European Journal of Pharmaceutics and Biopharmaceutics 140 (2019) 121–140

Contents lists available at ScienceDirect

European Journal of Pharmaceutics and Biopharmaceutics

journal homepage: www.elsevier.com/locate/ejpb

Review article

Expanding the applications of microneedles in dermatology

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ARTICLE INFO

Keywords:
Microneedles
Dermatology
Skin cancers
Psoriasis
Skin infection
Viral warts
Dermatitis

ABSTRACT

Since the first patent for microneedles was filed in the 1970s, research on utilising microneedles as a drug delivery system has progressed significantly. In addition to the extensive research on microneedles for improving transdermal drug delivery, there is a growing interest in using these devices to manage dermatological conditions. This review aims to provide the background on microneedles, the clinical benefits, and challenges of the device along with the potential dermatological conditions that may benefit from the application of such a drug delivery system. The first part of the review provides an outline on benefits and challenges of translating microneedle-based drug delivery systems into clinical practice. The second part of the review covers the application of microneedles in treating dermatological conditions. The efficacy of microneedles along with the limitations of such a strategy to treat diseased skin shall be addressed.

1. Introduction

Drug administration to the skin can be divided into topical, transdermal and intradermal delivery. A drug delivery system is considered topical when the intended site of action of the dosed drug is on the superficial layers of the skin. On the other hand, drug delivery systems fall under the transdermal group when the drug is delivered through the skin and into the systemic circulation. A delivery system is considered intradermal when the intended target site is within the deeper layers of the skin such as the dermis [1]. These transdermal and intradermal drug delivery systems have increasingly been used in the past 20 years. These systems offer various advantages over oral delivery, including avoidance of hepatic first-pass metabolism, localised treatment of skin pathologies, controlled drug delivery, and improved patient compliance [2,3].

Advancement in the mechanistic understanding of skin permeation started to emerge in in 1943 with a notable review by Rothman -*The Principles of Percutaneous Absorption* [4]. Years of research in the area of skin permeation culminated with the regulatory approval of first transdermal patch for the delivery of the antiemetic drug, scopolamine in 1979 [5]. Since then, along with the progress in biophysical techniques, our understanding of skin permeation has evolved substantially.

The success of transdermal and intradermal drug delivery systems is dependent on the ability of the drug to permeate into the skin in sufficient quantities at an acceptable concentration to achieve the desired therapeutic effect. However, due to the efficient barrier function of the *stratum corneum*, the range of therapeutics that are available for transdermal and intradermal delivery is limited [6]. For a compound to conventionally traverse the intact *stratum corneum*, without an enhancing methodology, a drug molecule should ideally possess the following attributes: Mw $<$ 600 Da, Log P: 1.0–3.0, low melting point, hydrogen bonding group $\leq$ 2, non-irritating and non-sensitizing [7–9]. The boom of biotechnology has produced new range of therapeutics such as peptides, antibodies, oligonucleotides with astounding therapeutic potential. However, such macromolecules possess high molecular weights and extreme physiochemical properties which limits skin permeation using conventional transdermal delivery systems that are dependent on the passive diffusion of drugs across the skin. The development of such novel therapeutics therefore needs to be complemented with the design of effective drug delivery strategies, which can deliver the macromolecules to and across the skin in an efficient manner. The invention of microneedle assisted drug delivery systems overcomes the limitation imposed on the range of pharmaceuticals or cosmeceuticals available for percutaneous administration. Such biomedical micro devices can

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https://doi.org/10.1016/j.ejpb.2019.05.001
Received 29 January 2019; Received in revised form 30 April 2019; Accepted 2 May 2019
Available online 03 May 2019
0939-6411/

breach the skin with minimal discomfort to generate transient microchannels. These channels may be utilised for the delivery of therapeutics that would otherwise be unsuitable for transdermal or intradermal delivery.

Being the largest organ in the human body, the skin acts as a barrier between the body and the external environment, while having an immense influence on appearance and self-confidence. Indeed, there is now a considerable body of evidence on how dermatological conditions can lead to psychological problems and a reduced quality of life [10]. Hay *et al* conducted the Global Burden of Skin Disease study in 2010 that highlighted skin conditions were the 18th leading cause of health burden worldwide [11]. In addition, Dalgard *et al* recently conducted an extensive European multicentre study highlighting how adult patients with common dermatological conditions suffer significant psychological co-morbidities such as depression, anxiety, and even suicidal ideation [12]. UK figures indicate that 23 to 33% of the population are affected at any one time with 54% experiencing a skin condition in any given year [13]. The scope of dermatological conditions is vast with an excess of over 2000 diseases being described in the literature [14]. Despite the astonishing prevalence and impact on the society, dermatological conditions receive relatively little attention within both national and global health debates.

The utilisation of microneedles for the management and treatment of dermatological conditions is of great therapeutic and commercial value, because microneedles have the advantage of conferring painless drug delivery with minimal tissue damage, as the devices only penetrate the non-innervated epidermis [15]. In addition, the simplicity of applying the microneedle patch onto the skin permits patient self-administration without the need of assistance from healthcare professionals [16]. From an industrial perspective, the high prevalence of dermatological conditions suggests that there is a wide market and demand for such a drug delivery system.

The first section of the review provides a general background on microneedle technology. This section covers the following topics-history and development, clinical benefits and translational challenges. The second section of the review places emphasis on potential utilisation of microneedles for intradermal delivery to treat dermatological conditions i.e skin cancer, psoriasis, atopic dermatitis, skin infections and viral warts. We acknowledge that chemical enhancement strategies can also play an integral role in enhancing transdermal and intradermal delivery, but this is outside the scope of this paper. For reviews on chemical enhancement in skin permeation, readers are signposted to reviews elsewhere [17,18]. It is hoped that this review will provide an introduction to clinicians, formulation scientists and researchers in the area of dermatology on the possibilities and impact that microneedles may provide in improving the treatment of dermatological conditions. Also, this paper also aims to stimulate a paradigm shift towards utilising microneedles for the treatment of more severe dermatological conditions as well as cultivating interest in the area.

2. Microneedles: A brief history

Since the invention of hollow needles in 1844, hypodermic needles have been used for intravenous administration of drug to patients. With an estimated 16 billion injections administered worldwide, it is undeniable that it is one of the most widely used medical devices [19]. The benefits of hypodermic needles as devices to systemically deliver drugs and bioactives are still evident today as many pharmaceuticals have poor gastrointestinal absorption and are susceptible to enzymatic degradation [20]. In fact, the first medical intervention that a majority of individuals will undergo is an intramuscular vitamin K injection that is administered right after birth to avoid ‘haemorrhagic disease of the new-born' (HDN) [21]. Also, such administration permits bolus drug delivery as well as careful titration of narrow therapeutic index drugs. However, intravenous administration via hypodermic needle is associated with both pain and psychological distress in needle phobic patients.

Given these limitations, considerable efforts have been devoted to revolutionise the design of the hypodermic needle into a patient-friendly and painless drug delivery system. These efforts have ultimately culminated in the conceptualisation of microneedles for transdermal and intradermal application. Described as a hybrid between hypodermic needles and transdermal patches [22], microneedles are biomedical microdevices consisting of rows of fine needles [23]. Mark Prausnitz, one of the researchers who pioneered the research in the field, classified microneedles as a third-generation transdermal drug delivery system [5]. Such devices result in micron sized pores when applied to the skin that can be exploited for drug delivery. Typically, microneedles have a shaft length between 250 and 1000 μm while possessing tips sharper than those of hypodermic needles [24]. Upon insertion, microneedles can breach the *stratum corneum* (SC) and improve the bioavailability of various therapeutics and large molecular weight compounds, a significant advantage relative to conventional transdermal delivery.

The first microneedle patent was filed in 1976 by Gerstel and Martin from Alza Corporation, and at the time it was proposed that such micron-scale needles could be utilised for transdermal drug delivery in a painless manner [25]. However, it was not until the emergence of microfabrication tools from the microelectronics industry in the 1990s that research on utilising microneedles for drug delivery started to gain much pace. With the help of microfabrication tools, microneedles of varying dimensions, sizes and materials were generated to meet specific drug delivery requirements. During this period, three main groups from Becton Dickinson, Alza Corporation and Georgia Institute of Technology pioneered microneedle research for drug delivery [26].

The first ever published paper on microneedle arrays was by Hashimi *et al* in 1995 who developed a hollow microneedle array that injected bacterial plasmid for genetic transformation of nematodes [27]. However, it was not until 1998 that the first publication by Sebastien Henry on the use of microneedles for transdermal application emerged [28]. In 2004, significant progress in the area of microneedle emerged when Mark Prausnitz proposed that microneedle arrays may be utilised to enhance the delivery of not only small molecular weight molecules but macromolecules such as peptides, proteins, oligonucleotides and even supramolecular complexes [29].

Since then, there has been an exponential rise in publications regarding microneedles for pharmaceutical application. It has been nearly five decades since the first patent for microneedles was filed. Currently, most microneedles that are available on the market are indicated for cosmetic purposes. More recently, microneedle devices for intradermal delivery of vaccines have been approved by regulatory authorities for seasonal influenza vaccination [30–35]. Despite these advances, microneedle-based drug delivery systems are yet to make a significant impact in a clinical setting as most devices are still in preclinical and clinical studies. However, based on the current progress in microneedle research as well as the rise in the number of commercialised cosmetic microneedle products, it is not unreasonable to predict the emergence of therapeutic microneedle products indicated for the management of either acute or chronic diseases in the near future.

3. Clinical translation

The translation of microneedles as drug delivery devices into clinical practice will be dependent not only on the ability of the device to perform their intended functions but also the acceptability to healthcare professionals and patients. An exploratory study by Birchall *et al* attempted to capture end-user views on the technology. Through the use of focus groups, Birchall and colleagues identified that 100% of the general public participants and 74% of the healthcare professional participants were positive on the potential benefits of microneedle technology. The participants identified and acknowledged the benefit of microneedle technology, including a reduction in pain, tissue trauma,

and disease transmission as well as the potential for self-administration. However, concerns were raised by healthcare professionals on the effectiveness of delivery, delayed onset, reliability in dosing, the possibility of accidental self-injection and the potential for abuse by the general public [16].

