



# CURRENT TRENDS IN POLYMER MICRONEEDLE FOR TRANSDERMAL DRUG DELIVERY : A REVIEW

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## ABSTRACTS:

TDD is a painless method of delivering drugs systemically by applying a medication formulation onto intact and healthy skin .The drug firstly penetrates through the stratum corneum and then passes through the epidermis and dermis without drug accumulation in the dermal layer. Transdermal drug delivery utilizing microneedles is increasingly gaining interest because to the issues related with oral drug delivery routes. Gastrointestinal route open the drug to acid and enzymes present in the stomach, leading to denaturation of the compound and resulting in poor bioavailability.Microneedle transdermal drug delivery resolves the problems linked to oral delivery and to relieves the discomfort of patients associated with injections to increase patient compliance.Microneedles can be classified into five types: solid microneedles, coated microneedles, dissolving microneedles, hollow microneedles, and hydrogel-forming microneedles. The materials used for the preparation of microneedles ditect the various applications and features present in the microneedle. Polymeric microneedle exhibit present an improved method for transdermal administration of drugs as they penetrate the skin stratum corneum barrier with minimal invasiveness. The review summarizes the significance of polymeric microneedle and discussed some of the most important therapeutic drugs in research, mainly protein drugs, vaccines and small molecule drugs in regenerative medication.

## KEY WORDS:

Skin,Transdermal route, Microneedles, Drug delivery system, Polymer microneedles.

## INTRODUCTION:

The efficacy of pharmaceuticals depends on not just the properties of the active drug component but the mechanism underlying its delivery to the body . Thus, it is critical to investigate an optimal method for drug delivery in accordance with the characteristics of the drug.Oral administration is a simple and convenient drug delivery method due to the patient can self-administer the drug; however, its application to biopharmaceuticals is challeng. Injections bring about high bioavailability and quick onset of drug action. However, expertise is required for administration of drug and patient compliance is low. Therefore, the ideal drug delivery method should be as simple as oral administration and should to show high bioavailability as with injection.

The skin is the outermost and largest organ of the human body, covering an area of 1.8 m<sup>2</sup> and making up close to one-fifth of an average person's total body weight. Being the first barrier to entry into the body, the skin protects against external

threats in the environment, including microbes, harmful UV rays, toxins, inflammatory agents and lack of hydration . Due to the large coverage area of the human skin tissue, it offers a convenient, selective, and painless route for drug delivery. The delivery of drugs via skin overcomes many of the issues associated with oral drug delivery, including the gastric irritation, elimination of hepatic first-pass metabolism, and less patient compliance. Moreover, it offers better release over time compared to oral drug delivery. In addition, transdermal delivery devices are available, replaceable, controllable, and could be self-administered in few cases. Scopolamine, with a primary indication for managing motion sickness nicotine for smoking cessation , and fentanyl for chronic pain are examples of the first generation trans-delivery drug administration is the solution for disease. The greatest challenge in the delivery of active ingredients across the transdermal route is the stratum corneum (SC) that acts as the primary protective layer of the skin and limit the drug absorption. This will significantly lessen the effectiveness of delivery of therapeutic agents and limit the types of drugs that can be delivered into the skin. Recently, there have been few studies on microneedles that penetrate the superficial skin barrier (SC) while avoiding contact with important nerves and capillaries in the epidermis to provide a more efficient and quick method for drug delivery compared to available transdermal drug delivery techniques. The novel approach combines between conventional injection and patch system. The drug is delivered transdermally while eliminating the pain and invasiveness associated with conventional methods in medicine .

Microneedles were first mentioned in a 1998 paper by the research group headed by Mark Prausnitz at the Georgia Institute of Technology that demonstrated that microneedles could penetrate the uppermost layer that is stratum corneum of the human skin and were therefore suitable for the transdermal delivery of therapeutic agents. Microneedles (MNs) have been conceptualized and introduced several years ago but were only successfully manufactured and applied in the 1990 s. The microneedles can be classified according to the function it performs: solid, coated, hollow, dissolving and hydrogel-forming microneedles . The mechanical properties and biocompatibility of the material chosen for the manufacture of MNs are of great importance to the performance of the MNs. Less production cost and high mechanical strength are general considerations for the choice of manufacturing materials. In such manner, polymers are the preferred materials for MNs fabrication as it does not elicit an immune response in the body, degrades in the body and can be tailored to perform with various qualities and function.

