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MICRONEEDLES: AN EMERGING TECHNOLOGY FOR THE EFFECTIVE TRANSDERMAL DRUG DELIVERY

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ABSTRACT: Topical drug delivery is the conventional route of drug administration to the surface of the skin. Barrier present in the various layers of skin hinders the permeability of drug molecules, specifically large size of drug substance into the systemic circulation. A small-sized needle in micron range is found to be a promising approach to penetrate the uppermost layer of the skin *i.e.*, epidermis to the dermal tissue. These needles are used in the delivery of drugs such as insulin, proteins, RNA and gene therapy due to the efficiency, convenience, safety, and painless nature of the needle. Moreover, the combination of non-carriers with the microneedle delivery system further highlights the application of these needles. This review will discuss the various types of microneedles (MNs) such as coated, solid, dissolving hollow and hydrogels for the effective delivery of drugs and the materials used as fabrication of microneedles. All the microneedles act differently to show its action such as solid MNs produce mini pores in the skin, whereas special channels will be formed into the dermal layer by the hollow MNs and dissolving MNs have explored their role in the delivery of vaccines. It possesses varied characteristics and has applications according to the material used in their formation. This review also focuses on the background, recent trend and summarization of its type along with applications.

INTRODUCTION: With the approximate surface of 20000 cm^2 in an average male, skin is the prime or largest organ of the human body formulates an indispensable barricade to the environmental conditions and an individual [1]. The vital function of the skin remains the containing all the inner organs and to defend them from foreign organisms, thereby acting as a passive barrier [2]. Human skin helps in the regulation of the body temperature and provides insulation. Moreover, the surface area of the skin keeps on changing depending on the age, sex [5], weight gain or loss [3, 4,] and height of the individual. The skin is a receptive organ to pain as well as heat. There are many layers of skin; these include dermis, epidermis, and subcutaneous (SC) tissue, to name a few [2]. SC is the non-living layer that acts as the foremost barrier to foreign bodies and drug delivery.

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Below this layer, we find the epidermal layer with living cells and the absence of blood vessels [6]. Drug molecules penetrate through layers of skin directly across the Stratum corneum by various possible mechanisms such as *via* transappengeal route through the sweat glands, hair follicles and sebaceous glands, offering high permeability to

larger polar molecules as well as ions [7]. Because of the small surface area, there is less data available on the study through this route. However, the transepidermal route acts as a straight pathway to deliver the drug through the Stratum corneum. This occurs through the transcellular or intracellular route. As the skin's surface area is different in different individuals, the thickness of the skin also varies that is important in the absorption of therapeutics [7, 8]. So, the analysis of the skin thickness is considered important, and is outlined in a study of skin thickness of Korean males and females conducted [5].

Trend of Micro Needles: The micron-scale needles can be named the Microneedles and are designed to overcome the limitations associated with their applications. These microneedles are small with a length of less than 1 mm [9]. Over the past few decades, MN has emerged in varied designs, categorized into two types, solid and hollow [10]. Also, a wide range of materials is used in their fabrication ranging from glass [11], silicon [12] metals, silk fibroin, and some biodegradable polymers. In recent research, it has been found that the fish scales are also used in the fabrication of MN. The materials used are non-toxic from a pharmacological standpoint and compatible with the ingredients and inert. The metals that are put to use for the fabrications include nickel that is coated with gold, stainless steel, palladium, titanium, and platinum.

Background: In the mid 1990s the microfabrication technology started to thrive. The rise in use of various armamentariums in the microfabrication industry that resulted in the formation of various microscopic devices ultimately led to the introduction of microneedles for the delivery of drugs. ALZA Corporation was the first to introduce the concept of microneedles in the year 1976.

However, the use and the fabrication of such needles for transdermal drug delivery applications was not included in the scientific literature as late as 1998, further extending the advent to high precision microfabrication tools and microstructure technology. And since then, many studies report the use of various techniques used in the making of different types of microneedles [13].

