REVIEW ARTICLE

Microneedles as A Magical Technology to facilitate Transdermal Drug Delivery: A Review Article

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ABSTRACT

Skin drug administration is the method used to provide drugs for local or systemic therapy, which is recognized for clinical usage. It is the third-largest method of medication delivery, after only intravenous administration and oral administration. Using a transdermal delivery method makes the administration easy, and blood concentration and adverse effects can be reduced. A microneedle is a micron-sized needle with a short height of no more than 500 micrometers and a width of no more than 50 micrometers. The needle comes into contact with the epidermal layer of the skin before it gets to the dermal layer, where there is no discomfort. Several materials, such as metals, inorganic, and polymer materials, are used to create microneedles. All different types of microneedles are employed in different scientific disciplines. In recent years, microneedles have been utilized as a drug delivery method to carry pharmaceuticals, genetic codes, proteins, and vaccinations. In chemotherapy, diagnostics, treatment, and immunotherapy, microneedles were utilized.

Keywords: Microneedles, Proteins, Transdermal drug delivery, Vaccine.

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INTRODUCTION

The Structure and Function of the Skin

Skin is a big and vital organ with an extensive barrier system comprising many layers of skin, which is classified as the epidermis, dermis, and hypodermis. The stratum corneum (SC) is the initial layer of the skin, with an average thickness of 20 to 30 μm, and the hardest substance to permeate for drug delivery consisting of several layers of keratinocytes.[1] Papillary and reticular layers make up the dermis, which is found in the center of the skin and consists of collagen and elastin. Other components of the dermal layer include blood vessels, lymphatic capillary networks, hair follicles, sensory nerve terminals, sebaceous glands, and sweat glands. The hypodermis is the fatty tissue that forms the bottom layer of skin and links the dermis to the muscles or bones.[2]

Applying Drugs through the Skin

The transdermal distribution of medicines refers to the method of administration through the stratum corneum and thus allows for both topical and systemic effects. It is the third-largest method of medication delivery, after only intravenous administration and oral administration. Because of the administration route, the administration route, and the potential to decrease volatility in blood drug concentration and adverse effects, the administration route warrants the use of the medication. Furthermore, because the medicine may skip the first pass side effect of the liver, it will ensure that the medication does not undergo first-pass hepatic metabolism and be destroyed in the gastrointestinal system. While the benefits of this method are numerous, its main drawback is the fact that the skin is a substantial barrier to the efficient transfer of chemicals and medicines.[3] Thus, improving the transdermal medication delivery efficiency is an absolute necessity. The ability of the permeable molecules to pass through the skin can be improved by using a chemical or physical technique. It includes the use of penetration enhancers that assist with chemical processes. Permanent changes in skin permeability might be made using penetration enhancers that work by altering the skin's structure.[4]

MICRONEEDLES

In the 1960s, microneedle technology first saw the light. In 1971, Alza Corporation found that it was in use. a microneedle device that has projections that resemble needles and delivery media (drug molecules) located within the needles, which can diffuse through the skin.[5] Microfabrication promotion was a subsequent development for microneedles. systems, applications in chemotherapy, diagnostics, treatment, immunotherapy, and microneedles were utilized.[6]

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To address the restrictions of the oral route, micro-needles are utilized to administer the medication to the skin. In microneedle applications, needles of micron size are mounted on a patch of micron-size thickness, forming a backing layer. A hypodermic injection may be used with the transdermal patch to create microneedles. One of the major problems connected with transdermal administration is that hydrophilic medicines can't get into the skin fast enough to treat the patient. Hydrophilic and high molecular weight medicines may be delivered to the skin's stratum corneum using microneedles.[7]

Sophisticated technique conveniences with Microneedle's technology, older patients are more compliant, able to self-administer, and have greater access to class III medicines such peptides and proteins.[8]

