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Review article

Dissolving microneedles: Applications and growing therapeutic potential

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ABSTRACT

Microneedles are a rapidly developing method for the transdermal delivery of therapeutic compounds. All types of microneedles, whether solid, hollow, coated, or dissolving function by penetrating the *stratum corneum* layer of the skin producing a microchannel through which therapeutic agents may be delivered. To date, coated and hollow microneedles have been the most successful, despite suffering from issues such as poor drug loading capabilities and blocked pores. Dissolving microneedles, on the other hand, have superior drug loading as well as other positive attributes that make it an ideal delivery system, including simple methods of fabrication and disposal, and abundantly available materials. Indeed, dissolvable microneedles can even be fabricated entirely from the therapeutic agent itself thus eliminating the requirement for additional excipients.

This focused review presents the recent developments and trends of dissolving microneedles as well as potential future directions. The advantages, and disadvantages of dissolving microneedles as well as fabrication materials and methods are discussed. The potential applications of dissolving microneedles as a drug delivery system in different therapeutic areas in both research literature and clinical trials is highlighted. Applications including the delivery of cosmetics, vaccine delivery, diagnosis and monitoring, cancer, pain and inflammation, diabetes, hair and scalp disorders and inflammatory skin diseases are presented. The current trends observed in the microneedle landscape with particular emphasis on contemporary clinical trials and commercial successes as well as barriers impeding microneedle development and commercialisation are also discussed.

1. Introduction

Percutaneous absorption and transdermal delivery are very long-standing concepts. From ancient Roman Unguentarii to Galen's cold cream [1], to more modern applications such as chemical permeability enhancers, iontophoresis, microdermabrasion, ultrasound cavitation, and microneedles [2], the impact of transdermal drug delivery has grown significantly. Drugs delivered via the transdermal route can bypass some of the issues related to oral and systemic delivery, including large swings in pH, extensive enzymatic activity, liver metabolism and in the case of systemic delivery via hypodermic needles, pain resulting from injections and needle stick injury.

Skin is part of the integumentary system alongside hair follicles, nails, and glands [3]. On the surface, our skin appears as a static barrier, protecting our fragile internal organs from outside environmental hazards [4]. It is nonetheless a highly active organ, integral to immunity, inflammatory response, and tissue repair [5–7] and remains a useful indicator of systemic disease [8]. Skin was historically only seen as a barrier to drug delivery [9], however it has more recently grown into an exciting field of research supporting a rich diversity of transdermal and intradermal technologies [2].

Transdermal delivery is not without limitations and remains challenging to formulators. Only small molecule, lipophilic compounds and generally those below 500 Da can passively diffuse through the *stratum corneum* to reach underlaying layers to achieve systemic absorption at required therapeutic levels [10]. In recent decades, microneedles have been studied to deliver drugs through the intradermal route in attempt to overcome the limitations associated with more conventional methods.

Microneedles are micron-sized (<1000 μm in length), conical, pyramidal, or multifaceted piercing protrusions which offer many advantages for intradermal drug delivery. Application of microneedles creates temporary channels in the outer layer of the skin, thus bypassing the barrier functionality and allowing the delivery of different therapeutic compounds which otherwise would be incapable of delivery via the transdermal route [11]. The short shaft of the microneedle is long enough to penetrate the *stratum corneum* but does not penetrate far enough to reach underlying nerve endings. Therefore, the application of

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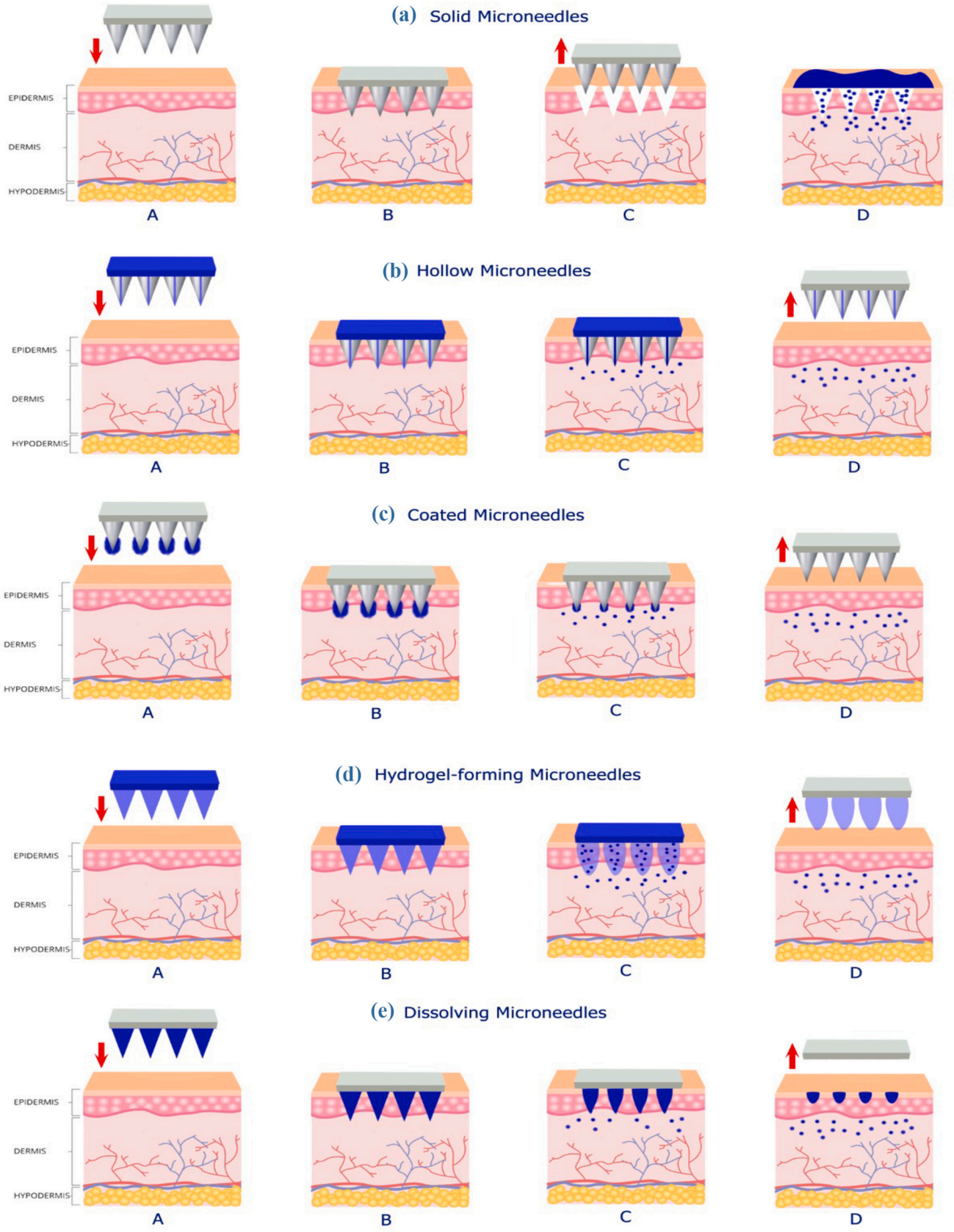


Fig. 1. Graphical representation of the different types of microneedles typically discussed in the literature. Including: (a) solid, (b) hollow, (c) coated, (d) hydrogel, and (e) dissolving microneedles.

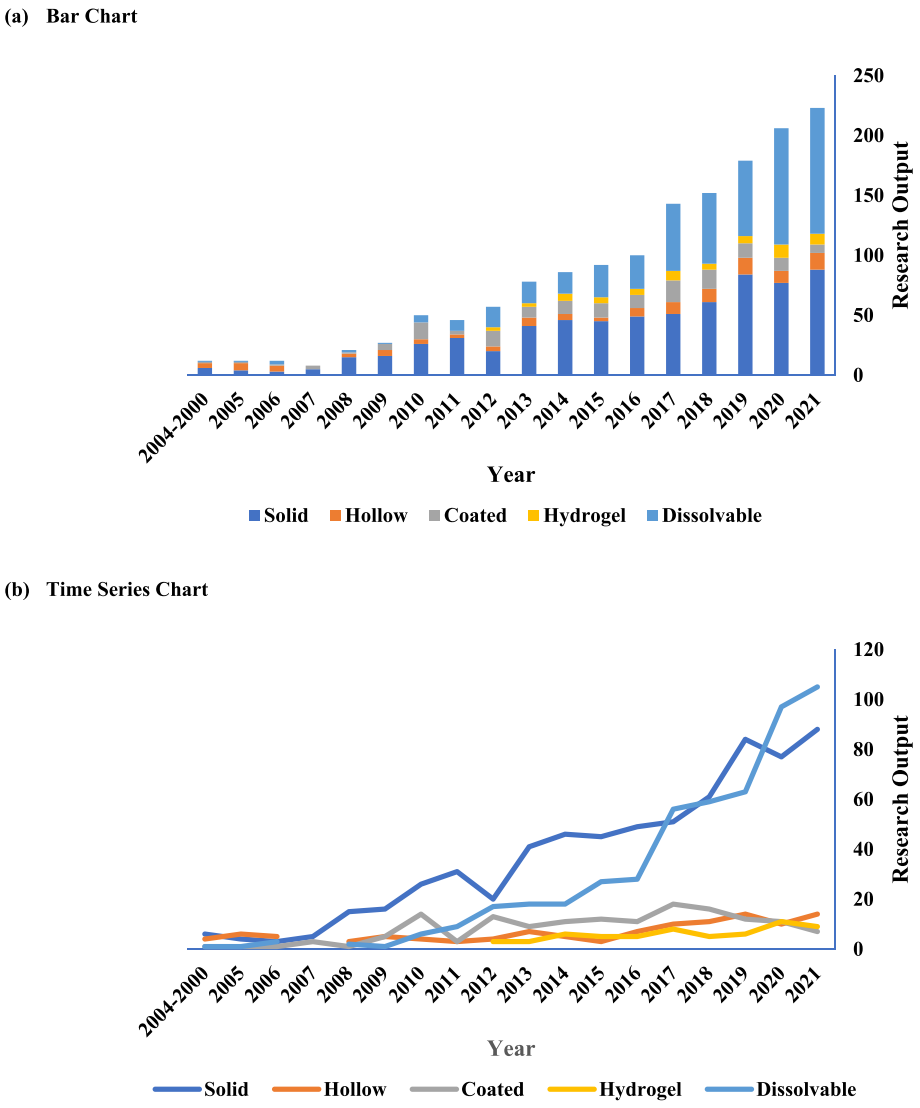


Fig. 2. (a) Bar chart and (b) Time series chart illustrating current research trends of microneedles reported in the literature, 2000–2021, (n = 1503). Derived from www.ncbi.nlm.nih.gov/pubmed/. Search query: '(microneedle) OR (microneedling) OR (micro-needle).

microneedles is essentially pain free. This results in increased patient compliance, especially in the case of people suffering from trypanophobia [12].

1.1. Microneedle design

There are several designs of microneedles that have been the focus of much attention over the last few decades. Each type of microneedle is classified according to their method of drug delivery namely: (a) solid, (b) hollow, (c) coated, (d) hydrogel and (e) dissolving microneedles, Fig. 1.

Solid microneedles are composed of materials and metals such as silicon [13], titanium [14], stainless steel [15] and in some cases polymers [16]. Solid microneedles are used in systems termed as 'poke and patch', whereby a two-step application of the solid microneedles creates microchannels through the skin before being removed and replaced with a drug-loaded backing layer, patch, solution or cream [16,17], Fig. 1 **(a)**.

Hollow microneedles consist of an empty cavity inside each needle and a bore on the needle tip, Fig. 1 **(b)**. This allows microvolumes of drug solutions to be injected into the skin via a 'poke and flow' mechanism. Hollow microneedles have been fabricated using ceramics, metal, silicon, and glass [18]. The benefit of hollow microneedles becomes clear when juxtaposed with one of the known issues with the 'poke and patch' approach. Following removal of the applied solid microneedles the skin quickly heals and collapses the microchannels that were created. Hollow microneedles play a dual role of bypassing the *stratum corneum* and providing non-collapsible microchannels that can be left in place as long as is required to deliver the desired therapeutic. However, hollow microneedles are not without issue, and can suffer from incidences of microchannel blockage, although this can be mitigated by designing the microneedles with an off-centre bore [18].

