Review Article

Contemporary Modernization in the Domain of Microneedles

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ABSTRACT

Microneedle arrays are one of the most predominant ways to produce desired bioavailability by transdermal delivery of the drugs. Microneedles are considered idea-inspiring technology which enchanted numerous scientific researchers. They are designed as most intrude and cause minimal pain which protrudes into the stratum corneum. These are some of the most evolving techniques compared to the other subcutaneous injections. They are micron scaled needles that are non-invasive, painless, causes less infection or injury with excellent skin permeability to a wide range of compounds viz., small molecular weight drugs, oligonucleotides, proteins thereby considering microneedles as third-generation transdermal drug delivery systems as they serve as a great platform for self-administration of drugs. Targeting a medicine to a specific skin location allows for desired drug administration. Moreover, a lot of research is being carried out that solves various obstacles to successfully launching microneedles into the market. This review provides in-depth information on microneedles, types, materials and methods, and emerging applications and summarises innovations of smart MNs describing magnificent functions.

Keywords: Microneedles; Microneedle array; Stratum corneum; Subcutaneous injection; Transdermal drug delivery systems; Smart microneedles.

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INTRODUCTION

The biggest organ in the body, skin covers the entire body. In the face of injury, heat, light, and infection, it acts as a protective shield. A transdermal drug delivery system bypasses first-pass metabolism by delivering medications via several layers of skin. It is the most effective route for systemic absorption. Anatomically the skin has many histological layers, and is divided into three layers:

1) Epidermis
2) dermis
3) hypodermis

The epidermis is the skin's outermost layer, which is made up of stratified squamous epithelial cells and has a thickness of 0.2mm. The epidermis contains five layers.[1]

1) Stratum corneum (Corneal layer)
2) Stratum lucidum (Clear layer)
3) Stratum granulosum (Granular layer)
4) Stratum spinosum (Prickle cell layer)
5) Stratum basale (Germinatum)

The stratum corneum is the epidermis' dense and outermost layer, made up of 20-30 layers of dead, flat keratinocytes that are constantly replaced by new cells from deeper layers. Despite being hygroscopic, it is impervious to water. The dermis is the deeper thicker layer of skin containing collagen fibres (provide strength), elastic fibres (provide flexibility), reticular fibres (provide support). It is separated into two layers structurally: the upper papillary layer and the lower reticular layer. Beneath the dermis, there is a layer of subcutaneous tissue comprising adipocytes (fat cells) and collagen fibres called hypodermis which acts as a shock absorber.

The principle mechanism of the transdermal drug delivery system is a diffusion of drug molecules from the drug reservoir in the transdermal patch through the epidermal layer of the skin. Skin acts as a barrier, major obstruction is posed by the stratum corneum thereby considering it as a rate-limiting membrane in TDDS. Stratum corneum allows only a few low molecular weight chemicals possessing lipophilicity to diffuse through it. Therefore, in the case of nonpolar compounds epidermis is considered as a rate-determining membrane[2]. Hence the latest technology of microneedle array came into existence to improve transdermal delivery of drugs. Microneedles are a new way to administer drugs through the skin. Microneedles provide effective bioavailability therefore maximum systemic absorption of the drug can be achieved. It is possible to self-administer microneedle which leads to enhanced patient compliance. Moreover, it is a painless and non-invasive approach and observed to deliver drugs by trespassing the barrier of the skin, stratum corneum.[2]

Microneedles provide effective transportation of small drug molecules, macromolecules, nanoparticles,[3] and elegantly deliver those APIs that finds difficult to pass through the stratum corneum. An important point to be considered is that the size of the drugs molecules delivered by microneedles is not a limiting element for their functional application[4,5.] With the benefits of advances in science and technology, the system of microneedles can achieve commercialization and implementation in everyday lives. This article summarises tremendous efforts that have been focused on innovations made in the field of microneedles, lists out various advantages and disadvantages of microneedles, providing in-depth information on the types, materials, and methods for their fabrication and functional applications of microneedles. This review provides a compendium on Smart microneedles-based drug delivery by outlining their functions.

Advantages[2]:

1) rapid onset of action.

2) Bypasses largest barrier of skin i.e., stratum corneum.

