

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, 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

38 which provide controlled release of medicines to patients in a minimally invasive manner.
39 However, large molecules cannot passively permeate through the stratum corneum (SC),
40 thereby, limiting the number of such transdermal drug products available to patients. Problems
41 can also arise from the TDP's peeling off due to the long periods for which they are required to
42 be applied. Several approaches have been researched to overcome the problems with TDPs
43 and allow delivery of compounds like proteins, DNA [4-9], so that they can permeate through
44 the skin.

45 **1.1 DD Routes**

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

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

68 However, there are disadvantages associated with TDPs, for example, the prevention
69 of large molecules from bypassing the SC, the outermost layer of the skin, which is the rate-
70 limiting barrier [18-21]. TDPs are applicable for molecules that are traditionally smaller than
71 500 Da [22]. Methods that have been employed to solve the short comings of both TDPs and
72 hypodermic injections are ultrasound [20, 23, 24], MNs, iontophoresis [25], electroporation,

73 chemical enhancers, and others [23, 26]. These techniques can overcome the protective SC
74 barrier as they allow the passage of large molecular compounds such as proteins and DNA [4,
75 5, 11, 27, 28]. MN technology in particular has grown over the past 15 years and can permit
76 drugs to bypass the SC layer by the insertion of micron sized needles that create micro
77 channels through the SC [29-31]. The MNs are small enough in length to avoid touching nerve
78 endings of a patient, thereby, causing little or no pain [32]. Furthermore, MN technology has
79 shown to be more advantageous in comparison to the other TDD techniques [33], such as the
80 ability to deliver large molecular molecules that are larger than 500 Da [22] and the versatility in
81 the application to allow solid or liquid formulations to be developed for disease specific
82 applications.

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

109 currently incomplete, therefore the analysis will give an indication of the trend till 2013 [51]. For
110 the completeness of the paper, we discuss other relevant issues as well as follows.

111 **1.2 Why microneedles?**

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

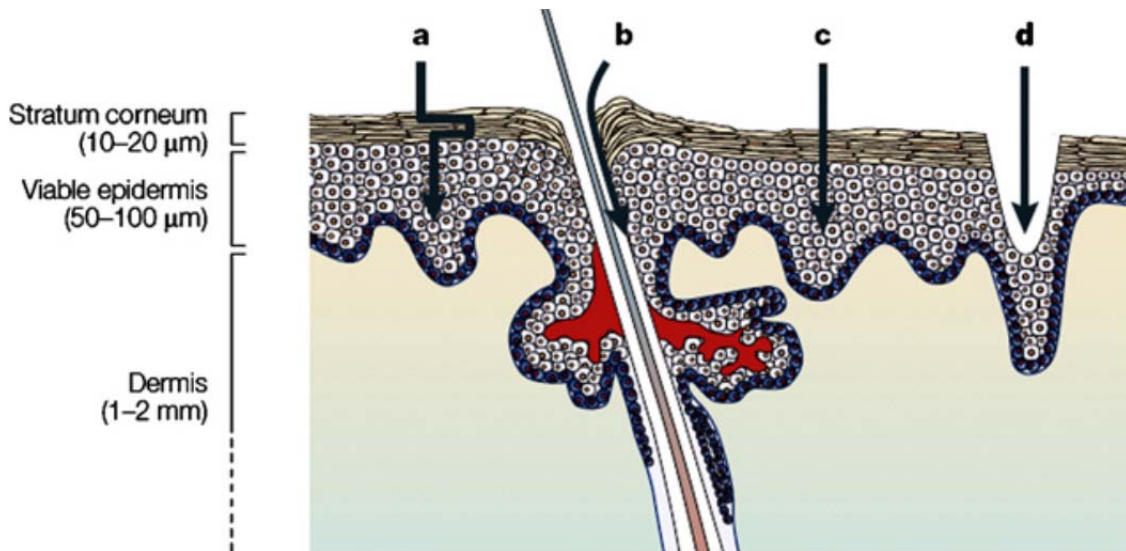
127 MNs have been made possible to make due to the technological advances that have occurred
128 in the last 20 years. Since the independent invention of the hypodermic needle in the mid
129 1850's [56] by Wood and Pravaz, hypodermic needles [57], or syringes, have been the most
130 common form to administer biotherapeutics [10]. MN use has the advantage of simple patient
131 administration of drugs with minimal invasiveness to the patients [58, 59]. The MNs would only
132 permeate the SC and not the nerve receptors, consequently, the patients would feel little or no
133 pain [32], though longer microneedles can also be used where deeper delivery of the drug is
134 desired. Therefore, the development of MNs is important as it has the potential to overcome
135 numerous disadvantages posed by the traditional DD systems [60].