Coated microneedles aim to eliminate the need for a two-step application by utilising a 'coat and poke' approach by coating solid microneedles with a thin layer of the desired therapeutic agent, Fig. 1 **(c)**. Coating is often achieved via dip coating, ink-jet printing, and various methods of spray drying [19]. Issues related to coated microneedles include the efficiency and uniformity of coating (for example the unnecessary coating of microneedle patch baseplate), the coated layer being removed during insertion and remaining on the surface of the skin, and the retention of the coated drug on the microneedles following removal from the skin [20]. Drug loading capability is limited by the thickness of the coating layer and the size of the needles.

Hydrogel microneedles are fabricated from swellable hydrophilic crosslinked polymers. Upon insertion to the skin, the hydrogel

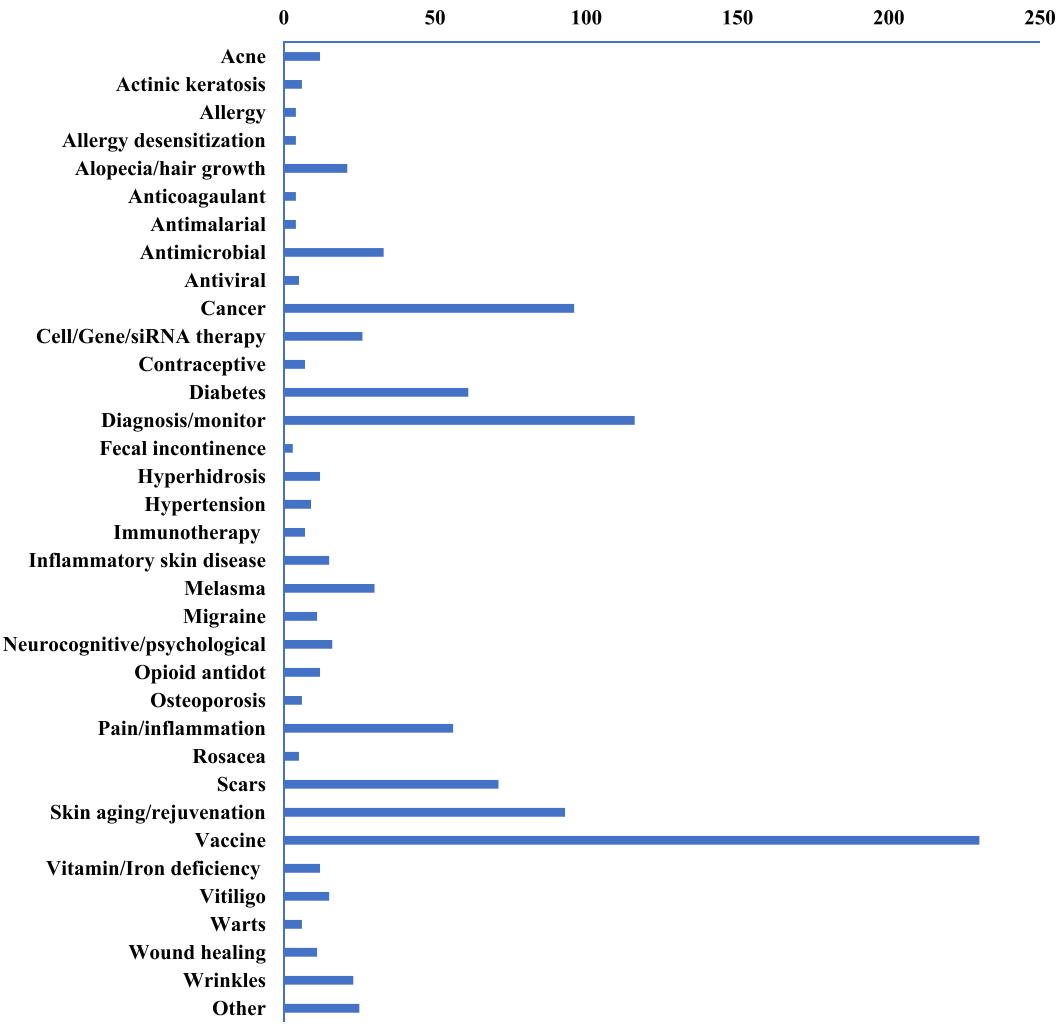


Fig. 3. Recent trends in the therapeutic applications of microneedles reported in the literature, 2000–2021 (n = 1067). Derived from www.ncbi.nlm.nih.gov/pubmed/. Search query: '(microneedle) OR (microneedling) OR (micro-needle) OR (micro array patch) AND (skin).

microneedle swells in the presence of interstitial fluid due to the inherent hydrophilic nature of the polymer, Fig. 1 **(d)**. Hydrogel forming microneedles are an interesting recent development in the field of microneedle technologies. This is due to their ability to act as a delivery device for drugs into or across the skin, as well as their ability to passively extract interstitial fluids, potentially allowing their use as a diagnostic tool [21]. One of the most commonly used polymers in the fabrication of hydrogel microneedles is poly(methylvinylether co-maleic acid) (PMVE/MA) crosslinked with poly(ethylene glycol) (PEG) [21]. Hydrogel microneedles are also not without challenges, where issues with slow fluid uptake, delay in swelling and maintenance of drug release within therapeutic levels following a burst release have been reported.

Dissolving microneedles are traditionally fabricated by encapsulation of the drug into biodegradable polymers [22–24]. After penetrating the *stratum corneum*, the polymer forming the needle architecture dissolves and releases the entrapped drug, Fig. 1 **(e)**. The application of dissolving microneedles involves a one-step approach since the microneedle is not removed following application. This can be described as a 'poke and release' type mechanism. Dissolving microneedles overcome several of the issues experienced with solid microneedles by nature of their mechanism of action, as they undergo no additional manipulation following insertion. The benefit of dissolving microneedles inside the skin essentially reduces the risk of injuries due to needle-stick post-application. Dissolving microneedles will be the focus of this review.

Additionally, there has been recent research into bioresponsive microneedles. Wang and co-workers describe microneedles composed of hyaluronic acid integrated with pH-sensitive dextran nanoparticles that encapsulate aPD1 and glucose oxidase (GOx), which converts blood glucose to gluconic acid. The resulting acidic environment promotes the self-dissociation of the nanoparticles and results in the release of aPD1 for treatment of melanoma [25]. Yu et al., showed that a single removable transdermal patch, bearing microneedles loaded with insulin and a non-degradable glucose-responsive polymeric matrix, and fabricated via in situ photopolymerisation, regulated blood glucose in insulin-deficient diabetic mice and minipigs [24]. The hyperglycaemic conditions induce the swelling of the polymeric matrix, promoting the rapid release of insulin. This proof-of-concept demonstration aided the development of other translational stimuli-responsive microneedle patches for drug delivery [26–28].

In this review, the advantages, and disadvantages of dissolving microneedles, as well as the materials and methods of fabrication are discussed. The potential application of dissolving microneedles as a drug delivery system in different therapeutic areas is highlighted. The primary focus of this review is highlighting the current trends observed in the microneedle landscape with particular emphasis on contemporary clinical trials and present commercial successes. Barriers impeding microneedle development and commercialisation are also discussed.

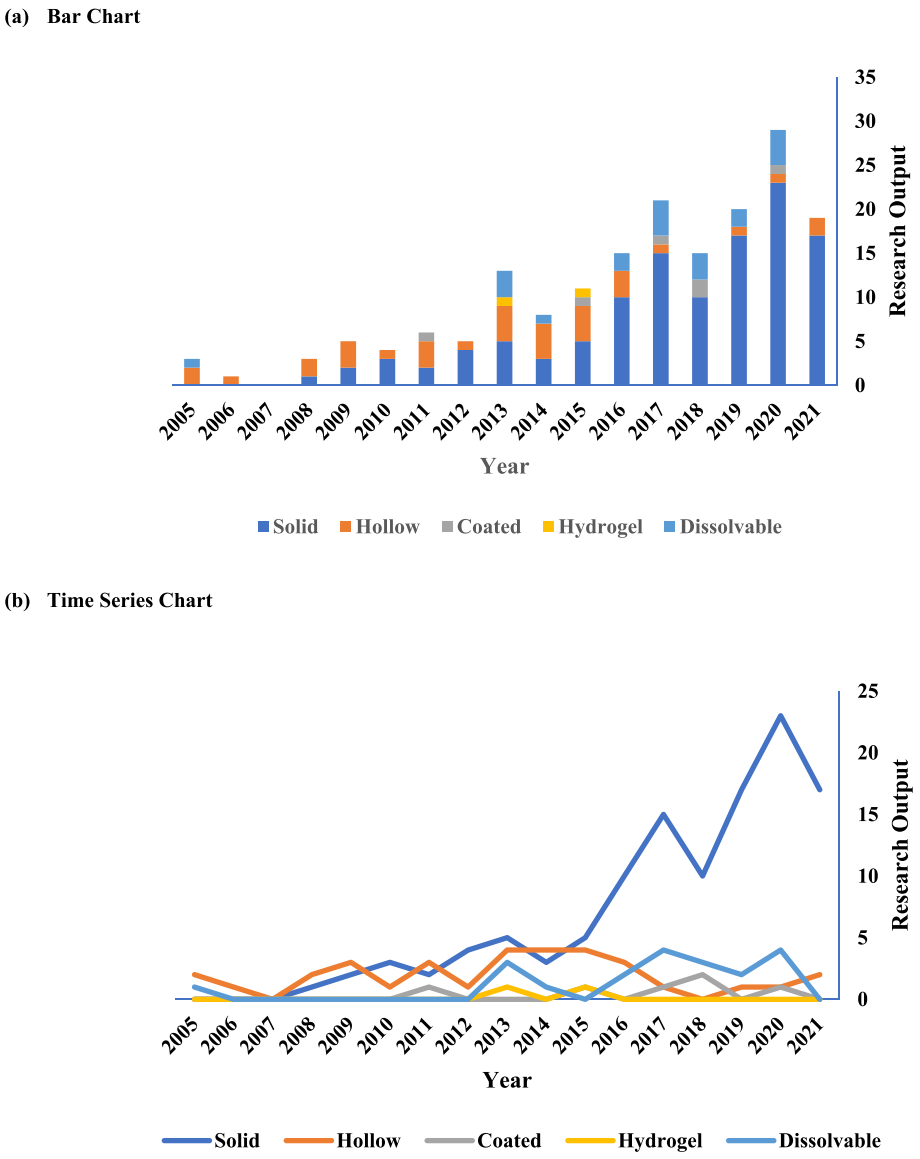


Fig. 4. (a) Bar chart and (b) Time series chart illustrating current clinical research trends of microneedles reported in the literature, 2005–2021, (n = 178). Derived from www.ncbi.nlm.nih.gov/pubmed/. Search query: '(microneedle) OR (microneedling) OR (micro- needle) OR (micro array patch) AND (skin).

1.2. Data collection and current trends

The authors commissioned a multi-step literature search to elucidate current trends of microneedles in both research and clinical settings. In the first instance, data regarding current microneedle research was collected by searching Pubmed (www.ncbi.nlm.nih.gov/pubmed/) using the following search criteria: '(microneedle) OR (microneedling) OR (micro-needle) OR (micro array patch) AND (skin)'. The timeframe was limited to post 2000 to present day (date of search December 2021). This search criteria returned 1946 results of which 443 were excluded due to irrelevance when examining the text or being a review article, resulting in 1503 relevant papers for inclusion. Data was extracted from these papers regarding microneedle type to illustrate and highlight current research trends in the literature, Fig. 2 **(a** and **b)**. It is shown, especially in the last decade, that there was a substantial increase in microneedle research overall, with solid and dissolvable types being the most prominent. It is quite evident that in recent years there has been a noticeable shift towards the research and development of dissolvable microneedles, where the number of research outputs of the dissolvable type of microneedle overtook research into the solid classification.

Microneedle research outputs from the literature were examined for target applications, Fig. 3, excluding applications in fabrication and safety (n = 436) resulting in the inclusion of 1067 applications. Unsurprisingly, microneedle applications in various combined areas of cosmetics were the most common overall. However, there is a clear trend towards research towards vaccine delivery, with increasing interest in the areas of diagnosis/monitoring, cancer, pain management and diabetes.

