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A Review on Recent Advancement in Material and Manufacturing Techniques of Microneedles and Their Clinical Development

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ABSTRACT

A Microneedle (MNs) is an advanced technology in transdermal drug delivery system for effective and efficient delivery of vaccines and therapeutic agents. It has many advantages over conventional needles; it is non-invasive, provides painless insertion, avoid first pass metabolism etc. Microneedles are designed and fabricated by using suitable materials like silicon, metals, polymers, ceramics, etc. MNs are classified according to their mechanism of action; structure and their plane of symmetry etc. Summary of the advancement made during recent years in the clinical translation were also streamlined. This review article highlights an overview of micro needle systems, applications, classification, material selection, manufacturing methods and clinical data of MNs.

Keywords: Microneedles (MNs); Applications; Silicon; Metals; Ceramics; Polymers; Clinical data

INTRODUCTION

Transdermal delivery and percutaneous absorption are relatively old ideas. The influence of transdermal medication administration has expanded dramatically throughout time, from the ancient Roman Unguentari to Galen's cold cream to more contemporary applications including chemical permeability enhancers, iontophoresis, microdermabrasion, ultrasound cavitation, and micro needles [1]. Transdermal drug delivery can avoid some of the problems associated with oral and systemic drug delivery, such as severe pH swings, intense enzymatic activity, liver metabolism, and, in the case of systemic distribution by hypodermic needles, discomfort from injections and needle stick injuries.

LITERATURE REVIEW

Along with hair follicles, nails, and glands, the skin is a component of the integumentary system [2]. Our skin appears to be a static barrier that shields our interior organs from external environmental dangers. It remains a helpful predictor of systemic disease despite being a highly active organ that is essential to immunity, inflammatory response, and tissue repair. Historically, skin was simply considered a barrier to drug administration, but more lately, it has developed into an attractive area of research enabling a wide range of transdermal and intradermal technologies (**Figure 1**).

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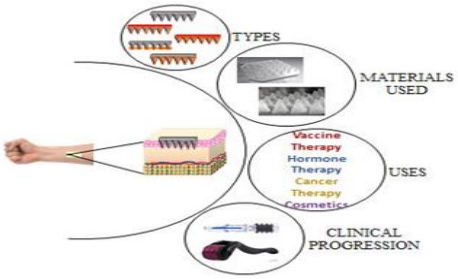

Figure 1: Types and materials used.

Transdermal delivery is not without drawbacks, and formulators continue to face difficulties with it [3]. To achieve systemic absorption at necessary therapeutic levels, only small molecule, lipophilic compounds generally those below 500 Da can passively diffuse through the stratum corneum to reach underlying layers. Microneedles have been researched recently to deliver medications *via* the intradermal route in an effort to get around the drawbacks of more traditional approaches. Microneedles are multifunctional, conical, pyramidal, or micron-sized (1000m in length), penetrating protrusions that have several advantages for intradermal medication administration. In order to overcome the skin's natural barrier function and enable the distribution of certain medicinal chemicals that would be impossible to distribute *via* the transdermal route, microneedles are applied to the skin [10]. The microneedle's small shaft is long enough to pass through the stratum corneum but not deep enough to reach the nerve terminals beneath. The first introduction of medication penetration *via* skin using a microneedle in 1976 [11] resulted in less pain and minimal invasion. Showed microneedle medication delivery system's mechanism and history of microneedles (**Figure 2**).

History of Microneedles

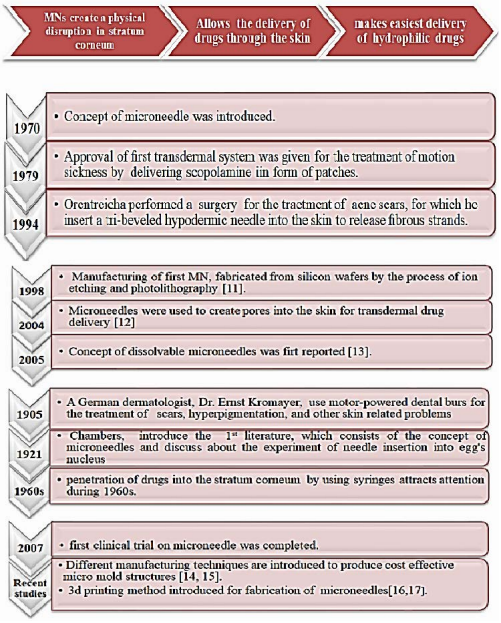

Figure 2: Mechanism of action and history of microneedles.

