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Review Article

Microneedle and drug delivery across the skin: An overview

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Abstract

The skin offers a route of administration with numerous advantages. However, one of the major limitations of this route is the limited number of drugs that possess the ideal physicochemical properties to passively diffuse through the skin barrier. Today, microneedle (MN) technology proved to be superior in the field of drug delivery. MN arrays are devices that consist of micron-sized projections which pierce the *stratum corneum* (*SC*), the main barrier for drug delivery across the skin. MN technology has the potential to provide a localised drug delivery with minimal toxicity and expand the range of drugs for transdermal and intradermal delivery. In this comprehensive review, MN technology was thoroughly discussed. Meeting regulatory standards and large-scale production is essential to advance MN technology into a cost-effectiveness commercial scale.

Keywords

Microneedle arrays, skin, topical, transdermal, drug delivery

Introduction

The function and structure of the skin

The skin is the largest and most accessible organ of the human body that provides protection from the external environment and maintains homeostasis (Ghasemiyeh and Mohammadi-Samani 2020). It consists of three main layers; epidermis, dermis, and hypodermis (Fig. 1), (Mojumdar and Sparr 2021). The epidermis is about 50–150 µm thick where keratinocytes are the chief component cells (Hadgraft and Guy 1989). The epidermis does not contain blood microcirculation and consequently, the transport of substances from the epidermal/dermal layer to the hypodermis circulation is supported by diffusion process (Benson and Watkinson 2012). The epidermis has two sub-layers; the viable epidermis and the *stratum corneum* (*SC*). A 70% of the viable epidermis is water and hence, considered as a hydrophilic layer. In contrast, the *SC* is hydrophobic in nature with only 13% water content. The *SC* is the outmost layer of the epidermis which is 10–20 µm thick (Mendelsohn et al. 2006). The *SC* is known as the rate-limiting membrane of the skin and the main barrier against the topical drug delivery (Scheuplein et al. 1971).

The dermis is hydrophilic in nature and is supplied with nerves and blood vessels. This layer is 600 to 3000 µm thick that is made up from connective tissue which gives the mechanical strength of the skin (Mendelsohn et al. 2006). Compounds that reach the dermis layer can find portal into the systemic circulation and this provides a concentration gradient that maintains the diffusion process. The dermis is demonstrated as a gel-like matrix of fibrous proteins network such as collagen and contains skin appendages such as hair, sebaceous and sweat glands. Cells such as; fibroblasts, melanocytes, macrophages, and mast cells are located in this skin layer (Hadgraft and Guy 1989; Benson and Watkinson 2012). The hypodermis or

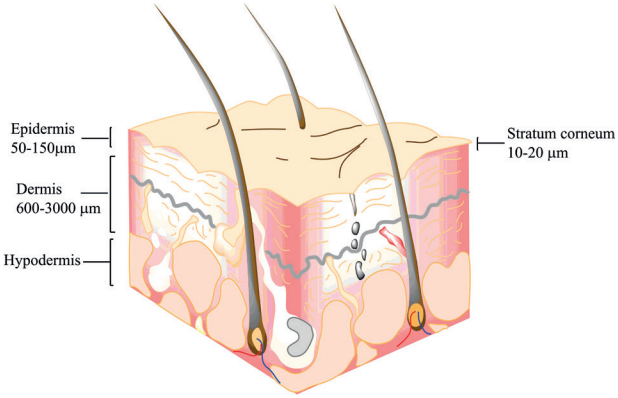

Figure 1. The structure of the skin. The epidermis, dermis, and hypodermis. This Figure is generated using ChemDraw professional 16.0.

the subcutaneous layer consists of adipocytes and is innervated and supplied with blood vessels. The primary functions of this layer are protection and heat insulation (Benson and Watkinson 2012).

Abbreviations

SC	*Stratum Corneum*;
MW	Molecular weight;
Da	Dalton;
MN	Microneedle;
TDD	Transdermal drug delivery;
CAGR	Compound Annual Growth Rate;
BSA	Bovine serum albumin;
NSAIDs	Non-steroidal anti-inflammatory drugs;
PTH	Parathyroid hormone;
CMC	Carboxy methyl cellulose;
PVP	Polyvinyl pyrrolidone;
PLGA	Poly(lactic-co-glycolic acid);
PMMA	Poly(methyl methacrylate);
PVA	Poly(vinyl alcohol).