Secondly, a similar Pubmed (www.ncbi.nlm.nih.gov/pubmed/) search was conducted using the same criteria and timeframes, but only limiting our search to clinical trials (date of search December 2021). This search returned 219 results of which 41 were excluded due to irrelevance, resulting in the inclusion of 178 papers published post 2004. Similarly, subjective data was manually extracted from these papers regarding microneedle type and target application to illustrate and highlight current clinical research trends, Figs. 4 and 5. The majority of microneedles recently tested in clinical trials are unsurprisingly of the solid type, comprising 65.73% of the total. This is possibly due to less regulatory scrutiny associated with the device having no additional drugs and excipients. This is followed by the hollow microneedle type

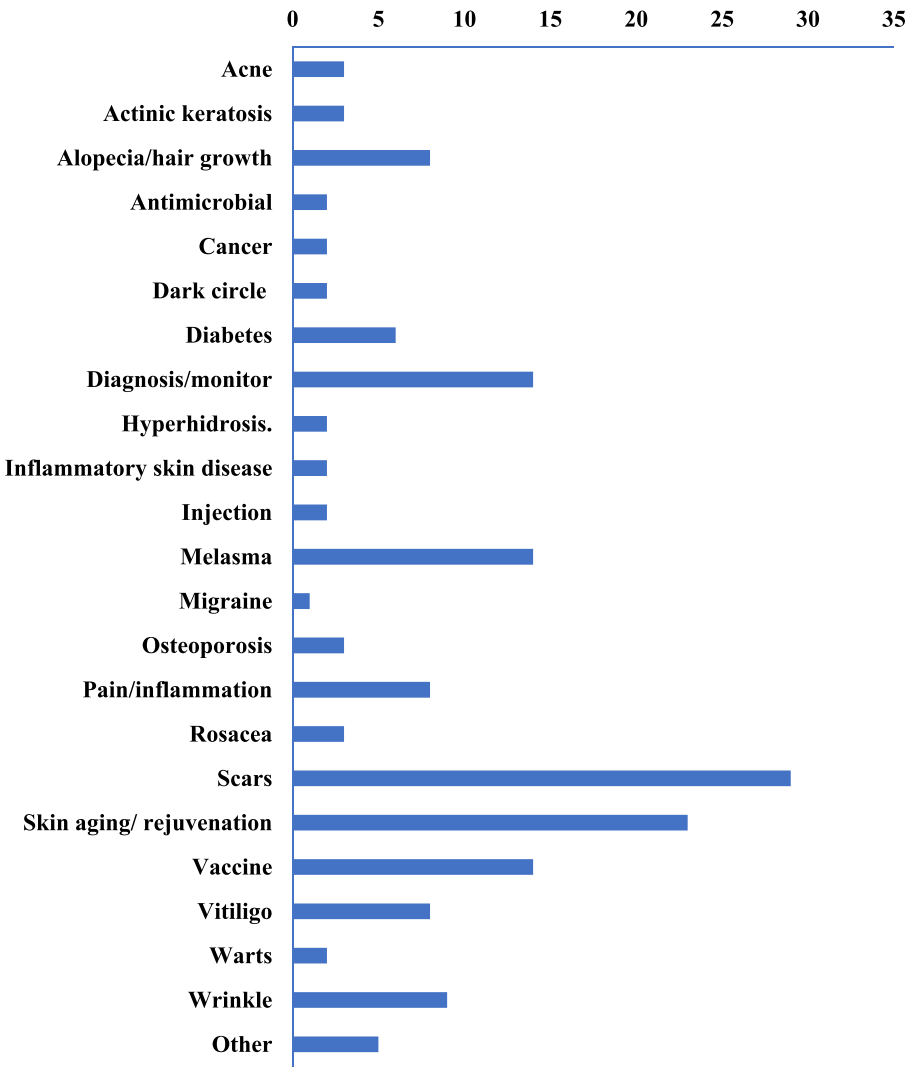


Fig. 5. Recent trends in the clinical applications of microneedles reported in the literature, 2005–2021, ($n = 165$). Derived from www.ncbi.nlm.nih.gov/pubmed/. Search query: '(microneedle) OR (microneedling) OR (micro-needle) OR (micro array patch) AND (skin).

with 18.54% of the total. However, it is evident that in recent years there has been a noticeable increase in the clinical use of dissolvable microneedles in the literature (11.23% of the total), which will be the primary focus of this review.

Clinical applications of microneedle research in the literature were examined, again excluding applications in fabrication and safety ($n = 13$) resulting in the inclusion of 165 applications. Also, not unsurprisingly most microneedle applications have been in cosmetics with treating skin conditions such as scars, wrinkles and skin rejuvenation being the most common. Evidence suggests that there has been a noticeable shift towards the development of microneedles for vaccine delivery and diagnosis/monitoring, Fig. 5. It should be noted that there is a clear decrease in the number of clinical trials conducted post 2020. This could be attributed to the on-going Covid-19 pandemic, in which there has been a substantial increase in restrictions and enhanced clinical focus on Covid-19.

Finally, a search of https://clinicaltrials.gov/, which is a database of privately and publicly funded clinical studies conducted globally, using the terms '(microneedle) OR (micro needle) OR (micro-needle) OR (microneedle array) OR (array patch) OR (microneedling)' was carried out. These data illustrate the state of microneedles in a clinical setting, which is indicative of the applications and type of microneedle which are currently closest to achieving commercial approval, Figs. 6 and 7.

The most common microneedle type currently being studied in clinical trials are the solid and hollow types (64% and 19% respectively). This, as stated previously, is unsurprising, as these types of microneedles are easier to manufacture and would face less regulatory scrutiny than their coated or dissolving counterparts due to having no additional excipients. The clinical trial data showed that dissolvable microneedles comprised 7% of past and present clinical trials ($n = 10$). In comparison, Ingrole et al., have shown that between 1998 and 2018, dissolvable microneedles represented 11.1% of industry-based and 27.9% of academic literature [20]. This is indicative of a substantial interest in dissolvable microneedles across academia and industry. The increase in the research into dissolvable microneedles will more than likely result in an increase in dissolvable microneedles undergoing clinical trials in the future. This will be further discussed in Section 2.4.1.

Similar to the data derived from the literature, these data also confirm that the clinical application of microneedles lies predominantly in the cosmetics industry and to treat skin disorders. There is also evidence suggesting that there has been a recent significant uptake in the use of microneedles for vaccine delivery.

2. Dissolving microneedle focus

Consolidating both the literature and clinical trial data, it is evident

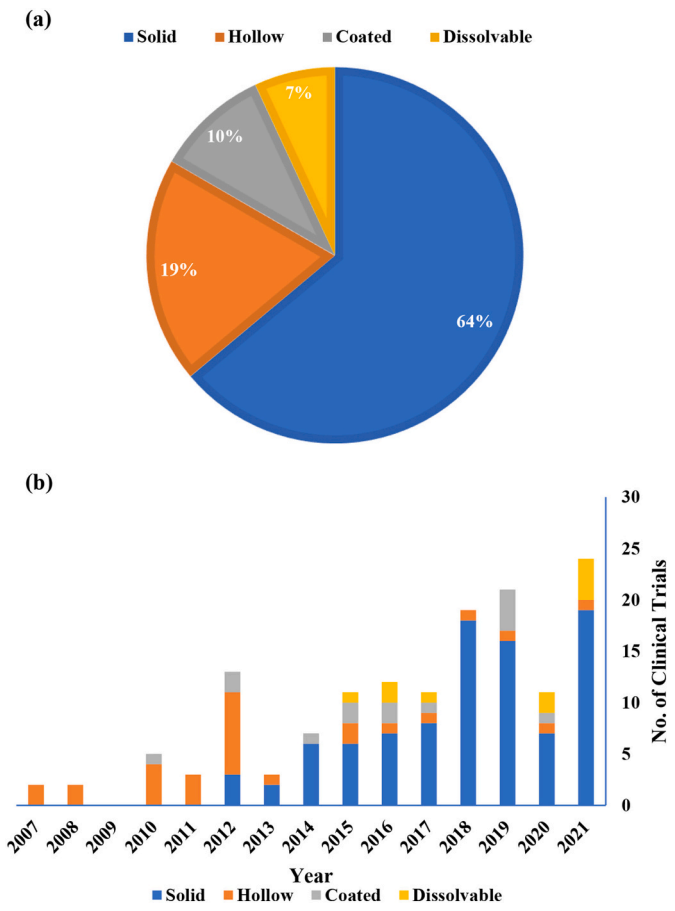


Fig. 6. The types of microneedles used in clinical trials, past and present (n = 148). Derived from https://clinicaltrials.gov/. Search query: '(microneedle) OR (micro needle) OR (micro-needle) OR (microneedle array) OR (array patch) OR (microneedling)'.

that in recent years there has been a substantial increase in interest in dissolvable microneedles across both academia and industry. There are also recent reviews that contributed to the focusing of this review towards dissolving microneedles [22,23]. The purpose of this review is to discuss the methods and materials of dissolvable microneedle fabrication, their varied potential applications, and their future therapeutic and commercial potential. Potential regulatory routes for microneedle commercialisation will also be highlighted.

2.1. Fabrication of dissolving microneedles

Most dissolving microneedles are prepared by microcasting or micromoulding, whereby a solution, slurry, or suspension of a material is filled (often using centrifugation or vacuum) into a microneedle mould, allowed to dry, harden, and is then removed from the mould [29], Fig. 8**(a)**. Researchers have investigated alternative preparation methods including modifications to the micromoulding technique that avoid the need for centrifugation or vacuum steps. For example, utilising an atomised spray process to fill the moulds allows the preparation of regular as well as horizontally and vertically layered microneedles composed of carboxymethyl cellulose and glycerine, all of which were shown readily capable of penetrating the epidermis [30], Fig. 8**(b)**.

Apart from micromoulding, other fabrication techniques have been investigated. For example Kim et al., used a droplet-born air blowing method to prepare microneedle arrays loaded with insulin that produced similar therapeutic results as a subcutaneous injection control in vivo [31]. The polymer droplet is shaped to the microneedle via air blowing. This method provides gentle fabrication conditions without heat or UV irradiation. The fabrication of dissolving microneedles from each droplet makes it possible to load the drug in the microneedle without loss of drug and provides easy manipulation of dosage by controlling the droplet volume and drug concentration, Fig. 8 **(c)**.

Alternatively, additive manufacturing techniques have shown potential, with one example by Johnson et al., who used continuous liquid interface production (akin to 3D printing) to prepare microneedles composed of biocompatible materials polycaprolactone, polyacrylic acid, and polyethylene glycol Fig. 8 **(d)** [32]. More traditional 3D printing techniques, such as stereolithography has been used to prepare microneedles composed of dental resins, that then had insulin plus a carrier (trehalose, mannitol, and xylitol) coated onto the surface of the microneedles by a piezoelectric dispenser, in essence 3D printing followed by 2D printing [33].

Overall, the majority of articles in the available literature suggest that micromoulding is by far the most common technique for dissolving microneedle fabrication. Indeed, Moore et al. has shown in a recent review that 85% of research articles, clearly specifying fabrication methods, used some type of micromoulding technique [34]. A Pubmed (www.ncbi.nlm.nih.gov/pubmed/) search was conducted using the same previous criteria and timeframes regarding dissolvable microneedle, but only limiting our search to clinical trials (date of search December 2021). This search returned that all of the dissolvable microneedles tested in clinical trials (n = 19) are either the micromoulding type, comprising 68.4% of the total, or the droplet air-blown, 31.6% of the total.

2.2. Materials used in the preparation of dissolvable microneedles

Over the years different drug carriers have been developed and tested for drug delivery and target applications, with polymers most commonly used [35]. The materials used must offer protection, be biocompatible, biodegradable, mechanically robust and must not impact on the safety, potency, and efficacy of the encapsulated ingredient. Drug release varies in complexity depending on the design and types of materials involved, with the mechanisms of drug release directly linked to drug diffusion, dissolution, and degradation of the carrier matrix [36]. However, other factors, such as interactions of the material and the drug, can also influence the release kinetics. In addition to physicochemical and morphological properties, the drug location within the matrix, and drug solubility are key parameters governing the release kinetics and, therefore, the efficiency and efficacy of treatment.

At the present time, only a small number of polymer materials have been administered in the human body. Of those materials, an even smaller subset, including examples of amphiphilic, hydrophobic and hydrophilic molecules, has been clinically validated as safe for systemic administration in the body [37]. A recently published review by Moore et al. [34] described the trends seen in the literature with regards to the materials used in the fabrication of dissolving microneedles containing drug or vaccine. This review illustrates the difference in the types of material used in the delivery of these ingredients, which mainly fall in to one of two categories – polymers or sugars. Polymers account for the majority of reported fabrication materials in both drug (84%) and vaccine (62%) containing dissolvable microneedles. Sugars such as trehalose, maltose, and sucrose are frequently incorporated into vaccine containing dissolving microneedles (35%) and are also used in drug containing dissolving microneedles but to a lesser extent (14%). Other materials reported in the literature for the preparation of microneedles include silks and salts (<1%).

