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Review Article

Microneedles- A new paradigm in transdermal delivery of therapeutic agents

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ABSTRACT

Microneedles are a new mode of transdermal delivery system that delivers the drug through micron-size pathways caused by disruption of the epidermis. It is an effective procedure with an array of applications in dermatology and drug delivery with a low side effect profile. Microneedles deliver the drug in the epidermis or upper part of the dermis, bypassing the toughest barrier of the stratum corneum, and resulting in a painless delivery. Microneedles are being investigated for the delivery of hormones, vaccines, peptides, and cosmetics. They are fabricated as dissolvable, solid, coated, or hollow depending on the type of drug loading. This review is a comprehensive collection of various aspects of microneedles. The authors focus to enlighten the readers on the mechanism of dermal penetration of microneedles, their fabrication materials, types, design strategy, specificity, and manufacturing. There are a few products already captured the market. A lot of research and clinical studies are yet to establish the scale-up and clinical efficacy of the product. They can be served as a novel modality for the enhancement of topical delivery of drugs at a low cost, well tolerated, and with low profiles of side effects.

Keywords:
Microneedles, Microneedling technique, Skincare, Transdermal drug delivery, Microneedle fabrication

1. INTRODUCTION

Microneedle is a novel type of transdermal drug delivery technique that improves drug permeation through the toughest barrier of the skin. The mechanism involves the creation of a larger pathway of transport of drug molecules through micron size hypodermic needles which can disrupt the stratum corneum and directly deliver the drug into the epidermis or dermis layer. "Collagen induction therapy", "derma rolling", "skin needling"[1], and "Percutaneous Collagen Induction"[2] are all terms used to describe microneedling process. Microneedle is a less invasive technique for treating a variety of dermatological problems[2]. It also eliminates a slew of issues of the traditional formulations like inter-subject variations in bioavailability, and patient compliance[1]. The advantageous features of this technology include faster action, improved permeability of larger molecules, self-administration, and better patient compliance.

The key feature is the disruption of the epidermal layer, which creates drug transportation through micronized routes straight to the epidermis or upper dermis[1]. It causes minimal damage to the epidermis that triggers dermal regeneration through the release of multiple growth factors. Neovascularization and neocollagenesis promote skin rejuvenation. Patients who are concerned about aesthetic changes caused by injury, sickness, or aging have recently been treated using this technique[3].

Solid, dissolving, hydrogel-coated, and hollow microneedles are some of the varieties of microneedles[4].

This technique has a long list of benefits in the treatment of acne vulgaris, scars, facial rejuvenation, dyspigmentation, alopecia, hyperhidrosis, and transdermal medication administration, as well as the treatment of diseases other than skin[5]. It is a low-cost and minimally invasive tool for transdermal drug delivery.

2. MECHANISM OF MICRONEEDLING

The transepithelial potential of the epidermis varies

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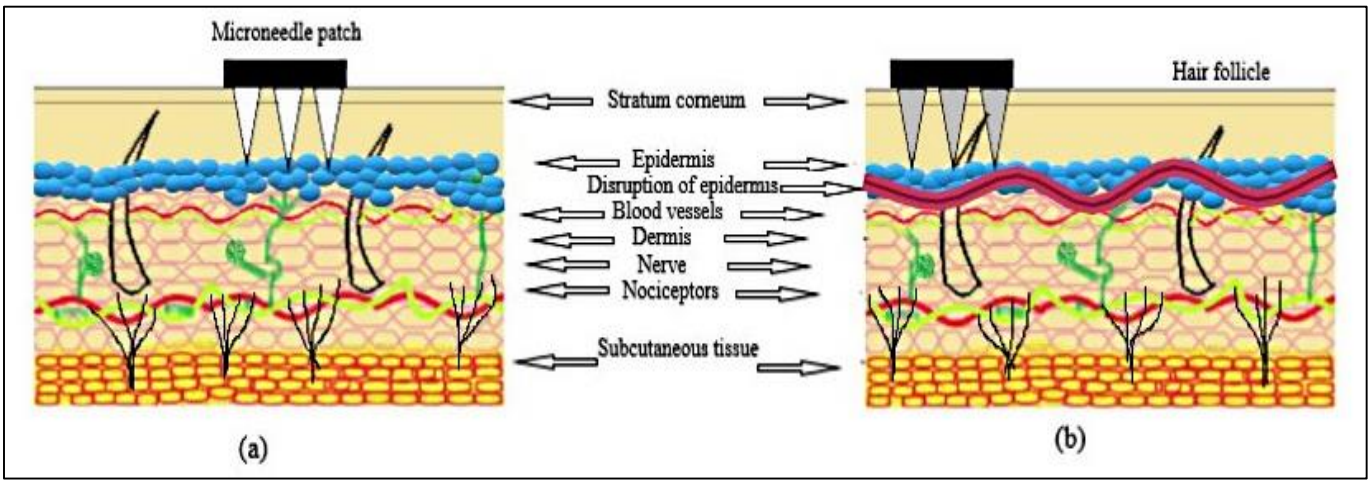

