Emerging era of microneedle array for pharmaceutical and biomedical applications: recent advances and toxicological perspectives

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Abstract

Background: Microneedles (MNs) are the utmost unique, efficient, and minimally invasive inventions in the pharmaceutical field. Over the past decades, many scientists around the globe have reported MNs cautious because of their superb future in distinct areas. Concerning the wise use of MNs herein, we deal in depth with the present applications of MNs in drug delivery.

Main text: The present review comprises various fabrication materials and methods used for MN synthesis. The article also noted the distinctive advantages of these MNs, which holds huge potential for pharmaceutical and biomedical applications. The role of MNs in serving as a platform to treat various ailments has been explained accompanied by unusual approaches. The review also inculcates the pharmacokinetics of MNs, which includes permeation, absorption, and bioavailability enhancement. Besides this, the in vitro/in vivo toxicity, biosafety, and marketed product of MNs have been reviewed. We have also discussed the clinical trials and patents on the pharmaceutical applications of MNs in brief.

Conclusion: To sum up, this article gives insight into the MNs and provides a recent advancement in MNs, which pave the pathway for future pharmaceutical and biomedical applications.

Keywords: Microneedles, Fabrication of MNs, Pharmaceutical and biomedical applications, Pharmacokinetics of MNs, Biosafety of MNs, Clinical trials and patents

Background

Several approaches to the drug delivery system have been adopted for the administration of the drug into the body. Out of this, the oral drug delivery system has been widely accepted due to its effortless administration and more patient compliance [1]. Meanwhile, many studies are looking into an oral or conventional route of administration. It leads to the conclusion that they were not fulfilling the appropriate purpose of the medication. Therefore, for satisfying the needs, other routes of administration have been developed after humongous research. The transdermal drug delivery system (TDDS) is among them, in which drugs are administered through external epithelia, i.e., stratum corneum (SC) [2]. However, this outermost layer of skin acts as a principal barrier for topically applied medications. It allows the transfer of drug(s) having molecular weight < 500 Da, adequate lipophilicity, and low melting point. Thus, to overcome the aforesaid limitations in the last earlier decades, we are dealing with the use of micro and nanotechnologies in drug delivery aspect to get the desired outcomes of the formulations/system as per our compendial requirements for intended use application [1, 3]. These pioneered systems are preferred because they

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have several advantages over the conventional route of drug delivery [1, 3–8], even though passing the drug particles through different skin barriers leads to developing a measurable hurdle in drug delivery [3]. In TDDS, drugs can be administrated to different pathways like transcellular and intracellular routes. In both pathways, the drug is delivered to the targeted site or the site of action by simple diffusion. The other important pathway is by microneedling through microchannels. Gerstel and Place firstly invented microneedle technology for the conveyance of drugs in 1971. At that time, inventors Gerstel and Place termed MNs as “puncturing projections.” However, the first prosperous attempts on MNs emerged in the 1990s [4]. These MNs are accomplished with several charismatic advantages like easy to use, easy to fabricate as per compendial requirements, and reduces the pain and irritation without extensive rupture to the skin. It offers a faster healing rate than conventional methods, bypasses the first-pass metabolism of the drug, and therefore can achieve required pharmacokinetics and pharmacodynamics response, and pretends to explore MNs as an excellent tool for the intended use. Fascinatingly, they are also applicable for quicker delivery of drug substances, administration of high molecular weight molecules, targeted and controlled drug delivery, etc.; due to which, they are widely accepted for pharmaceutical applications. Although the MNs suffer from some limitations like the necessity of careful handling, hindrance in the drug delivery due to some external factors like hydration of skin, damaging the veins due to the repetitive administration, or chances of injuring the skin while removing the patch if the MNs are broken. MNs are micron-sized needles that are used to open holes into the skin to create microchannels for the subsequent delivery of drugs. Generally, the MNs move in the epidermal layer of skin deprived of touching the nerves and consequently conveying the medicament transdermally without pain for both low and high molecular weight. MNs are 100 μm long, 1–50 μm wide at the tip, and about 50 to 300 μm at the base [1, 3]. Generally, MNs consist of a plurality of microprojections, ranging from 25 to 2000 μm in height, along with different shapes, which are attached to the base support [5].

MN are fabricated from a wide diversity of materials, viz., metal, polymer, glass, silicon, ceramic, hydrogel, and sugar [5]. Revolution in the microelectronics industry launches the various microfabrication technology tools that enabled the advancement in the manufacturing facilities necessary to produce microconduits in MNs [6]. In the earlier decades, the fabrication of diverse types of MNs via different techniques for the enhancement in the delivery of drugs and compatibility with a wide variety of physicochemical properties is extensively researched and has been demonstrated in in vitro, ex vivo, and in vivo experiments [7]. But still, its overwhelming applications in the field of cellular delivery, targeted delivery, DNA vaccine delivery, protein delivery, systemic delivery, etc. are not explored that much [8, 9]. Thus, in this present review, more emphasis has been given in depth to the existing applications of MNs in the release of active agent. Herein, we also deal with recent advancements made in fabrication materials and methods used for MN synthesis for intended use applications and discussed the variety of MNs. The review also inculcates the pharmacokinetics of MNs, which includes permeation, absorption, bioavailability enhancement, toxicity, and biosafety of MNs. The patent and clinical trials on pharmaceutical applications of MNs have been reviewed. Thus, this article gives insight about the MNs and also provides the recent advancement in MNs, which pave the pathway for future pharmaceutical application.

Main text
The material meant for the fabrication of MNs
Several types of material have been used for the fabrication/manufacturing of MNs. It includes polymeric materials (natural, biodegradable, non-biodegradable) and metals [10–12]. The general criteria for polymers, metals, and metalloids include good biocompatibility and mechanical properties [13]. In addition, it should be stable and should show chemical resistance. It should contain attractive physical properties that can make it a versatile material for pharmaceuticals as well as biomedical applications [12]. Furthermore, it should be socio-economic and safe for human health. Also, in most of the cases especially polymeric MNs or dissolvable MNs, the material should regulate the drug release rate (viz., controlled/sustained) [14]. In addition, they should show the admirable degradation at physiological conditions. The material should possess an acceptable molding ability. Despite the stability, the selected material should be highly stable in the fabrication and packaging process also [12]. Instead, the dissolving, hydrogel-forming, and biodegradable MNs contain polymeric material. It should follow the acceptance criteria of MNs [15]. Herein, we have summarized the types of materials with mostly acceptable examples (Table 1).

Types of MNs
MN are classified into two different groups based on the fabrication strategy, i.e., in-plane MNs and out-plane MNs. Concerning the facts of drug delivery, the MNs are classified as solid MNs, hollow MNs, coated MNs, dissolving MNs, and hydrogel-forming MNs (Fig. 1).
Solid MNs

Generally, solid MNs are performed by creating the holes in the SC layer of skin and are applied before the application of dosage form and detached thereafter or the drug may be coated onto the needles [16]. After removal of solid MNs, it leads to the formation of temporary microchannels where a drug can be placed in the form of cream, gel, solution, or transdermal patches. These microchannels recover soon afterward so that there is no secondary infection [16, 17]. The drug penetrates through the skin via microchannels and reaches to applicable site. In addition, solid MNs help to boost the transdermal transmission of different biologicals or therapeutics, which cannot be conveyed by passive diffusion. Solid MNs can increase the transdermal absorption of the small molecules by up to 4 folds. Additionally, these solid MNs are used to convey the bulky molecular weight compounds [17]. Solid MNs are made up of different metals like palladium, stainless steel, cobalt alloy, nickel, and silicon (Table 2). Besides, different materials are used for the formulation of solid MNs like maltose, sucrose ceramic, non-biodegradable, and biodegradable polymers [5]. Even though the drug delivery through solid MNs is a much considerable system, it encounters

| Polymers                  | Biodegradable | Non-biodegradable | Metals/metalloids |
|--------------------------|---------------|-------------------|-------------------|
| Natural                  |               |                   |                   |
| CS                       | PLGA          | Alginic acid      | Silicon           |
| CMC                      | PLA           | Gantrez AN-139    | Titanium          |
| Dextran                  | PVP           | Polyvinyl acetate | Stainless steel   |
| Zein                     | Polyglycolic acid | PVA          | Palladium-cobalt alloys |
| Galactose                | Polycarbonate | Carbopol 971 P-NF | Palladium         |
| Starch (thermoplastic)   | Polyvinylpyrrolidone | Polyetherimide | Nickel            |

Table 1 Material used for the fabrication of smart MNs

Fig. 1 Types of MNs based on drug delivery approach
some drawbacks, viz., the necessity of a two-stage process, the placement of sharp bio-hazardous residues, and the tendency of skin to self-regenerate which heals itself and inhibits transmission of molecules via microspores [25]. To overcome the aforesaid limitations, the researcher tested a co-drug strategy for the continuous delivery of a therapeutic drug, across the skin treated with solid MNs [26].

Coated MNs

These are the solid array of MNs made up of different metals and silicon and then further coated with a drug or mixture of drugs. After applying coated MNs on the skin, the coated material gets absorbed into the skin followed by penetration. MN coating is considered a prominent technique for quick and instant bolus delivery of molecules [26]. In addition, appropriate coating and proper drying of drug or surface modification of smart MNs may enhance their long-term stability. Dip coating and casting techniques are most wisely applied for the production of coated MNs [27]. Depending on physico-chemical adsorption, mechanism of chemical processing and surface alteration, numerous techniques, viz., dip coating, spray coating, and inkjet printing, brushing, electrohydrodynamic atomization, gas-jet drying, are used to produce coated MNs [17]. Gill designed MNs along with central openings termed “pockets” that were prepared in aqueous or organic solvents. The flexibility of the MN coating technique was showed by coating curcumin (hydrophobic molecule) and bovine serum albumin (BSA)/insulin (model proteins) using suitable solvent-based coating solutions [28]. Recently, transcutaneous vaccine delivery was investigated for the feasibility of fabrication and antigen delivery using coated MNs by Bhatnagar et al. [29]. As the layer of coating reduces, the mechanical strength as well as the sharpness of the MNs reduces, which confined the decrease in drug load on the surface of the MNs.

