



**MICRONEEDLES: A PARADIGM SHIFT IN MODERNISTIC
APPROACH OF TRANSDERMAL DRUG DELIVERY SYSTEM****KHAN S^{1*}, KASIM A², JATHAR V³ AND RIZVI A⁴****1:** M Pharm Student, Department of Pharmaceutics, HKCP, Mumbai, Maharashtra, India**2:** M Pharm Student, Department of Pharmaceutical Chemistry, Principal KMKCOP,
Mumbai, Maharashtra, India**3:** M Pharm Student, Department of Pharmaceutical Chemistry, VESCOP, Mumbai,
Maharashtra, India**4:** B Pharm Student, HKCP, Mumbai, Maharashtra, India***Corresponding Author: Ms. Saba khan: E Mail: khansabawahid@gmail.com****Received 8th June 2022; Revised 9th July 2023; Accepted 7th Aug. 2023; Available online 1st Sept. 2023****ABSTRACT**

Microneedles have emerged as a promising solution for overcoming the challenges of transdermal drug delivery. Conventional methods like hypodermic needles, topical creams, and transdermal patches face limitations due to the skin's stratum corneum layer, which acts as a barrier for molecules, restricting their entry and efficacy. Microneedles present an innovative approach by creating micron-sized pathways in the skin. These pathways breach the stratum corneum, enabling direct delivery of drugs to the epidermis or upper dermis. As a result, the drugs can enter the systemic circulation more efficiently, bypassing the barrier posed by the skin layer. These microneedles come in various types, including solid, dissolving, hydrogel, coated, and hollow variants, each designed based on the application and materials used. This diversity allows them to cater to a wide range of drug delivery needs, from oligonucleotide and vaccine delivery to insulin administration and cosmetic applications. The advantages of microneedles are multifaceted. They enhance drug delivery efficiency, reduce pain compared to traditional needles, and offer the potential for self-administration. However, there are challenges to address before widespread adoption. Ensuring consistent and precise drug delivery, refining microneedle design and fabrication techniques, managing potential skin reactions, and navigating regulatory approval processes are among the hurdles that need to be tackled. The trend in the field of microneedles is on the rise, with several products already in the market. Nonetheless, continued research and development are imperative to overcome the existing obstacles and

fully unlock the potential of microneedles for diverse applications. This technology holds promise as a groundbreaking method for delivering therapeutic agents, and its evolution will shape the future landscape of drug administration.

Keywords: Microneedle, Transdermal, Nanotechnology, Vaccine, Gene delivery

INTRODUCTION

The field of nanotechnology was first introduced by Professor Richard Feynman in 1959 [1]. The National Nanotechnology Initiative (NNI) was announced in January 2000 which acted as an impetus for nanoscale science and engineering [2]. Nanotechnology can be used in a variety of fields of research and different therapeutic applications. In particular, the technology of nuclear acid-mediated nanomaterials allows exclusive control for dimension, time, anisotropy and mechanics. Without toxic effects, it is capable of binding to various kinds of cells and tissue without affecting the induced immune response or breaking down most biological barriers [3]. Working at the atomic, molecular and supramolecular levels (on the scale of 1-100 nm) enables the understanding, development and use of material structures, devices and systems that have fundamentally novel properties and functionalities as a result of their nanoscale structure. Nanoparticles offer specificity, efficacy, controlled release and fewer side effects [1]. Improved bioavailability, drug-carrying capacity, stability within the body, controlled release

and target release have been obtained due to the physicochemical properties of nanoparticles, making them efficient drug delivery systems. Nanoparticles can be delivered by different routes, including intraocular, nasal, parental, transdermal and oral. The transdermal drug delivery system offers many benefits being non-invasive, avoiding first-pass metabolism and preventing gastrointestinal degradation [4]. Decisions regarding science policy should take into account the amalgamation of nanoscience with modern biology and medicine. To overcome the difficulties related to conventional medications used to treat many chronic diseases like cancer, asthma and diabetes, it may be necessary to use nanoparticles as drug carriers [1].

LIMITATIONS

It is difficult and expensive to formulate and manufacture nano-drug delivery systems. The microneedles have a major drawback concerning the chance of developing infections as they penetrate the skin and expose it to bacteria [5].