Microneedles play an important role in medical field applications for delivering different drugs ranging from small to macromolecules, especially protein drugs that use for the treatment of several diseases. Subsequently, biotechnology organization give more attention toward research and development of MNs loaded protein drugs . However, effective utilization of biotherapeutics is hindered by the large size, hydrophilic nature, poor absorption, and unstable nature of the drug, which prevent efficient uptake through the skin . The advantage in MNs research and production technology will lead to the delivery of clinically important drugs in the future.

#### **Advantages :**

- (1) large molecules can be administered,
- (2) painless administration of the active pharmaceutical ingredient
- (3) first-pass metabolism is avoided,
- (4) faster healing at injection site than with a hypodermic needle,
- (5) no fear of n,
- (6) ease of administration,
- (7) decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures only the epidermis,
- (8) specific skin area can be targeted for desired drug delivery,
- (9) enhanced drug efficacy may result in dose reduction,

(10) good tolerability without long-term oedema or erythema,

(11) rapid drug delivery References can be achieved by coupling the microneedles with an electrically controlled micropump, and

(12) the rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.

#### **Disadvantages:**

(1) dosage accuracy may be less than with hypodermic needles,

(2) careful use of the device may be needed to avoid particles 'bouncing off' the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees,

(3) the thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too,

(4) the external environment, like hydration of the skin, could affect delivery,

(5) repetitive injection may collapse the veins,

(6) the tip of the microneedle may breakoff and remain within the skin on removal of the patch,

(7) a small amount of drug (less than 1 mg) can be given by bolus, and (8) compressed dermal tissue can block hollow microneedles.

#### **Anatomy of the skin :**

The skin is a multi layered organ made of three important layers as presented in Fig. 1. The layer's function to protect the internal organs from a host of outside dangers including toxins, external mechanical tension, and microbial attack from pathogenic species. The skin also functions as a trigger for immune reactions due to the specialized antigen-presenting cells.

The principal skin layer, for example the epidermis layer, is roughly 150-200  $\mu\text{m}$  thick and is made out of viable cells. It is made of five layers according to a degree of cell keratinization: stratum corneum (SC, horny layer), stratum lucidum (clear layer), stratum granulosum (granular layer), stratum spinosum (spinous or prickle layer) and stratum germinativum (basal layer). The peripheral layer or horny layer SC (10–20  $\mu\text{m}$ ) has been 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". Under the SC layer is the viable epidermis layer, which contains the keratinocytes and pigment-creating cells, the melanocytes. This layer is responsible for most drug-related activities, such as drug binding, metabolism, active transport, and surveillance.

The second skin layer is the dermis (3–100  $\mu\text{m}$ ), which follows the viable epidermis layer. Here, the skin is made up a more complex mix of cells with different functions, for example connective tissue, vascular tissue, lymphatic vessel network, sweat and sebum glands, hair follicles and macrophages. This layer not only functions as a host layer for the network of functional tissue but also provides structural support in the skin because of the presence of fibroblasts.

The third layer of skin, the hypodermis (subcutaneous tissue), follows the dermis layer, which contains loose connective tissue. The exchange of molecules across the skin follows a complex series of steps involving many mechanisms. Intracellular absorption of molecules passes through keratin-filled corneocytes by partitioning across the cell membrane. Intercellular absorption, in which molecules surround corneocytes in lipid-rich extracellular regions. Pending absorption as molecules

move through shunts in hair follicles, sweat glands and sebaceous glands.

