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Review article

Recent advances in microneedle-based drug delivery: Special emphasis on its use in paediatric population

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ABSTRACT

Transdermal drug delivery offers several attractive advantages over the traditional oral and parenteral routes. Particularly, in case of paediatric patients, it helps to overcome the issues specific to this population, such as difficulty in swallowing and palatability of oral medicines as well as fear and pain associated with needles. However, due to the formidable barrier characteristic of the stratum corneum, it fails in the effective systemic delivery of broad range of therapeutic molecules, especially macromolecules and genetic material. Over the last two decades, microneedle technology has been portrayed as a strategy to infringe the stratum corneum, in a minimally invasive manner, and enable the successful passage of molecules by creating transient channels across the skin. There has been an exponential surge in the number of studies exploring the design, development and fabrication of microneedles. This article reviews the evolution of microneedle technology and provides a comprehensive summary of microneedle research to date. It provides a detailed overview of the microneedle types, advanced fabrication strategies including the biodegradability and compatibility of the new materials used in fabrication. Research on microneedle-mediated paediatric drug delivery as well as insights on the application of this novel technology has been discussed. The up-to-date progress in clinical translation of microneedles and the regulatory requirements for their commercialization are highlighted along with a brief perspective on the future prospects of microneedle-mediated paediatric drug delivery. This review proposes that advanced research can further contribute to the improved therapeutic efficiency of microneedle-based delivery of numerous molecules, which are otherwise difficult to administer via the conventional transdermal delivery mechanisms.

1. Introduction

Drug development for the paediatric population has always been a challenging task owing to the extremely diverse nature of the group, ranging from new-borns to adolescents. Skin maturation pattern, body water-to-fat ratio, metabolic capacity and extent of protein binding also vary with age [1]. Moreover, enzyme composition and regulation undergo drastic changes, particularly in the first few months of life, compared with older children or adolescents [2]. Therefore, there are specific requirements for suitable excipients and dosage forms, according to different age groups and disease conditions. Consequently, it is almost infeasible to design and develop a single drug formulation for the entire domain of developmental stages. Parenteral administration has always remained the first choice of treatment for neonates and also in emergency situations. However, there are several disadvantages associated with the use of hypodermic needles, for instance, emotional distress and pain associated with injections which lead to poor patient compliance. Also, the risk of disease transmission and the requirement of frequent clinical visits are inconvenient and distressful to paediatric patients [3]. Furthermore, hypodermic needles produce sharp and potentially dangerous bio-hazardous waste [4–6]. The transdermal route of drug delivery offers several advantages such as, avoiding hepatic/gastrointestinal metabolism and escaping the issues of hepatotoxicity, palatability and disease transmission. It also helps in improving the bioavailability and reducing overall doses. These consequently makes transdermal route an effective alternative to the available parenteral and oral routes [7–10]. Moreover, transdermal drug delivery helps to avoid the emotional trauma and needle stick injuries thus increasing patient compliance. These advantages are particularly attractive as well as beneficial as a non-invasive alternative to oral and intravenous delivery [11]. Unfortunately, the effective barrier properties of the skin make transdermal drug delivery not suitable for many drugs. The

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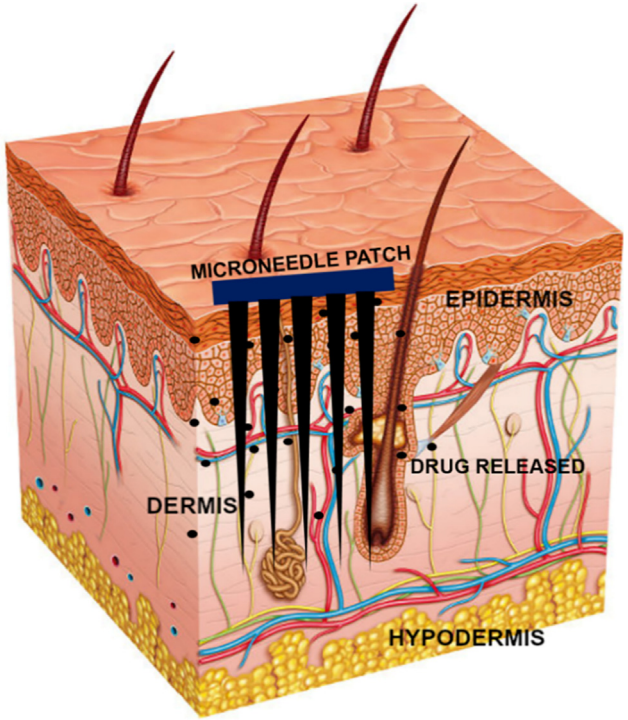

Fig. 1. Layers of the human skin depicting a MN patch application. Image adopted and modified from Lee [22].

effective permeation of certain active compounds, particularly those with high molecular weights, has not been quite satisfactory despite employing chemical enhancers, ultrasound, electric fields and thermal methods [12].

In 1976, a new and innovative technology named microneedle(s) [13] was first introduced with the aim to overcome the drawbacks of conventional transdermal systems. Microneedle (MN) technology is a unique and promising technique to ensure effective penetration of drugs into the skin in a pain-free manner through the use of multiple micron-scale needles attached to a supporting membrane (Fig. 1) [13,14]. During the past two decades, remarkable evolution has been witnessed in the development of MN-based drug delivery systems. The MNs can create micro-channels by piercing the stratum corneum, but without distressing the nerve endings and blood vessels in the inner skin layers of epidermis and dermis [15,16]. Consequently, increased types of drugs can be delivered with a dramatically improved efficiency and in a minimally invasive manner [15–18]. In regard to the paediatric population, MNs may offer particular benefits for example, pain-free and minimally invasive immunisation during childhood. Besides being painless, MNs offer other advantages such as a comparatively effortless application method, which makes them further desirable for long-term use [19,20]. It also leads to reduced risk of needle-stick injury and cross-contamination [19] as well as increased ease in disposal [21]. Moreover, the smaller doses required by children eases the attainment of therapeutic concentrations.

The following sections will provide a brief general introduction to transdermal drug delivery technology and development of skin barrier in children. The chronological evolution of MNs is also briefly discussed followed by the different types of MNs, their applications and the advances in fabrication techniques. Further, in this review, MN-based studies on paediatric population has been outlined along with an insight on the perspectives of children and paediatricians on MN technology as a prospective drug delivery device. The safety and biocompatibility issues in relation to MN materials have also been addressed briefly. Finally, an update on the clinical translation and commercialization of MN products highlighting the current state of the art of pharmaceutical research in the field of MN-assisted drug delivery systems is discussed.

1.1. Skin structure and transdermal drug delivery

Skin (*cutis*) is the largest human organ and is the body's first natural barrier. Accounting almost 15% of the total body weight of an adult, it has a surface area of about 2 m^2 and is 10^2–10^4 times less permeable than a blood capillary wall [23]. The skin is mainly composed of three histological layers commonly illustrated in relation to tissue layers i.e. the epidermis, dermis and subcutaneous layers [23]. Outer epidermis, a 5-layered assembly composed of keratinocytes (95% of cells), is generally 0.02–0.2 mm and typically 50–150 μm thin in humans. The outermost layer of the epidermis is the dead skin layer or the stratum corneum (SC), which is largely responsible for the barrier property of the skin due to its 'brick and mortar' structure [24]. The corneocytes of hydrated keratin comprise the 'bricks' embedded in a 'mortar', composed of multiple lipid bilayers of ceramides, fatty acids, cholesterol and cholesterol esters [25]. The layer beneath the epidermis is the dermis which is much thicker than the epidermis (usually 2–4 mm) and contains collagen (~70 wt%), some immunologically active cells, connective tissues, blood and lymphatic vessels, glands, hair follicles and nerve endings [26]. The subcutaneous layer or the hypodermis, lying underneath the dermis, is the innermost layer of the skin comprising primarily of adipose tissue (fat). The complex capillary network in the dermis and hypodermis is very critical for systemic delivery through transdermal route. Although it sounds straightforward, overcoming these obstructions is quite complex, especially for larger molecules such as peptides and proteins. The diffusion of most drugs across the skin is very slow and lag times to attain steady-state fluxes are in hours. Therefore, it is challenging to attain the therapeutically effective drug level without augmenting skin permeation. Recently, there has been intensive research on the strategies to invade the permeability barrier of the SC in a controlled and reversible manner. This will eventually widen the range of drugs delivered through skin [27]. Several physio-chemical methods to undermine the epidermis and thus enhance transdermal delivery have been proposed in the recent years. The approaches range from addition of chemical enhancers to MN technology, electroporation, iontophoresis, sonophoresis, thermal ablation or the synergistic combinations of two or more mechanisms [28]. In the recent time, MN arrays developed from various metallic and polymeric materials have been the main focus and is widely explored among the scientific community. These micron-sized devices promise to reduce the pain associated with hypodermic needle injections by only penetrating the top layer of skin, thus conveniently delivering molecules across the skin barrier.

1.2. Transdermal route as an alternative for paediatric drug delivery

The human skin is accountable for the control of vital mechanisms such as photo-protection, thermoregulation, hormonal synthesis, sensory perception, and immune and barrier functions [29,30]. Among these, barrier function is the most significant in the context of drug absorption. The skin barrier function in infants and older children efficiently restricts the percutaneous entry of compounds including drugs; however, the reduced doses required by children aids the attainment of therapeutic concentrations [31]. Yet, infants and children are the most challenging groups in relation to transdermal drug administration. A full-term neonate (but not premature infant) has a well-developed epidermis, similar to that of an older child or adult [31]. However, the comparatively thinner skin in infants and children may affect the pharmacokinetics of the delivered drugs. This can, on one hand, be beneficial with obvious therapeutic advantages, but may also have undesirable toxicity consequences. Therefore, it is obligatory to adjust the drug input in response to the rapidly developing skin barrier function and also to the age-dependent drug dose requirements. There

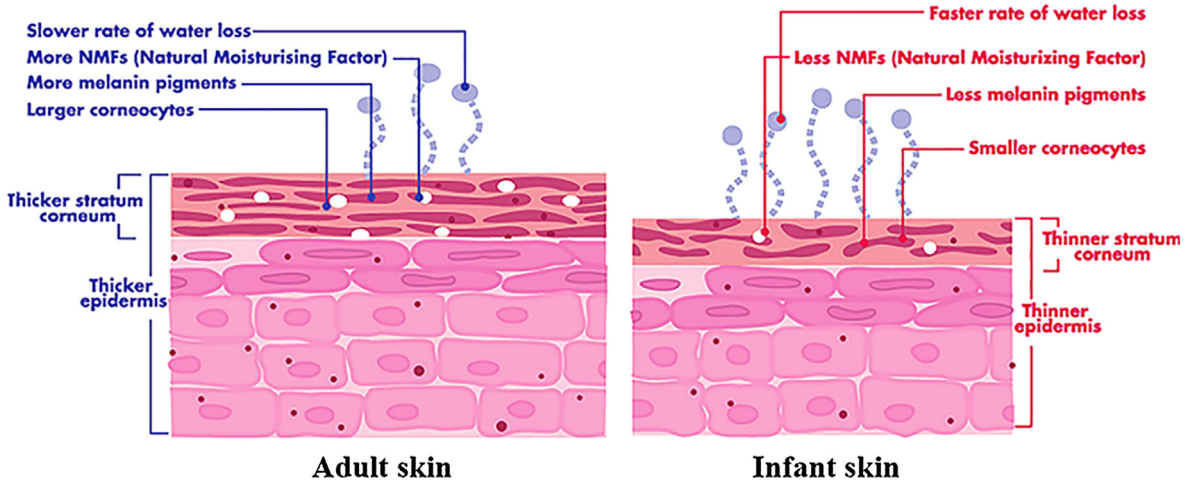

Fig. 2. Diagrammatic representation of the differences between adult and infant skin. Image adopted and modified from Ismail [34].

Table 1
Key structural/composition differences between infant and adult skin.

Parameters	Infant	Adult	References
Thickness of epidermis	~ 40–50 μm	~ 50–150 μm	[35]
Sweat glands	Not fully developed	Fully developed	[36]
Elastin fibres	Absent	Present	[37]
Collagen fibres	Less dense	Dense	[38]
Corneocyte and keratinocyte size	Smaller	Larger	[35]
Lipid content	Less	More	[39]
Melanin content	Lower	Higher	[36,37]
Skin surface-to-body weight ratio	700 cm^2/kg	250 cm^2/kg	[37]
Water content	Higher	Lower	[40]
Natural moisturizing factor	Significantly lower	Higher	[40]

Table 2
Key functional differences between infant and adult skin.

Parameters	Infant	Adult	References
pH	6.34–7.5	5–5.5	[31,41]
TEWL	Increased	Decreased	[40]
Cell proliferation	Faster rate	Slower rate	[35]
Skin barrier function	Weaker and evolving	Stronger	[42]

are additional differences between the infant and adult skin (Fig. 2) which need to be considered before designing a transdermal drug delivery device for paediatric application. Some of the key structural and functional differences have also been outlined in Tables 1 and 2. Moreover, care should be taken to consider any underlying developmental and disease conditions in the paediatric patients. In case of premature neonates, the formulation development procedure should consider additional criteria such as, suitability of a patch adhesive for fragile premature skin, potential risk associated with accidental overabsorption of an excipient and so on. This is because, the skin, which accounts for only ~3% in an adult, represents nearly 13% of the body weight of a pre-term infant [32]; thus, the area and site of application of a transdermal system may have an intense consequence on the safety and efficacy of a treatment in such population groups [11,33].

