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AN INNOVATION IN CLINICAL PRACTICE BY MICRONEEDLES: A REVIEW

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ABSTRACT

Transdermal drug delivery system (TDDS) provides controlled and continuous input of drugs, especially those with short biological half-life, they are designed to deliver therapeutically effective concentration of drug through patient skin. Normally hypodermic needles are used in clinical practice to deliver medication across the skin, especially vaccines. Injections with hypodermic needles are essential from clinical point of view, but they are painful, they may induce hypersensitivity reactions, bruising or bleeding at the site of injection. So, in order to overcome these drawbacks associated with hypodermic needles in clinical practice, we designed micro needles. Microneedles have been designed as novel drug delivery carrier for Transdermal drug delivery system, they are similar to traditional needles, but they are of the size range from 1 micron to 100 microns in length and 1 micron in diameter. Microneedles are also known as micro scale needles arranged on a Transdermal patch, these are micro structure system composed of micronized array projections coated with a drug or vaccine. They improve patient compliance as self-administration is possible, micro needles are divided into four types: hollow, solid, coated and polymer. Hydrogel forming micro needles with super swelling properties shows enhanced stability and better patient acceptability.

KEY WORDS

Transdermal, Microneedles, Clinical practice, Hydrogel, Biocompatibility.

INTRODUCTION

The main objective of any drug delivery system is to deliver therapeutic amount of drug to specific site in the body to achieve and maintain optimum therapeutic concentrations in the body and exhibit desired pharmacological action with minimum adverse effects. Therefore, to prevent frequent drug administration and maintain optimum drug level in body it is essential to administer drug by controlled release system [1]. Controlled drug delivery system(CDDS) is designed to obtain desired drug release profile for a longer period of time by formulating various available delivery systems like noisome [2], liposomes, transdermal patches [3], microspheres [4], etc. The objective of controlled drug delivery system is attained by maintaining optimum dosing frequency with desirable route of administration. the route through which drug is administered plays a vital role in treatment of patient [5-7]. Among various available routes, transdermal route is one of the most significant routes for drug delivery [8]. Transdermal drug delivery system (TDDS) provides improved route for administration of drugs due to enhanced patience and prevention of first pass metabolism, hence enhanced bioavailability [9], for those drugs that are having short biological half-life. TDDS can be defined as the self-contained, discrete dosage form which, when applied to the intact skin, delivers the drug through the skin at a controlled rate to

the systemic circulation, it is an integral part of novel drug delivery system (NDDS) [10-11]. The first transdermal system named as "Transderm-SCOP" was approved by FDA in 1979 for the prevention of nausea and vomiting [12]. TDD is also called as painless method for drug delivery of delivering by applying a drug formulation onto intact and healthy skin, so this delivery system serves as an important tool in administration of several vaccines, proteins and peptides [13], after application of TDDS, initially the drug penetrates through the stratum corneum and then passes through the deeper epidermis and finally the dermis region of skin without any drug accumulating in the dermal layer. When drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation [14-16]. The major aim behind the development of transdermal systems is to cross the stratum corneum. Drug administration with minimum pain to the patient is one of the most essential criteria for following clinical practice. Good Clinical Practice (GCP) is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses and reporting of clinical trials. GCP provides assurance that the data and reported results are credible and accurate, and that the rights, integrity and confidentiality of trial subjects are respected and protected [17]. It was finalized in 1996 and became effective in 1997. Several years from past the formulation scientists are striving hard to develop a delivery system that works as needle-free injection (NFI) [18], These NFI devices can improve patient compliance by evoking less pain and stress. Novel inventions regarding NFI includes intradermal layers of the skin, that are being targeted for vaccination with innovative devices [19]. TDDS has been classified as first, second and third generation respectively, first generation includes delivery of low dose lipophilic drugs, second generation involved delivery system that used chemical enhancers, iontophoresis etc for clinical implications. The most important third generation TDDS aimed on targeting the stratum corneum by using microneedles, thermal ablation, electroporation, microderma abrasion etc. Microneedles are one of the latest innovation in clinical practice that are designed through clinical trials, in the delivery of macromolecules and vaccines like insulin, parathyroid hormone, and influenza vaccine. The present review article is based on the use and development of microneedles as an effective and alternative strategy for transdermal drug delivery which significantly enhance the impact of drug delivery via transdermal route [20], From the past ten years, microneedles (MN) were proposed as a mechanical carrier which pierces through the stratum corneum to create pores for the drug delivery without stimulating the pain nerves. Since then, this system has been emerged as potential carriers for transdermal applications [21-26]. Presently, MN are being utilized to enhance transdermal delivery of small and large molecules.