Furthering this, Mooney *et al* conducted a qualitative assessment of the views of children and parents on using microneedles as an alternative method to conventional blood sampling techniques. Through interviewing focus groups, they discovered parents and children preferred the microneedle-based approach in comparison to conventional hypodermic needles. Parents displayed a preference for the microneedle approach as it resulted in less pain for children. However, concerns were raised about the likelihood of allergic reaction and reliability of such a system [36]. In a follow-up study, the group explored the views of children on the use and acceptability of microneedles, particularly hollow microneedles on blood and interstitial fluid sampling for monitoring purposes [37]. They found that the paediatric populations were more accepting of microneedle-based monitoring in comparison to conventional blood sampling by hypodermic needles. The group also suggested that in order for such technology to be more accepted among children, the microneedle patch ought to adopt an alternative name that avoids the term “needles” as it may instill fear among this group of patients.

More recently, Marshall *et al.* have conducted a comprehensive review on the perception and acceptability of microneedles among patients and healthcare professionals. They identified twelve pivotal studies that explored patients and healthcare professional views on microneedle technology with eleven of the studies displaying positive acceptance towards the device [38]. Thus, it can be seen that there is an acceptance for microneedle devices from end-users which allies with the demand that is primarily driven by the clinical advantages conferred by the microneedle delivery system. These advantages will be discussed in this section of the paper.

3.1. Clinical benefits

3.1.1. Painless

The pain associated with hypodermic needles can cause severe distress in patients, particularly in the paediatric population and those with needle phobia [39,40]. One of the most cited benefits of microneedles is the painless insertion of the device in comparison to hypodermic needles. This benefit is attributed to the micron size protrusion that pierces the *stratum corneum* without reaching the mechanoreceptors and nociceptors that reside within the dermis [15].

The pain associated with microneedles has been found to be proportional to the length of the microneedle, with longer microneedle having a higher tendency to reach and stimulate nociceptor within the viable epidermis [41]. However, there have been reports that some microneedles are still capable of achieving painless insertion despite penetrating into the superficial dermis [42]. This observation may be attributed to the small dimension of the needle tip used which reduces the likelihood of encountering and stimulating nerve endings [29].

One of the earliest trials to highlight the painless insertion of microneedles was by Kaushik *et al.* In their study, they compared the pain score between 26-gauge hypodermic needles with microneedle arrays (400 microneedles in an area of 3x3mm with needle of height of 150 μm). Despite the small sample size in their study (n = 12) the pain of insertion associated with microneedle was statistically less when compared to hypodermic needle [15]. Since then, there have been numerous reports from clinical studies that further corroborate the painless injection offered by microneedle patches [41,43–45].

3.1.2. Minimally invasive and small lesion size

Although conventional hypodermic injection is useful for systemic delivery of therapeutics, such an approach is viewed as crude and invasive. In comparison to hypodermic needles, microneedle applications are associated with less injection site damage and more rapid recovery [46]. In addition, various *in vivo* studies, both in human [47] and animal models [48] have shown that microneedle penetration results in minimal bleeding. Burton *et al* through their work on microneedle mediated delivery of proteins and molecules in a swine model, also support this observation. Even though the group noted that oedema and erythema were present at the insertion site, the severity was mild and resolved within an hour [49].

A clinical study conducted by Haq *et al* compared skin puncture induced by microneedles and hypodermic needles. In this study, the researchers found that the lesion and microchannel induced by platinum coated silicon microneedles showed minimal skin trauma with a more rapid recovery rate (8–24 h) in comparison to that induced by hypodermic needles [41]. Nevertheless, once the stratum corneum (the superficial layer of the epidermis) is penetrated by microneedles, the risk of infection increases regardless of the presence of blood circulation [50]. However, due to the skin’s self-defence mechanism, many studies report that the use of microneedle mitigates the potential risk of infection.[26]. Thus, it is clear that the minimally invasive nature of microneedle assisted drug delivery is another advantage of the device.

3.1.3. Ease of administration

Another advantage of microneedle delivery is the ease of administration which reduces the need for a trained health care professional for drug administration [51]. An example of a situation where microneedles provide ease of administration is the delivery of purified Tuberculosis (TB) antigen for the Mantoux test. Conventionally, the test involves the intradermal injection of the antigen into the forearm of a patient using a hypodermic needle at an angle of 5-15° with respect to the skin surface. Insertion of a needle outside this range would result in Mantoux test failure [52,53]. In an attempt to overcome this limitation, Jin *et al* fabricated solid chitin microneedles coated with TB antigen. The polymeric microneedles delivered the antigen into guinea pigs that resulted in a positive Bacillus Calmette–Guérin (BCG) vaccination test against TB. Although preliminary in nature, Jin and co-workers developed a microneedle-based TB test which is easy to administer and similar to applying a transdermal patch [54]. Such ease of delivery using a microneedle-based approach mitigates administration errors and as well as providing a possibililty for patients to administer the test themselves.

In addition, it’s a known fact that conventional hypodermic needle necessitates careful handling and disposal to avoid transmission of bloodborne pathogens. Despite exercising caution, needle stick injury is still prevalent with over 30 million healthcare professionals facing the risk of such injuries globally [55]. Such injury may lead to transmission of bloodborne infection such as HIV, hepatitis B and C [56,57]. In contrast to hypodermic needles, some microneedles are inherently self-disabling post-insertion, such as the dissolving and hydrogel-forming variants. Such microneedles provide a safeguard mechanism to healthcare workers and caretakers who might assist patients with drug administration. This will ultimately mitigate the risk of sharps injury and transmission of bloodborne infection. Another method to reduce the likelihood of disease transmission with microneedle reinsertion was developed by Chu *et al* via the use of separable arrowhead microneedles. Such microneedles consisted of micron-size polymer tips mounted on metal shafts. The tips of the needles rapidly separate from the metal shaft post-insertion leaving behind blunt metal shafts [58]. These microneedle arrays possess an excellent safety profile for patients as the residual blunt shafts post-insertion reduce the likelihood of re-insertion and disease transmission.

Another attractive feature of the microneedle patch is the discrete nature of the device due to the small size of the microneedle array. Furthermore, the ability of some microneedles to rapidly dissolve into the skin within a matter of seconds may promote ease of administration without the usage regime associated with a typical topical formulation such as a cream or gel [59]. Thus, drug administration via microneedles

could be achieved in a simple, quick and discrete manner by patients even in public spaces. Such patient-centred drug delivery systems may be more popular among patients resulting in improved compliance.

3.1.4. Stability of therapeutics

Another reported advantage of microneedle-based drug delivery systems is the enhanced stability of small drug molecules and biologics when they are formulated into the microneedle system either as coatings (for coated microneedles) or into the needle shafts (for dissolvable and hydrogel forming microneedles) [60,61]. Dissolvable and coated microneedle formulations usually consist of viscosity enhancers (such as carboxymethylcellulose (CMC)) to increase coating thickness, and sugars to stabilize biomolecules during and post-drying. The addition of sugar such as trehalose, into these formulations impart stability to the biologics via the formation of an amorphous sugar glass phase that minimises molecular mobility of biomolecules. This restricted mobility reduces the kinetics of possible chemical and physical degradation pathways, leading to improved stability. The second possible mechanism is the substitution of removed water molecules' hydrostatic interactions by hydroxyl groups from the sugars with the hydrogen bonding group on the biomolecules. Such substitution forms a stabilisation shell around the biomolecules thereby minimising dehydration induced changes during storage [62,63]. In addition, the addition of viscosity enhancing agents (such as CMC) into the microneedle formulation further suppresses molecular mobility. This mitigates the likelihood of the crystallisation rate and phase separation within the microneedle formulations leading to improved stability of therapeutics during storage [64].

Such advantage removes the need for cold chain storage and specialised transport systems. This is of great importance particularly in developing nations where cold chain storage facilities are scarce posing the risk of stability issues for some therapeutics. The enhanced formulation stability may substantially reduce logistic costs as well as the overall market price of microneedle products.

Such advantages have been documented by various research groups. For instance, Mönkäre *et al* showed that antibodies displayed enhanced stability when formulated into hyaluronan-based dissolving microneedles despite being stored at room temperature for up to 2 months [60]. Besides that, Mistilis *et al* demonstrated the effect of microneedle formulations in enhancing the stability of vaccines. In their work, Mistilis and co-workers highlighted that judicious selection of excipients such as lyoprotectants and stabilizer enhances the stability of monovalent vaccines for up to 2 years with no significant loss in immunogenicity despite being stored at 25 °C. Thus, further corroborating the enhanced stability profile conferred by microneedles [63].

Hirobe *et al* also investigated the stability of dissolving microneedles containing influenza vaccine when stored at 3 different storage temperatures 4 °C, 25 °C and 40 °C for 6 months. In addition, Hirobe and co-workers also studied the effect of long-term storage on the mechanical strength of microneedles in addition to stability of the vaccine. The group reported that long-term storage causes a decrease in the mechanical strength of the microneedle. However, such decrease was not significant as the microneedle still retained the mechanical strength needed to puncture the skin and elicit an immune response after a 6 month stability test [43].

Besides vaccines and antibodies, various studies have also reported that therapeutics integrated into the microneedle delivery system retain stability despite being stored at room temperature for prolonged periods. Such examples include ascorbic acid and niacinamide [65], human erythropoietin alfa [66], parathyroid hormone [67], insulin [68–70], desmopressin [71], and lidocaine [72].

3.2. Challenges towards clinical translation

From an economic perspective, it is estimated that strong demand and the need for a patient friendly formulation will influence production of microneedle devices. This will ultimately result in the fixed costs for microneedle fabrication be spread over more units of output, leading to an overall reduction in the final market price of the device. However, this is a very simplistic view, as the final price range may be highly dependent on parameters such as the material used to fabricate the needles such as polymers, drug of choice and potential excipients. In addition, as microneedles breach the skin there is a need for the device to be sterile prior to use, necessitating the use of aseptic manufacturing during microneedle fabrication. Such manufacturing techniques may lead to considerable production costs and overall final price of the product. Furthermore, as microneedles are a fairly new technology with respect to other, more established formulations (such as conventional transdermal patches), it is anticipated that the early market price for microneedles may be expensive until the technology gains popularity and acceptance from the public. Richter-Johnson *et al* have highlighted in their review that it is still too early to establish if microneedles are truly cost-effective with respect to current formulations [73]. For a more detailed review on the pharmacoeconomics of microneedles, readers are signposted to the review.

It is evident that microneedle technology has progressed significantly over the years. Such drug delivery technology boasts many clinical advantages that include patient-centred care. Despite these benefits, there are still considerable challenges that should be addressed before such technology will make an impact in clinical settings. Such challenges are discussed in this section.