Moore et al. described that polyvinylpyrolide (18.6%), hyaluronic acid (16.6%) and poly (methyl vinyl ether-*co*-maleic anhydride) (12.8%) are the most reported materials used to make drug-containing dissolvable microneedles [34]. Conversely, the most frequently used polymers in the fabrication of vaccine containing dissolving microneedles are polyvinyl acetate (15.2%), followed by trehalose, chitosan, and carboxymethylcellulose (10.6% each) and hyaluronic acid (9%).

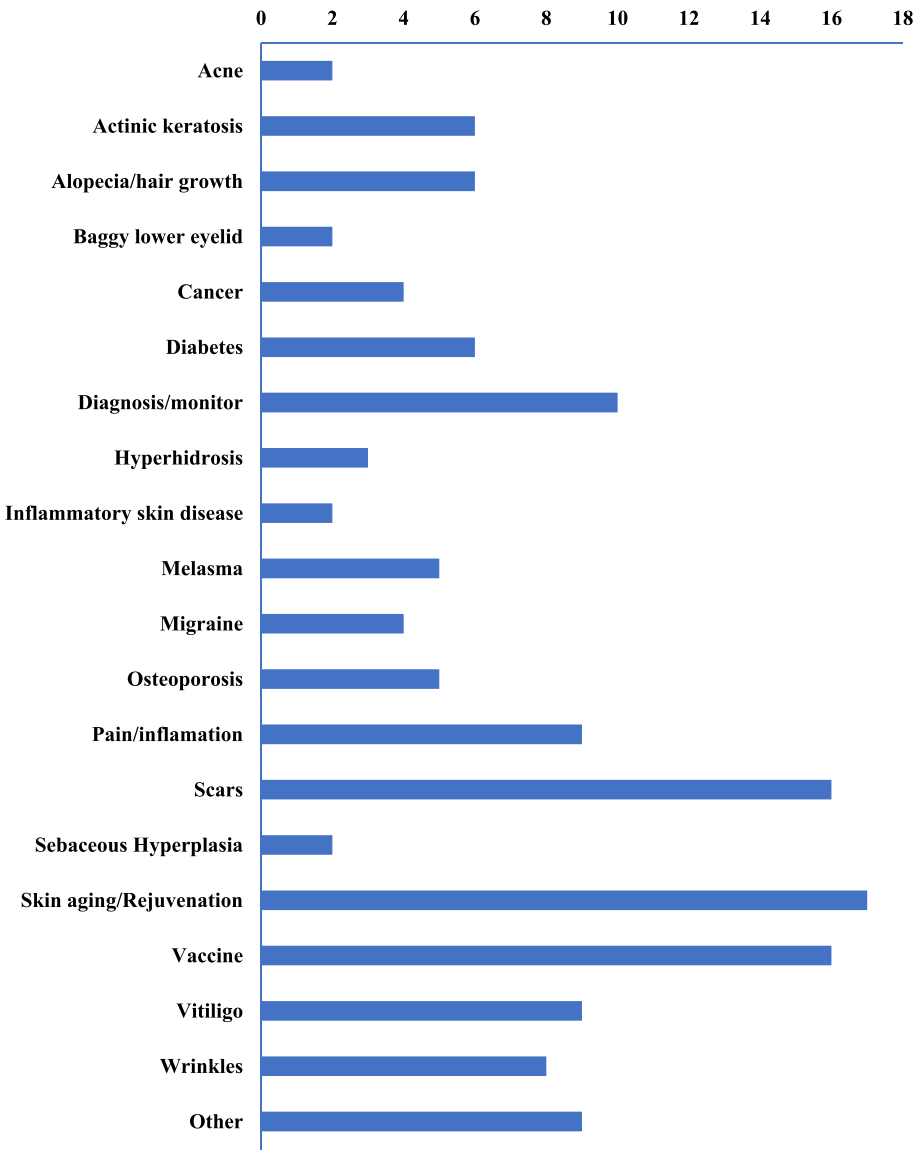


Fig. 7. Therapeutic Applications of microneedles in clinical trials, (n = 141). Derived from https://clinicaltrials.gov/. Search query: '(microneedle) OR (micro needle) OR (micro-needle) OR (microneedle array) OR (array patch) OR (microneedling)'.

Upon further examination of the clinical trial data derived from www.ncbi.nlm.nih.gov/pubmed/, it is evident that hyaluronic acid and its sodium salt are the materials that are used more specifically in the fabrication of dissolving microneedles which are at the stage of clinical trials (53% and 21%, respectively), Fig. 9. Hyaluronan or hyaluronic acid is a glycosaminoglycan polysaccharide, and is a major component of connective tissues throughout the body, including the skin [38]. It is quite commonly used in the preparation of microneedles in cosmetic research and will be discussed further in the dedicated section on microneedle applications in cosmetics, 2.4.2.1.

The main challenges facing these carrier systems is low drug loading capabilities, where the success of medical therapy depends on the appropriate delivery of the required drugs for treatment. Excipients are also a cause for concern from a regulatory perspective as so few have valid safety profiles and supporting data, especially for intradermal use. Even when an excipient is regarded as safe for oral dosage forms this does not confer complete safety for intradermal use. The lack of validated analytical procedures is often compounded by difficulties associated with the identification of various possible products of polymer metabolism, which is inherent due to the complexity of these polymer systems. These issues create problems when establishing criteria for manufacture and storage of polymer therapeutics, since the criteria applied to determine purity, stability and shelf life of those materials are often arbitrary. Furthermore, potential incompatibility between the polymer and the drug is another possible challenge [39]. Therefore, it may be beneficial to reduce the quantity of polymers used relative to the active ingredient, ideally avoiding the requirement for excipients entirely.

2.3. *Drug fabricated dissolving microneedles*

To circumvent the use of excipients and polymers and thus avoiding issues discussed, our research group have developed and patented a novel dissolvable microneedle technology fabricated from drug alone ***(Patent no. WO2020250210A1)***. This has been achieved in our laboratory with a method similar to micromoulding, in which molten drug is filled into poly(dimethylsiloxane) (PDMS) moulds under vacuum or centrifugation, Fig. 10. Suitable drugs for this method are characterised by being heat meltable with minimum degradation, possessing a glass transition temperature $>$ 25 °C and capable of forming stable,

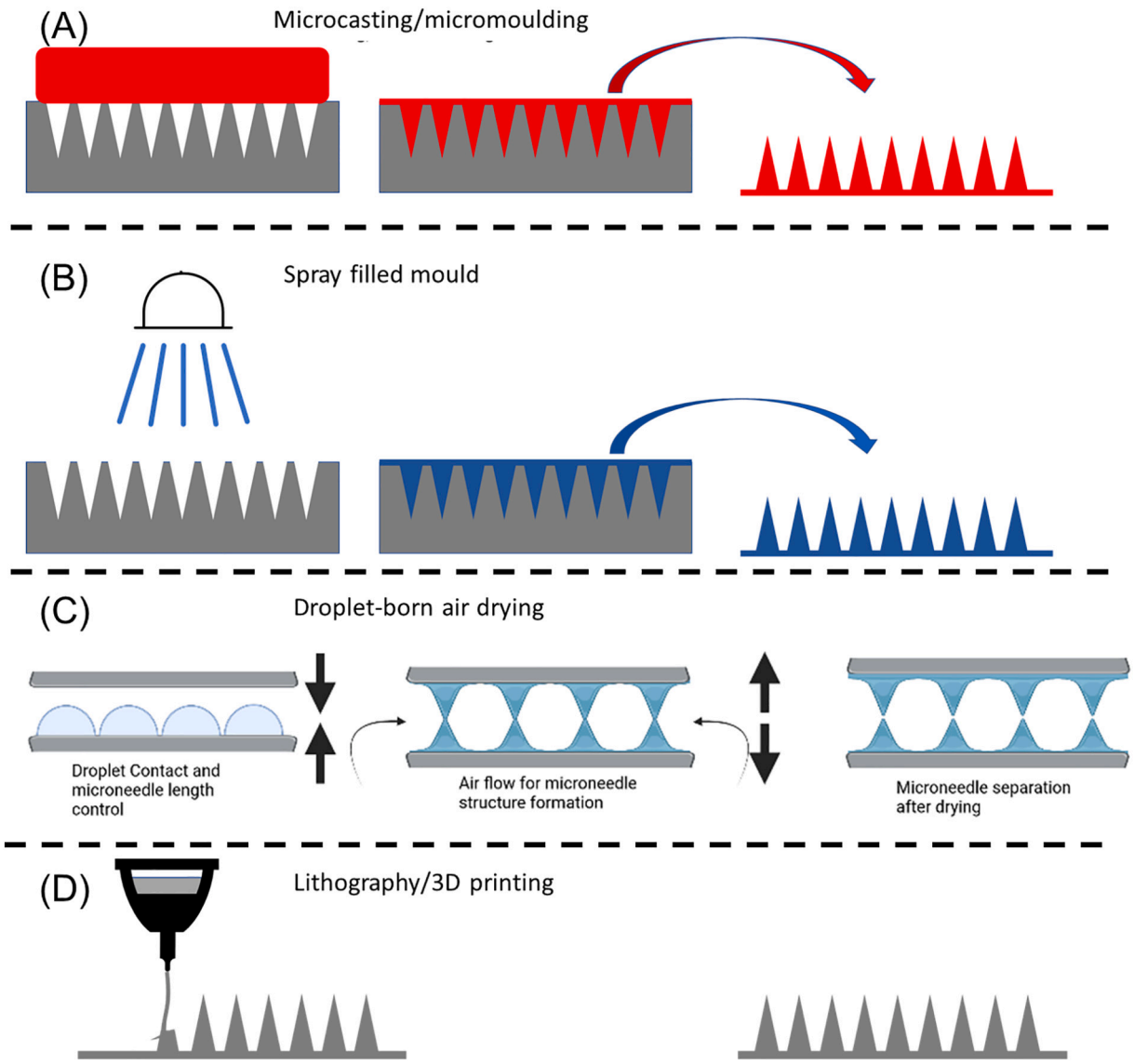


Fig. 8. Methods of fabricating dissolvable microneedles (a) micromoulding (b) micromoulding via spray methods, (c) droplet-born air drying and (d) Lithography/3D printing.

amorphous glassy states upon vitrification. Examples of such drugs are shown in Table 1.

Such microneedles have been successfully fabricated in our laboratory from indomethacin, oestradiol and itraconazole. Microscopy images illustrating examples of drug fabricated microneedles are shown in Fig. 11. These images demonstrate the highly defined needle point and octagonal pyramidal structure of the resulting microneedles. These microneedles demonstrate long term stability in the glassy amorphous state and possess mechanical strength properties capable of penetrating the skin (data not shown).

Dissolving microneedles fabricated from drug alone affords more benefits than those fabricated with polymers and other excipients. This approach will inherently introduce simplicities into the regulatory pathway and ongoing development of this technology. The absence of excipients means there is no need to worry about their presence in the final formulation from a biocompatibility and safety perspective.

Additionally, there are no issues with polymer testing, no polymer residues remaining in skin, higher drug loading capabilities, and the potential to deliver lower potency drugs thereby increasing the number of medicines that can be delivered intradermally. The use of simple manufacturing methods with few steps and minimal materials is also beneficial from an economical point of view. Although it is important to note that the manufacturing process may be a focal point for regulatory scrutiny as it involves the unconventional step of melting the active pharmaceutical ingredient.

2.4. Recommended applications of dissolvable microneedles

2.4.1. Dissolvable microneedles undergoing clinical trials: Therapeutic applications

Microneedles have been, and remain, a target of investigation across a wide range of therapeutic applications [20]. As previously discussed, dissolving microneedles are fast becoming an area of significant research, not only in academic circles but also in various therapeutic clinical applications where presently there are 10 clinical trials being undertaken involving dissolving microneedles (date of search Dec 2021). Fig. 12 and Table 2 illustrate different applications of dissolving microneedles across past and present clinical trials. This is a subset of the data illustrated in Fig. 6, extracted from a search of https://clinicaltrials.gov/. Dissolving microneedles undergoing clinical trials focus on cosmetics, anti-infectives (mainly vaccines), cancer, and skin conditions (mainly psoriasis).