MICRONEEDLES: INTRODUCTION

When introduced into the body the effectiveness of pharmaceuticals is influenced not solely by the attributes of the active drug compound, but also by the mechanism facilitating it [6]. Therefore, it is imperative to explore an optimal approach for drug delivery that aligns with the specific characteristics of the drug in question. While oral administration offers simplicity and convenience, allowing patients to self-administer, its application to biopharmaceuticals presents challenges [7]. In contrast, injections yield heightened bioavailability and rapid onset of drug effects, yet their administration necessitates expertise and often suffer from low patient compliance [8]. Engineering microneedle patches for vaccination and drug delivery to skin. Consequently, the ideal drug delivery method should combine the ease of oral administration with the high bioavailability associated with injections. Transdermal delivery has the notable advantage of circumventing the first-pass effect and enabling controlled, sustained drug release. Nonetheless, the stratum corneum poses a significant challenge to effective drug

delivery [9]. Addressing this issue, microneedles offer a transdermal drug delivery platform that is user-friendly and boasts substantial drug bioavailability [8]. Moreover, it is a minimally invasive and painless technique that directly traverses the skin's most substantial barrier, the stratum corneum [10]. By tailoring microneedle design and drug formulation, the dosage, administration rate, and drug effectiveness can be precisely controlled. Numerous studies have explored microneedles, utilizing diverse manufacturing methods and materials to deliver pharmaceuticals and cosmetics [11]. The efficacy and safety of microneedles have been substantiated through animal trials and clinical studies [12]. Within this review, we not only delineate the requisite microneedle types for varied applications but also expound upon the materials employed in fabrication and the manufacturing processes involved. Furthermore, we introduce recent advancements in biological applications and clinical trials in this field. The advantages and drawbacks of microneedles as a transdermal delivery system are succinctly outlined in **Table 1**.

Table 1: Advantages and Disadvantages of Microneedle Transdermal Drug Delivery Tool

Advantages	Disadvantages
Improved patient compliance	Potential for temporary inflammation and allergies
Enhanced drug delivery efficiency	Limited drug dose due to microneedle size
Minimally invasive and painless	Complex manufacturing processes for reproducibility
Bypasses the skin barrier	Need for storage containers for hygienic distribution