3.2.1. Infection risk

Permeabilization of the *stratum corneum* through microneedle puncture may pose a risk for microbial invasion that could lead to local or even systemic infection. Driven by this argument, Donnelly *et al* conducted a microorganism permeation study across Silescol® membrane and porcine skin in an attempt to elucidate the ability of microorganisms to traverse microneedle pores in comparison to hypodermic needle injection. The group discovered that microneedle puncture resulted in lower microbial penetration into the viable epidermis in comparison to hypodermic needle puncture [74]. However, it is worth noting that the group only used microneedles with a length of approximately 280 μm, which does not represent the range of lengths frequently utilised in microneedle assisted drug delivery. Besides that, the selection of microorganisms used in the permeation experiment did not reflect the actual skin microbiota which is far more complex than that presented on the Silescol® membrane using the *in vitro* set up [75]. Despite these limitations, this landmark study showed that microneedle puncture was safer than conventional hypodermic injection.

More recently, Vicente-Perez *et al* evaluated the effect of repeated application of microneedles on the skin barrier properties. In their work, they investigated the effects of repeated application of microneedles on a hairless mouse model. The group discovered through monitoring skin barrier function and serum biomarkers for infection, that neither skin integrity nor inflammatory markers were altered in the murine model upon repeated microneedle application [76]. This finding demonstrated that the chronic application of microneedles displayed a good safety profile with respect to skin barrier function and infection risk.

However, it may be argued that the propensity for infection to arise via microbial penetration through microneedle-induced pores is further reduced due to the antimicrobial properties of the skin. The skin is known to produce antimicrobial peptides such as cathelicidins [77] and β-defensins [78,79] that function as a chemical shield within the skin. These compounds orchestrate components of the innate and adaptive immune systems against infection. Furthermore, the risk of infection could be further mitigated by aseptic fabrication and application of microneedles [80].

On the other hand, advancement in polymer chemistry has recently led to unprecedented control over polymer physicochemical properties. Hook *et al* through high-throughput microarrays, have identified a

group of hit polymers that are resistant to bacterial colonisation and growth. These polymers were used to coat silicone catheters and demonstrated a reduction in bacterial attachment both *in vitro* and *in vivo* [81]. The authors suggested that these polymers might also be used in other medical devices to reduce the likelihood of iatrogenic or secondary infection. The utilisation of such polymers in fabricating and coating microneedles may help to mitigate bacterial adhesion and penetration into the skin during microneedle insertion. Furthermore, the group of polymers discovered by Hook *et al* are non-bactericidal. Application of non-bactericidal polymer during microneedle insertion avoids placing selective evolutionary pressure on dermal microbiota, thus avoiding the development of antimicrobial resistant bacteria.

3.2.2. Skin irritation

Although the likelihood of adverse effects associated with microneedles is low, the use of microneedles has been associated to some extent with skin irritation. Such localised reaction frequently manifests in the form of mild erythema and oedema. It has been shown that the primary factor that dictates the likelihood for the development of skin irritation is the material which is used in fabricating microneedles [82]. Only on rare occasions have adverse events occurred after the use of microneedles, these events have been attributed to inappropriate use of the device

Another factor to consider is the development of irritation from the delivered drug or biotherapeutics. Due to the limited dimensions of microneedle arrays, particularly for dissolving and coated microneedles, only a limited amount of drug can be administered per array. Utilisation of a more concentrated amount of drug per microneedle may serve as a solution to circumvent this dose restriction. However, the delivery of concentrated drug into the skin may increase the likelihood of skin irritation.

Even though microneedle puncture may result in some local irritation, such effects are usually transient [76,83–85]. This was demonstrated by Damme *et al* who conducted a prospective randomized trial in 180 adults to investigate the safety profile of low dose influenza vaccines delivered via MicronJet, a microneedle device used for vaccination. The group noted that microneedle mediated delivery of vaccine induced more local skin reaction (e.g., erythema, induration, and swelling) relative to intramuscular injections. However, such skin reactions were considered mild and short-lived. In addition, the participants preferred the microneedle device over intramuscular injection as it offered a more painless delivery of the vaccine [86].

The safety of microneedles with respect to repeated skin application is further supported by results of the extensive phase II clinical trial conducted by Zosano Pharma [87] and Corium [88]. In these studies, the repeated application of coated titanium and dissolving polymeric microneedle for delivery of parathyroid hormone analogues in postmenopausal women resulted in no adverse reaction, illustrating the safety of such drug delivery technology [89].

3.2.3. Delivery of payload

Despite avoiding pain and distress associated with conventional hypodermic needles, there are limitations with respect to the amount of drug that can be delivered with microneedles. In the case of solid microneedles, the duration that microneedle channels remain open is a limiting factor for this drug delivery approach. Such limitation is attributed to the regenerative nature of the skin. The duration that microneedle channels remain viable using the 'poke and patch' approach has been reported to be as short as 15 min [90] and up to several hours [91,92]. This may reduce the amount of drug that could be delivered with this approach. However, strategies have been developed to prolong pore viability for drug delivery. These include the use of non-specific cyclooxygenase inhibitor such as diclofenac [93], HMG-CoA reductase such as Fluvastatin [94] and even through simple occlusion [45].

To overcome this limitation, one may opt to use coated and dissolving microneedles to deliver the payload into the skin. These types of microneedles can deliver the drug directly into the skin upon insertion in a one-step manner. However, these types of microneedles suffer the disadvantage of incomplete insertion and delivery of the drug into the skin [95,96]. Another drawback, particularly in the case of coated microneedles is the propensity for the polymeric coating to flake and peel off on the skin surface during insertion. For the dissolving type, the microneedle arrays may not possess sufficient mechanical strength to pierce the skin causing the needle to fracture or buckle under pressure. Besides that, some dissolving polymeric microneedles may have a heating step in the manufacturing process that may lead to degradation of the therapeutic [95,97]. In order to eliminate this limitation, most dissolving microneedles are now made from aqueous polymer blends rather than hot polymer melts [98–100]. The most apparent limitation is the small dimension of the microneedle array may limit the amount of drug that may be fabricated into these type of microneedle systems [101].

Given these drawbacks, hollow microneedles may serve as an alternative to coated and dissolving microneedles when there is a need to deliver a more significant quantity of payload. Through the use of hollow microneedles, one may attach the microneedle system to an already available injectable formulation. This would allow pneumatic-driven delivery of formulations similar to conventional hypodermic injection. However, this approach limits the selection of therapeutic to a liquid formulation. The use of liquid formulation in hollow microneedles also introduces the risk of leakage which can contribute to concerns with regards to payload delivery. Also, the presence of a hollow bore in the design reduces the mechanical strength of hollow microneedles, leading to an increased risk of fracture upon insertion into the skin [102]. In addition, hollow microneedles may be blocked by compressed dermal tissue which limits the available outlets for the formulation to flow out [103].

Recently hydrogel-forming microneedles have been introduced to overcome the limitations associated with other classes of microneedles. Once inserted into the skin, this class of microneedle takes up the surrounding intestinal fluid to generate a network of hydrogel conduit for which drug may flow from the backing layer and into the skin. Furthermore, the reservoir in the backing layer allows more drug to be loaded in comparison to coated and dissolving microneedles [104,105]. However, due to the hydrophilic nature of the hydrogel conduit, this type of microneedle may not be suitable for the delivery of hydrophobic drug molecules. In addition, rapid delivery of actives may not be readily achieved with these hydrogel-forming microneedles due to the slow diffusion of actives from the reservoir into the skin through the hydrogel conduits.

There is no "one size fits all" microneedle system for the delivery of drug across and into the skin. Judicious selection of microneedle system tailored to the nature of the disease and physiochemical properties of the drug is paramount in the design of an effective microneedle system to deliver the payload. As an emerging pharmaceutical technology, microneedles display considerable advantages such as being patient friendly, easy to apply and remove, minimally invasive and painless. The versatility and diversity in microneedle designs allow the device to be tailored to nature of the disease intended to be treated. Such advantages may have a significant clinical impact in the foreseeable future. However, before such transition could occur, some of the current limitations and challenges associated with microneedle technology need to be addressed.

4. Application of microneedles in dermatological conditions

Diseased skin has been shown to display differences in physiological and metabolic profile compared to healthy skin [106]. While there has been significant progress in the area of transdermal application of microneedles to deliver drug systemically through the skin, it is only recently that there is growing interest in the utilisation of microneedles

for treating dermatological conditions [107]. Microneedles provide a unique opportunity for specific and precise delivery of therapeutic to the defined dermal region while minimising unwanted systemic side effects. However, the current application of microneedles in dermatology has been for cosmetic purposes. For those who are interested in the cosmetic application to treat mild and superficial dermatological conditions, readers are signposted to the review written by Hou *et al.* This comprehensive review highlights the application of microneedling in treating acne, scars, actinic keratosis, hyperhidrosis, melasma, and alopecia [82]. It is clear that there is an opportunity to expand the scope of intradermal application of microneedles to treat more severe dermatological diseases. Therefore, we dedicate this section of the paper to discuss several potential skin conditions where microneedle technology may improve therapeutic outcome.

4.1. Skin cancer

Skin cancer is the most common malignancy in humans, the incidence is escalating dramatically worldwide [108]. Risk factors that predispose an individual to skin cancers include genetics [109], sunlight exposure [110], immunosuppression [111], human papillomavirus infection [112], therapy with photosensitizing drugs [113] and tobacco smoking [114]. As a result, considerable efforts have been devoted to reduce the incidence and impact of the disease through public awareness campaigns and skin screening programs [108,115,116]. In general, skin cancer can be categorised into two main groups which are non-melanoma skin cancer (NMSC) and malignant melanoma (MM). NMSC can be further subdivided into basal cell carcinoma (BCC) and squamous cell carcinoma (SCC) [117].

Despite being the least aggressive form of skin cancer, early detection and intervention are pivotal in managing NMSC as these skin cancers can lead to significant damage and disfigurement to local tissue, cartilage and bone [118,119]. On the other hand, MM are tumours that arise mostly from mutated melanocytes in the epidermis. These are the most aggressive form of skin cancers that have a high propensity to metastasize. Despite accounting for less than 5% of all cutaneous malignancies, MMs are responsible for the majority of deaths due to skin cancer [120].

NMSCs are treated either through surgery or non-surgical interventions. Despite the effectiveness of surgical interventions, accurate detection of tumour margins prior to surgery is pivotal in ensuring complete tumour resection. Such prerequisites are both time-consuming and technical, which are major limitations of this treatment strategy [118,121–123]. In addition, not all NMSC patients are suitable for surgical intervention and some may opt for non-surgical treatment due to lower overall cost and better cosmetic outcomes [124,125]. Non-surgical modalities include cryotherapy, radiotherapy, photodynamic therapy (PDT), curettage and topical drug therapy [121,126].

