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REVIEW ON MICRONEEDLE DRUG DELIVERY SYSTEM

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ABSTRACT

In recent years, a transdermal drug delivery system which combines the technology of transdermal patches and hypodermic needles, have been the focus of research and development. Because traditional needles are hundreds of microns long, they cause extremely little or no discomfort. The stratum corneum, the outermost layer of the skin, functions as a lipid barrier for molecules, restricting their pharmacological effectiveness. As a result, only a few molecules make it to the action site. Microneedles are a brand-new delivery method. These delivery techniques help to improve medicine delivery through this channel while reducing the problems that standard formulations cause. Because the usage of micro-needles bypasses the stratum corneum barrier, it has gotten a lot of interest. The pharmaceutical technique necessitates breaking the epidermal layer, which has led to research into producing a micron-sized needle that allows the medicine to reach the systemic circulation without being obstructed. The mechanics and applications of microneedles were explained in this review. Microneedles can be made in a variety of shapes and sizes, including solid, dissolving, hydrogel, coated, and hollow. The kind and material of the microneedle usually determine the fabrication procedure. This technique has a broader use and significance in a variety of sectors, including cancer, vaccine administration, insulin delivery, and cosmetics. Many microneedle products have been offered on the market in recent years. Although much work and research is required to overcome the obstacles, it may also increase the performance of microneedles.

KEYWORDS: Microneedle, solid microneedle, coated microneedle, dissolved microneedle.

INTRODUCTION

The most often utilized formulations for topical drug delivery through the skin are

hypodermic needles and topical lotions. Patients are less likely to use needles because of the pain and irritation they cause. The skin acts as a primary barrier to the delivery of drugs via the topical mode of administration. The outermost stratum corneum layer, the middle epidermis, and the thickest of all, the deepest dermis layers make up the skin. The stratum corneum layer acts as a primary barrier, allowing just a few lipophilic compounds and medications with low molecular weight to pass through. Because skin is less permeable, there are some challenges in developing topical products.[1, 2]

Various topical or transdermal drug delivery systems, such as nano carrier loaded topical creams, transdermal patches, and micro needles, micro needle patches, and so on, have been researched for enhancing drug penetration activity via the skin. Researchers have conducted a number of experiments on the transdermal route of medication administration in order to reduce the constraints of traditional dosage forms.[2]

Microneedles are solid or hollow cannulas having an exterior diameter of not more than 300 mm and a length of 50–900 mm. For transdermal drug delivery, microneedles can be manufactured within a patch. Patches with microneedles have been tested for medication, biopharmaceutical, and vaccine administration, among other things. The microneedle gadget is made up of micron-sized needles that are organized on a small patch. In order to address the issues connected with the microneedle drug delivery method, which is a mix of the hypodermic needle system and the transdermal patch, was invented. The fundamental problem with transdermal drug administration is that many drugs do not pass through the skin at the required rate for therapeutic activity. Researchers have developed microneedles to inject hydrophilic high molecular weight compounds into the stratum corneum. As a result, more medication molecules can come into contact with the skin.[2]

Microneedles provide very accurate reproducibility and maximal bioavailability in addition to improved therapeutic application. It has a lot of benefits, but it also has some drawbacks. It may irritate or induce an allergic reaction in people with sensitive skin. Because the needle is so little and thin, similar to the thickness of hair, it's possible that the tip of the microneedle can break and remain inside the skin, causing a slew of difficulties. It occurs seldom, but can be avoided by carefully selecting microneedle materials.[2]

Microneedles provide the following advantages[3]

- Large molecules can be delivered.

- Painless administration.
- Avoidance of first-pass metabolism.
- When compared to a hypodermic needle, the injection site heals faster.
- Targeted drug delivery can be possible.
- It's possible that improved pharmacological efficacy will lead to a dose reduction.
- Tolerance is good, with no long-term oedema or erythema.
- By combining microneedles with an electrically regulated delivery device, rapid medication administration can be achieved.

Microneedle disadvantages include[3]

- Dosage accuracy may be less than with hypodermic needles.
- The medicine must be administered with care, otherwise it will bounce off the skin surface.
- Particle penetration depth may vary depending on the external environment and the thickness of the stratum corneum and other epidermal layers, which varies from person to person.
- The external environment, affect the drug delivery and bioavailability.
- Frequent and repetitive injection administration may collapse the veins.
- Compressed dermal tissue can block hollow microneedles.

Dimensions of Microneedles

Depending on the type of microneedle and the material utilized, microneedles can be made in a variety of sizes. Because the epidermis has a thickness of up to 1500 m, the needle length should be sufficient to deliver the medicine into the epidermis. Needles having a longer length and a thicker diameter might pierce the nerves, causing discomfort. They are typically 150–1500 microns long, 50–250 microns thickened, and 1–25 microns thick at the tip.