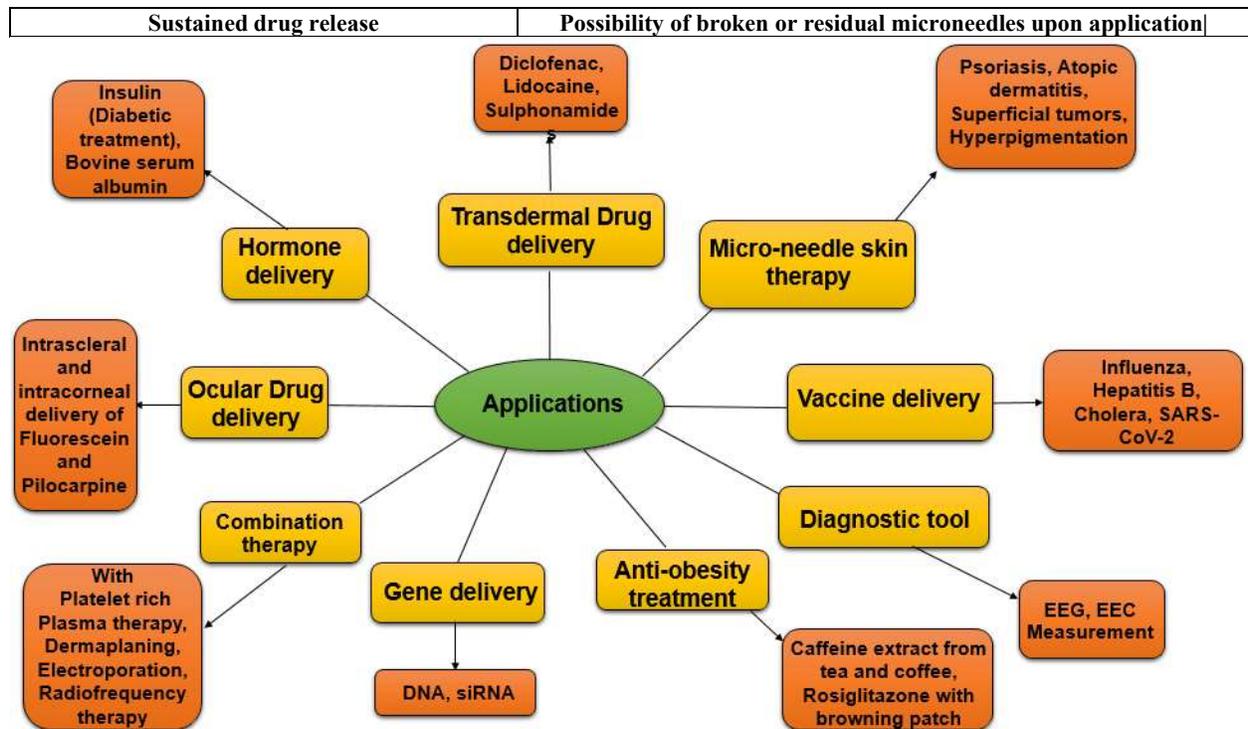


Figure 1: APPLICATION [13]

MATERIALS FOR MICRONEEDLE: The main challenge faced by the world is to manufacture microneedles at a cost which is affordable for all. The manufacturing of micro-needles requires an extensive study of materials that can soothe the skin with no injuries. A key aspect to keep in mind is the material and size of the needles. It plays a very important role in the piercing of microneedles. Microneedles have proved to have varied applications which are made from various materials like silicon in a variety of sizes and shapes. Biodegradable polymers like PLGA, polylactic acid (PLA) and polyglycolic acid (PGA) are used along with photolithographic epoxy. Other materials include metals like

titanium, stainless steel, silicon, and ceramics [15]. Materials used in the manufacture of microneedles are described here:

1. Silicon: Microstructures and microelectromechanical systems (MEMS) use silica for various reasons. A variety of desirable shapes and sizes of microneedles can be produced. To meet the plethora of requirements, monocrystalline or polycrystalline silica is used. Silicon substrates can be produced precisely and in large batches, which lowers costs [16]. A degree of shapes, sizes and densities of microneedles can be produced using silica. Mainly, there

are three main classes of Microneedles- Hollow, Solid and Coated microneedles [16]. Even though silicon has vast applicability, it has certain limitations too. High expenses, intricate fabrication, long fabrication hours and complicated multi-step procedures are some limitations. Biocompatibility of silicon is also a big concern [14, 16, 17].

2. **Metals:** Metals have long been used extensively in medicine [16]. Classic examples include titanium implants prosthetics and stainless steel hypodermic needles [17]. Since these materials are typically used in the production of medical devices, microneedle production shouldn't raise any additional safety concerns, easing the way for regulatory approval [14]. Microneedles can be produced using Titanium, Nickel, Palladium, Palladium-cobalt alloys and stainless steel [18]. Such metals have good mechanical qualities in addition to good biocompatibility [214, 16, 18, 19].
3. **Ceramics:** Ceramics is also amongst the materials used for producing microneedles [15]. The main

technique used to produce microneedles is by using ceramic slurry cast into micro mould. Microneedles are produced mainly using Alumina (Al_2O_3) [14]. Calcium sulfate dihydrate [Gypsum ($\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$)] and calcium phosphate dihydrate [Brushite ($\text{CaHPO}_4 \cdot 2\text{H}_2\text{O}$)] are other types of ceramic used [5]. Adjustment in the properties by varying the composition is an important feature of ceramics [14, 19].

4. **Silica Glass:** Silica glass is an alternative to all other materials [19]. Small-scale laboratories make use of silica glass microneedles of different geometries. They are physiologically inactive, the flow of fluid can be visualized easily and, finally, its dimensions are similar to microfabricated microneedles [14]. Glass microneedles are only used for experimental purposes. They cannot be used commercially on a larger scale in the transdermal drug delivery system [19].
5. **Carbohydrates:** Researchers have put significant efforts into finding the use of carbohydrates in the manufacturing of microneedles. Microneedles can be prepared by moulding hot

melts/slurries of carbohydrates into the main templates of silicon and metal microneedles [14]. Microneedles have been produced using sugars like mannitol, sucrose, trehalose, xylitol, maltose and galactose. Among these, maltose is the most commonly used sugar. The mechanical properties of these microneedle arrangements need extensive study. All the problems concerning the use of carbohydrate microneedles have been studied by Donnelly *et al* [20]. This type of microneedles possesses huge drawbacks like it cannot be treated thermally during the manufacturing process as this arrangement cannot load numerous compounds. Moreover, during the deliverance of the drug, microneedle-produced holes were sealed by partially soluble sugar. Storage of these microneedles also requires optimal temperature [14].

