine is small, therefore the dimensions of the MN are sufficient to allow coating and delivery of the vaccine • Needles long enough for rat dorsal thickness (700 μm–1000 μm) penetration • Cost effective manufacturing	• Produce bio hazardous sharp waste	Edens et al., 2013
Dissolving MN	• Starch/gelatin (1:1 ratio) • PDMS mould	600 μm height 300 μm base 5 μm tip	• Rapid dissolution of five minutes was achieved • Pharmacological activity retain in the starch/gelatin	• Time to reach minimum plasma glucose level slightly longer for MN than for subcutaneous injection of insulin	Ling & Chen, 2013

to insert the MNs, the permeation of the drug increased (Wei-Ze et al., 2010). 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 lists the main parameters of super short MNs in the study conducted by (Wei-Ze et al., 2010). 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.

ARIMA model has been applied to the 16 journal papers that have been published in the journal database Scopus with the search term ''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.

MNs patents

MNs have become more prominent within the past 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 (Rizwan et al., 2009; Sachdeva & Banga, 2011; Singh et al., 2011). Table 4 lists a summary of patents that have been taken out on materials to fabricate MNs. Table 5 lists some example patents on the methods of MN fabrication. Table 6 lists 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 patens 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 (Bariya et al., 2011).

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.

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

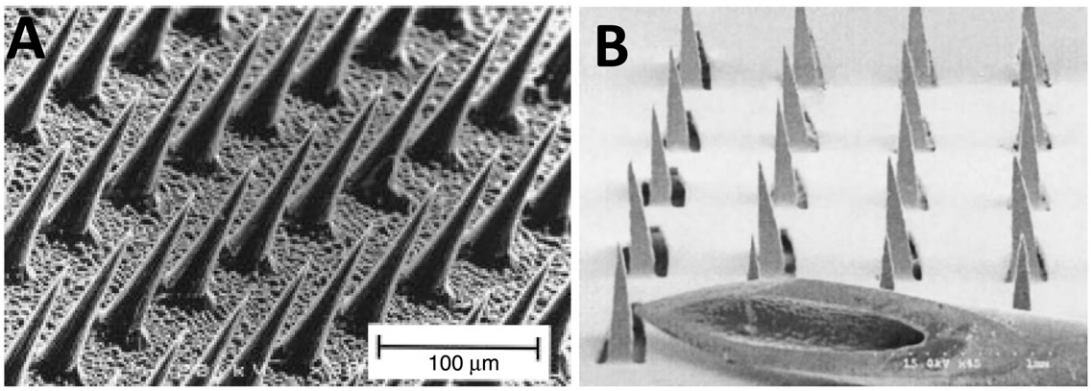


Figure 4. SEM images of various microneedles: (A) solid conical shaped microneedle (Henry et al., 1998), (B) solid microneedle next to a 27-gauge syringe (Martanto et al., 2004).