3) Accurate amount of drug can be delivered through the system of microneedles by managing its formulation.

4) Maximum drug bioavailability can be achieved.

5) Self-administration, which is painless, improves patient compliance.

6) Microneedle's accounts for a direct route of drug delivery as they cause micron-sized pore formation due to skin puncturing.

Disadvantages[2]:

1) Number of drugs administered into the body is relatively small due to the smaller size of microneedles.

2) Short-term inflammation and allergy can be possible at the site of application.

3) Most probably this system requires skilled expertise, knowledge, and advanced technology for the fabrication of microneedles.

4) If solid microneedles are used, there is a potential that they will break (or) remain in the skin.

History and Dimensions of Microneedles

Research in microneedles has a long and rich history. Microneedles were first conceptualized for the purpose of drug delivery many decades ago around the 1960s. Alza corporation was allotted a patent for microneedles in 1971[6]. With the exception of a scientific article published by Henry and co-workers on microneedles in 2000, microneedles were simply considered as an idea[6,7]. With sophisticated microfabrication technology, this microneedles concept was studied over 30 years later and became the subject of substantial research beginning in the mid-1990s.

In contrast to the conventional needles which are millimetres (or) even larger dimensions, microneedles are preferably shorter than 1 millimetre and allow drug delivery across the skin by increasing skin permeability to various compounds such as small molecular weight drugs, oligonucleotides, and proteins[8]. Microneedles are micron-scaled medical devices used to administer vaccines, drugs, and other therapeutic agents comprising a length of 50-900 µm less than 300µm in diameter, 50-250 µm in width. Microneedles contain approximately arrays of 20,000 MNs per cm square on the base plate that creates micron-sized pores on the upper layer of the epidermis. Microneedle extremities can be triangular, cylindrical, octagonal, pointed pentagonal, and a variety of other shapes and sizes[10,11].

TYPES OF MICRONEEDLES

Solid microneedles

These are used for the pre-treatment of the skin by forming pores/microchannels, through which the drug is directly delivered into the skin layers, bypassing through the main barrier of skin i.e., stratum corneum, thereby showing passive diffusion of the drug through skin layers. It's primarily employed in the poke and patch method. It includes two steps: in the first step, SMNs are used, which pierces the epidermis forming a microchannel, and then removed. In the second step: After the SMN is removed, the traditional drug formulation or dosage form (solution, cream, transdermal patch) is used as an external reservoir, allowing the API to diffuse through the microchannels via passive diffusion. This method is utilised when medicine needs to be delivered quickly. The major disadvantage of SMN is micropores only remain open for a limited time, thereby stopping/halting the drug delivery or delivery of API, in some cases, there will be a considerable risk of infections caused by these SMNs[4,10,12.]

Coated microneedles

The solid MNs are coated with the drug solution/drug dispersion before being applied to the skin. It's most commonly utilised in the coat and poke method. When these coated MNs are put into the skin, the drug dissolves, resulting in improved drug delivery. Drug diffusion across the deeper epidermal layers is possible with this method. These coated MNs work well with macromolecules such as vaccines, proteins, peptides, DNA, and so on. Although it is a simple one-step approach, certain aspects limit the usefulness of this approach. The main drawback is the amount of drug which is used for encapsulation on the outer layer of SMNs is very low, but it can be used in vaccination because the antigen dose needed to produce the immune response is very less i.e., in nano/micrograms and the coating in some cases may even decrease the sharpness of the microneedles, which mainly affect their ability to penetrate skin layers. Due to its limitations, it is hence used only in cases of potent molecules/drugs[4,12,13.]

Dissolving microneedles

Besides API these include a solid matrix where the MNs are fabricated with biodegradable polymers in which the drug is contained in a polymer and released after being inserted into the skin. After the insertion of the needle, dissolution takes place wherein drug releases in a single-step process, because the needles need not be removed after insertion like other types. As the release kinetics of the drugs depends on the dissolution of the polymers, we can control the drug delivery by adjusting the composition of polymers[4,10.]