Dissolving MNs

In the last few years, concerning the applicability of MNs, they are prominently used for the delivery of various kinds of compounds ranging from low molecular weight drugs to proteins, vaccines, and plasmid DNA. They are fabricated using common materials depicted in Table 2. The literature survey evinced that the researcher increased the skin penetration of therapeutics like docetaxel by applying elastic liposomes to the skin and that was penetrated with silicon-based MNs, while some were coated with DNA using a water-soluble formulation. However, their expensive material costs or an unwanted two-step administration method limits the use of these types of MNs [30]. To overcome these previously mentioned limitations, a biodegradable polymer or water-soluble carbohydrates have been utilized lately for the fabrication of MNs. Miyano et al. recorded the first dissolvable MNs in 2005. Also, to minimize the potentially hazardous sharp waste, the principle of poke and release-based dissolvable MNs was created, [30]. These MNs were entirely degraded/dissolved into the skin interstitial fluids and in that way releasing encapsulated active agent [30, 31]. Besides, many biopharmaceutical compounds, including small-molecular-weight heparins, insulin, leuprolide acetate, erythropoietin, and human growth hormone, were explicitly used to meet different medical needs [32]. Dissolving MNs can be manufactured from various materials like polylactic acid (PLA), hyaluronic acid (HA), poloxamer, silk fibroin (SF), polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP), and poly(lactic-co-glycolic acid) (PLGA) [17]. Nevertheless, the advances of dissolving MNs furnish the list of obstacles, viz., manufacture of smart MNs at elevated temperatures, admirable activities of their heat-labile cargoes

Table 2 Fabrication techniques for a variety of MNs

| Sr. No. | Type                  | Method of construction                                                                 | Ref.       |
|---------|-----------------------|----------------------------------------------------------------------------------------|------------|
| 1.1.1.  | Silicon MNs           | Microelectromechanical systems (MEMS) techniques, thin-film deposition on a substrate, chemical vapor deposition on a substrate, Silicon dry-etching process, isotropic etching, etc. | [17, 18]  |
|         | Metal MNs             | Three-dimensional laser ablation, laser cutting (stainless less), metal electroplating methods (palladium), wet etching photochemical etching (titanium), etc. | [19–21]   |
|         | Ceramic MNs           | Ceramic micro molding and sintering lithography, etc.                                   | [5]        |
| 2.      | Coated MNs            | Dipping or spraying, layer-by-layer (LbL) coating techniques                           | [5]        |
| 3.      | Hollow MNs            | Deep reactive ion etching of silicon, deep X-ray photolithography, wet chemical etching, and microfabrication, Integrated lithographic molding technique, etc. | [5]        |
| 4.      | Dissolving MNs        | Micromolding                                                                           | [5]        |
| 5.      | Polymeric MNs         | Photolithography, micro molding, casting, hot embossing, injection molding, investment molding, etc. | [5, 22–24]|

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such as peptides, and protein losses. In addition, carbohydrate-based MNs deformed readily under relatively humid conditions, which negatively affected the mechanical strength of the needles. Thus, dissolving MNs are drug delivery systems with the potential to administer the therapeutics required to fulfilling these requirements [33].

**Hollow MNs**

The method of drug delivery through hollow MNs involves the process of injection of drugs through a hollow bore, which is situated at the center of the needle. As the MNs are impaled into the skin, the hollow bore present inside bypasses the SC layer by creating microchannels into the different layers of the epidermis [1]. The hollow bore enhances the transmission of activity via the needles either by diffusion method or by the pressure-driven flow. This method of approach is more reminiscent of an injection than a patch. It is used mostly for high molecular weight substances like proteins, vaccines, and oligonucleotides [34]. Drugs can be distributed as needed constantly, without the removal of drug patches as in solid MNs. The hollow MNs were manufactured with a choice of methods listed in Table 2 [17]. Jiang et al. also showed the intrascleral distribution of the model drug, sulforhodamine, and combinations of microparticles/nanoparticles (NPs) using hollow glass MNs. For this analysis, hollow MNs were made from a micropipette tube with borosilicate cylindrical glass. These devices were produced using various materials such as silicone, rubber, glass, polymers, metals, and ceramics depicted in Table 2 [35]. Hollow MNs were commonly used to deliver insulin, to inject vaccines, protein antigen, nucleic acid, huge molecular weighted substances, and other therapies such as pilocarpine. Among them, vaccination is the most popular application of hollow MNs [36].

**Hydrogel-forming MNs**

Traditional soluble MN arrays or biodegradable MN arrays are furnished from a kind of dissolving/degradable polymers. These MN array consisting of drug or therapeutics dissolved or degraded into simulated fluid held with dermal microcirculation by crossing the barrier of SC via self-made microchannels, which allows the release of drug as per compendial requirements. However, they are only applicable to the drug with high potency which is delivered in low doses [32, 34]. The most recent addition to MN technology is hydrogel-forming MN arrays, which are fabricated from polymeric materials that have been cross-linked. The MN arrays pierce the SC and draw up interstitial fluids, leading to swelling of the polymeric matrix. Thus, the therapeutic agents enter to the dermal tissue by molecular diffusion through this swollen polymeric matrix. Hydrogel-forming MN arrays contain no active agent and, as such, instead, the active pharmaceutical ingredient can be loaded into an associated reservoir, viz., a polymeric film, directly compressed tablet/lyophilized reservoir due to which high amount of drug penetrates through the skin [37]. The employment of MN arrays recommended several improvements for estakamine (ESK) delivery that could be useful in TDDS. The proposed MNs transdermal delivery technology covers a narrative approach for facilitating the continuous delivery of ESK (with no pain) [38]. Surprisingly, notwithstanding the emergence of biotherapeutics and the merits furnished by hydrogel MNs, there has been very little research carried out to assess the capabilities of this delivery system to enhance the delivery of such molecules [37, 38].

**Other forms of MNs**

Fabricating the hydrogel-forming MNs is eye-catching to deliver the therapeutic as being more biocompatible with controllable degradation property. In addition, a smart or bio-responsive hydrogel can be intended to counter external environmental change. Bio-responsive MNs can be activated in reaction to biochemical stimuli like pH, glucose, reactive oxygen species, and enzymes, to deliver protein therapies. Since various kinds of physiological circumstances, including differences in the MN matrix or incorporated carriers, may undergo dissociation or deterioration, it provides opportunities for precise on-demand payload release [39]. Nowadays, another type of MNs namely porous MNs is also high in demand. MN array receives gains with less prominence due to its complex, time-consuming, high-cost fabrication, and easy fracture in comparison with solid and hollow MNs [40]. Silicon, polymer, ceramic, and metal (Table 2) can be employed to fabricate porous MN array. Li et al. developed a porous polymeric MN array via photopolymerization of an acrylate monomer in the existence of a pyrogen within a mold for quick fluid convey. Yan et al. fabricated Ti porous MNs by an integrated method of wire-electrode cutting and wet etching from a porous Ti wafer for the insulin injection. This production method is expensive and not suitable for the mass production of porous MN array [40].

**Fabrication techniques of MNs**

A range of methods was explored to prepare unique MNs. In this section, we address the list of techniques to the specific variety of MNs. In this line, the selection of fabrication methods for MNs solely depends on the kind of MNs, the geometry of MNs, and the sort of material utilized. The various techniques applied for different types of MNs have been described below in Table 2.
Characteristics of MNs
In the precision of MNs, versatile pharmaceutical, cosmetics, and medical applications have drawn the attention from the last decade. In comparison to the other conventional drug delivery methods, MNs are at the forefront. Furthermore, the MNs have drawn more attention in pre-clinical and clinical trials for a safe and efficient product. Besides this, it shows significant growth due to the notable outcomes of the clinical trials. The MNs as an adaptable and efficient promising carrier for pharmaceutical applications have been widely reported. It may due to its versatile and tunable characteristics. In this shade of light, we have enlisted the characteristics of MNs and their specific required description [1–7] into Table 3.

Characterization of MNs
The active pharmaceutical ingredient is loaded on the MN surface or inside the MNs. The various drug-containing formulation can be used for the loading of drugs which includes encapsulation form (example: liposomes, nanoliposomes, and NPs) and drug suspension or dispersion [41]. The active agent can use as a patch or coat into a polymeric solution. The characterization includes the size of particles, polydispersity index, zeta potential, and viscosity determination and that can be used for loaded drugs, which solely depend on the formulation employed in the invention of drug-loaded MNs [42]. The adhesion testing and permeation study were carried out for a patch-based approach that was normally used after pretreatment. The percent content, in vitro release evaluation has been performed for nearly many MNs. With nanocarriers, vesicle size, and internal structure analysis, crystallinity can be investigated. Moreover, the drug-containing dispersion can be tested for stability studies. The designed MNs also evaluated in biocompatibility studies. Besides the abovementioned characterization, MNs can also check at a different simulated condition such as pH, temperature, and in vivo physiological conditions [12, 43, 44].

Dimensions of MNs
It includes needle geometry, mainly for MN tip radius, height, length evaluation, etc. as depicted in Fig. 2. The various (optical or electrical) methods or techniques have been explored for dimensional evaluation of MNs which includes scanning electron microscopy and confocal laser microscopy [12]. This technique can provide the geometry of the 3-dimensional needle, which is more beneficial to the quality control purpose. Scanning electron microscopy provides detailed information about the surface topography of MNs, and a confocal layer microscope can be utilized for high-resolution images of MNs [45, 46].

Mechanical properties of MNs
As per the requirement of MN criteria, MNs should be enough sharp, slender, and strong, which can provide sufficient penetration and can avoid the MNs breaking while driving them inside the selected part of the body [12, 47]. The mechanical properties include insertion force, insertion depth, and failure force which are investigated using unorthodox methods such as dye marking, force-displacement test, electrical measurements, histological cryosectioning, staining, confocal microscopy, and optical tomography [48, 49]. The ratio of insertion forces to the failure forces is normally called a safety factor and it should be high as possible. Normally, the MN integrity and insertion force depend on the forces used during application. It is the most prominent fact for the synthesis of proficient and harmless design of MNs [12, 48].