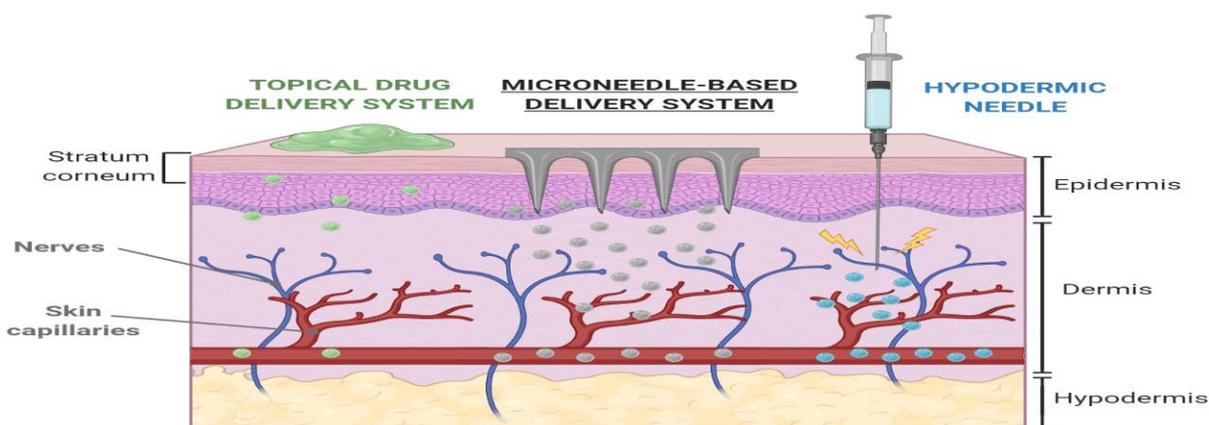


Fig 1: Structure of skin and routes of penetration of a molecules across the stratum corneum

### Transdermal drug delivery (TDD) :

Transdermal delivery is gaining interest as an option for drug delivery. Drugs reach the systemic circulation through the skin without drug loss while reaching their targets, improving bioavailability, improving sustained drug release, minimizing unwanted side effects, and improving physiology. improves therapeutic and pharmacological responses. For example, in testosterone replacement studies, transdermal administration bypasses the liver, overcoming the problems associated with oral and intramuscular administration. The drug initially penetrates through the layer corneum and then passes through the deeper epidermis. TDD is a painless method of delivering drugs systemically by applying a drug formulation onto intact and healthy skin. The drug reaches the dermal layer without drug accumulation in the dermal layer. At the point when drug reaches the dermal layer, it becomes available for systemic absorption via the dermal microcirculation. TDD has numerous advantages over other conventional routes of drug delivery. It can give a non-invasive alternative to parenteral routes, thus circumventing issues such as needle phobia. A large surface area of skin and simple entry permits numerous situation choices on the skin for transdermal ingestion. Besides, the pharmacokinetic profiles of drugs are more uniform with fewer peaks, thus minimizing the risk of poisonous side effects.

The drugs applied through transdermal drug delivery system required to take a convoluted course to bypass through consecutive skin layers containing both aqueous and lipid domains and reach the systemic circulation. A drug molecule must have ideal properties to pass through the SC layer; molecular weight must be less than 600 Da, Log P value between 1 and 3, high but balanced SC/vehicle partition coefficient and low melting point, correlating with good solubility as predicted by ideal solubility theory. Olanzapine is one of the drugs that require physicochemical properties for effective transdermal drug delivery. The poor oral bioavailability of olanzapine and susceptibility to loss during delivery mean that only 40% of the actual dose remains before entering the circulatory system. Together, these properties make olanzapine a good candidate for administration via transdermal patches.

1st generation transdermal drug delivery systems: There are two types of simple patch design. The original patch design is a liquid reservoir system where the patch consists of a backing material that is both protective and adhesive, a liquid drug reservoir, and a release membrane. A more recent design is the adhesive matrix system, where the adhesive and drug are combined in the same layer, leaving the patch with only three layers; a backing layer, a drug and adhesive layer, and a protective layer that will be removed before the patch is applied to the skin. Most of the currently available patches. 2nd generation TDDS attempt to improve the delivery of organic molecules across the stratum corneum by disrupting its barrier function and/or providing some sort of driving force for the movement of molecules across the epidermis. This disruption should be reversible and prevent skin injury. However, it can be difficult to break the barrier without causing damage or irritation, especially when using chemical enhancers. Furthermore, these 2nd generation enhancement techniques are

limited to small, lipophilic molecules and still have little effect on larger or hydrophilic molecules.. In the third generation, new chemical enhancers, electroporation, cavitation ultrasound, microneedles, thermal ablation and microdermabrasion were introduced, these techniques allowed biotherapeutics and large molecules to better penetrate the outer layer of the cornea, resulting in increased efficacy of transdermal delivery in human clinical trials. However, the techniques used abrasive methods, lasers, and heat and radiofrequency exposure that damaged the skin, caused patient discomfort, and led to drug application and treatment side effects. Such limitations can be solved by using micrometer-sized needles called microneedles.

