Can Microneedles Replace Hypodermic Needles?*

Painless Drug Delivery

B H Jaswanth Gowda, Mohammed Gulzar Ahmed and Sanjana A

With a history of almost 175 years, hypodermic needles are the most widely used systems for drug administration and sample extraction. But the major drawbacks associated with the use of hypodermic needles include pain, invasiveness, psychological distress, bio-hazardous waste, and the requirement of skilled healthcare professionals. Recently, the ‘microneedle system’ has been gaining interest as an efficient sample extraction (blood or interstitial fluid) and drug delivery system due to its various advantages over hypodermic needle based systems. As the name indicates, the microneedle system contains micron-sized needles—50–1500 μm in height—usually made of metal, glass, or polymer. The application of these needles creates micron-sized conduits in the skin, which is helpful to deliver a wide range of therapeutics both locally and systemically. This article describes the basics, history, and types of microneedles along with their drug delivery approaches. This article attempts to critically highlight the advantages of microneedle systems over hypodermic needle-based injections based on studies.

1. Introduction

The oral route of drug administration is the most widely accepted drug delivery approach globally. But its advantages are limited when drugs have properties such as poor absorption, irritation of the gastrointestinal tract (GIT), enzymatic degradation in GIT, first-pass hepatic transformation in the liver and hepatotoxicity. As a suitable substitute for oral administration of drugs, injections

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The transdermal drug delivery system (TDDS) is a better alternative to the above-mentioned drug delivery systems. TDDS can overcome all the drawbacks of oral and hypodermic needle-based drug delivery, along with some add-on benefits such as site-specific drug delivery for dermal conditions and controlled drug delivery for both dermal and systemic conditions. In 1943, progress in the mechanistic perception of skin permeation began to evolve with an eminent review by Rothman titled ‘The principles of percutaneous absorption’. Years of study on skin permeation finally resulted in the approval of the very first transdermal patch in 1979 for the delivery of the antiemetic medication scopalamine. Ever since, our knowledge of skin permeation has advanced significantly along with relative advancement in some physicochemical strategies. Being the outermost layer of the skin with 10–20 μm thickness, the stratum corneum (bed of dead corneocytes) serves
as the primitive barrier for all foreign particles. This barrier complications the drug delivery efficiency of many types of TDDS formulations. The drugs administered through TDDS need to take a tortuous route to bypass consecutive skin layers containing both aqueous and lipid domains and reach the systemic circulation [1]. To achieve this the drug must possess optimal characteristics such as low molecular weight (less than 600 Da), optimum log P value (1–3), balanced partition coefficient (vehicle/stratum corneum), and low melting point [2]. Until 2011, there were only about 20 drugs approved by the United States Food and Drug Administration (USFDA) as transdermal patches. Besides, the molecular weights of all these drug substances are less than 400 Da. Biotechnology has given rise to a new category of therapeutics, namely, peptides, antibodies, and oligonucleotides, all of which have significant therapeutic benefits. However, due to their large molecular weights and inappropriate physicochemical properties, these biomolecules have restricted skin permeation when used in conventional TDDS relying on passive diffusion across the skin. As a result, an efficient drug delivery system needs to be developed to successfully deliver large molecules across the skin.

Even though many strategies such as chemical enhancers, electric fields, ultrasound, and thermal methods have been used to improve the skin permeability of various small molecules, the large molecules still face permeability issues due to their high molecular weight. To overcome these disadvantages associated with oral drug delivery, hypodermic needle-based drug delivery, conventional transdermal and topical drug delivery, researchers have explored alternative techniques. Coming back to the previously discussed point, despite the many drawbacks associated with hypodermic needle-based drug delivery, the intense benefits of direct injection have led the researchers to reduce the size of the needles to micron size. Micron-sized needles minimize the pain, fear, and need for skilled healthcare professionals to administer the medication while still being able to deliver a broad range of drugs and biomolecules. A hybrid between the conventional hypodermic needle and transdermal patch, a microneedle (MN) is a

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biomedical device that is slowly transforming the area of transdermal and intradermal drug delivery [3].