Drug delivery across the skin

Skin stands as a route of drug administration for both local and systemic drug effects (Benson et al. 2019). The knowledge and understanding of skin permeation have led to the development of topical and transdermal delivery (Benson et al. 2019; Aldawood et al. 2021). Drug administration through the skin offers plenty of advantages including; sustained drug delivery, maintained constant plasma levels, low metabolism activity compared to other routes, less inter-subject variability (Iwata et al. 2020; Phatale et al. 2022), escaping first pass hepatic metabolism, less frequent dosing regimens (Lee et al. 2017; Waghule et al. 2019; Ghasemiyeh and Mohammadi-Samani 2020), ability to discontinue regimen by removal of the system (Iwata et al. 2020), accessibility and relatively large surface area available for drug absorption, and being a non-invasive and convenient means of delivering therapeutics (Hamdan et al. 2018; Baveloni et al. 2021; Tiwari et al. 2022). Hence, this route provides a good alternative to oral and parenteral administration as it overcomes considerable limitations encountered by these routes (Benson et al. 2019; Aldawood et al. 2021). The aforementioned advantages possibly can increase patient adherence and ultimately improve their quality of life (Iwata et al. 2020). However, the main restraint of drug delivery by this route is the skin's barrier properties. Generally, factors that determine skin permeability include; drug solubility, thermodynamic activity, partition coefficient (Benson et al. 2019), drug matrix-skin interaction, and temperature (Benson et al. 2019; Aldawood et al. 2021). Candidate molecules should have intermediate lipophilicity (Log P 1–3), be potent (Pandya et al. 2015), have molecular weight (MW) less than 500 Daltons (Da) (Mamta et al. 2010), and good aqueous solubility characterised by a low melting point (Williams 2003). It is difficult for hydrophilic substances to penetrate the hydrophobic *SC* layer. Whereas hydrophobic substances may be confined to it, as the following subsequent layer is hydrophilic (Supe and Takudage 2021). So far, limited number of therapeutics possess the optimum physicochemical properties to passively pass the skin's outermost layer, the *SC*, and consequently, limiting both topical and transdermal market (Nastiti et al. 2017; Roberts et al. 2017). Many technologies have evolved to enhance the delivery into the skin, thereby extending the number of therapeutics that can be effectively delivered *via* the skin (Benson et al. 2019). These technologies involve the utilisation of chemical penetration enhancers, micro and nano delivery systems (Nastiti et al. 2017; Roberts et al. 2017), ultrasound, iontophoresis, electroporation, and microneedle (MN) technology (Phatale et al. 2022). Among these approaches, MN arrays stand out as a simple and a relatively low-cost approach to deliver therapeutics (Hamdan et al. 2022).

Transdermal drug delivery

Transdermal drug delivery (TDD) deals with the drug administration through the skin to achieve systemic effect and is considered as a non-invasive alternative to parenteral route (Soni et al. 2022). The transdermal absorption is a stepwise process which involves (Dhote et al. 2012); (i) penetration: the access of a substance into a certain skin layer, (ii) permeation: the penetration of a substance from one layer of the skin into another, where both layers are functionally and structurally dissimilar, and (iii) absorption: the uptake of a substance into the systemic circulation. Primarily, the drug passes through the *SC*, then reaches into the epidermis and dermis microcirculation. The medication succeeds to enter the systemic circulation when it manages to reach the dermis (Waghule et al. 2019; Soni et al. 2022). TDD has several advantages such as; avoidance of first-pass effect, self-administration, prolonged drug delivery, less frequency of dosing, enhancement of patient compliance (Ghasemiyeh and Mohammadi-Samani 2020; Iwata et al. 2020). This route of administration is useful for patients who are unconscious

or vomiting. However, TDD is not suitable for high-dose and high molecular weight drugs, skin sensitisation and irritation at the site of application is a possibility.

