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Microneedles as a new approach for transdermal drug delivery system.

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ABSTRACT: There has recently been a lot of interest in transdermal medication delivery systems, which are introduced as a unique strategy, by reducing the strength of action and sustaining drug release, transdermal drug delivery systems lessen the side effects connected to oral therapy. Transdermal administration offers the benefit of avoiding the first-pass impact and enabling continuous medication release. Yet, due to the barrier that the stratum corneum creates, the drug distribution is restricted. With a high drug bioavailability, microneedles are a painless, minimally invasive, and self-administered transdermal drug delivery device. The main idea is to break the skin layer, resulting in micron-sized routes that take the medication right to the epidermis or higher dermis, where it can bypass the barrier and enter the systemic circulation. This article provides an overview of the several varieties of microneedles, as well as their designs, fabrication materials, and production processes. The ability of microneedles to load drugs can be improved in formulation technologies. Several microneedle products have entered the market in recent years. However, before the microneedles can successfully enter the market, a lot more study must be done to address the numerous issues.

KEYWORDS: Microneedles, stratum corneum, transdermal drug delivery.

I. INTRODUCTION :

A group of physicochemical technologies that can regulate the distribution and release of pharmacologically active compounds are collectively referred to as "drug delivery systems" (DDS).such that these active ingredients might exert their actions as effectively as possible in cells, tissues, and organs(1,2). Transdermal administration offers the benefit of avoiding the first-pass impact and enabling continuous medication release as that of oral and parentral administration. Drugs are administered by the transdermal route, which passes them through the skin and into the bloodstream. Yet, the stratum corneum (SC), the skin's top layer, is made up of dead cells called keratinocytes. These flat keratinocytes are encased in a lipid matrix. More than 90% of medications used topically may encounter this layer as a potential barrier, which restricts their absorption and lessens the effectiveness of this method of delivery.Hypodermic injections cause discomfort and are therefore unacceptably uncomfortable. Several innovative formulations have been created to address these issues(3,4,5). Micron-sized projections that resemble needles, as the name implies, make up microneedles. Their length can range from 100 to 1000 mm. They have the ability to pierce through the SC , but because of their small size , they are unable to get to the nerve terminals and do not cause pain. A tremendous amount of work has been put towards creating MNs made of a variety of materials, from metals to polymers, utilising different fabrication procedures(6). In this review, we summarize the types of microneedles required for microneedle design,materials used for fabrication, and manufacturing methods.

Advantages and Disadvantages of microneedles (7,2) :

Advantages:

1.) The stratum corneum serves as a direct route for drug delivery into the body.
2.) Drug action begins quickly (since there are capillary bed and associated lymphatic vessels in the superficial dermis)
3.) Controlling microneedle compositions allows for the delivery of precise medication doses.
4.) Avoids first pass metabolism and have high bioavailability.
5.) Because of their short length and small size, microneedles are safe and painless.
6.) The patch application requires less technical knowledge.

Disadvantages:

1.) Due to the microneedle's small size, the drug dose is restricted.
2.) Allergy and temporary inflammation are two possible causes.

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3.) When being distributed from the makers to the patients, microneedle patches must be held in a storage container to keep them clean and undamaged.
4.) A portion of the solid microneedles may break or remain in the skin after application.

TYPES OF MICRONEEDLES (8,9,10,11) :

1.) Solid microneedles :

When solid microneedles are put into the skin, they produce pores the size of a micron on the skin's surface. Solid microneedles are an array with microscale tapered sharp ends made of a single substance without any medications or excipients. These pores allow the medicine to easily pass through the stratum corneum, the greatest barrier of the skin, when it is applied to the treated area. This increases the drug's bioavailability by allowing the drug to reach the superficial dermis capillaries.

2.) Coated microneedles:

With coated microneedles, a water-soluble matrix is applied to the surface of a solid microneedle such that, following insertion, the medication dissolves quickly into the skin. The coating formulation should create a film on the microneedle's surface and retain adherence throughout storage and skin insertion. The coating recipe needs to have enough viscosity to accomplish this. It is important to think about where the coating formulation will be applied.It is usually more cost-effective to just administer the medications at the microneedle's tip, where the skin is really penetrated. By adjusting the depth at which the microneedle is dipped into the solution when dip coating, the drug-coated region may be managed.

3.) Dissolving microneedles:

The materials used to create the microneedles themselves can be water-soluble or biodegradable and include the medications.enough mechanical force to pierce the skin. A dissolving microneedle can be inserted into the skin without producing sharps waste because it dissolves or disintegrates quickly when it comes into contact with skin fluid. The main method for producing dissolving microneedles is solvent casting with a water-soluble biodegradable polymer. Often used cellulose-based biodegradable polymers include carboxymethyl cellulose (CMC) and methyl cellulose. The microneedles also contain saccharides, such as trehalose and sucrose, which aid in the formulation's breakdown and stabilise biomolecules.