Classification of Microneedles

MN is an advanced technology that allows for minimally invasive drug delivery across the stratum corneum into the skin's deepest layers [4,5].

There are many ways to classify microneedles on the basis of structure, method of manufacturing and according to their symmetry etc. Generally, MNs are classified into the five types as shown in **Figure 2**.

Hollow Microneedles

Hollow microneedles have a bore on the needle tip and an empty chamber inside each needle. Through a "poke and flow" method, this enables the injection of tiny amounts of medication solutions beneath the skin [6]. Glass, silicon, ceramics, and metal have all been used to create hollow micro needles. When one of the well-known problems with the "poke and patch" strategy is contrasted with the advantage of hollow micro needles, it becomes obvious. After the solid micro needles have been removed, the skin heals quickly and the micro channels that was formed collapse. In addition to avoiding the stratum corneum, hollow micro needles also offer non-collapsible micro channels that can be left *in situ* for however long is necessary to deliver the desired treatment [7]. While this can be avoided by constructing the microneedles with an off-center hole, hollow microneedles are not without problems and can experience instances of micro channel obstruction.

Solid Microneedles

Metals and minerals including silicon, titanium, stainless steel, and in some cases polymers make up solid micro needles. In "poke and patch" systems, solid micro needles are used to form micro channels in the skin in two steps before being withdrawn and replaced with a backing layer, patch, solution, or cream that contains drugs [8].

Coated Microneedles

By using a "coat and poke" strategy, coated micro needles aim to do away with the requirement for a two-step application. Solid microneedles are coated with a thin layer of the chosen therapeutic substance [9]. Dip coating, ink-jet printing, and other spray drying techniques are frequently used to achieve coating. The effectiveness and uniformity of the coating, as well as issues with the coated layer being removed during insertion and remaining on the skin's surface, as well as the retention of the coated drug on the microneedles after removal from the skin, are all connected to coated micro needles as shown in **Figure 2.** The drug loading capability is restricted by the thickness of the coating layer and the size of the needles.

Hydrogel Microneedles

Swellable hydrophilic cross linked polymers are used to create hydrogel microneedles [10]. Due to the hydrophilic properties of the polymer, the hydrogel microneedle expands when inserted into the skin when there is interstitial fluid present. An intriguing recent advancement in the field of microneedle technologies is the invention of hydrogel-forming microneedles.

This is because they can operate as a medication delivery system into or across the skin and passively retrieve interstitial fluids, which may enable their use as a diagnostic tool. In the creation of hydrogel microneedles, Poly (Methyl Vinyl Ether co-Maleic Acid)(PMVE/MA) cross linked with Poly Ethylene Glycol) (PEG) is one of the most widely utilised polymers.

Dissolving Microneedles

Traditionally, biodegradable polymers have been used to encapsulate drugs to create dissolving microneedles. The polymer comprising the needle architecture degrades after

entering the stratum corneum and releases the medication that was trapped inside. Since the micro needle is not removed after application, dissolving microneedles require a one-step application process. This kind of mechanism is known as a "poke and release." Due to the nature of their method of action, dissolving micro needles are able to address a number of the problems associated with solid micro needles since they require no more manipulation after insertion [11]. The advantage of having microneedles that dissolve under the skin essentially lowers the possibility of post-application needle-stick injuries.