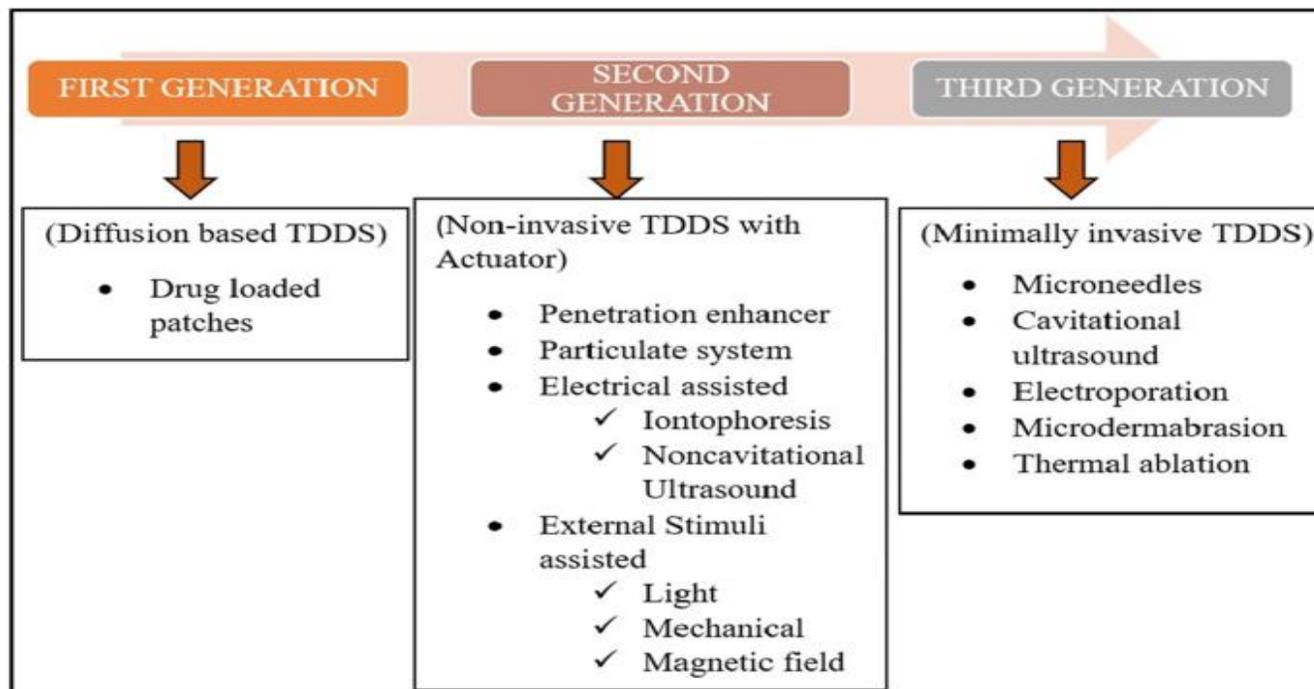


Fig 2 : Generations of Transdermal drug delivery

MNs technology has grown over the past 15 years and allows drugs to pass through the outer layer of the cornea by piercing the skin and creating microchannels in the outer cornea using micron needles. Compared to other transdermal delivery methods, microneedles are able to deliver molecules of larger sizes without disturbing the nerve endings in the skin, thus minimizing or completely preventing the pain experienced by patients. Furthermore, microneedles can be used in both solid and liquid preparations according to the desired disease specifications. MNs hold promise for the future of TDD to facilitate the delivery of drugs with large molecular weight and low lipophilicity, such as proteins, peptides, and vaccines, as well as drugs with poor efficacy at low doses.

#### Microneedle drug delivery system :

Microneedle (MN) technology uses tiny needles to deliver drugs across the SC layer to the underlying layers in a minimally invasive manner. The microneedles used in these delivery systems vary in length. They are only a few micrometers long, but some reach up to 2000  $\mu\text{m}$ . The short length of the MN allows penetration into the SC without touching the nerves of the underlying skin layer. The use of MNs is superior to conventional drugs due to the ease of delivery mechanisms, painless, and minimally invasive devices that offer the simplicity of transdermal application while offering the efficacy of invasive needles and syringes. preferred over the delivery method. Unlike traditional methods, MNs are designed for patient self-administration and do not require special skills or staff. Additionally, MNs are designed for single use. This minimizes the possibility of drug cross-contamination.