In this article, first, we discuss the anatomy of human skin and provide a structural and functional comparison of adult and children’s skin. Further, we brief the history and basics of the MN system, as well as their types and drug delivery approaches. Finally, the advantages of the MN system over the hypodermic needles-based system in terms of drug delivery efficiency and patient compliance are highlighted based on theories and research papers.

2. Anatomy of Human Skin (Adult and Infant)

Skin is the largest organ of the human body. It performs a major role in protecting the body from undue water loss and providing a protective shield against harmful influences like pathogens. It is also responsible for controlling crucial operations like hormone metabolism, sensory processing, photoprotection, and thermoregulation. Skin also serves as a trigger for immune reactions due to specialized antigen-presenting cells [4]. Human skin comprises three layers (Figure 1), namely:

- Epidermis
- Dermis
- Hypodermis

2.1 Epidermis

The epidermis is approximately 150–200 μm thick and is composed of viable cells. Based on the degree of cell keratinization, the epidermal layer is distinguished into five layers such as stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum germinativum. The outermost layer of the epidermis (stratum corneum) is approximately 10–20 μm thick. It is referred to as “a brick wall-like structure of corneocytes as
‘bricks’ in a matrix of intercellular lipids, with desmosomes acting as molecular rivets between the corneocytes”. The rest of the layers below the SC are called the viable epidermis. This section comprises keratinocytes, melanocytes, and interstitial fluid (ISF). The majority of drug-related activities, such as drug binding, metabolism, active transport, and monitoring, are managed by this layer. Specialized cells, like Merkel and Langerhans cells, are also found in this layer.

2.2 Dermis

It is the second layer of skin (300–2500 μm) after the viable epidermis and comprises a variety of components such as vascular tissue, connective tissue, nerve endings, lymphatic vessel network, sweat gland, sebum gland, and also blood. The presence of fibroblast in this layer furnishes the structural support for the skin.

2.3 Hypodermis

The hypodermis, also called the subcutaneous layer, is the third layer of skin containing loose connective tissue. This layer comprises a vital cell type called ‘adipocytes’ that helps in fat storage in the form of adipose tissue. Adipose tissue helps in regulating
the body temperature during cold by producing heat (thermogenesis), as well as, cushioning against external damage.

Transport of any substance through the skin follows either of these two transport mechanisms—the intracellular (transcellular) or intercellular (paracellular) pathways. The transcellular path involves the movement of substances via keratin-packed corneocytes by partitioning in and out of the cell membrane whereas, the paracellular pathway involves the passage of substances between the corneocytes. However, there is another mode called the appendageal pathway, where molecules diffuse through the shunts of hair follicles, sebaceous glands, and sweat glands.

Even though there is a distinct knowledge of the general structure of human skin, the points discussed above on the structure and size of skin are not exactly applicable for infants and older children (Figure 2). The lipid and melanin content and the natural moisturizing factors in infants are much lower compared to adults, while infants possess higher water content in the skin compared to adults. The size of corneocytes and keratinocytes in infants is smaller. In infants, the sweat glands are not fully developed, the collagen fibers are not dense, and elastin fibers are literally absent. The thickness of epidermis and skin surface-to-body weight ratio in infants ranges from 40–50 μm and 670–700 cm²/kg respectively. However, in adults, the thickness of the epidermis is 150–200 μm, and the skin surface-to-body weight ratio is 220–250 cm²/kg. Few more key functional differences between infant and adult skin include the pH (6.34–7.5 for infants and 5–5.5 for adults), the transepidermal water loss (TEWL) (increased in infants and decreased in adults), cell proliferation (faster rate in infants and slower rate in adults), and skin barrier function (weaker and evolving in infants and stronger in adults). Generally, intercellular transportation (percutaneous) of drug substances in infants and older children is restricted. But the smaller dose requirement in children enables the fulfillment of therapeutic concentrations [5]. A full-term neonate (but not a premature infant) has a well-developed epidermis, similar to that of an older child or adult. But, the presence of thinner skin layers than an
adult greatly affects the pharmacokinetics (absorption, distribution, metabolism, and excretion) of administered drugs leading to undesired toxicities [6].