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

144 1.3 Skin

145 We discuss skin and its properties briefly in this section because the skin barrier needs to be
146 understood and overcome before MNs can be designed and applied successfully. Human skin
147 is the largest organ in the human anatomy with an approximate surface area of 20,000 cm² on
148 an average human male, which spans the entire external surface of the body [70], in which its
149 main function is to contain all the internal organs, protect them against foreign organisms and
150 bacteria and act as a passive barrier. Some of the skin's other functions include the regulation
151 of internal body temperature, insulation, resistance against foreign bacteria and to provide
152 protection to the internal organs [71]. The surface area of the skin constantly changes
153 depending on age, weight loss and gain, [72, 73] height and sex of a human being [74]. It is
154 also a receptive organ to thermal heat and pain. The skin comprises of several layers of which
155 the main layers consist of the epidermis, dermis and subcutaneous tissue [71], see Figure 1.
156 The figure illustrates the SC, a non-living layer, which provides the first barrier to foreign bodies
157 and DD. Below the SC layer is the epidermis containing living tissue with no blood vessels.
158 Below this is where drugs are taken up by capillaries in the dermis layer [52]. As evident in the
159 figure, there are several pathways in which molecules can permeate through the skin which can
160 be categorised into two routes, the appendageal and transepidermal routes. The appendageal
161 route includes the movement through hair follicles and sweat glands (Figure 1b) and offers a
162 high permeability to ions and large polar molecules [22]. The surface area is considerably
163 small, and therefore, the exploration of passing drugs using this form of route is considered of
164 little importance. The transepidermal route is a direct pathway through the SC (Figure 1c). This
165 can occur via an intracellular (Figure 1a) or transcellular route (Figure 1c) [22].

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



177

178 Figure 1 Cross section through human skin a: intracellular, b: hair follicles and sweat glands, c:
 179 direct pathway through the SC and, d: depicts the micron sized holes that can be created by
 180 MNs upon the skin (modified from [52])

181 **1.3.1 Mechanical properties of skin**

182 Understanding the mechanical properties of skin and detailed knowledge on various skin layers
 183 [76] are important as the insertion of needles into the skin would alter the skins mechanical
 184 response to all skin layers [77]. Knowledge of the properties of skin would help better
 185 understand the effect MNs have and therefore help determine what needs to be overcome
 186 when designing or inserting a MN. Skin is a viscoelastic material in which research has been
 187 conducted to ascertain what factors can influence skin properties. These include the site at
 188 which a material can be located, the age of the patient, the thickness of the skin, orientation,
 189 etc. [76, 78-80]. It is a complex organ that continuously changes as we age [79]. A property of
 190 skin that has been studied is the skin's ability to fold upon itself, such as wrinkling [81]. Smalls
 191 *et al.* [76] investigated the body's biomechanical skin properties which showed a significant
 192 difference in elasticity, stiffness and laxity for the right side in comparison to the left side of the
 193 body. This was possibly the result of 90% of subjects being right handed, which illustrated that
 194 an increase in muscle tone can also have an effect on the biomechanical skin properties. Cua
 195 *et al.* [79]. concluded that the biomechanical properties of skin decreased with increasing age,
 196 which may be due to natural degeneration as we get older. SC thickness on human forearm,
 197 palm, cheek and lower leg were also studied to determine by using two non-invasive measuring
 198 techniques namely, confocal Raman spectroscopy and confocal laser scanning microscopy, to
 199 measure SC thickness which were then compared to the thickness in literature data. It was
 200 found that it was possible to accurately measure the SC thickness with both techniques [82].

201 **1.3.2 Increasing Permeability of Skin**

202 The use of MN as a drug delivery system is an important development as the potential to allow
 203 a wider scope of molecules to be transdermally delivered through the skin is greatly increased

204 [83-86]. The amount of drug that is delivered can also be increased. However, an
205 understanding of the permeability of skin would need to be established in order to determine
206 how to increase drug content [69, 87, 88]. It is important to look at skin thickness when
207 investigating increasing permeability of skin, as increasing skin permeability is important for
208 transdermal drug delivery (TDD). The invention of the MN can overcome this factor as the
209 needles bypass the SC layer, which is the rate dependent layer and can allow large molecular
210 weight proteins to pass into the blood stream [89]. A well-known method to quantify the drug
211 release through skin is the use of Franz diffusion cells, and therefore have been used in
212 literature extensively to calculate the permeability of skin [32, 90, 91].

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

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

228 Several review papers have been published on different types of enhancement techniques [15,
229 22, 96-103] which outline various uses of chemical enhancers like N-methyl-2-pyrrolidone, a
230 pyrrolidone [19] used in the application of insulin, ibuprofen and flurbiprofen. The applications of
231 these techniques for increasing skin permeability would be useful when delivering drugs
232 transdermally. Table 1 outlines some examples of enhanced protein/peptide delivery systems
233 across the skin and the outcome of the experiments.