On the other hand, MM may be managed through early detection and excision. However, once metastasis has been established, it is extremely difficult to treat MM [127,128]. According to the National Institute for Health and Care Excellence (NICE) guidelines on managing melanoma, surgical excision is the primary treatment strategy to manage stage 0-II MM. In addition, complete lymphadenectomy is usually implemented in managing stage III MM. Should the cancer progress to stage IV, patients are usually referred to specialist skin cancer team for more advanced treatments. In addition, the use of systemic anticancer agents such as vemurafenib, dabrafenibfor, ipilimumab, and dacarbazine are usually considered for metastatic cases of MM [129].

The two drugs that are commonly used in the topical treatment of NMSC are imiquimod (Aldara®) and 5-fluorouracil (Efudix®). Imiquimod Fig. 1 (a) is an immunomodulator which exhibits no direct antiproliferative activity towards BCC. When topically applied, the immunomodulator stimulates toll-like receptors (TLR-7) on dendritic cells and monocytes leading to an induction of cytokine and chemokine production. As a result, both the innate and cell-mediated immune responses are stimulated, which ultimately lead to its antitumour activity [125,130]. 5-fluorouracil (5-FU) Fig. 1 (b) on the other hand is an antimetabolite which is converted intracellularly to fluorodeoxyuridine monophosphate (FdUMP). This metabolite binds to the nucleoside binding site of thymidylate synthase and inhibits the enzyme causing a decrease in the synthesis of thymidine; a nucleoside essential in the DNA replication. Additionally, 5-FU may also be metabolised to other metabolites which are later incorporated into DNA of cancer cells leading to DNA damage and ultimately cell death [131].

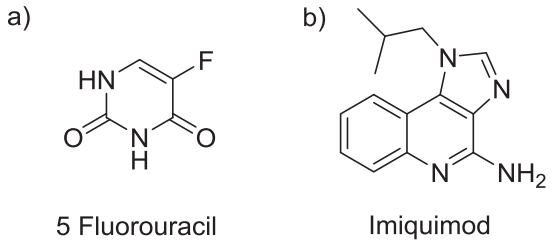

Fig. 1. Chemical structure of drugs used in the management of non-melanoma skin cancer (NMSC) (a) 5-fluorouracil and (b) Imiquimod.

Furthermore, PDT involves the eradication of cutaneous malignancy through the interaction of light of specific wavelength with a photosensitizing agent. Examples of photosensitising agents that are used in this treatment are 5-aminolevulinic acid Fig. 2 (a) and Photofrin® Fig. 2 (b). Upon topical administration, these compounds will accumulate in rapidly dividing cells. This is then followed up with irradiating the patient at the targeted dermal region with light of a specific wavelength that will elicit the generation of reactive oxygen from the photosensitizers. The interaction of reactive oxygen species with the cellular components at the target site will culminate in tumour death. [132–134].

Similar to photosensitisers, 5-FU and IMQ also possess physiochemical properties which limit their skin permeation and ability to reach deeper NMSC lesions [135–137]. Due to this limitation, 5-FU and IMQ are only currently licensed for the treatment of superficial BCC [121]. Therefore, there is a general need to improve the permeation profile of these drugs used in the management of skin cancers. Attempts to enhance the skin permeation of these drugs have been made either through the use of prodrug strategies or via chemical permeation enhancers. Despite the effectiveness of such strategies these methods suffer several weaknesses such as complexity in prodrug designs, toxicity, and irreversible alterations in the skin barrier caused by the use of chemical enhancers [136,138].

Additionally, topical therapy using these compounds is associated with side effects such as local inflammation, ulceration, and erosion which may reduce patient acceptability and compliance [139]. It has been suggested that a reduction in the topically applied dose may limit the likelihood of such side effects arising while improving compliance and overall therapeutic outcome [140]. In light of these limitations, a considerable amount of work has focussed on devising microneedle systems that could enhance the delivery of these compounds, to reach deeper tumour lesions in a dose-sparing manner and limit systemic side effects.

Research in utilising microneedles for delivery of therapeutics for the treatment of skin cancers was pioneered by Donnelly *et al* in 2008. Through the use of solid silicon microneedles and bioadhesive patches containing 19 mg aminolaevulinic acid (ALA) cm^{-2}, the group employed the 'poke and patch' strategy on a nude mouse model to enhance ALA delivery into the skin. This was the first study to demonstrate microneedles enhanced localised delivery of a photosensitiser to the skin. In addition, such a strategy also showed a reduced application time, and a reduction in the dose of ALA needed to elicit high-level of photosensitiser in targeted skin lesions [141]. Following these studies, various groups have explored different microneedle designs to deliver a

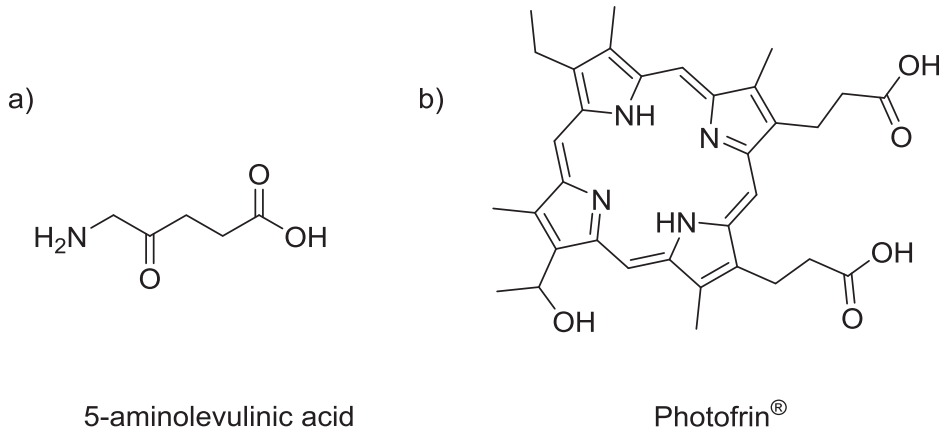

Fig. 2. Chemical structure of drugs used in photodynamic therapy for NMSC (a) 5-aminolevulinic acid and (b) Photofrin®.

range of anticancer drugs to the skin. Examples of such drugs include methyl aminolevulinic acid (MAL) [142], *meso*-tetra (N-methyl-4-pyridyl) porphinetetratosylate (TMP) [143], itraconazole [144] and 5-FU [145]. A summary of these studies is presented in Table 1.

For example, Jain *et al.* developed a 5-aminolevelunic acid (5-ALA) coated microneedle to improve dermal delivery of the photosensitizer to treat skin tumours. The group showed that the 5-ALA coated microneedle patch allowed improved delivery of 5-ALA deeper into the tumour lesion in comparison with topical application of 5-ALA cream. Interestingly, the coated microneedle also displayed better efficacy in the *in vivo* murine skin tumour model despite delivering a lower dose relative to topical cream application [146].

On the other hand, Naguib *et al.* demonstrated, using a murine model, the feasibility of using solid microneedles to enhance the intradermal delivery of 5-FU to treat skin tumours. In their *in vitro* work, the group demonstrated that 5-FU flux increased by 4.5-fold when 5-FU cream was applied on microneedle-perforated murine skin compared to cream application on intact skin. *In vivo* work using a mouse model with B16-F10 melanoma tumour showed that topical application of 5-FU cream (5%) on microneedle-perforated skin showed significant tumour inhibition relative to intact skin [145]. Although preliminary in nature, these studies highlight that microneedles hold great potential in improving intradermal delivery of antineoplastic agents to improve the treatment efficacy of skin cancer. More recently, several groups began to explore the strategy of delivering anti-melanoma vaccines as a method to treat and prevent the development of MM [120,147,148]. Recently, it has been proposed that delivery of anticancer agents into superficial skin tumours via dissolving microneedles may be more efficacious than nanosized carriers as microscale structures of microneedle enable long term retention of chemotherapeutics at tumour sites [149].

However, it is worth highlighting that due to the metastatic nature of MM, microneedles may not be a suitable standalone intradermal therapy, unless they are used for transdermal delivery of antineoplastic agents for systemic management of MM. In such a setting, microneedle-based treatment for melanoma ought to be used as an adjuvant to the standard MM care plan. Therefore, should research on utilising microneedles for the treatment of melanoma continue, researchers in the area ought to aware of the systemic nature of the disease and evaluate how microneedles may be able to be used to treat the MM that has invaded to other sites of the body. If such a strategy is deemed ineffective, research on microneedle-based skin cancer therapy ought then to focus on more localised tumours such as BCC or some variants of SCC.

4.2. Psoriasis

Psoriasis is a common, chronic papulosquamous disease with a prevalence of 1–2% in the general population [164,165]. The disease is not only confined to the skin but can be considered a systemic condition that may present with signs affecting the nails and joints as well. Psoriasis commonly presents itself as a scaly plaque on the elbow, knee, and scalp with varying degree of pruritus. Punch biopsy of psoriatic skin typically reveals acanthosis (epidermal thickening) and hyperkeratosis of the *stratum corneum*. Despite its prevalence, the aetiology of psoriasis is poorly understood with genetic predisposition and environmental triggers playing a pivotal factor in disease pathogenesis [166–168].

Despite the selection of treatments options for psoriasis, most of them are either suppressive or provide symptomatic relief with none being curative. In addition, some of these topical therapies have been reported to be cosmetically unacceptable and time-consuming to apply, while resulting in undesirable side effects such as irritation which limit patients' compliance [169,170].

Methotrexate is one of the drugs which is commonly used in the management of psoriasis. This folic antagonist is generally administered either parenterally or orally which leads to systemic exposure to methotrexate. This may eventually lead to side effects such as hepatotoxicity, nausea, vomiting, anaemia, thrombocytopenia and bone marrow suppression. Thus, efforts have been made to deliver methotrexate intradermally at psoriatic sites to limit the systemic exposure. Vemulapalli *et al* investigated the topical delivery of methotrexate via the use of solid maltose microneedles in combination with iontophoresis. The group found a synergistic enhancement of 25-fold in methotrexate delivery to the skin *in vivo* when microneedle and iontophoresis are used in combination in comparison with either modality alone [171].