TABLE 1: MATERIALS FOR THE FABRICATION OF MICRO NEEDLES

S. no.	Fabrication Material	Properties	References
1	Silicon	Anisotropic in nature, crystalline and possesses crystal alignment lattice, Fabrication process is time-consuming so limited use in the formation of microneedles. Due to is brittle nature, it exhibits biocompatibility issues	14, 16
2	Metal	Typically alloys for example palladium-nickel and palladium –cobalt are the major metals used as fabrication material. It possesses good mechanical properties and adequately robust to withstand breaking. Most suitable in comparison to silicon for use in the	17
3	Ceramic	Calcium sulfate dihydrate commonly known as Gypsum, calcium phosphate dihydrate [5] and $Al_2O_3$are the major examples of ceramics being used as fabrication material in the process of microneedles. In recent times, organic modified ceramics are gaining interest due to its good biocompatibility properties	18
4	Silica glass	Borosilicate glass composed of silica and boron trioxide is used for experimental purpose in the laboratory due to its elastic nature. Silica glass is inert physiologically but it exhibits brittle properties. Therefore, not suitable to use as it may have breaking in the skin	19
5	Carbohydrate	Mannitol Maltose, sucrose, xylitol are the certain examples of carbohydrates being used in the fabrication of microneedles. Silicone or metal templates are used to shape carbohydrate slurries. Carbohydrate-drug prepared mixture is loaded into the moulds. Carbs are inexpensive, non-toxic but it has drawback to degrade at higher temperature resulting into difficulty in fabrication	20
6	Polymers	Numerous polymers such as polyglycolic acid, poly lactic acid, poly-vinylpyrrolidone, polyurethanes, poly methyl methacrylate are used for the fabrication of microneedles due to their biodegradable nature	22, 23

Types of Micro Needles: Depending on the research validation and implementation, micro needles are classified into number of types as depicted in **Fig. 1.**

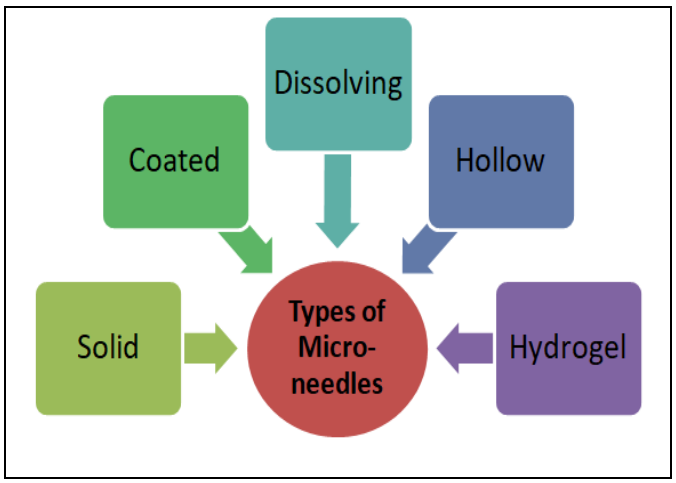

FIG. 1: TYPES OF MICRONEEDLES

Solid Micro Needles: The solid microneedles find their use in the skin pre-treatment as they result in the formation of pores. The pointed tips of these solid microneedles go deep into the skin and result in the creation of micron size channels. Through these channels, the drugs directly enter the skin tissue by applying the drug patch, resulting in increased penetration.

The drug so injected reaches the capillaries for systemic effects and local effects as well [24]. These microneedles help in the delivery of the drugs with passive diffusion in layers of skin [25, 26]. According to a study conducted on polylactic acid micro-needles, it was observed that the solid microneedles made out of biodegradable polymers have enough mechanical strength to go deep into the SC, resulting in the enhancement of the drug absorption [27].