Figure 1. Mechanism of microneedles for dermal penetration – (a) insertion of the device and (b) temporary disruption of the epidermis.

from 10-60 mV in different parts of the body[6]. During the delivery of the medicine, a diffusion mechanism takes place. Arrays of hundreds of microneedles are arranged on a narrow path to form a microneedle device that delivers enough medication to provide a therapeutic response. During the microneedling process, the skin is temporarily disrupted, leading to the generation of a short circuit and activation of Na^+/K^+ pump.

Micro channels thus form as a result of the physical shock that triggers dermal regeneration by inducing fibroblast growth factor, platelet-derived growth factor, and transforming growth factor (TGF)-a and TGF-b[3]. This triggers fibroblast proliferation and migration and consequently leads to neovascularization and neocollagenesis. In course of time tissue remodelling occur. Collagen type 3 deposits after a fibronectin matrix are formed. Type 1 collagen gradually takes over from type 3. The results of this remodelling process include skin tightening and scar reduction. This process thus benefits in repairing scars and photoaging.

The mechanism of action of microneedles is presented in Figure 1.

3. SKIN ANATOMY AND MICRONEEDLES

Skin is the largest complex organ in the human body to carry out multiple functions. It is a non-homogeneous structure of living and non-living cells of the body. It has three distinct layers. The outermost layer epidermis is 200-400 µm thick and consists of five layers -stratum corneum (20-30 cell layers), stratum lucidum (2-3 cell layers), stratum granulosum (3-5 cell layers), stratum spinosum (8-10 cell layers) and stratum germinativum[7]. The different types of cells present in the epidermis are keratinocytes, melanocytes, Langerhans cells, and Merkel's cells. The stratum corneum has a heterogeneous structure composed of proteins (70%), lipids (15%), and water (15%). Keratin and ceramide constitute the main protein and lipid parts of the stratum corneum respectively. The dermis, the next layer of the skin varies in thickness from 2-4 mm, where collagen is the main protein component. A rich blood supply through the arterial and venous system lies within 0.2 mm of the skin surface. Skin appendages and sebaceous glands are present in the region. The hypodermis, the innermost layer consists of fat cells, collagen, blood vessel, and nerves having a varying thickness throughout the body from 1 mm to 3 cm[8].

The length of microneedles varies from 25-2000 µm just enough to cross the stratum corneum and penetrate the viable layers of the epidermis. They reside mostly in the epidermis and avoid the nerves and blood vessels in the dermal layer. Hence, they are designed for pain-free delivery of small and large active pharmaceutical ingredients through percutaneous way[9]. Many studies reported with a low Visual analogous scale (VAS) score that the process is painless compared to hypodermic needle[10]. But, the sensation patient experiences on application and closure of the micropores or formation of erythema after removal of microneedles are of paramount importance in its design and application.

4. FABRICATION OF MICRONEEDLES

In microneedle devices, hundreds of microneedles are embedded over a small area of a standard transdermal patch and made to pierce only the 50 µm of the outer layer of the skin to deliver the medicine into the dermis layer. The array of these tiny needles ensures the delivery of drugs for achieving therapeutic response.
Silicon etching technology and micromechanical system manufacturing are used to make solid and hollow microneedles thinner than hair. They offer a painless delivery due to their small size and restricted penetration to the deeper layer of the skin.

The needles in the arrays are 150 µm long and tapered from an 80 µm base to a 1µm tip. The drawback of the silicon etching technology is the brittleness of the

Table 1. Fabrication techniques of microneedles.