Nevertheless, transdermal drug delivery has been well translated from adults to the paediatric population with different dosage forms. The benefits of this unique and non-invasive route ensure its wide popularity and acceptance.

2. The history of MNs

The term 'microneedle' was first used by Robert Chambers in as early as 1921 when they used MN for micro-dissection of echinoderm egg by injecting the needle into the nucleus of the egg [43]. However, the concept of MN-based drug delivery was first introduced by Martin S Gerstel and Virgil A Place in the year 1976 [13]. In their patent, they described both solid and hollow MNs for local or systemic drug delivery. The first drug-coated MN device was reported by Pistor Michel Louis Paul [44]. Even though the concept of MN-based drug delivery was first introduced by Gerstel and Place, the first significant evaluations and proof-of-concept analyses of MNs were demonstrated in 1998 by Henry et al. [16]. They described the use of silicon MNs, prepared by microfabrication technology, to enhance the delivery of calcein through human skin [16]. Moreover, they were the first to report the *in vivo* evaluations of MNs and the pain perception. In 2002, Mikszta et al. published the first report on silicon MN mediated immunization [45]. They also studied the safety of MNs by evaluating the erythema and edema scores. The first study on the MN-based transdermal delivery of macromolecules and nanoparticles was published in 2003 by McAllister et al. where they used solid and hollow MNs for transporting insulin, albumin and 100 nm sized latex beads respectively through human cadaver skin [46]. The first report on dissolving MNs was reported in 2005 by Miyano et al. [47]. They studied an array of maltose MNs that dissolve in the skin to release the model drug, ascorbate-2-glycoside into the epidermis and dermis. In 2005, the first report on MN assisted biological fluid sampling was published [48]. Furthermore, in 2005, Fernandes reported the first cosmetic application of MNs (collagen induction therapy), in which, he stated the use of MN roller for skin tightening and wrinkle reduction [49]. During the last two decades, other innovative and advanced applications of MNs have been claimed in diverse areas, apart from the cosmetic and drug delivery applications, and these have been described in detail in the subsequent sections of this article. Fig. 3 shows a sequential timeline of the significant events in MN development.

3. MN types and advances in fabrication technologies

MN arrays can be defined as a multiplicity of micron-sized projections, ranging from lengths as short as 25 μm to those as long as 2000 μm, assembled on one side of a supporting base or patch [50]. MNs have emerged as a particularly attractive type of drug delivery approach with the potential to deliver numerous therapeutic molecules across the biological membranes including skin, mucosal tissue and sclera as shown in Fig. 4. Modulation and alteration of MN geometry and composition can result in controlled drug delivery to various target

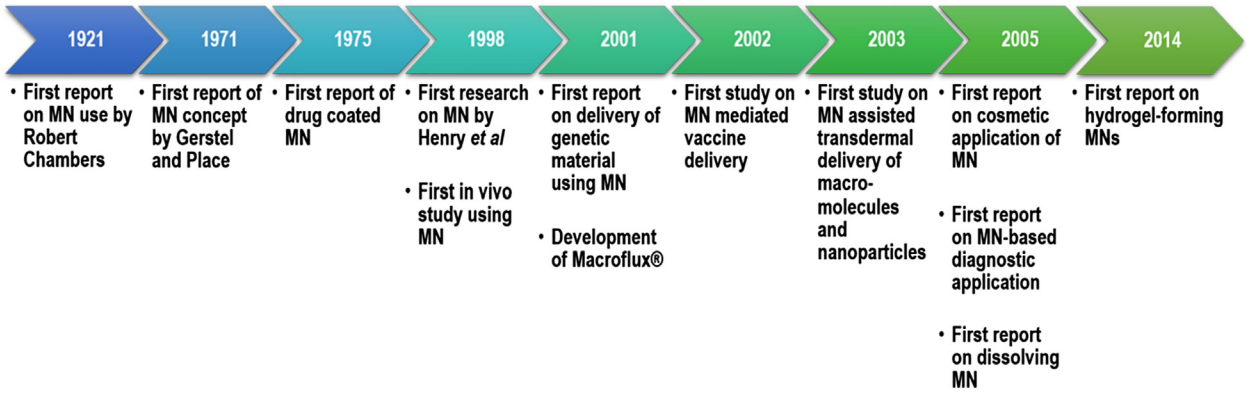

Fig. 3. A sequential timeline of the major events in MN development.

organs. Over the past few years, widespread research has been carried out concerning MN design and a multiplicity of fabrication methods have been reported [51–55]. In general, MNs developed for drug delivery can be broadly classified into five categories: hollow, solid, coated, dissolving and hydrogel-forming [56]. Fig. 4 provides an insight into the different MN-based drug delivery approaches.

3.1. Solid MNs

Solid MNs deliver drugs by generating microchannels in the layers of the skin and thus increasing the permeability of skin. Subsequently, a patch containing the drug of interest should be applied on the channels [58]. However, it is essential for the skin to retract, thus closing the microchannels, soon after the MN patch is removed from the skin. This will prevent undesired entry of toxic substances or infection by pathogenic microbes [58]. Fabrication of solid MNs from a wide range of materials has been reported in the literature. This includes non-biodegradable materials such as silicon [59,60] and polymers such as a copolymer of methylvinylether and maleic anhydride (PMVE/MA) [61], polycarbonate [62] and polymethylmethacrylate (PMMA) [63]. Other materials like biodegradable polymers [53]; maltose [64]; and metals including stainless steel [65,66], titanium [67], tantalum [68] and nickel [69]; and ceramics [70,71] have also been used. Olatunji et al. utilized biopolymer films extracted from fish scales of tilapia

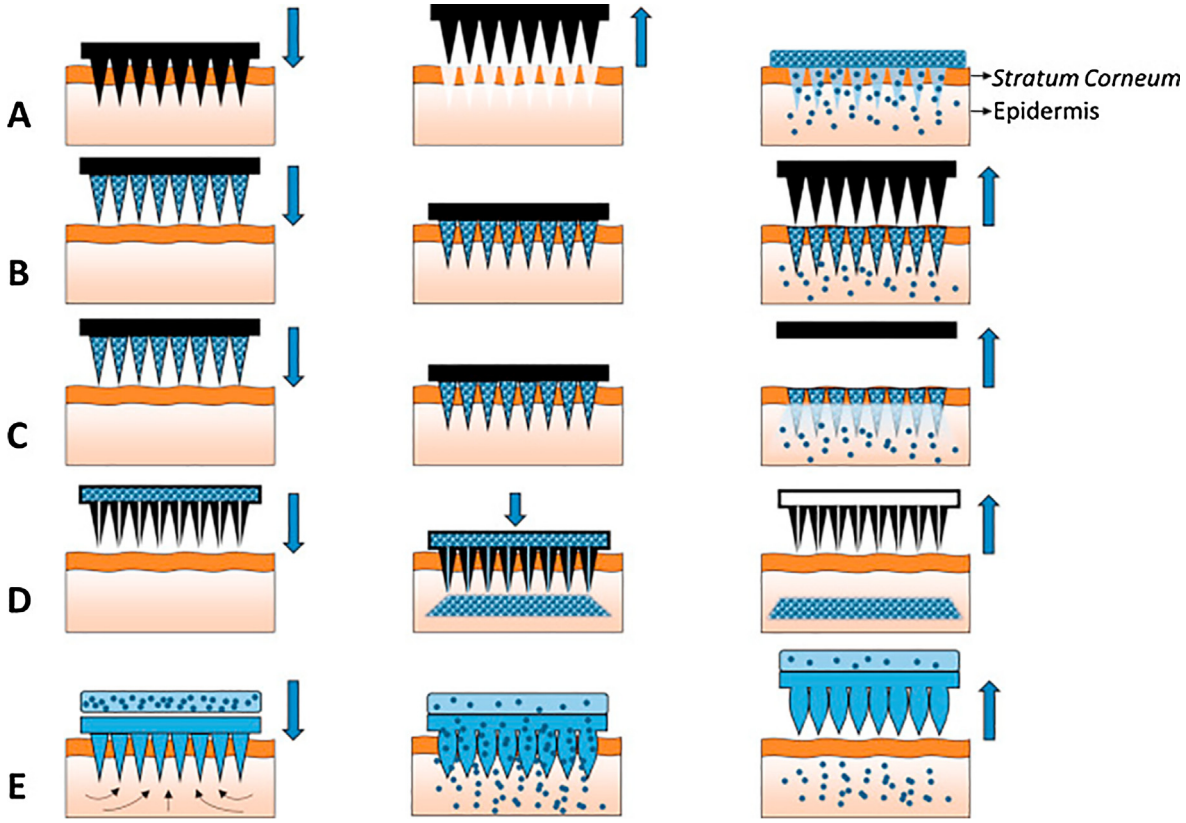

Fig. 4. A schematic illustration of the five different types of MNs and their drug delivery approaches. (A) Solid MNs increase the permeability of a drug formulation by creating micro-holes across the skin. (B) Coated MNs undergo rapid dissolution to release the coated drug into the skin. (C) Dissolvable MNs leads to a rapid or controlled release of the drug incorporated within the MNs. (D) Hollow MNs puncture the skin and enable release of a liquid drug following active infusion or diffusion of the formulation through the needle bores. (E) Hydrogel-forming MNs take up interstitial fluids from the tissue, causing swelling of the micro projections and thus inducing diffusion of the drug located in a patch through the swollen micro projections. This image has been reproduced with kind permission from Larrañeta et al. [57].

(*Oreochromiss* sp.) to prepare solid MNs [72]. Patches of solid MNs, containing a dry formulation, have proved to be promising and favours improvement in vaccine efficacy [73]. Edens used solid MN patch containing 100 pyramidal MNs to deliver 1000 tissue culture infectious dose (TCID50) of measles vaccine [73]. The permeation of different therapeutic molecules via solid MNs is dependent on various factors, for instance, MN insertion force, tip sharpness and MN density. The combined effect of solid MNs with other permeation enhancement approaches, such as iontophoresis, have also shown to be advantageous in the the transdermal delivery of several active molecules [15].

3.1.1. Fabrication of solid MNs

The first solid MNs from silicon were developed using microfabrication technology [16], which was then adopted by other research groups to prepare silicon-based solid MNs of varying dimensions [10,52,74]. Microfabrication technology, i.e. micro-machining or micro-electromechanical systems (MEMS), is conventionally utilized in the production of microprocessors and micron-scale devices, such as micropumps, microreactors etc. [75]. MEMS technology is currently being applied in the fabrication of MN devices [76]. The fabrication process of silicon MNs varies according to the needle material and geometry. Even though microfabrication techniques are promising for high throughput MN manufacturing, they are not very cost effective, require highly specialised handling and involve complex processing steps [77,78]. The MEMS process employs a series of controlled sequential operations and techniques. The three basic building blocks involved in MEMS are deposition of thin films of material on a substrate, photolithographic imaging to apply a patterned mask on top of the films, and etching the films selectively to the mask [79,80]. Optically curable polymers undergo photolithography imaging to produce master structures for replication, which are then employed to make solid polymeric MNs by molding as shown in Fig. 5. The ultraviolet (UV)-curable polymer SU-8 is extensively used to fabricate MNs [81–83].

Reactive ion etching, as well as isotropic etching, have been used to prepare silicon MNs [16,75,84]. Additionally, anisotropic wet etching of crystalline silicon has also been employed to formulate solid MNs [60,74,85]. There are also illustrations of combining both isotropic dry etching and anisotropic wet etching methods to produce MNs [75]. Acid etching approach has also been adopted to sharpen tips of pillars obtained by dicing a silicon substrate [86–89]. Solid MNs have also been fabricated using metals, such as stainless-steel, titanium and palladium employing numerous approaches, for example, electroplating (palladium), photochemical etching (titanium) and three-dimensional laser ablation (stainless-steel) [90–94].

Very recently, a novel magnetorheological drawing lithography method was efficiently used to fabricate solid MNs. In this technique, a droplet of curable magnetorheological fluid is drawn directly from a substrate to produce a 3D MN under an external magnetic field [95]. This is a one-step method and also eliminates the requirement for temperature adjustment.