234 **2. Trends in Microneedle (MN) Drug Delivery Method**

235 MNs can be considered to be a micron scale hybrid between TDPs and hypodermic syringes,
236 to overcome limitations that are associated with the individual application. They are small
237 arrays of needles that are generally less than 1 mm in length [104-107]. There are multiple MN
238 designs that have been created over the last decade. They can be categorised into two types,

239 solid or hollow MNs [108]. The materials that have been used to fabricate them range from
 240 metal [109], glass, silicon [110] and biodegradable polymers (polydimethylsiloxane) [111, 112]
 241 and silk fibroin [113]. More recently the use of fish scales have also been investigated [114].
 242 Ideally the materials used would be pharmacologically inert, non-toxic, compatible with
 243 pharmaceutical ingredients, etc. [19]. Metals traditionally used for MN fabrication consist of
 244 stainless steel, nickel coated in gold, titanium, platinum, palladium [47, 115, 116]. Although
 245 numerous journal papers have been published on the use of silicon as a primary substituent of
 246 MN formulation, the material itself has yet to be FDA approved [90].

247 MNs provide a direct pathway for drugs to access the viable dermis, allowing for a painless DD
 248 that by-passes the SC [4]. They also differ in shape, ranging from square, circular, flat tipped,
 249 sharp tipped etc., [32, 90, 116-121]. There has been a lot of research conducted on MNs for the
 250 delivery and monitoring of various drugs such as glucose control for diabetics [61, 46, 122-125],
 251 Alzheimer's disease [110], anti-cancer [126] and other conditions [127]. Vaccines have also
 252 been a prominent research field with numerous studies developed to allow dose sparing effects
 253 [63, 128, 129] . There have been multiple studies conducted to optimise the delivery of drugs
 254 using MNs with numerous methods to fabricate them.

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

Protein/Peptide	Delivery Method	Main Outcome	Reference
Bovine serum albumin	Polymeric microneedles	All drug released in 6 hours for in vitro permeation studies	[130]
Bovine serum albumin	Microneedles, ultrasound	BSA permeability of 1 $\mu\text{m/s}$ is achieved with a 1.5 mm height microneedle and 15 W ultrasound output	[20]
Bovine insulin and bovine serum albumin	Microneedles coupled with iontophoresis	MN design containing 361 MNs/cm ² of drug permeation in 6 hours on neonatal porcine skin in vitro	[6]
Botulinum toxin A	Stainless steel microneedles	Efficient diffusion through the dermis	[118]
Hepatitis B Surface Antigen	Elastic liposomes	Systemic and mucosal antibody response elicited in mice	[4]
Hepatitis B Virus DNA Vaccine	Jet propulsion (Powderject)	Application to healthy human volunteers resulted in both humoral and cell-mediated immune responses	[4]
Insulin	Insulin loaded dissolvable microneedle made of starch and gelatin	Dissolved in 5 minutes in rats to relative pharmacological availability and relative bioavailability of 92%	[21]
Influenza subunit vaccine	Microneedles Delivery	Application to intramuscular injection in guinea pigs. Hemagglutinin concentrations as high as 20.	[117]

		mg/ml	
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]

256

257 Park *et al.* [90] used biodegradable polymer MNs with sharp tips, to overcome problems
 258 associated with safety and disposal. They found that the use of biodegradable MNs increased
 259 skin permeability by three fold which increase the delivery of drugs transdermally. Gupta et al.
 260 [119] used hollow MNs for bolus delivery of lispro insulin in comparison to catheter infusion.
 261 They found that MNs inserted 1 mm into human skin showed rapid insulin absorption with no
 262 pain observed from the volunteers in comparison to catheter infusion [131].

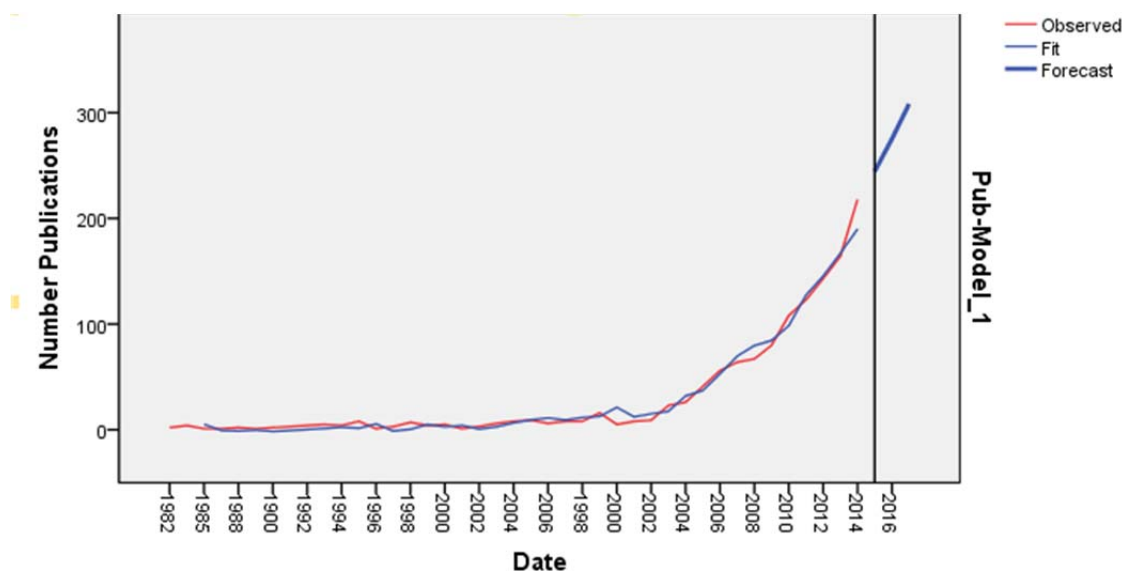
263 A method to fabricate MNs is important, as desirable attributes would be to have a simplistic
 264 fabrication method that is low cost and reproducible. This would be advantageous when mass
 265 producing MNs for industrial application [132]. However, the delivery of drugs using MNs can
 266 be conducted in four different ways. These can be known as “poke and patch”, “coat and poke”,
 267 formulating the API (active pharmaceutical ingredient) with a biodegradable polymeric MN [133,
 268 134] or by channelling the drug through the channels of a hollow MN [89]. Multiple MN designs
 269 have been fabricated that facilitate the piercing of the SC allowing the permeation of drugs
 270 [110].