Background on microneedles and mechanism of action

The investments in MN market were approximately $24 billion in 2013 (Azmana et al. 2020). By 2030, the market size of MN drug delivery system will reach to a $1.2 billion and Compound Annual Growth Rate (CAGR) record approaching 6.6% (Aldawood et al. 2021). MN has been extensively investigated in academia and industry to take this technology from laboratory settings in to clinic (Quinn et al. 2014). MN arrays are categorized as one of the direct physical methods and an alternative to conventional hypodermic needle (Benson et al. 2019). MN arrays are a micron-scale devices attached to a patch-like support (Wei-Ze et al. 2010; Benson et al. 2019; Hamdan et al. 2022) that pierce the *SC* barrier and generate conduits, subsequently, enhance the drug flux and its permeation through the skin (Prausnitz and Langer 2008; Donnelly et al. 2010a; Benson et al. 2019). Perforations created by MN arrays can physically disrupt the intercellular lipids and penetrate the corneocytes in the *SC* and increase the total surface area of the aqueous pores in the skin (Mikolajewska et al. 2010; Pattani et al. 2012). Pores created by MN projections have been shown to cure within two hours without occlusion, the later can extend closure time up to 24 hours (Gupta et al. 2011). MN arrays have been designed in several needle geometry and densities (25–2000 μm in height, 50–250 μm in base width, 1–25 μm in tip diameter, up to 2000 MN cm^{-2}) (Singh et al. 2013; Alkilani et al. 2015) without reaching nerve endings or blood vessels, thereby providing a painless administration (Gill et al. 2008) and avoiding needle-stick injuries (Indermun et al. 2014). Several researches have been thoroughly conducted to obtain an optimum MN arrays design (Davis et al. 2004; Verbaan et al. 2008). MN array have been designed in a 'poke and patch' or loaded forms (Benson et al. 2019) using various materials and microfabrication techniques (Prausnitz 2004; Lee et al. 2008; Donnelly et al. 2009a, 2010a; Singh et al. 2010; Garland et al. 2011; Migalska et al. 2011). It was found that the rate and extent of transdermal delivery were influenced by the configuration and application mode of the MN batch (Verbaan et al. 2008; Yan et al. 2010). It was reported that an increase in MN arrays height has led to an increase in the depth of MN arrays penetration into the skin (Donnelly et al. 2010b). However, the application of MN arrays with height 900 μm was perceived by volunteers to be relatively painful (Garland et al. 2012a). Further, higher MN arrays density resulted in a higher number of conduits formed within the skin. Yet, high MN density would affect bed of nail effect (Lee et al. 2008; Yan et al. 2010). Various combinations of MN arrays systems and other techniques have been studied for a number of drugs. All combined approaches enhanced the TDD of the tested compounds. MN arrays systems were coupled with iontophoresis (Katikaneni et al. 2009), 'in-skin' electroporation (Yan et al. 2010), phospholipid vesicle systems (Badran et al. 2009), sonophoresis (Chen et al. 2010), Skin occlusion (Gupta et al. 2011). A unique triple strategy based on MN arrays, iontophoresis and nanovesicle was also reported (Chen et al. 2009).

Advantages of microneedles

MN arrays proved to enhance skin permeability, and hence, drug penetration into the skin (Hamdan et al. 2018; Tekko et al. 2020). The rate limiting step to the drug delivery through the skin is mostly attributed to the diffusion of the drug solute to the underlying dermal capillary bed. Thus, the drug release kinetics is likely to be controlled by the delivery system, rather than the *SC* (Donnelly et al. 2011). MN systems are capable of delivering macromolecules and biotherapeutics which are considered not good candidates for transdermal delivery. Worthy to mention, the administration of such therapeutics is limited to the parenteral route, and are susceptible to degradation when administered orally (Quinn et al. 2014). MN arrays are minimally-invasive devices, and have delivery capabilities similar to hypodermic injection (Donnelly et al. 2011; Seok at al. 2016; Aldawood et al. 2021). MN arrays are short and thin to reach the underlying dermal nerves or capillaries, thereby, their insertion into the skin is generally perceived as being painless and causes no bleeding (Donnelly et al. 2010b, 2011; Mikolajewska et al. 2010). Risk to develop MN-associated skin infections is negligible (Donnelly et al. 2011; Johnson and Procopio 2019). MN arrays generate transient microscopic pores in the *SC*, with minimal or even without signs of erythema or local adverse skin reactions (Bal et al. 2008; Van Damme et al. 2009). Heavy occlusion to the MN-pre-treated area extends barrier disruption and improves the permeation of the drug into the skin (Haq et al. 2009). MN arrays are considered patient-friendly devices, easy to apply with no need for hospitalisation (Pattani et al. 2012; Larrañeta et al. 2016b). On the other hand, hypodermic needles cause skin trauma and bleeding. Needle-stick injuries are possible with parenteral injections, hence, safe and correct disposal are essential but rather challenging to accomplish in developing countries (Donnelly et al. 2009b, 2012b; Pattani et al. 2012). Generally, the advantages offered by MN arrays reflect the versatility of MN approach as a delivery system (Quinn et al. 2014)