MICRONEEDLES (MN)

Microneedles (MN) are one of the most innovative advancement in transdermal drug delivery system, similar to our traditional hypodermic needles, but the variation lies in its size, these are fabricated in the size range from 1-100 microns in length and 1 micron in diameter manufactured by silicon etching technology and micro mechanical system manufacturing (MEMS) technique. MN is also known as micro scale needles that are placed on transdermal patches, that are composed of micro sized array projections coated with drug or a vaccine [27-33]. The major advantage of microneedles is its pain free delivery of drug for small and large molecular weight pharmaceuticals, fabrication of microneedles has been observed to improve the transdermal delivery of a variety of molecules like anthrax vaccine, β-galactosidase, calcein, bovine serum albumin, desmopressin, diclofenac, erythropoietin, met methyl nicotinate, ovalbumin, plasmid DNA, insulin, etc. The micro needles are capable to deliver the drug deep into the epidermis and dermis, which subsequently resulted in the uptake by capillaries into the systemic circulation without disturbing the nerves. Silicon is used for the fabrication of micro needles. It contains very sharp tips which are meant for piercing the skin. Micro grams quantity of drugs can be delivered via micro needles. They act by temporary mechanical disruption of the skin. Drug in the form of bio molecules is enclosed within the micro needles which then undergo insertion within the skin in the similar way as drug is released from the patches into the blood stream. Needles undergo dissolution within a minute and released the drug at the desired targeted site . If we go into the history of microneedles, it indicates that the first microneedles system was designed in 1976, comprising of a drug reservoir and a plurality of projections

(microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug into the systemic circulation. Recently, The ALZA Corp had formulated a microneedle technology named Macroflux, that can be used either in combination with a drug reservoir or by dry coating the drug on the micro projection array. The dry coating method is being employed for better intra cutaneous immunization. Fabrication and development of microneedles has been subject to intensive research and development by researchers with some devices in clinical development stage along with others waiting FDA approval [34-35].

TYPES OF MICRONEEDLES

Micro needles are broadly classified into two types mainly, solid micro needles and hollow micro needles [36-38].

Solid Microneedles

Solid microneedles are the arrays of projections that are used for forming holes in stratum corneum and are applied before the application of a drug and then removed later, very conveniently they create micron scale holes in the skin by which drug molecules easily passes. It can also be said that that solid micro needles deliver the drug by the mechanism of passive diffusion by creating micro channels to increase skin permeability followed by the application of a drug loaded patch on the channels [39-46]. From a safety perspective, it is desirable for the microchannels to close soon after needle removal to prevent permeation of undesired toxic substances or infection by pathogenic microorganisms. A chromium masking material was first deposited onto silicon wafers and patterned into dots which had a diameter approximately equal to the base of the desired microneedles. The wafers were then loaded into a reactive ion etcher and subjected to plasma etching. The regions protected by the metal mask remained to form the microneedles. Vinaya Kumar *et al.* fabricated an array of rectangular cup shaped silicon microneedles [47]. Microneedles were either prepared as individual rows of needles or as two-dimensional arrays of needles cut into the plane of the stainless-steel sheet and subsequently bent at 90° out of the plane [48]. The stainless-steel MN arrays were manually cleaned with detergent. To prepare "out-of-plane" MN, stainless steel MN were first manually pushed out of the sheet using either forceps or a hypodermic needle and then bent at 90° angle with the aid of a single-edged razor blade. Stainless steel microneedles can also be made by wet etching photo lithographically defined needle structures from stainless steel sheets [49]. The authors used these MN to deliver a vaccine based on virus-like particles containing influenza virus heterologous M2 extracellular (M2e) domains (M2e5xVLPs). Solid MN can be fabricated from polymers. Olatunji *et al.* prepared MN from biopolymer films extracted from fish scales of tilapia (*Oreochromiss* sp.) using micro molding technique. The microneedles were successfully inserted into porcine skin and were shown to dissolve gradually at 0, 60, 120 and 180 s after insertion. The microneedles contained methylene blue as model drug and successfully pierced porcine skin [50].