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

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

283 Figure 2 represents the time series analysis in graphical form. The observed and fitted data
 284 show a good match which give the confidence that the ARIMA model is reliable in predicting the
 285 trend. The trend shows that there are some fluctuations in the number of publications in various
 286 years. However, overall, there is a considerable increase in the number of MN publications in

287 the past 10 years. The ARIMA fit shows a good prediction of the trend (beyond 2015) when the
288 total number of future MN publications are forecasted. The figure shows the yearly observations
289 of the number of publications published since 1982-2013 (1228 total publications) and
290 forecasted to 2016. The predicted NOJP for 2016 are shown to be approximately 300 which is
291 a significant increase from the 218 papers found in Scopus for year 2013.



292

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

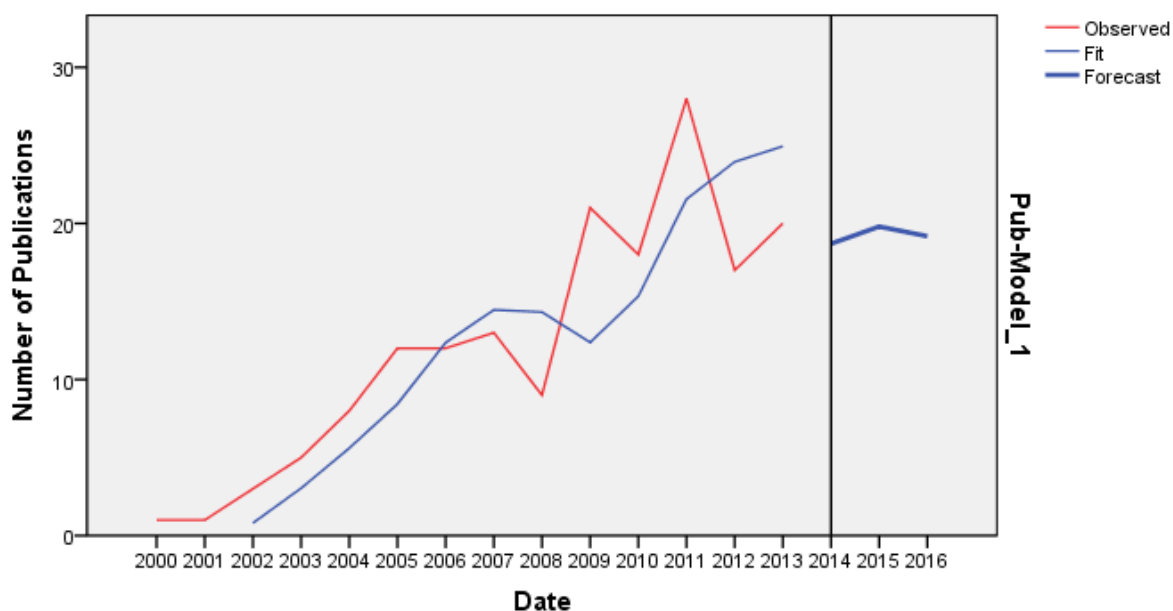
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296 2.1 Hollow MNs

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

313 Roxhed *et al.* [77] developed a method of fabricating MNs that combines a controlled flow of
314 drugs using out of plane MNs. Nordquist *et al.* [61] conducted a study using hollow MNs
315 fabricated from metal which improved the Griss and Stemme design. MNs of length 400 μm
316 and pitch 500 μm were produced.