Disadvantages of microneedles

Although MN have a lot of advantages, yet there are some drawbacks. The MN application may necessitate a good mechanical strength, extended application time, multiple patches (Jeong et al. 2017). The pharmacokinetic parameters are more likely challenging to acquire, and hence, adverse side effects may appear as a result of inaccurate dosing (Rzhevskiy et al. 2018). The shapes and conformation of needle structures may affect their efficacy and ability

to poke the skin (Kawahara and Tojo 2007; Ramadon et al. 2021). One of the major long-term safety issues of MN devices is the polymer deposition inside the body when using dissolving MN arrays, however, a 'one-off' delivery platform such in the case of vaccination would overcome this problem (Bal et al. 2008). The chances to develop immunological skin reactions such as; skin irritation, redness, pain, swelling (Kawahara and Tojo 2007; Ramadon et al. 2021).upon the application of MN arrays would be considered as a health concern issue (Bal et al. 2008).

Types of microneedles

The major MN types used for drug delivery purposes are solid non-coated/coated, hollow, dissolvable/swellable polymeric MN arrays devices (Aldawood et al. 2021).

Solid, non-coated microneedles

Solid, non-coated MN employ 'poke and patch' approach that involves two-steps which is not a preference for patients. First, the skin is pre-treated with MN that pierce the epidermis creating transient microchannels and then are removed. This temporarily enhances the skin permeability, and hence, facilitates diffusion of therapeutics from its matrix. The second step involves the application of a drug in a patch or topical formulation platform at the same site of MN application (Gupta et al. 2011; Quinn et al. 2014). Solid MN can be developed from various materials such as metals and silicon (Nagarkar et al. 2020). Multiple drugs delivered by this type of MN arrays have been assessed such as; bovine serum albumin (BSA), insulin, 5-aminolevulinic acid, 5- aminolevulinic acid methyl ester and a number of non-steroidal anti-inflammatory drugs (NSAIDs) (McAllister et al. 2003; Prausnitz 2004; Banga 2009; Mikolajewska et al. 2010; Donnelly et al. 2012b; Stahl et al. 2012). Some drawbacks arise for this type of MN arrays in terms of biocompatibility and skin issues, as these MN arrays may be subjected to brakeage inside the skin.

Coated microneedles

Coated MNs poke the *SC* and the drug payload is released into the skin (Li et al. 2017). Accurate coating is somewhat challenging, and the coated area is very limited that can only deliver a bolus minute amount of drug (<1 mg) (Donnelly et al. 2010a; Singh et al. 2010; Garland et al. 2011). Coated MN arrays have attracted particular interest for potent molecules and vaccines delivery (Dang et al. 2017; Du et al. 2018). Different compounds such as; DNA, fluorescein sodium, desmopressin, salmon calcitonin and parathyroid hormone (PTH) were delivered using coated MN arrays (Cormier et al. 2004; Pearton et al. 2012; Tas et al. 2012; Quinn et al. 2014).

Hollow microneedles

Hollow MN employ 'poke and flow' approach and has similar mechanism of action to the traditional hypodermic injections (Martanto et al. 2006). When A pressure is applied to the MN the liquid formulation starts flowing through a central hole (Prausnitz 2004; Donnelly et al. 2011; Indermun et al. 2014; Waghule et al. 2019). Hollow MN may be subjected to technical difficulties such as blockage due to compressed dermal tissue during their application as they possess a single port (Donnelly et al. 2010a; Singh et al. 2010; Garland et al. 2011; Dang et al. 2017). A hollow MN has the ability to deliver high MW compounds and vaccines with a controlled drug release rate (Sanjay et al. 2016). The delivery of drugs such as sulforhodamine solution and insulin were explored using hollow MNs (McAllister et al. 2003; Martanto et al. 2006).