3. History of Microneedles

In 1921, Robert Chambers introduced the term ‘microneedles’ (MNs) during the microdissection of an endotherm egg by injecting the needle into its nucleus. But, the concept of MN-based drug delivery was introduced only in 1971 by Martin S. Gerstel and Virgil A. Place from Alza Corporation. They filed a patent (US3964482) on two different types of MNs—hollow and solid—for painless and efficient delivery of drugs, both locally and systemically. Subsequently, the first drug-coated MN was patented by Pistor Michel in 1975. There was a huge gap of almost 15 years, during which not much advancement in MNs was observed. However, the 1990s saw the advent of microfabrication systems from microelectronic industries, and MNs with the necessary dimensions to establish efficient drug delivery systems

Figure 2. Comparison of adult and infant skin structure (Source: https://mypositiveparenting.org/2016/03/22/your-babys-skin-the-power-of-touch/).
The first proof-of-concept analyses of MNs were demonstrated by Sebastien Henry in 1998. He discussed the advantages of silicon MNs to improve the permeability of a model drug calcein prepared using reactive ion etching, a type of microfabrication technique. Besides, his team was the first to study and evaluate the permeability of microfabricated MNs in human epidermal skin in vitro and in vivo. In 2001, Therese B. Bevers first reported the delivery of genetic materials by MNs, and in 2002, Mikszta and team first reported vaccine delivery using silicon MNs. They also studied the safety of MNs by evaluating the scores of edema and erythema. The delivery of macromolecules and nanoparticles via the transdermal route using MNs was first reported by McAllister and team in 2003. They used solid and hollow MNs for transporting insulin, albumin, and 100 nm-sized latex beads through human cadaver skin. Many other macromolecules such as oligonucleotides, proteins, peptides, and supramolecular complexes delivery using MNs were reported in 2004 by Prausnitz. In 2005, Miyano and team reported dissolving MNs for the first time. In this, they studied an array of maltose MNs that dissolve in the skin to release the ascorbate-2-glycoside (model drug) into the epidermis and dermis. In the same year, MN-based biological fluid sampling for diagnostic purposes was first reported. The first cosmetic application of MNs in collagen induction therapy was reported by Fernandes in 2005. Fernandes and team reported the use of an MN-based roller for skin tightening and wrinkle reduction. However, it did not end there. In 2012, Donnelly and team introduced hydrogel-forming MNs (HFMNs), even though hydrogel-based MNs were reported way before 2012. All of them were swellable or expanding MNs. Donnelly and team also introduced the drug reservoir (lyophilized wafer) integrated HFMNs for the first time in 2014 to increase drug loading capacity (and thus long-term sustained drug delivery). This is how the MN drug were designed. In this timeline, three major research teams were involved greatly in MN-based drug delivery. In 1995, Hashmi and team published the first-ever paper on the hollow MN system intended to inject bacterial plasmid for the genetic transformation of nematodes. Although the MNs had taken a great stand since 1921, the first proof-of-concept analyses of MNs were demonstrated by Sebastien Henry in 1998. He discussed the advantages of silicon MNs to improve the permeability of a model drug calcein prepared using reactive ion etching, a type of microfabrication technique. Besides, his team was the first to study and evaluate the permeability of microfabricated MNs in human epidermal skin in vitro and in vivo. In 2001, Therese B. Bevers first reported the delivery of genetic materials by MNs, and in 2002, Mikszta and team first reported vaccine delivery using silicon MNs. They also studied the safety of MNs by evaluating the scores of edema and erythema. The delivery of macromolecules and nanoparticles via the transdermal route using MNs was first reported by McAllister and team in 2003. They used solid and hollow MNs for transporting insulin, albumin, and 100 nm-sized latex beads through human cadaver skin. Many other macromolecules such as oligonucleotides, proteins, peptides, and supramolecular complexes delivery using MNs were reported in 2004 by Prausnitz. In 2005, Miyano and team reported dissolving MNs for the first time. In this, they studied an array of maltose MNs that dissolve in the skin to release the ascorbate-2-glycoside (model drug) into the epidermis and dermis. In the same year, MN-based biological fluid sampling for diagnostic purposes was first reported. The first cosmetic application of MNs in collagen induction therapy was reported by Fernandes in 2005. Fernandes and team reported the use of an MN-based roller for skin tightening and wrinkle reduction. However, it did not end there. In 2012, Donnelly and team introduced hydrogel-forming MNs (HFMNs), even though hydrogel-based MNs were reported way before 2012. All of them were swellable or expanding MNs. Donnelly and team also introduced the drug reservoir (lyophilized wafer) integrated HFMNs for the first time in 2014 to increase drug loading capacity (and thus long-term sustained drug delivery). This is how the MN drug
delivery system has evolved over the past 50 years (Figure 3).