#### Types of microneedles:

Although the design of the microneedle varies depending on the route of administration, the type of microneedle, and the effect of the drugs being administered, most patches share some common features A typical microneedle has the shape

of a tapered sharp tip. Microneedles are usually made of metal, silicone, polymer, glass or ceramic. The drug is generally placed in or on the tip of the microneedle, which is attached to the underlying substrate underneath to form the field. The microneedle array is attached to the patch backing for ease of use; this pad contains skin adhesive to improve skin contact.

#### **Solid Microneedles :**

Solid microneedles are an array of sharp, microscopic tips made of a single material without any drugs or excipients. They are inserted into the skin, creating tiny holes in the skin's surface. When the drug is applied to the treatment area, it passes through the stratum corneum, the largest barrier of the skin, through these pores; it is easily delivered to the capillaries of the superficial dermis, increasing the bioavailability of the drug.

#### **Coated microneedles :**

In coated microneedles, the surface of the solid microneedle is coated with a water-soluble matrix, so that the drug dissolves quickly in the skin after the microneedle is inserted. The coating formulation should form a film on the surface of the microneedle and maintain adhesion during storage and insertion into the skin. To achieve this purpose, the coating composition should have adequate viscosity. Consideration should be given to where the drug is placed. In general, it is economical to place drugs only at the tip where the microneedle enters the actual skin. In the case of dip coating, the drug coated area can be controlled by controlling the depth to which the microneedle is immersed in the coating formulation. The drug-coated area can be determined by controlling the surface tension of the coating formulation, thereby controlling the spread of the microneedle. In coated microneedles, the drug can quickly dissolve in the skin, resulting in a rapid onset of action of the drug. Coating thickness can be increased by repeating coating formulations; however, it is not suitable for drug delivery as it requires a large dose due to dose limitations.

#### **Dissolving Microneedles:**

The microneedles themselves can be made of water-soluble or biodegradable materials that contain drugs and have sufficient mechanical strength to penetrate the skin. Inserting the dissolving microneedle into the skin does not produce sharp waste because it quickly dissolves or breaks down when it comes into contact with skin fluid. Dissolving microneedles are primarily produced using a water-soluble biodegradable polymer using a solvent casting method. Biodegradable cellulose-based polymers such as carboxymethyl cellulose (CMC) and methyl cellulose are often used. Carbohydrates (eg, trehalose and sucrose) are also included in the microneedles; they support formulation breakdown and stabilize biomolecules. The drug-containing tip formulation should exhibit compatibility with the drug, provide mechanical strength, and have low enough viscosity to fill the microscale mold space well without air bubbles. The drug-free base substrate may have a higher viscosity than the tip, may be mechanically weak, or may be a water-insoluble material.

#### **Hydrogel Microneedles :**

In hydrogel microneedles, the drug is contained in all areas of the microneedle tip, the base substrate and the back of the patch and is released at a slow rate while the patch is applied to the skin. Microneedle patches are primarily composed of hydrogel, and when they encounter fluids in the skin, they are hydrated but not dissolved. A large amount of the drug in the hydrogel reaches the skin by diffusion. Because the drug can be incorporated into the entire microneedle patch, this system is suitable for delivering large doses; however, its disadvantage is that the wearing time of the patch is long because the drug delivery rate is slow.