Hollow microneedles

Hollow microneedles contain a hollow bore in the center of the needle. When inserted into the skin, the hollow bore present bypasses the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis. These microneedles are mainly employed to inject the drug solutions directly into the skin [51-56]. These are very expensive to prepare and require expensive micro fabrication techniques. These micro needles contain hollow bore which offers possibility of transporting drugs through the interior of well-defined needles by diffusion or for more rapid rates of delivery by pressure driven flow. Hollow microneedles (HM) can be fabricated from a commercially available 30-gauge hypodermic needle. Pressure, and thereby flow rate, can be changed in HM for a rapid bolus injection, a slow infusion or a varied delivery rate. HM can also be used to administer a larger dose of drug solution. Verbaan *et al.* fabricated HM from 30G stainless steel needles [57]. The 4 × 4 pattern of holes was drilled in a poly ether ether ketone mold (diameter 9 mm). Then, the needles were placed through the holes at a predetermined length of 300, 550, 700 and 900 µm. Subsequently, the needles were cut and glued at the back of the mold. A manual applicator was also designed for the MN array. Aoyagi *et al.* fabricated long thin holes with a high aspect ratio of 100 (diameter: 10 µm, depth:1 mm) in biodegradable polymer material using a UV excimer laser [58]. Holes having diameters of 10, 20 and 50 µm were fabricated from the side surface of a polylactic acid (PLA) sheet. The laser fabrication approach was then

applied to a PLA microneedle, which were fabricated by a micro molding technique. A hole was fabricated along the centerline of microneedles using the above-mentioned approach and it was confirmed experimentally that blood plasma was taken into the hole by capillary force. For HM, it is important that adequate and constant flow rate is maintained for transdermal drug delivery, without compromising the mechanical strength of the needles. The main factor affecting the flow rate is the compression of the dense dermal tissue at the needle tip during insertion. By increasing microneedles bore may increase the flow rate; however, this results in a decreased MN strength and a reduction in sharpness. Another way to increase the MN strength is by applying a metal coating on the MN. However, this may decrease MN sharpness. Hollow out-of-plane silicon microneedles were fabricated. A sequence of deep-reactive ion etching (DRIE), anisotropic wet etching and conformal thin film deposition was used. Tip curvature was defined by lithography and the length of the needles varied between 150 and 350 micrometers [20]. Silicon MN are justified by their mechanical properties and their biocompatibility potential. However, inconveniences such as high production costs or fragility have spurred researchers to look for other options. Hollow silicon MN were fabricated by using isotropic etching followed by anisotropic etching to obtain a tapered tip Silicon MN of 300 micron in height, with 130-micron outer diameter and 110-micron inner diameter at the tip followed by 80-micron inner diameter and 160-micron outer diameter at the base were fabricated using this technique. In order to improve the biocompatibility of MN, the fabricated microneedles were coated with titanium (500 nm) by sputtering technique followed by gold coating using electroplating. A breaking force of 225 N was obtained for the fabricated MN, which is 10 times higher than the skin resistive force. Hollow microneedles can also be fabricated using other micro-electro-mechanical systems (MEMS) technologies such as laser micromachining, deep reactive ion etching, integrated lithographic molding technique, wet chemical etching and X-ray AdminPen® MN have also been fabricated [59], Hollow microneedles can deposit a compound directly into the viable epidermis or the dermis avoiding the stratum corneum. This is especially useful for the delivery of high molecular weight compounds such as proteins, oligonucleotides and vaccines [60]. It is desirable that hollow microneedles possess adequate mechanical strength and that the bores are not clogged during transdermal drug delivery.

