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Review

Microneedles: A smart approach and increasing potential for transdermal drug delivery system

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ABSTRACT

The most widely used methods for transdermal administration of the drugs are hypodermic needles, topical creams, and transdermal patches. The effect of most of the therapeutic agents is limited due to the stratum corneum layer of the skin, which serves as a barrier for the molecules and thus only a few molecules are able to reach the site of action. A new form of delivery system called the microneedles helps to enhance the delivery of the drug through this route and overcoming the various problems associated with the conventional formulations. The primary principle involves disruption of the skin layer, thus creating micron size pathways that lead the drug directly to the epidermis or upper dermis region from where the drug can directly go into the systemic circulation without facing the barrier. This review describes the various potential and applications of the microneedles. The various types of microneedles can be fabricated like solid, dissolving, hydrogel, coated and hollow microneedles. Fabrication method selected depends on the type and material of the microneedle. This system has increased its application to many fields like oligonucleotide delivery, vaccine delivery, insulin delivery, and even in cosmetics. In recent years, many microneedle products are coming into the market. Although a lot of research needs to be done to overcome the various challenges before the microneedles can successfully launch into the market.

1. Introduction

Hypodermic needles and topical creams are most commonly used when it comes to delivery of the drug through the skin. Needles are less accepted by patients due to pain associated with them and topical creams show less bioavailability. Skin serves as the major barrier for delivering drug through the topical route. Skin is made up of three main layers-the outermost stratum corneum, middle epidermis and the thickest of all, dermis. The stratum corneum layer behaves like a major barrier as it allows only certain molecules like lipophilic and low molecular weight drugs to pass through it. The relatively less permeability of the layer presents many problems in designing topical formulation [1,2]. Various topical or transdermal delivery systems have been investigated for improving drug permeation through the skin like nanocarrier loaded topical creams, transdermal patches, and microneedles [3,4].

The microneedles (MNs) have been studied by various researchers for delivering drug through the transdermal route and for overcoming the limitations of the conventional approaches. Microneedle device consists of needles of micron size, which are arranged on a small patch. Considering the problems of the hypodermic needle and the transdermal patch, microneedle drug delivery system was developed and is thought to be the hybrid of both. The major problem associated with transdermal technology is that many of the drugs are not able to cross the skin at the required rate necessary for the therapeutic action. Researchers have developed a refined technology using microneedles, which allow hydrophilic high molecular weight compounds to enter into the stratum corneum. Administration of drugs using the microneedle device allows the drug molecules to cross the stratum corneum layer, thus allowing more drug molecules to enter the skin. The characteristic features of this technology are the faster onset of action, better patient compliance, self-administration, improved permeability

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Table 1
Comparison between topical cream, transdermal patch, hypodermic needle, and microneedle drug delivery systems.

	Topical cream	Transdermal patch	Hypodermic needle	Microneedle
Description	Emulsion/ emulgel/ cream/ ointments	Adhesive patch to be placed on the skin	Fine, hollow tube having a sharp tip with small opening at the end	Micron size needles are aligned on the surface of a small patch
Onset of action	Slow	Slow	Faster	Faster
Pain	Painless	Painless	Painful	Painless
Bioavailability	Poor	Insufficient	Sufficient	Sufficient
Patient compliance	Less	Better	Less	Better
Self-administration	Possible	Possible	Not possible	Possible
Mechanism of drug delivery	Permeation through skin pores.	Drug has to cross stratum corneum barrier, thus poor diffusion of large molecules	Drug placed directly in the dermis	Bypass stratum corneum and drug placed directly into epidermis or dermis hence enhanced permeability

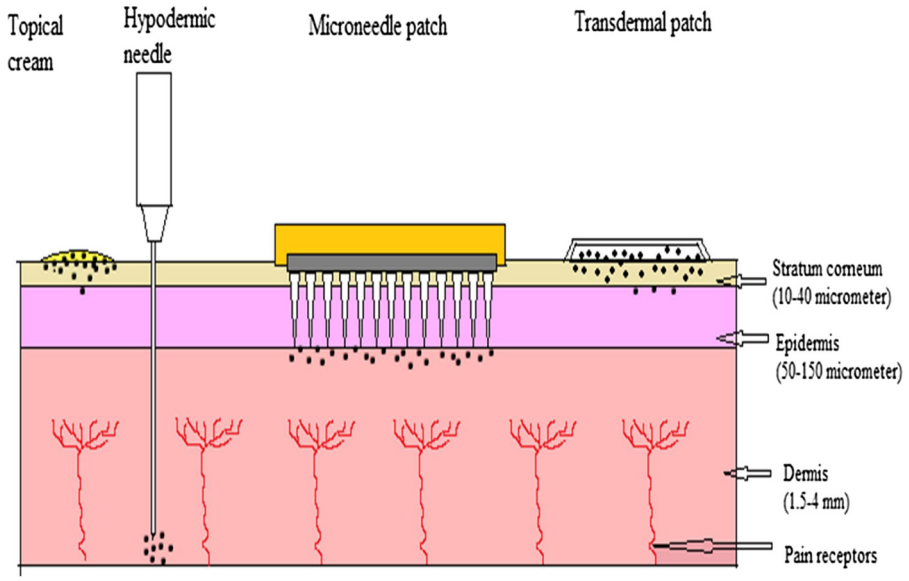

Fig. 1. Comparison of topical cream, hypodermic needle, microneedle patch and transdermal patch.