3.2. Hollow MNs

Hollow MNs have been manufactured from a wide variety of materials and in a varied range of heights and geometries. They have also been fabricated from commercially available 30 gauge hypodermic needles, where the individual MNs have a diameter of about 300 µm and a length tailored to 300 µm [93]. Hollow MNs have been mainly made out of silicon [96–98], metals [99], glass [100], polymers [101], ceramic [70] and carbohydrates [102]. Hollow MNs facilitate the continuous infusion of larger amounts of drug substances, in comparison to solid or coated MNs, which can only deliver small and definite amounts of drugs [97]. This approach employs diffusion, pressure- or electrically- driven flow to deliver molecules across the skin. After a detailed investigation, it has been reported that the flow rate of drug is directly proportional to the inner diameter of MN and inversely related to MN length [103]. A number of extensive analyses have established

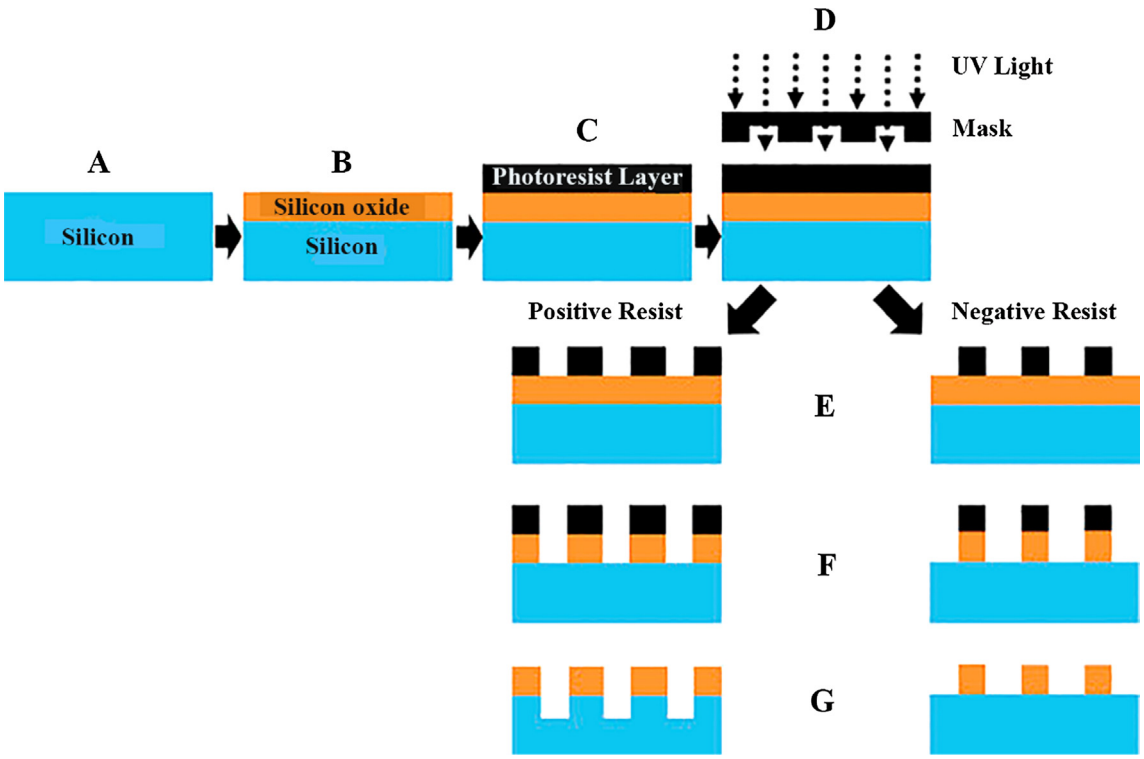

Fig. 5. The series of processes in the transfer of a pattern to the substrate surface: (A) Silicon wafer; (B) Silicon wafer with oxide coating; (C) spin-coated photoresistive material; (D) mask guided UV light exposure on the photoresistive material; (E) development process to remove the soluble resist material; (F) etching of SiO_2 film; and (G) photoresist removal. This image has been reproduced with kind permission from Larrañeta et al. [57].

that by altering infusion parameters, such as infusion pressure, insertion/retraction depths and MN tip dimensions, flow rates can be modified. This in turn assists in achieving controlled drug delivery [104]. However, the efficiency of hollow MNs can be hampered by the possible blockage of the needle bore-opening with tissue in the course of skin insertion [105]. Nevertheless, this concern has been taken care of by using inventive design which locates the bore-opening slightly off-centred, rather than at the extreme tip [55,96]. This not only prevents needle clogging but also increases the area of drug exposure to the tissue and retains tip sharpness. Additionally, flow resistance due to the compression of dense dermal tissue around MN tip represents a major drawback associated with the hollow MNs [106]. An investigation has demonstrated that withdrawing the needle partially, following its insertion into the skin, has enhanced the fluid infusion. This is owing to the relaxation of the compressed tissue which increases the flow conductivity of skin underneath the MN tip [100]. Chen and his group studied the combined effect of using hollow silicon MN with sonophoresis – termed SEMA (sonophoretic enhanced MN array) for the delivery of hydrophilic and large molecular mass compounds, namely calcein and BSA, across porcine skin. Synergistic enhancement of calcein and BSA permeability in skin was demonstrated by the application of SEMA. The hollow MNs breach the stratum corneum enabling deeper delivery of drugs, whereas ultrasound enhanced the diffusion rates by cavitation effect in the epidermis and also in the hollow MNs drug reservoir [107].

3.2.1. Fabrication of hollow MNs

A variety of hollow microneedles have been fabricated using MEMS techniques including laser micromachining [51], deep reactive ion etching of silicon [105,108], an integrated lithographic molding technique [109], deep X-ray photolithography [110], and wet chemical etching and microfabrication [111]. Bosch process was utilized to create hollow shell structures with high aspect ratio, which was subsequently followed by isotropic [111,112] and wet etching processes to achieve tip sharpness [105]. In addition to using chemical etching methods, sharp tips in hollow silicon MNs were also obtained using a dicing saw along with deep reactive ion etching [113]. Hollow microneedles made of glass, polymer and metal have been prepared from substrates by the traditional fabrication approaches. The glass micropipette technique has been used to make hollow glass MNs [100].

Hollow polymeric MNs are formed by a variety of techniques. Holes were drilled and then bevelled tip was moulded out of polyphenylsulfone polymer by milling [114]. Hollow MNs out of PMMA was fabricated by employing lithographic techniques [63,115]. In another case, a digital micromirror stereolithography instrument was utilized for the preparation of hollow polymeric MNs by polymerization of liquid resin [116]. A laser-based rapid prototyping system was also used to form hollow polymer microneedles by direct two-photon polymerization [117].

Metal MNs have been formed by drawing lithography and metal electroplating [118]. In another design, a polymeric micromold was prepared using UV laser, which was later coated with nickel by electrodeposition. Subsequent selective etching of the polymer mold releases the formed metal MNs arrays [51]. Hollow nickel MN arrays were also prepared by a sequential process of electro-less copper and nickel plating and copper wet chemical etching [69].

3.3. Dissolving MNs

Dissolving MN undergoes dissolution following its application to the skin and subsequently releases the encapsulated drug into the skin. They are made from a wide variety of materials such as, polysaccharides or other polymers and are fabricated on the basis of the “poke and release” principle [119]. Polymers such as polylactic acid (PLA) [53,91], polyglycolic acid (PGA), polylactic-co-glycolic acid (PLGA) [53], polyvinylpyrrolidone (PVP), poly (vinylpyrrolidone-co-methacrylic acid) (PVPMAA) [120] and poly (methyl vinyl ether-maleic anhydride) (PMVE-MA) [121] have been employed for the preparation of dissolving MNs. Biopolymers used in the fabrication of dissolving MNs include sodium hyaluronate [122,123], chondroitin sulphate [124,125] and carbohydrates, e.g. sugars, carboxymethyl cellulose and maltose [126]. Dissolving MNs have been shown to enhance transdermal and dermal delivery of numerous substances including insulin [127,128], 5-aminolevulinic acid [126], sulforhodamine B [119,129], low molecular weight heparin [129], ovalbumin [122,125], thymopentin (TP5)[130], adenovirus vector [122] and a variety of vaccine antigens [123]. In the dissolving MN arrays, selection of the constituent polymers, from which to formulate the arrays, plays an important role in governing the release kinetics of the incorporated drug. Moreover, controlled drug delivery can be achieved by regulating the polymeric composition of the MN array or by varying the fabrication procedure. The numerous advantages of the dissolving MNs, when compared to the other MN types, have led to their emerging acclaim. The favourable biocompatibility and biodegradability profiles exhibited by the majority of polymeric materials make them promising in the field of drug delivery technology. The use of water-soluble and biodegradable polymers or sugars eliminates the possible risk of leaving biohazardous sharp waste in the skin [53,131]. This approach also should significantly reduce any risk of infection transmission. Furthermore, the one-step application process proves to be convenient for patients. Regardless of the numerous advantages, there are various complications associated with the designing and development of dissolving MN structures. In some instances, drug loading and the fabrication procedures can distress the mechanical strength and stability of MNs or the incorporated drug or macromolecule. Donnelly and colleagues in 2009 prepared drug-loaded galactose MNs in a micro-moulding process by melting galactose powder at 160 °C and subsequent addition of model drugs: 5-aminolevulinic acid (ALA) and bovine serum albumin (BSA) [126]. The authors emphasised that the elevated temperature to facilitate polymer melting resulted in substantial degradation and eventual losses of the incorporated ALA and BSA. This has been claimed as the major limitation when dealing with thermolabile molecules. They even illustrated the difficulties associated with the processing and storage of the MN arrays. It was challenging to prepare more than two MN arrays at a time owing to the high viscosity of molten galactose and its tendency to solidify easily. This eventually leads to difficulty in scaling up and mass production. To circumvent these obstacles, alternative MN fabrication approaches have been recommended and these include fabrication by the thread forming technique [132]; room-temperature photo-polymerisation of the liquid monomer vinyl pyrrolidone [120]; employment of aqueous blends of different types of polymers [119] and low-temperature vacuum forming micro-moulding method [133]. Synergistic effects of dissolving MNs used in combination with other enhancing strategies have been reported by Garland et al. [134] when the use of drug-loaded dissolving poly (methylvinyl- ether-co-maleic-acid) (PMVE/MA). MN arrays was coupled with iontophoresis and it was observed that the permeation of the model drugs across neonatal porcine skin increased by two to three times, compared to MN alone. Dissolving MNs have also been investigated for their potential application in transcutaneous immunisation and the study highlighting the use of dissolving polymeric MN patches for influenza vaccination received worldwide media attention [135]. Additionally, dissolving MNs (MicroHyala™), fabricated by sodium hyaluronate, were able to induce a successful immune response in mice against tetanus toxoid, diphtheria toxoid, Se36 (malaria), influenza hemagglutinin, ovalbumin and adenovirus vector antigens [122,123]. Recently, Pan et al. developed, for the first time, a novel intradermal delivery system for STAT3 siRNA based on dissolving MNs for the treatment of melanoma [136].

3.3.1. Fabrication of dissolving MNs

Dissolving MNs can be fabricated using a wide variety of mould-based techniques including solvent casting [Fig. 6], drawing

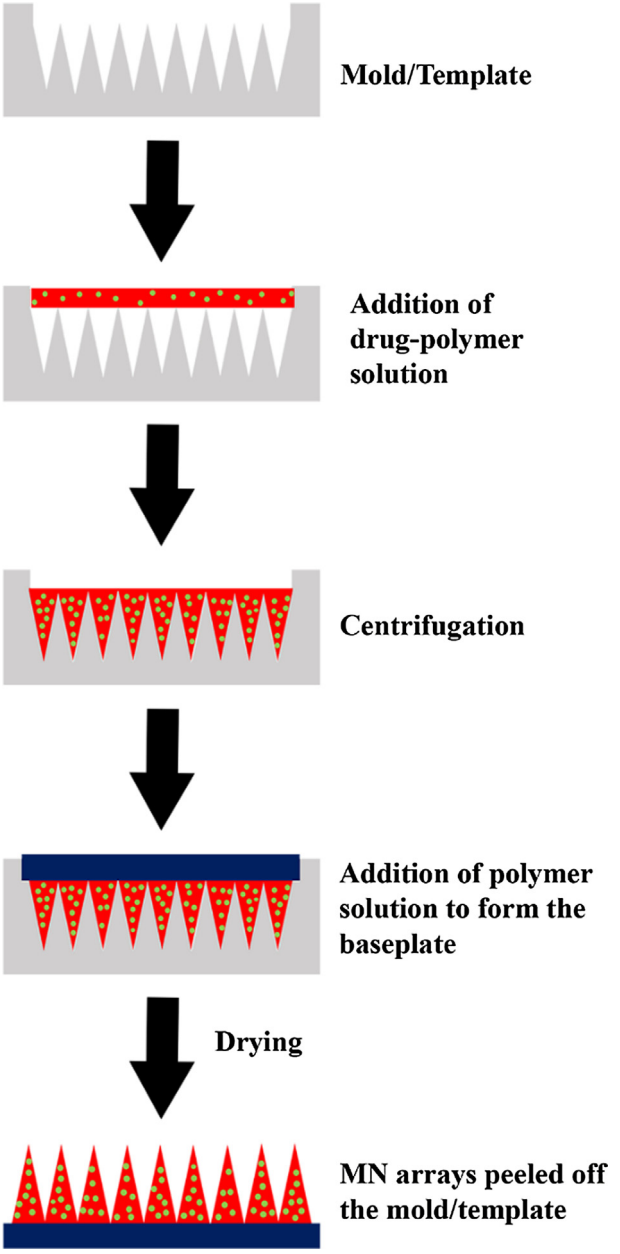

Fig. 6. Illustration of Solvent Casting method used to fabricate dissolving MNs.

lithography, droplet-born air blowing, laser machining, hot embossing, microinjection moulding and ultrasonic welding.

Solvent casting is the most common method for fabrication of dissolving MNs [Fig. 6]. The polymers or other constituents are dissolved in appropriate solvents, filled into the mold cavities and allowed to dry, sometimes with the additional use of vacuum and/or centrifugal force [137]. In another fabrication method, tapered MNs are formed by drawing up liquid preparations which later solidify in position [138,139]. This approach was used to prepare MNs containing dextrin, chondroitin sulfate and albumin, where each needle was fabricated by drawing using pipette tips [132,140]. Dissolving MNs are also prepared using ultrasonic welding method in which the polymers are fused together without heating and thus causing negligible damage to the encapsulated molecules [141,142].