Advantages and Disadvantages of MNs

There are various benefits and drawbacks associated with various types of microneedles. Solid microneedles are strong, rigid, and have good mechanical properties; nevertheless, the manufacturing process is relatively expensive and complex, and delivery involves two steps: Pricking and sticking [12]. Coated microneedles are used to administer vaccines, but loading is poor because there is only one stage of micro needle penetration into the skin. Although hollow microneedles can quantitatively and precisely regulate the rate at which vaccines are delivered, there is a chance that the hollow catheter will become blocked. This will reduce the effectiveness of the delivery and make the microneedles challenging to clean during the manufacturing process. Hollow microneedle production calls for more precise technology, which is more expensive [13]. Additionally, solid sharps debris can become trapped in the skin when solid, coated, or hollow micro needles break after use. Dissolving microneedles dissolve into the skin after penetration and don't cause subsequent injuries by producing sharps waste. Delivering higher doses is also made possible by the fact that dissolving microneedles can carry more medication or vaccine material than other varieties. However, the production technology for these microneedles still needs to be improved in terms of quality control throughout fabrication. To solve the blockage issue of hollow micro needles, hydrogel-forming micro needles absorb tissue fluid in the skin to build a continuous, non-clogging pipe. However, since a new substance is used in the manufacturing of hydrogel microneedles, its safety has not yet been examined (**Figure 3**).

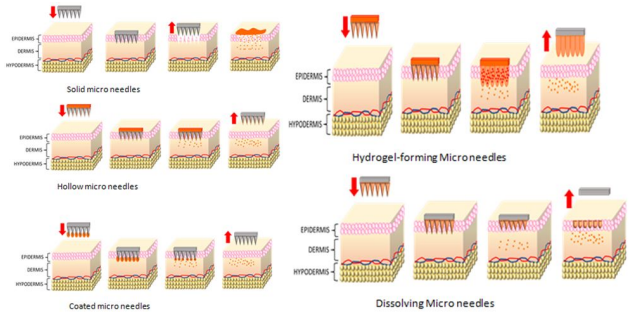

Figure 3: Classification of microneedles with their mechanism.

Drug Delivery Mechanism

The diffusion mechanism is used to administer the medicine *via* the topical route. The skin is momentarily damaged during

the medication delivery process using microneedles. In order to administer enough medicine to produce the necessary therapeutic response, a microneedle device is created by arranging hundreds of microneedles in arrays on a tiny patch (similar to that of a typical transdermal patch available on the market). By cutting through the stratum corneum, it avoids the barrier layer [14]. The medicine is immediately injected into the epidermis or upper dermis layer, where it enters the systemic circulation and, upon reaching the site of action, produces a therapeutic response.

RESULTS AND DISCUSSION

Production and Materials used for MNs Construction

Numerous researchers have worked to create techniques to produce various types of micro needles using various materials since the first successful manufacturing of solid micro needles made of silicon using the reactive ion etching method. Microneedle manufacturing materials should have a high tensile and mechanical strength, be non-immunogenic, non-irritating, non-corrosive, and biocompatible. Microneedles are currently made mostly from silicon, glass, ceramic, metal (nickel, titanium), polymer, and other materials [15]. Laser cutting, atomized spraying, micro-molding, droplet-borne air blowing, Three-Dimensional (3D) printing, hot embossing, deep reactive ion etching, and electrochemical machining are the most often used techniques to create microneedles, depending on the material.

For drug delivery and target applications, several drug carriers have been created and tested over time, with polymers being the most popular choice. The chosen materials must provide protection, be biocompatible, biodegradable, mechanically durable, and not affect the safety, potency, or effectiveness of the encapsulated substance. The complexity of drug release varies depending on the design and types of materials used, with the mechanisms of drug release being closely related to drug diffusion, dissolution, and carrier matrix degradation. The release kinetics, however, can also be influenced by other variables, such as interactions between the substance and the medicine [16].

The placement of the drug inside the matrix and the drug's solubility are important factors regulating the release kinetics and, consequently, the effectiveness and efficiency of the treatment, in addition to physicochemical and morphological features. There are different types of materials used for the manufacturing of MNs enlisted in Figure 4.