The purpose of a microneedle device is to develop a micron-sized drug delivery system. The needles' diameter is controlled to a few microns. Microneedle tips come in a variety of forms and sizes, including cylindrical, triangular, pointed, pentagonal, and octagonal.[4]

Microneedle Fabrication Materials

Silicon

In the 1990s, silicon was used to create the first microneedle. Silicon has a crystalline

structure and an isotropic characteristic. Its qualities are determined by the crystal lattice solid's orientation, which has distinct elastic moduli (50 to 180 GPa). Their ability to adjust enables for the creation of needles of various sizes and forms. Because of its physical qualities, it is a more adaptable material. Silicon can be precisely fabricated and mass-produced in large quantities. Silicon is inexpensive, yet it is a time-consuming process to produce. Furthermore, because silicon is brittle by nature, some parts may break and remain in the skin, posing a major health risk.[5,6]

Metals

Stainless steel and titanium are the most common metals used in fabrication. Also utilized are palladium, nickel, and palladium-cobalt alloys. They are biocompatible and have good mechanical qualities.

Metals are more suitable for microneedle manufacture than silicon because they are robust enough to prevent breakage. For the first time, stainless steel was employed in the production of Microneedle. Titanium is also a good stainless steel substitute.[7, 8]

Ceramic

Because of its chemical resistance, ceramic alumina (Al2O3) is commonly utilised. Because of the highly energetic ionic and strong covalent interactions between Al and O atoms, they form a stable oxide.[9] Gypsum (CaSO40.2H2O is a calcium sulphate dehydrate and brushite (CaHPO4.2H2O) calcium phosphate dihydrate are two more forms of ceramics utilized. Ormocer®, an organically modified ceramic, has also been employed in recent years.[10]

It's a copolymer that's three-dimensionally cross-linked. During the polymerization process, different organic components can be used to create a polymer with a variety of properties. Typically, they are made using a micro-molding process. A micro-mold is filled with ceramic slurry. Micro-moulding procedures are less time-consuming than casting processes, and they can easily be scaled up.[11]

Silica glass

Silica glass is a biologically inert and brittle material. The elasticity of borosilicate glass, which is made up of silica and boron-trioxide, is stronger than that of type I glass. Glass MNs are no longer used commercially and are solely used for utilitarian reasons.[12]

Carbohydrate

One of the most often utilised sugars is maltose, which is a carbohydrate. Other sugars such as mannitol, trehalose, sucrose, xylitol, and galactose, as well as polysaccharides, can be used. Silicon or metal templates are used to make carbohydrate slurries. The drug-loaded carbohydrate mixture is poured into the molds to make the microneedles. The controlled breakdown of carbohydrate regulates medication distribution into the skin. Carbohydrates are cheap and safe to eat, but they deteriorate at extremely high temperatures, making the manufacturing process difficult to use.[13]

Polymer

Microneedles can be made from polymers such as polymethyl methacrylate (PMMA), polylactic acid (PLA), polylactic-co-glycolic acid (PLGA), poly glycolic acid (PGA), polycarbonate, cyclic-olefin copolymer, polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), polystyrene (PS), and poly methyl vinyl. Microneedle and hydrogel microneedle arrays are made with these polymers. These polymers' microneedles are less strong than those formed of other polymers, but they are more durable than glass and ceramic.[13]

Microneedle Types

Generally, four types of microneedles have been used. Solid microneedles (SMNs), hollow microneedles (HMNs), dissolving microneedles (DMNs), and coated microneedles are the four varieties of microneedles that are commonly used (CMNs).[14]

Solid microneedles (SMNs)

There are several different varieties of microneedles that are upgraded ideal designs of SMNs. SMNs are hypothesised to be a way of pre-treating additives before they pass through the skin. After injecting and extracting SMNs, micron-sized channels may persist at the skin's surface. A channel's shape, depth, and diameter ratio are described using the SMN design. There are a total of 20 SMN phases, ranging from 5 to 20. After SMNs are administered, small pores in the epidermis and dermis are unable to move as quickly, preventing the patch from becoming a more efficient drug delivery mechanism. The very simple "poke and patch" procedure, which represents an early stage in microneedle formation, demonstrates the SMN mechanism. In later devices, microneedles and combination patches have become prevalent.[15,16]

Hollow microneedles (HMNs)