Very recently, Huh et al. compared two droplet-based fabrication methods (centrifugal lithography and droplet-born air blowing by evaluating the change in activity of the encapsulated drugs. From their study, they concluded that centrifugal lithography exerts less stress during the manufacturing processes and thus minimizes activity loss of the encapsulated drugs. This method can, therefore, be preferred to prepare dissolving MNs with fragile biological drugs [143].

3.4. Coated MNs

Coated MNs are coated with the drug-containing dispersion [56] and are considered particularly attractive for rapid bolus delivery of high molecular weight molecules such as vaccines, proteins, peptides and DNA to the skin [90,144–149]. Once inserted into the skin, the drug is rapidly released from the coating into the tissue. However, one serious limiting factor in attaining a relevant drug release profile is the infinitesimal surface area of the MN structures which leads to the limited extent of drug that can be successfully coated onto them. Besides, there are additional issues of concern such as consistency, uniformity, reproducibility and stability of the MN coating materials. In addition, precautions should be taken such that there is negligible deleterious drug loss from the MN surface during the coating process and also prior to insertion into the skin [65]. Coated MNs have also been demonstrated for the efficacious and minimally-invasive delivery of therapeutic nucleic acids such as small interfering RNA (siRNA) etc. for various clinical symptoms including genetic vaccinations [21,150]. Coated MNs are also particularly attractive candidates for vaccine delivery to the skin, as antigens can be released in the skin to target the Langerhans cells in the epidermis or the dendritic cells in the dermis for a more effective immune response [151]. To demonstrate this, ovalbumin, a model antigen, was coated onto microneedles and delivered to guinea pigs to induce a pronounced immune response [152]. Furthermore, as only small quantities of antigen are required to elicit an immune response, the restricted quantity of drug that can be coated onto MNs does not actually hamper their utilization in vaccine delivery [94]. In a recent study, drug-coated poly (L-lactic acid) (PLLA) MN arrays were fabricated to induce rapid and painless local anaesthesia in the skin [153].

3.4.1. MN coating methods

A broad range of materials have been utilized and techniques have been developed to ensure effective coating of MN arrays with specific drugs. For instance, Gill et al. proposed the micron- scale dip-coating procedure using different aqueous, organic solvent-based or molten liquid formulations [65,154]. This was designed to successfully deposit a range of molecules with varied physicochemical properties onto the surface of MNs. The most significant parameters to be considered during the dip-coating process are surface tension and viscosity of the coating solution. Gill and Prausnitz showed that by reducing the surface tension (by adding surfactants) and increasing the viscosity (using viscosity enhancers), a thick and uniform coating of MNs can be achieved [65,154]. Layer-by-layer coating techniques have also been applied to coat MNs [155–157]. In case of DNA/protein molecules, MNs are coated by alternately dipping into solutions containing oppositely charged solutes, such as negatively charged DNA and positively charged polymer. This leads to the formation of a polyelectrolyte multilayer on the MNs. In some instances, coating solution has also been sprayed onto silicon MNs, using an atomizer, to produce coated MNs [158]. A simple and versatile coating technique utilising gas jet was described by Chen et al. [152] to uniformly coat a wide variety of molecules (OVA, rhodamine-labeled dextran, ethidium bromide) on densely packed microprojections. In another study, piezoelectric inkjet printing process was utilized to deposit drug coatings onto the surfaces of polymeric MNs for antifungal applications [159]. The different coating methods for microneedles have been illustrated in Fig. 7.

3.5. Hydrogel-Forming MNs

In recent times, multiple novel technologies are targeting at overcoming the biocompatibility problems and the potential for

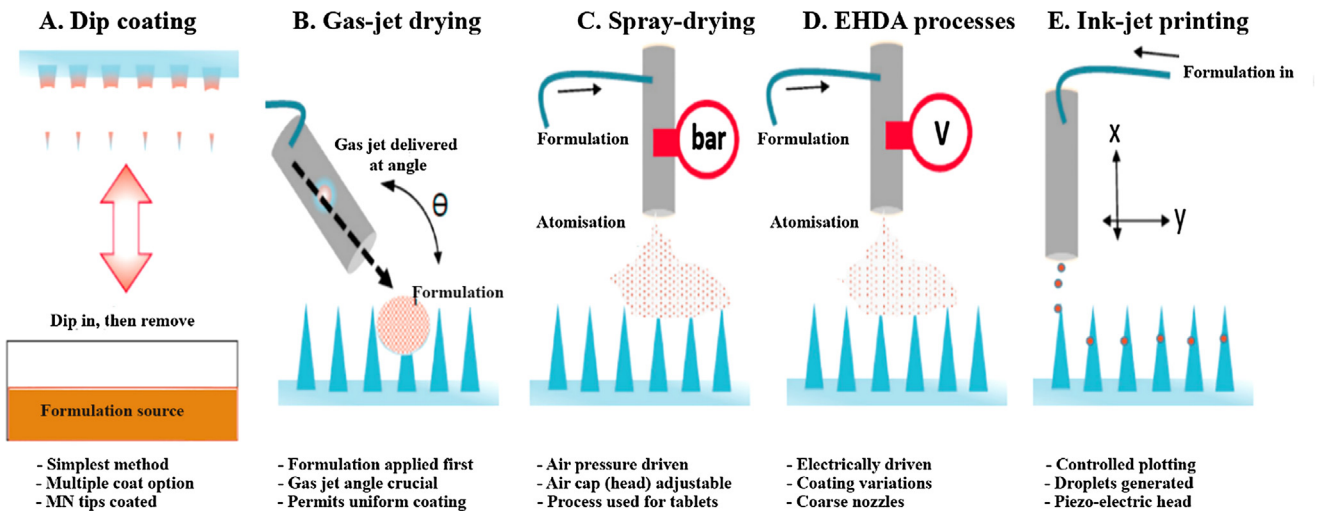

Fig. 7. Illustrated examples of techniques used to coat MNs. (A) Dip coating; (B) Gas-jet drying; (C) Spray drying; (D) Electrohydrodynamic atomization (EHDA) processes; (E) Ink-jet printing. [Reproduced with permission from Haj-Ahmad et al. [160]].

inappropriate re-use associated with silicon or metal MNs. One of these approaches emphasizes the use of hydrogel-forming MNs [161]. The principal advantage of hydrogel-forming MNs when compared to regular dissolving polymer MNs is that in case of hydrogel-forming MNs, the delivered doses of drugs are no longer restricted to what can be loaded into the needles themselves. This approach was first explored by Donnelly et al. who employed "super-swelling" polymeric compositions to prepare a hydrogel-forming MN array with an attached patch-type drug reservoir [162]. The arrays contain no drug themselves, however, upon penetration, they rapidly imbibe skin interstitial fluid and form channels between the dermal microcirculation and the drug reservoir [162]. Such MNs act initially as a tool to breach the stratum corneum and eventually swell to become a rate controlling membrane. Fluid uptake range in one hour was 0.9–2.7 μL, which is of the same order of magnitude as the rates of interstitial fluid uptake for hollow MNs and microdialysis [163]. Hydrogel MNs also overcome some of the characteristic limitations related to the conventional MN arrays, i.e. particularly reduced drug loading capacity, difficulty in precise drug coating and controlling the extent and rate of drug release. The possibility of incorporating active pharmaceutical ingredients in a separate reservoir provides the opportunity to deliver increased amount of medications. Hydrogel-forming MNs also prove to be advantageous in the specifics that they can also be fabricated in wide-ranging geometries, can be easily sterilized and detached absolutely intact from the skin [164]. Various polymeric compositions have also been examined in order to screen robust materials which are capable of rapid swelling, but simultaneously sufficiently hard in the dry state to pierce the skin [162]. Additionally, the interesting ability of the hydrogel MNs to imbibe interstitial fluids could be exploited for the extraction of molecules of interest from the skin for consequent analysis [50]. This strategy is expected to be extremely beneficial for vulnerable patients such as neonates and the elderly [165]. In a recent study, a novel *in situ* forming hydrogel MNs were designed and evaluated for transdermal drug delivery using a biocompatible thermosensitive copolymer [166]. Maltose MNs were used to pierce the skin and create microchannels, followed by application of poloxamer-based drug formulation. The solution streamed inside the microchannels and got converted into gel at skin temperature thus attaining the shape of the MNs. These *in situ* formed hydrogel MNs ensured a sustained delivery of the encapsulated drug [166]. A hydrogel-based MN device can be endorsed for its versatility as the delivery profile can be personalized based on the requirements of different drugs with differing therapeutic windows. The application of hydrogel-forming MN is promising, and further effort should be focussed at widening the range of materials for fabrication of these systems and to include medications that are administered for the management of chronic disorders.

4. Biocompatibility and biodegradability of MN materials

It is mandatory for the materials chosen for MN production to be biocompatible because the MN tips disrupt the protective barrier and get exposed to the viable skin tissues. A biocompatible material can exist in harmony with tissues without leading to any immunogenic response and detrimental transformation of the tissues. However, there is a lack of adequate research studies on the skin biocompatibility of the MN constituents.

The biocompatibility of silicon has been widely scrutinized owing to its extensive use in MEMS technology [167]. Silicon and silica glass are brittle materials and hence probable breakage of MN tips, made with such materials, in the skin is an area of concern. There have been significant studies examining the biocompatibility of brain and subcutaneous implants made of silicon [168–170]. No significant toxicity was exhibited by nanocrystalline silicon as reported by Bayliss et al. [171]. On the contrary, there are additional studies narrating cases of silicon- and glass-related granulomas [172]. There have been few incidences of granuloma formation by accidental implantation of silica into a wound [172].

Ceramics are well recognized for their good biocompatibility and great strength. For this reason, ceramic materials have been increasingly used in repair and replacement treatments [173]. Alumina is reputable in the field of orthopaedics due to its 25 years of use in bone and dental implants [173]. Therefore, its biocompatibility has been extensively studied [174,175]. In spite of demonstrating favourable biocompatibility profile, some studies indicated the possibility of aluminium release from long-term bone implants [176]. However, ceramic MNs intended for short-term application should not present major problems [176].

Metals used in the fabrication of MNs are generally biocompatible and are the principal structural biomaterials used in medical relevance [177]. The most widely used surgical stainless steel, 316L, shows comparatively decent biocompatibility, however to a less acceptable degree to other metals, such as titanium, because of its elevated corrosion rates [177]. However, the MN devices are unlikely to raise significant problems due to their short application times [178]. Titanium alloys are known to have superior biocompatibility profiles largely due to their excellent corrosion resistant properties [177]. Therefore, they are considered relatively safe for human and animal use. However with reported allergies accompanying some first generation titanium alloys

[177], other metals like palladium and platinum show good biocompatibility [179,180]. However, nickel should be used with caution as it is known to be carcinogenic and there are reports stating adverse allergic reactions with nickel-containing biomaterials [181].

Natural sugars have long been employed in the fabrication of drug delivery systems [47]. Maltose is largely used in the production of carbohydrate-based MNs and several FDA- approved parenteral formulations. Polysaccharides have also been extensively used in other biomedical applications and they are well accepted by the human body [182]. However, certain polysaccharides are incapable of proper biodegradation leading to undesired accumulation within the body [183].

Polymers with both biocompatible and biodegradable properties are the most widely accepted materials for MN fabrication [184]. Majority of polymers such as polycarbonates, PMMA, PVA, PVP, PLGA, PLA, and PGA are known to possess both the properties and have been extensively employed for medical purposes [185–187]. The epoxy-based polymer SU-8 is extensively used in microfabrication purposes for medical devices [188]. Nemani et al. investigated the biocompatibility of SU-8 and demonstrated its suitability as an implant material [188].

For the paediatric population, the biocompatible nature of the MN materials is of great importance because of the immature and rapidly evolving skin barrier function of this age group. Prior to designing and developing a MN device, the constituent materials should be comprehensively examined with respect to their safety and toxicity attributes. The materials should have the required strength to pierce the skin to effectively deliver the dose, however, without causing any adverse tissue reaction. Also, the materials must be neither systemically or locally toxic. Thus, it is crucial to investigate the potential toxicity of the materials' degradation products, as well as the safety profiles of the reactive groups on polymers. Ensuring these required characteristics will help in the successful clinical translation of this unique and non-invasive technology for drug delivery to the vulnerable paediatric population.

5. Pain perception of MNs

MN technology has demonstrated encouraging results from drug delivery studies and clinical trials. However, its popularity and advantages will be limited if it causes pain and distress in patients. Needle phobia, a fear of needles, syringes, injections, and intravenous accessories, can range from being mild to severely disabling or even life-threatening and can seriously compromise treatment of both paediatric and adult patients [189–191]. Quite a few studies have reported and validated the scale of pain related to MN application in children, as well as adults, by determining the extent of disruption to the protective function of the skin [Table 3].