6. Polymer: A promising alternative that has been found is the use of polymers to produce microneedles. Some polymers have proved to have high-quality biodegradability, biocompatibility, low toxicity, and strength and it is inexpensive.

Compared to silicon, metals, ceramic and glass, they have lower strength but provide better toughness [14]. Different types of polymers can be produced using dissolving/biodegradable polymeric microneedle arrays. Swelling or hydrogel-forming microneedle arrangements are other main types of polymeric microneedles [15]. Their function is to deliver the drug as a result of the swollen polymer when body fluid is absorbed. Thus, after removal from the skin, there are no residuals of polymer left [15]. This type of microneedle is good for skin penetration [14].

METHODOLOGY

Microneedle fabrication techniques:

- 1) Laser-mediated fabrication techniques: LMF is a process of eliminating the material freely little by little through the rapid ablation effect caused by encroaching laser beams [24]. Laser precision cutting, laser engraving or carving, laser milling and laser drilling are the different processing techniques used in LMF based on the parameters [24]. There are two methods to fabricate the microstructures on the substrate a) Laser cutting and b) Laser ablation

- a) Laser cutting: It is the elimination of the materials directly using a focused laser beam, which at the same time controls a movable stage with the computerized numerical control (CNC) to create patterns. It involves trimming a polymer into 2D structure [25].
 - b) Laser Ablation: It is the removal of some part of the solid surface metal or polymer by focusing the laser beam. It involves trimming a polymer into a 3D structure [25].
- 2) Photolithography: Photolithography is a process wherein the light having radiant energy is focused onto the patterned layer (usually made of Quartz) which allows the chemical changes on the surface of the coating material providing it a definite pattern [21]. In this process, a photoresist is used to provide a specific pattern which is used to shape the substrate made from a mixture of polymers [22]. The photoresist is coated on the surface of the substrate such that the focused radiating light when falls provides a specific pattern [22]. It is applied in the preparation of prototype/original devices such as magnetic oxide tunnelling junctions, field effect transistors etc. [23].
- 3) Etching: Etching is an intaglio printmaking process which uses a strong acid to incise the uncovered part of the substrate to provide a

specific etch or a tapered shape. There are two types of Etching I) Dry etching and II) Wet etching [27].

I) Dry etching: It is a type of etching which takes place in the plasma phase where different chemicals at the gaseous phase are used. It is also known as Anisotropic etching which is suitable for a wide range of materials [15, 26]. It is divided into two types, namely reactive ion etching and ion beam milling [26, 27]. In reactive ion etching the gas at an excited state reacts with the substrate [27]. The gaseous pressure is responsible for controlling the influence of ions on the degree of isotropy [27]. It has a low etching rate and a high width-to-height ratio that is difficult to maintain. In the Ion beam milling process, etching material is fragmented via the acceleration of inert ions [26].

II) Wet etching: It is the type of etching which takes place in the liquid phase where the liquid phase chemicals are used for etching [27]. It is also known as Isotropic etching which is suitable for crystalline materials. It is used to remove layers of material such as silicon wafers. Wet etching may need strong basic or acid solutions or temperatures much higher than room temperature for their action [26, 27].

EVALUATION OF MICRONEEDLES
[28, 29]

1) Moisture Content:

Record the weight of each patch and place them in a desiccator. After a certain time, again record the weight of the patches. Calculate moisture content (%) by the given formula.

$$\text{Moisture content (\%)} = (w_i - w_f) / w_i \times 100$$

Where,

w_i = initial weight of patch.

w_f = final weight of patch.

2) Thickness of the patch: A digital absolute micrometre was used to obtain the average thickness of the patch. The measurements were recorded for the various areas of the patch. Glass slides were taken and their thickness was measured. Place the patches between two glass slides and measure the thickness with the help of a micrometre. Subtract the thickness of the glass slides for the thickness of the patch.

3) Tensile Strength And Mechanical Strength Of Needles A known approach with certain modifications was used to assess the tensile strength of the patches using an auto tensile tester. Pull the patch using a force and measure it. The tensile strength was calculated by the following equation.

$$\text{Tensile strength} = \text{Force applied to break (N)} / \text{Cross-sectional area of a patch (cm}^2\text{)}$$

Mechanical strength:

A compression test was followed with the help of a Universal testing machine (Testometric, UK) to assess the mechanical strength of the microneedles. On the metallic platform of the probe, the developed microneedles were placed facing downward. The average mechanical strength was recorded in “N”.