Hollow microneedles (HMNs) have a structure and mechanical qualities comparable to hypodermic needles with a channel, there are holes in the centre of the needle tubes as well as holes on the needle tips. A strain device activates the hollow cavity of the needle, supplying the additives. The ability of compounds stored inside the needle to flow into the frame may be completely controlled utilising custom-built mechanisms, resulting in a bespoke architecture for one-of-a-kind drug delivery requirements. HMNs are used for high molecular weight compounds such proteins, vaccines, and oligo nucleotides, according to earlier research.[17]

Coated microneedles (CMNs) and dissolving microneedles (DMNs)

After injection into the layer of the pores and skin, and with enough contact time to the watery surrounds of the tissue, the coated drug layer of CMNs remains water soluble, allowing the medication to be released from the outer layer. Bleomycin-coated microneedles were developed to administer bleomycin therapy deep into the epidermis, resulting in an effective and safe kind of wart therapy that does not cause discomfort or fear in patients. CMNs are now being studied for use in the treatment of peanut hypersensitivity reactions. A CMN group treated with peanut protein extract had much better clinical symptoms and elevated Th1 cytokines than an untreated group, demonstrating that a CMN technique with faster immune regulation, including the Th1 pathway, can be used successfully. CMNs are also important in eye disease treatment; a more detailed explanation can be found elsewhere.

DMN devices are made of biodegradable polymers that contain the therapeutically active substances that will be administered, as previously stated. The needle's tip will dissolve, flow into, and metabolise within the human body, therefore material selection is critical not just to meet a range of biological parameters such as mechanical strength and durability, but also to ensure bio-friendliness. The rate at which the polymer component dissolves determines the medication release.[17, 18]

Microneedles Fabrication

For many years, individual little microneedles have been handcrafted for scientific purposes, and since the 1970s, low-cost microneedles have been used for medicine delivery. The microelectronics sector did not provide the micro fabrication tools needed to design microneedles suited for pharmaceutical purposes until the 1990s.

The majority of microneedle fabrication techniques are based on classic micro fabrication methods for adding, deleting, and replicating microstructures using photolithographic processes, silicon etching, laser cutting, metallic, and other methods.[17,18]

Table 1: Fabrication methods for a variety of microneedle kinds.[1]

Types of Microneedle	Fabrication technique
Silicon microneedle	Silicon dry-etching process, Isotropic etching, Anisotropic wet etching, Dicing a silicon substrate and then acid etching. Three-dimensional laser ablation,
Metal microneedles	Laser cutting, Wet etching, Metal electroplating methods.
Polymer microneedles	Photolithography.
Ceramic material microneedles	Ceramic micro moulding and sintering lithography.
Coated and covered microneedles	Microneedles that have been coated and covered by using an aqueous solution containing a surfactant to dip or spray the microneedles, the active agent, and a stabilising agent to retain more formulation after drying. Microneedles can be immersed in a coating solution once or multiple times, each microneedle can be dipped into a medication solution-filled microwell., or a film of drug solution can be applied previously created on the roller. Coating processes that are applied layer by layer.
Dissolving microneedles	Micro moulding.
Hollow shaped microneedles	Micro moulding.

Applications of the Microneedle Drug Delivery System

The microneedle drug delivery system can be used to treat a variety of genetic skin diseases, as well as malignancies and infectious diseases. It can also be used for immunization. Because numerous cells may be treated at once, the microneedle medication delivery method of gene is superior than the microinjection technique. As a result, microneedles can distribute bioactive substances both systemically and locally. Antiviral, anti-diabetic, genetic, oncological, anti-osteoporosis, dermatological, and other forms of action should be the focus of future research and studies.[3]

Microneedle in Cosmetics

The stratum corneum, which is only 10–20 m thick and effectively blocks the delivery of most molecules into the body, is the primary barrier in the case of skin. Microneedle patches (MNPs) are meant to penetrate the stratum corneum with micron-scale pores large enough to allow drugs, including macromolecules, to enter the skin with the least amount of pain, irritation, and needle anxiety. MNPs, which are made up of solid microneedles that encapsulate or coat pharmaceuticals, are the subject of the research. This review excludes

hollow microneedles, which can be used as tiny hypodermic needles for injection.[19]

This concept has led to the development of a wide range of MNPs with different transport mechanisms for transdermal delivery of drugs that would otherwise require injection. In a 1 cm2 region, MNPs are made up of an array of 102–104 microneedles. Every microneedle is typically 100–1,000 m long and is made of either (a) a non-water-soluble cloth lined with a drug system, or (b) a water-soluble cloth containing saccharides and/or polymers to encapsulate medication inside the microneedle matrix.[2]

The procedure aids and stimulates skin's natural restoration while producing no long-term damage to the epidermis.[3] The majority of cosmetic items that adapt themselves to microneedle technology are for non-surgical and non-ablative treatment of skin conditions such as ageing (wrinkles, lax skin), scarring, and other skin conditions (acne, surgical),photo-damage, hyper pigmentation (age/brown spots), and hair loss (alopecia).[3]

Microneedle used in cancer

The patch should give an upgraded transport system for immunotherapeutic medications, a recent increase in precision, and most cancers research, according to a recent invention published in Nano Letters. These therapeutic techniques do not directly attack the tumour cell; rather, they disrupt the mechanism by which malignancies avoid being detected by the body's immune system.