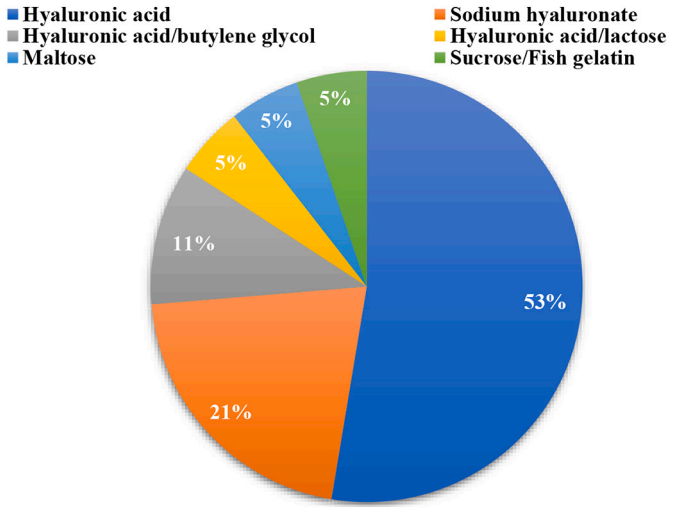


Fig. 9. Materials used in the fabrication of dissolvable microneedles undergoing clinical trials. Derived from www.ncbi.nlm.nih.gov/pubmed/. Search query: '(microneedle) OR (microneedling) OR (micro-needle) OR (micro array patch) AND (skin)'.

2.4.2. *Literature-based applications of dissolving microneedles*

2.4.2.1. Cosmetics. Microneedle technologies are to a certain extent already established in the field of cosmetics [40]. However, dissolvable microneedles remain an open area of research, and have been developed for the purpose of delivering cosmetic compounds to the skin or stimulating skin rejuvenation. One of the most commonly used materials is hyaluronic acid, which as a natural component of connective tissue, is well suited for its role in the preparation of microneedles for intradermal delivery and cosmetic applications [41]. For example, Kim et al., prepared dissolvable microneedles composed of hyaluronic acid loaded with ascorbic acid or retinyl retinoate. These were evaluated quantitatively for their capacity to improve the appearance of wrinkles in 24 human volunteers, ultimately resulting in statistically significant improvements [42]. Another study using a similar ascorbic acid-loaded dissolving microneedle composed of hyaluronic acid supports the earlier study, whereby the microneedle patch produced significant anti-wrinkle effects with no skin sensitisation or irritation [43]. Some groups have looked to incorporate adenosine, an anti-wrinkling agent, into their dissolving microneedle technologies. One example involved the preparation of polyvinylpyrrolidone microneedles containing adenosine, whereby the permeation of adenosine through porcine skin was significantly improved by microneedles compared to direct application of adenosine, although the methodology of the direct application were not clearly defined [44]. Another paper describes a hyaluronic acid microneedle system loaded with adenosine, the microneedles were compared with an adenosine cream, and showed similar or better efficacy across selected measurements (wrinkles, skin density, hydration, and elasticity), notably the dose in the microneedles was 140 times lower than the cream [45]. More recently, Jang et al., showed that dissolvable microneedles composed of hyaluronic acid and containing adenosine produced statistically significant improvements to skin wrinkling, elasticity, and dermal density, using a randomised clinical trial of 23 humans [46].

Table 1
Examples of the different drug classes potentially suitable for the preparation of dissolvable microneedles made exclusively from the active pharmaceutical ingredient. Adapted from Patent no. WO2020250210A1.

Class of medicinal compound	Examples of compounds with suitable properties
Antifungals	Itraconazole, Clotrimazole, Ketoconazole, Fluconazole
Corticosteroids	Oestradiol, betamethasone valerate, Testosterone
Anti-inflammatory drugs	Celecoxib, Diclofenac, Sulindac, Indomethacin
Antimicrobials and Antibiotics	Cefuroxime axetil, Chloramphenicol
Cardiovascular and Antihypertensives	Carvedilol, Nifedipine
Autonomic nervous system and Psychiatric drugs	Droperidol
Antilipidemics	Probucol, Simvastatin
Gastrointestinal	Famotidine, Omeprazole
Anti-migraine	Zolmitriptan

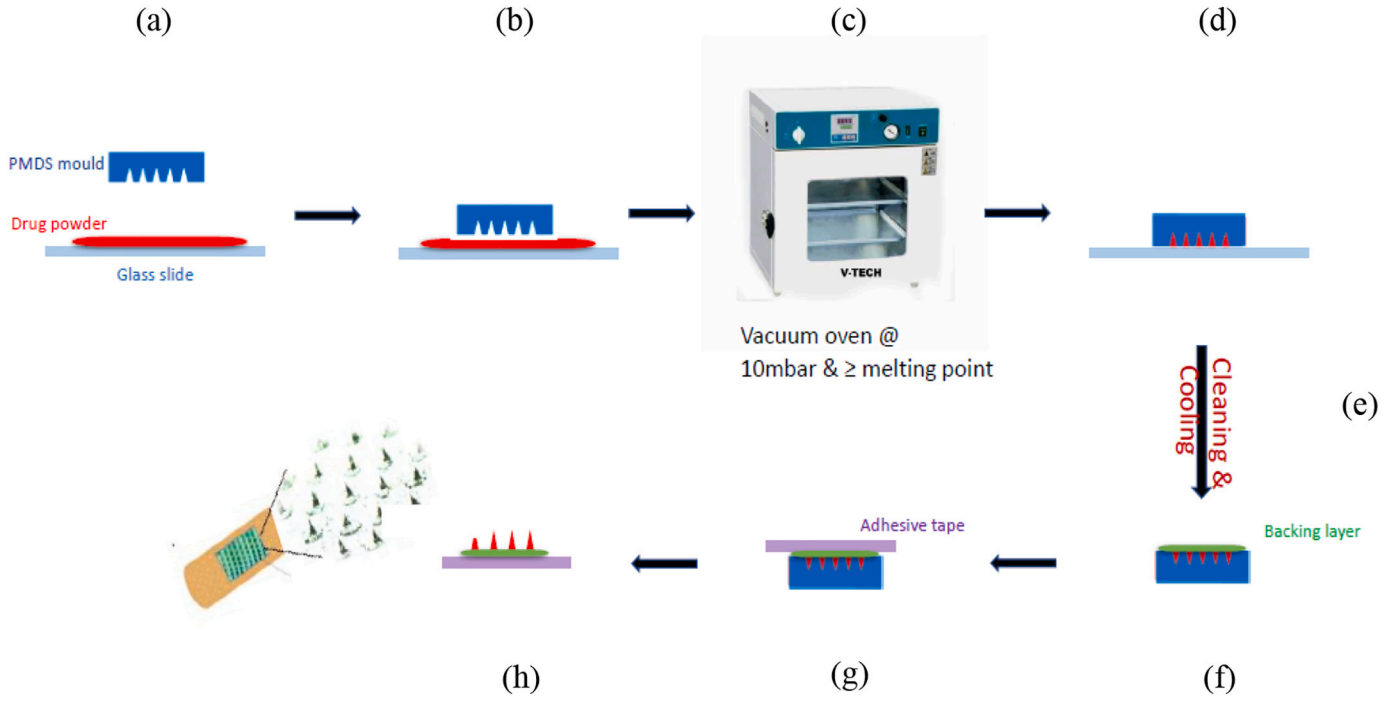


Fig. 10. Manufacturing process of drug fabricated dissolving microneedles (Patent no. WO2020250210A1).

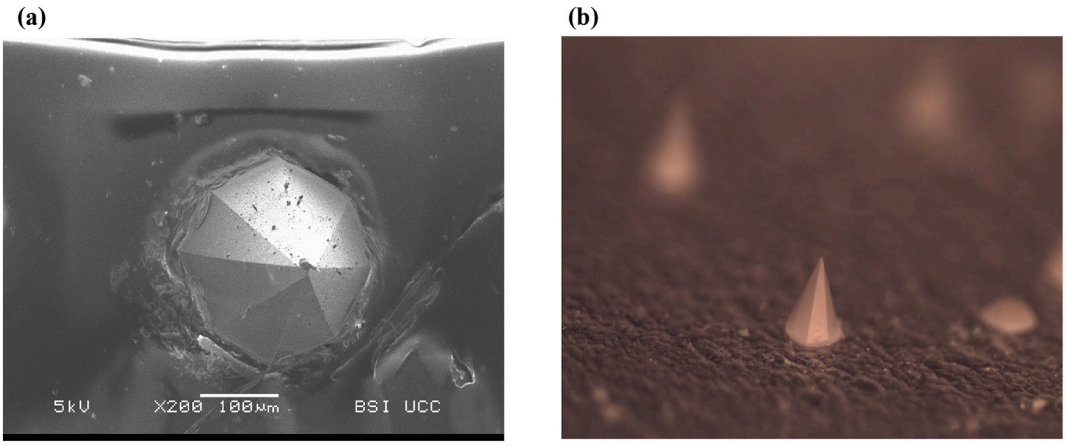


Fig. 11. (a) SEM and (b) microscope images of drug fabricated microneedles developed in our laboratory.

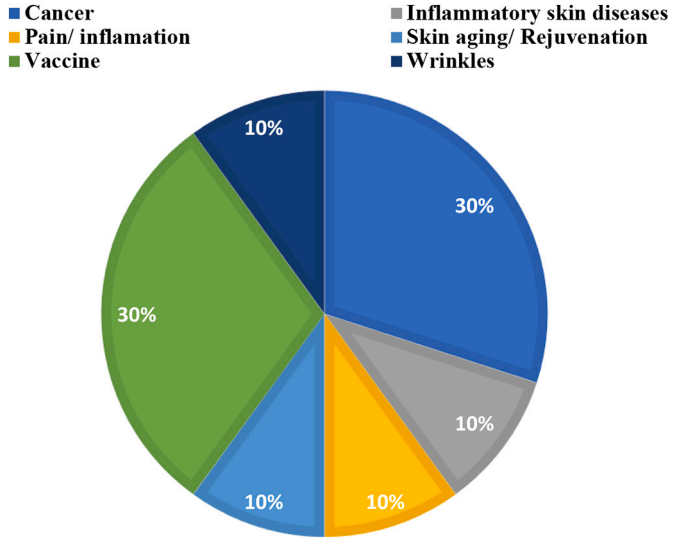


Fig. 12. Dissolving Microneedles: Applications in clinical trials, (n = 10). Derived from https://clinicaltrials.gov/. Search query: '(microneedle) OR (micro needle) OR (micro-needle) OR (microneedle array) OR (array patch) OR (microneedling)'.

Some have looked at combination therapies, such as combining dissolvable hyaluronic acid microneedles with adenosine cream, which together produced superior anti-wrinkle effects than microneedling alone [47].

2.4.2.2. Vaccines. Trypanophobia is one of the primary reasons most people avoid getting vaccinated. Therefore, developing an alternative pain-free method of vaccination using microneedles has been a significant area of research. The skin is an organ known to be rich in antigen presenting immune cells, including dendritic cells, monocytes, and macrophages [48], and so vaccination via the skin or the intradermal route of administration was the original concept of immunisation.

Quickly dissolving microneedles (≈5 mins) coated with inactivated influenza virus have been prepared for the presentation of influenza antigen to the skin [49]. Aptly for these times, Kim et al., prepared carboxymethyl cellulose microneedles incorporating the SARS-CoV-S1 protein. The microneedles were applied to the abdomen of mice for 10 min for initial and two-week later booster doses, eliciting potent antibody responses beginning two weeks after immunisation [50]. Rouphael et al., have shown in phase 1 clinical trials that their gelatin based microneedles were capable of producing a robust antibody response towards an influenza vaccine, a response not significantly different from an intramuscular injection [51]. Edens et al., prepared dissolvable microneedles carrying measles antigen composed of sucrose and carboxymethyl cellulose. These microneedles were applied to rhesus macaques and produced antibodies at levels correlated with protection. Furthermore, the result was not significantly different from subcutaneous injection [52]. Joyce et al., used the same design of microneedle to deliver measles and rubella vaccines to rhesus macaques and produced antibody responses at least equivalent to those seen for subcutaneous injection [53]. Pattarabhiran et al., prepared microneedles composed of polyvinylpyrrolidone and polyvinylchloride, containing tetanus vaccine. The microneedles produced antibody responses comparable to those of an intramuscular injection control when administered to Swiss albino mice [54]. Donadei et al., prepared dissolvable microneedles composed of trehalose and polyvinyl alcohol, containing a poliovirus vaccine, producing an immunogenic response in rats comparable to an intramuscular positive control [55].