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



327
328 Figure 3 Forecasted, fitted and observed results on the trend of publications on hollow
329 microneedle using the keyword "hollow microneedle"

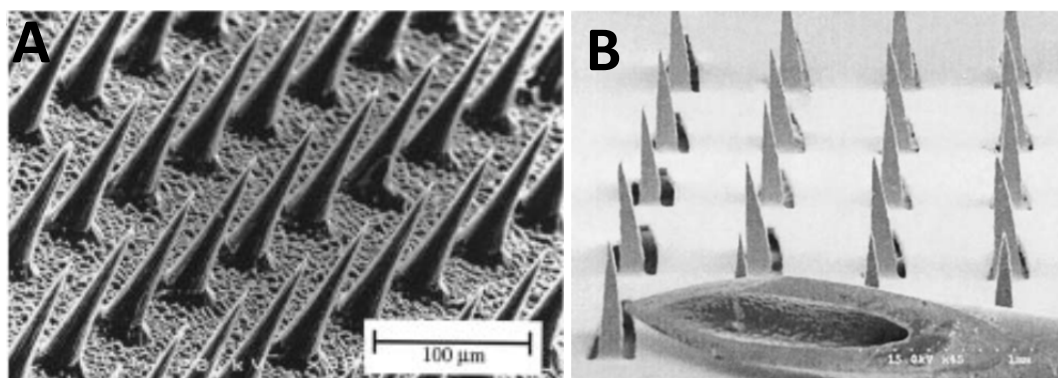
330 2.2 Solid MNs

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

335 The first reported case of solid MNs in literature was in the study of gene therapy [141].
336 However, Henry *et al.* [32] was the first to demonstrate the feasibility of delivering drugs

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

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



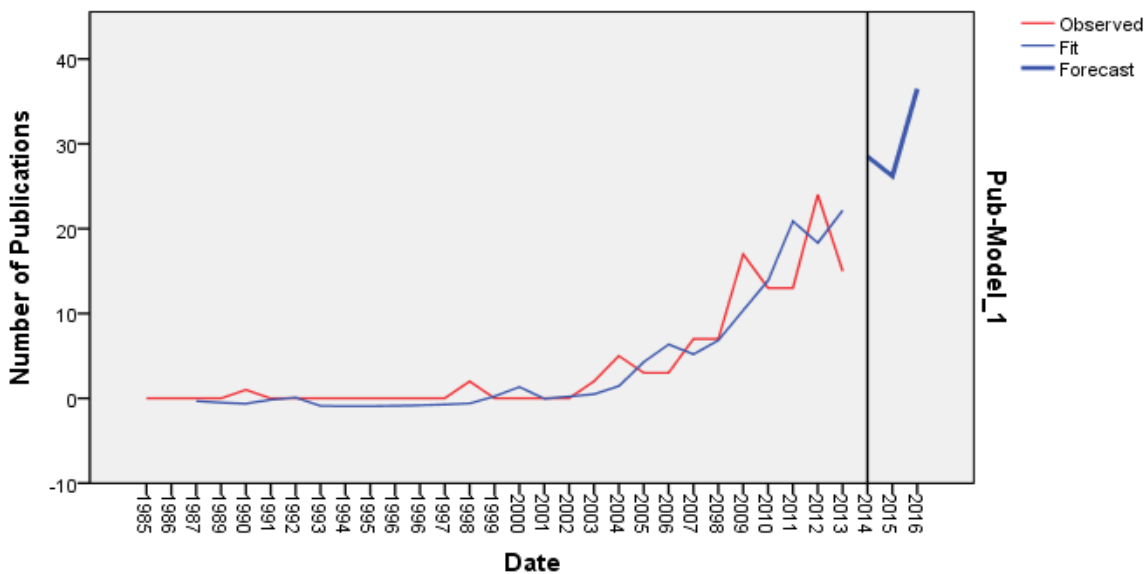
359
360 Figure 4 SEM images of various microneedles: (A) solid conical shaped microneedle [32], (B)
361 solid microneedle next to a 27-gauge syringe [47]

362 As shown in Table 2, silicon has been widely researched when developing MNs.
363 Polydimethylsiloxane was used by Chu and Prausnitz [111] to show the material combined the
364 mechanical strength that metal MNs can provide and the useful properties of silicon drug based
365 arrow head (Figure 6). They showed that the production of a blunt metal shaft with a detachable

366 drug encapsulated arrow head on the end could provide drug to the viable epidermis within
367 seconds to porcine and human cadaver skin.

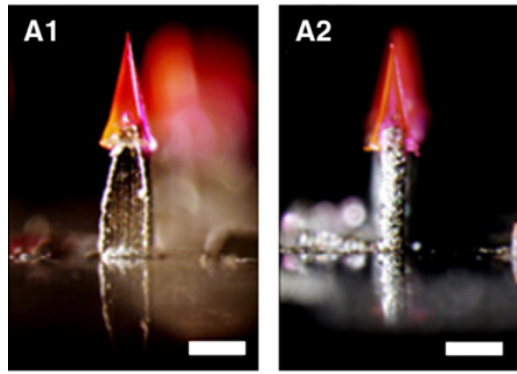
368 There have been several types of polymer MNs that have been created to overcome the non-
369 biocompatible and non-biodegradable properties of metal and silicon MNs [90, 143-145]. The
370 biodegradable MNs were fabricated using a lithographic approach. Dissolving MNs were
371 fabricated by Ito *et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