Dissolvable microneedles

Dissolvable MN employ a 'poke and release' delivery strategy (Rodgers et al. 2019; Guillot et al. 2020). These MN arrays are polymer-based systems with the drug dissolved or suspended into the MN formulation (Donnelly et al. 2011; Hamdan et al. 2018; Benson et al. 2019). These MN array formulations consist of water soluble and/or biodegradable polymers that dissolve and/or degrade in contact with the skin interstitial fluid to release the drug payload. Several advantages were attributed to this type of MN (Dang et al. 2017; González-Vázquez et al. 2017). The polymers are of low cost and leave no biohazardous or sharp waste within the skin. These MN arrays are self-disabling which assure their safe disposal and avoid their reuse (Park et al. 2005; Prausnitz and Langer 2008). Many researchers have used a wide variety of polymeric materials for their fabrication (Tekko et al. 2020; Hamdan et al. 2018). Some have used aqueous blends of carboxymethylcellulose and amylopectin, (Lee et al. 2008). others have fabricated dissolving MN arrays from hydrophilic polymers of various molecular weights. Hydrophilic polymers of low molecular weights dissolve in minutes providing a one-step bolus drug delivery, offering a minimized application time into the skin. (McCrudden et al. 2014). However, drug loading in such systems can significantly affect their mechanical strength (Migalska et al. 2011; Pattani et al. 2012), and hence, drug loading of therapeutically relevant concentrations of low potent drugs could be challenging, (Tuan-Mahmood et al. 2013). Dissolving MN arrays proved successful enhancing the delivery of a range of drugs including small molecules such as caffeine and lidocaine and macromolecules such as insulin, human growth hormone (Lee et al. 2011; Migalska et al. 2011; Dangol et al. 2017; Lee et al. 2017; Zhao et al. 2018), and a variety of vaccine antigens and diagnostics materials (Rodgers et al. 2018; Jin et al. 2019; Leone et al. 2019).

Swellable microneedles

Swellable MN arrays are hydrogels typically developed from a crosslinked polymers where the needle matrix contains no drug (Donnelly et al. 2012b; Tekko et al. 2020). When poked into the skin, these MN arrays imbibe skin interstitial fluid, swell, and form an open-channels that connect a patch-type drug reservoir to the underlying dermal microcirculation (Donnelly et al. 2014b, d; Seong

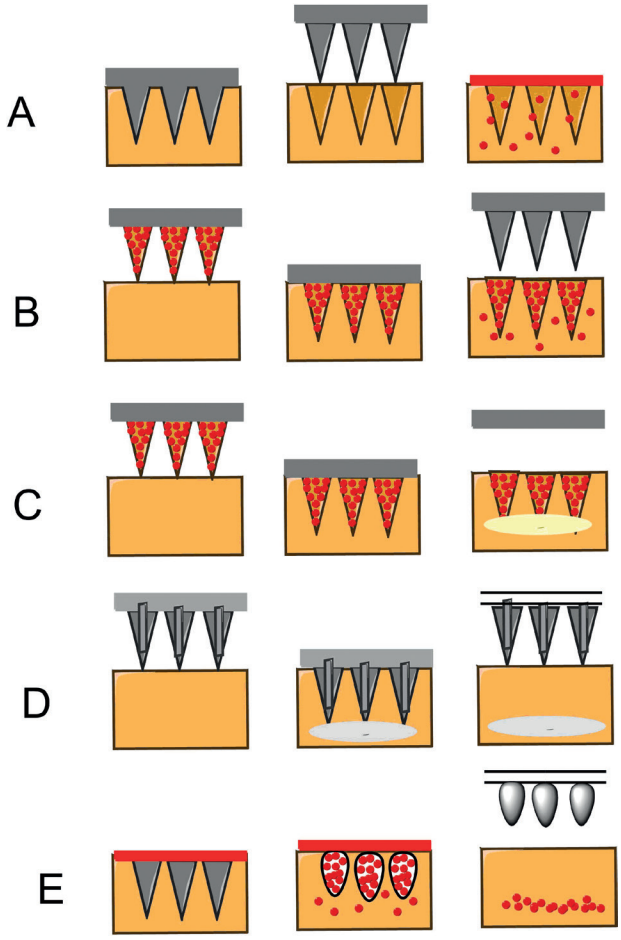

Figure 2. Schematic representation of MN types and delivery approaches. **A.** Solid non-coated; **B.** Solid coated; **C.** Dissolving; **D.** Hollow and **E.** Swellable MNs.

et al. 2017). Swellable MN arrays are capable of delivering small and macromolecules, such as metronidazole and insulin respectively (Donnelly et al. 2012b, 2014a; Chang et al. 2017). In such hydrogel system, the rate and capacity of polymer swelling, and subsequently, the drug release rate, can be tailored by varying the polymer crosslink density. As the drug concentration in interstitial fluid usually reflects plasma drug concentration, MN arrays are applied in drug diagnostic monitoring (Donnelly et al. 2014a; Chang et al. 2017). Compared to dissolving MN arrays in which polymer deposition is a cumbersome, hydrogels are removed completely intact and cannot be re-inserted (Donnelly et al. 2012b). The later reflects appreciable mechanical strength of the swollen hydrogel and eliminates material safety concerns. Hydrogels are known to possess inherent antimicrobial properties which reflect their safe use (Donnelly et al. 2012b; Hong et al. 2013; McCrudden et al. 2014).