and efficacy [2]. In addition to improved therapeutic advantages, microneedles give highly accurate reproducible results with minimum inter-subject variability in bioavailability. Though it has many advantages it also possesses some limitations. There is the possibility of skin irritation or allergy to sensitive skin. Since the needle size is very small and thinner as compared to the thickness of hair, breaking of microneedle tips may take place which if remained inside the skin, can cause problems. These limitations are very rare and can be overcome with advanced material selection for microneedles. The main objective of developing this technology is to create larger transport pathway of micron size which is larger than molecular dimensions and smaller than holes by hypodermic needles, to disrupt the stratum corneum to allow large molecules to pass through thus increasing the permeability [5]. Conventional methods like electric methods- iontophoresis and electroporation, chemical/ lipid enhancers create pores of nanosize which improve the permeability up to some extent but fail for large molecules [6]. A comparative discussion is compiled for various transdermal drug delivery systems in Table 1. The drug delivery by various transdermal systems is presented in Fig. 1. The topical cream spreads only on the skin surface. It has been reported that only 10–20% of total drug loaded in cream is being permeated through the skin [3]. In case of a transdermal patch, the drug has to pass the stratum corneum barrier thus it also shows less bioavailability. Addition of permeation enhancer in the transdermal patch can improve the drug permeation but up to a very limited extent [4]. The hypodermic needle goes deep into the dermis where pain receptors are present. Thus it can deliver 90–100% of the loaded drug but it is very painful which results in poor patient compliance. Microneedle patch bypasses the stratum corneum barrier and delivers the drug directly into the epidermis or upper dermis layer which delivers 100% of the loaded drug without pain [5].

2. Mechanism of drug delivery

The delivery of the drug through the topical route follows the diffusion mechanism. In the microneedle drug delivery system, the skin is temporarily disrupted. A microneedle device is made by arranging hundreds of microneedles in arrays on a tiny patch (the same as that of a normal transdermal patch available in the market) in order to deliver sufficient amount of drug to give a required therapeutic response. It pierces the stratum corneum thus bypassing the barrier layer. The drug is directly placed in the epidermis or upper dermis layer which then goes into the systemic circulation and shows a therapeutic response on reaching the site of action [6,7]. Mechanism of drug delivery through microneedles is depicted in Fig. 2.

3. Dimensions of microneedles

Microneedles can be formulated in varying sizes depending on the type of microneedle and the material used. Since the epidermis is up to 1500 μm thick so the needle length of up to 1500 μm is sufficient to release the drug into the epidermis. Needles larger in length and thicker in diameter can go deep into the dermis, damage the nerves and cause pain [5]. Mostly they are 150–1500 microns long, 50–250 microns wide, and have 1–25 microns tip thickness. As discussed earlier the need for microneedle device is to create micron size transport pathway, the diameter of needles is kept between few microns. Microneedle tips

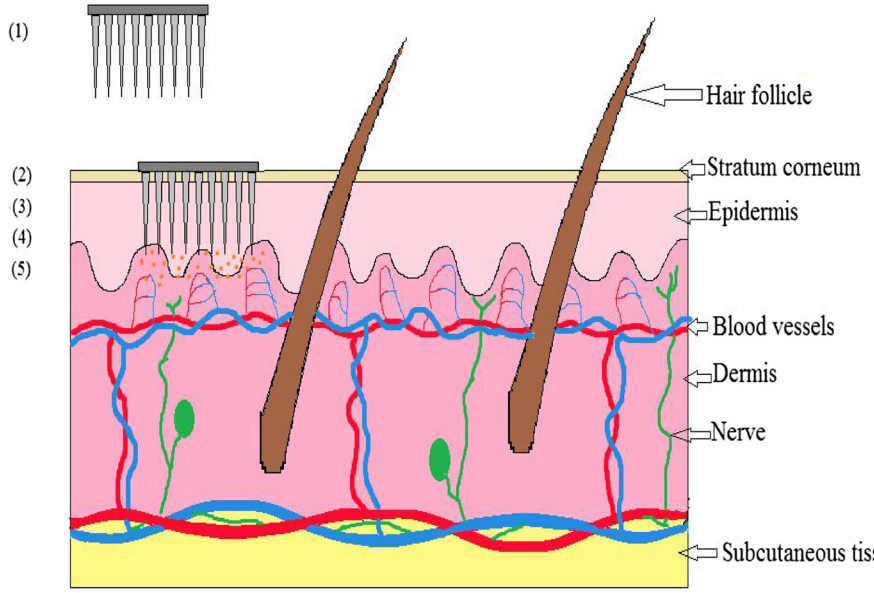

Fig. 2. Mechanism of drug delivery by microneedle device: (1) Microneedle device with drug solution; (2) Device inserted into the skin; (3) Temporary mechanical disruption of the skin; (4) Releasing the drug in the epidermis; (5) Transport of drug to the site of action.

can be cylindrical, triangular, pointed, pentagonal, octagonal and are available in many more shapes [7].