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



383

384 Figure 5 Forecasted, fitted and observed result on the trend of publications on solid
385 microneedle using the keyword "solid microneedles"



386

387

Figure 6 Images of an arrow head microneedle [111]

388 **Table 2 Methods of fabricating solid MNs**

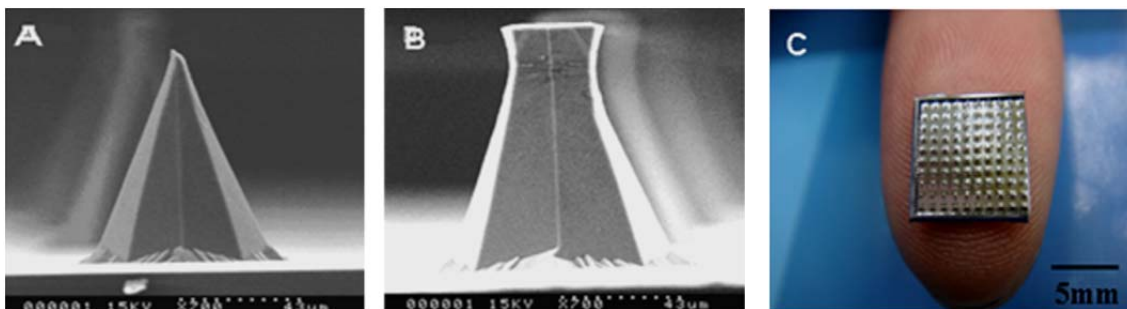
Methods	Materials	Dimensions (µm)	Advantages	Disadvantages	Reference
Separable dissolving Arrow Heads	<ul style="list-style-type: none"> • (polydimethylsiloxane (PDMS) Sylgard 184,) • Metal shaft • Water soluble excipients-PVP, sucrose • PLGA 	600 µm-long PVP/PVA arrowhead capped onto a metal shaft with an exposed length of 600 µm and a 100 µm overlap.	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Difficult insertion into skin as requires wider needle geometry (non-blunt shaft) • Non reusable • fibrotic reaction 	[111, 146]
Dissolving	<ul style="list-style-type: none"> • Mixture Insulin, water, dextrin 	basal diameter: 3.24±0.16 and 0.55±0.03 mm	<ul style="list-style-type: none"> • Bio-compatible 	<ul style="list-style-type: none"> • Produce bio hazardous sharp waste • Large tipped 	[46]
Pyramidal dissolving Polymer	<ul style="list-style-type: none"> • polyvinyl alcohol (PVA), Polyvinylpyrrolidone (PVP) • A = Pyramidal MN • B= Extended pyramidal MNs • C = Pedestal MNs 	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	<ul style="list-style-type: none"> • Ability to increase drug capacity and localise to the MN tip • Allowed a deeper insertion • Higher increase of drug to be dissolved 	<ul style="list-style-type: none"> • Produce bio hazardous sharp waste 	[147]
Deep reactive Ion etching	<ul style="list-style-type: none"> • Chromium • Silicon wafers 	120 µm length, <1 µm tip diameter	<ul style="list-style-type: none"> • Mechanically strong 	<ul style="list-style-type: none"> • Reusability questionably • Top 5- 10 µm of MN damaged for a few samples 	[32]
Dissolving. Fabricated by a	<ul style="list-style-type: none"> • Maltose 	1200 µm length 60 µm tip diameter	<ul style="list-style-type: none"> • Requires no moulds, therefore no sharp waste 	<ul style="list-style-type: none"> • Complicated process 	[148]

drawing technique to create a sharp tip					
Cutting metal using infrared laser, manually bending the MN structure, electropolished	<ul style="list-style-type: none"> • Metal 	1000 µm length, 50 µm x 200 µm cross section at base, tapered to a sharp tip (angle 20°), 106 array	<ul style="list-style-type: none"> • A short MN insertion time was better than a longer insertion time to facilitate drug permeation 	<ul style="list-style-type: none"> • Insertion of large array was difficult by hand without external device • Strong acids used 	[47]
Silicon master mould to make PDMS inverse mould	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Fast dissolution of drug into skin • Use of simple sugars to create biodegradable MNs 	<ul style="list-style-type: none"> • MN patch needles to be left on the skin for potentially over 20 minutes 	[149]
Stainless steel MN produced by chemical etching	<ul style="list-style-type: none"> • Stainless steel 	750 µm height 200 µm x 50 µm at the base. Single row of 5 MNs	<ul style="list-style-type: none"> • 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 	<ul style="list-style-type: none"> • Produce bio hazardous sharp waste 	[63]
Dissolving MN	<ul style="list-style-type: none"> • Starch/gelatin (1:1 ratio) • PDMS mould 	600 µm height 300 µm base 5 µm tip	<ul style="list-style-type: none"> • Rapid dissolution of 5 minutes was achieved • Pharmacological activity retain in the starch/gelatin 	<ul style="list-style-type: none"> • Time to reach minimum plasma glucose level slightly longer for MN than for subcutaneous injection of insulin 	[21]