In vitro testing of MNs
The in vitro testing is conditioned to hit upon the permeation or active (drug) release from MNs into the selected dissolution media [47]. In vitro study of smart MNs is generally performed using the diffusion cell apparatus. The pig ear skin is preferred for evaluation of the permeation of active agent [12]. Besides this, the cumulative permeation profile is tested for both cases which include MN treated skin and untreated skin penetration and this compared permeation profile can be helpful for the progress of efficient MNs [50].

In vivo testing of MNs
In vivo testing of MNs was performed for analysis of key objectives such as biosafety (safety and toxicity) and

| Table 3 Characteristics of MNs |
|--------------------------------|
| **Sr. No.** | **Property of MNs** | **Description** |
| 1. | Ruggedness | Should be able to resist the insertion force without being featured. |
| 2. | Penetration | Must be penetrated the drug at the required depth of tissue. |
| 3. | Dimensions | Length: > 100-900 microns; Base width: 50-300 microns; Tip diameter: 1-50 microns |
| 4. | Margin of safety | The force required for piercing the SC |
| 5. | Effect of the MN length on pain | As the length of the needle increases from (i.e., 500–1500 μm), the pain increases. Also, an increase in the digit of MNs from 5 to 50 resulted in the increases in the pain. |
| 6. | Transepidermal water loss | Intact animal skin, sing diffusion cell as well as probes that evaluate transepidermal water loss before and after MN application |
| 7. | Biological safety test | Extract chemicals from MNs by immersing them in physiological saline and apply them on intact human skin. |
in vivo pharmacokinetic and pharmacodynamic evaluation of the active pharmaceutical ingredient. Here, the hairless animal (for example mice/mouse, rabbits, guinea pigs, and monkeys) can be applied for the in vivo testing study [47]. In addition, we can evaluate the various parameters such as transepidermal water loss (TEWL), bioavailability, skin irritation, or inflammation. TEWL testing was performed before and after microneedling using the Delfin vapometer [50].

**Drug delivery methods**

A plentiful literature survey reported the delivery of active agent using MNs by the various method for the targeted/local site or regiospecific and systemic delivery [51]. Out of numerous sites, the delivery of active agent into the epidermis layer of skin and ophthalmic route, nail route, etc. has gained additional interest [52, 53]. For delivery of active agent, various methods have been reported which include direct transport pathway, wherein small holes are created on the application site using MNs, and then the drug-containing patch was placed in those holes. Another drug delivery approach is considered, viz., coating of MN surface by drug solution. Herein, the drug-loaded MNs are scrapped on the application site. Drug-loaded biodegradable MNs have been extensively applied for active delivery in the pharmaceutical field [12, 51]. In transdermal drug/active delivery via MNs, the unique approaches can be used to deliver the active agent into the epidermis layer. One approach is to fill the drug solution into the hollow space of the synthesized hollow MNs. The next approach includes the incorporation of active agent into biodegradable polymers and further synthesized MNs using polymer and active mixtures. The next approach involves the dipping of the tip of MNs into the prepared active/drug solution and scrapes the MNs on the local area of skin, where drug/active agent is left behind into the developed abrasions by needles [12, 14, 54]. Besides this, the surface of smart MNs was coated using a drug solution (coating solution); herein, the coated MNs are inserted into the selected local area where the drug is dissolved from the surface-coating layer on the needle. Another approach is to poke the selected area of the site with MNs to create the holes, and after successively creating a hole, the drug-loaded patch is applied over the holes, wherein the holes provide the direct path to the drug to deliver across the skin. Besides this, the electric field applied for an excellent outcome [1, 12, 47]. Many strategies have been explored to deliver the active agent to the ocular site and MNs (hollow, soluble, and coated) are one of them [53]. With this fact, majorly the ocular delivery of drugs has been reported using drug-loaded biodegradable (dissolvable) MNs, wherein the drug-containing hydrogel was prepared using suitable polymers and molded into the dissolvable MNs [55]. Meanwhile, the drug molecules were delivered by coating the drug on
the surface of stainless steel MNs and MNs were delivered into the frontal segment of the eye [53]. Another study reported the delivery of the medicine by hollow glass MNs in the form of microparticles/NP formulations [35, 56]. Chiu et al. have accomplished drug delivery through the nail. In this study, it delivered the active agent-loaded NPs via a nail. The NP formulation post-application has been performed on an MN-prorated nail [57]. Aksit and team reported the ultra-sharp full metallic MN-based active delivery tool for the inner ear. The design of MNs was based on gold-coated metallic MNs and can be potentially used for the release of the drug round window membrane with different drug delivery approaches [58].

Pharmaceutical and biomedical applications of MNs
Several pieces of research have been done on the utilization of MNs in different pharmaceutical and biomedical applications. MNs have been shown to have an outstanding drug release as well as have been used for several biomedical applications. MN-based platforms possess excellent drug/protein/peptide loading and targeted/controlled/sustained release ability as well as many additional applications that can be explored to develop the versatile platform for pharmaceutical and biomedical applications. Apart from transdermal drug/protein delivery, these MNs have been reported to be an excellent carrier for an alternative strategy for drug delivery through nail, nasal, ocular, and ear. The various pharmaceutical and biomedical applications of MNs have been discussed in detail to get an insight into the potential of these MNs in several safe and effective human applications (Fig. 3).

Applicability of MNs through transdermal route
Owing to the drawbacks of the oral and conventional route of administration the transdermal route has been widely accepted, due to imperative characteristics that help to reach required plasma concentration at the target site for a prolonged period [59]. Thus, MNs are considered as a more promising tool for TDDS as microchannels created by them allow the easy and painless delivery of therapeutics as compared to that of hypodermic needles [60]. For enhancing the therapeutic

![Fig. 3 Pharmaceutical and biomedical applications of MNs.](a) MNs for drug delivery to the brain. (b) MNs as a sensor. (c) Applicability of MNs through transdermal route. (d) MN drug delivery to nails. (e) MN drug delivery to the ear. (f) MNs for ocular delivery. (g) MNs for vaccine delivery.
efficacy of therapeutics by transdermal delivery, various kinds of MN formulations are used [61]. Wu et al. fabricated sumatriptan succinate (SS)-loaded MN arrays from sodium hyaluronate to enhance their therapeutic efficacy for transdermal delivery. The in vitro experiment demonstrated came with finding that the microchannels created by MNs immediately healed the skin damage and it was reversible. The study also evinced that the desired plasma concentration of drug was obtained by delivery through SS-MNs in rats with equivalent absorption to that observed after subcutaneous injection with high bioavailability (90%), which is greater in comparison with oral administration [62]. The literature survey evinced that the partial studies have been performed for the delivery of several therapeutics like a poorly soluble drug, antibacterial drug, and antiretroviral drug-using liposomes, ethosomes, cubosomes, and microemulsion. The poor stability, high cost, and complex technique limit the application of these nano-vesicular systems on a large scale, while microemulsion applications are not considered as a suitable approach for the long-term delivery of therapeutics. Therefore, an original approach in which drug-loaded NPs were accomplished with MN insertion was utilized for the delivery of drugs especially with small molecular weight and drugs having short half-life to enhance the stability of formulation [63]. Ramadan et al. developed polymeric lamivudine (LAM)-loaded NPs for transdermal delivery via passive diffusion and MN-mediated transport then further investigated for long-term stability and penetration enhancement. The studies revealed that this delivery could be enhanced notably by MN pretreatment of skin with long-term stability [64].

The plentiful literature revealed that the MNs used for transdermal delivery have many advantages, even though these MN-based drug delivery is a passive manner regardless of the changing physiological circumstances of patients. It is often difficult to completely avoid the toxicity caused by overdose or the inefficacy attributable to underdosing [65]. Thus, to overcome this mentioned limitation, transdermal delivery is decorated with the advanced bio-responsive method which is specifically used to treat the different kinds of diseases like diabetes and cancer. Diabetes mellitus is a challenging global disease around the world. The disease is caused by increasing blood sugar level either due to low-level secretion of insulin or less cellular uptake of secreted insulin within the body. Thus, various approaches have been explored for daily insulin administration, e.g., oral, nasal, pulmonary, and transdermal [66]. Literature survey unveiled that insulin delivered through the skin does not suffer from a scarcity of chemical and enzymatic degradation concerns. Furthermore, its convenient nature may considerably increase patient adherence [67]. Currently, subcutaneous self-injection is considered a widespread method for insulin administration. Nevertheless, this process is painful and inconvenient, reduces patient compliance, and also leads to microbial contamination, local tissue necrosis, and nerve damage [68]. Hence to overcome aforesaid limitation, an artificial pancreas-like, closed-loop, glucose-responsive insulin transport system that can “secrete” insulin in response against elevated blood glucose would provide a desirable way of regulating glycaemia with minimal patient effort and potential improvements in glycemia and quality of life [69]. However, several challenges are related to such unique devices for example guaranteeing precise signal feedback and avoiding biofouling [70]. Yu et al. reported a glucose-responsive insulin delivery device by using a painless MN patch coined as a “smart insulin patch” that contains glucose-responsive insulin and glucose oxidase (GOx)-loaded vesicles. This smart and new insulin MN patch successfully regulated blood glucose of chemically induced diabetes type 1 in the mouse model. The sooner responsiveness of this method holds great promise in avoiding hyperglycemia and hypoglycemia if translated for human therapy [71]. Chen et al. investigated a smart MN based on semi-interpenetrating network (semi-IPN) hydrogel that was prepared using SF and phenylboronic acid/acrylamide for exceptional glucose-responsive insulin delivery. The hybrid MNs originally released insulin well similar to the glucose alteration pattern and suggesting the possibility for sustained delivery [39]. In 2018, Liu et al. prepared MN-based near-infrared (NIR) responsive photothermal therapy (PTT) for diabetic care as an attractive alternative to combine with chemotherapy and it could serve as a promising platform for delivering other therapeutic drugs via transdermal delivery [72]. Yu et al. have developed the MNs of alginate and hyaluronate for transdermal delivery of insulin. In brief, MN (650 μm) patches are made with alginate and hyaluronate loaded with insulin. It showed admirable pharmacologic availability (90.5%) and relative bioavailability (92.9%) of insulin from MNs in mice [73]. Kolli et al. divulged the upshot of iontophoresis and MNs for TDDS of methotrexate (MTX). The synergistic effect was found due to iontophoresis and MNs. It has been showing a 25-fold enhancement of delivery in vivo in combination (MN-iontophoresis), compared to each one alone [31]. Gomaa et al. reported the laser-engineered dissolving MNs to nadroparin calcium to the transdermal delivery. The fabrication of laser-engineered dissolving MN arrays was fabricated by poly(methylvinyl-lether-co-maleic anhydride) with nadroparin calcium. The MNs offer immense potential as a relatively low-cost functional delivery system [74]. In 2008, Wermeling et al. have claimed for TDDS of naltrexone using MNs to the skin in medication to humans. Briefly, a clinical
study confirmed the MNs for enhanced naltrexone delivery in a transdermal patch [75].