4. Microneedle fabrication material and its properties

4.1. Silicon

The first microneedle was made from silicon in the 1990s [6]. Silicon is anisotropic in nature and has a crystalline structure. Its properties depend on the alignment in the crystal lattice, which shows different elastic moduli (50 to 180 GPa) [8–10]. Its flexible nature allows producing needles of different sizes and shapes. Its attractive physical properties make it a versatile material. Silicon substrates can be precisely manufactured and are capable of batch production. The cost of silicon and its time-consuming complex fabrication process limits its use in microneedle. In addition, there are some biocompatibility issues, as silicon is brittle, some part may break and remain in the skin thus causing some health issues [8].

4.2. Metal

The main metals used are stainless-steel and titanium. Palladium, nickel, palladium-cobalt alloys are also used [11]. They have good mechanical properties and good biocompatibility. Metals are strong enough to avoid breaking, thus more suitable as compared to silicon for microneedle production. The first metal used in the production of microneedle was stainless steel [12]. Titanium is a good alternative to stainless steel [8,13].

4.3. Ceramic

Alumina (Al_2O_3) is mainly used because of its chemical resistance. It forms a stable oxide because of the highly energetic ionic and covalent bonds between Al and O atoms [14]. Other types of ceramics used are calcium sulfate dihydrate [Gypsum ($CaSO_4$ $0.2H_2O$)] and calcium phosphate dihydrate [Brushite ($CaHPO_4.2H_2O$)] [5]. In recent years an organically modified ceramic called Ormocer® has been used. It is a three-dimensionally cross-linked copolymer [15]. A polymer with different properties can be produced by using different organic units during polymerization. Mainly they are produced using a micro-molding technique. Ceramic slurry is cast into a micro-mold. Micro-moulding techniques are cheaper processes, and also have the potential for scale-up [8].

4.4. Silica glass

Varying geometries can be produced on small scale using glass. Silica glass is physiologically inert but brittle in nature [16]. Borosilicate glass which is made up of silica and boron trioxide is more elastic. They are mostly fabricated manually, thus are less time efficient [17]. Glass MNs are not used now commercially, but only for experimental purposes [8].

4.5. Carbohydrate

Maltose is one of the most common sugars used [18]. Other sugars, such as mannitol, trehalose, sucrose, xylitol and galactose, polysaccharides can also be used [19]. Carbohydrate slurries are moulded by making use of silicon or metal templates. The drug-loaded carbohydrate mixture is casted into the moulds to get the microneedles [20]. The time-based dissolution of carbohydrate regulates the drug release inside the skin. Carbohydrates are cheap and safe for the human health but degradation at high temperatures makes the fabrication process difficult [8].

4.6. Polymer

A wide variety of polymers including poly (methyl methacrylate) (PMMA) [21], polylactic acid (PLA) [22], poly (lactic-co-glycolic acid) (PLGA) [23], polyglycolic acid (PGA) [17], poly (carbonate) [24], cyclic-olefin copolymer, poly (vinylpyrrolidone) (PVP) [25], poly (vinyl alcohol) (PVA) [25], polystyrene (PS) [26], poly (methyl vinyl ether-co-maleic anhydride) [27], SU-8 photoresist [28] are reported for microneedles preparation. Mostly, dissolving or biodegradable and hydrogel-forming microneedles arrays are made from these polymers. Microneedles fabricated with these polymers have less strength than other materials but are tougher than glass and ceramics [8,9].

5. Types of Microneedle

Different types of microneedles fabricated and investigated for their application in drug delivery are solid, coated, dissolving, hollow, and

