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Review

Microneedles: an emerging transdermal drug delivery system

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Abstract

Objectives One of the thrust areas in drug delivery research is transdermal drug delivery systems (TDDS) due to their characteristic advantages over oral and parenteral drug delivery systems. Researchers have focused their attention on the use of microneedles to overcome the barrier of the stratum corneum. Microneedles deliver the drug into the epidermis without disruption of nerve endings. Recent advances in the development of microneedles are discussed in this review for the benefit of young scientists and to promote research in the area.

Key findings Microneedles are fabricated using a microelectromechanical system employing silicon, metals, polymers or polysaccharides. Solid coated microneedles can be used to pierce the superficial skin layer followed by delivery of the drug. Advances in microneedle research led to development of dissolvable/degradable and hollow microneedles to deliver drugs at a higher dose and to engineer drug release. Iontophoresis, sonophoresis and electrophoresis can be used to modify drug delivery when used in concern with hollow microneedles. Microneedles can be used to deliver macromolecules such as insulin, growth hormones, immunobiologicals, proteins and peptides. Microneedles containing 'cosmeceuticals' are currently available to treat acne, pigmentation, scars and wrinkles, as well as for skin tone improvement.

Summary Literature survey and patents filled revealed that microneedle-based drug delivery system can be explored as a potential tool for the delivery of a variety of macromolecules that are not effectively delivered by conventional transdermal techniques.

Introduction

Development of functional delivery systems for new active pharmaceutical ingredients is a challenging task. Drug can be administered through most common routes like the oral, parenteral, ophthalmic and transdermal route, as well as less explored routes such as nasal, pulmonary and buccal.[1] Each of these routes have specific merits and disadvantages. Oral drug delivery systems offer advantages such as patient compliance, large surface area with rich blood supply for absorption, low cost, ease in engineering of drug release in stomach/intestine, etc. However, limitations, like drug degradation in the gastrointestinal tract, first-pass metabolism, poor absorption, local irritation and variability in absorption (due to factors like pH, motility, food, mucus layer, etc.), are associated with these drug delivery systems.[2,3] The parenteral route offers advantages like quick onset of action, accurate drug delivery and continuous drug delivery by infusion; its limitations include pain associated with the injections, expertise required to deliver the drug, risk of infection and difficulty in obtaining sustained drug delivery.[4]

Transdermal drug delivery involves the transport of drug across the skin. Optimal physiochemical properties are required in drug candidates for delivery via transdermal patches. Traditional transdermal patches can be divided into two categories – reservoir-based and matrix-based – according to their physical structure. Transdermal drug delivery offers advantages like patient compliance, avoidance of first-pass metabolism, large surface area of skin over which to deliver the drug, quick termination of dosing, etc.[5,6] However, only a few drug products with optimum characteristics have been successfully marketed to deliver a drug

through the skin. This is due to the resistance to drug transport offered by the stratum corneum.[7] The problem of poor drug transport can be addressed by development of micron-sized needles, which deliver the drug painlessly across the stratum corneum.[8]

Skin anatomy and transdermal drug delivery systems

Skin can be divided into three regions: (1) the outer most cellular layer, epidermis, which contains stratum corneum, (2) the middle layer, dermis, and (3) the inner most layer, hypodermis (Figure 1).[9] The epidermis layer is 150–200 μm thick and is made up of viable cells without a vascular network. This layer obtains its nutritional needs by passive diffusion through interstitial fluid.[10] The outermost layer of the epidermis (10–20 μm) consists of dead cells, known as the stratum corneum, which act as a rigorous barrier.[11] The dermis, an integrated fibro-elastic structure, provides mechanical strength to the skin. This layer contains an extensive nervous and vascular network. The pain associated with parenteral drug delivery is due to possible damage to the nerves endings within the dermis. For drug delivery across the skin, the challenge is to cross the intact stratum corneum layer without causing damage to nerves endings. Only a few potent drug molecules having high lipophilicity and small molecular weight (<500 Da) can be administered directly through passive diffusion.[10,12]