Delivery strategies assisted by microneedles

The delivery of several compounds assisted by MN arrays has been attained *via* four main strategies:

- 'poke-with-patch' approach: the MN arrays are applied to the skin surface to create microchannels, then detached to apply drug formulation such as drug-laden patch, gel or solution (Martanto et al. 2004).
- 'coat-and-poke' approach: the formulation of the drug is coated onto the projections of MN arrays, then MN arrays are inserted into the skin (Matriano et al. 2002).
- 'poke and-flow' approach: hollow MN arrays pierce the skin and the liquid drug payload is injected into the skin (Davis et al. 2005).
- 'poke-and-release' approach: the drug molecules and the polymeric material are combined in to a matrix, the resulting MN arrays matrix are subsequently inserted into skin (Park et al. 2006).

Materials used in microneedles fabrication

A variety of materials are used to fabricate MN arrays. Generally, selected materials should be available, inert, non-brittle, biocompatible, have a good mechanical strength and of low cost.

Silicon

Silicon has a good mechanical strength and is a flexible material which facilitates the manufacture of MN arrays into different shapes and sizes. Solid-uncoated, solid-coated, and hollow MN arrays were reported to be fabricated from silicon (Larraneta et al. 2016a). However, fabrication of MN from such material is intricate, time consuming and expensive (Badilescu and Packirisamy 2016; Donnelly et al. 2018). The fracture of silicon-based MN arrays in the skin may compromise its safety profile (O'Mahony 2014).

Metals

Metals such as stainless steel, titanium, palladium, nickel (Norman et al. 2013), platinum, and gold (Invernale et al. 2014) possess a good mechanical strength (Rad et al. 2021), which helps their penetration into the skin (Shirkhanzadeh 2005). Metal-based MN arrays have been mainly used in the fabrication of solid coated/non-coated (Shirkhanzadeh 2005; Dharadhar et al. 2019) and hollow MN (Norman et al. 2013). Nevertheless, metal MN arrays may cause skin issues such as skin sensitisation (Donnelly et al. 2012a).

Glass

Hollow MN arrays are most commonly fabricated from glass (Gupta et al. 2011; Van der Maaden et al. 2014), which has a good mechanical strength to pierce the skin (Martanto et al. 2006). Main drawback of silica glass type is its brittleness and possible fracture. If the broken needle tip fragments reside inside the skin, this may lead to inflammation and granulomas (Finley and Knabb 1982). Nevertheless, borosilicate glass type possesses a good biocompatibility (Gupta et al. 2011).

Ceramics

Ceramic such as; alumina and calcium sulfate dihydrate have been used in the fabrication of solid and hollow MN arrays (Waghule et al. 2019). Scaled-up production of ceramic MN arrays at low cost was possible and successful (Indermun et al. 2014), however, ceramic MN arrays are fragile (Bystrova and Luttge 2011). Alumina is considered biocompatible but brittle material (Bystrova and Luttge 2011). In contrast, calcium sulphate is biocompatible and has a better mechanical strength compared to alumina (Dharadhar et al. 2019).

Polymers

Various polymers have been utilised in the fabrication of dissolving/swellable MN arrays (Dharadhar et al. 2019). These polymers include; methylcellulose, hyaluronic acid, carboxymethycellulose (CMC), alginates, poly (methylvinylether/maleic anhydride), polyvinyl alcohol, polyvinylpyrrolidone (PVP), poly(lactic-co-glycolic acid) [PLGA]), poly(methyl methacrylate) (PMMA), (Donnelly et al. 2014c; Larraneta et al. 2016a; Waghule et al. 2019). These materials are biocompatible and of low cost (Jeggy 2004), yet their mechanical strength is lower compared to silicon and metals (Monteiro-Riviere 2010).

Sugars

Sugars like maltose, mannitol, galactose (McGrath et al. 2014) were used in the production of MN arrays. Sugar-based MN arrays can penetrate the skin, however, their instability and the need for high processing temperatures have been considered as a major drawback (Donnelly et al. 2009b).