Additionally, the findings are repeatable to a great extent. The fundamental mechanism of microneedles technology is to produce holes as a conduit for larger-than-drug-molecule-size micron-sized particles and smaller-than-molecule-size particles. This leads to skin disruption and the ability to let big molecules penetrate the skin. For lower molecular weight medicines, physical techniques such as iontophoresis, electroporation, and chemical enhancers can make nano-sized pores, but not Microneedle pores.[9]

These classical topical treatments, such as creams and ointments, are designed to have a topical impact and merely coat the skin's surface. 20% of the total drugs applied as semisolid dose forms can penetrate the skin. Another kind of transdermal drug administration utilizes transdermal patches that allow the medication to pass through the stratum corneum barrier, although the penetration rate is slower than microneedles.[10]

Transdermal medication patches often utilize permeation enhancers to promote penetration, although only a little amount. The needle inserts deeply into the dermis because of its length and diameter. When the needle is inserted, 90% of the loaded medication is injected. Additionally, it is unpleasant, does not occur frequently, and is delivered in little doses, making it difficult for patients to administer it on their own.[11]

Microneedle technology delivers the medication straight into the dermis layer of the skin, avoiding the stratum corneum, and it also provides a physical boost, avoiding discomfort. Vaccine formulations were utilized for different infectious illnesses, such as diphtheria, hepatitis B, and hepatitis C, using the microneedle.[12] Micro-needles may inject medication beyond the skin barrier, and in the dermis, it will allow for faster absorption, better pharmacokinetics, and more immunogenicity of the vaccine. The future use of microneedles for the delivery of medicines and cosmeceuticals has great promise. Drug delivery, excellent patient compliance, lower costs, and prolonged storage are all assured with microneedles.[13]

Features of the Microneedle Patch

The microneedles range in length from 50 to 900 μm, and their diameter is one μm. Microneedles must be able to pierce through skin layers and get access to the deep dermis without leaking or breaking. To avoid the insertion force, microneedles must have mechanical stability. Efficient medication distribution from the microneedles, such as hypodermic needles, should occur rapidly. The long-term performance and endurance of microneedles need to be enhanced, as well as the capacity to contain no leakage while delivering the medication as a liquid into the skin layers.[14]

Microneedle Manufacturing Materials

Silicon

The first Microneedle was created in the 1990s using silicon. Silicon is anisotropic and has a crystalline structure. It has various elastic moduli because of how the atoms are arranged in the crystal lattice. Silicon is malleable, which enables microneedles of various sizes and forms to be produced. Its appealing physical characteristics, as well as its large-scale manufacturing capabilities, enable it to be mass-produced. Because silicon costs and manufacturing processes are time-consuming, silicon is used sparingly in microneedle preparation. Also, the silicon used in most components is brittle and thus may shatter. Because of this, some biocompatibility problems may arise.[15]

Metals

In the process of micro-needling, stainless steel and titanium are the main metal types that are utilized. The palladium-cobalt alloys are good alternatives, too. For metal, strong mechanical characteristics are matched by a high degree of in-vivo biocompatibility. This resin is rather difficult to shatter, so it is more suited for the manufacture of microneedles than silicon. The first stainless steel was utilized in the microneedle manufacturing process.[16]

Ceramic

Aluminum oxide is formed due to energetic, ionic, and covalent connections that hold Al and O atoms together to create an oxide. Additionally, calcium sulfate dihydrate and calcium phosphate dihydrate are other kinds of ceramics. Ormocer® is a recently available biologically modified ceramic.[17] The copolymer is cross-linked using 3D cross-links. Depending on the combination of organic molecules used in polymerization, several kinds of polymers may be made. The ceramic slurry is cast into a micro-mold that has been produced using a micro-molding method, and the finished pieces are taken out of the mold. Micro-molding methods are a lower-cost manufacturing technology that may be utilized for large-scale production.[18]

Glass Made From Silica

Glass may be used to create variable geometries on a small scale. Physiologically inert yet brittle silica glass is often known as "silica glass". Borosilicate glass, which is produced by the reaction of silica and boron trioxide, is much more flexible. They are mostly constructed by hand; therefore, they are more time-consuming. Glass microneedles are exclusively employed to develop new products in the experimental setting.[19]

Sugars

Microneedles are most often made using maltose sugar, the most prevalent carbohydrate used in milk production.