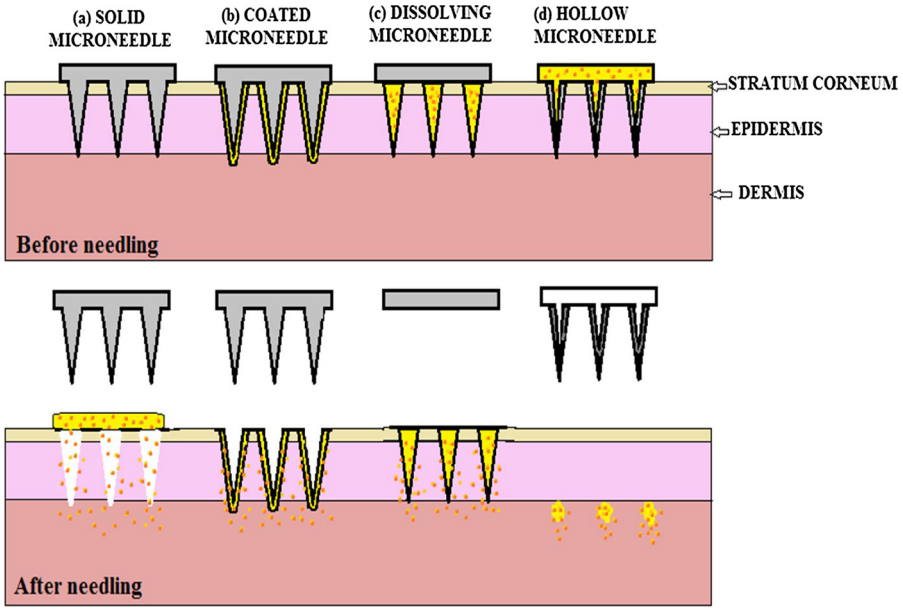

Fig. 3. Different types of microneedles (a) Solid microneedles use poke with patch approach, are used for pre-treatment of the skin; (b) Coated microneedles use coat and poke approach, an coating of drug solution is applied on the needle surface; (c) Dissolving microneedles are made of biodegradable polymers; (d) Hollow microneedles are filled with the drug solution and deposit the drug in the dermis.

hydrogel microneedles. Different types of microneedles with their unique properties are displayed in Fig. 3. Each type of microneedle has its own way of delivering the drug into the epidermis. Some are used just to create pores in stratum corneum, some are precoated with the drug solution on their surface, some are dissolvable and some are prefilled with the drug solution [29–32].

5.1. Solid microneedles

Solid microneedles are mostly used for pre-treating the skin by forming pores. Pointed tips of the needles penetrate into the skin; create channels of micron size, through which the drug directly enters the skin layers on the application of a drug patch, thus increasing the permeation. The drug is taken up by the capillaries to show a systemic effect. It can be used for a local effect also [29]. Solid microneedles deliver the drug with passive diffusion to skin layers [1,30]. Narayanan et al fabricated solid silicon long and tapered microneedles using tetramethylammonium hydroxide etching process. Microneedles with an average height of 158 μm and base width of 110.5 μm were successfully fabricated [33]. Later he also fabricated the gold-coated solid silicon microneedles with the dimension of 250 μm in height, the base width of 52.8 μm, the aspect ratio of 4.73, tip angle and diameter of 24.5° and 45 μm. The results demonstrated improved bioavailability and mechanical strength [34]. Li et al studied polylactic acid microneedles and found that biodegradable polymer solid microneedles have sufficient mechanical strength to pierce the stratum corneum and can enhance the absorption of the drug. The microneedles having 800 μm depth and density of 256 MNs per cm^2 was found to enhance the drug permeation [35]. Stainless steel microneedles are also studied by various researchers. Enhanced delivery of captopril and metoprolol tartrate was studied after application of stainless steel MN arrays [1].

5.2. Coated microneedles

The microneedles are surrounded with the drug solution or drug dispersion layer [1]. Subsequent dissolution of drug from the layer takes place and the drug is delivered quickly. The amount of drug that can be loaded depends on the thickness of the coating layer and the size of the needle which is usually very less [29]. Baek et al loaded lidocaine on poly L-lactide (PLLA) microneedle arrays. The loaded lidocaine released rapidly in phosphate buffer saline and was found to be stable for 3 weeks [36]. Coated microneedle also explored for delivery of multiple agents through same formulation. Li et al coated each microneedle with different formulations and drugs thus allowing co-delivery of multiple agents with different properties. These delivered water soluble and water insoluble dyes simultaneously [37]. Chen and co-workers coated PLA microneedles with sulforhodamine B and found the drug delivery efficiency to be approximately 90%. The in-vitro studies in mice confirmed the continuous drug delivery [38].

5.3. Dissolving microneedles

Dissolving microneedles are fabricated with biodegradable polymers by encapsulating the drug into the polymer. After inserting microneedle in the skin, dissolution takes place which releases the drug. The application involves only a single step as the microneedle is not to be removed out after insertion as in other cases. The polymer gets degraded inside the skin and controls the drug release. The bio-acceptability and dissolution of the polymer inside the skin make it one of the best choices for long-term therapy with improved patient compliance [1]. Effective needle drug distribution is an important factor which faces problems while developing dissolving microneedles. Hence, polymer-drug mixing is a critical step in such fabrication [30]. Chen and his group developed tip dissolving microneedles which showed rapid and efficient drug delivery without skin irritation [39]. Dissolving microneedles take time to dissolve and complete insertion is difficult. Zhu et al developed rapidly separating microneedles mounted on solid microneedles which gave sufficient mechanical strength to the microneedles and approx 90% delivery efficiency was observed in 30 s [40]. Wang et al introduced the addition of bubbles to the dissolving microneedles to prevent drug diffusion in the entire microneedles. These were found to achieve about 80% of drug delivery efficiency in 20 s [41]. Separable arrowhead microneedles were developed by Chu et al. Sharp polymer tips encapsulated with the drug were mounted on blunt metal shafts which separate or dissolve on insertion in the skin within a few seconds. These modifications in dissolving microneedles showed that possibilities of the rapid drug delivery with controlled release kinetics [42].