Type of microneedles	Fabrication techniques	Fabrication materials
Solid microneedle	• Silicon dry-etching process, • Isotropic etching, • Anisotropic wet etching[1] • Dicing and acid etching, • Three-dimensional laser ablation [1]	Silicon
Metal microneedle	• Laser cutting • Wet etching • Metal electroplating methods[1]	Metals - stainless steel, titanium, palladium, nickel, palladium-cobalt[1]
Polymer microneedle	• Photolithography[1]	**Natural polymers:** Amylopectin Chondroitin sulphate CMC Dextran[13] **Biodegradable synthetic polymers:** Thermoplastic Starch PLA PLGA Polycorbonate PMVE/MA Copolymer PVA PVP[13]
Ceramic microneedle	• Ceramic micro-moulding • Sintering lithography[1]	Aluminium oxide Zirconia[13]
Coated microneedle	• Layer-by-layer coating techniques[1]	Stainless steel sheets[14]
Dissolving microneedle	• Micro-moulding[1]	Polydimethylsiloxane (PDMS) micromould[15]
Hollow microneedle	• Micro-electro mechanical systems (MEMS) techniques-laser micromachining • Deep reactive ion etching of silicon • Integrated lithographic moulding technique • Deep X-ray photolithography • Wet chemical etching • Microfabrication[1]	Ceramics Metal Silicon Glass[16]

silicon which led to the breakage of the microneedle, resulted in the loss of medication, and enhanced the risk of infection and toxicity. To overcome these challenges, small gauge metal and plastic microdevices are employed to make short and sharp needles for deep skin penetration.

Maltose has recently been used to create biodegradable microneedles[11]. Kolli C.S. et al, conducted a study on *in-vitro* transdermal delivery of therapeutic antibodies using maltose microneedles. Microneedles manufactured using maltose are easily disintegrated upon piercing and they are used in transdermal administration of therapeutic molecules. Maltose microneedles were stable and strong enough to penetrate the skin of hairless rats. They provided a channel for the percutaneous transport of macromolecules on insertion. An *in-vitro* study was also performed to administer purified human IgG and a model monoclonal antibody and observed that the efficacy of the treatment was influenced by the number of microneedles, length of microneedles, and donor concentration[12].

To use microneedles for transdermal drug administration, a variety of delivery techniques have been used[11] and are illustrated in Table 1. The preferred materials for microneedles are silicon, ceramic, and metal.

4.1. Silicon

Silicon being an anisotropic material, has several appealing physical features, making it a flexible and appealing material for the creation of micro needles[17]. High elastic modulus and mechanical strength facilitate piercing and transdermal delivery. They show versatility in shapes, heights, and densities in making solid, hollow, and coated microneedles[18-19]. The high price, intricate manufacture, long production periods, and multi-step handling intricacy of silicon are some of its major downsides.

Silicon's biocompatibility has also been questioned. Many researchers have proved that they don't have significant cytotoxicity while others have reported on the formation of granulomas in the subcutaneous tissues [20-21]. Some silicon microneedles may shutter in the skin due to their brittle nature, posing a health risk. Numerous researches have been conducted to examine the reliability of their biocompatibility[22].

4.2. Silica Glass

Silica glass offers a distinctive advantage for microneedles being physiologically inert, versatile in microfabrication into different dimensions and easy visualization of liquid with high elasticity. They are biocompatible but are brittle, and can cause granulomas inside the skin if inserted for a long time.

4.3. Ceramic

Ceramic offers the suitability of being another material for the preparation of microneedles. Mostly, Alumina, Gypsum, and Brushite are used for this purpose. A ceramic slurry is molded through micro-molding technique to prepare the microneedles. Alumina being a stable oxide shows chemical resistance but is brittle under stress. They offer good drug loading because of high porosity and microneedles are mostly prepared by the coat and poke technique. Gypsum and Brushite offer good mechanical properties and drug loading. They impart good biocompatibility and are bio-resorbable[22]. Ormocer an inorganic-organic copolymer of ceramic polysiloxane and dimethacrylate monomer, has shown potential for biomedical material because of its biocompatibility[23].

4.4. Metal

Metals that are commonly used in the preparation of microneedles are stainless-steel 316L, titanium, palladium, palladium-cobalt alloys, and nickel[24]. They are biocompatible, possess good mechanical properties and elasticity, mostly a preferred material for subcutaneous implants. Microneedles are made by electro-plating, or by sputtering a metal seed layer onto polymer or silicon micro molds. They are biocompatible, show insignificant mutagenicity, and have excellent corrosion resistance[25].

4.5. Carbohydrates

Microneedles are prepared by casting carbohydrates slurry onto the master templates of silicon and metal microneedles. Generally, sugars such as trehalose, sucrose, mannitol, xylitol, and galactose are used[26]. There are many disadvantages associated with sugars in the processing and storage of microneedles. The requirement of thermal treatment during processing limits the use of many compounds. Even improper storage can adversely affect the properties and stability of the microneedles. Drug release is hindered because the partial dissolution of the sugars, results in the blocking of the holes[26]. Dissolving microneedles are mostly prepared with macromolecules like carboxy methyl cellulose, amylopectin, dextrin, hydroxypropyl cellulose, and alginates.