Coated Microneedles

As the name suggest, coated microneedles are those which are coated with the drug containing dispersion. In order to formulate coated microneedles extensive studies had been done, in one method electro hydrodynamic atomisation (EHDA) principle was used in the preparation of smart microneedles coatings [61-68]. Stainless steel (600–900 micron in height) microneedles were coupled to a ground electrode (in the EHDA coating set-up) with the deposition distance and collecting methodology varied for an ethanol: methanol (50:50) vehicle system. Ma and Gill used a polyethylene glycol matrix containing a water insoluble drug lidocaine to coat solid microneedles. Uniform coatings were obtained on microneedle surfaces. *In vitro* dissolution studies in porcine skin showed that microneedles coated with PEG-lidocaine dispersions resulted in significantly higher delivery of lidocaine in just 3 min compared with 1 h topical application of 0.15 g EMLA®, a commercial lidocaine-prilocaine cream [69]. Pearton *et al.* used coated microneedles to delivery plasmid DNA. Optimization of a dip-coating method enabled significant increases in the loading capacity, up to 100 µg of plasmid DNA (pDNA) per 5-microneedle array. Coated microneedles were able to reproducibly perforate human skin at low (less than 1N) insertion forces.

Dissolving Microneedles

Fabrication of dissolving microneedles is of high interest, as it serves several advantages; these include only one step application process. Dissolving MN are fabricated on the basis of the “poke and release” principle, these are made from polysaccharides or other polymers, they release encapsulated drug into the skin following application and dissolution. Micro moulding is the preferred fabrication method for making dissolving microneedles. Certain drugs and vaccines are thermolabile so moulds are often filled with solutions of drugs and excipients and then dried under mild conditions. The fabrication process involves pouring the polymer solution into female molds, filling the micro cavities of the mould under vacuum or pressure, drying under ambient conditions, centrifugation or pressure. Lee *et al.* fabricated master molds by thermal drawing and replicated high aspect ratio silk fibroin

microneedles from these master molds multiple times [70-73].

Hydrogel Forming Microneedles

The latest innovation in microneedles formulation is the development of hydrogel forming microneedles, as these hydrogels forming micro needles showed enhanced bioavailability and biocompatibility as they overcome the problem associated with previous silicone or metal formulated microneedles that remained completely intact after removal from the skin. The first two microneedles-based products, just recently marketed, Soluvia® and Micronjet® are based on metal and silicon, respectively [74]. In current era of microneedles research the major influence is focused on biocompatibility of dosage form, hence they formulated super swelling polymeric compositions comprising hydrogel-based microneedles. These are microneedle arrays, prepared under ambient conditions, which contain no drug themselves instead, they rapidly imbibe skin interstitial fluid upon insertion to form continuous conduits between the dermal microcirculation and an attached patch-type drug reservoir. Such microneedles act initially as a tool to penetrate the stratum corneum barrier. Upon swelling, they become a rate controlling membrane. Fluid uptake range in one hour was 0.9–2.7 µL which is of the same order of magnitude as the rates of interstitial fluid uptake for hollow microneedles and micro dialysis. Other advantages of hydrogel-forming microneedles are that they can be fabricated in a wide range of patch sizes and geometries, can be easily sterilized, resist hole closure while in place and are removed completely intact from the skin [75]. Recently, there was a report on the investigation of various polymeric compositions in order to find materials capable of rapid swelling, but which would be sufficiently hard in the dry state to penetrate the skin. These materials, once swollen, should maintain structural integrity and be reasonably robust during handling. Stock solutions of Gantrez S-97 (40% *w*/*w*) or AN-139 (30% *w*/*w*) were prepared using deionized water. Hydrogel films were then prepared using varying concentrations of the co-polymer, PEG 10,000 and the modifying agent, sodium carbonate. Films were cured at 80 °C for 24 h to induce chemical cross linking between the PMVE/MA and PEG by ester formation. Swelling studies were conducted and the results used to select optimal polymeric compositions. A microneedle formulation with enhanced swelling capabilities from aqueous blends containing 20% *w*/*w* Gantrez S-97, 7.5% *w*/*w* PEG10,000 and 3% *w*/*w* Na_2CO_3 and using a drug reservoir of a lyophilized wafer-like design was selected. These microneedle-lyophilized wafer compositions were robust and effectively penetrated skin, swelling extensively, but they were removed intact. Significantly, *in vitro* delivery experiments across excised neonatal porcine skin showed that approximately 44 mg of the model high dose small molecule drug ibuprofen sodium was delivered in 24 h, equating to 37% of the loading in the lyophilized reservoir. The super swelling microneedles delivered approximately 1.24 mg of the model protein ovalbumin over 24 h, equivalent to a delivery efficiency of approximately 49%. Silicon MN arrays to be used as master templates in microemulsion of hydrogel-forming arrays were first microfabricated. Using the above silicon MN arrays as master templates, silicone elastomer micromoulds were then prepared. The authors fabricated microneedles with enhanced swelling capabilities from aqueous blends containing 20% *w*/*w* Gantrez S-97, 7.5% *w*/*w* PEG 10,000 and 3% *w*/*w* Na_2CO_3 and utilized a drug reservoir of a lyophilized wafer-like design. In *in vitro* delivery experiments across excised neonatal porcine skin, approximately 44 mg of ibuprofen sodium was delivered in 24 h, equating to 37% of the loading in the lyophilized reservoir. The hydrogel-forming microneedles also delivered approximately 1.24 mg of the model protein ovalbumin over 24 h, equivalent to a delivery efficiency of approximately 49%. In a recent report, investigators incorporated caffeine and lidocaine hydrochloride into transdermal microneedle systems using novel laser-engineered polymers. Potential pediatric applications were studied. The authors prepared adhesive patches using aqueous blends consisting of 10% *w*/*w* PMVE/MA and 5% *w*/*w* tripropyleneglycol methyl ether [76]. Facilitated transdermal transport of caffeine and lidocaine HCl were observed using drug-loaded dissolving MN and integrated hydrogel- forming MN in comparison to their corresponding control patches/cream across dermatomed skin over a period of 24 h. The application of hydrogel-forming microneedles is highly appreciable, hence more effort and light should be thrown on further research in these hydrogels forming microneedles.