Drug delivery using a micro-needle patch is currently being investigated for a variety of purposes. A patch, according to a researcher from the Centers for Disease Control (CDC), will be a "game-changer" for measles vaccination.[20]

Microneedle used in myocardial infarction

A microneedle patch with cardiac stromal cells (MN-CSCs) for mending coronary heart tissue after acute myocardial infarction was employed in myocardial infarction (MI). To carry out mobileular-based totally coronary heart reproducibility, cells are injected with drug into the coronary heart via direct muscle injection, intravascular infusion, or epicardial patch transplantation. The software of the MN-CSC patch effectively enhanced coronary heart capacities and stronger angio myogenesis in the rat MI version investigation. MN-CSC patch software proved to be reliable and resulted in coronary heart feature protection in a pig MI model investigation. The MN system is a modern method of drug delivery to healing cells for

coronary heart regeneration.[21, 22]

Microneedle used in pain therapy

An analgesic microneedle (AMN) patch for the painless transdermal delivery of selective CGRP antagonist peptide for the treatment of localized neuropathic pain is becoming more sophisticated now days. Measurement of behavioral ache sensitivity in response to thermal and mechanical stimuli was used to assess local analgesic effects in rats using concerned aching models such as spared-nerve injury and diabetic neuropathy ache, as well as a neurogenic inflammatory ache model induced by UVB radiation.[23]

Because of the high specificity of the injected peptides against the CGRP receptors, the microneedle patches provided effective analgesia for neuralgia without affecting the rat's normal nociception and motor function. Unlike many standard medications, the AMN patches did not cause skin infection or have a systemic effect. Finally, they demonstrate that CGRP antagonist peptide delivered by dissolvable microneedle patches is a potent, safe, and simple technique for relieving neuropathic pain that outperforms current treatments.[24, 26]

Approved Marketed Products

Derma roller was the first microneedle product on the market. Many microneedle devices are now available on the market, all of which are FDA-approved for medical and aesthetic applications. Microneedle items are sold by several companies in Germany, the United States, Europe, and Japan.[24,25,26]

Table 2: Approved Microneedle Products.

Product name	Company name	Description of the product	Uses
Dermaroller®	Dermaroller® Germany, White Lotus.	A cylindrical roller with solid or metal microneedles, 0.2–2.5 mm in length.	Improve skin texture, treat scars and hyper pigmentation.
C-8 (Cosmetic type)	The Dermaroller Series by Anastassakis K.	A needle length of only 0.13 mm (130 μm).	Used to enhance penetration of topical agents.
CIT-8 (Collagen Induction Therapy	The Dermaroller Series by Anastassakis K.	A needle length of 0.5 mm (500 μm)	Used in collagen induction and skin remodeling.
MF-8 type	The Dermaroller Series by Anastassakis K.	A needle length of 1.5 mm (1500 μm)	Treat scars.
MS-4	The Dermaroller Series by Anastassakis K.	A Small cylinder, 1 cm length, 2 cm diameter, and	Used on facial acne scars.

		4 circular arrays of needles which are 1.5 mm in length	
MicroHyala®	CosMed transdermal drug deliver	Dissolving microneedle patch with hyaluronic acid	Wrinkle treatment
LiteClear®	Nanomed skincare	Solid silicon microneedles are used as pre-treatment and then drug applied topically.	Treats acne and skin blemishes

CONCLUSION

Microneedles are a new technology that can deliver pharmacological macromolecules both systemically and locally. Excellent permeability through the stratum corneum is a feature of this device. As a result, the research focused on the development of new extraordinary types. Microneedles are used to treat diseases such as cancer and heart attacks. In conclusion, Microneedles were structured by cramming as many patents as possible to cover the invention.

This field is particularly important for the future since it allows for the improvement of therapeutic index through the use of Microneedles. Although microneedles have advantages over typical transdermal methods in terms of drug delivery, it should be noted that the MNP is still in its infancy, and many approaches to model design and fabrication aren't ideal.

In uncommon cases, the overall performance of matrix fabric fluctuates, and analogous invention is desired. Many factors have an impact on the most recent industrial cost. MNP is an intrusive procedure that involves the use of chemicals on the skin, and the risk of infection must be considered. More research and study into MNP software is desired in order to overcome current challenges and expand the scope of software.

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