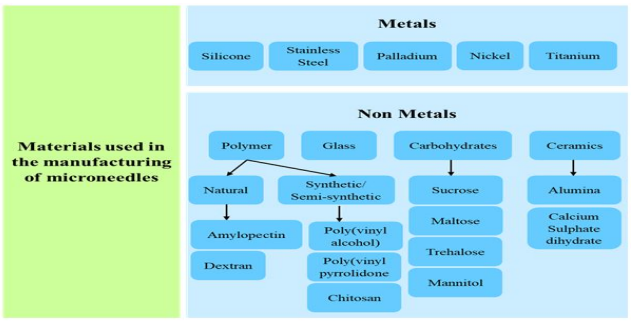

Figure 4: Materials used in the manufacturing of microneedles.

Silicon

The first material utilised to create micro needles was silicon. With the advancement of technology, there are currently numerous ways to create silicon microneedles, including electrochemical machining and etching (dry etching, wet etching, reactive ion machining, deep reactive ion machining, etc.). Microneedles that are made can be solid, coated, or hollow [17]. Microneedles can be made from the same inorganic substances as are used to make ceramics, such as alumina, calcium sulphate, and calcium phosphate. Micro molding or the conventional ceramic sintering procedure can be used to create solid ceramic micro needles. Pulling pipettes in a high-temperature liquid state allows glass made of silicon dioxide and other oxides to be stretched into the shape of microneedles, although this technique can only be used to create hollow micro needles.

Metal

Micro needles can be made from metals such as nickel, titanium, stainless steel, and other materials; stainless steel was the first metal to be used in this way. Metal microneedles can be created using dry etching, wet etching, electroplating (or electro deposition), electrochemical machining, laser cutting, micro stereo lithography, and micro-molding alone or in combination. However, because to their expensive price, metal microneedles are mainly solely employed as microneedle dies.

Polymer

Micro molding, droplet-born air blowing, hot embossing, 3D printing, and other techniques can be used to create microneedles made of sucrose, trehalose, hyaluronan, polyvinyl alcohol, poly vinyl pyrrolidone, carboxy methyl cellulose, and other sugars or polymers [18]. The droplet born air blowing technique has the benefit of being a low-cost, low-cost, ambient temperature preparation process for direct and quick creation of microneedles. However, due to human factors, the microneedle arrays made in this manner are not uniform. Hot embossing can create a consistent microneedle array, but because high temperatures are needed during the production process, it is not recommended for the delivery of non-heat-resistant materials. 3D printing can be used to generate homogenous microneedle arrays under mild settings, overcoming the drawbacks of the other two techniques, however the required equipment is expensive and the production efficiency is low [19]. The micro-molding technique has grown to be the most popular way to make polymer microneedles due to its benefits of quick production, comfortable working conditions, reusable moulds, and low cost. Microneedles that dissolve, generate hydrogels, or are coated can all be found in manufactured products.

Silica Glass

On a tiny scale, glass can be used to create a variety of forms. Although biologically inert, silica glass is brittle by nature. More elastic is borosilicate glass, which is composed of silica and boron trioxide. They take longer to produce because they are primarily made by hand. Glass MNs are currently only utilised experimentally and not commercially.

Ceramic

Chemical resistance is the primary reason that Alumina (Al_2O_3) is employed. The highly energising ionic and covalent interactions between Al and O atoms lead it to form a stable oxide. Additionally, Calcium Sulphate Dihydrate (Gypsum, $CaSO_4$ $0.2H_2O$), and Calcium Phosphate Dihydrate (Brushite, $CaHPO_4.2H_2O$) are utilised as ceramic materials. Ormocer, an organically altered ceramic, has been utilised recently. It is a cross-linked copolymer in three dimensions. Different organic units can be used during polymerization to create a polymer with various characteristics. They are mostly made with a micro molding process. A micro-mold is filled with ceramic slurry. Techniques for micro moulding are less expensive methods with scalability.