Moreover, these microneedles, which are 800 µm deep and 256 MNs per cm^2 wide, enhance the drug penetration. Many researchers have studied stainless steel microneedles. After the stainless steels were applied to MN arrays, this led to the enhancement of delivery of captopril and metoprolol tartrate [29]. These solid microneedles can be formed from the master mold through casting [31] and electroplating. Such microneedles are used as skin pre-treatment. The formation of microchannels is done through the insertion and removal of the microneedles on the surfaces of the skin across the epidermis and dermis, facilitating the drug diffusion pathways in the body [31, 32]. The most commonly used materials for fabrication can be divided into four groups. These are the non-degradable polymers like titanium dioxide, metals, various water-soluble compounds, degradable polymers. The solid microneedles fabricated with water soluble and degradable polymers materials like galactose, maltose, hyaluronic acid and polyvinyl alcohol (PVA) are considered the dissolving/polymeric microneedles. Reactive ion etching microfabrication technique had to make use of silicon for fabrication for the making of the first SMN [27]. This study also stated the use of fabricated microneedles resulting in the enhancement of transdermal drug delivery. With the use of various micro-electro-mechanical systems (MEMS) techniques, McAllister *et al.* published substantial work on microneedle fabrications with many materials [22]. There is another scientist used a solid silicon microneedle for the study [28].

Hollow Micro Needles: A good representation of hollow microneedles (HMNs) reduces the conventional hypodermic needles to the micro size in terms of length and diameter. Such a needle is used for high molecular weight compounds like vaccines, proteins, and oligonucleotides [29]. If the drug is to be given by the rapid bolus injection, this microneedle helps manage the drug flow and the release pressure. Such needles can be used in order to administer larger doses. This is because the needle has empty space for the accommodation of the drug. However, it is essential to maintain the constant flow [13].

This includes the attachment of single or multiple needles to a plate connected to a device, providing an external driving force for injecting fluid or drug through the internal bore [31]. HMNs were extensively researched during the early stages of the development of microneedle [32]. Existing injectable formulations are used by the HMN for drug delivery, therefore not requiring any additional research for the new formulation. Also, these microneedles allow easy controlling of the doses depending on the needs of the patients. Although, the volume of the drug and the rate of delivery is limited depending on the compaction of the skin [33]. However, such limitations can be overcome by partial retraction. Moreover, one must

note that the clogging of the lumen of HMNs can be done during the insertion because of the density of dermal tissues [35, 36]. So, the drug delivery can be impacted by the design of HMN. One study reported the placement of the lumen hole on the side of the microneedle for the investigation on novel HMN design. Also, in spite of utilizing astraight-walled HMNs the clogging of the lumen holes can be prevented by tapering the needle shaft [37]. Moreover, there have been advancements in HMN fabrication, like the digitally controlled HMN injection system. This also includes the research in the area of HMN-mediated vaccine delivery with the FDA approval of BD Soluvia TM and Micron Jet® for the purpose of vaccination.

Coated Micro Needles: Such microneedles are enclosed with the solution or dispersion layer of the drug [29]. The drug is distributed rapidly into the skin with its dissolution in the layer. Factors like the thickness of the coated layer and the dimensions of the needle influence the amount of the drug to be loaded. Making the use of such coated microneedles that are fabricated with the varied biocompatible and biodegradable materials helps in the administration of molecules possessing high molecular weight. Also, studies have shown that microneedles with drugs in solid-phase are stable in the long term. It was stated by Cormier *et al.* [34] that the desmopressin coated on microneedles showed their stability for around six months when stored under nitrogen at the room temperature. Metals or silicon microneedles were used as the base structure for giving them enough penetrating strength [38].

However, the limitation regarding the proper disposal of the needle and the biohazardous waste post insertion remains the same. So, for the successful coating of the microneedle, few factors need consideration. First and foremost, it includes the accurate placement and uniform coating of the solution. This is to offer accurate dose control, reproducibility and also to maximize the dose. To maintain the drug integrity, efficient coating conditions, as well as proper material, are required. Proper optimization of the materials and methods of coating is required for providing good adhesion of the coating. This prevents their wiping off on the skin at the time of insertion. Finally, the delivery profile is affected by the dissolution kinetics in the skin that is sustained and rapid release [24]. Many methods like roll coating, dip coating, spray coating, layer-by-layer coating were studied [39]. The most popular method is dip coating because of its cost-effectiveness as well as its simplicity. Pharmacodynamic studies are performed on the mice using nanoparticle-coated micro needle-mediated immunization with diphtheria toxoid [40]. Layer by a layer coating method is used for the coating of microneedles with nanoparticles. It was reported that with an increase in coating phases about 3-4 times, the amount of loaded drug is increased [38].