For TDDS of functional therapeutics, MNs have been extensively used in a noninvasive manner. However, launching an easy and widespread way to assure balanced filling of a large number of drugs is still imperative especially for nucleic acid-based drug delivery. To discourse the issue, universally applicable ribonucleic acid (RNA)-based transdermal delivery was endorsed to manufacture purpose-oriented MNs [76]. Although the hypodermic needles used efficiently deliver siRNA via SC, the main issue is that this method is painful. Thus, MNs may signify a superior way to distribute siRNAs across the SC [77]. Currently, methods like cavitational ultrasound, electroporation, iontophoresis, or intradermal injection have been used to overcome the barriers using cell-penetrating peptides [78]. However, the first three methods are complicated, time-consuming, expensive, and not so “patient-friendly.” Thus, overcoming the aforesaid limitation delivery of siRNA into the skin by MN devices was investigated [78]. Dang et al. first time evaluated silicon solid MN array for cholesterol delivery with advanced housekeeping gene (Gapdh) siRNA to the skin (in vivo) (Fig. 4). The study evinced MN use to deliver the siRNA, which should generate little or no pain. Thus, the application of MN array could effectively transport the SC, deposit siRNA into the epidermis, and silence the Gapdh gene [80]. Wang and colleagues developed NP-powered MN patches of siRNA that contain a disolvable HA. The study performed revealed that once a transdermal patch was inserted into the skin, the HA matrix dissolves, and mSiO2-coated upconversion NPs (UCNPs@mSiO2) diffuse in the skin tissue before entering the cells for delivering the loaded genes. Thus, as a proof of concept, this system is used to deliver the molecular beacons (MBs) and siRNA comprising targeting transforming growth factor-β type-I receptor (TGFβ) matrix and UCNPs@mSiO2 potentially used for scar treatment [79].

In the last years, protein and protein-peptide-based therapeutics gain vital importance for the development of the new drug; however, this process suffers from a lot of difficulties and obstacles as peptides face hurdles like instability under high temperature, light, and high/low pHs, and digestion by gastrointestinal enzymes during oral delivery [81]. MNs hold the potential to avoid oral uptakes, considered an effective tool for protein and peptide. Coating the needles with protein-based therapeutics is the simplest method for the invention of the same. However, optimization and adjusting by suitable excipients is a prominent requirement of coating formulations to achieve a uniform and sufficient coating [28]. Preloading drugs into the needles during the fabrication is an alternative way [82]. Liu et al. reported peptide delivery with poly(ethylene glycol) diacrylate (PEGDA) MNs through swelling effect. Herein, they introduced the loading of PEGDA-MNs with peptides. The peptide-loaded MNs were successfully applied to a keloid scar model, which showed inhibition expression of collagen I (a predominant marker of a keloid scar), therefore showing its potential therapeutic effects [83]. Chen et al. investigated MNs for a smart and new exendin-4 (Ex4) delivery along with dual mineralized particles that separately contain active agents namely Ex4 and GOx. The study evinced that the incorporation of mineralized particles can improve the mechanical strength of alginate-MNs via cross-linking to make easy skin penetration [84]. Zhang and co-authors reported the hydrophilic peptides in vitro delivery through transdermal MN array pretreatment. In this way, it improved genetic immunization by way of micromechanical disruption of the skin [85].

Over the decades, hypodermic needles were conventionally used for vaccination due to their rapid and direct delivery of the vaccine. Despite the familiarity, universal use, and proven efficacy of the hypodermic needle accompanying unintentional needle stick injury, the spread of blood-borne infections as well as phobias, pain, and significant anxiety is still present [86]. Besides, unless an individual gained specialized training to become an expert in injection technique and needle disposal, they are not easy to use through self-administration. To overcome these limitations, vaccination through the oral route is considered an acceptable alternative. However, this mode of immunization is less effective, as vaccine antigens undergo gastrointestinal digestion before the induction of an adequate immune response [87]. Vaccination through a diffusion-based transdermal route has also been investigated. However, it allows the prevention of vaccines to pass through different skin layers due to the outer SC layer. Charles Mantoux (French physician) investigated (1910) the first tuberculin intradermal injection as a diagnostic purpose for tuberculosis disease [88]. However, vaccination through intradermal injection is considered more challenging and required trained or expertise operators for their use and been associated with adverse events such as pain, inflammatory changes, and the development of abscesses. Thus, taking into consideration the limitations of parenteral, oral, and traditional transdermal, and intradermal vaccination, the concept of the MNs emerged as a solution to these issues [89]. Shin et al. developed cyclic di guanylate monophosphate (C-di-GMP) with the influenza vaccine, which showed improved and shifted immune reactions in MN vaccination in the skin. They also demonstrated the applicability, immunogenicity, and protective efficacy of c-di-GMP. Thus, this study proved that GMP is an efficient adjuvant for
influenza MN vaccination [90]. In 2018, Duong et al. demonstrated that the MNs along with charge reversal pH-sensitive copolymers perk up antigen-presenting cells-homing DNA vaccine delivery and immune responses. In vivo demonstrated DNA delivery of a vaccine encoding Aβ fusion protein to antigen present cells induced a robust antigen-specific immune response [91]. Zhu et al. 2017, reported the boosting skin vaccination is accomplished by dissolving MN patch encapsulating the extracellular domain (M2e). The results of these studies evidenced receiving recombinant flagellin (tFliC). MNs (4M2e-tFliC) of carboxymethyl cellulose (CMC) boost immunization of the array which has 100 MNs (250 and 650 μm, diameter and length, respectively [92]. In 2015, Hirobe et al. reported the clinical study of transcutaneous influenza vaccination using a dissolving MN patch. In that, the MNs of HA with hemagglutinins of influenza for vaccination induce a strong immune response [93]. Edens et al. showed the MN patch containing the measles vaccine is immunogenic in non-human primates. Herein, vaccination with MNs was loaded with an antibody of measles that was immunogenic in non-human primates [94]. Hiraishi et al. divulged the Bacillus Calmette-Guérin (BCG) vaccination using a MN patch. Herein, the vaccination patch was coupled with MNs, preloaded with BCG for the treatment and prevention of tuberculosis [95]. Coated MNs for transcutaneous delivery of live virus vaccines were studied by Vrdoljak et al. Silicon MNs were coated using a spray containing adenovirus antigen and virus Ankara that stimulated CD8 cells of the immune system [96].

Sustained and controlled delivery of drugs can be achieved by encapsulating drugs in biodegradable or synthetic polymer, and it increasingly becomes the trend of MN technology. To achieve release of incorporated therapeutics as per compendial requirements, the matrix of biodegradable MNs often chosen is made from polymers like chitosan (CS), PLA, polyglycolic acid, or poly(lactide-co-glycolide) [97]. Gao et al. reported novel polydimethyl siloxane (PDMS)-based negative mold with cavities packed with SF scaffold for rapid fabrication of polymeric MNs, which comprise primarily the
composition of PEGDA and sucrose as the needle matrix. Briefly, rhodamine (RhB), doxorubicin (DOX), and indocyanine green (ICG) were selected as a model drug. The prepared PEGDA/sucrose MNs were evaluated for effective transdermal delivery and controllable release of therapeutic molecules by regulating the sucrose content. The experimental evidence has proven that the presented method provides a simple strategy for quick fabrication of polymeric MNs toward transdermal and controlled drug delivery applications [98]. Additionally, He et al. reported intradermal implantable polyactic glycolic acid (PLGA) MNs for etonogestrel (ENG). They designed the implantable MN array via a controllable casting-mold method that allows ENG sustained intradermal delivery [99]. A literature survey revealed that the MN system is used for transmission of drugs, proteins, genes, RNA, vaccines, and other biological macromolecules, and they are highly efficient, convenient, and harmless [100].

Recently, the MN-based TDDS has provided a broad application prospect for skin cancer [101]. Tham et al. demonstrated a mesoporous nano vehicle with dual loading of photosensitizers and clinically relevant drugs to facilitate their penetration into the deep skin tissue. The developed mesopores of the NPs were further loaded with dabrafenib and trametinib (small-molecule inhibitors). The experimental data obtained from the present study evinced that the prepared nano vehicle could significantly inhibit the proliferation of tumor cells in a 3D spheroid model in vitro. Porcine skin fluorescence imaging demonstrated that MNs could facilitate the penetration of nano vehicles across the epidermis layer of skin to reach deep-seated melanoma sites. Tumor regression studies in a xeno-grafted melanoma mouse model confirmed superior therapeutic efficacy of the nano vehicles through combinational PDT and targeted therapy [102]. Hao et al. reported a NIR light-responsive 5-fluorouracil (5-Fu) and ICG-based monomethoxy-poly (ethylene glycol) polycaprolactone (MPEG-PCL-NPs) (i.e., 5-Fu-ICG-MPEG-PCL). Then 5-Fu-ICG-MPEG-PCL was integrated with an HA-MNs to get 5-Fu-ICG-MPEG-PCL-loaded HA-MNs for treating skin cancers, including human epidermoid cancer and melanoma. They investigated that 5-Fu-ICG-MPEG-PCL composite could be delivered through the smart and dissolvable MNs throughout the skin. The release performance of the active ingredient in the developed NPs could be controlled by NIR light for accomplishing a single-dose treatment of skin cancer, progress in a cure rate of cancer, and offering a new proposal and prospect for the clinical management of skin cancer [103].