2.4.2.3. Anti-Infectives. Skin infections, whether bacterial, viral, or fungal, are common [56] but also difficult to treat using conventional topical formulations due to the obstruction of the *stratum corneum* [57]. Therefore, microneedles capable of penetrating the *stratum corneum* or indeed the entire epidermis represent a promising research topic. This is especially true in cases that currently require extended treatment duration, such as fungal infections deep in the skin or extending to the nails [57]. To this end, Qin et al., prepared microneedles composed of poly ionic liquid polymers (which have intrinsic antibacterial properties) [58], coupled with salicylic acid, for the treatment of acne caused by *propionibacterium acnes* [59]. This microneedle design exhibited therapeutic efficacy both *in vitro* and *in vivo*, illustrating the potential benefit of fabricating the microneedle array itself from functionally active materials rather than simply acting as a vector for the delivery of antimicrobials [59]. Dissolving microneedles have also been developed for the treatment of neonatal sepsis, whereby sodium hyaluronate and polyvinylpyrrolidone acted as the microneedle matrix and backing layer, respectively. In vivo, the microneedle arrays produced sustained therapeutic plasma concentrations of 2–5 μg/ml, over 1–6 h, compared to an intramuscular injection given as a control. It is important to note that the highest concentration required the application of four microneedle arrays, which when scaled to humans would necessitate a patch size of 15 cm^2 [60].

Permana et al., produced a dissolvable microneedle delivery system that utilised nanocrystalline itraconazole for cutaneous candidiasis. This formulation resulted in superior distribution of the antifungal compound in ex vivo porcine skin samples compared to a conventional antifungal cream. However, this particular design results in itraconazole forming only 2% of the overall mass of the microneedle array [61],

Table 2
Dissolving Microneedles: Clinical trial information, (n = 10). Derived from https://clinicaltrials.gov/. Search query: '(microneedle) OR (micro needle) OR (micro-needle) OR (microneedle array) OR (array patch) OR (microneedling)'.

Trial name	NCT Code	Clinical trial phase	Therapeutic application	Needle name/method of fabrication/needle length
Soluble Hyaluronic Acid Microneedle VS. Non-ablative Fractional Laser on Infraorbital Wrinkles	NCT04989361	Not Applicable	Cosmetic	Micromoulding 600 μm
Placebo Microneedles in Healthy Volunteers (Part I) and Efficacy/Safety of Doxorubicin Microneedles in Basal Cell Cancer Subjects (Part II)	NCT04928222	Phase 1 Phase 2	Cancer	Micromoulding 750 μm
Evaluate the Efficacy and Safety of Brightening Micro-needle Patch on Facial Solar Lentigines	NCT04583852	Not Applicable	Solar lentigines, skin condition	AIVÍA, Ultra-Brightening Spot Micro-needle Patch N/A
Measles and Rubella Vaccine Microneedle Patch Phase 1–2 Age De-escalation Trial	NCT04394689	Phase 1 Phase 2	Vaccine	Micromoulding 650 μm
Open-Label Dose Escalation Trial to Evaluate Dose Limiting Toxicity and Maximum Tolerated Dose of Microneedle Arrays Containing Doxorubicin (D-MNA) in BCC	NCT03646188	Phase 1	Cancer	Micromoulding 750 μm
Microneedle Patch Study in Healthy Infants/Young Children	NCT03207763	Not Applicable	Vaccine	N/A < 1000 μm
Microneedle Patch for Psoriatic Plaques	NCT02955576	Not Applicable	Psoriasis	HA-fabricated microneedle patches (Therapass® RMD-6·5A 650 μm
Inactivated Influenza Vaccine Delivered by Microneedle Patch or by Hypodermic Needle	NCT02438423	Phase 1	Vaccine	Micromoulding 650 μm
Micro Needle Array-Doxorubicin (MNA-D) in Patients With Cutaneous T-cell Lymphoma (CTCL) (MNA-D)	NCT02192021	Phase 1	Cancer	Micromoulding 600–850 μm
Efficacy of Transdermal Microneedle Patch for Topical Anesthesia Enhancement in Paediatric Thalassemia Patients	NCT05078463	Phase 2	Anesthesia	N/A 400 μm

limiting the dosage of itraconazole that can be incorporated in the delivery device. The same group used a similar method to prepare polymeric, dissolvable microneedles containing doxycycline, albendazole, and ivermectin towards a new approach to the treatment of filariasis [62], and showed significant delivery of all the aforementioned agents to the dermis of neonatal porcine skin.

2.4.2.4. Diagnosis and monitoring. Our own analysis of clinical trial data (Fig. 5 and Fig. 7 and evidence from available literature has shown that the diagnostic/disease monitoring applications of all types of microneedles in clinical trials are significant [63]. This interest also extends to the field of dissolving microneedles, although the microneedles in question would be more accurately described as hydrogel microneedles. Nonetheless, dissolving microneedles can be used to measure both small and large molecules. For example, a potential diagnostic use of microneedles is for tuberculin testing, Wang et al., demonstrated this using a dissolving microneedle design composed of sodium hyaluronate and containing a tuberculin antigen, which after application to the skin produced redness and induration of the skin in human volunteers with tuberculosis and latent tuberculosis, but had no effect in healthy volunteers [64]. There is also a substantial interest in the use of microneedles in tumour and cancer diagnosis [65–67]. Meanwhile, Chang et al., used a swellable microneedle system to measure glucose and cholesterol in interstitial fluids as potential management tool for diabetes, atherosclerosis, thrombotic risk, and cardiovascular disorders [68]. Dissolving microneedles have also been investigated as a potential applicator or test device in skin allergy tests, whereby dextran microneedles, containing L-arginine as a test allergen, were applied to rats and elicited a response similar to conventional 'needle scratch/prick' tests [69]. Another group is developing a polyvinylpyrrolidone-methacrylic acid dissolvable microneedle for the same purpose [70].

2.4.2.5. Anticance. Anticancer endeavours in the field of transdermal delivery have generally been associated with prevention and pain management. In particular nicotine patch users are significantly more likely to quit smoking [71], thus contributing to a reduction in the risk of lung cancer [72], while buprenorphine and fentanyl patches are safe and effective for managing cancer pain [73]. The efficacy of transdermal delivery of cancer therapeutics is less clear, nonetheless there is a growing body of literature using microneedle technologies (including dissolvable microneedles) to improve upon severe chemotherapeutic side-effects by improving tumour targeting [74]. Some examples of dissolving microneedles developed to treat cancers include those by Pan et al, who prepared dissolvable microneedles composed of dextran, hyaluronic acid, and polyvinylpyrrolidone. The microneedles were loaded with STAT3 silencing RNA (STAT3 is known to be involved in melanoma metastasis). In vivo the microneedles were effective in suppressing the development of melanoma as determined by reductions in tumour mass and volume [75]. Other research groups have also looked to incorporate small molecules, such as doxorubicin and docetaxel, which have been incorporated into polyvinylpyrrolidone microneedle formulations for the management of breast cancer, whereby drug-loaded microneedles significantly slowed tumour growth in a xenografted breast cancer mouse model [76]. Doxorubicin and trametinib have been used synergistically as part of a dextran methacrylate microneedle system, with the drug-loaded microneedles producing a significant inhibition of tumour growth in a melanoma cell xenograft mouse model [77]. Another group targeted melanoma by preparing hyaluronic acid dissolving microneedles loaded with doxorubicin and photothermal therapy gold nano-cages, which resulted in slowed tumour growth in mice [78]. A similar article describes hyaluronic acid microneedles loaded with gold nano-rods and doxorubicin. However, the microneedles alone had no anti-tumour effects towards an epidermoid carcinoma in mice, instead showing a smaller synergistic effect alongside the more significant photothermal therapy brought about by the near infra-red irradiation of the gold nano-rods [79].

2.4.2.6. Pain and inflammation. Various approaches have been proposed to develop fast and painless intradermal drug delivery for pain management and anti-inflammatory therapeutics [80]. Nowadays, microneedles have obtained substantial attention as a promising tool to deliver a variety of these molecules. Lee et al., prepared dissolving microneedles composed of carboxymethyl cellulose and containing lidocaine. Applied in vivo, the microneedles produced a significant reduction in the nocifensive response of rats for over an hour [81]. In this case the microneedles were prepared using centrifugal lithography, which is useful as a one-step method for the preparation of microneedles where centrifugation both shapes and dries the needle structures [82]. Zhan et al., prepared dissolvable microneedles loaded with lidocaine, producing statistically significant anaesthetic efficacy. However, due to

the water-soluble lidocaine making up 70% of the microneedles by weight, the anaesthetic effect was only maintained for 16 min compared to over 200 min for a positive control [83].

Another potential target of microneedle therapeutics is the neurological condition, migraine. Tas et al., prepared dissolvable polyvinylpyrrolidone microneedles loaded with dihydroergotamine mesylate, which following application to hairless rats showed a relative bioavailability and plasma levels that were not statistically significantly different compared to a subcutaneous injection [84]. Ergot derivatives are a second choice in migraine following a failure to respond to the triptan family of drugs, which themselves have also been a major target of microneedle research. Specifically, Zolmitriptan is used in the Qtrypta™ device, which is a coated microneedle system, but is one of the most developmentally advanced microneedle projects and may soon be approved for commercial use if it can overcome issues related to inconsistent pharmacokinetics [85].

Xie et al., prepared dissolvable microneedles loaded with a selective antagonist of calcitonin gene related peptide, a neuropeptide involved in the sensation of neuropathic pain. The group used several models of neuropathic pain to show increases in rats pain threshold towards thermal and mechanical stimuli [86].

2.4.2.7. Diabetes. The most common method of delivering insulin is parenterally via hypodermic needle, with all the difficulties hypodermic delivery entails, including: pain, potential needle-stick injury, and requiring professional handling [87]. Hence the need to explore alternative delivery pathways, such as delivery intradermally using microneedles.

The delivery of insulin is a common target in the field of drug delivery, with microneedles being no exception. For example, Kim et al., developed a dissolving microneedle composed of a carboxymethylcellulose shell with a hollow core containing insulin powder. This technique allowed the researchers to load more than double the amount of insulin compared to more conventional microneedles where the carboxymethylcellulose and insulin were homogenously mixed. Ultimately, the two methodologies resulted in similar bioavailability of insulin in vivo. However, it should be noted that the superior loading of the shell-based device means that when the data is extrapolated to humans, the patch size for the homogenised microneedles would be 9 cm^2 compared to a significantly smaller 3.8 cm^2 [88]. Chen et al., prepared microneedles composed of gelatin and carboxymethyl cellulose loaded with insulin. In vivo, the insulin-loaded microneedles produced significant reductions in plasma glucose levels similar to those of a subcutaneous injection control. The group also conducted skin penetration tests on human cadaveric skin to identify suitable locations for microneedle application, with the posterior auricular and forearm skin showing the highest rates of penetration [89]. Zhang et al., delivered insulin intradermally using an alginate/maltose composite microneedle that produced an effective hypoglycaemic effect with insulin bioavailability equivalent to that of a subcutaneous injection [90].

Despite these promising studies, it is important to highlight that bypassing the *stratum corneum* does not guarantee success. Indeed, in one study, leuprolide was incorporated into dissolving microneedles composed of chondroitin sulfate, and despite circumventing the *stratum corneum* the achieved bioavailability was only ≈ 30%. The authors endeavoured to show that the leuprolide was being degraded, likely by enzymes in the epidermal region of the skin and calculated a degradation half-life of 16.3 min for leuprolide in the skin [91]. This study highlights the importance of in vivo investigations into the pharmacokinetics and bioavailability of microneedle delivery, rather than just issues of permeability. Another interesting paper on this type of in situ degradation of peptides is one by Keea Kim et al., whereby several formulations of dissolving microneedles composed of hyaluronic acid containing human parathyroid hormone were prepared. The different formulations included additional materials, namely trehalose or polyvinylpyrrolidone. Both additives improved bioavailability compared to additive-free microneedles by a 3- and 10- fold increase in the peak serum concentration, respectively, an effect ascribed in part to polyvinylpyrrolidone providing protection to the protein from enzymatic degradation [92].

2.4.2.8. Hair and scalp disorders. Alopecia and hair loss are one of the most prevalent dermatologic conditions, it is viewed mostly through the lens of its cosmetic consequences and that is why it has a separate section. Lahiji et al. described carboxymethyl cellulose fabricated dissolvable microneedles containing valproic acid for the treatment of androgenetic alopecia [93] and evaluated the formulation for hair regrowth in a mouse model following transcutaneous implantation. Following 28 days, all mice of the microneedle treated group, and two out of seven mice in the topical valproic acid control group demonstrated induced hair growth, with only the microneedle group displaying uniform coverage. The control groups showed no hair regrowth.