4.6. Polymers

Microneedles are prepared with a wide variety of biodegradable and biocompatible polymers like poly methyl methacrylate), Poly Lactic acid, Polyglycolic acid, Polylactic glycolic acid, polycarbonate, polyvinyl pyrrolidone, polyvinyl acetate, styrene, etc. They are mostly used in the production of dissolving and hydrogel-forming microneedle arrays. Microneedles prepared with Gantrez AN-1391, a copolymer of poly methyl vinyl ether co maleic anhydride exhibited better resistance and plasticity for the skin penetration[27].

5. CLASSIFICATION OF MICRONEEDLES

Microneedles can be classified in several ways. Different types of microneedles are mentioned in various research articles and are generally termed as solid, dissolving, hollow, coated, and hydrogel-forming microneedles. Depending on their mode of delivery (Table 2) through the stratum corneum the classification is mainly of four types. The different types of micro-needles are presented in Figure 2.

5.1. Hollow microneedles

Hollow microneedles are used to inject liquid drug formulations into the skin through microneedles bores. They have a lumen or interior tube (5-70 µm wide) which is filled with drug dispersion. The holes at the tip of the microneedles allow the drug to deposit at a constant rate in the inserted layer of the skin.

They act as a reservoir of drugs through which drug is diffused at a predetermined rate. A large dose of drug can be administered safely. The advantages of this microneedle type are its ease of manufacture, low prices,

Table 2. Different approaches of Microneedling techniques.

Approaches	Highlights
Poke with patch	• Application of electric field • Transport of drug via diffusion or iontophoresis
Coat and Poke	• Drug-coated needles scrap across the skin
Biodegradable	• Biodegradable, polymeric microneedles for controlled drug release
Hollow	• Injects drug with hollow bore needle • Resembles injection rather than a patch

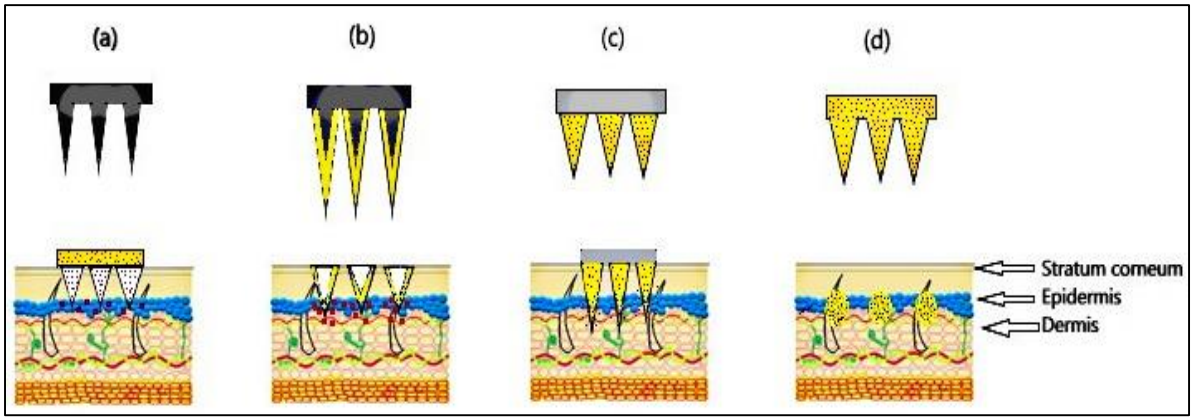

Figure 2. Different types of microneedles (a) Solid microneedles (b) Coated microneedles (c) Dissolving microneedles (d) Hollow microneedles.

and precise drug release control. Incorporating a chip with microfluids or micro-pump within the slew of microneedles can also be used to provide controlled active pharmaceutical ingredients (API) release[13]. This type of microneedles is studied to deliver proteins, vaccines, and oligonucleotides[28].

5.2. Solid microneedles

Solid microneedles are used for creating micro-sized pores and channels to allow the drug to penetrate through the skin effectively from a transdermal patch. This type of microneedles is thus used for the pre-treatment of skin before administration of drug from the external source. The drug is delivered by passive diffusion and can be used to achieve both systemic and local action[29]. The "poke and patch" strategy, the "poke and release" approach, and the "coat and poke" approach are the three major ways by which solid microneedles can transport medications through the skin.

Using the poke and patch microneedles are used to create channels inside the epidermis and drug formulation is allowed to pass from a reservoir-type transdermal patch through the created path. This method is used with iontophoresis and increases the penetration of the drug in many folds. The micropores must remain open during the drug application. But this method suffers drawbacks as extended opening times can increase the danger of infection[30].