4. Microneedle System

Microneedle is a specialized drug delivery system comprising an array of needles whose length ranges from 50–1500 μm, permitting drugs to cross the stratum corneum by puncturing and creating micron-sized conduits (Figure 4). MNs can incorporate solid, semi-solid, or liquid formulations depending upon their type. These systems are future TDDS, especially for delivering large molecules such as proteins, peptides, vaccines, etc. They are painless and minimally invasive since they do not affect the dermal region, where sensory and pain receptors are present. Also, it doesn’t require skilled healthcare professionals to administer MNs, making them more convenient and patient compliant compared to conventional hypodermic needles. The MN system is not just intended for delivering therapeutics, but also to diagnose various disease conditions and cosmetic purposes. In the case of diagnostic applications, the MN system can extract extracellular fluids such as interstitial fluid (ISF) and blood without pain, fol-
Figure 4. Macroscopic and microscopic visuals of microneedle arrays (Lau et al., 2017, Seong et al., 2017, Yao et al., 2019 and Vora et al., 2020).

Followed by its conventional analysis. Nowadays, sensor-embedded MNs are available for instant diagnoses of many disease states [3].

5. Types of Microneedles

Microneedles are broadly categorized into five types based on the mechanism of drug delivery (Figure 5) [3]:

- Solid microneedle
- Coated microneedle
- Hollow microneedle
- Dissolving microneedle
- Hydrogel-forming microneedle
5.1 Solid Microneedle

Solid microneedles are a unique system that works on the ‘poke and patch’ principle. Initially, the skin is pretreated using MNs to create micron-sized channels, followed by the application of drug-loaded formulation in the area where microchannels are created. This enables drug molecules to diffuse either from a conventional transdermal patch or a semi-solid formulation (ointment, cream, gel, or lotion) and pass through the micron-sized channels to reach the dermis. This can be used either for local effect in the skin or for systemic delivery after uptake by skin capillaries. The commonly used materials are glass, polymer, metal, etc. A study showed that the micropores created using solid MNs remained unclosed up to 72 h when the occlusive tape was applied onto the micropores. However, in the absence of occlusive tape, the micropores closed in less than 2 h upon the removal of MNs, without any trace of secondary infection by microorganisms. Another principle of solid MNs is the ‘scrape and patch’ method, in which MNs, microprojections, or microblades are scraped over the skin to generate microabrasions. The drug-containing viscous solution with a patch is applied to these microprojections. A specific kind of solid MNs is a roller with microprojections, available commercially for cosmetic purposes such as skin pore opening therapy. This, also called a ‘derma-roller’, can pierce the stratum corneum multiple times as the roller spins on the skin. A study on the effect of transdermal flux using a cylindrical surface MN system to deliver antihypertensive drugs resulted in 5–8 times increased transdermal flux than conventional gel formulation.