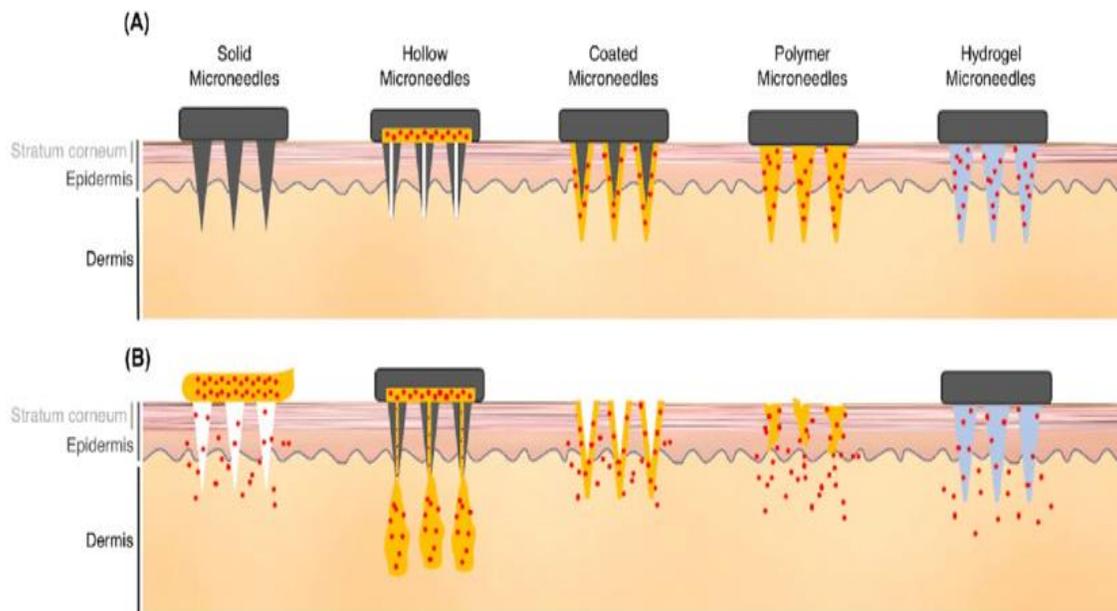


Fig : (A) The structures of solid, hollow, coated, polymer, and hydrogel microneedles.

Fig : (B) Each of these microneedles has different drug delivery properties.

### Polymeric microneedles :

Silicon is fragile and does not metabolize in the body; therefore, the use of other materials such as polymers promoted the fabrication of microneedles. Polymers are preferred due to their low cost, biocompatibility, biodegradability, hygienic use, swelling and dissolving capabilities. This feature reduces the possibility of infection in the body. Polymers are mainly used in the production of dissolving and hydrogel-forming MN arrays. Still, there are few studies using polymers to fabricate coated solid and hollow MNs. This is because the polymer has weak mechanical strength and may fail during insertion.

Polymeric MNs can be classified according to materials, composition, MN construction, and in vivo performance; In solid polymer microneedles, the drug is not encapsulated in the solid microneedles and they are effective in creating holes through the SC. Likewise, hollow microneedles act as an external drug reservoir applied after the formation of microchannels in the skin. Drug formulation and polymers can also be coated onto MNs using various coating methods such as dip coating, cast coating techniques, spray drying, and inkjet printing. However, the drug content of the MN coating layers is limited due to the limited amount of MN. Dissolving MN polymers is considered the most efficient approach and has many applications; drug incorporated into soluble or degradable polymeric MNs. Compared to coated MNs, these MNs can significantly increase drug loading capacity by encapsulating drug molecules throughout the needle instead of coating on its outer surface. Drug release depends mainly on the dissolution and degradation properties of the polymer in the skin. Soluble MNs can be used to rapidly deliver and release molecules. This strategy ensures that drugs are delivered to specific targets and taken up immediately, which is acceptable for short-term applications.

On the other hand, MNs made of biodegradable polymers dissolve over a period of time and find interesting applications in extended/sustained drug delivery, the choice of biodegradable polymers is critical to manipulate and control the gradual release profile of drugs according to their degradation rate. . In addition, hydrogel forming MNs prepared mainly from a polymer that absorbs interstitial skin fluids and swells to form a hydrogel mass to regulate drug release depending on the crosslinking strength of the hydrogel network. This allows for a slow release of the drug over several days. An advanced MN approach combining polymer and micro- and nanoparticle formulations to deliver many different types of therapeutics through the skin. For example, microparticulate insulin embedded in MNs chips provides a greater hypoglycemic effect compared to MNs insulin chips alone. In addition, recent developments have focused on the fabrication of smart MNs

(bioresponsive) for drug delivery control. Unlike soluble and biodegradable MNs, bioresponsive MNs release the drug smartly according to the change of physiological signals, which is achieved by embedding drugs in bioresponsive polymers or encapsulating drugs in physiological signal-sensitive micro- or nanoparticles, such as pH responsive drug release, surface activation of nanoparticles commonly used in cancer therapy, insulin-incorporated glucose in MN array tips, reactive oxygen species (ROS)-responsive microneedle patch for acne treatment, and enzymes that trigger or suppress drug release through inactivity or excessive enzyme expression.