A novel finasteride delivery system to treat androgenetic alopecia was described by Kim et al. [94]. Finasteride in powder form was encapsulated within a dissolvable carboxymethyl cellulose fabricated microneedle and coupled with a topical diffusion enhancer. Encapsulating drug powder in a hollow within the microneedle structure circumvents insolubility issues experienced with lipophilic drugs during the conventional dissolvable microneedle fabrication process. Compared with a topical finasteride gel, the dissolvable microneedles showed a higher efficacy in promoting hair growth in a mouse model with increased amount and density of hair. The formulation demonstrated continuous delivery of finasteride for 3 days with daily application of a diffusion enhancer, delivering 2.80 times more drug on the same application area than the topical gel.

2.4.2.9. Inflammatory skin and autoimmune conditions. Microneedles, in their different varieties, have been investigated across a number skin and autoimmune conditions, including dermatitis, atopic dermatitis, eczema, Psoriasis, prurigo nodularis, dry skin and seborrheic keratosis. A common condition, atopic dermatitis, lacks a defined cure and relies on management of recurrent flare-ups. To this end, Jang et al., prepared dissolving microneedles containing triamcinolone acetonide for the treatment of atopic dermatitis. This microneedle system utilised a triamcinolone suspension resulting in a delivery system containing 30% triamcinolone by mass, and when utilised in a murine model of atopic dermatitis, the drug-loaded microneedles produced significant reductions in erythema, scaling, and lichenification comparable to triamcinolone creams and intralesional injection [95]. Chen et al., prepared dissolvable poly-glutamate microneedles set atop a supporting polycaprolactone substrate. In vivo, the microneedles produced reductions in lesions associated with atopic dermatitis, and furthermore reduced mast cell infiltration by downregulating immunoglobulins [96].

3. Barriers facing microneedles

3.1. Physiological and scientific barriers

Microneedles are not without limitations, with one well known barrier encountered in microneedle research being the issue of rapid skin healing and closure of induced microneedle channels. Gualeni et al., used optical coherence tomography to show the rate of change in the depth of microchannels after microneedle application in vivo, finding that complete closure takes between 4 and 24 h [97]. This timeframe is in agreement with other sources available in the literature [98,99]. It is useful to note that the rate of skin micropore closure can be different depending the characteristics of the skin in question, for example more melanistic skin has shown significantly extended microchannel duration, by as much as 50% [100]. Additionally, older skin also recovers more slowly following microneedle insertion [101]. Improved

understanding of the biomechanics of skin may help in ensuring consistent microneedle penetration into the skin. For example, Kim et al., investigated the effect of stretching and mechanical vibration of the skin on microneedle penetration taking inspiration from the mechanism of action of mosquito and bee stings [102]. Dissolvable microneedles, by nature of their design, overcome this barrier as they are not removed at any point, instead remaining in place until fully dissolved.

Furthermore, the manufacturing process of dissolvable microneedles is generally more complex than other skin-related methodologies (for example, topical creams and ointments), especially regarding the various methods (vacuum, centrifugation) and excipients used in microneedle fabrication. In addition to the possible sterility requirements of the final product [103], and the potential costs of microneedles may result in them being uncompetitive against less efficacious but still more cost-effective options. Another issue related to dissolvable microneedles that may hinder cost-effectiveness is the susceptibility to material wastage, especially when using the most common fabrication method, micromoulding [104].

Microneedles may present a small infection risk, however there is evidence showing that microneedles result in lower microbial penetration than hypodermic needles [105], indicating a potentially lower infection risk. A more recent systematic review on the topic maintains that infection risk remains a possibility, however concludes that microneedling is a relatively safe procedure whose adverse effects may include erythema, pain, oedema, and skin irritation [106].

The need to understand the ADME profile of any encapsulated material will largely focus on the time taken for the active ingredient to reach a maximum concentration in plasma. This will be a critical factor and indicates the absorption that can be achieved from the microneedle platform and also the potential of the drug to act locally, when this would be beneficial. The non-clinical ADME testing of the microneedle product is specific to each product. In this context, Ito et al., 2011, reported a low bioavailability of leuprolide acetate in a rat model after the application of two-layered dissolving microneedles of which acral portion contained active ingredient [91]. The enzymatic degradation of leuprolide acetate in the skin tissue resulted in low bioavailability after percutaneous administration by dissolving microneedles. In contrast, So et al., 2009, showed a higher plasma concentration of ketoprofen in rats following microneedles treatment versus a topical gel formulation alone [107]. Inconsistent pharmacokinetics was also evidence at phase 3 trial with Zolmitriptan coated microneedle system which is used in the Qtrypta™ device [85].

Limited dosing capacity is a self-evident difficulty with microneedles, given the dimensions of the microneedles themselves, and the limitations that will be imposed on the size of the patch by patients and customers' demands [108]. By nature of their design, dissolving microneedles are generally capable of delivering greater quantities of an active pharmaceutical ingredient than other types of microneedles. To elaborate on this, coated microneedle arrays can often be loaded with no more than 1 mg of drug [109]. For example, Gill and Prausnitz, prepared microneedle arrays made up of 5–50 microneedles, 600 μm in height, coated with up to 6.4 μg of riboflavin per microneedle [110]. Compared to McCrudden et al., who prepared a dissolvable polymeric microneedle array composed of 361 microneedles, 600 μm in height, that contained up to 37.24 ± 2.25 mg of ibuprofen sodium [111]. It is important to note that the majority of the 37.24 mg likely resides in the microneedle backing layer rather than the microneedles themselves.

There are only a few variables that can be tweaked when aiming to improve the limited dosing capacity, these are to encapsulate more drug, to increase the density of needles or needle size, and to enlarge patch size. One potential microneedle design that may help overcome several design and cost issues, is the preparation of microneedle patches and arrays exclusively from medicinal compounds. As previously discussed, our research group have designed and patented a method for the fabrication of such microneedles ***(Patent no. WO2020250210A1)***, which also highlights several pharmaceutical compounds with physicochemical properties pertinent to this method, Table 1.

The use of excipients is often a cause for concern from a regulatory perspective as so few have valid safety profiles and supporting data, especially for intradermal use. The metabolism of polymers is still an uncharacterised process, and the lack of long-term studies on polymer deposition in the skin following microneedle application, mainly for dissolving microneedles, is another safety issue to be investigated. If the deposited polymer is not efficiently metabolised by the body, the polymer will be distributed throughout the body, accumulated in the liver and/or build-up in the dermal tissue after repeated applications [112]. These issues create problems when establishing criteria for the manufacture and storage of polymer therapeutics, since the criteria applied to determine purity, stability and shelf life of those materials are often arbitrary. This concern with dissolving microneedles suggests that this particular design is more suitable for 'one-off' delivery. Therefore, it may be beneficial to reduce the quantity of polymers used relative to the active ingredient, ideally avoiding the requirement for excipients entirely. This approach was expressed in our recent patent ***(Patent no. WO2020250210A1)***, whereby a dissolving microneedle array was manufactured with drug material alone.

3.2. Regulatory and commercial barriers

One of the main challenges to commercialisation will be to convince clinicians and patients about the benefits of microneedle products in light of other well established and low-cost products. Additional technical evidence and early engagement with stakeholder Key Opinion Leaders (KOLs) will be crucial to raising awareness of the microneedle benefits. To enter the market for disease specific applications, there will be a challenge to get health insurers to pay for the treatment. Reimbursement will depend on a cost/benefit analysis. Microneedles will be in a good position if the efficacy of the treatment outweighs healthcare costs associated with the treated condition and those costs associated with the patient non-adherence to treatments due to the systemic side effects and drug-drug interactions of other standard care treatments.

The regulatory position of microneedles is still unsettled, and several of its commercial barriers are still unclear. Under the United States' Food and Drug Administration Code of Federal Regulations: Title 21/Chapter 1/Sub-chapter A/Part 3/Sub-part A/3.2., dissolvable microneedles would likely be regulated as a drug/device combination product. Conversely, under the European Union framework, namely Directive 2001/83/EC or Regulation No 726/2004, dissolvable microneedles would likely be classified as a medicinal product. Therefore, the development will proceed in compliance with the regulatory framework of drug development. The development of microneedle platforms and indeed any drug delivery platform has a financially restrictive bottleneck at the non-clinical stage.

For any microneedle prototype, the ability to navigate successfully through an evolving regulatory process presents a significant commercialisation threat. Manufacturers interested in microneedle technology and the production scaleup wait for guidelines pertaining to pharmacopoeial standards and accepted quality control tests. Specific regulatory guidance relating to patient use are also required, concerning factors such as sterility, packaging, ease of use, assurance of correct use, disposal and safety issues. However, Zosano Pharma has advanced its Qtrypta product through the FDA system and has established a blueprint for other companies.

Sterility and endotoxin testing are fundamental requirements of parenteral drug products. Microneedles lie between this level of risk and a standard transdermal patch. Even the most conservative drug developer will consider microneedles to be closer to transdermal patches in terms of risk than parenteral products. To date, regulatory agencies have directed that microneedle patches be sterile and pass a standard pharmacopeial test for endotoxin.

A significant cost in formulation development and processing is the aseptic processing of microneedle platforms and this is only used when

there are no alternatives. Biologic drugs are typically manufactured in this way due to their inherent instability and their parenteral route of administration. There have been a number of microneedle products that failed due to regulatory pressures reducing their financial viability. The sterility of the microneedle patch becomes hugely significant especially when the manufacturing process and active ingredient do not support terminal sterilisation. In such cases, the only option is to manufacture using sterile processing reducing the cost-effectiveness of the product. Manufacturers have even stated that it would be not make financial sense for them to replace their own injectable products with complex microneedle formulations if the benefit to the end user is limited to convenience or marginal clinical gains. A case-by-case basis for sterility of microneedle patches will be the likely approach until the intradermal route of administration becomes more established.

Another area of interest which is becoming increasingly important across all industries is sustainability. Should the developed technology be able to demonstrate environmental positivity then this would be clearly advantageous. Reducing waste and increasing use of sustainable input materials mainly in packaging is recommended. The ability to make claims around this area will be of importance when entering the market and be beneficial to potential customers.

However, assuming that the non-clinical stage of development is overcome, of which will be further discussed, there still remains further commercial barriers encountered by all types of microneedle technologies. An overview of these is presented in the following subsections of this review.

3.3. Non-clinical safety

When a drug is no longer protected by patent or data exclusivity, the regulatory framework in most markets allows the drug developer to place their product on the market having only established that the pharmacokinetic profile of their product 'matches' the innovator's marketed product. As the intradermal route is completely different, there is uncertainty over what can be assumed from the safety profile of the innovator's drug that was delivered via the oral, topical, or injectable routes. This uncertainty presents as enhanced animal testing in comparison to the generic drug application path. This is prudent by the Regulatory Agencies and expected, however the risk averse position to change inevitably presents a barrier to the clinical testing of microneedle formulations.

Whilst a significant proportion of the standard non-clinical testing programme for a New Chemical Entity (NCE) does not apply to an established active ingredient with a known safety profile, it is important to be aware of these requirements in order to provide a scientifically sound rationale to exclude them. The specific active ingredient to be delivered will dictate the overall program but there are obvious tests that can be excluded such as genotoxicity and immunotoxicity.

The preclinical testing of a potential candidate prior to clinical testing must demonstrate the safety of the molecule in standard models if possible. The following preclinical development summary relates to the safety of a NCE with the route of administration being IV Bolus, however the generic preclinical programme presented should give a general indication of the current regulatory expectations. Bespoke elements are usually required for vaccines, biological drugs and oncology products which are cytotoxic or cytostatic.

In general, a standard NCE non-clinical development programme would take 7–8 months to complete and involves the use of a rodent and non-rodent model which is usually a beagle dog. The only regular alternative being porcine models including the Gottingen mini-pig for transdermal products. It is important to emphasise that pivotal preclinical toxicology studies should be conducted in accordance with Good Laboratory Practice (GLP). Failure to do so will render any information invalid for regulatory submissions. There will also be less regulatory scrutiny if the pivotal toxicology testing is conducted in an OECD country.

Regardless of the experience in the research team, it is highly advisable to engage the Regulator in formal scientific advice at early stages. Discovering that a preclinical testing programme is insufficient after submitting a Clinical Trial Authorisation results in a very significant delay. There are sometimes situations when an aspect of the programme will need to be negotiated with the regulator, but this should be done upfront for example the need for a viable model of disease for a previously untested cellular therapy may render non-clinical safety testing impossible.