5.2 Hollow Microneedle

Hollow microneedles can be called mini-conventional hypodermic needles since both are alike except in size. In this system, the drug delivery principle includes the pressure-driven flow of liquid formulation (‘poke and flow’). The pressure and flow rate can be modulated for either a rapid bolus injection to achieve instant drug delivery or a slow infusion to achieve long-term con-
trolled drug delivery. The commonly used materials are glass, polymer, metal, etc. An investigation on the efficiency of metal-based hollow MNs on insulin delivery using diabetic rats shows that MNs are as efficient as a conventional hypodermic injection in delivering insulin [7]. However, the manufacturing process of hollow MNs is quite difficult due to their structure and fragility. In addition to the conventional hollow MN system, they can also be modified as syringes to inject large volumes of liquid drug formulation. Many methods have been suggested to integrate a hollow MN system with a suitable actuator to generate liquid flow through hollow MNs resembling hypodermic injections. One such example includes the attachment of hollow MNs to a drug solution filled polydimethylsiloxane-based reservoir, where the flow of liquid through the hollow MNs can be controlled by CO₂ gas pressure, piezo-electric micropump, syringe pump, etc.

5.3 Dissolving Microneedle

This microneedle system works on the principle of ‘poke and release’. They are usually made of polysaccharides or biodegradable polymers that can dissolve within a few minutes to hours. The commonly used materials are sodium hyaluronate, polyvinyl pyrrolidone, poly-lactic-co-glycolic acid, hyaluronic acid, polyvinyl alcohol, gelatin, starch, maltose, hydroxypropyl cellulose, etc. The therapeutic drug is commonly embedded in the above materials and fabricated as the dissolving MNs. As the dissolving MNs are applied onto the skin, the needles dissolve as soon as the skin interstitial fluid comes in contact, thereby releasing the drug into the dermal region painlessly. One of the major advantages of dissolving MNs over solid and hollow MNs is their ease of manufacturing and one-step application.

5.4 Coated Microneedle

The coated microneedle is based on the principle of ‘coat and poke’ to deliver the drug. This kind of MNs is also called modified solid MNs since the needles are coated with drug solutions.
The commonly used materials are polyethylene, polyisobutylene, polystyrene, polyvinylpyrrolidone, poly-lactic-co-glycolic acid, poly-lactic-acid, etc. In this system, the solid MNs help create micron-sized conduits, while the coating on the solid MNs help in delivering the required drug into the dermal region either for a skin condition or systemic condition. The most commonly used method to coat the MNs is dip coating. However, there are other methods such as spray coating, aerosol coating, etc. This type of MNs holds an advantage over solid MNs due to its one-step application. But the drawbacks such as low drug loading capacity due to less surface area and inefficient coating of accurate drug concentration onto the MNs make this system un convincing compared to dissolving and hydrogel-forming microneedles.

5.5 Hydrogel-forming Microneedle (HFMN)

The main principle behind this microneedle system is ‘poke and swell release’. These MNs adopt hydrogel as a basic material to deliver drugs via swell and diffuse strategy. Hydrogel was first reported by Witchterle and Lim in 1960. Hydrogels are three-dimensional networks of hydrophilic polymers that can swell in water and hold a large amount of water while maintaining the structure due to the chemical or physical cross-linking of individual polymer chains. Adoption of the basic hydrogel principle into MNs was relatively novel and was first reported by Ryan F Donnelly and team in 2012 [8]. Upon application, the HFMNs absorb the interstitial fluid and undergo rapid swelling, thereby releasing the drug directly into the dermal region by a simple diffusion mechanism. The commonly used materials are polyvinylpyrrolidone, carbopol, poly(methyl vinyl ether co-maleic anhydride), guar gum, pectin, sodium alginate, chitosan, etc. Compared to dissolving MNs, HFMNs have concerns regarding mechanical strength and physical stability due to their swelling behavior. But the use of stronger materials that can pierce the epidermis can overcome this issue. Unlike dissolving MNs, HFMNs do not leave needles in the skin—a significant safety advantage. Additionally, the HFMNs stand above the solid, coated and dissolving
Figure 5. Different types of microneedles and their drug delivery approaches (A) Solid microneedle, (B) Coated microneedle, (C) Dissolving microneedle, (D) Hollow microneedle, and (E) Hydrogel-forming microneedle (Larrañeta et al., 2016).

MNPs due to their ability to integrate with the drug reservoir. Unlike all other MN types, the drug delivery can be controlled to a greater extent in the one-step application of HFMMs.