Furthering this, Nguyen and Banga have also demonstrated the utility of using polylactic-co-glycolic acid (PLGA) microneedles, via the poke and patch approach to enhance delivery of methotrexate across porcine and human cadaver skin. However, the researchers also showed that skin pre-treatment using laser ablation resulted in greater enhancement of methotrexate across the skin in comparison to PLGA microneedle skin pre-treatment [172]. Although skin pre-treatment with laser ablation showed superior enhancement in the delivery of methotrexate across skin relative to microneedles, such approaches necessitate the use of complex, bulky and expensive equipment. Furthermore, the technical skills needed for safe and effective use of laser ablation may result in higher overall treatment costs for psoriasis. The simplicity of applying a microneedle patch followed by a formulation on the treatment site, might be more clinically translatable, as such treatment strategies may easily performed by patients and hence could be more cost-effective.

In addition, anti–TNF–α antibody therapy has been shown to be efficacious role in the management of psoriasis. The chimeric monoclonal antibody results in a rapid and significant decrease in epidermal inflammation in psoriatic lesions through neutralizing transmembrane-

Table 1
Summary of microneedle studies focussed on intradermal delivery of therapeutics for skin cancer. Abbreviations: ALA (aminolaevulinic acid), TMP (*meso*-tetra (N-methyl-4-pyridyl) porphinetetratosylate), MAL (methyl aminolaevulinic acid), protoporphyrin IX (PIX), 5-Fluorouracil (5-FU) programmed cell death protein 1 (PD1), ultraviolet (UV), signal transducer and activity of transcription 3 (STAT3), small interfering RNA (siRNA), Polyethylene glycol (PEG), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, chitosan/methoxy polyethylene glycol - polylactic acid (CPP), near infrared (NIR).

Microneedle design	Delivered therapeutics	Model to evaluate microneedle efficacy	Outcome	Refs.
7 × 7 hydrogel-forming microneedle array. 7 × 7 dissolving microneedle array	ALA and TMP	*Ex vivo* (neonatal porcine skin)	Both microneedle systems enhanced transdermal delivery of ALA and TMP *in vitro*. However, the hydrogel-forming microneedle was superior in delivering the larger molecule (TMP) than the dissolving microneedles over 24 h	[105]
6 × 7 solid silicon microneedle arrays that are 270 μm in height	ALA	*Ex vivo* (murine and porcine skin) *In vivo* (murine model)	Application of ALA bioadhesive patch on microneedle perforated skin enhanced delivery of ALA to the deeper regions of the skin in murine and porcine skin. Application of ALA bioadhesive patch on microneedle perforated skin demonstrated a dose-sparing effect and shorter application time but generated higher PIX concentration for photodynamic therapy	[141]
6 × 7 solid silicon microneedle arrays that are 270 μm in height	TMP	*Ex vivo* (murine and porcine skin) and *in vivo* (murine model)	Application of TMP bioadhesive patch on microneedle perforated skin enhanced both intradermal and transdermal delivery of TMP. However, the amount delivered is still small due to large molecular size of TMP. Application of TMP bioadhesive patch on microneedle perforated skin enhanced intradermal delivery of TMP with minimal transdermal delivery thus limiting unwanted systemic delivery	[143]
121 microneedles per array. Polymeric microneedle made of copolymer of methylvinylether and maleic anhydride.	ALA and MAL	*In vivo* healthy human volunteer (n = 14)	Application of 2% and 8% ALA or MAL, but not with 16% ALA or MAL, on microneedle perforated skin enhanced PIX production *in vivo*. No significant difference in erythema and photodynamic induced pain was observed between microneedle pre-treated and non-pre-treated skin	[142]
Disposable plastic stamps (DermaStamp and Dermaroller) with stainless steel solid bore needles, 100 μm in width and 2000 μm in length	ALA	*In vivo* human with actinic keratosis or Bowen's disease (n = 3)	Microneedling resulted in moderate to severe erythema with pinpoint bleeding, that was immediately managed with a sterile saline solution pad. Upon nanoemulsion application, conventional PDT was carried out. Complete resolution of AK and Bowen disease was achieved but at the expense of post-treatment erythema and crusting	[150]
700 μm ALA coated microneedle array. 57 microneedles per array	ALA	*Ex vivo* (porcine skin) using Franz cell set up *In vivo* (murine model)	The coated microneedle gave a delivery efficiency of 90% in *ex vivo* porcine skin. *In vivo* dermal study showed that the ALA coated microneedle delivered a lower dose of ALA relative to the topical cream application but achieved higher and deeper (480 μm) intradermal formation of PPIX. In addition, despite delivering a low dose (1.75 mg) via coated microneedle relative to topical cream (5 mg), coated microneedles managed to suppress tumour progression in murine tumour model. An effect that was not observed with only topical application of ALA cream	[146]
An array of 225 dissolving microneedles made from hyaluronic acid crosslinked with methylene bis(acrylamide) on a 9x9 mm^2 patch. Each microneedle is conical in shape with a needle height of 600 μm	anti-PD1 antibody in a self-dissociating nanoparticle	*In vivo* B16F10 murine model of melanoma	Microneedles efficiently penetrated the epidermis and released the self-dissociating nanoparticle containing Anti-programmed death (PD)-1 receptor antibody and glucose oxidase. The nanoparticles selectively released the antibody at the tumour site in a sustained manner. Significant tumour inhibition was observed. 40% of the mice in the treatment group survived while 0% mice survived in the control group	[151]
15 × 15 array of dissolving microneedle fabricated from hyaluronic acid. The microneedles had a height of 800 μm	anti-PD1 antibody (aPD1) and 1-methyl-DL-tryptophan	*In vivo* B16F10 murine melanoma model	The group treated with microneedle containing both aPD1 and 1-methyl-DL-tryptophan showed 70% survival at 40 days compared with 0% survival for the other control groups.	[152]
One-by-four arrays of 642 μm long solid polyglycolic acid microneedles followed by topical application itraconazole solution.	Itraconazole	*In vivo* human basal cell carcinoma murine model	Preliminary *in vivo* results indicated that microneedles may be used to facilitate delivery of itraconazole resulting in shrinkage of	[144]

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Table 1 (*continued*)

Microneedle design	Delivered therapeutics	Model to evaluate microneedle efficacy	Outcome	Refs.
Arrays of 85 hollow stainless steel 800-μm-tall microneedles attached to syringes.			the basal cell carcinoma tumour graft in comparison to the untreated group	
Dermaroller® with 150 μm needle length	Melanoma vaccine microparticle	Tumour challenge study using *In vivo* murine model	Mice vaccinated with melanoma vaccine microparticles using the 'poke and patch' approach showed no measurable tumour growth 35 days post tumour injection into the back of the mice. In comparison, the non-vaccinated group displayed tumour growth	[120]
Dermapen®	Nanoparticles containing DNA vaccine for malignant melanoma (MM) therapy	Tumour challenge study using *In vivo* murine model	Using the 'poke and patch' approach mice elicited a protective immune response when challenged with melanoma xenograft. The microneedle treated group displayed a survival rate of 80% while the control group showed 0% rate after 95 days	[147]
Coated microneedle with an immune polyelectrolyte multilayer. 77 microneedles per array with a length of 800 μm	human melanoma antigens and adjuvant	*In vitro* cell culture using dendritic and T cells.	The vaccine was released from microneedles which promotes internalisation and activation of dendritic cells. In addition, the released vaccine also promoted T-cell proliferation and generation of effector cytokine involved in the immune response against melanoma.	[153]
		In vivo murine model	*In vivo* studies showed expansion of $CD8^+$ T cells which play an essential role in anti-tumour response	
Dermarollers® with 182 needles per roller. Needles were 500 μm in length	5% 5-FU cream	*In vitro* Franz Cell setup using mouse skin *In vivo* B16F10 murine model of melanoma	Microneedle treated skin, showed a 4.5-fold increase in 5-FU flux across mouse skin using an *in vitro* Franz cell set up. After 17 days, the mice treated with 5-FU with microneedles pre-treatment displayed minimal tumour growth compared to the other control groups.	[145]
Microneedle roller with needle length 3000 μm.	ALA-loaded polylactic-co-glycolic acid (PLGA) nanoparticles	*In vivo* hairless murine model with SCC induced through UV irradiation	Through in situ fluorescence examination of PIX, a biotransformation product of ALA, the microneedle treated group displayed higher intensity compared to other treatment groups. This indicates that pre-treating tumour lesion with microneedles enhances delivery of ALA-loaded nanoparticles to intra-tumour lesion	[154]
Dermapen®.	5% Imiquimod cream	*In vitro* Franz Cell setup using porcine skin	Microneedle treated skin prior to 5% imiquimod cream application, showed enhanced intradermal delivery of imiquimod into the skin using *in vitro* Franz cell set up. Microneedle treated skin also showed enhanced lateral permeation of imiquimod that was visualised using time-of-flight secondary ion mass spectrometry.	[155]
9 × 9 array of embeddable polycaprolactone microneedle with a dissolvable poly(vinylalcohol)/polyvinylpyrrolidone supporting array patch. Needles were 600 μm in length	Lanthanum hexaboride nanoparticles and Doxorubicin	*In vitro* drug release into (porcine cadaver skin). *In vivo* severe combined immunodeficient (SCID) murine model bearing 4T1 tumours	Drug release took place in a stepwise manner. When the porcine skin treated with microneedle was irradiated with NIR laser, a steep increase in drug release. Negligible drug release occurred when the laser was switched off. 4T1 tumour was eradicated within 7 days after single microneedle application followed by three cycles of NIR laser treatment. Upon irradiated, the lanthanum hexaboride absorbs the laser energy and converts it into heat, promoting the release of doxorubicin from the polycaprolactone needles embedded in the tumour. The photothermal effect of lanthanum hexaboride coupled with the chemotherapeutic effect of doxorubicin resulted in tumour destruction.	[149]
10 × 10 array of dissolving microneedle fabricated from hyaluronic acid. The microneedles had a height of 450 μm	Doxorubicin and gold nanocage	*In vitro* B16F10 mouse melanoma cell line. *In vivo* B16F10 murine model of melanoma	Gold nanocage showed localisation around the nuclei of melanoma cells. When exposed to NIR laser, gold nanocage exhibited photothermal effect that resulted in reduced melanoma cell viability. Biodistribution study showed that the gold nanocage distributed mostly in liver, kidney and lung with maximum concentration at 24 h with most being excreted in 72 h. After four rounds of treatments the tumour volume in due to chemo-photothermal effect were lowest in mice treated with hyaluronic acid loaded	[156]

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Table 1 (*continued*)