Kaushik et al. conducted the first MN safety assessment study in human subjects [17] including a total of 12 healthy, male and female volunteers aged between 18 and 40 years. They used silicon MN arrays consisting of 150 μm long 400 needles with a base diameter of 80 μm and tip radius of 1 μm. Pain-scores from the subjects were documented on a visual analogue scale and it was observed that MN application was painless and, no skin damage or inflammation was noticed. In another study, safety aspects and disruption of the barrier property of skin following the application of MN arrays with varying lengths and shapes of tips were evaluated [192]. A total of 18 healthy volunteers were examined for different parameters such as barrier function of skin (assessed by quantifying Trans-epidermal Water Loss (TEWL)), erythema and pain-score. Treatment with MN arrays of 400 μm height resulted in considerably increased TEWL and erythema when compared to MN arrays of 200 μm height. However, irritation was transient and lasted for less than 2 h, for all the MN arrays regardless of their different designs. It was also noted that the application was perceived as painless.

Haq et al. investigated the pain and sensory responses in 12 human subjects [19]. Hypodermic needle piercing was found to be significantly more painful than MN insertion. Moreover, it was observed that longer MN leads to higher pain score compared to the shorter MNs. The subjects even perceived hypodermic insertion as 'sharp' and 'stabbing' and MN insertion as 'pressing' and 'heavy'. In several other studies, focused mainly on the assessment of the efficacy of MN-assisted drug delivery to human subjects, the evaluation of pain and discomfort was also carried out. Wermeling et al., while studying the MN-mediated systemic delivery of naltrexone (NTX) in human volunteers, also assessed the acceptability and pain score of the MNs themselves and also the MN arrays in combination with drug preparations [94]. They found that skin piercing by MN insertion was four times less painful than insertion of a hypodermic needle and the erythema observed was short-lived as well. However, applying the NTX preparation after MN treatment produced more prominent skin reactions, which were attributed to the constituents of the NTX formulation, rather than the MN array itself. In another study, 200 μm-long silicon MNs were used to deliver methyl nicotinate solution to human subjects. The application of MN was mostly perceived to be pain-free by the participants [193]. Likewise, MN-mediated insulin delivery was found to be less painful when compared to administration via catheter and hence more preferred, compared to the later route [194]. Van Damme et al. observed that erythema and swelling were more frequent in case of MN-based delivery of influenza vaccine (using MicronJet™) in comparison to intramuscular injections. However, they found the reactions to be mild and transient [195]. Additionally, Gupta et al. (2011) have suggested in their study that pain score depends on the volume of formulation discharged from the MNs during insertion. If the injection volume exceeds the limit of 1 ml, the human subjects perceived increased pain owing to the higher pressures required to infuse such volumes [196]. A very recent study reported that dissolving MN patches were well tolerated, easily self-applicable and immensely accepted by human subjects and this paves the way for the further clinical application of this technology [197].

Needle-related fear and needle phobia are more common in children and adolescents than in adults often presented as significant needle-related distress and behavioural consequences [189]. Children who require frequent injections, such as those with juvenile idiopathic

Table 3
List of studies reporting the scale of pain related to MN application.

MN material/drug	Length of MNs	Comments	References
Silicon	150 μm	Painless, no skin damage, no inflammation observed	[17]
Stainless steel	200 μm and 400 μm	Painless. Transient irritation	[192]
Silicon	180 and 280 μm	Transient skin disruption, repairs within 24 h. Significantly lower pain sensation than hypodermic needle	[19]
Stainless steel/NTX	620 μm	MN array caused just one-fourth of the pain caused by the hypodermic needle	[94]
Silicon/ methyl niconitate	200 μm	Painless application	[193]
Borosilicate glass/ Insulin	1 mm	Less painful then catheter-based delivery	[194]
Silicon/ influenza vaccine	450 μm	Mild and transient erythema and swelling observed	[195]
Borosilicate glass/Insulin	500 μm, 750 μm, 1 mm and 4 mm	Painless. If injection volume is higher than 1 ml, pain increases	[196]
Polyvinyl alcohol and sucrose	650 μm	Painless and well-tolerated. Transient and mild erythema observed	[197]

arthritis, often develop psychological side effects, such as anticipatory nausea and behavioural distress in anticipation of the treatment [198]. In such situations, MN devices can be utilized owing to their minimally invasive and less painful mechanism. In 2014, Mooney et al. reported children's appreciation of MN-based drug/vaccine delivery in their study involving a total of 86 schoolchildren aged 10–14 years. The study indicated that the reduced pain associated with MN application and the elimination of needles have resulted in the widespread approval of this technology among children. Also, many children felt that MNs were suitable for people of all ages owing to their pain-free mechanism [199]. In conclusion, MN arrays have been demonstrated to be a comparatively less painful technique and hence well-accepted among the paediatric population.

6. Safety evaluation of MN devices

MN devices operate by puncturing and penetrating the defensive layer of skin and hence are not equivalent to the conventional transdermal patches, which are just applied on to the skin surface. Moreover, MNs can occasionally penetrate deep into the sterile domains of viable epidermis and dermis [200]. Consequently, it is obligatory for the MN products to be entirely devoid of microorganisms which can cause local and systemic toxicities. The bioburden of the MNs should be regulated as well, to avoid activation of the immune cells present in the viable epidermis and dermis [201].

The prospects of infection, by microorganism infiltration through MN-created holes in the skin have been studied by several research groups [60,126,202]. Donnelly et al. have demonstrated that representative Gram-positive *(S. epidermidis*) and Gram-negative (*P. aeruginosa*) bacteria and fungi (*C. albicans*) were efficient of traversing the micron-sized pores created by MNs in the Silescol® membranes or excised porcine skin. The results of this study suggested that when compared to conventional hypodermic needles, microbial influx through MN-created conduits is negligible and considerably lower [126,202]. Wei et al. studied the extent of *Staphylococcus aureus* infection through microconduits created by MN treatment, macro-needle puncture and abrasion *in vivo* in rat animal model. The progress of infection was evaluated by quantifying the white blood cells, leukomonocytes and neutrophil granulocyte levels in blood. They demonstrated that there was no substantial difference in the cell populations between MN treated group and control group indicating the absence of microbial invasion. However, macro-needle puncture and abrasion resulted in the increase of all the three cell types, signifying the development of an infection [60]. The infusion of microorganisms can be further controlled or reduced by cleaning the application site with 70% isopropanol before MN treatment, as shown by Cormier et al. [90].

Recently there are instances of MN production using materials having antimicrobial properties and this further reduces the possibilities of infection [161]. MNs fabricated using the acid anhydride copolymer, Gantrez® AN-169 BF, demonstrated antimicrobial effects against numerous microorganisms, highlighting the potential for further application of this polymer and its derivatives in MN research [203].

Production of sterile MN devices can assure patient safety and helps to avoid any device-related toxicity. However, careful consideration should be given while deciding on the sterilization procedure as some methods can irreversibly alter the original attributes of the product and might multiply the manufacturing costs. For instance, terminal sterilisation using moist heat, microwave or gamma irradiation could degrade certain types of MNs. McCrudden et al. studied the effectiveness and the consequences of different sterilisation procedures on dissolving and swelling MN devices [204]. Wermeling et al. ensured sterility of the fabricated stainless-steel MNs by using a laminar hood to assemble them into a patch, which was followed by ethylene oxide sterilization [94]. In case of polymeric dissolving MN products, another key concern is the deposition of polymer in the skin. Generally, the polymers used in the fabrication of MNs have been previously categorized as biocompatible and non-toxic. However, some of these polymers might have never been employed previously for intradermal delivery. Hence, the selection of polymers and their safety evaluation is a mandatory aspect, especially while designing dissolving MN systems.

Pore closure following MN treatment is another important aspect to be considered while designing MN systems. Open pores may subsequently result in complications such as irritation and infection and might also affect the optimal delivery of drugs. In their study, Kalluri and Banga reported that the defensive property of skin in a hairless rat model was re-established within 3–4 h after poration with soluble MNs. However, complete closure of pores was not noticed until 15 h and incorporation of an occlusive material further delayed pore closure for up to 72 h *in vivo* [205]. Additionally, Haq et al. demonstrated that MN treated skin showed signs of healing 8–24 h after poration whereas disruption triggered by a 25 G hypodermic needle was significantly noticeable even after 24 h post-insertion [19].

Young children are more susceptible to bloodstream infections and surgical site infections than older children and adults [206]. Device-associated toxicities often lead to bloodstream infections in paediatric patients. This is frequently due to the migration of microbes from the skin at the site of insertion along the device and into the blood flow. As the MN technology is less invasive, there are relatively reduced chances of MN-associated infectious complications. However, it is imperative to follow sterile manufacturing conditions to assure the safety of MN devices and also minimise the possible allied risks. Also, the patient should be supervised and monitored for any potential infection, particularly when a new device or procedure is initiated. The paediatric population group is significantly vulnerable to the risks associated with excessive and undesirable drug exposure due to their moderately effective skin barrier function. Consequently, comprehensive advice and education on accurate usage is crucial to avoid any incidence of toxicity, with respect to the site and duration of application.

7. Applications of MNs

7.1. Drug delivery and vaccination

During the last 20 years, a wide variety of studies have reflected the considerable drug delivery enhancing effects of MNs. As detailed above in Section 1.2, Henry et al. published the first research work using MN for transdermal drug delivery [16,134] and since then, this technology has been extensively reported in scientific literature. There have been extensive reports of MN arrays being used for the percutaneous delivery of small molecules such as caffeine, lidocaine, metronidazole [134], ibuprofen sodium [119,207], sulforhodamine B [119], 5-aminolevulinic acid [59] and macromolecules including insulin [127,128], BSA [80], low molecular weight heparin [129], ovalbumin [122,125], leuprolide acetate [124], erythropoietin [140] and human growth hormones [208]. MN pre-treatment has also been explored for enhancing the permeation of certain photosensitizers [5- aminolevulinic acid, 5-aminolevulinic acid methyl ester and mesotetra(N-methyl-4-pyridyl) porphine tetratosylate] [59,209], non-steroidal anti-inflammatory drugs (diclofenac, ibuprofen, ketoprofen, paracetamol) [210], naltrexone (NTX) and dyclonine [94,211]. In many instances, this approach was used in conjunction with other permeation enhancement techniques, such as iontophoresis or sonophoresis, in order to have a synergistic influence on the transdermal delivery of macromolecular compounds [212,213]. In addition to a wide variety of drugs, coated MNs have been also used for the delivery of genetic material [150] thus offering an attractive alternative for the management of genetic skin diseases. Moreover, *in vitro* and *in vivo* silencing of gene expression has been achieved by coating metal MNs with RNA [21]. So far, insulin has been the most widely investigated molecule for MN-mediated delivery [51,97,100]. The pharmacokinetic and pharmacodynamic profiles for MN delivery of insulin is comparable to subcutaneous injection and in

the first clinical trial, intradermal MN delivery of insulin demonstrated rapid glucose uptake and a faster insulin action with shorter T_{max} compared with subcutaneous injection [214–216]. MN mediated delivery of insulin also leads to improved patient compliance due to the low pain-scores upon MN insertion into the skin and also due to its ability to be self-administered without the need of expert handling [217]. There are a number of ongoing clinical trials related to MN-assisted insulin delivery and further investigations in this regard may clinically introduce this technology [127]. MNs loaded with Parathyroid hormone (PTH) has also been clinically studied. Zosano Pharma's PTH loaded patch (ZP-PTH) has shown a rapid plasma profile for PTH with three times greater T_{max}, and two times shorter half-life in comparison to FORTEO®, the marketed PTH subcutaneous injection [218]. The MN based device was also demonstrated to be safe, effective and well-tolerated in the considered patient population. Very recently, dissolving MN arrays have been proposed for their application in obesity treatment. In this study, nanoparticles encapsulating rosiglitazone, glucose oxidase, and catalase were loaded onto MN arrays for sustained delivery into subcutaneous adipose tissue. This would inhibit the adipocyte hypertrophy and consequently improve the metabolism [219]. Furthermore, hydrogel-forming MN arrays have been exploited for delivering clinically relevant doses of low potency, high dose drug candidates (e.g. ibuprofen sodium) and also for protein and peptide delivery [163,164].