In the poke and release approach, microneedles must remain on the skin until the medicine is delivered. Drug depot gets created and provides controlled release of the medication from the microneedles. Hence the microneedles should be made with biodegradable materials or they should be porous or dissolving type[30].

The coat and poke approach uses drug-coated microneedle arrays as a single-unit drug delivery device to improve drug uptake through the skin. Coating of the microneedle should be done with the optimum quantity of medications since thick coatings result in slow delivery and also diminishes the sharpness of micro-needles. As a result, coated microneedles are useful for transdermal delivery of vaccines[30].

5.3. Dissolving/degradable microneedles

Dissolving/degradable microneedles completely dissolve in the skin, releasing medications or vaccines embedded in the matrix of microneedle. They are fabricated with drug encapsulated biodegradable polymers. The advantage of this type of microneedles is that there is no need for removal after insertion. The choice of polymer, its bio-acceptability, and its release pattern make it suitable for long-term therapy. The critical step for this fabrication is the uniform distribution of drug-polymer mixing[1].

5.4. Coated solid microneedles

Coated solid microneedles are covered with the dispersion of drug. After insertion, dissolution of the coating results in the delivery of drug. The thickness of the coating determines the drug loading[28].

5.5. Hydrogel microneedles

The polymers having high swelling index are used to make hydrogel microneedles. Swelling of the polymers in presence of interstitial fluid causes formation of channels between dermal microcirculation and the drug reservoir in the transdermal patch. The swellable polymer acts as a rate-controlling membrane and sustained the delivery of the drug. Drug release can be controlled by varying the crosslinking of the polymer hence the swelling capacity. Hydrogel microneedles are generally easier and more cost-effective to make from materials that are more biocompatible and have FDA approval[31].

Table 3. Special characteristics of the various microneedle devices.

Microneedling device	Length of needles	Purpose for use	Important characteristics
Deeper devices	0.1-3.5 mm	Removal of Deep acne scarring, surgical and deeper scars, wrinkles,	Usage in health care facilities[3].
More superficial devices	0.15 mm	Home use	
Automated devices	Depends on the area being treated	Pen-shaped and enable for easy adjustment of needle penetration depths	Disposable, reducing the danger of infection and allowing for the treatment of small regions[3].
Microneedles with radio-frequency and light-emitting diodes		To treat scars, wrinkles, and skin laxity	Fractional radio-frequency type, uses insulated needles that release radiofrequency currents upon skin penetration, resulting in dermal remodelling and neo-collagenesis[3].
Microneedling pens			Hollow needles to administer medication straight to the dermis[3].

6. MICRONEEDLING MANUFACTURING TECHNIQUES

The fabrication of microneedles varies with the type, shape, and construction material as described in Table 1-3.

6.1. Microneedling process

6.1.1. Design theorem

Human skin constitutes of epidermis (100-200µm), dermis, and hypodermis. The microneedles aim to cause damage to the viable layer of the epidermis. There are three fundamental regions of the device: Region 1- the staff, Region 2- styles, and Region 3- the body structure. The functions of each region are restricted to the piercing ability of the microneedles through the skin. Region 1 helps to clutch the device. Region 2 aids to deliver the drug through piercing. Hence the shape of the needles becomes a critical parameter for the design. The preferred shapes are monoclinic trihedral, cone, or cantilever beams. Region 3 has a hollow structure to form small channels to deliver drugs uninterrupted and a solid structure to shatter the epidermis and aid entry of drug[32].

6.1.2. Design of instruments

The design of the microneedle device was first explained by Fernandes. He proposed the design of creating a cylindrical device that could be pushed back and forth to obtain intact bleeding[3].

Microneedle should be designed in such a way that it must give association between drug reservoir and patient's body to deliver the drug, for that the length must be such that they should penetrate through the epidermis and should not enter or pierce the dermis layer to avoid pain. Hence the length of microneedle should be in the range of 100 µm-300 µm.

Microneedles can be fabricated using materials such as silicon, metal, ceramic, silicon dioxide, glass, and polymer in different sizes and shapes[33].

The various types of microneedling devices are described in Table 3 with their special characteristics.

6.1.3. Device specificity

A variety of cylindrical mechanical devices are distinguished by the length, quantity, diameter, and substance of the needles. They act by rolling perpendicularly across the skin's surface until superficial bleeding occurs.

The standardized microneedles device, the Dermaroller®, has 192 pins that are 2 mm and 0.07 mm in diameter, and when used 15 times on the skin, incurs around 250 perforations/cm^2 towards the papillary layer, depending on the loaded tension, avoid harming the epidermis.