Microneedle design	Delivered therapeutics	Model to evaluate microneedle efficacy	Outcome	Refs.
			with doxorubicin and gold nanocage. This was similar to intratumour injection of doxorubicin and gold nanocage	
12 × 12 array of dissolving microneedle fabricated from a mixture of hyaluronic acid, dextran and polyvinylpyrrolidone. The microneedles had a height of 650 μm	STAT3 siRNA encapsulated with polyethylenimine	*In vitro* B16F10 melanoma cells line. *In vivo* B16F10 murine model of melanoma	STAT3 siRNA encapsulated with polyethylenimine were taken up by B16F10 cells and resulted in STAT gene silencing and hindered cancer cell proliferation. Mice treated with STAT3 siRNA via dissolving microneedles displayed STAT3 mRNA downregulation which indicated successful gene silencing *in vivo*. In addition, mice treated with the microneedles showed lower tumour volume and weight and enhanced tumour necrosis compared to control (untreated) group	[157]
14 × 14 array of dissolving microneedle fabricated from a mixture of Gantrez® S-97, tripropyleneglycol monomethylether, sodium carbonate, and poly(vinylalcohol). The microneedles had a height of 600 μm	Redaporfin™	*In vitro* Franz Cell setup using porcine *In vivo biodistribution studies*	*In vitro* drug deposition studies showed that the microneedle dissolves upon application and was able to deliver the photosensitizer (Redaporfin™) down to 5 mm intradermally. Mice treated with Redaporfin™ dissolving microneedles showed significant fluorescence at the application site, as opposed to the IV group, which displayed distribution to the entire body. Decline in fluorescence intensity at the application site for the microneedle treated group began to occurr after 7-days. Trace levels of Redaporfin™ were seen in mice kidneys at 7 days but no drug was detected in their livers or spleens. On the other hand, mice that received IV Redaporfin™ showed appreciable drug concentrations in liver and kidneys	[158]
8 × 8 array of coated microneedle fabricated by coating stainless steel microneedles with octaarginine/siRNA nanocomplexes suspension. The microneedles had a height of 750 μm	octaarginine/BRAF siRNA nanocomplexes	*In vitro* A375 human melanoma cells line. *In vivo* A375 murine model of melanoma	Octaarginine, a cell penetrating peptide was able to successfully transfect the cells with BRAF-siRNA. Real-time polymerase chain reaction and western blot showed BRAF mRNA an protein expression were downregulated when treated with octaarginine/BRAF siRNA nanocomplexes. In addition, A375 cells treated with the nanocomplexes exhibited reduced cell proliferation. The tumor in the group treated with R8/siBraf nanocomplexes coated microneedles decreased over the 13 day *in vivo* experiment period. In addition, staining experiment indicated presence of apoptosis in microneedle treated groups	[159]
20 × 20 array of coated microneedle fabricated from hyaluronic acid. The microneedles had a height of 480 μm	PEGylated gold nanorod and doxorubicin	*In vivo* Release study in murine model *In vivo* A431 murine model of melanoma	Microneedle was inserted into right side of balb/cA- nu mice mice's skin and treated under an NIR laser for 5 min. The skin was isolated post treatment and *in vivo* imaging system showed release of doxorubicin and PEGylated gold nanorod. When the mice were treated with dissolving microneedles loaded PEGylated gold nanorods and doxorubicin followed by irradiation with 808 nm laser for 5 min, the photothermal effect from the gold nanorods coupled with the release of doxorubicin led to tumour apoptosis. Tumour bearing mice survived without tumour recurrence under only one treatment cycle.	[160]
10 × 10 array of solid microneedles. The microneedles had a height of 500 μm. Solid microneedle was used for skin pre-treatment	mesoporous organo- silica nanoparticles covalently linked with dabrafenib and trametinib	*Ex vivo* (porcine skin) *In vivo* A375 murine model of melanoma	When the drug loaded nanoparticles were applied onto skin pre-treated with microneedles, enhanced nanoparticle penetration into the epidermis and dermis were observed after one hour. For nanoparticles applied on intact skin, nanoparticles were observed to have penetrated only into the epidermis after one hour. Microneedle-assisted nanoparticle treatment was conducted twice weekly for two consecutive weeks. Subsequently, 730 nm NIR laser treatment was applied to the tumour site. Tumour growth curves indicated that mice receiving microneedle-assisted nanoparticle delivery had significant tumour regression compared to other treatment groups.	[161]

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Table 1 (*continued*)

Microneedle design	Delivered therapeutics	Model to evaluate microneedle efficacy	Outcome	Refs.
10 × 10 array of dissolving microneedle fabricated from polyvinyl pyrrolidone. The microneedles had a height of 600 μm	Mesoporous silica nanoparticles loaded with doxorubicin hydrochloride and indocyanine green	*In vitro* viability of MG-63 osteosarcoma cell line. *In vivo* murine model of osteosarcoma	Cell lines treated with dissolving microneedles incorporated with drug loaded silica nanoparticles, followed by irradiation with a 808 nm NIR laser, resulted in the highest osteosarcoma apoptosis compared to other treatment groups. Mice treated with dissolving microneedles incorporated with drug loaded silica nanoparticles, followed by irradiation with a 808 nm NIR laser, caused the most tumour shrinkage compared to other treatment group	[162]
3 × 27 array of maltose microneedles that possess a height of 500 μm. Admin Pen™ 1200 that contain 43 microneedles per patch with needle height of 1100 μm. Admin Pen™ 1500 that contain 31 microneedles per patch with needle height of 1400 μm	Vismodegib	*In vitro* Franz Cell setup using porcine skin. *In vitro* skin irritation test using reconstructed human epidermis model.	Significant enhancement in permeation of vismodegib through microneedle-treated skin was observed. Increasing the length of microneedles from 500 to 1400 μm, resulted in a five-fold increase in the amount of vismodegib delivered across the skin. However, skin disposition studies showed that there was no significant difference in amount of drug retained in the skin from the three types of microneedle treatment used. It was also shown that an increase in the needle insertion time from 1 and 2 min to 4 min resulted in a significant increase in the amount of drug delivered across the skin. Vismodegib formulated in in propylene glycol was non-irritant (NI) to the reconstructed human epidermal model. The results suggested suggest that formulation could be applied safely on the skin without any irritation using the poke-and-patch approach	[163]

bound and soluble circulating TNF- α [173,174]. Korkmaz *et al* explored the potential to use microneedles for localised delivery of anti–TNF–α using carboxymethyl cellulose dissolving microneedles. The group showed that the critical biomarkers of psoriasiform inflammation were reduced when the anti-TNF-α microneedle was applied to a psoriatic mouse model. This proof of concept study highlights the potential for microneedles to improve the treatment outcomes for psoriasis [175].

With the limitation in the current therapies for psoriasis, there is a general need to explore novel compounds which may improve the treatment outcome for psoriatic patients. Pentaerythritol tetrakis (3,5-di-*tert*-butyl-4-hydroxyhydrocinnamate) (PTTC), a compound from the extract of mate tea has been shown to have anti-psoriatic properties. The cinnamate tetraester has been shown via *in vitro* studies to have proteasome inhibitory activity which is beneficial in the treatment of psoriasis [165,176,177]. Despite the potential benefit in the treatment of psoriasis, PTTC has a very high Log *P* of 23 which results in poor solubility and selective partitioning into the *stratum corneum*. Gujjar *et al* explored the potential of utilising microneedles to improve intradermal delivery of PTTC for the treatment of psoriasis. Upon pretreating dermatomed human skin with microneedles followed by application of an oil in water emulsion of PTTC, Gujjar *et al* showed enhanced PTTC permeation into the epidermis. Furthermore, this group also evaluated the efficacy of the compound using 3D psoriatic cell culture and showed reduced interleukin-6 (IL-6) production, a proinflammatory marker which is typically upregulated in psoriatic lesions [178].

Jeong *et al* have generated dissolving microneedles from hydroxypropyl cellulose for the intradermal delivery of highly hydrophobic and large molecular weight drug Cyclosporin A (CyA) for the treatment of psoriasis. The 600 μm long, 250 μm wide dissolving pyramidal microneedles displayed sufficient mechanical strength to pierce porcine skin in an *in vitro* setting. In addition, the group conducted a pharmacokinetic study using eight-week-old Sprague-Dawley (SD) rats. They showed that therapeutic dose of CyA for treatment of psoriasis could be delivered intradermally with minimal systemic toxicity due to the slow absorption of CyA form the delivery site in comparison to oral delivery of CyA [179]. Despite the promising nature of this microneedle formulation, it should be noted that the performance of the fabricated microneedles was evaluated using porcine and murine skin which does not mimic the hyperkeratotic nature of psoriasis plaque which may hinder and reduce the true penetration achievable by microneedle patches.

Recently, a pilot clinical trial was carried out to evaluate the efficacy of a microneedle patch on the treatment of psoriatic plaques. The microneedle patch was fabricated from hyaluronic acid (Raphas Co., Ltd., Cheonan, South Korea) which was used in tandem with the topical Diabovet® gel that contained the active ingredients calcipotriol and betamethasone dipropionate [180]. Ten psoriatic patients were enrolled in the pilot study. After one week, the researchers reported that the hyaluronic acid microneedle patch enhanced the treatment outcome of the psoriatic patient with two patients having complete resolution. Despite these positive outcomes, the small patient number and lack of placebo control in the trial are major limitations of the study [181].

Examples of drugs molecules that have been investigated for delivery via microneedles for treatment of psoriasis are illustrated in Fig. 3.

Due to the poorly understood pathogenesis of psoriasis, there is plenty of scope to explore and identify potential therapeutics for the management of psoriasis. Although the number of studies using microneedles for the treatment psoriasis is small, the outcomes of these studies are promising. The ability of microneedles to deliver new and conventional psoriatic drugs in the form of microneedle patches may be appealing to psoriatic patients. This is because conventional topical psoriatic creams have been reported by patients to be cosmetically

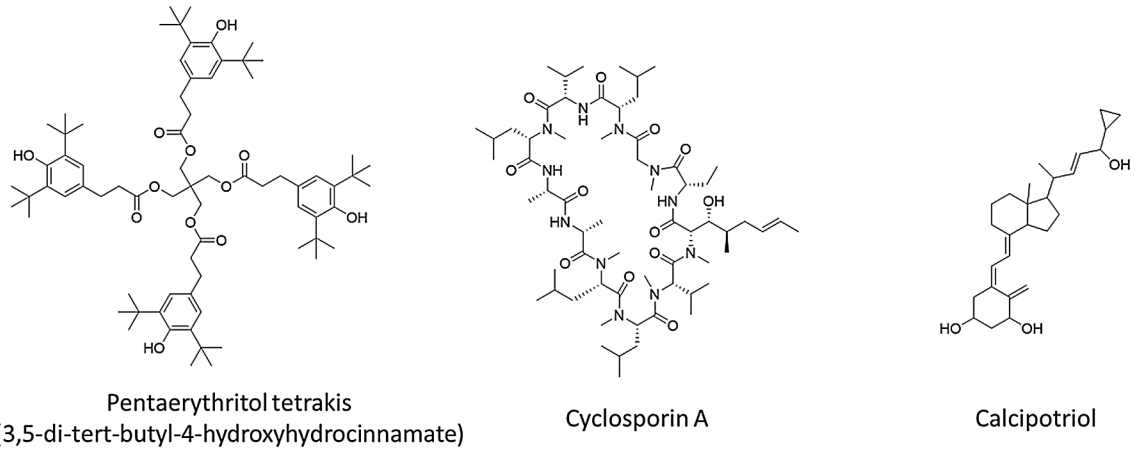

Fig. 3. Drug molecules that have been investigated and successfully delivered into the skin for the treatment of psoriasis using microneedle delivery system.

unacceptable, to stain clothes and to exude unpleasant odours. However, such an approach may only be applied to small localised psoriatic plaques in contrast to extensive psoriatic lesions. Also, it is worth highlighting that microneedles that are intended for the treatment of psoriasis need to be more mechanically robust due to the hyperkeratotic and acanthotic nature of the plaque which may limit microneedle penetration.