Mannitol, trehalose, sucrose, and galactose are other sugars that may also be utilized. Carbohydrates serve as a source of moisture and nutrients by using silicon or metals as templates to grow mold. Medicated microneedles are manufactured by injecting a drug-loaded carbohydrate mixture into a mold. During the dissolving of carbohydrates, drug release is increased through the skin. The low cost and biocompatibility of carbohydrates are offset by their rapid breakdown when exposed to high temperatures.[20]

Polymers

Polyvinyl alcohol (PLGA), Polyvinyl pyrrolidine (PVP), and others were all used to form microneedles. Dissolving and hydrogel-forming microneedles arrays are formed using dissolving and hydrogel-forming microneedles. These polymers' microneedles have lower strength and stiffness compared to other materials.[21]

TECHNOLOGIES FOR MICRONEEDLE PREPARATION

Lithography, microfabrication, thin-film disposition, etching, and laser cutting all contribute to fabrication technology.[22] The different-sized and shaped microneedles are suitable for use. Like solid, hollow, sharp, and flat, microneedles come in a wide variety of various kinds. Design approaches utilized include in-plane and out-of-plane techniques, which change based on the orientation of microneedles to the backing. Complex processing methods, including both in-plane and out-of-plane processes, have also been used. Microneedles in in-plane designs are parallel to the surface on which they are manufactured, while microneedles in out-of-plane designs are perpendicular to the surface.[23]

Fabrication on a Microscale

Micro-electromechanical systems (MEMS). Micron-scale devices, including micropumps, microreactors, and micromirrors, are made using it.[24] With MEMS (micro-electro-mechanical systems), structures ranging from sub-centimeter to sub-micrometer may be created. Integrated circuit technology has been used as the foundation for MEMS technology. Three main MEMS methods are patterned light-sensitive mask deposition, thin film deposition, and selective etching.[25]

Lithography

Micromachining and microelectronics processes use photolithography (litho-stone and graphene-to-write). Selective exposure to a high-intensity radiation source is used to transfer the master pattern to the surface of a substrate (e.g., a silicon wafer) that has previously been covered with a photosensitive substance. Photolithography is one of the most often used types of lithography.[26]

The Thin Film Deposition on a Substrate

Patterning utilizing photolithographic and appropriate etching methods is used in this procedure on the substrate's surface (e.g., a silicon wafer). Silicon dioxide and silicon nitride are among the most common materials. Substrate thin-film deposition may also be performed utilizing other materials, such as metals, for example, gold. During PVD-based methods, the source material is released and then deposited on the substrate.[27]

Etching

It is very important to etch the films before depositing the images. Wet etching and dry etching are the two most common kinds of etching techniques.[27,28]

METHODS USED TO CREATE THE MICRONEEDLE DESIGN

High-precision Laser Cutting

Laser cutting is used to produce metal microneedles which are then molded into the appropriate shape. Microneedles are created as a solid using a laser to create consistent, laser-cut microneedles from stainless steel or titanium. The design of the necessary microneedles using Computer-Aided Design (CAD) tools like Fusion 360, such as the desired shape, depth, and outside and inner diameters.[29]

Laser Ablation (Ablation by a Laser)

For metals, a laser ablation is a top-down approach. Laser light pulses were used to create solid metal arrays on a metal plate. Solid polymeric microneedles (made utilizing laser ablation of steel molds) were launched in 2020. Polymeric microneedles are injection molded using this kind of mold. Microneedles may be adjusted so the tip of the needles is sharp, and the radius of the needles may be changed using this technique.[30]