Smart MNs offer opportunities to provide controlled drug delivery based on physiological responses to certain disease states. utilized glucose-responsive nanoparticles to encapsulate rosiglitazone as a browning agent, which was further coupled into an array of polymeric MNs. The pH-sensitive nanoparticles gradually degraded under physiological glucose conditions to release browning agents into subcutaneous adipocytes in a sustained manner, leading to increased whole-body energy expenditure and amelioration of type 2 diabetes in a mouse model of diet-induced obesity. The most commonly used matrix materials for dissolving polymeric MNs are sodium hyaluronate, which occurs naturally in the skin, sodium carboxymethylcellulose, poly(vinyl alcohol) (PVA), poly(vinylpyrrolidone) (PVP), methyl vinyl ether-co-maleic anhydride, dextran, sodium chondroitin sulfate, hydroxypropyl cellulose (HPC), carboxymethyl cellulose (CMC), hydroxypropyl methyl cellulose (HPMC), sodium alginate and hyaluronic acid (HA). Meanwhile, other biodegradable polymers used in MN production, such as polylactic acid, chitosan, polyglycolic acid or poly(lactide-co-glycolide) (PLGA), degrade in the skin after application. In addition to bioresponsive polymers such as cross-linked methacrylate HA (MeHA), cross-linked polyvinyl alcohol (PVA) and cross-linked alginate.

Ideal polymeric microneedles should be biocompatible, nonimmunogenic, mechanically strong, and able to carry large complex drugs without damage. Therefore, the development of polymer microneedles must consider the type of polymer used, the manufacturing process, and the design of the length, width, and shape of the MN tip. Each polymer in the studies provides its own characteristics in terms of strength permeation ability and drug release either immediate or sustained release. The main problem associated with polymeric MNs is the penetration of MNs through the skin layer. Mostly, the mechanical strength of water-soluble polymers is weaker compared to insoluble materials such as silicon or metal, and drug encapsulation can further degrade the strength of MNs. The mechanical strength, modulus of elasticity and fracture toughness of the MN polymer are important; reflects the ability to insert arrays of polymer-based microneedles. Stronger needles will be able to withstand the forces without bending or breaking. Therefore, researchers can combine two or more polymers and other materials to improve the mechanical strength of MNs. In addition, the target tissue for the MN, either transdermal or non-transdermal, must be considered when selecting MN polymers. Non-transdermal targets such as eye tissue, vascular tissues, and the digestive system are often required for MNs that are flexible and easy to use surgically, when targeting soft tissues that may not be able to handle, the right balance of strength and flexibility needs to be considered. pressure of high strength insertion MN. Another factor that makes sense to consider is environmental humidity, as higher humidity levels weakened the strength of MNs depending on the polymer used and the humidity level. In addition, the active ingredient added to the MN polymer patch could increase the mechanical strength, but sometimes increasing the drug content led to a decrease in the mechanical strength of the MN. In addition, the mechanical strength of MNs could be reduced if the drug is distributed in the needles and base plates of the MN arrays, which is manifested by the cracking of the base plate after mechanical evaluation, while the localization of the drug in the needles not only solves the problem of mechanical strength, but also leads to reducing drug waste.

Microneedle design is a fundamental aspect determining the effectiveness of MN form and function. Microneedles are organized as an array of structures in either a cone or pyramid shape that work by piercing the human skin to deliver drugs. The material used in the fabrication of the MN is the most important design factor as it determines the mechanical strength and drug-releasing properties of the MN. Other factors to consider include the density of the material, the height of the microneedle, and the diameter width of the tip and base of the microneedle. Microneedles are arrays of cone- or pyramid-shaped structures made of various materials, generally 250 to 2000  $\mu\text{m}$  in height, that could pass through the human skin barrier to deliver targeted drug molecules. Several researchers have varied MN length, width, thickness, and tip size to

optimize penetration, pain sensation compared to conventional needle injection, and drug delivery efficiency, using different MN designs/geometries could lead to maximizing drug dose efficiency.

Polymeric MNs are commonly produced using compression molding techniques, this method allows for larger scale production, it has limitations as it usually involves multiple time-consuming steps such as template preparation, mold making, plasticization of thermoplastic polymers above their glass transition temperature, hence heat resistant . drugs cannot be used. Researchers solve the problem of thermo-resistant drugs by filling drug and polymer solutions into a mold under vacuum or pressure and drying under ambient conditions, centrifugation or pressure. 3D printing has also recently been described in published reports as an alternative manufacturing technique for MNs. The manufacturing process of microneedles should take into account factors such as the sharpness of MN tips, take place at ambient temperature, the absence of organic solvents, and the preservation of the biological activity of charged drug molecules. Polymeric MNs are capable of enhancing the flow of molecules ranging from small hydrophilic molecules such as alendronate to macromolecules including heparins, insulin, and vaccines. Several studies have demonstrated the efficacy of the MN suite for transdermal delivery of low molecular weight drugs, biological therapies, and vaccines. Biotherapeutics are more complex and expensive than a small molecule pharmaceutical product; they produce by a biological process from living organisms rather than by chemical synthesis including biotechnological methods. Unlike small molecules, macromolecules and proteins are too large to diffuse into the blood capillaries, but are able to enter the lymphatic vessel.