Intramuscular or subcutaneous routes are comparatively painful, and they even bypass the skin's immune system consequently delivering vaccines to regions with no significant concentration of antigen presenting cells [151]. On the other hand, MNs deliver drugs in the epidermis and the dermis, containing an enriched network of antigen presenting cells. This has facilitated their recognition as an effective alternative route for vaccination. According to scientific reports, MN-based vaccinations have shown comparable or even greater immunogenicity and a higher level of antigen stability to conventional routes of administration [195,220,221]. Soluvia™ microinjection (BD Bioscience) and MicronJet ™ (Nanopass technologies) are clinically approved hollow MN systems for intradermal delivery of influenza vaccine [195,222,223]. Moreover, influenza antigen coated MN system developed by Kommareddy et al. could elicit comparable antibody titres to intramuscular injection [224]. Furthermore, the MicronJet™ has presented encouraging results in a Phase III study for delivery of inactivated polio vaccine (IPV) in 6–14 week-old infants sponsored by the U.S. Centres for Disease Control and Prevention (CDC) and the International Centre for Diarrheal Disease Research, Bangladesh [225]. Recently, MicronJet™ injection has been clinically utilized to compare the intradermal polio vaccine in HIV-infected patients against the conventional intramuscular injection [226]. This is particularly beneficial for the immunocompromised population, such as the HIV patients who have a reduced immune response to most vaccines. Matsuo et al. investigated hyaluronic acid MNs (Microhyala1®) for efficiency against tetanus, diphtheria, influenza and malaria and observed immunisation results analogous to the conventional parenteral route in all the cases [123]. The same research team tried developing a vaccine for Alzheimer's disease by using similar hyaluronic acid MN array. They could well demonstrate the attainment of effective anti-amyloid-beta immune responses, despite the fact that the results did not indicate enhanced brain activity in the treated population [227]. Additionally, a recent study suggested the delivery of an Alzheimer's disease vaccine using coated MNs [228]. MN systems are even studied to deliver vaccine against the Edmonston-Zagreb virus [229] and also DNA and RNA vaccines [230,231]. An alternative vaccination strategy was to incorporate multiple vaccine-components in a single device and this particular approach was studied by Morefield and his team, who delivered a combination vaccine against anthrax, botulism, plague and staphylococcal toxic shock in rhesus macaque monkeys using hollow MN systems [232]. In another instance, Ono et al. developed novel double-decker MN patches, by stacking two tapered-cone MNs vertically, for the safe and effective transcutaneous vaccine delivery [233]. Groot et al. have revealed for the first time, the potential of nanoporous MN mediated intradermal immunization with subunit vaccines (diphtheria and tetanus). This study indicated the future possibilities of MN assisted intradermal vaccination [234]. In a recent study, a digitally controlled hollow MN injection system (DC-hMN-iSystem) was developed for minimally invasive and potentially pain-free induction of cytotoxic and helper T-cells for therapeutic cancer vaccination. In some cases, this system resulted in higher induction of antigen-specific T-cell responses in blood and spleen than those achieved by using a conventional hypodermic needle [235].

7.2. Diagnostic applications of MNs

MNs offers the opportunity for a pain and blood free monitoring/diagnosis system and have the potential to overcome other conventional needles allied limitations including the requirement of skilled handling and the risk of infection. Samples extracted using MNs can later be analysed or an integrated system comprising a diagnostic system with the MN assembly can be employed. In recent times, the advancements in MN technology has paved the way for the development of a number of MN-based diagnostic strategies which have demonstrated successful results in sampling and testing *in vitro* and in animal models [236–239]. The MN extraction systems were initially designed based on the capillary action of interstitial fluid but, eventually started including complex strategies such as vacuum or osmotic pressure [240]. Hollow glass MNs have been designed for glucose monitoring using interstitial fluid and the results showed that the glucose concentrations in interstitial fluid can be correlated with blood glucose [48]. Another alternative for interstitial fluid extraction is the use of hydrogel-forming MN arrays. When applied to the skin, they absorb the interstitial fluid and swell depending on the extent of polymer cross-linking. Later the MN patch can be examined for the quantification of different analytes and/or biomarkers [236,240]. In a recent study, the design and implementation of a MN-based device have been described for painless and automated capillary blood collection. In this device, the sample gets mixed with anticoagulant throughout the collection process and the sample is stored for subsequent analysis [241]. Another research presented the fabrication of an improved silicon MN array for low cost, minimally invasive human interstitial fluid extraction for nucleic acid profiling in order to identify potential biomarkers of disease [242].

7.3. Other applications

During the last few years, several novel routes have been tried for MN application such as ocular, oral, vaginal and nails. For the ocular delivery of drugs, MN technology has been proposed to be a comparatively minimally invasive alternative to the existing routes [243]. The conventional routes including systemic administration via oral and parenteral routes, intravitreal injections, and surgical implantation of drug vehicles into the ocular or periocular tissues, and targeted topical delivery using injections and conventional topical medications are effective to treat certain ocular ailments. However, these routes also present some serious disadvantages, for example, requirement of high doses of medications, highly invasive procedures of implantation of drug vesicles, possibility of intraocular pressure increment, bacterial invasion, decreased bioavailability of drugs due to being washed away by the lacrimal fluid and the requirement of skilled medical staff [244]. Recently, MN delivery has been studied to improve the treatment of both anterior and posterior eye ailments [245]. Being minimally invasive, MN technique decreases the pain sensation, tissue injury and the probability of microbial infection in comparison to the hypodermic injections. Additionally, MN systems can be self-administered and thus increase patient compliance. Jiang et al. were the first to carry out *in vitro* and *in vivo* experiments to estimate the potential of MNs for ocular

drug delivery. They found the designed coated MNs to be safe in terms of post-applicative inflammation and tissue damage [243]. Hollow MNs have also been used to deliver drugs to the sclera and the suprachoroidal space of the eye [246–252]. Palakurthi, et al. have investigated the toxicity of methotrexate loaded biodegradable MNs, surgically implanted into the rabbit eye sclera, and have described the absence of any adverse effects [253]. Also, Thakur et al. in their study, could successfully show the feasibility of rapidly dissolving MNs to deliver macromolecules to the eye via the intrastromal or intrascleral route [254].

Several delivery systems have been developed and studied for boosting the transfer of molecules across these barrier properties of mucus and the epithelial tissues [255] and also to protect the orally delivered drugs from the enzymes inhabiting oral cavity and gastrointestinal tract [256–261]. Lately, MNs have been explored in this regard. Wang et al. tried to develop an effective, convenient and stable mucosal vaccine against hepatitis B virus. Liposomes loaded with antigens were filled into MN molds and dried to form MN arrays. A single application to the oral mucosa of mice could induce robust systemic and widespread mucosal immune responses [262,263]. Another study investigated the possibility of inducing systemic immune responses using coated MNs to deliver vaccines into the oral cavity [264]. Traverso et al., for the first time, studied the use of MNs for the delivery of biologics via the gastrointestinal tract. They compared the bioavailability of insulin delivered via the MN-equipped pill with that of conventional subcutaneous injection. They even investigated the potential tolerability of the formulated MN devices and found that they can be passed and excreted from the gastrointestinal tract safely without resulting in any tissue damage [265].

In recent times, there are studies showing the use of biodegradable MN arrays to effectively eliminate the mucosal barriers to deliver vaccines [263,264]. Oral mucosal vaccination via MNs could produce impressive mucosal immunity in the oral cavity and intestinal lumen. However, it could not induce an adequate immune response in the reproductive duct to establish an optimum defence against sexually transmitted infections, such as HSV, HIV and HPV. N.Wang et al. for the first time, designed a promising MN-assisted vaginal mucosal vaccine adjuvant-dual delivery system, loaded with liposomes containing antigens, against infectious pathogens causing STDs [266].

Drug administration via nails is generally preferred for drugs to treat various nail diseases such as onychomycosis and nail psoriasis [267]. However, its efficacy is limited due to the low permeability of the drugs across the keratinized structure of nail plate. This again demands a prolonged presence of the drug formulation onto the nail plate, which in turn leads to evaporation of the drug vehicle and eventual immobilisation of the drug [268]. Chiu et al. suggested a method for MN-based drug delivery onto nails, where a commercially existing dermaroller, with 250 μm long MNs, was rolled onto the fingernail clippings. This was subsequently followed by topical application of Nile Red-loaded poly-(ε-caprolactone) nanoparticles [269]. It was reported that the permeation of Nile Red across the MN-treated nails was substantially higher in comparison to the nails which were not MN-treated. The promising results suggested that the technique of nail poration by MN treatment followed by the subsequent application of drug formulation can be further investigated for future applications.

Apart from the applications mentioned above, MN technology has also been widely explored in cosmetic applications. The most relevant microneedling device in the field of cosmetics is the Dermaroller® (Dermaroller GmbH, Wolfenbüttel, Germany), which is available in a number of designs intended for different applications. According to reports, a standard Dermaroller® produces nearly 250 pores per square centimetre when rolled over the skin for fifteen times and depending on the applied pressure, these pores can spread up to the papillary dermis [270]. Dermaroller® is effectively used to treat fine wrinkles, lines and small stretch marks; however, it shows nominal results against deep wrinkles and lines, and larger stretch marks on the skin. In order to address the limitation of Dermaroller® to accurately aim the target skin area, a compact form of Dermaroller® termed as MS-4 model has been designed for usage in smaller areas with precision. Moreover, Dermaroller®, MF-8 model, containing 1.5 mm long needles, is used for larger collagen scar bundles and stretch marks [271]. Dermapen® (Dermaroller GmbH, Wolfenbüttel, Germany) is a motor operated microneedling device that uses electrical power to deliver pulsating-stamp like motion to the skin at a low (412 cycles/min) or high speed (700 cycles/min) [272]. Similarly, Dermastamp® is used for collagen induction therapy and is helpful in treating skin scars, age spots, varicella scars and wrinkles. It is also motor operated with back and forth movement of needles similar to the stamp-like motion. Another device manufactured by Dermaroller®, Germany is the Beauty Mouse®, which is claimed to create microchannels in the skin and thus enhance the penetration of anti-cellulite creams. In another instance, the microneedling device, DermaFrac™ combines microneedling with a concurrent infusion of serum containing active agents inside the skin. The newer DermaFrac™ designs also contain light emitting devices (LEDs) with wavelengths specific for skin conditions. Moreover, MN dermabrasion is used to treat different types of scars by piercing the skin multiple times and thus encouraging collagen growth [272–276]. There are also instances of drug-loaded MN devices employed for the self-treatment of cosmetic diseases [277,278].

8. MN application devices

Appropriate and reproducible piercing is essential for the medical application of MN devices. This entails the use of a MN applicator, even in the case of sharp MN arrays. There are certain mandatory, as well as desirable, requirements that should be considered for the clinical use of the applicators. Primarily, the applicator itself should not cause any pain, because one of the chief reasons to develop MNs is to eliminate pain sensation and thus lessen patient discomfort. Besides, an applicator should be capable of inducing an effective, consistent and depth-controlled insertion of MNs into the skin and should decrease the possibilities of MN fracture. Also, the applicators should be user-friendly [15,19,78,93,100,279].

Till date, several MN application devices with varying configurations have been designed and developed. A hand-operated applicator based upon the reduction of insertion forces was designed for hollow MNs. It operates by drilling individual MNs into the skin to a predetermined depth [100]. Another hand-held MN applicator used a single rolling motion at an angle of 45° to 135° to insert the MNs in the skin [19]. Certain application devices make use of vibrations to lower the insertion forces [54,100]. Mostly the application strategies are based upon impact insertion, which essentially decreases the insertion forces, bypassing the skin's elasticity. These impact-based applicators range from basic hand-operated systems, which insert the MNs into the skin either manually [19] or by a mechanically-driven device [280–283], to more sophisticated electrically-driven systems [93,192]. For a single administration, a mechanically-driven applicator proves to be an economic option however, the electrical applicators result in more stable forces over time and hence generally preferred in case multiple administrations are required (e.g. repeated dose, multiple patients). Hence, the requirement and design of the MN applicators are solely governed by the geometry, sharpness and density of the MNs and their proposed applications.

8.1. Smart MN devices

In case of the conventional MNs, once they are inserted into the skin, drug diffusion is irreversible and hence it is difficult to regulate the duration and dose. In smart MNs, there is an amalgamation of various elements like sensors, actuators and the drug formulation. Their combination leads to a complete network for individualized treatment. Sensors track the physiological conditions and elicit the medication

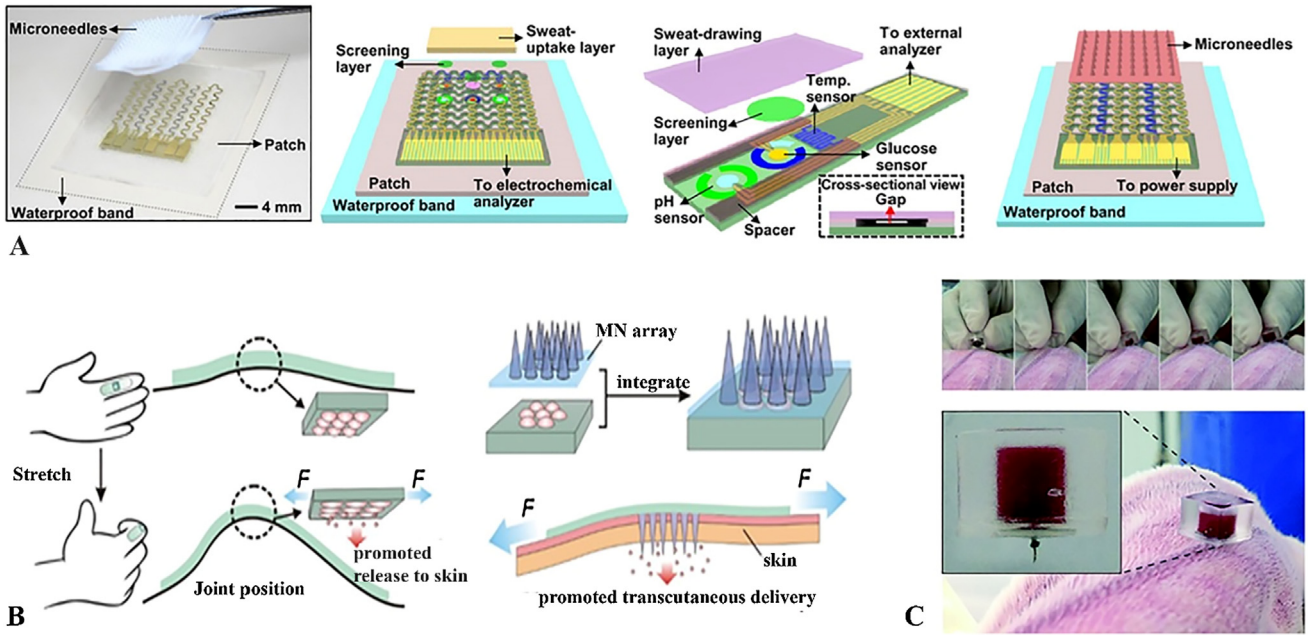

Fig. 8. A schematic representation of smart MN devices: (A) Wearable/disposable sweat monitoring device and MN-based transdermal drug delivery module. Replacement-type MNs are assembled on a three-channel thermal actuator [286]. (B) Stretching-induced drug-loaded wearable device integrated with a MN array patch [285]. (C) *In vivo* blood extraction using the self-powered one-touch blood-extraction system [288].

while the actuators control the release pattern and dose of the delivered drug. The smart MN patches maintain the tailored drug release, without the need of any expert medical involvement, until the disease indications improve. These automated devices can provide a patient-friendly and feedback-controlled delivery, unlike the traditional MN systems. MNs can be made responsive to external stimuli (e.g., heat, laser, and mechanical strain), which can easily be regulated by patients [284,285]. This can be particularly beneficial, when MN devices are developed for paediatric patients. The dose, time and release pattern can be optimized for individual patients according to age and the severity of treatment required.