Microneedles manufacturing methods

MN array system, by design and necessity, should be sharp enough to puncture the skin with low insertion force i.e. below its break force (Davis et al. 2004; Park et al. 2005; Gill et al. 2008). The performance of MN arrays can be optimised by controlling needle dimensions, design, type of material, and fabrication technique (Aldawood et al. 2021). Several methods have been developed for MN fabrication including laser ablation, lithography, micro-molding. injection molding, additive manufacturing (Prausnitz 2017; Rodgers et al. 2018; Ye et al. 2018; Juster et al. 2019; Parupelli and Desai 2019; Aldawood et al. 2021).

Laser ablation

Laser ablation manufacturing method saves time and involves the use of an optical light beam to generate MN arrays (Nejad et al. 2018). Numerous types of laser light were evaluated for the production of MN arrays such as; CO_2 (Nejad et al. 2018) and femtosecond laser machine (Zheng et al. 2007). The laser beam consumes less than 100 nanoseconds to approach the corresponding material sheet for shaping (Aldawood et al. 2021). This method produces heat at the touching contact that may alter the structure and the mechanical properties of the material being treated. The laser ablation method is expensive and not feasible for large scale production.

Lithography

The lithography method involves transfer of a defined geometries of a matter template onto outer surface of a substrate material (Aldawood et al. 2021). Lithography technique can form products using different substrate materials such as: glass, plastics, metal, and ceramics (Tran and Nguyen 2017). The finished product generally possesses a very well-defined geometries and smooth surfaces (Aldawood et al. 2021). Drawbacks associated with such method include the requirement for designated facilities and the prolonged time of manufacture (Nejad et al. 2018).

Micro-molding

Micro-molding method uses laser milling technique to form MN master moulds of varying configurations using silicon sheets (Donnelly et al. 2011). The generated silicon moulds are then casted with various polymer solutions such as; Polyvinyl alcohol (PVA), alginic acid, Carbopol 971 and Gantrez AN-139 (Donnelly et al. 2012a). This method proves to be superior because of its ability for mass production and being cost effective (Aldawood et al. 2021). The MN arrays produced from various polymers using this technique may vary in penetration depth into the skin, drug loading capacity, and mechanical properties (Kim et al. 2018).

Injection molding

The injection moulding process involves the use of a master template which is mounted on a movable top plate of the injection moulding machine. Silicon rubber base and curing agent are combined and introduced into the injection moulding machine *via* a hopper, and injected into the metal moulds that define the shape of the moulded part. The latter is cured and ejected out using ejector pins (Hamdan et al. 2022). This method is considered reproducible and allows for mass production at low cost. However, the injection moulding equipment is expensive (Aldawood et al. 2021).

Additive manufacturing

Recently, additive manufacturing (3D printing) has gained attention which involves printing or building the MN arrays from a desired material by layering (Parupelli and Desai 2019). This technique allows for a versatile MN arrays design in a very limited time for processing (Johnson and Procopio 2019).

Mechanical characterization of microneedles

The fundamental knowledge of the mechanics of needle insertion into the skin is very essential to optimise the

performance of MN devices. Needles that have sharp tips are capable to poke the skin with the minimum force for insertion. However, the later would reduce the strength close to the needle tip and bending of needles tips may take place, especially for needle prototype with very thin tips (< 20°) (Zhang et al. 2009). It was documented that the higher the thickness of the needle wall, the higher is the fracture force, therefore, needle prototypes with small tip diameter and high wall thickness are preferable for insertion (Prausnitz 2004; Zhang et al. 2009). Needle density of a baseplate of a certain area can also affect the penetration force. The high needle density would result in the bed of nails effect. Generally, there are two kinds of failure styles related to the insertion of the needles into the skin; fracture or buckling (Zhang et al. 2009). Failure takes place when the load leads to either fracture or buckling. Consequently, MN mechanical characterization during their design is of paramount importance (Khann et al. 2010). The main mechanical tests which include; axial force, transverse force, and insertion force are usually conducted for MN arrays and are listed in (Table 1).

Table 1. MN mechanical tests: Description of the mechanical tests (Aldawood et al. 2021).