5.4. Hollow microneedles

Hollow microneedles have an empty space inside which is filled with the drug dispersion or solution. They have holes at the tips. On inserting into the skin, the drug is directly deposited into the epidermis

or the upper dermis layer. Mostly it is used for high molecular weight compounds such as proteins, vaccines, and oligonucleotides [1]. The drug flow rate and release pressure can be adjusted if the drug is to be given by a rapid bolus injection. These microneedles are capable of administering a large dose of the drug as more amount of drug can be accommodated into the empty space inside the needle. Maintaining a constant flow rate is essential here [32]. Increase in the microneedle bore can increase flow rate but lead to reduced strength and sharpness. Sometimes a metal coat is applied on the microneedle to increase the strength of the microneedle but this can make the needles sharp [1]. Mishra et al developed hollow microneedles aligned on the silicon substrate having a length of 500–600 μm and 100 μm outer diameter. The flow rate of 0.93 μl s^{-1} was achieved at 2 K Pa pressure difference [43]. Maaden and co-workers fabricated fused silica hollow microneedles using hydrofluoric acid etching. These microneedles were able to inject very less amount of vaccine into the skin in an automated manner thus overcoming the drawbacks of the hypodermic needle [44]. Interestingly Suzuki and colleagues developed hollow microneedles which were mimicking the action of mosquitoes and the designed microneedles showed improved penetration in the skin [31].

5.5. Hydrogel-forming microneedles

This type of microneedle is recently developed. Super-swelling polymers are used to make microneedles. The polymers constitute the hydrophilic structure which makes it capable of taking up a large amount of water into their three-dimensional polymeric network. These polymers swell when inserted into the skin due to the presence of the interstitial fluid. This leads to the formation of channels between the capillary circulation and the drug patch. Before needling, these microneedles are just used to disrupt the skin barrier. On swelling, they behave as a rate controlling membrane. They have flexibility in size and shape. Easy sterilization and intact removal from the skin are the unique properties of such microneedles [45]. Migdadi et al studied hydrogel-forming microneedles to administer metformin transdermally so as to decrease the gastrointestinal side effects associated with the oral delivery. Results demonstrated the improved permeation and bioavailability of the drug with designed microneedles [46]. Cross-linked polymers are also utilized for fabricating swellable microneedles for drug delivery.

6. Methods of delivering drug

Various methods can be used to deliver the drug into the epidermis layer. One approach is to poke the skin with the microneedles to create holes, followed by removal of the microneedle and application of the drug-containing patch over it. This creates a direct transport pathway for a drug to travel into the skin. The electric field can be applied for better effect. The second approach is to cover the microneedle surface with a coating layer containing the drug. The coated microneedles are inserted into the skin where drug dissolution takes place from the coating [6]. The third approach is to dip the microneedles into the solution containing drug and scrape the needles on the skin. The drug is left behind into the abrasions. Another approach is to incorporate the drug into a biodegradable polymer and fabricate the microneedles from the mixture. One can design a hollow microneedle where the drug solution can be filled into the hollow space of the microneedles [8,34].

7. Fabrication techniques

The selection of fabrication or manufacturing method for microneedles depends on the type, geometry and the material of the microneedle [29]. Various techniques used for different type of microneedles are mentioned in Table 2 [47–49].

8. Evaluation of microneedles

8.1. Characterization methods

The drug can be loaded onto or into the microneedles either in suspension/dispersion form or encapsulated form (liposomes, nanoparticles, nanoliposomes) [37]. The drug can be coated with the polymer solution or can be applied as a patch. Various physicochemical characterizations including particle size, polydispersity index, viscosity, and zeta potential can be evaluated for loaded drug depending on the type of formulation used in the microneedles [50]. Drug release, adhesion, permeation tests are performed for a patch which is applied after pre-treatment. The size, internal structure, and crystallinity of the liposomes or nanocarriers can be performed using a dynamic light scattering, X-ray scattering, and transmission electron microscopy technique. Stability studies of drug dispersion and microneedles can be studied at a different temperature, pH and simulated in-vivo physiological conditions (cell line or tissues). Other tests like solubility studies, drug content, in-vitro release tests, and biocompatibility studies are also performed on designed microneedle [5,15].

8.2. Dimensional evaluation

Various methods are used to evaluate the needle geometry and to measure the tip radius, length, height of the microneedle. Most common methods are optical or electrical microscopy. Analysis of a 3D image gives a better picture of needle geometry and helps in quality control. Scanning Electron Microscope (SEM) and confocal laser microscope have been used for this purpose. SEM produces an image of a sample by making use of a focused beam of electrons which interact with the atoms in the sample while scanning and produce various signals which give information about sample surface topography and composition. Confocal laser microscope produces high-resolution images [51,52].