The guidance relevant to standard preclinical safety testing is as follows:

- ICH guideline M3(R2) on non-clinical safety studies for the conduct of human clinical trials and marketing authorisation for pharmaceuticals (EMA/CPMP/ICH/286/1995).
- Repeated Dose Toxicity (CPMP/SWP/1042/99).
- Safety Pharmacology (CPMP/ICH/539/00 and CPMP/ICH/432/02).
- Genotoxicity (EMA/CHMP/ICH/126642/2008).
- Toxicokinetics (CPMP/ICH/384/95).

There are many guidance documents compiled by other regulators and stakeholders globally and compliance with some of them will be necessary, for example FDA guidance on bioanalytical validation should an **Investigational New Drug** (IND) application need to be sought. It is important from an early stage in the research programme to determine which markets and clinical trials sites will be relevant for the drug candidate.

3.4. First mover (dis)advantage

Whilst innovation is key to the development of better products and treatments, the relative novelty of microneedles as an intradermal delivery technology, with few examples on the market available for comparison, presents a fundamental barrier to the potential success of microneedles going forward. Developers of intradermal drug formulations have few of the benefits afforded to other extensively used routes of administration such as oral or intravenous delivery. This includes the accessibility of guidance documents from regulatory agencies; safety and pharmacokinetic data from previous use of a drug intradermally; safety and pharmacokinetic data from previous use of excipients intradermally; and the confidence of regulatory assessors.

3.5. Lack of existing infrastructure

The manufacture of microneedles is generally more difficult than traditional dosage forms such as topicals, orals or injectables. This is directly connected to the unique nature of these products, but the refined structural parameters necessary for successful drug delivery presents a risk to manufacturers trying to scale-up production to commercial batch sizes of current good manufacturing practice compliant products. The use of microneedle technologies in cosmetics is likely the biggest contributor to infrastructure development in Asia, however for therapeutic applications, further scientific developments and breakthroughs are required to bring in the required investment. Alternatively, the industry must rely on so-called angel investors, such as the Bill & Melinda Gates foundation's support in the development of microneedles for measles and rubella vaccination. Another example is the Program for Appropriate Technologies in Health (PATH) Centre of Excellence, which is part of a program spanning over a decade, which aims to develop microneedles for vaccine applications in regions with less access to essential medical resources.

3.6. Cost of goods

The cost of goods is another important barrier to microneedle success, as currently there is little to no developed manufacturing capacity

or infrastructure for microneedle development. Large scale manufacturing must be established in order for microneedles to compete with existing hypodermic methods [113]. Microneedles may never be able to compete with oral dosage forms, however competition with injectable drugs is expected [114]. The short term safety of microneedles may be promising [112], however, microneedle technologies must confer a significant advantage over current treatment option to overcome the complexities stated above. Microneedle products could fail due to regulatory pressures reducing their financial viability. For example, microneedles have been suggested as an alternative route of delivery for vaccination, and the sterility of microneedle patches becomes hugely significant especially when the manufacturing process and the active pharmaceutical ingredient do not support terminal sterilisation. In such cases, the only option is to manufacture using sterile processing, ultimately reducing the cost-effectiveness of the product. Manufacturers have even stated that it would not make financial sense for them to replace their own injectable products with complex microneedle formulations if the benefit to the end user is limited to convenience or marginal clinical gains. The likely eventuality would be that microneedle technologies would be assessed on a case-by-case basis until the intradermal route of administration becomes more established. Finally, increasing regulatory conservatism relating to the health and safety issues of microneedles for repeated use, or use over longer durations, presents a substantial barrier to microneedle technologies, which are lacking in long term study data.

The limiting factors regarding further progress for clinical applications of microneedle based delivery systems include the cost of the active ingredients, excipients, manufacturing capabilities and storage conditions. All of which contribute to the amount of time and resources spent in in the research and development phase. The future development in the cost control of the microneedle formulation should be carefully considered. Using generic medications can provide significant cost savings and are nearly always preferred by prescription insurance plans. One approach in this concern, which is developed by the authors own research group, is the use of a dissolving microneedle array made only from the drug ***(Patent no. WO2020250210A1)***. This increases the availability of the drug, reduces costs, and simplifies the production process. Critically, the fact that the microneedles are manufactured from 100% drug is a major advantage. In the authors experience, dissolving microneedle arrays could be classed as a new medicine when excipients are used to retain the structure and the use of bridging studies removed. Any outcome that avoids the new drug classification is highly favoured with the impact of being classed as a new drug being instrumental in dictating the project plan. Increased costs, time to market and risks are significant. The pharmaceutical history of generics is well established, and regulators will be assured by the safety profile of the drug if the dosage is within the prescribed safety limits. The key questions to address are safety (biocompatibility), efficacy, and that mass-produced devices give a repeatable reliable dose when used. However, factors for establishing the physical robustness in use and stability of the device using 100% drug will be required.

4. Commercial successes

The market for microneedles is forecast to continue to grow at a compound annual growth rate of 7.1% through to 2027 [115]. Though some companies now have GMP licenses for the production of microneedles, currently no intradermal microneedle array-based drug delivery product has yet been marketed, and there are only a handful of other microneedle based devices currently available commercially [115]. The earliest example is the Soluvia® microinjection system developed by Becton Dickinson, although different in many regards from what has been described herein. This device is essentially a hollow microneedle system of 1500 μm length, connected to a handheld prefillable applicator [116]. Intanza®, is a similar system developed by Sanofi, primarily for the delivery of vaccines [117]. Other similar devices include MicronJet® developed by Nanopass Technologies [118], and the Microstructured transdermal system developed by 3M [119]. Most marketed devices are for cosmetic applications, and the most common of which include Dermapen® which can contribute to the reduction of acne scars [120] and Dermaroller® which can contribute to the reduction of facial wrinkles [121]. However, it is important to note that all these microneedle-based devices are outside the scope of dissolvable microneedles.

There are several microneedle array-based drug delivery products currently undergoing clinical trials. These microneedle devices are meant for single use and thus reduce the risk of infection. The length of these microneedles is relatively small, as they are designed to deliver medication intradermally, which makes them less likely to cause pain. A review of the published clinical trials suggests that most of the dissolving microneedles are designed for cosmetic applications (skin aging and wrinkles) and for the delivery of cargoes for the treatment of infectious diseases (typically through vaccines), cancer, psoriasis and for pain management, Fig. 12.

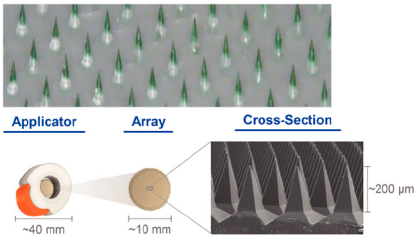
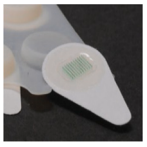
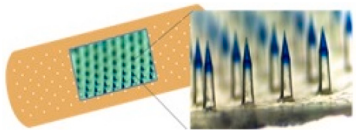
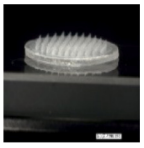
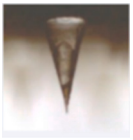
Within the evolving market landscape, it is important for developers to keep up with the changing business environment and assess their respective strengths and invest in them. Criteria, for example company size, USP, and product protection should be considered. By searching for microneedle spinouts, we identified several companies that developed dissolvable microneedle products that are at an advanced stage of development. VaxMat & DrugMat, were developed by TheraJect. DrugMat is designed to deliver proteins, vaccines, cosmeceuticals, genetic materials, and large molecules. This microneedle delivery system has a needle length of 500 μm and can administer compounds through transbuccal and transdermal routes. Micron Biomedical's dissolving microneedle patch, Peel & Stick, allows administration of drugs and vaccines. Moreover, the company's proprietary formulation and manufacturing process provides thermostability to encapsulated drugs, and thereby reduce and sometimes eliminate the need of cold chain entirely. Another example is BioSerenTach, who developed a dissolvable microneedle chip consisting of 100–300 projections of 500 μm in length. This product is touted for the administration of vaccine antigens, insulin, erythropoietin, interferon, and growth hormone.

Vaxess Technologies is developing a series of products based on the MIMIX smart release patch. MIMIX is a microneedle array patch technology, which can be used for the intradermal delivery of a wide range of therapeutic products, including both biologics and small molecules. Self-administration potential and better drug stability are two important features of this technology, but the most novel aspect is that it enables sustained release. The patch is required to be applied to the skin for only a few minutes. However, depending on the desired release kinetics, it has the ability to deliver therapeutics continually in the skin for anywhere from a few minutes to a few months in a controlled release manner.

Corium's MicroCor system utilises dissolving microneedles. This technology can be combined with small molecules, peptides, proteins, monoclonal antibodies, and vaccines. For example, the MicroCor PTH (1–34) aims to compete with Eli Lilly's Forteo® (teriparatide [rDNA origin] injection), which is approved for the treatment of osteoporosis. MicroCor PTH (1–34) has successfully completed Phase 2a clinical evaluation (ACTRN12615000195550). Corium claims to have established GMP manufacturing facilities, systems for scale-up, and cost-effective manufacturing processes to support early-stage through to clinical development.

LTS Lohamann micro array patch technology is also based on dissolvable microneedles, and seeks to incorporate small molecules, large molecule biologics, and vaccines. Devices developed by MEDRx, Innoture Medical Technology, SkinJect and FUJIFILM Pharmaceuticals have been also developed. Table 3 summarises some of the dissolvable microneedle products in an advanced stage of development.

Table 3
List of dissolvable microneedle products in an advanced stage of development.

Device name	Developer name/ Clinical Phase	length	Type of treatment	Image/Diagram
Dissolvable Microneedle Chip[a]	BioSerenTach Phase I	500 μm	Small molecule drugs, vaccine antigens, insulin, erythropoietin, interferon, growth hormone	
MicroCor®[b]	Corium international Phase 2a	200 μm	Osteoporosis	
Peel & stick[c]	Georgia Institute of Technology & Micron Biomedical Phase 1/2	Not mentioned	Small molecule drugs, vaccine	
Un-Named[d]	FUJIFILM Pharmaceuticals, Unclear	100–2000 μm	Influenza virus	
Un-Named microneedle patches[e]	Innoture Medical Technology, Preclinical		3D precision printing.	
Micro Array Patch (MAP)[f]	LTS Lohamann, Unclear	200–1000 μm	Small molecule drugs, biologics, and vaccines	
SkinJect™ patch[g,h]	SkinJect, Inc. & University of Pittsburgh, Phase1/2	<1000 μm	Non-melanoma skin cancer, basal cell, and squamous cell carcinoma	
Microneedle Array "Patch Vaccine"[i]	MEDRx INDA application		Large molecule drugs and vaccines	
DrugMAT and VaxMAT[j]	TheraJect, Unclear	500 μm	Small molecule drugs and vaccines	
MIMIX[k]	Vaxess Technologies, Phase 1		Small molecule drugs and vaccines	

[a] http://www.bioserentach.co.jp/e-technologies.html
[b] https://www.corium.com/propietary-platforms.html
[c] https://micronbiomedical.com/technology/
[d] https://www.fujifilmpharma.com/contract-services
[e] https://innoture.co/our-platform-technology/
[f] https://ltslohmann.de/en/micro-array-patches/
[g] https://mirm-pitt.net/news-archive/university-of-pittsburgh-licenses-novel-microneedle-patch-to-pittsburgh-company/
[h] https://skinjectpatch.com/
[i] http://www.medrx.co.jp/english/business_6.html

[j] http://www.theraject.com/welcome/more_welcome.html
[k] https://www.vaxess.com/mimix-therapies

5. Conclusions

Dissolving microneedles, and indeed microneedles in general, have undergone a rapid growth in the volume of clinical trials and research articles exploring their potential across various applications. Microneedles are likely to continue to develop as innovations shift the balance away from conventional solid and hollow microneedles towards dissolving microneedles which overcome several barriers associated with the former. We have reviewed how dissolving microneedles can potentially be used across a wide variety of medical applications, including cosmetics, vaccine delivery, diagnosis/monitoring, cancer, pain and inflammation, diabetes, hair and scalp disorders and inflammatory skin diseases.

However, it is important to recognise that it is the commercial viability of these therapeutic applications that is driving the growth of microneedle technologies. The market for microneedles has great potential and is expected to continue growing, which will likely spur continued interest in dissolving microneedles for the foreseeable future.

Declaration of Competing Interest

None.

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