Various chemical and physical approaches have been employed to improve drug penetration across the skin.[13] Chemical approaches include the use of penetration enhancers, like surfactants, fatty acids/esters and solvents to dissolve the stratum corneum lipid or to increase the solubility of drugs. Physical approaches, like electroporation, iontophoresis, magnetophoresis and sonophoresis, have been found suitable to create pathways for only a few drugs across the skin.[14]

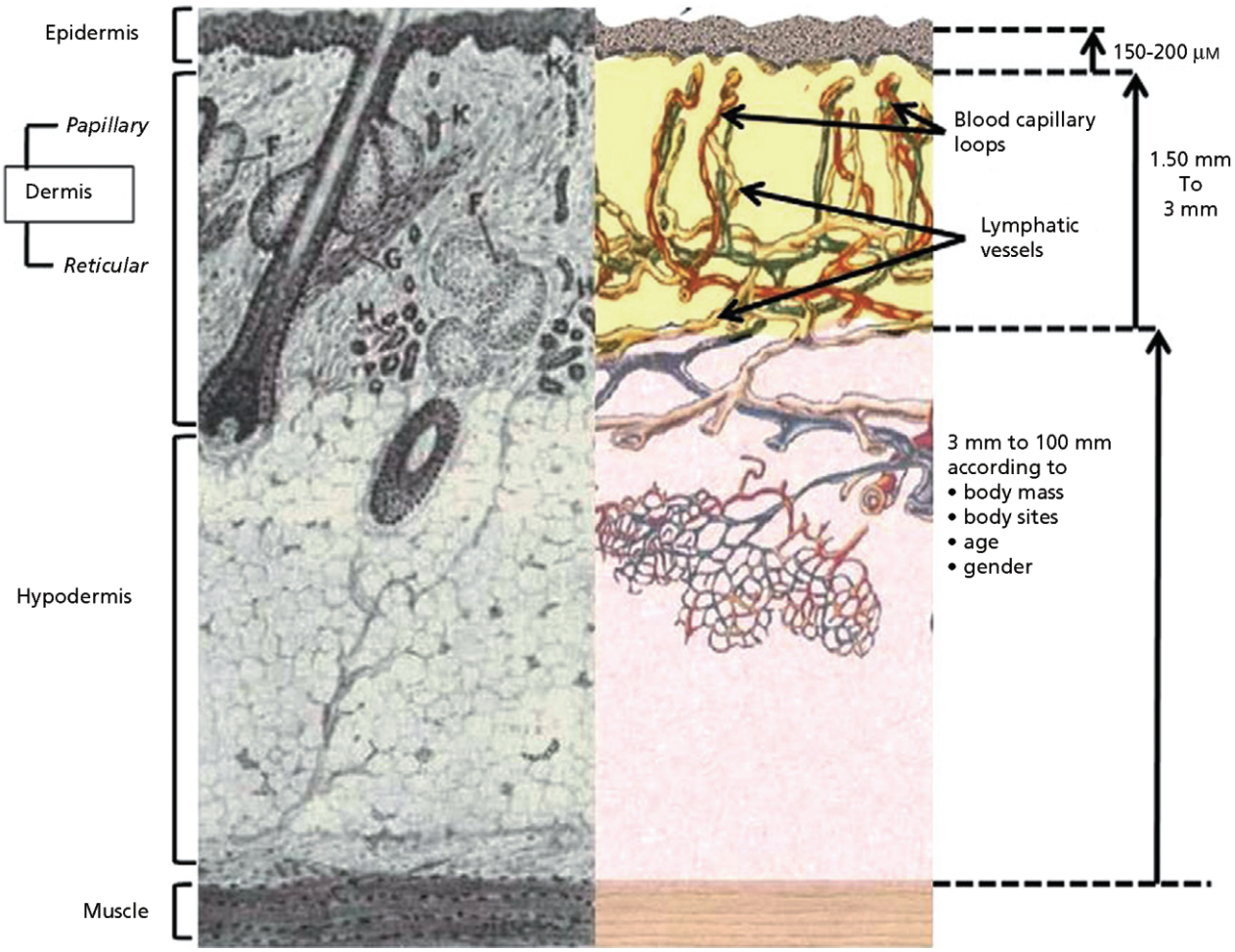

Figure 1 Skin structure showing three major regions: epidermis, dermis and hypodermis (with the thickness range). Reproduced with permission from Elsevier.[9]