8.3. Mechanical properties or insertion forces

A microneedle must be sharp and slender enough so that it can easily penetrate into the skin and also be strong enough so that it does not break when inside the skin. Mechanical tests which are performed on microneedles are given in Table 3. Two important factors for a safe and efficient design of microneedles are the force at which the microneedle loses its structural integrity and the insertion force. The ratio of these two forces is called as the 'safety factor'. The ratio is preferred to be as high as possible [53].

8.4. In-vitro skin permeation studies

Diffusion cell apparatus is used to find the permeation of the drug through the skin. Pig ear skin is mostly used in the experiment which is mounted between the receptor and donor compartment. The cumulative permeation profiles of microneedle treated and untreated skin are compared [54].

8.5. In-vivo animal model studies

Hairless rats can be used for the study. A suitable technique to anesthetize the animal shall be used. One of the parameters considered is trans-epidermal water loss (TEWL) which is measured before and after micro needling. Delfin Vapometer is used to measure this parameter [54].

Table 2
Fabrication techniques for different types of microneedles [47–49].

Type of microneedle	Fabrication techniques
Solid microneedle	
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 microneedles	Ceramic micro moulding and sintering lithography.
Coated microneedles	Dipping or spraying the microneedles with an aqueous solution of increased viscosity to retain more formulation during drying and which contains a surfactant, the active agent and a stabilizing agent. Microneedles can be dipped one time or more than one time into a coating solution, each individual microneedle can be dipped into a microwell containing drug solution or a film of drug solution previously formed on the roller can be applied. Layer-by-layer coating techniques.
Dissolving microneedles	Micro moulding.
Hollow microneedles	Micro-electromechanical systems (MEMS) techniques-laser micromachining, deep reactive ion etching of silicon, an integrated lithographic moulding technique, deep X-ray photolithography, wet chemical etching and micro-fabrication.

Table 3
Mechanical characterization tests [29,53].

Parameter	Tests
Insertion force	Dye marking, Force-displacement tests or Electrical measurements
Insertion depth	Histological cryosectioning and staining, confocal microscopy and Optical tomography
Failure force	Pressing the device on a rigid surface, Displacement force tests

9. Patient compliance and safety

9.1. Skin recovery process

When a microneedle device is inserted into the skin and removed after the treatment, it leaves behind holes of micron size. It may take time to reseal these pores. These holes need to be resealed quickly, otherwise may cause infection. The time taken by the skin to recover its barrier properties is important. Pore resealing can be studied by electrical impedance measurement. It can take 2–40 hrs to recover depending on whether the skin is occluded or not and also the geometry of the needle. TEWL and tissue staining can also be used to study pore resealing [29,30].

9.2. Skin irritation

The normally used transdermal injections even show a small swelling around the site. This is because the skin layer is disrupted while a foreign material is being inserted into the skin [29].

9.3. Skin irritation and infection

As the skin is exposed to various environmental stresses, skin carries various defense mechanisms to protect itself. In case of sensitive skin, use of microneedles can cause mild to moderate skin irritation or allergy. Redness, pain, swelling can be seen. Itching can cause patient discomfort [55]. Holes caused by inserting microneedles into the skin can be a site of infection unless the needles are sterile. Although the pores created by microneedles are very small as compared to that of a hypodermic needle, thus show less microbial penetration [29].

9.4. Pain

The microneedles do not reach the pain receptors which are deep into the dermis, thus cause less pain as compared to that of a hypodermic needle. The intensity of pain depends on the number of microneedles on a patch, length of the microneedle and the tip angle or needle shape [29]. Gill et al confirmed that microneedles cause less pain than a 26-gauge hypodermic needle. Lesser the microneedles length and number on the patch, less is the pain associated with the therapy [56].

10. Applications

10.1. Oligonucleotide delivery

Oligonucleotides are short DNA or RNA molecules. Delivering oligonucleotide to their intracellular site of action is difficult. Therefore various techniques to enhance the delivery were discovered. An attempt to deliver 20-merphosphorothioated oligodeoxynucleotide was made using the microneedle approach. Solid microneedles made up of stainless steel or titanium were tried to deliver oligonucleotides using the poke with patch approach. More amount of drug was found to reach the site of action as compared to the intact skin. Using iontophoresis along with microneedle approach gave better results than iontophoresis alone [2,57].

10.2. Vaccine therapy

A vaccine is a biological preparation. It provides active acquired immunity to a particular disease. Vaccine constitutes a killed or weakened form of disease-causing micro-organism, its toxins or one of its surface proteins. Vaccine therapy stimulates the immune system of the body and provides protection against the future micro-organism encounter. Microneedle approach was found to be effective in vaccine therapy [29,30].