Other devices[34] that are available with their unique specificity are presented in a tabular way in Table 4.

The varieties of fabrication processes that are used to make microneedles are lithography, micro molding, molecular imprinting, photopolymerization, etc. Dry and wet etching lithography was used initially for the fabrication of microneedles using alkaline solution and reactive ions. Later on, with the use of fabrication materials like glass, silicon, and polymers, the photolithograhy, replica molding, and Polymer micromachining are employed[35].

7. APPLICATIONS OF MICRONEEDLES IN COSMETIC AND THERAPEUTIC DELIVERY

7.1. Microneedling as an adjunct therapy for facial melasma

Lima E.V.A et al, did an open pilot study with women who had faced refractory melasma. They were not allowed to receive any treatment for the previous 30 days other than sunscreen. Patients were given two microneedling sessions with Dr. Roller TM (1.5 mm). After two sessions of microneedling, all participants reported a reduction in melasma, as well as a subjective

Table 4. Specificity of various microneedle devices.

Device	Specificity	Use
Dermaroller®	Length 0.15 mm. Used twice or thrice a week at the very least	To reduce penetration depth, subtle wrinkles, and sebum production.
Derma-stamp	Length from 0.2 to 3 mm. Pressing the device on skin while piercing	Localised scars such as varicella scars are repaired with this product
Dermapen®	Pen-like tool with the capacity to modify needles.	Disposal needles are used to resurface a vehicle mechanically.
Dermafrac®	Micro-derm abrasion Use light emitting diode therapy	Commonly used to provide immunizations

improvement in facial skin smoothness and brightness. Histologically, epithelial thickening, decreased epithelial melanin pigmentation, and densification of upper dermis collagen were all seen. They have reported that to maximize the efficacy of microneedling treatment and fixation of the regimens to ensure long-term results, further randomized controlled trials were needed[36].

7.2. Microneedling in skin rejuvenation

For face rejuvenation, microneedling has proven to be a precise and safe solution. Dyspigmentation, rhytids, elasticity loss, and collagen loss are all symptoms of aging skin. The extracellular and cellular components of the skin are changed by cumulative intrinsic and external forces. Microneedling allows collagen and elastin neogenesis by mechanically stimulating the dermis while avoiding harm to the epidermis. Clinically, skin rejuvenation is defined as a reorganization of dermal architecture.

Microneedling disrupts dermal collagen and scar anchoring, resulting in a pro-inflammatory response with subsequent collagen and elastin remodelling. The variation in the needle length from 0.5-3 mm can cause mechanical damage from the stratum corneum to the papillary dermis, hence they are capable of delivering medicine to any layers of skin.

Microneedling reduces the incidence of post-inflammatory hyperpigmentation, infection, scarring, and milia by maintaining the epidermis and dermal-epidermal melanocytes[3]. El-Domyati and colleagues used reported a significant clinical improvement in photoaged skin[37].

Microneedling has demonstrated promising outcomes in facial rejuvenation. Clinically and histologic alterations that aid in the reduction of wrinkles and skin laxity have been identified in previous studies. It has a positive safety profile due to its low invasiveness. Microneedling is a rejuvenation technique that reduces the likelihood of hyperpigmentation and is a safe and effective treatment option that can be used alone or in conjunction with other agents or treatments[37].

7.3. Vitiligo

The effectiveness of microneedles as part of a vitiligo treatment regimen is unknown[38]. Yomna Mazid El-Hamd Neinaa et al, explored the use of narrow-band ultraviolet B and topical 0.005% latanoprost solution for the treatment of vitiligo, with and without Dermaroller. The results were promising and the therapeutic efficacy of latanoprost was enhanced significantly in the treatment of nonsegmental vitiligo[39].

7.4. Verruca

Konicke and Olasz saw the usefulness of microneedle as a technique of transdermal delivery of bleomycin for the treatment of verruca vulgaris, without tissue necrosis[40]. The cure rates with the application of this technique were found to be a promising approach for ensuring 100% cure rates in plantar warts. The findings prompted a requirement for a large-scale clinical trial to establish the efficacy of microneedles in the treatment of wart[40].

7.5. Anti-aging

Microneedling, is becoming increasingly popular to arrest the aging of the skin. The use of microneedle rollers to improve facial cosmesis by inducing collagen and increasing the penetration of topical cosmeceuticals has been widely studied. This therapy doesn't cause epidermal harm as laser therapy. This provides a less expensive treatment. The procedure can be carried out in a doctor`s office and does not necessitate any lengthy special training or costly equipment[41]. MicroHyala®, an FDA-approved product of dissolving hyaluronic acid microneedles is prescribed for wrinkle treatment[42]. Dermaroller®, solid metallic microneedles are used for improving the texture of skin[1].