Micro-Molding

Dissolving microneedles are made by preparing a mold with a liquid formulation and then filling it with a liquid (Solvent Casting). To produce the mold, a silicon wafer was used as a starting material, and the wafer was subsequently oxidized at 1000 degrees Celsius. Polymeric solutions are put into prepared molds, then allowed to gel. Next, a vacuum or centrifuge is used to remove the air bubbles; the molds are then placed in an oven set to a certain temperature to dry. See Figure 1 for microneedles that are removed after being cooled.[29] This technique enables the low-cost manufacturing

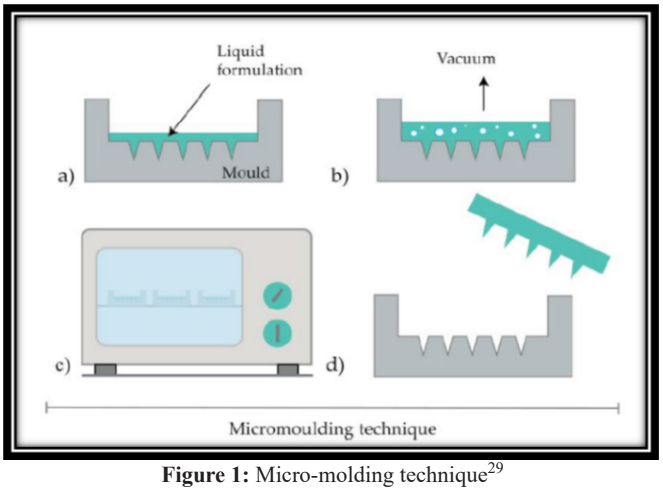

Figure 1: Micro-molding technique[29]

of microneedles at a temperature that doesn't exceed ambient. Using natural or synthetic polymers with the correct shape and adequate strength, one may create biodegradable polymeric microneedles. In the past several years, micro-molding has been used in the manufacturing of ceramic microneedles.[31]

Spraying Technique Using Atomized Spraying Guns

This technique bypasses difficulties in producing dissolving type microneedles with the proper stiffness, geometry, and other physical properties. Because of the larger-scale manufacturing capabilities of dissolving microneedles. Microneedles that dissolve may be made using sugars or polymers (PVA, PVP, CMC, HPMC, and sodium alginate). An atomized spray is produced by a liquid-liquid formulation using a nozzle that is linked to an air source. Once the formulation is pumped into the mold, it is left to dry for two hours at 25ºC. Another way to produce dissolving microneedles that are laminated and laid horizontally is to use atomization.[32]

Fused Deposition Modeling

Beginning to create microneedles using CAD software and CAD software starts with printing microneedles with conventional fused deposition modeling (FDM) printers. The filament used in this 3D printer is suitably thermoplastic, which is fed into the machine via rollers. The temperature is barely over the glass transition temperature (Tg), and the material is transformed into a molten state.[33] In the commercially available printer head, the filaments typically have a length of 1.75 mm and 3 mm. On the other hand, the application of fused deposition modeling in microneedles production is very cost-effective. Another problem is that the resolution of the printer is too low, although this is surmountable by utilizing a high-resolution printer.[34]

Direct Metal Laser Sintering

Microneedles are most frequently fabricated using the stereolithography technique for these reasons: It has excellent resolution, precision, and flawless surface finishing. The premise of this technique is that photosensitive monomers are polymerized with liquid resin through ultraviolet light exposure. Forging the last layers of resin in the presence of high-energy UV light produces microneedle mold. Because the resin surface is coated with a laser beam, which allows the resin to have a precise depth, the shape of the microneedle is formed.[35] After the unpolymerized resin residues have been removed by washing the microneedles in an alcohol solution, they are cured in a UV chamber. Stereolithography is costly and slow, but it produces high-quality components that meet the resolution requirement. Due to biocompatibility, printing materials are kept to a minimum.[36]