DNA vaccine was delivered using microneedle. Immune responses seen were much better than that of the normal injections [58]. An attempt to develop a microneedle patch which can be used for administering influenza vaccine was also made [59]. A less dose is required when the drug is administered using hollow microneedles as compared to intramuscular injection. Administration of anthrax and rabies vaccine using hollow microneedles was also studied [8]. Ogai and colleagues fabricated hollow microneedles from poly-glycolic acid to enhance the vaccination efficiency by the intradermal route. The precise delivery of the drug in the upper dermis provides enhanced immunity. After the vaccination, the antibody titers were significantly higher with

intradermal vaccination with microneedles as compared to subcutaneous injection on 15th day [60]. Dissolving microneedles were also investigated for intradermal vaccination [61].

10.3. Peptide delivery

Peptides are enzymatically degraded when administered through the oral route. Transdermal delivery avoids this but less amount of peptide is able to cross the skin. Peptide delivery through microneedles can help overcome poor skin penetration of the peptides. Desmopressin is a synthetic form of vasopressin, a potent peptide hormone. It is used to replace low levels of vasopressin. This medication is used to treat diabetes insipidus, bedwetting in young children and hemophilia A. Use of microneedle approach to deliver desmopressin was studied which showed that microneedle delivery was safe and more efficient as compared to other routes [2]. Cyclosporin A is a water-insoluble and high molecular weight cyclic peptide which is used to treat various skin diseases. Dissolving microneedles containing cyclosporine A with the dimension of 600 μm in length and 250 μm wide were prepared by molding process. Fabricated microneedles with 10% cyclosporine A was pressed into the porcine skin for 60 min which showed dissolving of approx 65% of microneedle with 34 ± 6.5 μg drug delivery [62]. In one study, GAP- 26 which is a gap junction blocker loaded polyethylene glycol diacrylate based microneedles were fabricated by Liu et al for delivering peptides through swelling effect. The designed microneedles showed improved permeation of loaded peptide which confirmed with the inhibition of the proliferation of keloid fibroblasts and the collagen I expression [63].

10.4. Hormone delivery

Insulin is a peptide hormone. The medication is used to lower the high blood sugar levels. Delivering insulin using microneedle was found to lower blood glucose levels more efficiently [64]. Li et al fabricated solid microneedles and studied the effect on blood glucose levels in diabetic mice on delivery of insulin. The results demonstrated the reduced blood glucose level to 29% of the initial level at 5 h which confirmed the improved permeability of insulin to the skin using microneedle [35]. Ye and co-workers investigated microneedles integrated with pancreatic β-cell capsules which sense the blood glucose levels and secrete the insulin. But the patch was not found to function effectively. Thus microneedle matrix containing synthetic glucose signal amplifiers (GSAs) was developed which was consist of nanovesicles containing glucose oxidase, α- amylase and glucoamylase enzymes. These amplifiers showed the secretion of insulin from the β-cells capsules [65]. The results of clinical study conducted for parathyroid hormone (I-34) coated microneedles demonstrated the 3 times shorter T_{max} and 2 times shorter apparent $T_{1/2}$ compared to conventional injection therapy [66]. These studies indicated that microneedle can be utilized efficiently for the hormonal therapy. Further, these can also be modified for sustained action with the use of suitable polymers [67]. Additionally, iontophoresis in combination with microneedles can also be explored for delivery of various hormones [68].

10.5. Cosmetics

Microneedle use in cosmetics is gaining importance; especially to improve the skin appearance and to treat skin blemishes and scars. An attempt to deliver some cosmetic active ingredients like ascorbic acid, eflornithine, retinyl retinoate was made using the microneedle approach [8]. Melanin was incorporated into phosphatidylcholine liposomes (nanoliposomes) which showed increased solubility in lipids. Amount of pigment that reached deep near the hair structures was found to be more on application by an e-roller [69]. Enhanced delivery of melanostatin, rigin and pal-KTTKS was also investigated through the use of microneedles [70].

10.6. Lidocaine delivery

Lidocaine is used for local anesthesia. Administering lidocaine through microneedle causes less pain as compared to hypodermic injection and thus shows better patient compliance [29].

Baek et al coated the microneedle tips with lidocaine. These microneedles showed consistent in vitro skin penetration and enhanced delivery of the drug in 2 min. Hence, microneedles can be used for pain-free and rapid local anesthesia [36]. In one study, microneedles coated with PEG-lidocaine dispersions showed improved drug delivery within 3 min compared to the topical formulation [1].

10.7. Pain therapy

Meloxicam loaded polymeric microneedles were prepared using polydimethylsiloxane molds. The in-vitro permeation studies showed approx 100% drug release in 60 min. The drug deposition was found to be 63.37% and improved transdermal flux of 1.60 μg/cm^2/hr was observed. The permeation increased 2.58 times compared to free drug solution [71]. Neuropathic pain is usually difficult to treat. The available treatments are not able to provide sufficient pain relief and show certain side effects. Dissolvable microneedles were explored for treating neuropathic pain. These delivered selective calcitonin gene-related peptide (CGRP) antagonist peptide and showed high specificity against the receptors. The analgesic microneedle patch showed no skin irritation and side effects. About 75% microneedle dissolved within 20 min on the application [72]. The effective delivery of therapeutics through microneedle has opened the huge opportunities for the industries for pain management.