4.3. Atopic dermatitis

Described as an eczematous eruption, atopic dermatitis is a prevalent inflammatory skin disorder which appears to be on the rise. The skin disorder tends to have an early onset in life with periods of exacerbation and remission. The main symptoms of dermatitis include pruritus, xerosis, ichthyosis and in some circumstances cheilitis. The disease tends to be more common in the paediatric population and has a serious effect on patients' quality of life. The disease may lead to sleep disturbance, disruption in social plans as well as impacting personal relationships [182].

The disease is typically treated with topical corticosteroids to reduce skin inflammation. However, the use of topical corticosteroid is associated with adverse effects such as skin atrophy, telangiectasia and striae. The chronic use of topical steroids in the management of atopic dermatitis also faces the potential issue of tachyphylaxis (progressive decrease in effectiveness with continued use). The response is usually to increase the potency of applied topical steroids which increases the risk of adverse effects [183]. Topical calcineurin inhibitors such as tacrolimus and pimecrolimus are also used in the management of atopic dermatitis. This class of drug is also associated with side effects such as site irritation and a transient burning sensation during treatment [184].

Although current therapeutic options for the management of atopic dermatitis is, in most cases, effective; the side effects associated with the therapy particular in chronic atopic dermatitis may result in poor patient compliance and ultimately therapeutic failure. Thus, considerable efforts have been made to find therapeutic alternatives to manage and treat atopic dermatitis. Plant flavonoids such as quercetin [185], chrysanthemin [186], tannic acid [187,188], naringenin [189], and resveratrol [190] have recently emerged as a potential class of drug for the management of atopic dermatitis. These molecules have antioxidant, anti-allergic and anti-inflammatory properties which may be of significant therapeutic benefit in the management of atopic dermatitis. However, despite their therapeutic potential in atopic dermatitis, these molecules have poor aqueous solubility and rapid first-pass metabolism when delivered orally.

Thus, the utilisation of microneedles to improve the delivery of flavonoids to the viable epidermis, which is the main site of action, would be of great value. Paleco *et al* have explored the potential of such a strategy by delivering lipid microparticles (LM) loaded with quercetin on microneedle perforated porcine skin. They observed an increased permeation in quercetin level through the *stratum corneum* and localised in the viable epidermis, which is the primary site of action of the molecule [191]. To date, the study by Paleco *et al* is the sole study that attempted to explore the use of microneedles in treating dermatitis. The limited interest in the area may be attributed to the fact that patients with dermatitis already suffer from reduced skin barrier function. Application of microneedles on such skin may lead to an even higher risk of microbial penetration which is not observed in healthy skin [192]. In addition, the increased likelihood of dermatitis as a side effect of microneedle treatment may also contribute to the lack of interest in this area [45].

4.4. Skin and soft tissue infections

Skin and soft tissue infections (SSTIs) are caused by microbial invasion into the skin and underlying tissue. The most common SSTIs manifest in various forms ranging from mild localised superficial infections to severe deep tissue infections leading to sepsis and death. SSTI affects up to 10% of hospitalised patients [193]. The aetiology of SSTI may be due to bacteria, virus, fungi, and parasite with bacterial infection being the most prevalent [193–195]. In Europe, the microorganisms most frequently associated with skin infections are *Staphylococcus* and *β-haemolytic streptococci* [196].

Ideally, treatment of SSTIs is based on the causative microorganism. However, in most cases the exact aetiology is unknown. Under such circumstances, broad-spectrum antibiotics are prescribed empirically until clinical results are available to guide the treatment with narrow spectrum antibiotics. Gentamicin is an example of a broad-spectrum antibiotic that is used in the management of some skin infections such as ecthyma gangrenosum and folliculitis[197]. However, the hydrophilic nature of the drug limits its permeation across the skin to treat deeper skin infections. In light of this limitation, it is believed that the use of microneedles may aid the delivery of gentamicin into the skin. The development of antimicrobial microneedles was initially developed as an effort to mitigate the risk of infection that may be associated with the movement of microorganism through microchannels post microneedle insertion.

Gittard *et al* were the first to fabricate antimicrobial microneedles for this purpose. Through the use of two photon photopolymerisation-micromolding, the group generated antimicrobial microneedles containing gentamicin sulfate. These novel microneedles were shown to release gentamicin and inhibit the growth of *Staphylococcus aureus* when evaluated using an agar plating assay [198]. However, the group did not evaluate the microneedle efficacy using any skin models to establish if the drug release profile in skin matrix would be similar to

that observed in the agar plating assay. Should the drug delivery profile be lower in the skin, this may result in sub-inhibitory concentrations in the skin and ultimately antimicrobial resistance. Furthering this, González-Vázquez *et al* fabricated dissolving microneedles that contained gentamicin. Through the use of *in vitro* Franz cell diffusion experiment and *in vivo* rat model, it was shown that the dissolving polymeric microneedle system was able to release gentamicin into and across the skin within a matter of 5 min [199]. Although the microneedle system was intended for the treatment of sepsis, the design may be optimised and tailored to treat more localised skin infections. In order to do so, gentamicin, which is more suited for systemic infections [200], ought to be swapped for other antimicrobial agents which are more suited for localised skin infections such as neomycin, mupirocin and polymyxins [201].

Over the years, there has been a realisation that antimicrobial microneedles may be utilised for the treatment of SSTI. In light of this information, Gittard *et al* fabricated acrylate-based solid microneedle arrays coated with either silver or zinc oxide films. This is because SSTIs (particularly those that are caused by meticillin-resistant *S aureus* (MRSA) have been shown to respond to topical application of nanocrystalline silver [202] and zinc oxide [203,204]. The metal oxide coated microneedle arrays demonstrated antimicrobial activity via agar diffusion studies against two common two bacteria strains frequently associated with skin infection, *Staphylococcus epidermidis* and *Staphylococcus aureus* [205].

Interestingly, it has been shown that some polymeric microneedles that are made from an acid anhydride copolymer without the inclusion of any antimicrobial agent, displayed antifungal and antibacterial activity by itself [206]. However, when such copolymers are used as coatings for solid microneedles, the polymers did not display similar antimicrobial activity. This was attributed to the low amount of acid anhydride copolymer present on the surface of the microneedle compared to when the copolymers are used as the bulk material to fabricate the entire microneedle. Such a low quantity of polymer on the surface of microneedle was ineffective at eliciting antimicrobial activity [207]. This demonstrates that careful selection of the potential material used in fabricating or coating microneedle system play an essential part in the overall antimicrobial effect of the system [50,68,104,208].

This promising potential for microneedles to be used in the treatment of SSTIs has led to the emergence of several patents for the use of microneedles to deliver antimicrobial agents [209,210]. Based on such promising results and if future research in area continues to prove the utility of microneedle in SSTI, it is envisioned that antimicrobial microneedles may emerge as a promising biomedical device for the treatment of skin infections. However, much work in the area is still necessary. Table 2 summarizes some of the studies that have focussed on the development of antimicrobial microneedles. One limitation that could be observed in the area of antimicrobial microneedles is that evaluation of efficacy has largely been limited to agar plating assays. There are limited studies that use an *in vivo* model of SSTI to evaluate the full efficacy of antimicrobial microneedles. The development of such antimicrobial microneedles accompanied with careful evaluation of efficacy using a suitable *in vivo* model will be necessary to move the field forward.

4.5. Viral warts

Viral warts are benign epidermal proliferations which are caused by a human papillomavirus (HPV) infection. This form of cutaneous proliferation is ubiquitous with a prevalence of 7–12% in the general population [220]. There are various clinical subtypes of viral warts with verucca vulgaris being the most common, often manifesting on the hands, plantar warts presenting as hyperkeratotic plaques on the feet, and genital warts normally transmitted from sexual contact. The infection is transmitted by simple contact or frequently by skin lesions, abrasions or traumas [221].

Observational studies have highlighted that most cases of viral warts tend to be self-limiting without any treatment, albeit after a period of up to two years [222]. Although such dermal infection may be viewed as benign, the cosmetic outcome of such disease may impact an individual's self-confidence and relationships with others, thus highlighting the need to treat this skin condition.

There are a variety of treatments for viral warts which may be used alone or in combination. Common topical preparations used in the management of viral warts include salicylic acid, lactic acid, podophyllin and 5-FU preparation which chemically ablate the infected epidermal cells while ameliorating the hyperkeratotic epidermis. In addition, the immunomodulator, imiquimod is licensed for topical use for genital warts Although the clearance of warts through topical application in most cases is good [223], various studies have shown that patients' compliance with such treatment are poor which is attributed to local irritation, poor cosmetic outcomes and treatment difficulties [223–225]. Cryotherapy with liquid nitrogen also serves as an alternative for the management of viral warts. However, a Cochrane review has highlighted the limited effectiveness of such treatment [223]. In addition, the need for multiple visits, the complexity of the treatment along with the risk of blistering limits patient compliance [226]. Another strategy to manage viral warts is through the use of intralesional bleomycin which is a well-known cytotoxic agent. Bleomycin exerts its therapeutic effect through intercalating between DNA strands and inducing strand scission[227]. Although this treatment strategy has been reported to be more effective than cryotherapy in the management of viral warts [228,229]; the pain induced during injection, poor cosmetic outcomes along with the expertise necessary to perform the injection are significant drawbacks of this treatment strategy [230,231].