6. Advantages of Microneedle System Over Conventional Hypodermic Needle Based System

6.1 Painless

The pain involved in hypodermic needle-based injections can be extremely distressing especially to children, as well as adults with needle phobia. MNPs can serve as an alternative to hypodermic needles since they do not reach the pain receptors (nociceptor) and mechanoreceptors which are deep in the dermis, and hence result in much less pain compared to hypodermic needles. In the MN system, the severity of pain majorly relies on three factors namely, (a) the number of needles on a patch, (b) the length of the needle, and (c) the tip angle or needle design. Therefore, the MN system should prove its stance to be painless. Because, if at all its application causes any pain and distress in patients, the whole
concept would not be so imperative. As a result, several studies have been performed to determine the severity of pain involved with MNs penetration into the skin, as well as the transient extent of the impairment of the role of the skin barrier. Various studies have explained the higher tendency of longer MNs to reach and stimulate pain receptors (nociceptor) and mechanoreceptors within the viable epidermis. However, there have been reports that some MNs are still capable of achieving painless insertion despite penetrating the superficial layer of the dermis. This observation may be attributed to the use of a small dimensional needle tip which reduces the stimulation of nerve endings [1]. A 2001 study involved the first-time evaluation of MNs safety in human volunteers. In this study, a silicon MN system comprising 400 needles, which were 150 μm long, with a base diameter of 80 μm and tip radius of 1 μm were used on 12 healthy male and female volunteers, aged 18–40 years. All the participants expressed no pain based on the visual analog scale [9]. However, a study conducted in 2009 stated that all the human subjects expressed verbal comments such as ‘sharp’ and ‘stabbing’ on hypodermic needle insertion and ‘pressing’ and ‘heavy’ for MNs insertion. Nevertheless, the relationship of MNs with pain did not end there; a study on human subjects involving the infusion of a few micro-liters of saline using hollow MNs exhibited mild sensation with no pain. But, the same infusion, using hollow MNs up to 1 ml, caused slight pain, specifically during high flow rates [10].

6.2 Minimally Invasive

The hypodermic needle-based injection is crude and invasive and when used to deliver any drug, results in persistent skin damage. Studies on both animal and human models have shown that penetration of MNs leads to milder bleeding compared to hypodermic needles. Also, the application site of MNs show less injection site damage and more rapid recovery. As reported in some studies, a minor erythematic condition is sometimes observed upon MNs application. However, it usually resolves within an hour after the removal of MNs. The results of a study comparing the degree of

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skin puncture caused by platinum-coated silicon MNs and hypodermic needles are in favor of MNs. The results indicate minimal trauma with a rapid recovery rate of about 8–24 h in the case of MNs compared to hypodermic needles. Thus, minimal invasiveness is one of the major advantages of the MN system [10].

6.3 Ease of Administration

Administration of therapeutics via hypodermic needles requires trained healthcare professionals to avoid injuries from the sharp elongated needles. But, globally, there are approximately 30 million healthcare professionals who are facing challenges due to hypodermic needle injuries as a result of faulty reinsertion. Hypodermic needle injuries can transmit diseases like HIV, hepatitis, etc. To prevent the transmission of blood-borne pathogens, it becomes mandatory to carefully dispose of the used needles. MNs, on the other hand, are patch-like devices bearing micron-sized needles, almost invisible to the naked eye. Therefore, there is no need for trained healthcare professionals for administering the therapeutics, thus easing the process. For example, during the Mantoux test, injecting purified tuberculosis (TB) antigen intradermally to the forearm of a patient using a hypodermic needle at an angle of exactly 5–15° with respect to the skin surface is mandatory. If the needle is not injected in the specific range, the Mantoux test might fail. To overcome this problem, researchers have developed polymeric MNs coated with TB antigen. These MNs eliminate hypodermic needle-based errors by creating a way for patients to administer the test themselves. A study investigating the use of a patient information leaflet on self-application of 400 μm MNs by human volunteers without the aid of an applicator device indicated that there is no significant difference between patients’ self-application and application by experienced researchers. This study suggests that patients can apply MNs without any help from skilled medical professionals and applicator devices [11]. In addition, dissolving MNs is safe in terms of controlling the spread of blood-borne pathogens to healthcare workers and caretakers. Chu and Prausnitz developed separable,
sharp arrowhead, dissolving MNs with metal shafts. Post administration of this MN, the polymeric tip gets separated by dissolving instantly, leaving the blunt metal shaft behind. Therefore, post application, the incidence of faulty reinsertion and disease transmission are low [12].