Formulation Design Parameters of Microneedles

In fabrication of microneedles the basic idea should be applied that these fabricated microneedles must have sufficient strength to get inserted into the skin without breaking. The polymers selected in formulation must have sufficient mechanical strength and must be biocompatible. The size and shape of microneedles is also essential, along with the sharpness of tip of needle. The materials required for constructing micro needles include glass, silicone, metals such as stainless steel, solid or coat of gold over nickel, palladium, cobalt and platinum and biodegradable polymers.

Characteristics of Microneedles

Ruggedness: Micro needles developed must be capable of insertion deep into the skin without breaking. They should be manufactured by taking optimum size and if they are too long, upper portion of micro needles may not have enough rigidity and could undergo breakage before penetration. They must be able to withstand the insertion force without delaminating, or fracture.

Controlled drug release: The micro needles should deliver the controlled amount of drug at a definite and predetermined rate.

Penetration: The micro needles should be able to penetrate the drug to the required depth in the tissues of the body. Painless insertions of micro needles into the skin can be accomplished by gentle pushing, using approximately 10 Newton forces.

Dimensions of microneedles: The dimensions of micro needles can vary depending on the types of microneedles, generally the size ranges from 150-1500 microns in length, 50-250 microns in base width, and 1-25 microns in tip diameter. The tips of microneedles are of different shapes like triangular, rounded or arrow shaped. The hollow microneedles arrays are fabricated with lumen diameter of 30 micro meters and height 250 micro meters. Centre to center hollow micro needle array 150µm and the axis of lumen is fabricated with the distance of 10 micro meters to the axis of outside column.

Advantages of Microneedles [77-78]

- Painless drug delivery system.
- Possible self-administration.
- Rapid onset of action.
- Improved patient compliance.
- Good stability.
- Efficacy and safety comparable to approved injectable products.
- Cost effective.

Evaluation Parameters

In-Vitro study of Microneedles: In vitro evaluation micro needles are accomplished by using various mediums like agarose gel and methanol to insert the microneedles. In vitro tests are used to determine the characteristics of new test device or compound. The main key objectives of the in vitro testing of microneedles involves optimization of the microneedles, finding out the penetration force and bending force, evaluation of strength of microneedles, determination of the dissolution rate of coating material and the estimation of the efficiency of drug delivery. Various methods employed for conducting in vitro studies are as follows

Method 1: *In vitro* methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Paradimethylsiloxane (PDMS) biochip and black ink is injected by the microneedles into the petridish *In vitro* methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Paradimethylsiloxane (PDMS) biochip and black ink is injected by the microneedles into the petridish, which contains methanol. The right triangular microneedles with 8.5 and 15 tip taper angles and isosceles triangular microneedles with 9.5 and 30 tip taper angles have been used for this purpose [79].