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

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

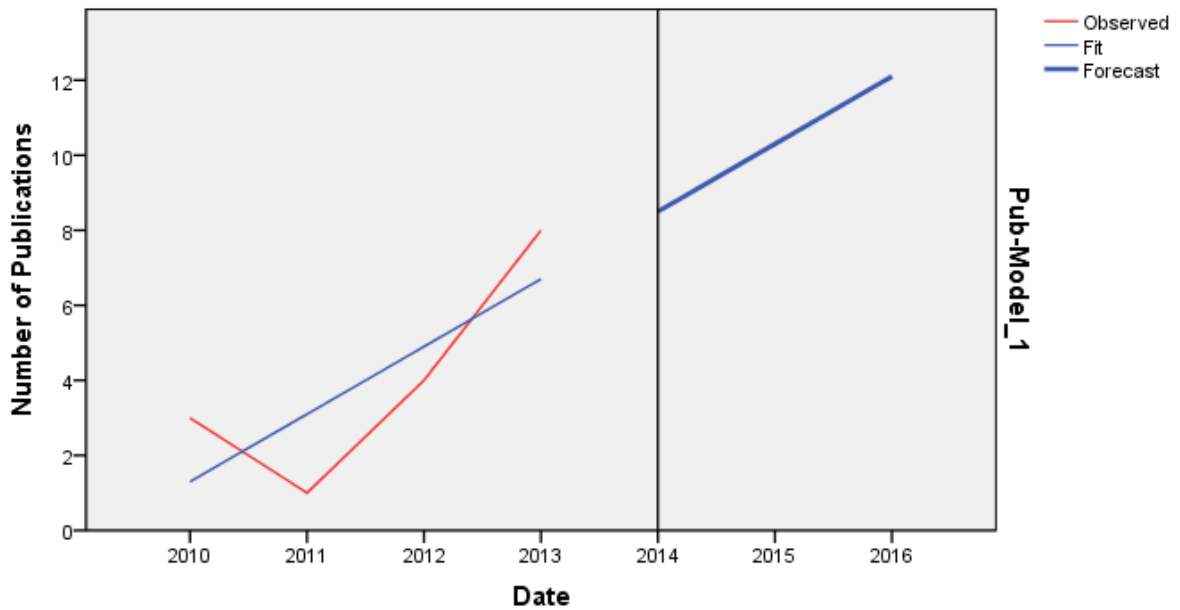
399 Solid MNs have been shown in the literature to have a typical length of 150 μm -350 μm .
400 However, studies into the fabrication of super short MNs with a length of 70-80 μm were
401 conducted by Wei-Ze *et al.* who have shown that super-short MNs are capable of
402 successfully delivering galanthamine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



415

416 Figure 7 Super-short microneedles used in this study, SEM images of A: a single sharp
417 tipped super-short microneedle, B: a single flat tipped super-short microneedle and C: an
418 angled view of a flat tipped super-short microneedle array [110]

419 ARIMA model has been applied to the 16 journal papers that have been published in the
420 journal data base Scopus with the search term “dissolvable microneedle”.



421

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

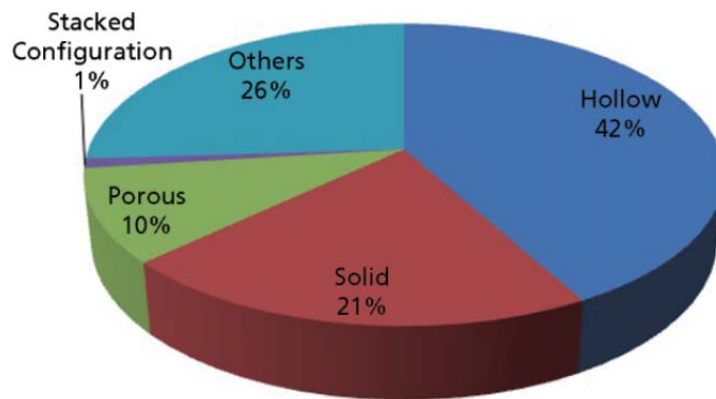
424 There is little data on the publication of dissolvable MNs. However there is a growing trend in
425 the use of dissolvable MNs, which is apparent due to the benefits of incorporating active
426 drug directly to the manufacture of MNs. Although the ARIMA forecast in Figure 8 seems to
427 fit this trend due to the lack of observations the forecast would not be a useful estimate of
428 the mean as there would essentially only be one observation per mean. Therefore this
429 forecast would not be an ideal assumption of the predicted NOJP for 2016.