Transdermal administration is a favored route of administration due to its advantages mentioned earlier [104]. SC barrier noticeably limits the larger molecules (proteins and therapeutic genes) transdermal delivery. To enhance the SC permeability, several techniques, viz., ultrasound, electroporation, iontophoresis, microdermabrasion, and thermal ablation, have been developed. However, the majority of these techniques failed to owe to the possibility of skin irritation that is intolerable in a clinical setting [105]. To overcome the challenges subjected, previously mentioned MNs arrays gain significant interest in both TDDS and transdermal diagnostics. Vora et al. reported pullulan (PL)-based dissolving MN arrays for enhanced TDDS of small and large biomolecules. They reported for the first time, the preparation and characterization of a dissolving MN system from the carbohydrate biopolymer, PL. Model molecules and protein/peptide were loaded into PL-dissolving-MNs and characterized. The stability of fluorescein isothiocyanate-labeled bovine serum albumin (FITC-BSA) and insulin (model biomolecules) following dissolving MN manufacture was assessed via circular dichroism (CD). This study showed that PL-dissolving-MNs show to be a potential tool for efficient transdermal delivery of small as well as large molecules [106].

**MNs for ocular delivery**

Several peoples from the universe have been suffering from the loss of vision due to age-related ocular diseases [107]. Auspiciously, great expansions of the latest tactics were accepted for ocular drug delivery, including biologics [108]. Up to date, various kinds of approaches have been established, such as systemic, topical, periorcular (or transcleral), and intravitreal routes that have been adopted. Ocular delivery of drug topical (e.g., through eye drops) and systemic (e.g., oral tablets) routes could not achieve the required therapeutic concentration of drug due to multiple ocular barriers, a high amount of dose is needed to administer leading to scarcity requiring administration of unnecessarily drug-related toxicity and producing low treatment efficacy [109]. To overcome the ocular barrier function and to enhance the localization of the drug close to the target tissues, intravitreal, intracorneal, and intrascleral injections were investigated [110]. However, this method does not gain the required bioavailability of therapeutics due to delay in the diffusion in the ophthalmic cavity. Besides, the use of traditional injection frequently over a prolonged period can put forth several complications and poor patient compliance indicates the need for less-invasive technologies that will enhance patient compliance and allow localized, precise drug delivery to the eye [111]. Thus, considering the facts of care, the application of minimally invasive MNs for ocular active delivery is a relatively new concept. Singh et al. developed rapidly dissolving polymeric MNs for minimally invasive intraocular drug delivery. MNs were fabricated using PVP...
polymer of various molecular weights namely fluorescein, sodium, and fluorescein isothiocyanate–dextrans (MW of 70 kDa and 150 kDa). These MNs showed a quick dissolution rate, and in vitro testing of MNs showed noteworthy improvement of macromolecule permeation. Furthermore, the confocal images demonstrated that the macromolecules created depots within the tissues that guide to sustained permeation rate [55]. Than et al. reported self-implantable double-layered microdrug reservoirs for efficient and controlled ocular drug delivery. These MNs can be implanted as micro reservoirs for controlled drug delivery with enhanced therapeutic efficacy. The study evinced the anti-angiogenic monoclonal antibody (DC101) delivery via such eye patch generates a ~ 90% reduction of the neovascular area with synergistic therapeutic outcome [112]. In 2016, Khandan and co-authors have been fenestrated vascular area with synergistic therapeutic outcome [112].

Moreover, the restriction imposed on the infiltration of the drug molecules’ brain barrier allows the entry of only a small molecule having a molecular weight (especially less than 400 Da) or for the lipid-soluble drug [116]. Thus, the scenario created the necessity to develop techniques for crossing the BBB. Several advances have been made to explore the properties of BBB for the effective treatment of brain diseases, like the delivery of drug-using nanocarrier or NPs as noninvasive techniques to enhance brain drug uptake. In the past few decades, syringe injection has been used for the delivery of drugs to the brain. But these approaches are entitled with smoke limitations like serious issues regarding the probability of infection and inflammation at the site of injection together with the occurrence of pain and anxiety, which has drawn attention toward some alternative mode of drug delivery and incompetency toward the patient [117]. Kearney et al. investigated the donepezil hydrochloride (Alzheimer’s drug)-loaded MN patch. In brief, MNs are made up of PVP or poly(methyl vinyl ether co-maleic anhydride/acid) polymers. Furthermore, in vitro permeation of donepezil hydrochloride across neonatal porcine skin from the patches was investigated, with 854.71 lg ± 122.71 lg donepezil hydrochloride delivered after 24 h, using patch formulation, signifying the accomplishment of this delivery proposal for donepezil hydrochloride to take care of brain disorder [118]. Another study reported that the silicon-based MNs for drug delivery in the deep brain. In this regard, MN array fabricated on silicon intended for infusion of activity in the brain to recognize connections as well as neuronal activities [119].

MNs as a sensor

Current therapeutic drug monitoring approaches rely on discrete blood measurements, being invasive, and limit the temporal resolution of the information obtained. Moreover, they are labor-intensive and not practical in a clinical environment. There is an immediate necessity for a minimally invasive approach for therapeutic drug monitoring [120]. There is a quickly rising interest in the use of transdermal MN-based electrodes in favor of molecular-based biosensing and drug delivery [121]. Examples of MN-based biosensors have been revealed for continuous screening of metabolic markers such as glucose and lactate as well as for the drug theophylline and organophosphate nerve agents [122]. These sensors only penetrate the SC and therefore do not cause pain or draw blood, as they do not reach the nerve endings as well as capillary blood vessels in the dermis. As a result, such sensors provide a minimally invasive means of sampling the interstitial fluids for drug or metabolite monitoring [123]. Gowers et al. developed a minimally invasive MN-based sensor for constant monitoring of β-lactam antibiotic concentrations in vivo. The biosensor is coated with a pH-sensitive iridium oxide layer, which detects changes in local pH because of β-lactam hydrolysis by β-lactamase immobilized on the electrode surface. These biosensors were found to be stable up to 2 weeks at ~ 20°C and to withstand sterilization. Sensitivity was retained after application for 6 h in vivo. These preliminary results showed the potential of this MN-based biosensor to provide a minimally invasive means to measure real-time β-lactam concentrations in vivo, representing an important first step toward a closed-loop therapeutic drug monitoring system [124]. Wang et al. divulged the MN electrode array on a flexible substrate for long-term EEG monitoring. The utilization of MNs (silicone height of 190 μm) has been used that could be capable of electrocardiograph (EEG) monitoring. MNs can be adapted to the skin providing robust contact with skin [125]. The MN array electrodes for continuous glucose monitoring sensors are reported by Sharma et al. The use of MNs eliminates this interference to detect glucose in comparison with other devices’ glucose [126]. The nitrogen-incorporated ultra
nanocrystalline diamond MN arrays intended for electrochemical biosensing are demonstrated by Skoog et al. The nitrogen-incorporated ultra-crystalline diamond-coated titanium alloy MN arrays can sense electrochemical signals (dopamine and uric acid) [127]. The MN biosensor is meant for real-time electrical recognition. Owing to this in situ cancer, Keum et al. have accomplished biosensing using MN array. This system can use a new platform for the detection of cancer [128].

**MNs for cosmetics applications**

Considering the capability of the MNs to act more efficiently by application to the skin surface, they are widely considered to treat different skin disorders like seborrheic keratosis, scars, striae, anti-aging, wrinkles, or depigmentation. “Dermaroller” is the best example of MN-based instrument. Tranexamic acid (TXA) is not only used for the treatment of post-acne but also in anti-aging therapy with no sequelae. Machekposhti et al. generated MNs of PVP and methacrylic acid loaded with TXA. These MNs had adequate properties to be used to the skin and have a release in the TXA with the possibility of being an alternative for the management of melasma [129]. Another case of pigmentation is seborrheic keratosis or senile lentigo normally seen in people > 50 years of age; the treatment is with all-trans retinoic acid (ATRA). Hibrobe et al. developed an ATRA-loaded microneedle patch (ATRA-MNs) to enhance the permeability of ATRA and microneedle patch loaded with retinoic acid. ATRA-MNs were applied on the lesion site of each subject once per week for up to 4 weeks (Fig. 5). This study has proven that MNs are promising as a safe and effective therapy for seborrheic keratosis and senile lentigo [130].

In this study, skin needling is a treatment for acne scarring and management of hypertrophic scar after burn wounds using MNs reported by Doddaballapur [131]. Seo et al. divulged the skin rejuvenation by MN

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*Fig. 5* The investigational skin of four subjects in which the SC is desquamated. ATRA-MNs applied to the lesion site of each subject for 6h once per week for 4 weeks. The investigational skin is observed every week. Each image shows the ICDRG score and the presence of desquamation (taken with permission from [130]. Copyright© 2016 Elsevier Inc.)
fractional RF and a human stem cell-conditioned medium. Fractional RF was used with MNs in the skin using stem cells for skin rejuvenation. The therapy with percutaneous collagen offers a modality with which to rejuvenate [132]. Triamcinolone acetonide-loaded MNs for alopecia areata have been claimed by Chandrashekar et al. [133]. Application of corticosteroids using MNs resulted in promoting blood supply to hair follicles for the alopecia areata treatment [133, 134].