7.6. Aesthetic uses

The fact that microneedling may be used for a variety of aesthetic treatments is one of the key reasons for its growing popularity. This comprises the treatment of

i. Anti-ageing / skin rejuvenation - Revive-microneedle procedure kit consist of moisturizer, cleaner, and topical serum used to improve post-operative healing of the skin[4].

ii. Hyper-pigmentation - ScarLet™ was found to improve skin pigmentation and laxity[43].
iii. Hair loss by inducing stem cells in the scalp[44]- Dhurat et al. reported the positive use of minoxidil lotion with Dermaroller® device for the treatment of alopecia.
iv. Scarring and Stretch marks- Dermapen® and Dermastamp® is claimed to be effective for scar, wrinkles, and skin lessions[45].

7.7. Insulin delivery

Insulin is one of the most challenging medications to deal with for drug delivery technologists. Martano et al, used microarrays to deliver insulin to hairless diabetic rats[46].

Solid stainless-steel microneedles with a length of 1 mm and a tip width of 75 m were implanted into the rat skin and employed with poke and patch procedure. Over four hours, blood glucose levels dropped by as much as 80%[46].

7.8. Vaccine delivery

Conventional delivery of vaccines is painful and requires cold storage. Microneedles can be used effectively for vaccination without the requirement of cold storage and reduce medical waste[,29,47]. Intramuscular administration of DNA vaccines exhibits a weaker immune response due to the inefficient delivery of plasmid DNA into host cell[22]. A suitable delivery system is of prime importance to improve immunization of DNA vaccines. DNA vaccines were loaded in microneedles and studies revealed that they could deliver plasmid DNA effectively into the host cell[48]. Hence, it can be considered an optimistic delivery method for DNA vaccines[49].

7.9. Delivery of peptide and protein

The main goal of microneedling drug delivery system is to deliver the drug through transdermal irrespective of its molecular weight and polarity. Protein-based substances rarely penetrate the skin because of their hydrophilic nature and high molecular weights.

In the context of the cosmetic sector, research is currently being done on the intra-dermal delivery of peptide cosmeceutics through microneedle devices. Melanostatin, rigin, and Palmitoyl-Pentapeptide (pal-KTTKS) are studied for microneedling process for enhanced skin delivery for cosmetic purposes[50]. Pal-KTTKS induces the formation of collagen when administered through the skin. The study compared the effects of microneedle use on the penetration and distribution of these peptides in the skin versus passive diffusion of the same peptides and reported that an increased penetration and distribution of the peptides, were seen with the use of microneedles[42].

Proteins play an important role in the treatment of diseases like inflammation, genetic diseases, cancer, vaccination, etc. The primary mode of administration is by the parenteral route and the main concern is the stability of the formulation[51]. Oral delivery suffers from the limitations of degradability. Stratum corneum limits the delivery of proteins. Hence the present research is focused on microneedles which can painlessly penetrate the stratum corneum and brings out the maximum stability and bioavailability of proteins. Hollow, coated, biodegradable, swellable, and bioresponsive micro needles are in research for the delivery of proteins through percutaneous way[52].

7.10. Cancer treatment

Every year, cancer strikes a large number of people around the world, and cancer treatment is fraught with difficulties. Microneedles have been studied for the delivery of anticancer medicines. Anti-PD-1(aPD1) was delivered in a sustained manner using self-degradable microneedles for melanoma treatment. Microneedle delivery of anti-PD-1 and glucose oxidase-loaded pH-sensitive dextran nanoparticles[53]. Basal cell carcinoma is treated with a topical cream containing 5-fluorourail. Upon application of the cream to skin that had been treated with solid microneedles, the permeability of 5-fluorouracil was increased by up to 4.5 times. Microneedle efficacy was further confirmed by significant tumor growth inhibition[54]. Bhatnagar et.al, investigated the use of microneedles to administer chemotherapeutic drugs such as tamoxifen and gemcitabine for the treatment of breast cancer. The negative effects of these medications could be reduced if they were delivered locally[55]. Skin cancer and localized administration of anticancer medications were also explored using polymeric microneedles[56].

The marketed microneedle devices are listed out here in Table 5.

7.11. Delivery of biopharmaceuticals

Microneedles are investigated to be a useful means for the delivery of drugs to improve bioavailability and therapeutic activity.