Author ling and chem introduced a dissolving MN containing starch, gelatin, and insulin as a drug model, during an in-vitro test. As a result, MN releases practically all of the insulin content in less than 5 minutes. It is most commonly seen in the poke and release method, in which the dissolving microneedle controls the dissolution rate of the polymers used in DMNs to maintain regulated drug release over a longer period of time. The major advantage of these MNs is that it is a one-step process, thereby reducing the drug administration process. Another added advantage is it avoids the generation of waste, thereby minimizing the cost and needle-stick injuries. On the other hand, rapidly separated microneedles are developed as a hybrid of coated and dissolving MNs, with limited drug loading and inability to penetrate through the stratum corneum. The fundamental goal of this hybrid is to inject a drug-loader, water-soluble matrix into the skin, together with SMNs, which are made of an insoluble polymer, so that the water-soluble matrix stays in the skin and solid MNs may be readily removed[12].

Hollow microneedles

As the name itself indicates the hollow microneedles, have an empty hollow space inside them, where the drug solution is filled, and have holes on their tops. When these HMNs are inserted into the skin the drug is directly released into the epidermis or upper dermis. High molecular weight molecules like as proteins, vaccines, and oligonucleotides are typically handled by these MNs. These can administrate a large dose and a large amount of drug can be filled in the hollow space inside the needle. A constant flow should be maintained. The drug flow and release pressure can be adjusted in the desired cases. When the flow increases, the strength and sharpness of the MN decrease; in this instance, a metal coat is added to the MN to increase the strength and sharpness. It is employed in the flow and pokes strategy. The medication compositions are administered by skin perforations, similar to hypodermic needles. Due to its micrometric size, it is difficult and expensive to prepare a hallow MN, on the contrary, it is a smaller size, which encourages patient acceptancy when compared to the traditional injections [14,12.]

Hydrogel microneedles

This was a significant advancement in the realm of MNs. it was first described in 2010. It includes an integrated system and with super swelling, cross-linking polymers forming a patch containing API the polymer has a hydrophilic structure, which enables it to take up a large amount of water in its 30 networks. Upon the administration, these MNs uptake the intestinal fluid by the process of diffusion through the patch, and therefore the polymer swells. As a result, channels between the capillary and the medication patch form. The polymers are flexible in size and shape. After the uptake of intestinal fluid, they swell and behave as a rate-controlling membrane. The merits of this approach include easy sterilization and easy removal from the skin with improved permeation and bioavailability. Phase transition MNs, a subcategory of this hydrogel MNs, like it releases API after swelling of the polymer. After application, they may or may not leave a residue. Traditional dissolving MNs, on the other hand, contain a high concentration of the medication. The matrix contains a significant number of needles, which may disintegrate or degrade in the skin, making it less suitable for everyday usage. Hydrogel MNs, which do not dissolve or deteriorate in the skin but release the API in a controlled manner, are the most convenient type of MN[4,12,10]. The drug delivery mechanism of various microneedles is schematically represented in **Figure1.**