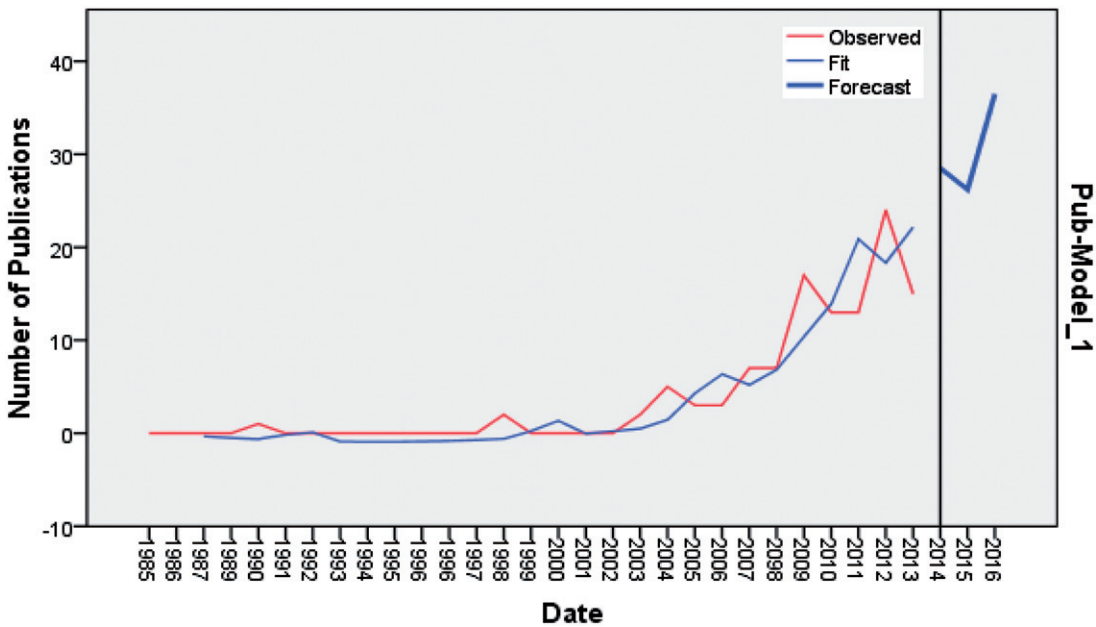


Figure 5. Forecasted, fitted and observed results on the trend of publications on solid microneedle using the keyword ''solid microneedles''.

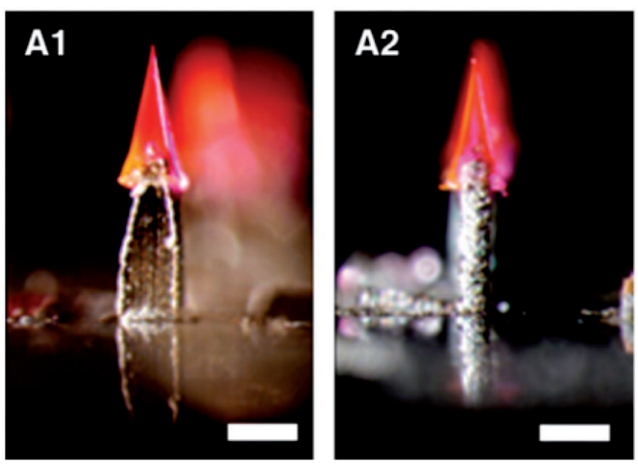


Figure 6. Images of an arrow head microneedle (Chu & Prausnitz, 2011).

bioequivalence (Guy, 1996). 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 & Namjoshi (2008). Various MN designs and fabrication methods have been explored in the literature ranging from the fabrication of, hollow, solid, dissolvable, sharp and short MNs. The 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