Method 2: In this method, the diluted form of Rhodamine B dye is injected through the microneedles into the 1% agarose gel to evaluate the penetration and flow of the solution after penetrating into the 1% agarose gel.

Method 3: Inserting microneedles into the porcine cadaver skin and pig cadaver skin for 10 to 20 SEC and 5minutes respectively are evaluated by this method. This method is used to test the delivery efficacy, dissolution rate of the coated material, which is coated on the microneedle tip, coated with vitamin B, calcein or sulforhodamine.

In Vivo Testing of micro needles: To conduct the *in vivo* preclinical study, generally mice, rabbits, guinea pigs, mouse and monkey etc are used. The main motive of the *in vivo* testing is the determination of safety as well toxicity of the tested compound. The key objectives behind *in vivo* testing of the microneedles includes to perform skin toxicity test, determination of penetration force in different skin, mechanical stability, bending breakage force, to perform various non-clinical safety study and pharmacological study, determination of

various parameters like immunogenicity, genotoxicity, skin sensitization and allerginisation, study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

Method 1: This *in vivo* method involves testing of microneedles by pricking the microneedles into vein of the tail of hairless mice. It is used for the determination of the penetration force of the microneedles into the skin.

Method 2: This method of *in vivo* testing of the microneedles, Rhodamine B is injected into tail of laboratory mouse-tail and anaesthetized for the determination of penetration force and bending breakage force.

Method 3: This method has been performed for the evaluation of vaccine delivery via microneedles. Ovalbumin is used in this method, as a model protein antigen and administered into hairless guinea pig by using solid metal microneedles at the rate of 20 µg ovalbumin in 5s up to 80 microns [80].

Method 4: In this method rabbits have been used to evaluate the vaccine delivery. The anthrax vaccine containing recombinant protective antigen(rPA) of Bacillus anthracis has been administered in the rabbits via solid and hollow microneedles.

Table 1: Marketed formulations of Microneedles. [81]

Market Formulation	Details	Manufacturer
AdminPatch™	Microneedles array	Admin Med [82]
Macroflux®	Microneedles array	Macroflux® Corporation Inc. [83]
Microcore®	Dissolvable peptide microneedles patch	Corium [84]
Microjet®	Intradermal microneedles injection system	Nano Pass [84]

CONCLUSION

The present review paper highlights the points that enumerate highly efficient use of the most innovative transformation of transdermal drug delivery via microneedles in clinical practice. Microneedles have also undergoing further research to have use in clinical implications to make them a better system to be effective in therapies, vaccinations and other useful applications in the field of pharmaceuticals. After deep review of the topic we can finally conclude that microneedles provide an alternative to traditional needles and thus a means of overcoming one of the biggest barriers to patient compliance for the treatment of chronic diseases and routine vaccination. Various delivery systems that target the skin have attracted growing attention during the last years. Needle-free delivery systems are associated with significant advantages, particularly with regard to safety issues, microneedles-based drug delivery also has the potential to be a transformative technology for the delivery of biologics and vaccines. By the use of micro-electro-mechanical systems (MEMS) technologies, highly efficient microneedles have been developed. Microneedles either in the form of patch or an array have been observed as a potential carrier for the delivery of numerous macromolecular drugs for the effective transdermal delivery. Along with high rates of achievements with microneedles, still tremendous amount of research being carried out to study the influence of microneedles on transdermal drug delivery. Apart from various advantages, several challenges are still to be overcome regarding clinical application of microneedles like, irritation, microbial contamination and the delivery of therapeutically relevant concentrations of drugs. There is also a limited choice of appropriate biomaterials, lack of mechanical strength, poor control of drug delivery, limitation of drug loading dose an products of biotechnology. There is also the concern that some fabricated microneedles from silicon and some polymers may not have adequate mechanical strength to pierce the skin. The ideal scenario is to fabricate MN with a low insertion force and a high fracture force. It is also cumbersome for MN to be applied in a two-step manner, that is to porate the skin first and then apply a patch, with this regard, the use of hydrogel-forming microneedles is particularly interesting. There is also the need to balance penetration enhancement with painlessness. Still along with so many challenges to be overcome, microneedles provide a wide scope of research in development of an efficient transdermal drug delivery system with high clinical efficiency.

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CONFLICTS OF INTEREST:

The author has no conflict of interest to declare.

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