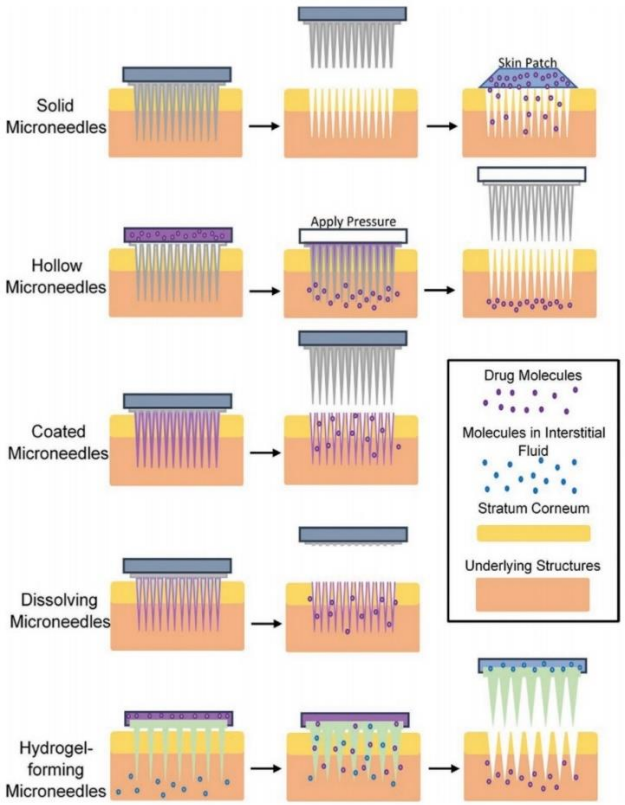

Figure 1: The drug delivery mechanism of (A) a solid microneedle (solid MN) and (B) a coated microneedle (coated MN), (C) dissolving microneedle (dissolving MN), (D) hollow microneedle (hollow MN) (D) hydrogel forming microneedles (hydrogel forming MN) is depicted in the schematic diagram (the graphical presentation of this model was used in the study by Alexey S. Rzhevskiy)[28.]

MATERIALS USED IN THE FABRICATION OF MICRONEEDLES

The world of microneedles comprises a wide range of intriguing materials with outstanding physical and chemical characteristics and properties. Microneedles have been made out of a variety of materials, which are briefly described here.

1) Silicon: Earlier MNs are fabricated by using silicon i.e., around the 1990s. silicon is one of the most useful elements which is anisotropic in nature and exhibit crystalline structure[10]. Silicon-based MNs can be produced into a variety of forms and sizes. Solid and coated microneedles are mostly made of silicon[2].

Fabrication process: Etching, lithography[12].

Advantage: Desirable mechanical properties[12].

Disadvantage: Material cost is high, Tedious fabrication process[12].

2) Metal: Metals are high-melting-point, high-density materials. It acts as a good conductor of electricity. In the manufacturing of microneedles, metals are chosen over silicon. Stainless steel, titanium, palladium, and nickel are examples of metals utilised in the manufacture of microneedles, with stainless steel and titanium serving as the primary metals for solid, coated, and hollow microneedles[2].

Fabrication process: Laser cutting, laser ablation, etching, electropolishing, lithography, and micro stereolithography[4].

Advantages: Good mechanical properties, Desired biocompatibility, Duct ability.

Disadvantages: Certain metals show poor bioavailability, Stainless steel shows rapid corrosion, Titanium alloys are more expensive, Possibility of breakage of MNs inside the skin.

3) Inorganic materials: The most extensively used inorganic materials are ceramic and silica glass.

Ceramic: It is a hard, brittle, heat resistant, material. Examples of ceramics include alumina (Al_2O_3), calcium sulphate dihydrate/gypsum ($CaSO_4.2H_2O$), calcium phosphate dihydrate/ brushite ($CaHPO_4.2H_2O$). Among these, alumina is most widely used due to its benefits like chemical resistance and stable oxide formation. A 3D cross-linked copolymer called Ormocer®; an organically modified ceramic is being used in modern days[10,2].

Fabrication process: Lithography and ceramic sintering[12].

Advantages: Relatively lightweight, Corrosion-resistant when compared to metal, Desired biocompatibility.

Disadvantages: Brittle in nature, zero ductility and poor tensile strength, Difficult to mould.

Silica glass: Glass made of practically pure silica in amorphous form is known as fused silica, fused quartz, or quartz glass. Silica glass microneedles can be produced into a variety of forms and sizes. Solid MNS, coated MNs, and hollow MNs are all made with these materials. Silica and boron trioxide combine to make borosilicate glass more elastic. The majority of these are made by hand[10].

Fabrication process: Pulling pipettes.

Advantages: Good biocompatibility, good chemical resistant, Excellent electrical insulator.

Disadvantages: Used only for experimental purposes but not commercially, Brittle in nature.

Carbohydrates/sugar molecules: Because of their physicochemical characteristics these are most widely used in the manufacturing process of MNs in past years. Some of the examples of sugars that can be used for the fabrication of MNs include maltose, mannitol, trehalose, sucrose, xylitol, and galactose. Maltose is most used among all other sugars. The rate of drug release into the skin is based on the dissolution of drug-loaded carbohydrates. Carbohydrates are mainly employed in the manufacturing of solid and dissolving microneedles[10,15].

Fabrication process: Solvent casting/ micro moulding.

Advantages: Desired biocompatibility, Cheap and safer for public health.

Disadvantages: Poor stability and poor mechanical strength, Degrades rapidly at elevated temperature.