Biotherapeutics classified into different types including products based on vaccines, blood components, allergens, gene therapies, human tissues, proteins and peptides. These biotherapeutics are usually delivered by injection with a needle due to their poor properties. However, it is well documented that patient compliance with this route is poor due to pain and the potential for contamination and infection. The introduction of MNs, which are able to penetrate the skin at a constant depth, allows the introduction of macromolecules to their targets in a fast and efficient way, while avoiding the pain associated with injections due to the absence of contact with nerve endings in deeper layers and skin. In addition, delivering biotherapeutics such as vaccines via MNs that induce a stronger long-lasting immune response with less vaccine compared to subcutaneous or intramuscular injection, as the vaccines would be closer to the antigen-presenting cells present in human skin, as biotherapeutics usually do, may not be administered in large doses, meaning that the dose limitations associated with coated or dissolving microneedle systems are not an issue. Furthermore, with improvements in vaccine stabilization technologies, it may be possible to create microneedle vaccines that avoid the need for refrigeration. Overall, this suggests that microneedle vaccines should be able to be stored under much less expensive conditions and possibly in more locations.

#### **Polymeric MNs—Challenges, Research Gaps, and Future View points:**

Even if the polymeric MNs are found to be biocompatible under the assumption of polymeric material accretion in the human or animal bodies when they are injected, they may cause impairment issues in the hepatic system accompanied by some detrimental immune-based reactions when the se materials are inserted.

Simultaneously to see that there will be a good balance off lexural strength when working with soft-based tissues, which fail to with stand high pressures and high rigidity during the insertion process of the polymeric-based MN. We would like to show case and project what the future holds in the area of polymeric microneedle technology, emphasizing the wide scope for next-generation methods of processing and manufacturing these microneedles according to the requirements of additive-based manufacturing techniques and the sabilityof COVID-19 testing strategies and safe means of in oculation procedures. There area good number of transdermal products which are facilitated by MNs; however, there is a wide scope for development and commercialization. However, there are certain hurdles to ensure in the field of manufacturing these microneedles and their cost-effectiveness.

### Next Generation of Microneedle Technology :

Several studies have been conducted through *in vivo* means of fabrication of MNs, which is used to transport pharmaceutical drugs and vaccines. The daunting task is to fabricate the MN, which can efficiently transport the macro-sized molecules with good molecular loads and a high amount of hydrophilicity. There are varieties of derma rollers available in the commercial markets.

### Microneedle and Additive Manufacturing:

As mentioned earlier, the research community and the pharmaceutical and biotechnology-based industries are heavily applying the concept of 3D printing. The use of this technology is shown to be promising compared to conventional manufacturing methods in terms of the amount of time consumed for production and cost effectiveness.

### Impact of microneedling on COVID-19:

Microneedling has found its way into the global problem of the COVID-19 pandemic. The research team – Chen et al. – developed and presented MN-based oropharyngeal swabs that substantially reduced false-negative results of testing procedures. This concept greatly helped doctors and testing personnel to identify the difference between a positive and a negative sample. If vaccines are incorporated into these microneedles, people can easily administer the vaccine themselves, reducing the risk of long exposure during vaccination at vaccination centers and making life easier for them.

### CONCLUSION:

Polymer microneedles (MN) are a powerful technology for delivering small chemical molecules into large complex biotherapeutics with established clinical efficacy. Transdermal MN-based drug delivery addresses the shortcomings associated with the oral and parenteral routes and is intended for self-administration at home. The successful development of polymeric MNs depends to a large extent on the type of polymer used, single polymer or mixture of polymers, biocompatibility with the drug, design and mechanical strength of the MN. In addition, animal studies and human studies must be included to evaluate MN skin penetration, drug release, pharmacological and toxic properties. Basic studies and commercialization programs need to be combined to accelerate the large-scale production of polymeric MNs, and more efforts are required to develop guidelines regarding the sterilization process and further awareness about the long-term adverse effects and side effects of polymeric MNs in regenerative medicine.

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