4.) Hydrogel microneedles:

The medicine is present throughout the hydrogel microneedle's tip, base substrate, and patch backing.and is released gradually as the patch is put on the skin. Since the microneedle patches are mostly made of hydrogel, they are hydrated but not dissolved when they come into contact with epidermal fluids. Diffusion allows for the delivery of a significant amount of the medicine in the hydrogel to the skin. This technology is appropriate for big dose distribution since the medicine may be integrated throughout the microneedle patch; nevertheless, one drawback is that the patch-wearing duration is lengthy because the drug delivery rate is slow.

MATERIALS USED FOR MICRONEEDLES :

Microneedles can be made of a variety of materials, including metal and polymer, depending on the patch's design or component parts. In general, materials for microneedles should for skin implantation, the mechanical strength must be sufficient. Non-dissolving microneedles can be inserted into the skin without triggering an immune reaction since they are inert, biocompatible, and powerful enough. The matrix of coated and dissolving microneedles, in contrast, ought to typically be water-soluble and biocompatible. Moreover, it must degrade or dissolve in the body without producing toxicity.

Throughout the production, storage, and transportation of the microneedle patches, drug and matrix compatibility is essential. The following is a description of the properties of several materials used in microneedles.

Silicon (12,13,14,15):

Silicon produces microneedles with high mechanical strength, allowing them to penetrate skin with ease. Solid, hollow, and coated microneedles can all be made from silicon. It can be used to create microneedles of various heights and shapes. The main drawbacks of silicon are its high cost, difficult fabrication specifications, protracted fabrication periods, and multi-step, elaborate processing. A skin fracture that could potentially compromise safety is one of the risks associated with silicon microneedles. On the other hand, silicon has been extensively utilised to

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improve and facilitate transdermal medication delivery.

Metal (16,17) :

Stainless steel, titanium, palladium, nickel, platinum, alloys, and gold are the most often utilised metals in the manufacture of microneedles. Metals are used to create solid, hollow, and coated microneedles as well as their basis. Metals have the advantage of having ideal mechanical characteristics and high tensile strength , which makes SC simple to penetrate. A lot of stainless steel is utilised in the manufacture of microneedles.However, compared to titanium alloys, it has higher rates of corrosion. In comparison to stainless steel, titanium alloys offer greater mechanical strength. Less is known about the use of platinum and palladium in microneedles manufacturing. Nickel should not be used without caution because it has problems with biocompatibility.

Glass (18,19,20) :

Glass microneedles with a range of shapes have been produced and successfully penetrate SC. Most often, the hollow kind is manufactured. The main drawback of silica glass is its brittleness and potential for needle points to break inside the skin, which can result in irritation and granulomas. Yet borosilicate glass has demonstrated strong biocompatibility.

Ceramic(21,22,23):

Alumina, calcium phosphate, and calcium sulphate [50] are materials that are frequently utilised. These components are used to create microneedles that are solid, hollow, or coated. OrmocerVR is a hybrid material created by modifying silicon alkoxide and monomers .It is biocompatible to use alumina. Nonetheless, it has been demonstrated that it will shatter brittlely when manually compressed. Contrarily, calcium phosphate and calcium sulphate have demonstrated the capacity to endure fracture when subjected to insertion in porcine skin , in addition to being biocompatible. It is well established that OrmocerVR is safe to use and has strong biocompatibility.

Polymers(24,25,26,27):

In order to create microneedles that dissolve, are biodegradable, or form hydrogels, polymers have been utilised. Frequently employed polysaccharides include hydroxypropyl methylcellulose, hyaluronic \sacid, carboxymethycellulose (CMC), alginates, or synthetic polymers \slike poly (methylvinylether/maleic anhydride) i.e. \sGantrezVR , polystyrene [58], polyvinyl alcohol, polyvinylpyrrolidone \s(PVP) , polylactic acid, polyglycolic acid, and their co-polymers \s(poly (lactic-co-glycolic acid) [PLGA]). Polymers' biodegradability and biocompatibility are key benefits.

Sugars(28):

Microneedles that can pierce SC are created by sugars such maltose, trehalose, raffinose, mannitol, xylitol, and galactose [63]. However, they also have issues with instability, the requirement for high processing temperatures, and quick pore resealing.

FABRICATION TECHNIQUES FOR MICRONEEDLES (29,30,31) :

The type, geometry, and material of the microneedle all affect the fabrication or manufacturing method that is used. There are numerous methods utilised for various types of microneedles stated in Table 1.