6.4 Efficient Drug Delivery

The major benefits of MNs include overcoming the drawbacks of hypodermic needles such as pain, invasiveness, psychological distress, etc. But, these advantages alone do not make MNs an efficient alternative to hypodermic needles. The efficiency of drug delivery by MNs compared to hypodermic needles has been taken into concern. The ideal MN system should penetrate the epidermis and reach the underlying dermal tissue before releasing the drug for efficient drug delivery. Also, an increased pressing force and time of MNs attachment to the skin can improve the permeability, thereby increasing drug delivery efficiency. It has to be noted that the drug loading capacity in MNs also greatly influences the treatment. Researchers found that the longer the length of the MNs, the higher the drug delivery efficiency due to the release of the drug, where the dermal microcirculation will rapidly take up the released drug into the systemic circulation. But the increased length of MNs is associated with pain. Therefore, the idea is to increase the number of needles and densely pack the MNs to overcome the issues discussed above. A study on determining the drug delivery efficiency of highly dense industrially scalable MNs (600) in comparison to less dense MNs (196) found that the highly dense industrially scalable MNs delivered the same amount of drug as less dense MNs [13]. Despite all the above-mentioned issues, additionally, the MN geometry plays an important role in drug delivery efficiency. Another investigation on the effect of four different MN geometries (cone, pyramid, cross-shaped, pedestal shape) found that cone and pyramid-shaped MN arrays can efficiently deliver drugs [14].
6.5 Minimal Microbial Contamination

The influx of microorganisms at the site of MN-created skin conduits has been hypothesized and the possibility of associated risk of skin infections analyzed. In 2009, a study was conducted to determine the ability of specific microorganisms (Candida albicans, Pseudomonas aeruginosa, and Staphylococcus epidermidis) to penetrate through the conduits in the skin created by both MNs and hypodermic needles (21 gauge). The results indicated that the 0.5 mm² area pore created by a hypodermic needle show greater penetration of the above-mentioned microorganisms compared to the pores created by MNs with a combined area of 1.5 mm². This revealed that the risk of microbial contamination associated with MNs insertion is much lower than the risk associated with hypodermic needles [15]. However, the usage safety of MNs can be further improved by aseptic or sterile manufacture and fabrication of MNs from self-disabling materials such as dissolving or biodegradable polymers.

6.6 Patient Compliance and Safety

In the quest of delivering necessary therapeutics to the patients, compliance plays a major role along with the prevention and cure of diseases. In hypodermic needle-based injections, the patients are highly susceptible to various complications such as pain, psychological disturbances, tissue damage, high risk of infection, and limited self-administration ability. However, the micron size of needles enables easy and painless self-administration with less tissue damage, faster recovery, and a low risk of infection. Most importantly, psychological distress due to needle phobia is eliminated. MN patches have been found favorable in focus group surveys of public and healthcare professionals. According to various vaccination studies, most doctors and the general population favor hollow MN-based injection of influenza vaccine to conventional intramuscular injection, owing to the smaller needle size and greater immunogenicity of intradermal vaccination. Both physicians and patients believe that an MN-based delivery system
could expand the vaccination rates. A study on human subjects above 65 years to investigate the feasibility and acceptability of MNs compared to human subjects aged 20–30 years shows that apart from a slow skin recovery rate after the removal of MNs, every other aspect such as acceptability and convenience are similar in both the age groups [16].