10.8. Ocular delivery

Many posterior segment indications can be treated by targeting drug delivery. Iontophoresis was used to deliver nanoparticles through the suprachoroidal space. Without iontophoresis, the particles were found to localize at the injection site. When combined with microneedles more than 30% of nanoparticles were delivered to the posterior segment of the eye [73].

10.9. Cancer therapy

Cancer affects many people every year in the world and cancer treatment faces lots of challenges. Microneedles have been investigated for various anticancer drugs delivery. Self-degradable microneedles were investigated for melanoma treatment by delivering anti-PD-1 (aPD1) in a sustained manner. Anti-PD-1 and glucose oxidase loaded pH-sensitive dextran nanoparticles were delivered through microneedle [74]. A topical cream containing 5-fluorouracil is used to treat basal cell carcinoma. The permeability of 5-fluorouracil was enhanced up to 4.5 times when the cream was applied on the skin treated with solid microneedles. Significant inhibition of tumour growth further confirmed improved efficacy using microneedles [75]. Bhatnagar et al investigated the delivery of chemotherapeutic agents- tamoxifen and gemcitabine through microneedles for the treatment of breast cancer. Localized delivery of these drugs would help to reduce the side effects [76]. Polymeric microneedles were also investigated for skin cancer and localized delivery of anticancer drugs [77].

11. Approved products

The first microneedle product was derma roller. Many microneedle products are coming in the market and are approved for medical and cosmetic use [2,29,78]. Some of them are mentioned in Table 4. Many companies in Germany, US, Europe, Japan are selling microneedle products [9].

Table 4
Approved microneedle products [2,29,78].

Product name	Company name	Description of the product	Use
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 hyperpigmentation.
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 4 circular arrays of needles which are 1.5 mm in length	Used on facial acne scars
MicroHyala®	CosMed transdermal drug delivery	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
Soluvia®	Sanofi Pasteur Europe	Hollow microneedle attached to a syringe	Influenza vaccination
h-patch	Valeritas	Small adhesive machine like patch is used	To deliver drugs in subcutaneous tissue (insulin)
Microstructured transdermal system	3M	Hollow microneedle	To deliver biologics and other small molecules

12. Clinical trials and safety

A lot of pre-clinical studies were carried out on microneedles and were found effective in many aspects but only a few gain successes in human subjects. Kaushik et al conducted the first study for microneedles in human subjects in the year 2001. The aim was to find whether the silicon microneedles are small enough to prevent pain as compared to a 26-gauge hypodermic needle. The microneedles were applied to the forearm of the 12 male and female healthy volunteers selected for the study. The study concluded that the pain caused by the microneedles was less than that caused by the hypodermic needles [79]. Arya and co-workers conducted trials to find whether microneedles cause local skin reactions and acceptable by patients or not. The study was conducted on 15 human subjects. The study demonstrated that the microneedles did not cause any swelling, pain or erythema at the site of application of the patch. The patients were able to self-administer the patches by hand without the need of the applicator. The human subjects preferred these more than the conventional needles [80]. The randomized clinical trial was conducted on 21 men to investigate the enhanced delivery of lidocaine after pretreatment with microneedles. Topical 4% lidocaine cream produced anesthesia after 60 min of the application. With the microneedles pre-treatment, anesthesia was produced within 30 min. [81]. An open trial was conducted on 10 patients for hyaluronic acid-based microneedle patch to investigate the therapeutic effects to treat psoriasis. Calcipotriol-betamethasone ointment was applied on the skin. Microneedle patch was applied over this once every day for a week. The one-week application significantly reduced the psoriatic plaques and thus was found efficient compared to the conventional cream application [82].

13. Current research, challenges, and future trends

The first microneedle was made up of silicon. A study was conducted to explore if microneedle can be used to deliver drugs through the skin more efficiently or not. Initially, the permeation studies were done on cadaver skin to see if large molecules like albumin, insulin can pass through the skin on using microneedles. Further studies confirmed better delivery of large molecules by microneedles. Currently, many new exciting microneedle concepts are coming out which will be of great help in the future [2].

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 microneedle. 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 is 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 [1].

A number of technologies are developing to deliver the drug through the skin. Various modifications have been investigated in the conventional microneedles. 3M's hollow microneedle is one of them. This emerging technology is flexible enough and can be used to administer some hundreds of milligrams of proteins, which go directly into the systemic circulation [83]. Combination of ultrasound and transdermal drug delivery is also studied in order to further increase the drug permeability [84]. Thus, microneedles can be fabricated with a variety of modifications in order to smartly deliver the drug through the skin providing a new direction and revolution in the field of transdermal drug delivery systems.

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