Manufacturing Methods of Micro Needles

Numerous researchers have worked to develop techniques to produce various types of micro needles using various materials since the first fruitful production of solid microneedles made of silicon using the reactive ion etching method. Microneedle manufacturing materials should have a high tensile and mechanical strength, be non-immunogenic, non-irritating, non-corrosive, and biocompatible. Microneedles are currently made mostly from silicon, glass, ceramic, metal (nickel, titanium), polymer, and other materials. Laser cutting, atomized spraying, micro-molding, droplet-borne air blowing, Three-Dimensional (3D) printing, hot embossing, deep reactive ion etching, and electrochemical machining are the most often utilised techniques to make micro needles, depending on the material (**Table 1**).

Table 1: Different techniques for manufacturing micro needles from various materials and types of microneedle used.

Material used	Method of manufacturing	Type of microneedle used
Silicon	Etching (silicon dry-etching, isotropic etching, anisotropic wet etching).	Solid, hollow and coated microneedles.
Metal	Laser ablation, etching, injection mold, metal electroplating.	Solid and hollow
Ceramic	Micro-moulding, lithography	Solid and hollow
Polymer	Lithography, injection molding, casting, laser ablation	Solid, hollow, coated and dissolving.
Titanium	Micro Electro Mechanical Systems (MEMS)	Solid, hollow and coated.
Glass	Pulling pipettes	Hollow
Stainless steel	Laser cutting, laser ablation, etching, electroplating, electro polishing, lithography and micro stereo lithography coated	Solid, hollow, coated
Nickel/iron	Laser-ablated ion, Micro molding, electro less plating, wet etching.	Solid, hollow and coated
Thermoplastic starch	Electro-discharge machining process.	Dissolving
PVA	Atomized spraying process.	Dissolving and hydrogel
PVP	2PP, atomized spraying process.	Dissolving and hollow

Application of MNs

The capacity of a molecule to permeate the skin determines the efficacy of a transdermal application. Due to their large molecular weight, many compounds, primarily peptides and vaccines, have encountered difficulties during production and application. MNs have demonstrated successful intradermal administration of such compounds, and in some situations, they have been found to be more efficient at delivering smaller dosages for the same therapeutic benefit than the existing conventional delivery systems. For instance, when MN was used instead of a conventional intramuscular injection, a similar change in the hemaglutinin inhibitory antibody titer was observed with less than half the drug concentration. The fact that numerous regulatory bodies approved the seasonal influenza vaccine administered *via* MN was proof of the MN systems' performance. Besides this, MNs also possessed numerous applications listed below.

Vaccine Therapy

A biological preparation is a vaccination. It offers a disease-specific active acquired immunity. A vaccine is made up of a disease-causing microorganism's toxins, one of its surface proteins, or a deceased or weakened version of the microbe. Vaccine therapy boosts the body's immune system and offers defence against coming into contact with microorganisms in the future. The use of microneedles in vaccination therapy has been proven to be successful.

A microneedle was used to administer the DNA vaccination. Immune responses were substantially more favorable than with standard injections. Additionally, an effort was undertaken to create a microneedle patch that might be used to administer the influenza vaccination. In comparison to intramuscular injection, a smaller amount is needed when the medicine is delivered using hollow microneedles. Hollow micro needles used in the administration of the rabies and anthrax vaccines were also investigated. To improve the intradermal method of immunisation efficacy, Ogai and colleagues created hollow microneedles from poly-glycolic acid. The medicine is precisely delivered to the top dermis, enhancing immunity.