Mechanical test	Description
Axial force	The force is applied vertically onto the needle tip
Transverse force	The force is applied onto the MN base in parallel way
Insertion test	The MN array is applied into a skin or a simulated membrane

Clinical trials on microneedles

Many clinical trials were completed on MN-based delivery for multiple conditions. One study that demonstrated the use of MN devices to deliver insulin had reached to phase III trial (Norman et al. 2013). It was revealed that the delivery of insulin using a single, hollow MN array was perceived with less pain and faster onset of action. Another phase III clinical study had tested zolmitriptan-containing MN system which is indicated for the treatment of migraine (Spierings et al. 2018). It was shown that the drug delivered through the MN device provided significant pain relief and lessened symptoms associated with migraine compared to placebo (Spierings et al. 2018). There are ongoing clinical trials and recruiting for patients to prove the feasibility of MN system to deliver various drug substances used for multiple clinical conditions.

Microneedles and Covid-19 pandemic

To prevent the COVID-19 pandemic, global mass vaccination is a necessity. The vaccine strength, transport chain, needle phobia, and needle waste are major challenges for global outreach (Hassan et al. 2022). The delivery of vaccines *via* the skin using MN arrays is a good alternative to conventional invasive hypodermic needle and syringe-associated needlestick injuries (Benson et al. 2019). The use of MN arrays for COVID-19 vaccination is painless, secures higher vaccine coverage, offers higher product thermal stability and shelf-life, and allows for self-administration. Many researches support the use of dissolvable MN-mediated COVID-19 vaccination system (Hassan et al. 2022). On the other hand, MN-based oropharyngeal swabs were introduced for COVID-19 testing and monitoring (Chen et al. 2020). The latter allow reduction of false COVID-19 tests and perform testing with high accuracy.

Microneedles in the market, challenges and future outlook

Despite the extent and diversity of research in the field of MN technology, there are few marketed MN products (Table 2) (Butola 2022). MicronJet and Soluvia (Arora et al. 2008; Benson et al. 2019) are MN devices which demonstrated superior immune responses to influenza vaccine compared to IM injection. Commercially, there exist no biodegradable polymer-based MN device (Li et al. 2017), nor protein- loaded MN device (Al-Japairai et al. 2020). The regulatory bodies may ask for MN finished product sterilization or their manufacture under aseptic conditions to assure the safety of the final product (Bal et al. 2008). MN devices classification whether it is transdermal or intradermal delivery, transdermal patch platform or injection is still unclear (Donnelly et al. 2012b). Regulatory bodies are concerned with the guidelines and instructions of MN devices in terms of scale-up instructions (Quinn et al. 2014), packaging, disposal, directions to use, and safety issues (Larrañeta et al. 2016b). The optimisation of MN array products with respect to engineering, design, and usability will facilitate their approval within the regulatory bodies. The perception for easy-to-use product and the contemplation of long term safety profile for MN devices will certainly extend the degree of acceptance of these devices in the market (Quinn et al. 2014). Moving forward with MN technology in terms of their manufacture and commercialisation require consensus on a harmonised specifications for MN system (Quinn et al. 2014; Larrañeta et al. 2016b). Although these hurdles exist, MN-based skin delivery shows a promising future toward the management of chronic diseases and global vaccination programs particularly in pandemics (Benson et al. 2019).

Table 2. Marketed MN-based products (Butola 2022).

MN product	Uses
Dermaroller	Cosmetic uses, acne treatment
Nanojet	Intradermal delivery of drugs, diagnosis
Soluvia	Intradermal delivery of drugs and vaccines
Micronjet	The delivery of drugs, protein, and vaccines
Macroflux	The delivery of peptides and vaccines
Dermapen	The treatment of acne, hair loss, stretch marks
Microcore	The delivery of small and large molecules

Conclusions

Drug formulation and the delivery logistics are at the core for the success of any drug product. The skin is an attractive route of administration for both local and systemic drug delivery. It has unique features and offers several advantages yet, rela tively impermeable. MN delivery strategy overcomes the SC barrier, and hence, can extend the range of increasingly sophisticated therapeutics to be efficiently delivered across the skin. MN technology has a significant and far-reaching impact benefiting both patients and healthcare providers. This paper summarized the various types of MN arrays i.e. solid, coated, hollow, dissolvable and swellable MNs. MN arrays are fabricated using a wide range of materials such as, silicone, glass, metals, sugars, and polymers. Various manufacturing methods including micro-molding, lithography and 3D printing found applicability in MN fabrication. Many researches have been conducted on MNs in terms of characterization, safety, and efficacy. Meeting regulatory standards of product safety and efficacy and large-scale production is essential to advance the technology to a commercial scale. Once optimised, MN technology has the potential to provide a sophisticated adaptable platform for the treatment of various diseases.

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