Dissolving Micro Needles: The fabrication of such microneedles is done by the biodegradable polymers through the encapsulation of the drug in the polymer. After the insertion of the microneedles in the skin, the dissolution occurs that releases the drug. Unlike the other cases, the drug application through these needles is a one-step procedure as it does not require the removal of the needle once inserted [41].

The polymer degraded the skin resulting in the controlled drug release. The process of dissolution of the polymer and the bio-acceptability of the microneedle make them the best choice for long-term therapies [42]. While the development of the dissolving microneedles, the major factor that faces problems is the effective needle drug distribution. Therefore, the major step in the fabrication is the polymer-drug mixing [50].

Tip dissolving microneedles were developed that showed fast and efficient delivery of the drug without causing any irritation of the skin. The complete insertion of the dissolving microneedles is difficult and also it takes time to dissolve [25, 43]. Rapidly separating microneedles were developed by Zhu *et al.*, that were mounted on solid micro needles. This gives them enough mechanical strength with an approximate 90 percent delivery efficiency in 30 sec. To prevent the drug diffusion in the micro needles, another report stated the presence of bubbles in dissolving micro needles. These have resulted in the 80 percent drug delivery efficiency in 20 seconds [44]. Such modifications in the dissolving micro needles reflect the possibility of rapid drug delivery along with controlled release kinetics.

Hydrogel-Forming Micro Needles: Such microneedles have been developed recently, making the use of super swelling polymers. These polymers have a hydrophilic structure that helps them take large amounts of water in their 3-D polymeric network [45]. The presence of interstitial fluid results in the swelling of the polymers when inserted into the skin, thereby resulting in the channel formation between capillary circulation and the drug patch [46]. Donnelly and co-workers developed such microneedles making use of hydrogel-forming polymeric matrices. These needles absorb the intestinal fluids rapidly, leading to hydrogel swelling. They result in the generation of unblocked, continuous hydrogel conduits for the penetration of drugs in the skin [47]. The rate of the delivery from such drugs can be regulated by the crosslink density of hydrogel fibers which allows controlled drug delivery kinetics [48]. Such microneedles are used in bio-diagnostic purposes through the analysis of interstitial fluid that get absorbed in the MNs upon their insertion in the skin. These MNs are subtypes of the polymeric microneedle, in which the polymers convey the hydro gel's physicochemical properties [49]. Because of the identical existence of the polymers, regardless of whether or not they have hydrogel properties, the fabrication methods are the same. Centrifugation and vacuum application are used to spin cast micro needles onto moulds.

The properties of the polymers, rather than the fabrication process, control the drug release and permeation profiles to a large extent. Certain cross-linked polymers that have been esterified can be difficult to dissolve when used. This, on the other hand, causes a particular drug release profile, such as bolus release followed by sustained release [48]. The following penetration into the skin, such microneedles breach the stratum corneum, serving as a continuous drug delivery conduit by drawing skin interstitial fluid to the skin's surface at the drug reservoir's place. This allows for the quick delivery of higher protein doses.

Advantages of Micro Needles:

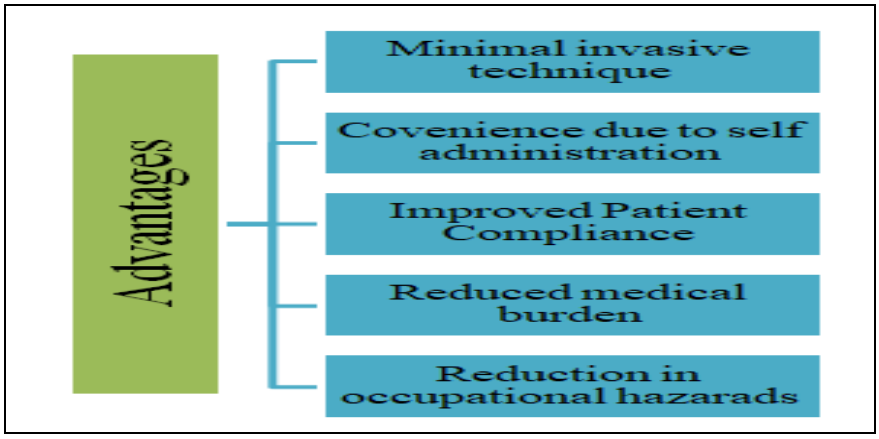

FIG. 2: ADVANTAGES OF MICRONEEDLES, KINDLY STRETCH THIS FIGURE, IT IS NOT CLEAR

Characterization or Testing of Micro Needles:

Physical Characterization: Microneedle output is determined by a number of interdependent variables, including microneedle fabrication materials, manufacturing processes, and parameters, as well as the nature and architecture of microneedle arrays. To pierce the stratum corneum, microneedles must have the right mechanical strength, durability, and stiffness, as well as the ability to resist fracture and buckling failure. Visual analysis, stereo microscopy, and scanning electron microscopy (SEM) have all been used to assess microneedle geometry in previous studies [50, 51]. Microneedle measurements, surface morphology, and needle distribution pattern on the array can all be visualized using this method. The radius of curvature is an important characteristic in microneedle design since it determines insertion efficiency [52, 53].

Fracture Test: The axial compression test, also known as the needle failure test, is the most common test used to determine the mechanical strength of microneedles. A microneedle array is

connected to a test probe, which forces the microneedle at a predetermined speed against a flat metal block of aluminium until the force-distance curve reaches a peak limit. This is also known as the microneedle fracture force [54]. The gradient of the force-displacement slope can also be used to determine the brittleness of the microneedle. The brittleness of a microneedle is related to the gradient's steepness [55]. The microneedles are visually examined after each mechanical compression test to determine any deformation (such as buckling or bending) that occurred during the compression stage of the test procedure.

Insertion Evaluation: Extracted animal skin [52, 56,] and human skin [57] have been used in microneedle insertion tests. To imitate the underlying soft tissue, excised skin is placed with the stratum corneum facing upwards on a flat surface such as parafilm or a wooden cork. Microneedles are manually inserted into the skin as the appropriate treatment site is gently extended to even out any skin folds. The investigator will then add a dye to the treatment site after the microneedles have been inserted and extracted. Microneedle channels are generally stained by two dyes, *i.e.*, Crystal violet [51] and methylene blue [52] . These dyes being hydrophilic in nature, can move downwards and remain inside the hydrophilic channels formed by puncturing the skin, enabling visualization of microneedle channels. Furthermore, these dyes have specific binding ability to the nucleated cells of epidermis and dermis, but it doesn't bind to a nucleated stratum corneum, resulting in staining. A number of dye-stained spots found and the total number of microneedles per array can be used to measure the penetration performance ratio of microneedles [55]. A microneedle must be sharp and slim enough to easily penetrate the skin while still being sturdy enough not to break while within the skin.

In-vitro Characterization: The *in-vitro* release profile of the drug through the skin is studied on Franz Diffusion Cell using skin of pig ear. The drug diffuses into the receptor compartment *via* an effective permeation region of 2.303 cm^2. Phosphate buffer (pH 6.8) as receptor fluid is filled in the receptor compartment to the maximum capacity. The temperature of donor compartment is maintained at 37 ± 2 °C. Then the skin as control is impregnated between both the compartments, *i.e.*, donor and receptor by ensuring the contact of the dermis with buffer solution followed by magnetic stirring 100 ± 20 rpm for 2 h. Then the receptor fluid is replaced with fresh media. The skin is again mounted between the receptor and donor compartment, and drug formulations is applied to the epidermal trimmed skin surface. Samples are withdrawn from the sampling port at predetermined time intervals. Receptor fluid volume is maintained by replacing with fresh buffer after withdrawing each sample. The samples are analyzed using the appropriate analytical method.

CONCLUSION: A large number of drugs use the microneedle approach; however, it needs to meet various challenges before coming into the market like preclinical and clinical studies, to get approval. Major problems linked with the microneedles technology include the irritation, hypersensitivity, and inflammation of the skin. Also, a restricted quantity of the drug can be added into the microneedle. The passage of macromolecules and hydrophilic substances through the skin is a challenge. Moreover, a material that has an adequate strength and insertion force needs to be selected for the fabrication of these microneedles.

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