Polymer: Polymer materials are to be the best materials that focus on the production of desired MNs. Ideal characteristics of polymers entitled for manufacturing of MNs must be water-soluble, biocompatible, desired mechanical property to aim in the insertion of a drug through the skin[2]. Solid MNs, coated MNs, dissolving MNs, and hollow MNs are all made with polymeric materials. Polymers such as poly(methyl methacrylate) (PMMA), polyacrylic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), polyglycolic acid (PGA), poly(carbonate) cyclic-olefin copolymer, polystyrene hyaluronic acid (HA), polyvinyl pyrrolidine (PVP), fibroin, sodium alginate, chitosan, zein[10].

Fabrication process: Solvent casting/ micro moulding

Advantages: Favourable biocompatibility and biodegradation, Devoid of waste after use.

Disadvantages: Poor mechanical strength.

SMART MICRONEEDLES

In recent years, the majority of efforts have been focused on improving smart microneedles by giving them exciting qualities including adhesion, responsiveness, and regulated drug release. Smart microneedles have been shown to be bionic and biocompatible. This review provides knowledge on unique properties, application, and fabrication methods of smart microneedles in **Figure 2.** Smart microneedles are advised to be an ideal medical device and could be guaranteed for medical use[16]. The evolving functions of smart microneedles and their description were mentioned in **Table 1.**

Table 1: Describing the functions of smart microneedle

Function	Description	Advantage	Method of fabrication
Adhesive ability	Due to the repulsion of skin, conventional MNs finds it difficult to adhere to the skin whereas the skin adhesion ability of smart microneedles gets rid of such limitation.[16]	• Long-term drug delivery. Improves the comfort of users.	• Specially structured MNs [29] • Using swellable MN materials.[30] Making supportive adhesive layer.[31]
Dissolvability	MN tips dissolve in less than 30 mins and deliver drugs rapidly.	• The complete release of drug Do not leave any remains of fractured MNs in the skin.	Fabricated using PVP, HA, PVA, CMC (carboxy methyl cellulose), TREHALOSE.[16]
Separability	Upon application onto the skin, the supporting layer of separable MNs gets detached from tips and removed.	• Less wear time. • Reduce irritation and inconvenience. Sustained drug delivery.	• Fracture of tip and supporting layer.[32] Dissolvable supporting layer.
Responsiveness	Responsive MNs bring about responses to external/internal stimulations thereby precisely controlling the release of drugs.	Controls release of the drug.	EXTERNAL STIMULUS: Prussian blue nanoparticles and photosensitive nanomaterials such as lanthanum hexaboride were used inside MN tips. INTERNAL STIMULUS: composed of P^H sensitive cellulose acetate phthalate.
Antibacterial ability	MNs incorporated with the antibacterial ability.	Treats wounds and other sites susceptible to infection.	Fabricated by chitosan/ silver nanoparticles, antibacterial peptides.

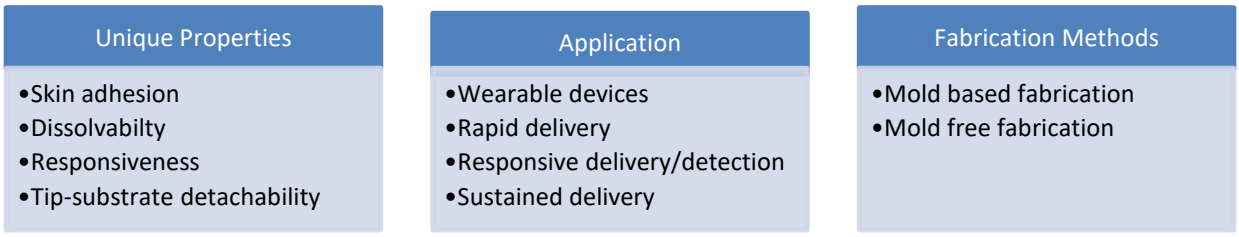

Figure 2: Describing unique properties, applications, and fabrication methods of smart

EMERGING APPLICATIONS OF MICRONEEDLES

The transdermal form of medicine delivery has become increasingly popular in recent years. In the transdermal method of medication delivery, microneedles are thought to be the best option. To date, microneedles have a broad range of applications and are being used in cancer therapy, vaccine therapy, oligonucleotide delivery, peptide and hormone delivery, pain therapy. This review discusses certain salient applications like:

Alzheimer's

It is a common degenerative disorder of CNS and is also claimed as a primary reason for dementia in elderly people over 65 years[17]. Alzheimer's is a disorder in which patients experience a gradual loss of memory, learning, executive and losses track of time. It is mainly due to the production of amyloid plaques and neurofibrillary tangles in the CNS. Certain anti-Alzheimer's drugs include acetylcholinesterase inhibitors (AChEIS), cerebral blood flow, and brain metabolism improver. Huperzine A, which is produced from the Chinese herb, *Huperzia serrata*, is considered an effective Ach EI and is known to improve memory of patients with Alzheimer's[18]. HuperzineA (Hup A) is available in various pharmaceutical dosage forms Viz tablets[19], capsules[20], and injections (IM). One of the most encountered disadvantages of frequent administration of HupA is that it is difficult to achieve steady plasma concentration thereby leading to GI side effects. Qinying, Weiweiwang designed a dissolving MN patch (DMNP) for delivering hupA through layers of skin and investigated *in vitro* and *in vivo* parameters[17]. Skin penetration and intradermal tests revealed that blank DMNP has acceptable permeability through the skin and could dissolve rapidly ≤5 mins. In vitro tests concluded that 80% of HupA can permeate from DMNP within 3 days indicating sustain release kinetics.

Mary Carmel et al. performed the formulation & characterization of an integration microneedle patch loaded with the drug, donepezil which is employed in the treatment of Alzheimer's[21]. The hydrogel-forming microneedle was used in conjunction with the donepezil-containing film to create the integrated patch. The author examined in vitro permeation tests of donepezil HCl across neonatal porcine skin from drug-loaded patches & observed 854.71 ug + 122.71ug donepezil HCl delivered after 24h & succeeded.

Cancer therapy

Cancer is a disease in which aberrant cells multiply uncontrollably and cause tissue destruction. cancer can occur at any age but 67% of cancer deaths occur in people above than 65yrs. They are 2 types of tumours, malignant tumours that spread in other areas in the body& benign tumours which stay in one place. Cancer treatment may include surgery, chemotherapy &radiation therapy. Even so, these approaches are associated with reduced efficacy & severe side effects. Parenteral administration of anticancer drugs results in the spreading of the drug to various other organs which not only results in reduced bioavailability but also destroys normal cells. Cancer treatment can be enhanced by delivering the drug in the right quantity, at the right time, and right site. This type of approach can be achieved by tiny needle-like structures called microneedles which are magnificent carriers for delivering small & large molecules to cancer patients[6].

Tejashree waghule et al. investigated self-degradable microneedles to deliver anti-PD-1(aPD1) for the treatment of melanoma in a sustained manner[10]. Wang et al. investigated apd1 & glucose oxidase (Gox) loaded with P^H Sensitive nanoparticles & found that Gox converted blood glucose to gluconic acid. This P^H-sensitive nanoparticle system is combined with HA dissolving microneedles which could effectively penetrate mouse skin. The *in vivo* studies were performed in a mouse bearing tumour B16F10 & concluded that the group treated with P^H sensitive nanoparticle system in conjunction with HA dissolving microneedles has remarkable antitumor efficacy & increases the retention period of a PD1 at tumour sites. Therefore, immune cells can easily recognize cancer cells & destroy them.

Breast cancer is one of the most common cancers in women that leads to mortality. To treat breast cancer the drug needs to be delivered directly to underlying tissue i.e., tumours in the breast to minimize the circulating concentration of the drug thus protecting normal healthy cells. Bhatnagar and colleagues investigated MNs loaded with zein which delivers tamoxifen and gemcitabine for the treatment of breast cancer. Even though the ratio of tamoxifen was much more than that of gemcitabine, the studies revealed that gemcitabine showed excellent permeation with regard to tamoxifen. Finally, Bhatnagar and colleagues concluded in their study that optimal water solubility of the drug is required to achieve appreciable permeability in the case of zein-loaded MNs[22].