Sr no	Method	Type of microneedles produced
1	Laser cutting	Solid metallic
2	Laser ablation	Solid metallic
3	Vapor deposition	Solid silicon
4	Photolithography	Dissolvable/hydrogel forming, solid ceramic, hollow type
5	Deep X-ray lithography	Dissolvable/hydrogel forming, hollow type
6	Dry etching	Solid silicon, hollow type
7	Wet etching	Solid silicon, solid metallic, hollow type

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8	Pulling pipettes	Hollow glass
9	Metal electroplating	Solid metallic, hollow type
10	Drawing lithography	Dissolvable/hydrogel forming, hollow type
11	Micromolding and melt casting	Dissolvable/hydrogel forming, solid ceramic
12	Droplet born air blowing	Dissolvable/hydrogel forming
13	Two photon polymerization	Dissolvable/hydrogel forming, solid ceramic, hollow type
14	Dipping	Coated type
15	Spraying	Coated type
16	Microstereolithography	Solid silicon, solid metallic

Table 1 ., Fabrication techniques for microneedles.

EVALUATION OF MICRONEEDLES :

1) Characterization methods (32,33,) : Either in suspension/dispersion form or encapsulated form (liposomes, nanoparticles, nanoliposomes), the medicine can be placed onto or into the microneedles. Depending on the type of formulation utilised in the microneedles, several physicochemical characterizations such as particle size, polydispersity index, viscosity, and zeta potential can be assessed for loaded medication. For a patch that is worn following pre-treatment, testing for drug release, adhesion, and permeation are carried out. The measurements of the liposomes or nanocarriers' size, internal structure, and crystallinity can be made with the help of the dynamic light scattering, X-ray scattering, and transmission electron microscopy techniques. Drug dispersion and microneedle stability investigations can be conducted under a variety of temperature, pH, and simulated in vivo physiological settings (cell line or tissues).
2) Dimensional evaluation (34,35) : The tip radius, length, and height of the microneedle are measured using a variety of techniques to analyse the needle geometry. The most popular techniques are electrical or optical microscopy. A 3D image analysis improves understanding of needle shape and aids in quality assurance. This has been accomplished using confocal laser microscopes and scanning electron microscopes (SEM). By using a focussed beam of electrons to interact with the sample's atoms while scanning, SEM creates an image of the sample that contains details about the sample's surface topography and chemical makeup. High-resolution images are produced by a confocal laser microscope.
3) Mechanical properties or insertion forces (36) : A microneedle needs to be robust enough to stay intact while inside the skin while simultaneously being sharp and thin enough to easily penetrate the skin. Table 3 lists the mechanical tests that are run on microneedles. The insertion force and the force at which the microneedle loses structural integrity are two crucial aspects of a safe and effective microneedle design. The "safety factor" is the ratio of these two forces. It is desirable that the ratio be as high as feasible.
4) In-vitro skin permeation studies (37) : With a diffusion cell equipment, it is possible to measure how well a drug penetrates the skin. In the experiment, pig ear skin is primarily employed and mounted between the donor and receptor compartments. We compare the cumulative permeation patterns of skin that has been microneedled and untreated skin.
5) In-vivo animal model studies (37) : The study can be conducted using hairless rats. The animal must be put to sleep using a safe method. Trans-epidermal water loss (TEWL), which is assessed before and after microneedling, is one of the factors taken into account. This parameter is measured with a Delfin Vapometer.

CLINICAL TRIALS AND SAFETY : Many pre-clinical experiments on microneedles were conducted and were successful in many ways, but few of them involved human participants. In 2001, Kaushik et al. carried out the initial investigation on microneedles in humans. The question was if silicon microneedles were smaller than a 26-gauge

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hypodermic needle to lessen pain. The 12 healthy participants who were chosen for the study had the microneedles inserted into their forearms. According to the study's findings, microneedles didn't cause as much agony as hypodermic needles did (3). To determine whether microneedles elicit local skin reactions and are accepted by patients, Arya and colleagues conducted tests. 15 people participated in the study as participants. The study showed that there was no erythema, discomfort, or edoema at the patch application site as a result of the microneedles. Without the applicator, the patients were able to apply the patches themselves. They were more popular among the human test subjects than the standard needles(38). The 21 males who participated in the randomised clinical study were examined to see whether pretreatment with microneedles improved lidocaine delivery. After 60 minutes, 4% topical lidocaine cream induced anaesthesia. Anesthesia was produced after the pre-treatment with microneedles in 30 minutes(39).

II. SUMMARY AND FUTURE PERSPECTIVES :

A micro-sized device has tremendous promise as a painless minimally invasive device while taking into account the necessity and drawbacks of the current TDD systems for the treatment and diagnosis of various diseases and occurrences. To address these issues, a number of TDD systems have been created, including non-invasive transdermal patches, oral delivery, topical lotions, and conventional hypodermic needles. These technologies are still unable to solve the primary problem, which is painless penetration without device breakage while also being continuous and controlled or quick drug release. Microneedles have the potential to combine the requirements for painless application and regulated drug delivery, as well as beneficial qualities like excellent bioavailability and increased skin permeability without skin irritation or allergic reactions (40). With an emphasis on the synchronisation of the load and release of these components, research on the development of microneedles is investigating their potential as a drug delivery system for the regulated and localised distribution of cells, growth factors, and small compounds.

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