Hormone Therapy

Insulin is a peptide hormone. To lower the elevated blood sugar levels, medication is needed. It has been discovered that administering insulin with a microneedle lowers blood glucose levels more effectively. Li, et al., created solid microneedles and investigated how the delivery of insulin affected the blood glucose levels in diabetic mice. The outcomes showed a decreased blood glucose level to 29% of the initial level at 5 hours, demonstrating better insulin permeability to the skin when employing a microneedle. Ye and colleagues studied pancreatic beta-cell capsules that are combined with microneedles that sense blood glucose levels and produce insulin [20]. But it was discovered that the fix did not work well. Thus, synthetic Glucose Signal Amplifiers (GSAs) were created using microneedle matrix and nano vesicles that included the enzymes glucose oxidase, -amylase, and gluco amylase. These amplifying devices demonstrated the release of insulin from -cell capsules. The results of a clinical trial using microneedles coated with parathyroid hormone (I-34) showed that they had a 3 times shorter Tmax and a 2 times shorter apparent T1/2 than standard injectable therapy. These investigations showed that hormone therapy can effectively use microneedles. Additionally, they can be

altered for long-lasting activity by using the right polymers. Additionally, the use of ion tophoresis in conjunction with microneedles to administer different hormones is a possibility.

Cancer Therapy

Every year, millions of individuals throughout the world are affected by cancer, and cancer treatment is incredibly difficult. For the delivery of several anticancer medicines, micro needles have been studied. In order to cure melanoma, self-degradable micro needles were tested for their ability to administer anti-PD-1 (aPD1) over an extended period of time. Anti-PD-1 and glucose oxidase loaded dextran nanoparticles that are pH-sensitive, delivered through MNs. Basal cell carcinoma is treated with a topical 5-fluorouracil cream. When the cream was applied to skin that had been pricked with solid microneedle, the permeability of 5-fluoro uracil was increased by up to 4.5 times. Significant tumour growth inhibition provided additional evidence of the increased effectiveness of micro needles. Tamoxifen and gemcitabine administration by microneedles for the treatment of breast cancer were the subjects of research by Bhatnagar, et al. The negative effects of these medications could be decreased with localised distribution. Polymeric microneedles have also been studied for localised administration of anticancer medications and skin cancer.

Cosmetics

The usage of microneedles in cosmetics is becoming more popular, particularly to enhance skin look and heal scars and blemishes. The use of microneedles was attempted to administer several cosmetic active substances, such as ascorbic acid, eflornithine and retinyl retinoate. Phosphatidyl choline liposomes (nano liposomes), which displayed improved solubility in lipids, were modified to include melanin. On application with an e-roller, it was discovered that there was more pigment that penetrated deep near the hair structures. The use of micro needles to improve the distribution of melano statin, rigin, and palmitoyl-penta peptide (pal-KTTKS) was also studied.

Approved Products

The derma roller was the first item with micro needles. There are numerous microneedle items on the market that can be used for both medicinal and aesthetic purposes. **Table 2** lists a number of them. Micro needle items are sold by numerous businesses in Japan, the US, Europe, and Germany.

Table 2: Currently available approved MNs devices and their applications.

S. no.	Company name	Marketed product	Applications
1.	Nano biosciences	Admin patch® Micro needle arrays.	MN contain six stainless steel screws and permits continuous delivery of drugs by laminated the transdermal patch on the back surface of the micro needle.
2.	Valeritas Inc., bridge water, NJ, USA	V-Go	A disposable insulin wearable patch like device.
3.	Nano pass technologies	MicronJet™	Single-use MNs, used for intradermal delivery of drugs, proteins and vaccines.
4.	Becton dickinson, franklin lakes, NJ, USA	BD Soluvia™	Allow intuitive, simple and reliable delivery of drug. The first hollow micro needle approved for vaccination.
5.	Zosano pharma Inc., United Sta	Adhesive Dermally Applied Microarray (ADAM)	Used for the delivery of zolmitriptan.
6.	DermaIndia, Chennai, India	Derma roller® microneedle rollers	Helps to treat some skin conditions.
7.	Sanofi Pasteur, swift water, PA, USA	Fluzone® intradermal quadrivalent	Used for delivery of the seasonal influenza vaccine.
8.	Debioject	DebioJect™	Connected with any standard syringes to ensure the full penetration of the microneedle into the skin.