Skin carcinoma is the most common type of cancer and one in 5 individuals are being affected by skin cancer. Lu and co-worker investigated MNs loading with dacarbazine for treatment of skin cancer which is fabricated by micro stereolithography. Controlled delivery of dacarbazine can be achieved for about 5 weeks[23].

Keloids

Keloids are noncancerous fibrous proliferation that can occur in the dermis after trauma or injury to the skin. It is a result of abnormal collagen deposition in healing skin wounds. Keloids are notoriously difficult to cure and have a high recurrence rate. Multiple treatment modalities have been advocated including pressure therapy, cryotherapy, lesional (intra) corticosteroids, radiation treatment, laser treatment and so on. Among these, a microneedle patch was made using FDA-approved liquid crystalline polymer in accordance with good manufacturing practises. Compared with other conventional needles, these microneedles are shorter and thus penetrate the stratum corneum without contacting the nerves surrounding the dermis. This treatment promotes the formation of new skin cells and accelerates healing. At the same time, it breaks down old scar tissue. This type of treatment is safer and causes less damage to the skin. Microneedles can be used on any area of the body such as necks, arms, legs. After the proper amount of medicine has been administered, the microneedle patch can be easily peeled off[8].

Insulin delivery

Insulin is a hormone created by the pancreas that regulates the amount of glucose in the body. Insulin is one of the hormones that has been studied the most. Resnik et al. investigated hallow silicon MNs to microinject insulin and got succeeded with the satisfactory result[12]. To concentrate insulin in the needle tip, Lee et al. used a two-step casting and centrifugation technique to create dissolving MNs made of gelatin and CMC. This approach has a higher transdermal delivery efficiency. *Ex vivo* results provided 50% of insulin was liberated and perforated into the skin after 1h with cumulative permeation reaching 80% of initial dose after 5h besides *in vivo* testing demonstrated bioavailability of insulin from MNs of 95.6% and 85.7% respectively[24].

One of the idea inspiring works brought up by Chen et al. is that MNs which are comprised of poly-c-glutamic acid(c-PGA) and polyvinyl alcohol (PVA)/polyvinyl pyrrolidine (PVP) are meant to be dissolved within 4mins upon insertion onto the skin. In the rat model, the results appeared to provide a hypoglycaemic effect which was achieved with insulin-loaded MNs when compared to that of conventional subcutaneous insulin injection. The bioavailability of insulin was observed in the range of 90- 97 %[25].

Ling et al. fabricated a dissolving polymer MN patch containing starch and gelation with an intention to deliver insulin to diabetic rats. After insertion of MN onto the skin it has proven to dissolve completely and deliver insulin

within 5 mins[26]. Tong et al. fabricated PVA/PVP comprised of glucose and hydrogen peroxide(H_2O_2) responsive polymeric vesicles loaded with insulin which is used under hyperglycaemic conditions[27]. Vesicles are made up of a self-assembling method and composed of 3 polymers: poly (ethylene glycol), poly (phenylboronic acid), and poly (phenylboronic acid pinacol ester). The contents of the vesicles are covered with glucose oxidase, an enzyme that converts glucose to glucuronic acid and then hydrogen peroxide when exposed to oxygen. Polymeric vesicles showed controlled release of drug by release of nanoparticle study at different glucose and hydrogen peroxide concentration (200 or 400mg/dL). The existence of glucose oxidase in particles impart a faster release of insulin due to the breakage of bonds in the poly (phenylboronic acid pinacol ester) which is catalysed by the generation of hydrogen peroxide. Diabetic rats had glucose-sensitive patches implanted and their systemic glucose levels were measured. MNs comprised of polymeric responsive vesicles which are proven to be the best alternative when compared to subcutaneous insulin injection. The schematic representation of insulin loaded glucose and H_2O_2 responsive polymeric vesicles containing polyvinyl pyrrolidine (PVP) /polyvinyl alcohol (PVA) was specified in **Figure 3.**

Authorized products: The first authorized microneedles product was derma roller. A great deal of products are making their appearance into the market. Certain list of microneedles are tabulated in the following table**. Table 2**