Spray-Applied Coating

Using fluid pressure to create a spray of liquid droplets is called spraying. Droplets are produced on the microneedles, and the film is then dispersed and collected. First, small droplets are atomized to produce fine droplets. These are followed by the deposition and adhesion of droplets, which occur simultaneously to create large droplets on the surface of the substrate. Finally, the substrate is covered in a film of droplets, which then coalesce and create a protective layer.[37] The concentration of the polymer, as well as the nozzle's shape, all influence the preparation process (viscosity, surface tension, and density).[38] On apply an unbroken, micron-sized film-coat to silicon microneedle arrays and create dissolving type microneedles, you may utilize the spray coating technique. A coating solution consisting of hydroxypropyl methylcellulose (HPMC), critical micelle concentration (CMC), and surfactant will generate polymers that form a film on the surface of the microneedle array and help the droplets formed during injection to coalesce.[39]

MICRONEEDLE'S CLASSIFICATIONS

There are several categories of microneedles, depending on their function and drug formulation distribution method. The needles in the products above have no active substances, are seldom used, and don't pierce the skin. After insertion and removal of solid microneedles, further application of the drug formulation is needed. Hollow microneedles, which have no opening, allow their application and drug administration in one step. Some people use drugs that are contained in a biodegradable polymeric matrix, which removes the need to physically remove remnants of any drugs after treatment.[40]

Strong, Sharp Solid Microneedles

One single material in the form of an array with a microscale design serves as the core component of the array. This array does not include any medicines or excipients with which it is linked. These microneedles enter and remove. Afterward, the points create tiny holes on the skin's surface. To improve the medication's penetration into the skin, applying the formulation to the pores may increase both local and systemic drug delivery.[41]

Microneedles Fabricated as a Hollow Structure

There are many similarities between these and hypodermic injections, with the primary distinction being the diameter of the micron range injections. These structures are interlaced, forming a single-strand connection in the center of each. The medicines are normally injected into the skin layers with the liquid formulation, although they are utilized to penetrate the skin layers with liquid, as well as with diffusion.[13]

Coated Microneedles

The layers of the skin are coated with an appropriate liquid formulation of the medication, which is then released into the layers of the skin to provide effective medication administration. Microneedles are inserted after that, coating in situ dissolves, followed by medication release, and removal of the device is no longer required.[7]

Biodegradable/Dissolvable/Hydrogel-Forming Microneedles

The drugs may be encapsulated within the microneedle matrix, and the polymers of sugars may be used to produce the microneedles. Once the microneedles are applied, they will disintegrate or degrade locally, allowing the medication to be

released. As the needle tip of a hydrogel-forming microneedle swells in the epidermal layers, it absorbs water and the resulting pressure aids in the release of medication. they enable the medication to be released from the reservoir and transported throughout the body.[5]

Separating Microneedles

In this kind of microneedles, the medication is encapsulated in a water-soluble matrix. To decrease skin deformation during insertion, the biodegradable polymer is sandwiched between two polymer arrays and acts as the spacer. The drug-loaded microneedles disintegrate after implantation into the skin and enter the interstitial fluid. Remnant patches may be peeled off against the skin with little resistance.[7,42]

CONCLUSIONS

In addition to being used to transport medicines and biomolecules, microneedles have also been proposed as a drug delivery method. It is seen as a skin-layer delivery method that enhances physical capabilities. Additionally, this technique is regarded to be a new, and therefore distinct, form of transdermal administration compared to the conventional delivery system. As this study demonstrates, it is feasible, repeatable, and cheap to manufacture transdermal patches. Compliance will be improved using microneedles, particularly for medicines with high bioavailability given more than daily. The formulation eliminates injections using hypodermic needles and with minimal toxicity. Instead of oral medication, this method avoids the first-pass effect. Vaccine-like influenza administration is being done using microneedles since fresh investigations on the production of covid-19 are underway. Microneedling is a viable delivery option for anticancer medicines that may cure a variety of conditions.

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