Scale-Up of Manufacturing of MNs and Their Clinical Development

Since their creation in the 1970's, microneedles have undergone steady development. In the years thereafter, the study of MNs has advanced dramatically. Glass and stainless steel, two well-known materials, have been used in the MN mode of drug delivery to many different polysaccharides. The fabrication technology has become simple and commercially successful thanks to a solid understanding of the microelectronics industry and its growth. MNs have been created using a variety of polymers. Through these technologies, a precise control over drug distribution has been made possible. MNs create possibilities and offers doors to reshape the field of drug delivery for molecules of all sizes. Researchers have been working continuously for the past 20 years to translate their scientific findings into clinical claims. Furthermore, the recent clinical development data of MNs are also depicted in **Table 3**.

Table 3: Clinical data of MNs that have completed clinical trials.

S.no.	Drug	Condition	Company	Registry No.	Phase	Status
1	Pilocarpine microneedle patch	Cystic fibrosis	Emory university Georgia institute of technology	NCT04732195	Not applicable	Suspended in 2021
2	Microneedle patch	Healthy	University of Iowa	NCT03332628	Not applicable	Completed in 2021
3	AIVIA, ultra-brightening spot microneedle patch	Solar lentigines	Panion and BF biotech Inc.	NCT04583852	Not applicable	Enrolling by invitation in 2021
4	Hypodermic needle	Oral cavity disease		NCT03855397	Not applicable	Completed in 2019
5	Microneedle	Vaccination skin absorption	Emory university micron biomedical, inc	NCT03207763	Not applicable	Completed in 2020
6	Microneedle patch	Topical anaesthesia	Innoture ltd	NCT03629041	Phase 1	Completed in 2019
7	Microneedle Device	Psoriasis vulgaris	Janssen research and development, LLC innovaderm research Inc.	NCT03795402		Completed in 2019
8	ZP-Zolmitriptan	Acute migraine	Zosano pharma corporation	NCT02745392	Phase 2 phase 3	Completed in 2018

Current Research, Challenges and Future Trends

Silicon was used to create the first micro needle. A study was done to determine whether or not medications could be delivered *via* the skin more effectively using microneedles. In the beginning, cadaver skin was used for permeation studies to determine whether or not big molecules like albumin and insulin could pass through the skin when injected with microneedles. Additional research supported microneedles superior delivery of big compounds. Many intriguing new micro needle concepts are now being developed, and they will be very useful in the future.

Microneedle approach is being applied to a number of drugs, but it has to encounter various challenges before it can release to the market. A lot of studies have to be conducted to get it clinically approved. The main problems associated with the microneedles technology include, skin allergy, redness and irritation. A limited amount of drug can be loaded into the micro needle. Passing hydrophilic and large compounds through the skin is a major challenge. A proper material has to be selected in the fabrication of these needles, which has adequate mechanical strength and insertion force. The main objective sssis to increase the permeation without causing pain. It could be difficult for a patient to first poke with a needle and then apply the patch. There is a chance of infection if the skin pores do not close after application.

To deliver the medication through the skin, various technologies are being developed. The standard microneedles have undergone a number of alterations; 3M's hollow microneedle is one of the best example to explain. This cutting-edge technology is adaptable enough to be used to administer hundreds of milligrams of proteins that enter the systemic circulation. To further improve medication permeability, a combination of ultrasound and transdermal drug delivery is being researched. As a result, microneedles can be created with a range of alterations in order to cleverly distribute the medicine through the skin, offering a new path

and revolution in the field of transdermal drug delivery systems.

CONCLUSION

MNs have changed the transdermal medicine delivery industry from straightforward skin patches to point-of-care tools. With two MN devices already available on the market for clinical usage and a huge number of MN devices under clinical trials, the development of MNs as a drug delivery technology has advanced exponentially quickly. The choice of construction material has become crucial to the design and advancement of MNs. Different materials offer various benefits and difficulties for MN design, production, and drug loading. The commercial viability of these therapeutic applications, it is crucial to understand, is what is promoting the development of microneedle technology. For the foreseeable future, interest in dissolving microneedles is likely to remain high given the market potential and anticipated growth for micro needles.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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