4) Percentage elongation: Elongation, stretching and deformation occur due to the applied tensile stress. Measure the Percentage elongation when the patch broke by the applied force. An auto-tensile tester was used to measure the initial and final lengths of the patch at breakage. Percentage elongation was calculated by the formula.

$$\text{Percent elongation} = (l - l_0) / l_0 \times 100$$

Where,

l_0 = initial length of patch.

l = final length of patch.

5) Measurement of insertion force into human skin: A proposed parafilm M (PF) based method was adopted to assess the ability of microneedles to penetrate the skin. The parafilm M sheet was folded to achieve a film of eight layers (approx. 1 mm). The film was placed on a flat surface and for 30 seconds pressed a microneedle patch against it. The parafilm M sheet was opened and on a microscope counted the number of holes on each layer.

6) **Skin irritation study:** Acclimate Female Balb/C mice of weight 20 ± 1 g to the laboratory environment for one week. Anaesthetize the mice with 2.5% isoflurane and using an electric shaver, their backs were shaved. To the dorsal part apply the patch by applying pressure with the thumb for 30 s. The skin was observed for sensitization and irritation for 24 hours.

7) **SEM analysis:** Microneedle patches were examined using SEM for their structure and size.

8) **In-vitro drug release stud:** The release of the drug from the microneedle patch was carried out by fixing it on a dialysis membrane in a Franz diffusion cell. The dissolution medium was a phosphate buffer solution of pH 7.4 having 1% SLS maintained at a temperature of $37 \pm 1^\circ\text{C}$ on a hotplate magnetic stirrer. At specified time intervals, an adequate amount of the sample was withdrawn and diluted to the required concentration. The receptor phase was filled with an equal volume of fresh buffer solution. The absorbance was read on a UV-spectrophotometer.

9) **Ex-vivo permeation study:** The Franz diffusion cell was used for the *ex-vivo* permeability study. Albino mice skin was used as the model membrane between the donor and receptor compartment. The

phosphate buffer solution of pH 7.4 having 1% SLS was poured into the receptor compartment and maintained at a temperature of $37 \pm 1^\circ\text{C}$ using a hotplate stirrer. The samples were withdrawn at specific time intervals and diluted to the appropriate concentration. Refill the receptor compartment with an equal volume of fresh buffer solution. The absorbance was read on a UV-spectrophotometer.

10) **Skin distribution study:** The skin was removed after 48 hours from the cell. By extracting the drug from the tissue, the amount of drug release was calculated using a UV-spectrophotometer.

11) **Transepidermal water loss (TEWL): [30]**

For this, the mice were acclimatized in the laboratory and the dorsal hair of the mice was removed a day before the experiment. Tewameter was used to determine the TEWL at different time points. The probe was placed horizontally on the treated skin at a constant pressure. TEWL measurements were also recorded for the control group.

Challenges in the production of Microneedles: Although delivery of drugs through microneedle technology has advanced very much in the last two decades, it still faces some challenges. The microneedle parameters like geometry, tip diameters,

sharpness, and length have to be taken care of. The dose accuracy, cost and packaging are some challenges which the manufacturers face a lot [31]. Another big challenge is patient compliance and safety concerns like irritation, immune response, and sensitization. The biocompatibility, biodegradability and stability of materials is a serious issue [32]. The microneedle transdermal drug delivery system is facing the test of clinical adaptation measures and its regulatory approval [28].

CONCLUSION

Transdermal drug delivery systems (TDDS) are emerging as a promising field for delivering macromolecules, both systemically and locally. The primary hurdle faced by TDDS is the limited permeability of the stratum corneum, which can be effectively addressed using microneedles. This has led researchers to concentrate on developing diverse microneedle types to facilitate the administration of macromolecules, immunobiologicals, medications, and even the extraction of tissue fluids. Additionally, physical approaches have been integrated with microneedles to amplify the efficacy of drug delivery through the skin. In conclusion, microneedles have garnered considerable scientific interest as an innovative strategy for administering various molecules. This enthusiasm is underscored by the numerous

patents that have been filed to safeguard these inventive concepts, underscoring the expansive potential of microneedles in addressing the complexities associated with macromolecule delivery. The utilization of microneedles holds the promise of achieving enhanced therapeutic outcomes, marking a significant stride in the advancement of drug delivery techniques.

SOURCE OF FUNDING

“There are no sources of funding to declare.”

CONFLICT OF INTEREST

"The author(s) declare no conflict of interest."

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