Recently, it has been shown that it is feasible for real-time health monitoring to achieve controlled transdermal drug release by using a wearable device-assisted thermo-responsive MN device [286,287]. Its effectiveness is confirmed in diabetic mice, in which the MNs triggered controlled transcutaneous drug release using thermal actuators, successfully bringing down the blood glucose levels [Fig. 8(A)].

Also, drug-loaded wearable devices can be attached comfortably to the finger with the microdepots area on the finger joint. Finger flexion triggers the promoted release to the skin. The drug-loaded wearable device integrates with a MN array patch. Stretching of the device promotes the drug release from microdepots, which further diffuses into the needle for transcutaneous delivery [285] [Fig. 8(B)].

Guo Li et al. have designed and developed a novel self-powered one-touch blood-extraction system by integrating a smart polymer-capped hollow MN and pre-vacuum actuator. This is a disposable system that works based on the negative pressure-driven force developed in the pre-vacuum actuator with no need for an additional electrical power source [288]. Another one-touch-activated blood multi-diagnostic system was designed by the same group, and it consists of a biocompatible hollow MN and a paper-based multiplex biosensor integrated into a single device [Fig. 8(C)]. All the functions of blood collection, separation, and detection are automated, and the device requires only one-touch activation without the need of additional processes [239]. Very recently, another touch-actuated transdermal delivery patch was developed to achieve effective controllable permeation from a small MN unit. This system facilitates real-time dose regulation and can be beneficial for diseases requiring careful supervision, for instance, nerve disorders [289]. The smart MN devices represent a significant advancement in drug delivery science as they have the potential to detect and even treat health abnormalities in a personalized manner.

9. Studies and perceptions on MN-based paediatric drug delivery

MNs can efficiently bypass the SC and hence can be used to deliver large molecular size entities. Nevertheless, as MNs are most appropriate for the delivery of comparatively small doses, they have been mostly utilized for the administration of large and potent drugs such as biopharmaceuticals. MNs have been reported to be advantageous for delivering disease modifying antirheumatic drugs in children, however they have been tested on only limited instances [290]. Cormier et al. have studied the potential of administering desmopressin using coated MN array (Macroflux®), to treat enuresis in young children [90]. They used hairless guinea pigs as animal model and found the treatment to be efficient and well tolerated. There have been two studies for confirming the effectiveness of MN devices for insulin delivery in children and adolescents with type 1 diabetes [214,223]. In the first study, intradermal insulin delivered via a single hollow MN was compared with subcutaneous insulin administered via a conventional catheter in 5 participants [214]. They suggested that intradermal MNs facilitate improved postprandial glucose control with better patient compliance, particularly among children and adolescents, and enhanced health outcomes. These factors can prove to be critical for the management of diabetes and also for reducing the complications associated with diabetes. The second study compared intradermal (MN-based) and subcutaneous (syringe pump) routes of administration in 16 (10–18 years old) subjects. They also reported that intradermal insulin delivery using a hollow MN device leads to less pain scores and faster onset and offset of insulin pharmacokinetics in children and adolescents [223]. There was another study in 384 (4–66 months) children, in which the authors investigated the thickness of skin at four different body sites (deltoid, suprascapular, upper back and lumbar area). This aspect is particularly significant while designing intradermal vaccine delivery devices such as MNs for children [291]. The study reported that although skin thickness is not dependent on age, gender, body mass index, and phototype, it was considerably higher at the suprascapular area than the deltoid, and

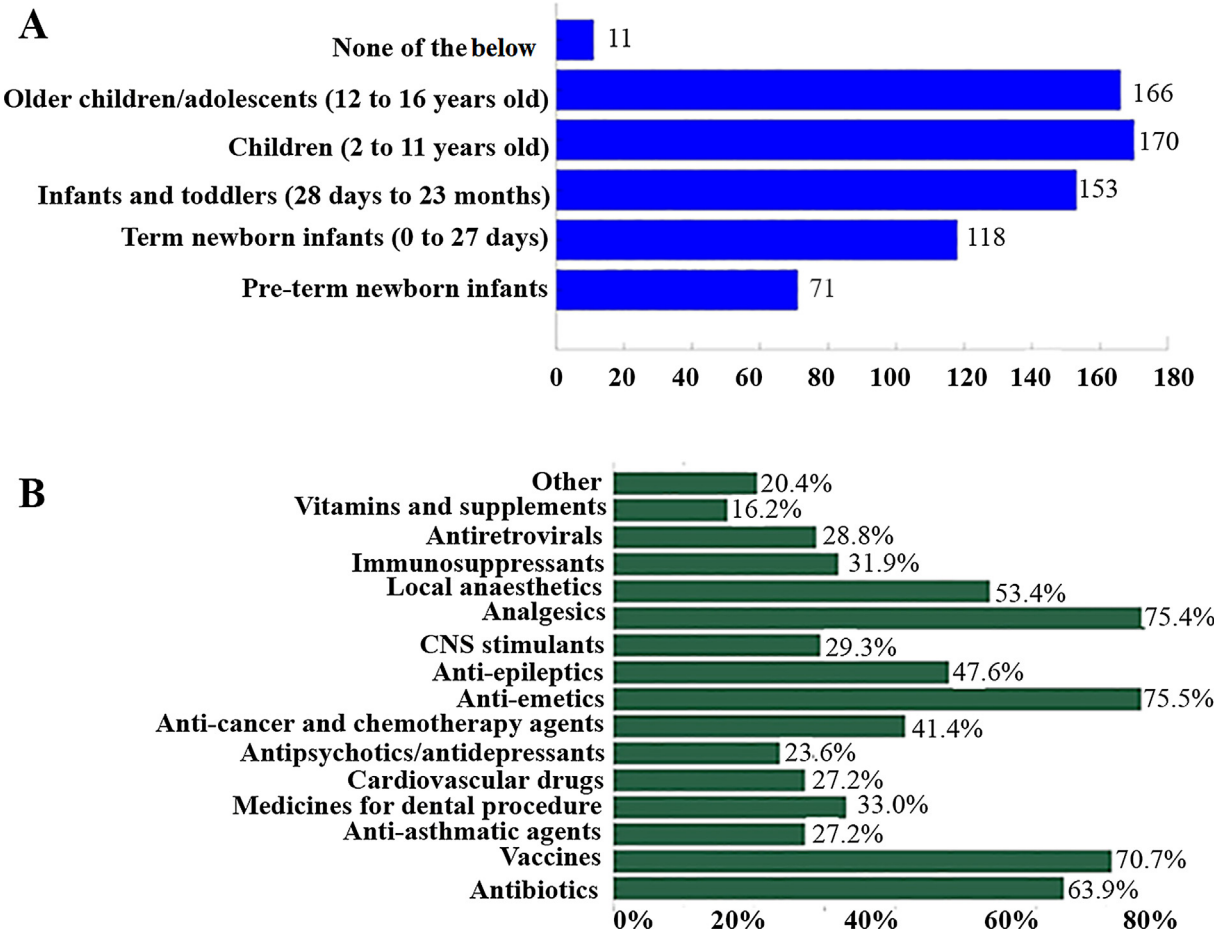

Fig. 9. (A) Number of paediatricians and their opinions on the potential suitability or appropriateness use of MN to different age-groups listed (n = 191); (B) Percentage of paediatricians and their opinions on different types of medicines that could potentially be beneficial for delivery using MN (n = 191). [Reproduced with permission from Caffarel-Salvador et al. [295]].

also on the upper back than the lumbar area. Nevertheless, there was no clinically relevant heterogeneity among the variables and hence there is no necessity of MNs of differing lengths for immunization of children aged up to 5 years.

Another research highlighted the potential of transdermal drug delivery using novel laser-engineered polymeric dissolving MNs and hydrogel forming MNs for paediatric applications. In this study, two drugs commonly used in paediatric patients (caffeine and lidocaine hydrochloride) were incorporated in the MNs and their efficacy for paediatric dosing was assessed via *in vitro* and *in vivo* studies [237]. They have also demonstrated the ability of hydrogel-forming MNs to detect and quantify different analytes from interstitial fluid *in vivo*. This technique could substantially reduce the need for medically-skilled personnel and the allied costs.

Another recent study showed the successful formulation of dissolving MN arrays to deliver therapeutically relevant doses of the antibiotic, gentamicin for the potential treatment of neonatal sepsis. They reported that this promising technology could be explored as an antibiotic treatment for infants with severe infection during the neonatal period [292].

Very recently, Maurya et al. have reported the use of rapidly dissolving MNs containing ferric pyrophosphate (FPP) as a prospective therapeutic approach for management of iron deficiency anaemia (IDA) in children. The ability of FPP-loaded MNs to replenish iron was examined in anaemic rats and the *in vivo* data could demonstrate significant improvements in haemoglobin and serum iron levels after 2-week treatment with FPP-loaded MNs [293].

It is critical for the recognition and acceptance of a novel technology among prospective end-users for the technology to be successful. Children and paediatricians' perspectives and acceptance are very imperative for the successful clinical translation of MN technology.

Birchall et al. explored the views of the general public and also the health care professionals on MN technology and majority of the participants interviewed identified it as being "good for children" and around 26% of healthcare professionals were neutral about the MN approach for drug delivery [294]. Mooney et al. also investigated the opinions of MN-mediated interstitial fluid or blood sampling in 86 children, aged 10–14 years old. The children expressed a better acceptability of MNs in comparison to the conventional hypodermic needles, however they showed their concerns regarding possibility of allergy and inaccuracies during MN-based drug delivery. Furthermore, the children suggested for an alternative name to describe MN technology and to exclude the word "needle" to improve acceptance of this approach [199]. Salvador et al. tried to explore children's views on MN use for drug delivery by conducting group discussions involving 66 children (46 female and 20 male), aged 9–15 years [295]. Among them, 14 children had underlying medical conditions for which they receive regular prescriptions from one to seven items for chronic ailments. The reports stated that children discussed the limitations related to conventional routes of drug delivery, (oral and IV routes) and expressed their positive views on the potential advantages of MNs. Regarding the typical routes, the children mentioned about the difficulty of swallowing oral medicines, pain, fear, anxiety and related adverse risks related to hypodermic needle, mostly based on their own negative experiences. In contrast, they were found to have a strong interest in MN technology and were eager to use MNs in future, provided they are

reassured about its safety and efficacy. Few of the children were, however, apprehensive about the potential high costs related to the development of MN devices. For the survey of paediatricians, there were a total of 191 participants and the majority were of the opinion that the use of MNs, in comparison to conventional needles, was expected to cause considerably reduced anxiety and distress for the children themselves (87.5%), the parents (88.5%) and even to the healthcare providers who are required for handing and administration (71.7%). They also expressed that it would be crucial to provide appropriate instruction and training for MN usage to the healthcare staff (99.5%), parents and/or guardians (87.4%) and older paediatric patients for self-administration (83.3%) [295]. Fig. 9(A) shows the views of paediatricians on the potential suitability of MN for drug delivery in different age-groups. Unexpectedly, paediatricians stated that thinner skin and skin immaturity in pre-term infants make them unsuitable for MN application. The prime professed concerns identified by paediatricians regarding the use of MN are potential allergic reactions or skin irritations (72.8%), associated high costs (66%), poor accuracy in drug delivery (61.3%) and possible accidental use (46.1%). Also, they mentioned that MN technology would be most beneficial for children who need to inject medicines frequently and reported that the analgesics, anti-emetics and vaccines would be ideal candidates for potential delivery using MN in children [Fig. 9(B)].

These studies have shown that there are endless opportunities for MN-mediated paediatric drug delivery and childhood immunisations via MN-based devices can be significantly prospective for commercialization.

10. Clinical trials of MNs in children

There have been a wide variety of clinical trials related to the application of MN-based devices. There has been a total of around 43 clinical trials (ongoing, recruiting or completed) of MN-based therapeutics till date and out of that 5 trials were carried out on paediatric participants. Most of the trials are focused on influenza vaccination and insulin delivery. Moreover, there are extensive studies evaluating the MN-mediated delivery of parathyroid hormone and lidocaine and other local anaesthetics. Table 4 enumerates the clinical trials carried out to determine the safety and efficacy of MN-based delivery of therapeutics in paediatric population. It can be comprehended that there has been a remarkable increase in the number of clinical studies related to MN during the last 5 years. Consequently, further clinical development is expected to substantiate the efficacy of MN-based paediatric drug delivery.