Miscellaneous application of MNs (delivery of the drug to ear, nails)
From its inception, drug/active delivery into the cochlea (a fluid-filled cavity within the temporal bone of the skull) is a long-standing issue and yet crucial to treat various hearing disorders, viz., sudden or progressive sensorineural hearing loss and tinnitus and vestibular disorders (Meniere’s disease). In this shade, it is well known that the inaccessibility as a fluid-filled cavity within the temporal bone of the skull is a major challenge to the researcher for the development of active delivery into the inner ear. Instead of this, the round window membrane (RWM) is the only active delivery portal from the middle ear to the inner ear that does not require perforation of bone. The plentiful literature revealed that MN fabrication enables the RWM to be perforated safely with polymeric MNs as a means to enhance the rate of drug delivery from the middle to the inner ear. Unfortunately, the polymeric materials are not admirable and biocompatible and lack the strength of other materials. In 2020, Aksit and co-authors have designed and developed the gold-coated metallic MNs that are appropriate for RWM perforation using two-photon template electrodeposition fabrication technology. It accomplished the negligible degree of trauma in a guinea pig RWM. In addition, MNs themselves remain undamaged during inducing a perforation. Therefore, these innovative MNs open the RWM for enhanced active delivery into the inner ear for therapy of a range of ear diseases and disorders [58]. The conventionally engaged topical nail drug delivery system has a certain major limitation. It includes evaporation of the volatile solvent and low diffusivity of active ingredient across the nail plate due to its compact keratinized structure. In this regard, there is an urgent necessity to develop an advanced approach for the management of several nail diseases, for example, nail psoriasis and onychomycosis. Chiu et al. divulged the polymeric NPs as a suitable drug reservoir for topical (sustained) drug delivery into MN-treated human nails. Herein, dorsal side microporation of hydrated human fingernail clippings (at least 8 mm in length) has been achieved using commercially available dermaroller (250 μm long titanium needles) via rolling it back and forth (5 times). The star-shaped PCL with 5,10, 15,20-tetrakis-(4-aminophenyl)porphyrin (TAPP) was synthesized using TAPP, stannous octoate (0.0025 mmol), and €-caprolactone. Besides this, Nile red (NR) (lipophilic fluorophore)-loaded PCL-NPs were prepared by the solvent displacement method. In vitro nail permeation NR has been performed using vertical Franz diffusion cells. The results offer clear confirmation that NPs can function as reservoirs for NR (lipophilic compounds) and sustain their local release for several days. Therefore, the MNs in nail drug delivery are paving the substitute for the management of major health issues in biomedical and pharmaceutical fields [57].

All drugs designed to be used in vivo should require excellent pharmacokinetic parameters, i.e., proper and good absorption, delivery to the specific site, access to the target site, should attempt required circulation time in blood, and half-life clearance [135]. The drug, which attains these properties, is considered to be practically safe for use. Pharmacological and toxicological characteristics in any pharmaceutical product must be identified. The in vivo kinetics, bio-distribution, and absorption relationship helps in designing the MNs in various applications [136]. Incorporating the drug or its particles into dissolving MNs can significantly enhance its dermato-kinetic profiles, compared to conventional dosage forms (Fig. 6a) [137].

The pharmacokinetics and bio-distribution rely on its physicochemical characteristics including length, shape, aggregation, surface modifications, chemical composition, and permeation which can be enhanced by developing the functionalized MNs [138]. For the drug to become effectively bio-available, the drug-loaded (functionalized) MNs or arrays should be capable of prominent absorption from the site of administration. Drugs absorbed from the site of absorption are carried forward to the specific site of action through the blood or lymphatic system.

In vivo and in vitro toxicity of MNs on an original model
The major concern with MN-based applications is skin irritation, skin allergy, and redness. If the skin pore does not close after the MN patch application, it can develop a skin infection,[12, 21]. Much research has been carried out to test the MNs in vivo and in vitro toxicity by using different animals (mice/rat) and cell lines to observe whether the MNs are associated with perceived undesirable human health effects [12, 96, 139]. Table 4 shows the current updates on the toxicity studies of MNs performed.

Recent MN patent as a drug delivery system
From the last decades, MNs are most widely studied as delivery carriers. In this light, the researcher pays much attention to explore and improve the MN material and
its properties. In this way, it can be efficiently utilized for effective drug delivery along with low toxicity. There are various patents related to MNs including fabrication methods and drug delivery. The innovative strategy for targeted/systemic delivery of active agent using MNs has resulted in the number of patents as summarized in Table 5.

Clinical trials on MNs
The MNs are potential targeted and systemic drug delivery systems. With this, we can load the numerous kinds of drugs in MNs to achieve efficient pharmaco-therapeutics. It provides plentiful merits such as biocompatible, less or nontoxic, controlled release, self and safe administration, and minimally invasive device for effective drug delivery [152, 153]. Owing to this, there is a recommendation to develop the MN-based advance dosage form. From the last decades, undoubtedly, continued growth has been found with new formulation and fabrication methodologies for MNs [152, 154]. And we witnessed that MNs have successfully applied for the administration of drugs, cosmetics, proteins, vaccines, and peptides [47]. Out of this, the various products have been successfully availed clinically [12]. Despite the huge milestone, safety, and efficacy of MNs, the formulation is a major concern that has been raised. For human use, the MNs should shift to clinical trial and it is the key demand of government bodies of the respective country involved in the pharmaceutical and biomedical market [155]. The product was based on MNs developed by various industries to treat various health issues which showed exceptional safety and efficacy in clinical trial phase III [47, 155]. Besides, they completed successfully the list of product clinical trials and many more in the process [47]. Table 6 shows the example of completed clinical trials up to 2020 as per the ClinicalTrials.gov (resource provided by the U.S. National Library of Medicine).
Table 4: In vivo and in vitro toxicity of MNs on a different model

| Sr. No. | Study Observation | Toxicity effect | Result/inference | Ref. |
|---------|------------------|-----------------|------------------|------|
| 1.      | The standard Draize skin irritation method was used to measure erythema and edema of the thiolated CS-MNs patch of tacrolimus. | After 1 h, the removal of thiolated CS-MNs loaded tacrolimus has increased erythema score. | No edema was exhibited | [140] |
| 2.      | A piece of rat dorsal skin was defrosted naturally, and then the curcumin micelle-loaded dissolvable composite MNs were inserted with the thumb using a force (5 N). Then MNs were removed after the insertion and the skin was exposed to trypan blue solution for 5 min. | The blue dot matrix was found on the surface of rat skin after being washed with a saline solution. | No any inflammation and irritation occurs | [141] |
| 3.      | The hair on the back of each rat was shaved, and the aconitine loaded diethyleneglycol monoethyl ether-mediated microemulsion assisted MNs was applied once daily for 7 consecutive days. | The cell morphology of each layer was found to be normal after the exhibition of the test. | No obvious irritant reaction and no inflammatory reaction were found. | [142] |
| 4.      | 5-Fu loaded monomethoxy(polyethylene glycol)-polycaprolactone NPs integrated HA dissolvable MNs was evaluated for in vitro cytotoxicity by human epidermoid cancer cell line-A431 and the human melanoma cell line-A375 through MTT assay. | It was demonstrated the cell inhibition ability almost similar to 5-Fu and showed a better inhibition at 48 h. | MNs have exhibited no obvious cytotoxicity without NIR laser. | [103] |
| 5.      | The gelatin methacryloyl and β-cyclodextrin (Gel-MA-β-CD) based MNs have penetrated the epidermal layer after 1 h of topical implantation. | No MN array-related damage or inflammation was found for up to 3 days. | No irritation and inflammation occur. | [143] |
| 6.      | In this study, two amifostine-armored MNs patches have been topically administered on the shaved dorsal skin (12 h). | No noticeable weight loss | No toxicity and inflammation in the major organs were exhibited | [139] |
| 7.      | Acute skin irritation of 3 min treatment by the MTX-HA-dissolvable (MTX-HA) MNs was performed by using the dorsal skin of mice. | No erythema and swelling | No obvious irritative reaction | [144] |
| 8.      | The cytotoxicity study of drug-free PEGDA/sucrose MNs was performed by human umbilical vein endothelial cells (HUEVCs) by MTT cell viability assay. | The cell viabilities were all above 90% at the 1:20, 2:20, and 3:20 mass ratio of (sucrose/PEGDA), which is significantly higher than the viability of those incubated with MNs made of pristine PEGDA or PEGDA plus fibrin scaffold. | No cytotoxic reaction occurs | [98] |
| 9.      | The study was carried out by applying MNs (without drug) followed by NIR light irradiation. | No noticeable tissue lesion took place in this study. | No cytotoxic reaction and irritation occur. | [72] |
| 10.     | The Ex4 tip-loaded MN arrays and subcutaneous injections were compared for their acute efficacy in type 2 diabetic GK/Scic rats. | The pores created by MNs were much greater (disappeared at 24 h after application) than the one pore created by subcutaneous injection (remained visible even at 72 h after). | No inflammation | [145] |
| 11.     | The in vitro EpiDerm™ skin | The skin irritation test showed that | No irritation occurs | [18] |
Table 4 In vivo and in vitro toxicity of MNs on a different model (Continued)

| Sr. No. | Study Observation | Toxicity effect | Result/inference | Ref. |
|---------|------------------|-----------------|------------------|------|
| 1.      | Irritation experi | The vismodegib s | No cytotoxicity | [19] |
| 2.      |         | olution was non- |                       |      |
| 3.      |       | irrant to the re |                       |      |
| 4.      |   |constructed human |                       |      |
| 5.      |     | epidermal model Epiderm. |                       |      |
| 6.      |   | It showed the better |                       |      |
| 7.      |     | biocompatibility of the dissolving MNs. |               |      |
| 8.      |   | MNs. |                       |      |
| 9.      |     | MNs showed in vivo and in vitro toxicity. |               |      |
| 10.     |   | It was observed that the dissolving MNs containing β-sodium Glycerol-phosphate and hydroxypropyl β-cyclodextrin induced slight mechanical damage. |                       | [136]|
| 11.     |     | The MNs can undergo hydrolysis to form a nontoxic by-product. |                       | [84] |
| 12.     |   | The viability of HUVECs incubated vehicle dissolving MNs was higher than 80%. |                       |      |
| 13.     |     | No cytotoxic reaction. |                       |      |
| 14.     |   | The skin irritation caused because of dissolving MNs has mild and transient. |                       | [20] |
| 15.     |     | The histopathological tissue section was exhibited. The mild inflammation in the cell infiltration is seen in the dermis. |                       |      |
| 16.     |   | The less invasiveness of the MNs patch to the skin suggested that the Ex4-MNs patch is a highly biocompatible treatment. |                       |      |
|         |     | The skin irritation of vismodegib solution. |                       |      |

**MN-approved products**

Despite the availability of plentiful fabrication strategies, the admirable scalability and reproducibility of the formulation is a major concern because of the non-availability of regulatory guidance on manufacturing requirements of MNs and subsequent validation of process to assure uniformity of quality product. And as a formulation scientist, these issues related to fabrication majorly remains unanswered. In recent times, numerous safety trials on admirable applications of MNs for drugs, cosmetics, proteins, peptides, and vaccines among small population groups provide the basis for successful commercialization of a range of MN-based products [156]. Out of them, many are successfully coming into the market and approved by the government for medical and cosmetic purposes [157]. Interestingly, MNs present significant merits over the conventionally applied formulation in terms of delivery of activities to the targeted site or systemic delivery. Owing to this, from the past decade, there has been high growth in scientific and industrial activity in this field [14]. It is groundbreaking that the derma roller was the first approved MN-based product [12]. In the present review, we have enlisted some approved products (Table 7) of many companies [12, 49, 156–158].