6.7 Ease of Manufacturing

Among all the MNs fabricated using metal, ceramic, or other materials, polymeric MNs can be economical in terms of large-scale manufacturing due to the usage of inexpensive polymers such as polyglycolic acid, polylactic acid, etc., in less quantity. The most commonly adopted method for manufacturing the MNs is the micromolding technique. Initially, a male micromold is produced from metal or silicon, from which a female PDMS micromold is produced. Finally, the female PDMS mold is used to fabricate the MNs using appropriate polymers. Thus it is quite easy to manufacture in large quantities with minimum production cost. Typical manufacturing methods like conventional injection molding, casting, as well as hot embossing procedures can also be used to fabricate polymeric MNs.

6.8 Pediatric Compliance

Among all others, the pediatric population is the majorly suffering category due to hypodermic needle-based injections. The pain intolerance and hypodermic needle phobia cause physiological distress in the pediatric patient group. As we discussed in the previous section, the pain due to MNs is directly proportional to the length of the MNs. Since the infants’ and children’s skin is physiologically different compared to adults’, the reduction in MNs length is ideal to deliver therapeutics or for diagnosis in the pediatric population. Considering the benefits, MNs are worthy candidates for extensive research in the area of pediatric healthcare.
6.9 Stability of Therapeutics

In hypodermic needle-based injections, the drugs usually come in two different forms—direct solutions and powders reconstituted to solutions. However, most of these drugs/therapeutics cannot be stored at room temperature and needs to be refrigerated to ensure their stability. Long-term storage of large and small molecules without refrigeration would significantly benefit developing countries. In this context, MNs draw considerable attention as they stabilize both small and large molecules. The polymers and sugars (such as carboxymethyl cellulose, trehalose, poly(methyl vinyl ether/maleic acid), etc.) used in dissolvable, coated, or HF MNs can maintain the stability of impregnated large and small drug molecules. Other materials which have been reported to increase the stability of drugs and biotherapeutics stored at room temperature for long period include ascorbic acid and niacinamide [1]. Studies have reported the use of trehalose in MNs’ formulation improving the stability of incorporated biotherapeutics. The conjecture mechanism involves the formation of an amorphous sugar glass phase that minimizes the molecular mobility of biotherapeutics. Another possible mechanism includes the “substitution of removed water molecules” hydrostatic interactions by hydroxyl groups from the sugars [17]. Substitution forms a stabilization shield around the biotherapeutics leading to minimized dehydration caused changes during storage. Carboxymethyl cellulose stabilizes the storage of biotherapeutics at room temperature by suppressing molecular mobility, thereby reducing the phase separation and crystallization rate within the MN system. A study investigating the effect of excipients such as lyoprotectants and stabilizers shows improvement in the stability of vaccines. The results suggest that monovalent vaccines could remain stable for up to 2 years at room temperature without losing their immunogenicity [17]. Overall advantages of MNs towards stability can eliminate the need for refrigeration, cold chain storage, and sophisticated transport system. This helps the developing countries overcome the challenges of cold chain storage, leading to a reduced cost of treatment via MNs formulation.
7. Conclusion

Hypodermic needle-based injections are the most widely used drug delivery system since 1844. The major advantages of these needles include efficient delivery of therapeutics to those who suffer from poor oral absorption, GIT irritation, enzymatic degradation, and first-pass hepatic transformation. The collection of blood samples for the diagnostic purpose unquestionably involves sharp hypodermic needles. However, the pain, invasiveness, and psychological distress in children and needle-phobic patients are major concerns. The hypodermic needle-based injection necessitates skilled healthcare professionals to administer them. Furthermore, hypodermic needles produce sharp and biohazardous wastes, which require special disposal. To overcome all these issues, a novel ‘microneedle system’, which consists of many arrays of micron-sized (50–1500 μm) needles can be used either to deliver the therapeutics or to collect samples (blood or ISF) for diagnostic purposes. The advantages of microneedles over hypodermic needle-based injections include painless, minimally invasive, safe, and inexpensive delivery of drugs, ease of administration, minimal microbial contamination, stability of therapeutics, and adult and pediatric patient compliance. Taking all the above advantages into consideration, microneedle systems can be greater alternatives to hypodermic needles in almost all aspects. We can also expect the microneedle system to take over the market of conventional hypodermic needles in the near future to benefit the people.

8. Acknowledgement

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