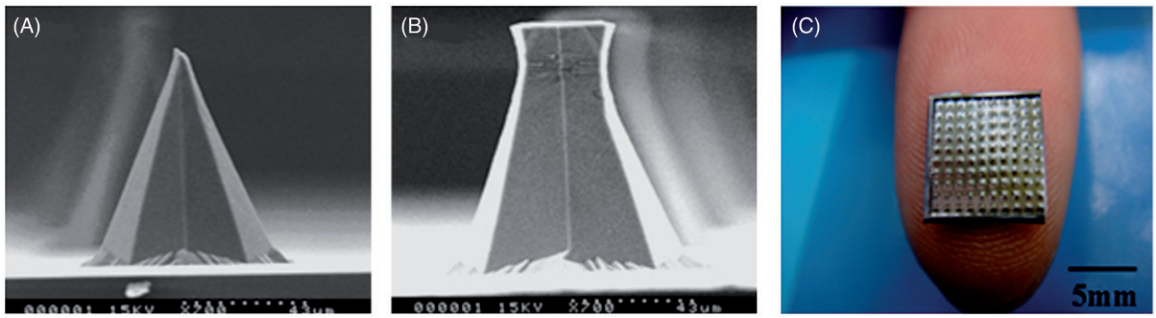
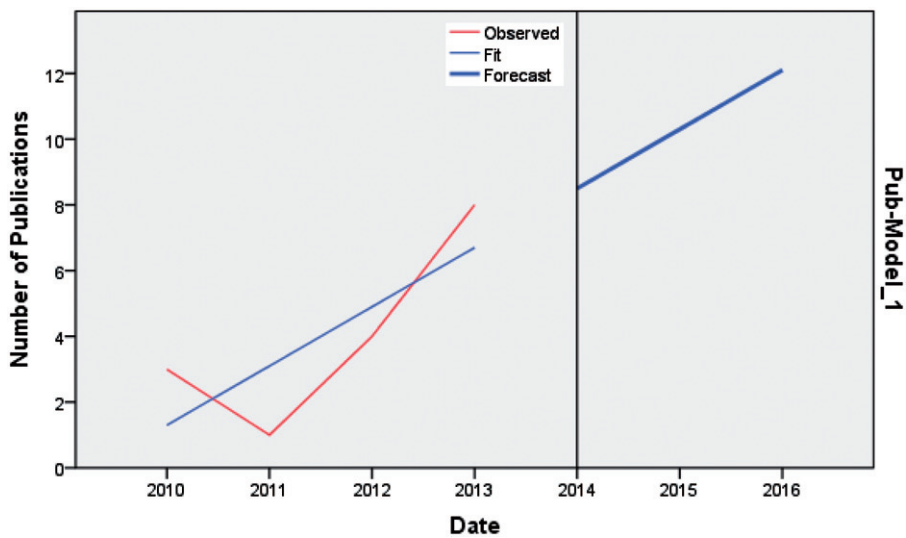


Figure 7. Super-short microneedles. SEM images of (A) a single sharp tipped super-short microneedle, (B) a single flat tipped super-short microneedle and (C) an angled view of a flat tipped super-short microneedle array (Wei-Ze et al., 2010).

Table 3. Parameters of super short MNs (Wei-Ze et al., 2010).

Method	Materials	Dimensions (μm)	Advantages	Disadvantages
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 with 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

Figure 8. Forecasted, fitted and observed results on the trend of publications on dissolvable microneedle using the keywords ''dissolvable microneedle''.



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 MNs, solid and hollow, this was possible. However this was not sufficient for dissolvable MNs.

Table 4. Example patents on microneedles technology.

Patent number	Date of filing	Applicant	Key invention	Country	References
US 2010042050	16 April 2007	Nemaura Pharma Ltd, USA	Applicator for microneedles.	USA, European, Japan, China, India	Chowdhury, 2010
WO 2011016230	4 August 2010	Medrx Co., Ltd., Japan	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.	Japan	Kobayashi & Hamamoto, 2011
WO 2011084951, US 20110172645	4 January 2011, 8 January 2010	Ratio, Inc., USA	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.	USA	Moga et al., 2011
WO 2011014514	27 July 2010	3 M Innovative Properties Company, USA	This disclosure relates to apparatus, assemblies, combinations and methods for infusing fluids by hollow microneedles.	USA	Gonzalez et al., 2011
CA 2696810 JP 2011078618 WO 2011043086 AU 2010201434 KR 2011067009 EP 2343102 A1	15 January 2010	Bioserentach Co. Ltd., Japan	Microneedle sheets are produced by injecting a needle raw material into a stamper formed with a concavity in a base material.	Japan	Honda et al., 2011
WO 2013096026	12 December 2012	3 M Innovative Properties Company, USA	Assembly of a microneedle adhesive patch. The assembly can include a backing and an adhesive and a matrix coupled to the backing.	USA	Cantor & Stockholm,2013
WO 2013066262	2 November 2011	Singapore	Invention relates to plastic microneedle strips that are used in TDD for increasing the DD rate through the skin.	Spain	Lim et al., 2013

Table 5. Example patents on methods of microneedle fabrication.