**Biosafety of MNs**

The system is based on MNs having plentiful pharmaceuticals along with biomedical applications. Owing to this, the optimization of MN formulation is gaining more importance for their successful utilization (Fig. 6b) [45]. It has been used to deliver the active agent into the selected side painlessly and safely [159]. Regardless of the benefits of MNs, the challenges about safety and biocompatibility are still acting as a barrier for development [12, 159]. As per literature, the drug-loaded MNs remain innocuous [12], but some of them are unsafe and may be dangerous to tissue and body part. The application of MNs has a chance to cause skin irritation, tissue necrosis, and redness of the skin which can convert into severe infection and damage the part of the body [12, 45]. Besides this, many reports claimed the considerable
safety of MN-based drug, protein, and peptide drug delivery via the original route such as a transdermal route [12]. Also, there are claims for MN toxicity depending on the kind of materials utilized [21], the drug delivery approach [77], and the shape or dimensions of MNs [142]. Besides, the insertion of MNs through the skin can produce inflammation because of the breakdown of cells and produces free radicals that cause skin damage [65, 129]. However, there are few biosafety conflicts that have not yet been settled. Some studies showed significant findings, which boost confidence regarding the utilization of MNs in pharmaceutical applications as well as and biomedical applications [12, 14, 144]. The toxicity of MN-based applications can reduce through the relevant use of the drug delivery approach, types of materials used, and release of drug from MNs. The toxicity of MNs can also be controlled through maintaining the bio-distribution and circulation time of drugs. The dose-dependent toxicity can be monitored by innovative and suitable material and types of MNs. Concisely, the dose can be customized, which resulted in the maximum benefits, and subsequently, toxicity can be avoided.

Expert opinion
As per the recent decade's research headway with rapid advancement in technology, the MNs are gaining significant attention from researchers. It is noteworthy that the MNs comprise various nontoxic materials and can extensively be applied for effective transdermal, ophthalmic, and nasal delivery. Based on a survey of the various databases, the future of the MNs seems perspicuous and it is worth informative that the number of scientific fraternities is actively working on MN advancement. Owing to this, with the upcoming challenges of MNs, the numbers of research teams and publication counts are rapidly rising in recent years. From its inception, the successive clinical application of the MNs paves the alternative pathways that show a positive impact on the clinical (pharmaceutical or biomedical or cosmeceutical) and untimely patient’s compliance. Besides, this major

| Sr. No. | Publication number | Conditions or diseases | Description/summary | Ref. |
|---------|--------------------|------------------------|---------------------|------|
| 1.      | 13/2019 20181104930 | Electrochemical biosensing in body fluid | In this invention, it has developed a modern method for MNs that prints assembled screens. Electrode fixes the biosensing electrode to print the screen that sensing of blood glucose, cholesterol HbA1C and like. | [22] |
| 2.      | 48/2018 201720147985 | Treatment of hyperkeratosis, injury, and pain in conditions like warts, corns, calluses, acne, psoriasis, keloids, microtrauma, eczema | The MNs patches based topical drug delivery system incorporated with keratolytic agents. The patch comprises micron-scale protrusions that penetrate via the SC and delivers the active pharmaceutical ingredient across the SC to improve the permeation of drugs. A keratolytic agent reduces the intercellular cohesiveness of the horny cells and thus enables speedy shedding of keratinized cells. | [23] |
| 3.      | 42/2018 201720172103027 | Management of anxiety | In this patent novel, the buspirone microemulsion method has developed using the phase titration method and tested for its efficiency in the skin. It enhances transdermal delivery. | [24] |
| 4.      | WO/2010/013601 | Enhancement of immunogenicity | It has enhanced immunogenicity using an MNs for the Japanese encephalitis virus antigen derived from kidney cells of monkey and concluded that antibody against a Japanese encephalitis virus antigen has efficiently enhanced. | [146] |
| 5.      | WO/2010/001671 | Enhancing the immunogenicity against influenza virus | Polyactic acid-coated MNs of an influenza vaccine that is the H1N1 strain, H1N2 and types B strain, and brought into direct skin contact that enhances immunogenicity against influenza virus. | [147] |
| 6.      | 20150290163 | To treat pimples, stains, or wrinkles | MNs contains a substrate, water-swelling polymer, and retinoc acid. It dissolves in an enormous amount of water. | [148] |
| 7.      | 20200170940 | Local anesthesia | The invention provides immediate acting local anesthetic MNs easily applied to the oral cavity or site, in which a needle part dissolves in a mucous membrane when applying to an oral mucous membrane or gums. | [149] |
| 8.      | 20170209553 | Botulinum toxin to treat diseases | To treat disease, disorder, or condition therapeutic amount of toxin was added to the MN array | [150] |
| 9.      | 20100030100 | Diagnosis of allergy | This is an invention of a diagnostic MN device for the detection of an allergy. It holds at least one allergen that enables to perform skin tests with an effortless process in the diagnosis of allergies. These MNs have been prepared using non-metallic synthetic or natural resin material. | [151] |
| Sr. No. | Study title | Intervention | Condition | Status | Year |
|--------|-------------|--------------|-----------|--------|------|
| 1.     | 2010/2011 trivalent influenza vaccination | - Biological: TIV 2010/2011 influenza vaccine<br>- Biological: INT | Influenza | Completed | 2011 |
| 2.     | A study to assess the safety and efficacy of an MNs device for local anesthesia | Device: MicronJet | Local anesthesia | Completed | 2013 |
| 3.     | Optimization of tuberculosis intradermal skin test | - Medical device: MNs BD 1.5 mm 30G<br>- Drug: Tubertest®: tuberculin (purified protein derivative)<br>- Device: medical device: lance 26G X 16 mm<br>- Drug: Tubertest® | Healthy volunteers | Completed | 2013 |
| 4.     | A pilot study to assess the safety, PK and PD of insulin injected via MicronJet or conventional needle | Device: MicronJet | Intradermal injections | Completed | 2013 |
| 5.     | A study to assess the safety and efficacy of an MNs device for local anesthesia | Device: MicronJet | Local anesthesia | Completed | 2013 |
| 6.     | Dose sparing intradermal S-OIV H1N1 influenza vaccination device | - Biological: S-OIV H1N1 vaccine | Influenza infection | Completed | 2013 |
| 7.     | Routes of immunization and flu immune responses | - Biological: INTANZA®<br>- Biological: Vaxigrip®<br>- Biological: INTANZA®<br>- Biological: Vaxigrip®<br>- Biological: INTANZA®<br>- Biological: Vaxigrip® | Influenza | Completed | 2013 |
| 8.     | A pilot study to evaluate the safety and immunogenicity of low dose flu vaccines | - Biological: Flu Vaccine (FLUARIX®) | Influenza | Completed | 2013 |
| 9.     | Insulin delivery using MNs in type 1 diabetes | Device: MNs<br>Device: Subcutaneous insulin catheter | Type 1 diabetes mellitus | Completed | 2014 |
| 10.    | Safety demonstration of MN insertion | Device: Gold- or silver-coated, or uncoated nickel MNs | Allergic reaction to nickel | Completed | 2016 |
| 11.    | The use of MNs in photodynamic therapy | Device: MNs<br>Drug: Aminolevulinic Acid Radiation: Blue light | Actinic keratosis | Completed | 2017 |
| 12.    | Site selection for intracutaneous saline delivery | - Device: Injection to deltoid<br>- Device: Injection to forearm<br>- Device: Injection to thigh | Intracutaneous drug delivery | Completed | 2017 |
| 13.    | Intracutaneous delivery of varied dose volumes of saline | Device: FLUGEN 101.2 device | Influenza | Completed | 2017 |
| 14.    | The use of MNs with topical botulinum toxin for the treatment of palmar hyperhidrosis | Device: MNs<br>Device: Sham MNs<br>Drug: Botulinum Toxin Type A<br>Other: Saline | Hyperhidrosis | Completed | 2017 |
| 15.    | Fractional MNs radiofrequency and I Botulinum Toxin A for primary axillary hyperhidrosis | Device: Fractional MNs<br>Radiofrequency | Primary axillary hyperhidrosis | Completed | 2017 |
| 16.    | Suprachoroidal injection of triamcinolone acetonide in subjects with macular edema following non-infectious uveitis | - Drug: 4 mg CLS-TA<br>- Drug: 0.8 mg CLS-TA | Uveitis, macular edema | Completed | 2017 |
| 17.    | Glucose measurement using MN patches | Device: MNs patch<br>Device: Intravenous (IV) catheter<br>Device: Lancet | Diabetes | Completed | 2018 |
| 18.    | Suprachoroidal injection of CLS-TA alone or with aflibercept in subjects with diabetic macular edema | - Drug: IVT Aflibercept<br>- Drug: SC CLS-TA | Diabetic macular edema | Completed | 2018 |
| 19.    | A split-mouth trial to compare MNs vs. standard needles in dental anesthetic delivery | Device: MNs Device<br>(Experimental)<br>Device: 30-gauge Short Hypodermic Needle | Dental pain<br>Anesthesia | Completed | 2018 |
| 20.    | The effect of MN pretreatment on topical anesthesia | Device: Sham MNs<br>Roller Device: MNs Roller | Pain | Completed | 2018 |
milestone of translation of MNs from research to clinical trial and, finally, into the patient application, necessitates good science, engineering, and significant funding from government agencies and pharmaceutical industries. In a nutshell, the appropriate number of financial support can resolve the economic issue and it will pave the way to MN product development and its clinical trial. We witnessed that we are suffering more challenges to translate the research into new medicinal products, which can provide improvement in patients. Out of various concerns, the development of economic, scalable, and trustworthy manufacturing of the MN-based product, and its real-time benefit to the patient health improvement is still the major challenge to researchers. Concisely, the uncertainties are present with the beginning of any innovative medical technology. It includes the targeted administration of a lower dose of drug/vaccine in humans or animals via MNs without irritation with the predefined rate (slow or fast uptake into the blood). The animal immunogenic response provided by MNs and human immunology might show the same or different or smaller amount of responses. Besides, when the active