Given the limitations of current treatment modalities, there is a general need to improve the local delivery of drugs in the treatment of viral warts. It is only recently that the idea of using microneedles to treat viral warts began to emerge. This idea was first explored in small clinical cases by Konicke and Olasz. They investigated the effect of combining the use of commercial Dermapen® with topical bleomycin in four patients with plantar warts. The authors reported complete cure rate in all the four clinical cases with minimal pain [232].

However, the idea to fabricate designer microneedles for the purpose to treat viral warts was pioneered by Lee *et al*. This research group developed a microneedle system that consists of poly-lactic-acid (L-PLA) solid microneedles coated with bleomycin. The microneedle system displayed sufficient mechanical strength to pierce thick skin similar to that seen in viral wart lesions. In addition, the group also conducted a pharmacokinetic study using the microneedle system in a rat model and showed that bleomycin delivered using coated microneedles provided more localised dermal delivery of the drug in comparison to conventional intralesional injection. This study demonstrates the utility of microneedles for localised delivery of drugs to the skin [233]. Furthering this, Ryu *et al* conducted the first clinical study to investigate the effectiveness of local delivery of bleomycin using coated microneedles in comparison to cryotherapy. The group reported that treatment efficacy using the microneedle approach was comparable to cryotherapy but was significantly less painful. Although published research on utilising microneedles to treat viral warts is scarce, these preliminary studies highlighted here show the potential that microneedle drug delivery may have in improving patient treatment outcomes [234].

5. Conclusion

Microneedles have been investigated in a variety of medical applications ranging from diagnostic to therapeutic delivery. Since the first paper on microneedle-mediated drug delivery was published in 1998, the field has progressed significantly. This has opened new avenues for the delivery of a wide array of therapeutics both to and across the skin. Extensive research in the area, driven by patient-centered care has led

Table 2
Summary of antimicrobial and antifungal microneedle studies.

Microneedle Design	Delivered therapeutics	Model to evaluate microneedle efficacy	Outcome	Refs.
5 × 5 microneedle arrays were fabricated from polyethylene glycol 600 diacrylate	Gentamicin sulfate	*In vitro* agar plating assays	Agar plating assay revealed that the antimicrobial microneedle resulted in zone of inhibition for *S. aureus*	[198]
Acrylate-based solid microneedle with four different geometries. Height ranged from 1000 to 1250 μm. The solid microneedles were deposited with antimicrobial coating	Silver and zinc oxide	*In vitro* agar plating assays	Agar plating assay revealed that the microneedle resulted in zone of inhibition for *Staphylococcus epidermidis* and *Staphylococcus aureus* but not for *Escherichia coli*	[205]
14 × 14 array of dissolving microneedle from aqueous blends of Gantrez® AN-139 (co-polymer maleic anhydride and methyl vinyl ether). Microneedle height ~600 μm	Methylene blue	*In vitro* biofilms assay	Kill rates of > 96%, were obtained for *S. aureus* while > 99% for *E. coli* and C. *albicans* when methylene blue delivered via microneedle in combination with photodynamic therapy at a wavelength of 635 nm	[211]
1 × 5 array of dissolving polymeric microneedle from Gantrez ® AN 169 BF (co-polymer maleic anhydride and methyl vinyl ether). Microneedleheight ~800 μm	None	*In vitro* agar plating assays	Gantrez ® AN 169 BF microneedle dissolved when evaluated in the agar plating assay. The polymer coating itself, upon dissolution, resulted in a large zone of inhibition for *E. coli, S. aureus, E. faecalis* and *B. subtilis*. However, no zone of inhibition was observed for P. aeruginosa and C. albicans	[206]
19 × 19 arrays of dissolving polymeric microneedles were fabricated from sodium hyaluronate and polyvinylpyrrolidone. Microneedle height ~500 μm	Gentamicin sulfate	*In vitro* Franz Cell setup *In vivo* rat model	Dissolving polymeric microneedle was shown to effective to dissolve and deliver gentamicin transdermally as mean to treat neonatal sepsis. Pharmacokinetics study showed that maximum plasma level in the range of 2–5 μg/ml was observed within 1–6 h after microneedle application	[199]
120 × 120 array dissolving polymeric microneedle fabricated from a mixture of hyaluronic acid and green tea extract. Microneedle height of ~500 μm	Green tea extract	*in vitro* cytotoxicity assays *In vitro* agar plating assays *In vivo* rat model displaying infected wound.	*in vitro* cytotoxicity assays showed that microneedle containing green tea extract are non-toxic in Chinese hamster ovary cells (CHO-K1), human embryonic kidney cells (293 T), and mouse muscle cells (C2C12). *In vitro* agar plating assays that the microneedle caused a growth reduction in all bacteria strains tested (*E. coli, B. subtilis, P. putida, S. aureus,* and *S. typhimurium*). Microneedle fabricated with green tea extract reduces bacterial growth in animal model with infected wound whilst promoting wound healing simultaneously compared to negative control.	[212]
1 × 4 biodegradable polyglycolic acid microneedles with height of ~750 μm	Voriconazole	*in vitro* agar plating study	Voriconazole-modified microneedles displayed antifungal activity against *Candida albicans* but not against *Escherichia coli, Pseudomonas aeruginosa,* or *Staphylococcus aureus*	[213]
1 × 5 array of microneedles fabricated from Gantrez 169 BF which is coated with antifungal drug using piezoelectric inkjet printing. Microneedle height of ~900 μm	Amphotericin B	*In vitro* agar plating study	Amphotericin B coated microneedles displayed antifungal activity against *Candida parapsilosis*. This provided proof-of-concept to utilise this type of microneedle for the treatment skin and nail infection	[214]
1 × 4 polyglycolic acid microneedle arrays. Microneedles height of either ~900 μm or 1500 μm when coated with 1040 mg/mL and 2080 mg/mL of Amphotericin B respectively	Amphotericin B	*In vitro* agar plating study	Microneedle loaded with amphotericin B displayed concentration-dependent antifungal activity against *Candida albican*	[215]
1 × 5 microneedle array fabricated from Gantrez® AN 169 BF which later coated with antifungal drug via piezoelectric inkjet printing	Miconazole	*in vitro* agar plating study	Microneedle array coated with miconazole displayed inhibitory activity against *C. albican*	[216]
1 × 4 Poly (glycolic acid) microneedle arrays. Microneedles were coated with poly (methyl vinyl ether–co-maleic anhydride) and itraconazole via piezoelectric inkjet printing. Microneedle height of ~640 μm	Itraconazole	*In vitro* agar plating study	The microneedle arrays did not show any inhibitory effect on the growth of E. coli and S. aureus but displayed activity against the growth of C. albican	[207]
15 × 15 arrays of dissolving microneedle fabricated from carboxymethyl cellulose. The microneedles had a height of 700 μm.	Nanosilver	*In vitro* agar plating study *In vitro* cytotoxicity study using human dermal fibroblasts	The microneedle arrays showed inhibitory effect on the growth of against Gram positive S. aureus and S. epidermidis and Gram-negative E. coli and P. aeruginosa. Human dermal fibroblasts retained more than 90% cell viability demonstrating that the microneedle formulation is unlikely to have adverse effects on healthy skin tissue upon microneedle treatment.	[217]
10 × 10 arrays of gold-coated polystyrene microneedles. The microneedles had a height of 650 μm	Zinc oxide nano-bushes	*In vitro* agar plating study *In vitro* cytotoxicity study using normal dermal fibroblasts	The microneedle arrays showed inhibitory effect on the growth of against Gram positive *S. aureus* and *S. epidermidis* and Gram-negative *Salmonella.* Alamar Blue cell viability assay showed that the antibacterial microneedles have minimal negative influence dermal fibroblasts	[218]
10 × 10 arrays of hyaluronic acid microneedles. The microneedles had a height of 600 μm. The microneedle base plate was made from methacrylated hyaluronic acid (m-HA)/diatomaceous earth	Clindamycin	*In vitro* agar plating study *In vivo* murine model of *P. acnes*-induced inflammation.	The polyvinyl pyrrolidone-clindamycin gel used to fabricate the needle arrays showed an inhibitory effect on the growth of *P. acnes*. The inhibitory effect was more pronounced in the presence of an oxidising agent i.e·H_2O_2 that promoted the release of clindamycin from the gel. Mice treated with oxidation responsive microneedles showed a 90% reduction in swollen skin volume. Portions of the swollen region even began to disappear after five days	[219]

to the development of novel and intelligent microneedle systems. This is evidenced by the transition from the simple 'poke and patch' approach to the development of bioresponsive systems such as hydrogel-forming and dissolving microneedles. As the field continues to flourish, we are slowly seeing the emergence of new hybrid systems which encompass the properties of different classes of microneedles into one. This trend is attributed to the need to overcome the limitations associated with each type of microneedle while tailoring the requirements for application in more complex diseases.

The ease of delivering drugs in a simple and painless manner are some of the advantages of microneedles. Although there are challenges associated with translating microneedles into clinical practice, new design strategies are being investigated to overcome these limitations. Also, exploratory studies on the views of patients and clinician towards microneedles have highlighted that there is a demand and acceptance for the technology to be included in clinical interventions. In addition, it is estimated that the global transdermal drug delivery market will be worth $95.57 billion by 2025 [235]. From an economic perspective, it is envisioned that part of this market would potentially be dominated by microneedles as such devices offer an easy and pain free drug delivery strategy compared to the more painful hypodermic injection-based delivery.

Despite the impact of microneedles in transdermal delivery, it is only recently that there is a paradigm shift towards utilising microneedles for treatment of dermatological conditions. Given the widespread nature of skin conditions in our society, there is a growing need to improve the way we treat diseased skin. Microneedles are slowly making an impact in the area of dermatology as evidenced by a number of studies involving microneedle systems designed for more localised drug delivery to treat diseased skin. However, it is apparent that some dermatological conditions are gaining more attention than others (such as skin cancers and cutaneous infections) due to the severity and prevalence of the disease. For microneedles to have a true impact in managing severe skin pathologies, clinicians (particularly dermatologists) ought to be made aware of such devices. In addition, establishing a research partnership between dermatologists, academia, and industry is paramount in promoting and translating microneedle research into dermatological practice.

Declaration of Competing Interest

None.

Acknowledgements

This work was supported by the Engineering and Physical Sciences Research Council (EPSRC) [grant number: EP/L01646X/1] via a PhD sponsorship for Akmal Sabri; at the Centre for Doctoral Training for Advanced Therapeutics and Nanomedicine at the University of Nottingham.

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