A novel two-layered dissolving MNs for fluconazole ocular administration was fabricated to administer the drug intra-corneally for the infection against *Candida albicans*. It has shown a promising effect on fungal keratitis[67].

Antihypertensive agents were shown to give promising effects on animals. Stainless steel microneedles of verapamil in pig skin showed a significant

Table 5. Marketed microneedle-based transdermal products

Brand name	Manufacturer	Description	Application
Demaroller®	Derma spark, Canada	Metallic microneedle array Two versions are, Standard dermaroller versions Miniature version	Therapy of acne, stretch marks, wrinkles, facial rejuvenation inducing collagen induction[57].
MicroHyala®	CosMED Pharmaceutical Co.Ltd., Japan	Dissolvable microneedle patch	Presence of hyaluronic acid to cure wrinkles[58].
VaxMat®	TheraJect Inc., USA	Dissolvable microneedle patch. Biodegradable patch[59]	Transdermal delivery of proteins, peptides, and vaccinations[58].
Micro-Trans®	Valetiras Inc., USA	Silicon microneedle patch [60]	Drug delivery into the dermis without limitations of drug size, structure, charge, or the patient`s skin characteristics[58, 60].
Drugmat®	TheraJect Inc., USA	Dissolvable microneedle patch	Rapid drug delivery through the stratum corneum into the epidermal tissue.
Nanoject®	Debiotech, Switzerland	Microneedle array-based on biocompatible MEMS technology	Improvised intradermal and hypodermic drug delivery and interstitial fluid diagnostics[61].
Soluvia®	Becton Dickinson, USA	Hollow microneedle array	Glass prefilled syringe, Used in influenza vaccine[62].
IDflu®/Intanza®	Sanofi Pasteur, Lyon, France	Intradermal microneedle injection	Prefilled with influenza vaccine for intradermal influenza vaccination[63].
Micronjet®	NanoPass Inc., Israel	Intradermal microneedle injection	Painless delivery of drugs, protein, and vaccines[64].
Macroflux®	Zosano Pharma Inc., USA	Metallic microneedle array	Delivery of peptides and vaccines and desmopressin[65].
Microcore®	Corium International Inc., USA	Dissolvable peptide microneedle patch	Delivery of small as well as large molecules, like proteins, peptides, and vaccines[66].
Dermapen®		Microneedle array-based device	Therapy for acne scars, burn scars and photo ageing[42].
Microstructured transdermal patch	3M Corp., USA	Hollow microneedle array	Transdermal delivery of proteins, peptides, and vaccines[59].

improvement in permeability of the drug[68]. Transdermal fluxes for amlodipine besylate exhibited significant improvement with solid and microneedle rollers[68].

Some examples of the performance of microneedles such as needle length and molecular weight of active ingredient are listed in Table 6.

8. CONCLUSION AND FUTURE PERSPECTIVE

Transdermal delivery of drug is limited to a specific number of drugs considering their molecular and physicochemical properties. Microneedling technique has revolutionized the aspect of transdermal delivery beyond any boundary of drug characteristics.

Starting from cosmetic use to the delivery of peptides, hormones, and vaccines it is found to be profusely effective. The development and regulation of microneedle are gaining more important focus in the present era. Microneedling techniques are safe, effective, and aesthetics, and provide minimal invasive dermal treatment for cosmetic or dermatological use, to produce local and systemic action. The present review highlights the science and design of microneedles and their application in various aspects. As with every novel process, the transdermal delivery of drugs through microneedling suffers from scalability and clinical issues like skin irritation, redness, and allergy on application. Hence more research on the properties, fabricating material and a vast number of clinical trials should be conducted for the establishment of the exciting concepts of microneedles.

Table 6. Performance of microneedles.

Drug	Microneedle type	Microneedle property	Utility
Acyclovir (Mol wt of 225.21 Da)	solid silicon microneedle	Length (100–1100 μm) and density (400–11 900 MN cm^{-2})	Dramatic increase in drug flux with longer needles[69].
Calcein (Mol wt ~ 622 Da) Insulin (Mol wt ~ 5800 Da), and bovine serum albumen (BSA) 67 kDa	solid silicon microneedle	150 μm in height	Significant improvement in permeation[70].
parathyroid hormone 1–34	titanium microneedle array w	length 190 μ, width 115 μ	Safe effective for post-menopausal women for the treatment of osteoporesis[71].
Piroxicam	Polymethylsiloxane micromold	Length 150 μm	Higher skin deposition of drug[72].
Lidocaine	Poly (L-lactide)) microneedle	length 650 μm	Rapid local anesthesia without pain[73].

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