Patent number	Date of filing	Applicant	Key invention	Country	References
EP 2289843	31 August 2009	University College Cork-National University of Ireland, Cork, Ireland.	The invention relates to a method of fabricating a microneedle device of the type comprising an array microneedles on a flexible polymer support layer.	European	Cork University Patent EP 2289843
JP 2011083387	14 October 2009	Kyushu Institute of Technology, Japan; Nichiban Co., Ltd.	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.	Japan	Akiyoshi, 2012
CN 102000020	17 November 2010	Beijing Pharmaceutical Research Institute, Henan Lingrui Pharmaceutical Co., Ltd., People Republic of China;	The title polymer (molecular weight: 1000–1000 000) is selected from poly(*p*-dioxanone) or *p*-dioxanone	China	Huizhen et al., 2011

(*continued*)

Table 5. Continued

Patent number	Date of filing	Applicant	Key invention	Country	References
		Beijing Lingrui Hi-tech Co., Ltd.	containing copolymer (containing *p*-dioxanone 10–100 wt.%), such as poly(*p*-dioxanone-lactide), poly(*p*-dioxanone-glycolide), etc.		
CN 103263727	22 May 2013	Tsinghua University, People Republic of China.	A metallic microneedle array, including substrate and a metal sheet fixed on the surface of the substrate.	China	Yue & Wang, 2013
US 20130030374 A1	11 October 2012	Toppan Printing Co., Ltd.	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.	USA	Sugimura et al., 2013
CN 103181887	30 December 2011	Shanghai No.7 People's Hospital, People Republic of China.	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 diameter of the microneedle is 100–300 μm and array d. is 9–100 needles/cm^2.	China	Zhang & Wu, 2013

Table 6. Patents on chemicals used for microneedle transdermal delivery system.

Patent number	Date of filing	Applicant	Key invention	Country	References
GB2472778A	17 August 2009	PANGAEA LAB LTD	Microneedle roller.	Great Britain	Saacs & Cobbledick, 2011
WO 2011026144 or S 20110052694	31 August 2009	AllTranz Inc., USA	DD system for pharma-active ingredients (e.g. cannabidiol and prodrugs of cannabidiol).	USA	Stinchcomb et al., 2011
US 20110118560, US 20110118656, US 20110117150, US 20110118652, US 20110118696, US 20110118653, US 20110118697, US 20110118698, US 20110118652 US 20110118656	13 November 2009, 19 February 2010, 9 March 2010	Searete LLC, USA	Provides one or more medicines to mammalian subject.	USA	Eckhoff et al., 2011
CN 101991846	17 November 2010	Chifeng Boen Pharmaceutical Co., Ltd., People Republic of China	The invention relates to inactivated vaccine for immunoprophylaxis of bovine mastitis caused by *Escherichia coli* and its preparation method.	China	Li et al., 2011a

(*continued*)

Table 6. Continued

Patent number	Date of filing	Applicant	Key invention	Country	References
US 20130171722	3 January 2012	City University of Hong Kong, Hong Kong	Injection of a substance into a subject including elongate non-hollow micro-nano-needles for delivering bioactive substance including drug and gene molecules such as plasmid DNA, siRNA, miRNA and shRNA.	USA	Chen & Zhang, 2013

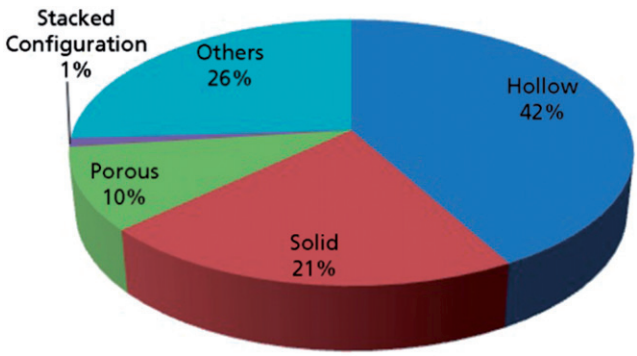


Figure 9. Division of patents filed based on type of MNs (Bariya et al., 2011).

Declaration of interest

The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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