430 Table 3 Parameters of super short MNs [110]

Method	Materials	Dimensions (µm)	Advantages	Disadvantages
Sharp tipped Super Short microneedles	<p>Microneedle: Silicon with 30% potassium hydroxide</p> <p>Patch:</p> <ul style="list-style-type: none"> • Backing: polyethylene • Adhesive: polyisobutylene 	75	<ul style="list-style-type: none"> • Strong material which does not break with insertion forces exceeding 8 N • Reusable 	<ul style="list-style-type: none"> • 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	<p>Microneedle: Silicon with 30% potassium hydroxide</p> <p>Patch:</p> <ul style="list-style-type: none"> • Backing: polyethylene • Adhesive: polyisobutylene 	80	<ul style="list-style-type: none"> • 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

431 **3. MNs Patents**

432 MNs have become more prominent within the last decade. The use of MNs as a method for
433 the transdermal delivery of drugs has become a more appealing technique as it overcomes
434 many disadvantages such as discomfort and pain that can be caused by hypodermic
435 needles or the non-bioavailability that oral dosage forms provide. Therefore it is important to
436 look at patents that have been filed within the last decade to correlate the trends of MNs
437 [150-152]. Table 4 shows a summary of patents that have been taken out on materials to
438 fabricate MNs. Table 5 illustrates some example patents on the methods of MN fabrication.
439 Table 6 shows patents on chemicals used for MN transdermal delivery system. Figure 9
440 illustrates the number of patents taken for various MN designs. It can be seen that there is a
441 considerable amount of MN patents taken out on hollow MNs. This may be due to the fact
442 that hollow MNs have the advantage of delivering a higher dosage in comparison to other
443 methods [108].



444
445 Figure 9 Division of patents filed based on type of MNs [108]

446 Transdermal delivery of drugs is a continually growing field with an abundant of journal
447 papers being published each year on MN technology and an increasing number of patents
448 filed. Therefore an increase in development for more commercially viable MN products
449 would need to be conducted.

450

451 **Table 4 Example patents on microneedles technology**

Patent Number	Date of Filing	Applicant	Key Invention	Country	Reference
US 2010042050	16 th April 2007	Nemauro Pharma Ltd, USA	Applicator for microneedles	USA, European, Japan, China, India	[153]
WO 2011016230	4 th Aug 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	[154]
WO 2011084951, US 20110172645	4 th Jan 2011, 8 th Jan 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	[155]
WO 2011014514	27 th Jul 2010	3M Innovative Properties Company, USA	The present disclosure relates to apparatus, assemblies, combinations, and methods for infusing fluids by hollow microneedles.	USA	[156]
CA 2696810 JP 2011078618 WO 2011043086 AU 2010201434 KR 2011067009 EP 2343102 A1	15 th Jan 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	[157]
WO 2013096026	12 th Dec 2012	3M 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	[158]
WO 2013066262	2 nd Nov 2011	Singapore	Invention relates to plastic microneedle strips that are used in TDD for increasing the DD rate through the skin	Spain	[159]

452

453 **Table 5 Example patents on methods of microneedle fabrication**

Patent Number	Date of Filing	Applicant	Key Invention	Country	Reference
EP 2289843	31 st Aug 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	[160]
JP 2011083387	14 th Oct 2009	Kyushu Institute of Technology, Japan; Nichiba n 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	[161]
CN 102000020	17 th Nov 2010	Beijing Pharmaceutical Research Institute, Henan Lingrui Pharmaceutical Co., Ltd., People Republic of China; Beijing Lingrui Hi-tech Co., Ltd.	The title polymer (molecular weight: . 1000-1000,000) is selected from poly(p-dioxanone) or p-dioxanone containing copolymer (containg p-dioxanone 10-100 wt.%), such as poly(p-dioxanone-lactide), poly(p-dioxanone-glycolide), etc.	China	[162]
CN 103263727	22 nd 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	[163]
US 20130030374 A1	11 Oct 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	[164]
CN 103181887	30 Dec 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 diam. of the microneedle is 100-300 μm and array d. is 9-100 needles/ cm^2 .	China	[165]

454

455

456 **Table 6 Patents on chemicals used for microneedle transdermal delivery system**

Patent Number	Date of Filing	Applicant	Key Invention	Country	Reference
GB2472778A	17 th Aug 2009	PANGAEA LAB LTD	Microneedle Roller.	Great Britain	[166]
WO 2011026144 or S 20110052694	31 st Aug 2009	AllTranz Inc., USA	DD system for pharma active ingredients (e.g., cannabidiol and prodrugs of cannabidiol.	USA	[167]
US 20110118560, US 20110118656, US 20110117150, US 20110118652, US 20110118696, US 20110118653, US 20110118697, US 20110118698, US 20110118652 US 20110118656	13 th Nov 2009, 19 th Feb 2010, 9 th Mar 2010	Searete LLC, USA	Provides one or more medicines to mammalian subject.	USA	[168]
CN 101991846	17 th Nov 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	[169]
US 20130171722	3 rd Jan 2012	City University of Hong Kong, Hong Kong	Injection of a substance into a subject including elongate non-hollow micro-needles for delivering bioactive substance including drug and gene molecules such as plasmid DNA, siRNA, miRNA, shRNA,	USA	[170]

457 **4. Conclusion**

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

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

480 **5. Declaration of Conflicting Interests**

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

483

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486

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