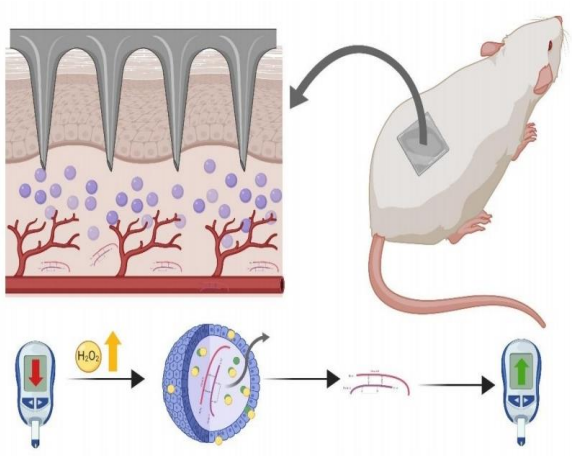

Figure 3: The figure represents insulin loaded glucose and H_2O_2 responsive polymeric vesicles containing polyvinyl pyrrolidine (PVP)/polyvinyl alcohol (PVA) MN, therefore, permitting an uncomplicated penetration of vesicles directly near the dermis vessels. Insulin is released in a controlled manner when the constituent polymers of vesicles get hydrolysed at hyperglycaemic state in the presence of H_2O_2 stimulus. This tactic provides an effectual and long-living hypoglycaemic activity when compared to subcutaneous injections. (Graphical presentation of this model was used in the study by Tong's et al)[27].

Table 2: List of approved microneedles for pharmaceutical administration till date

Product name	Manufactured by	Illustration of product	Significance
Dermaroller®	Dermaroller® Germany, white lotus	A cylindrical roller with 0.2mm to 2.5mm in length	Enhance skin texture, treat scars and hyperpigmentation.
Dermaroller™ MS-4	The Dermaroller series: Anastassakis k	A small cylinder with 1cm length, 2cm diameter, and 4 circular arrays of microneedles with 1.5mm in length	Employed for treatment of facial acne scars.
h-patch	Valeritas	A tiny adhesive machine-like patch	Transports drugs(insulin) in subcutaneous. To deliver biologicals and other small molecules.
Liteclear ®	Nanomed skincare	Pre-treated with solid silicon microneedles and then drug is applied topically.	Treats acne and skin blemishes.
MicroHyala ®	CosMED pharmaceutical Co. Ltd	Dissolving microneedle patch containing hyaluronic acid which dissolves slowly and is less irritating.	Wrinkle treatment
Microstructured transdermal system	3M	Hollow microneedle	Delivers biologics and other small molecules.
BD Soluvia ®	BD, Sanofi Pasteur Europe	1.5 mm long hypodermic needle	Used for influenza vaccination.
Dermaroller™ MF-8 type	The dermaroller series: Anastassakis K	A needle of 1.5mm in length	Treatment of scars.
Dermaroller™ C-8 (cosmetic type)	The dermaroller series: Anastassakis K	A needle with a length of 0.13mm, 24 circular arrays of 8 needles each	Used to enhance the penetration rate of topical agents.
CIT-8 (collagen induction therapy)	The Dermaroller Series: Anastassakis K	A needle length of 0.5mm	Used in collagen induction and skin remodelling.

CONCLUSION

Microneedles are innovative systems in the field of transdermal drug delivery systems. The past few decades have experienced significant leaps and bounds in the field of the microneedle array. These microneedles are reusable, inexpensive, and pain-free. MNs manufacturing methods are more sophisticated due to the advancement of MN technologies. In the future, MN-based transdermal drug delivery plays a significant role in the modern health care system. Initiating from the classification of microneedles, this review focussed on the different intriguing materials used for the fabrication of MNs. This review provides a summary of smart microneedles that have been imparted with novel and advanced features such as skin adhesion, rapid dissolvability, separability, responsiveness, and antibacterial activity. Unlike other reviews, this review provides a summary of the unique properties of smart microneedles and their excellent advantages. Besides this review provide detailed information on the role of MNs in the treatment of chronic diseases like Alzheimer's, cancer, keloids, diabetes. The importance of these devices in therapeutic indications was gaining more interest worldwide in the scientific community because of many clinical trials in MNs. The success of these MN devices provides a wide range of therapeutic opportunities for buccal, oral, vaginal, rectal, and ocular drug delivery.

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