Table 6 MN product clinical trials completed (Source: ClinicalTrials.gov) (Continued)

| Sr. No. | Study title | Intervention | Condition | Status | Year |
|--------|-------------|--------------|-----------|--------|------|
| 21.    | MNs lesion preparation prior to ALA-PDT for AK on face | • Drug: Aminolevulinic acid  
• Drug: Topical Solution Vehicle  
• Device: IBL 10 mW | Actinic keratosis | Completed | 2018 |
| 22.    | Clinical evaluation of healthy subjects receiving intradermal saline using the MN adapter (Model UAR-2S) | • Device: MNs Adapter (Model UAR-2S)  
• Device: Hypodermic needle + syringe | Intradermal injection | Completed | 2018 |
| 23.    | Safety and efficacy of ZP-zolmitriptan intracutaneous MN systems for the acute treatment of migraine | • Drug: ZP-Zolmitriptan  
• Drug: Placebo | Acute migraine | Completed | 2018 |
| 24.    | Suprachoroidal injection of CLS-TA in subjects with macular edema associated with non-infectious uveitis. | • Drug: 4 mg CLS-TA Suprachoroidal Injection  
• Drug: Sham Procedure | Uveitis, posterior uveitis | Completed | 2018 |
| 25.    | A study to evaluate the long-term safety of M207 in the acute treatment of migraine | • Drug: MJ07; MNs System | Migraine | Completed | 2019 |
| 26.    | The use of MNs to expedite treatment time in photodynamic therapy | • Device: MN roller  
• Drug: Aminolevulinic acid  
• Radiation: Blue Light | Keratosis, actinic | Completed | 2019 |
| 27.    | A study of the use of MN patches to deliver topical lidocaine in the oral cavity | • Device: MNs Patch  
• Device: Patch with no MNs | Topical anesthesia | Completed | 2019 |
| 28.    | Inactivated influenza vaccine delivered by MN patch or by hypodermic needle | • Biological: Inactivated influenza vaccine  
• Other: Placebo | Influenza | Completed | 2019 |
| 29.    | Safety study of suprachoroidal triamcinolone acetonide via MN to treat uveitis | • Drug: Triamcinolone acetonide | Uveitis, intermediate uveitis, posterior uveitis | Completed | 2019 |
| 30.    | Extension study of patients with non-infectious uveitis who participated in CLS1001-301 | • Drug: 4 mg CLS-TA Suprachoroidal Injection | Uveitis | Completed | 2019 |
| 31.    | Suprachoroidal injection of CLS-TA in subjects with non-infectious uveitis. | • Combination Product: 4 mg CLS-TA | Uveitis | Completed | 2019 |
| 32.    | Analysis of noninvasively collected MN device samples from mild plaque psoriasis for use in transcriptomics profiling | • Device: MN device | Psoriasis vulgaris | Completed | 2019 |
| 33.    | Comparison of 1,550-nm laser and fractional radiofrequency MNs for the treatment of acne scars in ethnic skin | • Device: Fraxel Restore  
• Device: Fractora | Acne scars | Completed | 2019 |
| 34.    | Minimally invasive sensing of beta-lactam antibiotics | • Drug: Phenoxytmethyl Penicillin  
• Device: MN array | Healthy volunteers | Completed | 2019 |
| 35.    | Pain and safety of MNs in the oral cavity | Other: MNs  
Other: Hypodermic needle  
Other: Flat patch | Oral cavity disease | Completed | 2019 |
| 36.    | MNs patch study in healthy infants/young children | Device: MNs Formulation 1  
Device: MNs Formulation 2 | Vaccination  
Skin absorption | Completed | 2020 |
administration via MNs in a large population is set as a contrast to the clinical trial, the finding of a clinical trial in a controlled environment may or may not be like the outcomes from a larger population in the normal daily condition of individual patients. Owing to the advanced technology, the daily use of MNs can require more practice. Despite this, pharmaceutical industries have confidential mass production methods due to competitive interest and this might be a major barrier for the progress of innovative MNs. Thus, from a future point of view, it is a primary requirement to develop cost-effective, reliable MNs on a large scale through the current good manufacturing practice. To overcome the abovementioned concerns, it is desirable to convince industries and research groups for advancing the MN research arena. Many of MN products are under the initial phase of clinical trials, which can be launched as a modern pathway for the management of numerous ailments. Additionally, day by day, the interest of the pharmaceutical industry in MN product development is rapidly increasing and the milestone of cosmetic MNs is encouraging to the patient for MN applications. Therefore, in upcoming years, the smart new MN product can pave the bright prospect for the pharmaceutical industry.

**Conclusion**

Even though multiple drug delivery systems continue to be introduced on a nanoscale designed for the targeted delivery of active substances, MNs are unique because of their versatile properties and characteristics. In the active pharmaceutical ingredient delivery using MNs, it has provided the pioneering way out for life-threatening illnesses. The MNs have already verified to be more proficient and a safe alternative to earlier reported methods of drug delivery systems. The present review provides insight into fabrication materials and methods used for MN synthesis. The role of MNs in serving as a platform to treat various ailments has been explained by unusual approaches. Moreover, the review also inculcates the pharmacokinetics of MNs, which includes permeation, absorption, and bioavailability enhancement. Besides this, the in vitro/in vivo toxicity, biosafety, and marketed product of MNs have been reviewed. Overall, the application of MNs has gained lots of attention and an enormous amount of ongoing research works; we can be soon observing various groundbreaking commercial applications in the management of various health issues. Besides, findings obtained in synthesis, functionalization (with active agent/s), and the design of MNs have led extensively to promising advances in

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**Table 7 MNs approved product for pharmaceutical applications**

| Product name | Manufactured by | Types of MNs | Specifications | Applications |
|--------------|----------------|--------------|----------------|--------------|
| Dermaroller* | Dermaroller* Germany, White Lotus | Solid or metal MNs, | Cylindrical roller shape and 0.2 mm to 2.5 mm in length | Use to improve skin texture and treatment of scars and hyperpigmentation. |
| Dermaroller™ MS-4 | The Dermaroller Series: Anastassakis K | – | Small cylinder, 1 cm length, 2 cm in diameter, 4 circular arrays of needles (total 96 needles) | Use to treatment on facial acne scars |
| MicroHyla* | CosMED Pharmaceutical Co. Ltd | Dissolvable MNs | Slowly dissolved | Use to wrinkle treatment |
| h-patch | Valeritas | – | A small adhesive machine like the patch is used | To deliver drugs (insulin) in subcutaneous |
| Microstructured transdermal system | 3 M | Hollow MNs | – | To deliver biologics and other small molecules |
| Dermaroller™ MF-8 type | The Dermaroller Series: Anastassakis K | – | A needle length of 1.5 mm (1500 μm) | Used for the treatment of scars |
| CIT-8 (collagen induction therapy) | The Dermaroller Series: Anastassakis K | – | A needle length of 0.5 mm (500 μm) | Used in collagen induction and skin remodeling |
| LiteClear® | Nanomed skincare | Solid silicon MNs | – | Utilized to treats acne and skin blemishes |
| Dermaroller™ C-8 (Cosmetic type) | The Dermaroller Series: Anastassakis K | – | A needle length of 0.13 mm (130 μm), 24 circular arrays of 8 needles each (total 192 needles) | Used to enhance the penetration rate of topical agents |
| BD Soluvia* | BD, Sanofi Pasteur Europe | Hollow MNs | 1.5-mm-long hypodermic needle | Used for Influenza vaccination |
different fields. The FDA for clinical application has already permitted a few products, and many more are under clinical trials. The notable achievement of these smart MNs for numerous clinical appliances paves the evolutionary pathway for active agent-based MNs for clinical use. MNs have been used for drug/vaccine delivery by skin penetration in the preceding decade. The plentiful research literature has demonstrated the importance of MNs in therapeutic applications through a different route of administration. Similar to its counterpart, MNs possess unique and versatile properties, which can be explored for various pharmaceutical and biomedical patents. The ability to deliver active agent(s) to the targeted site with improved pharmacokinetics and bring about higher safety and efficacy further makes it a most effective platform for pharmaceutical and biomedical applications. The MNs can be further investigated, and advances in the utilization of MNs in the different challenging fields can be further promoted. Inclusively, the most recent MN investigations have revealed a precise beneficial forecast of whatever manufacturing is in store for the future of medicine.

Abbreviations

- MNs: Microneedles; TDDS: Transdermal drug delivery systems; SC: Stratum corneum; BSA: Bovine serum albumin; CS: Chitosan; PLA: Polyactic acid; HA: Hyaluronic acid; SF: Silk fibroin; PVA: Polyvinyl alcohol; PVP: Polyvinyl pyrrolidone; PLGA: Poly(lactic-co-glycolic acid); CMC: Carboxymethyl cellulose; NPs: Nanoparticles; MEMS: Microelectromechanical systems; Lbl.: Layer-by-layer; DNA: Deoxyribo nucleic acid; ESK: Estakamine; TEWL: Transepidermal water loss; SS: Suranmitprat narrate; LAM: Lamivudine; GOx: Glucose oxidase; Semi-IPN: Semi-interpenetrating network; NIR: Near-infrared; PTT: Photothermal therapy; MTX: Methotrexate; RWM: Round window membrane; TAPP: 5,10,15,20-tetrakis-(4-aminophenyl)porphyrin; NR: Nile red; Gel-MA-βRWM: Gelatin methacryloyl cellulose coated with antigen-loaded mSiO 2-NPs; ALA-PDT: Aminolevulinic acid photodynamic therapy

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