11. Commercialization of MN products

11.1. FDA regulatory requirements for commercialization

MN technology is a relatively new and innovative field and therefore there are no separate regulatory requirements established for the MN-based products to date. The conventional transdermal patches are merely applied to the exterior surface of the skin; whereas MNs pierce the stratum corneum barrier and at times even infiltrate into the viable epidermis and dermis. Disrupting the defensive layer of the skin is an entirely different mechanism of action and this provokes the inception of additional scientific/ regulatory demands. Hence, from a regulatory perspective, new specifications should be defined for the MN systems apart from the well-defined requirements for the pre-existing transdermal patch systems. Some of the significant regulatory queries that need to be addressed when planning for commercialization of MN devices are [57]:

1. Needle characteristics, including materials, length, adjustability, sharpness, and geometry should be appropriately designed.
2. Satisfactory microbiological standards should be retained by the MN devices.
3. The MN systems should maintain uniformity of content.
4. Quality manufacturing aspects, as well as safe and secured packaging, should be applied.
5. A self-disabling mechanism, assuring a single-use only, may be required for the MN systems made of non-biodegradable materials to avoid the possibility for re-use by patients or others. Moreover, safe and non-hazardous disposal procedures should be outlined for these MN systems.
6. Cleaning or disinfection information, if the MN device is reusable, should be provided.
7. The issue of safe deposition of MN materials in the skin, without causing any adverse skin reactions should be addressed, especially for the MN products intended for long-term use.
8. Proposed labelling for the MN device, including package labelling and instructions for use should be given.
9. MN systems should be easy to use and, also, give reproducible results without complications. They should also be used with proper application device to ensure correct insertion and pain-free delivery.
10. Immunological safety assurance may be required to be provided for the MN systems.
11. The long-term safety profile of MN application should be addressed for the MNs requiring intermittent and repeated applications.

11.2. Existing MN products in the market

In the recent years, there have been substantial industrial activities in the area of MN devices. At present, a number of MN-based devices are being designed and developed by different companies. This include: Becton-Dickinson (BD) Technologies (USA), Zosano Pharma (USA), Microneedle Therapy System (USA), Sanofi Pasteur MSD (USA), Valeritas (USA), Nanopass Technologies (Israel), 3 M (USA) [301], Rodan + Fields (USA), Vaxxas (Australia), Corium (USA) and, more recently, Lohmann Therapie- Systeme AG (Germany/USA), the world's largest transdermal patch manufacturer [302].

Microstructured Transdermal System® [Fig. 10(A)], developed by 3 M, consists of coated MN arrays and allows the rapid and improved delivery of certain drugs and vaccines. This device could demonstrate a rapid and sustained delivery of lidocaine [303]. Another type of device designed by BD Technologies is the Microinfusor [Fig. 10(B)], a hollow MN system having a capacity of 0.2–15 ml which allows the delivery of

Table 4
List of clinical trials using MNs in children [Retrieved from clinicaltrials.gov].

Title of the study	Investigated condition	Starting year	Phase	Reference
Glucose Measurement Using Microneedle Patches	Diabetes	2017	N/A	[296]
Enhanced Epidermal Antigen-Specific Immunotherapy	Type 1 Diabetes	2016	Phase 1	[297]
Microneedle Patch Study in Healthy Infants/Young Children	Vaccination Skin Absorption	2017	N/A	[298]
Insulin Delivery Using Microneedles in Type 1 Diabetes	Type 1 Diabetes Mellitus	2008	Phase 2 Phase 3	[299]
The Use of Microneedles with Topical Botulinum Toxin for Treatment of Palmar Hyperhidrosis	Hyperhidrosis	2015	Phase 1	[300]

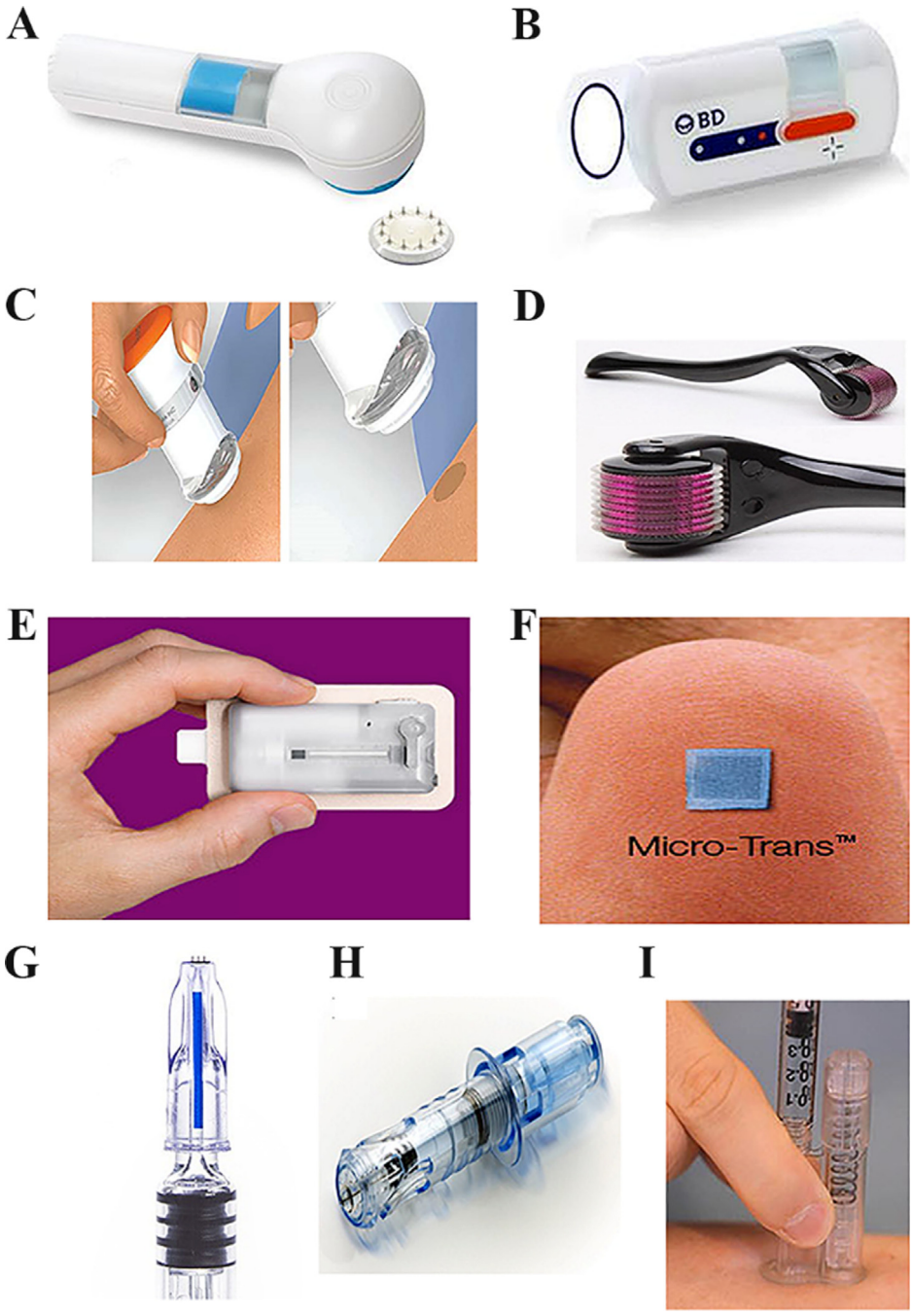

Fig. 10. Commercially available MN devices: (A) Microstructured Transdermal System (MTS). (B) BD Microinfusor. (C) Macroflux®. (D) MTS Roller™. (E) Vaaleritas h-patch™ (F) Valeritas Microtrans™. (G) MicronJet®. (H) Intanza®. (I) DebioJect™.

drugs to the subcutaneous tissue over a varied period of time, ranging from a few seconds to several minutes. This is an automated hands-free system and preclinical studies showed the effective delivery of influenza vaccine with comparable results to conventional intramuscular injection [304]. Macroflux® developed by Alza/Johnson & Johnson uses coated titanium microprojections for the improved delivery of biopharmaceuticals [280]. This device incorporates an applicator system that allows a consistent regulation of skin penetration depth [Fig. 10(C)].

Clinical studies have revealed that the use of MN rollers is more effective than other conventional ablative and non-ablative treatments in stimulating the production of collagen and elastin for cosmetic purposes including scar management [275]. This encouraged the increase in commercialization of the MN rollers during the last few years. The patented MTS Roller™ [Fig. 10(D)] is approved by the FDA for cosmetic applications [301] and the device is perfect for the non-ablative and non-surgical treatment of several skin disorders such as hyperpigmentation, ageing and scarring.

The two types of MN-based devices developed by Valeritas are the Micro-Trans™ and the h-Patch™ [Fig. 10(E) and 10(F)]. Micro-Trans™ device allows the painless dermal delivery of drugs and h-Patch™ is a simple and disposable system used for controlled delivery of drugs to the subcutaneous tissues [301].

Nanopass Technologies developed MicronJet®, consisting of four hollow silicon needles shorter than 500 μm that can be attached to any conventional syringe for intradermal injection [Fig. 10(G)]. This device was used for delivering influenza vaccine and it showed comparable immunogenicity with only 20% of the conventional flu vaccine dose

[301]. Micronjet® received FDA clearance in 2010 [305]. The Swiss company Debiotech developed a similar injector system called Debio-Ject™ [Fig. 10(H)], containing silicon MNs [223]. Moreover, Sanofi Pasteur MSD Limited used the same approach to design an intradermal microinjection system for influenza vaccine and named it as Intanza® [Fig. 10(I)] [301]. It uses the Soluvia® injector developed by BD technologies.

Presently, Soluvia® and MicronJet® are the only MN-based medical systems available in the market for therapeutic applications. In addition to Intanza1, Soluvia® is currently commercialised worldwide as IDflu® and Fluzone Intradermal® for intradermal vaccination [306].

Rodan + Fields Dermatologists® developed a dissolving MN array containing hydrolysed hyaluronic acid for cosmetic application and this product is available in the market since October 2014 [307].

The commercialization of the MN-based products will definitely encourage the expansion of MN research and motivate those working for the development of more innovative and diverse MN devices to move towards large-scale manufacturing.

12. Future perspective

Over the past two decades, a substantial progress has been witnessed in the field of MN-mediated drug delivery. Advancement in the microfabrication technologies has stimulated the design and development of a number of MN-based products. The positive and welcoming views and opinions of children, paediatricians and members of the general public ascertain the potential of MN technology for paediatric applications. With effective delivery, improved patient compliance and ease of storage, MNs have been recognised as a convincing route for vaccination, which is particularly advantageous for children. Moreover, this technology can be utilized for delivering drugs used on a long-term basis and for managing chronic paediatric conditions, such as diabetes. The current clinical outcomes and the ongoing research endeavours indicate the promising future of MN technology. With further innovations in polymer science, 3D printing and fabrication technologies, MN products can be expected to be employed for the delivery of a broader range of drugs for the management of difficult-to-treat conditions. Additionally, the next-generation transdermal drug delivery systems incorporate multiple features into a single device. The one-step process of detection and treatment, in case of the smart MNs, has the potential to tailor the therapy to ensure better patient care by the customized treatment. More advanced research can contribute to the improved therapeutic efficiency of MN-based delivery of large hydrophobic proteins and peptide molecules, which are otherwise difficult to administer by means of conventional transdermal delivery mechanisms. However, there is utter need for scientists and researchers involved in MN related research to address and consider the health and safety aspects, particularly for potential paediatric clinical applications and strict manufacturing regulations, specifically for the MN products, should be proposed. Taken together, an exponential growth of MN-assisted drug delivery can be expected with advances in fundamental studies, proficient clinical translation and enhanced commercialization conditions. The dissolving MNs could be tailored according to the dose required for different conditions and by different age groups. This will eventually result in better disease management with enhanced patient compliance.

13. Conclusions

This article presented a comprehensive appraisal of the therapeutic and other potential applications of MN technology, with a focus on the paediatric population. It also provided a detailed review on the MN types and the recent advances in their fabrication methods. MN technology has been widely documented for its efficacy in accelerating the natural healing of the skin and thus aiding skin rejuvenation. However, its applications are not limited to cosmetics only, and there is an enormous volume of literature describing its relevance in diverse areas such as drug delivery, vaccination, disease-diagnosis and many more. Compared to the conventional drug delivery systems, MN patches have demonstrated numerous advantages, such as providing pain-free, non-invasive and controlled delivery of therapeutics, avoiding first-pass effects, as well as decreasing needle-stick injuries and transmission of blood-borne infectious diseases. MN patches have presented a great potential particularly for the paediatric population. By meticulously designing and accurately considering their safety aspects, the MN arrays can be utilized for paediatric delivery of a wide range of drugs. The versatility of the MNs can be further explored in depth to promote the well-being of patients. Therefore, increased clinical trials should be implemented to establish the safety and efficacy of MN-based devices for paediatric application and for their successful translation to commercialization.

14. Disclosure statement

The authors have no conflicts of interest to disclose.

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