Table 1 Comparative efficacy of different approaches to drug delivery across the skin (+ – low efficacy, ++ – Moderate efficacy – High efficacy). Reprinted with permission from Nature[7]

Delivery method	Increased transport	Sustained delivery	No pain/ irritation	Low capacity/ complexity
Hypodermic needle	+++	++	+	+++
Chemical enhancer	+	+++	++	+++
Iontophoresis	++	+++	+++	+
Electroporation	++	+++	++	+
Ultrasound	++	+++	+++	+
Microneedles	++	+++	+++	+
Jet injection	+++	+	+	+
Thermal poration	++	+++	+++	+

+, Low efficacy; ++, moderate efficacy;+++, high efficacy. Reprinted with permission from Nature.[7]

The aforementioned approaches are associated with certain bottlenecks: chemical approaches are often associated with higher skin irritation and are applicable only to small molecules while physical methods typically require a device with a power supply which adds to the cost and complexity.[15,16]

Research is focused in the development of transdermal drug delivery systems for existing molecules to improve the pharmacokinetic and pharmacodynamic profiles. Each of such developed TDDS suffers with one or other type of demerits. Table 1 shows comparative efficacy of such delivery systems in terms of increase in drug transport, sustained drug release, pain sensation and complexity.

The search for an inexpensive and reliable mode of administering the drug safely to the epidermal layer without damaging the nerve cells, and minimising chances of microbial penetration, led to the development of microneedles.[17]

Microneedles

Microneedles can be defined as solid (Figure 2a–d) or hollow (Figure 2e) cannula with an approximate length of 50–900 μm and an external diameter of not more than 300 μm.[18] Microneedles can be fabricated within a patch for transdermal drug delivery. Patches containing microneedles have been evaluated in the delivery of drugs, biopharmaceuticals, vaccines, etc. A quick response can be observed due to disruption of stratum corneum by microneedles.[19] Although microneedles were first proposed in 1976, the technology needed to make needles of micron dimensions was not widely available until 2000s.[20] Using the low-cost mass-production tools of the microelectronics industry, needles have been fabricated out of silicon, metals and other materials.[21] Microneedles have been designed to penetrate through the epidermis up to a depth of 70–200 μm. Microneedles are thin and short and do not penetrate the dermis layer with its nerves; hence painless application is possible.[3,22] Microneedles are more capable of enhancing the transport of drug across the skin as compared with other transdermal delivery methods.

Advantages of microneedles

The advantages of microneedles are: (1) large molecules can be administered, (2) painless administration of the active pharmaceutical ingredient, (3) first-pass metabolism is avoided, (4) faster healing at injection site than with a hypodermic needle,[23–25] (5) no fear of needle, (6) ease of administration, (7) decreased microbial penetration as compared with a hypodermic needle, the microneedle punctures only the epidermis, (8) specific skin area can be targeted for desired drug delivery, (9) enhanced drug efficacy may result in dose reduction, (10) good tolerability without long-term oedema or erythema, (11) rapid drug delivery can be achieved by coupling the microneedles with an electrically controlled micropump, and (12) the rate of drug delivery can be controlled more effectively by this system as compared with drug delivery via the stratum corneum.

Disadvantages of microneedles

The disadvantages of microneedles are: (1) dosage accuracy may be less than with hypodermic needles, (2) careful use of the device may be needed to avoid particles 'bouncing off' the skin surface; if the device is not held vertically, the dose may escape or can penetrate the skin to differing degrees, (3) the thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too, (4) the external environment, like hydration of the skin, could affect delivery, (5) repetitive injection may collapse the veins, (6) the tip of the microneedle may break off and remain within the skin on removal of the patch, (7) a small amount of drug (less than 1 mg) can be given by bolus, and (8) compressed dermal tissue can block hollow microneedles.

Materials Used to Constitute Microneedles

Microneedles can be broadly divided into three categories: solid, degradable/dissolvable and hollow. Selection of the

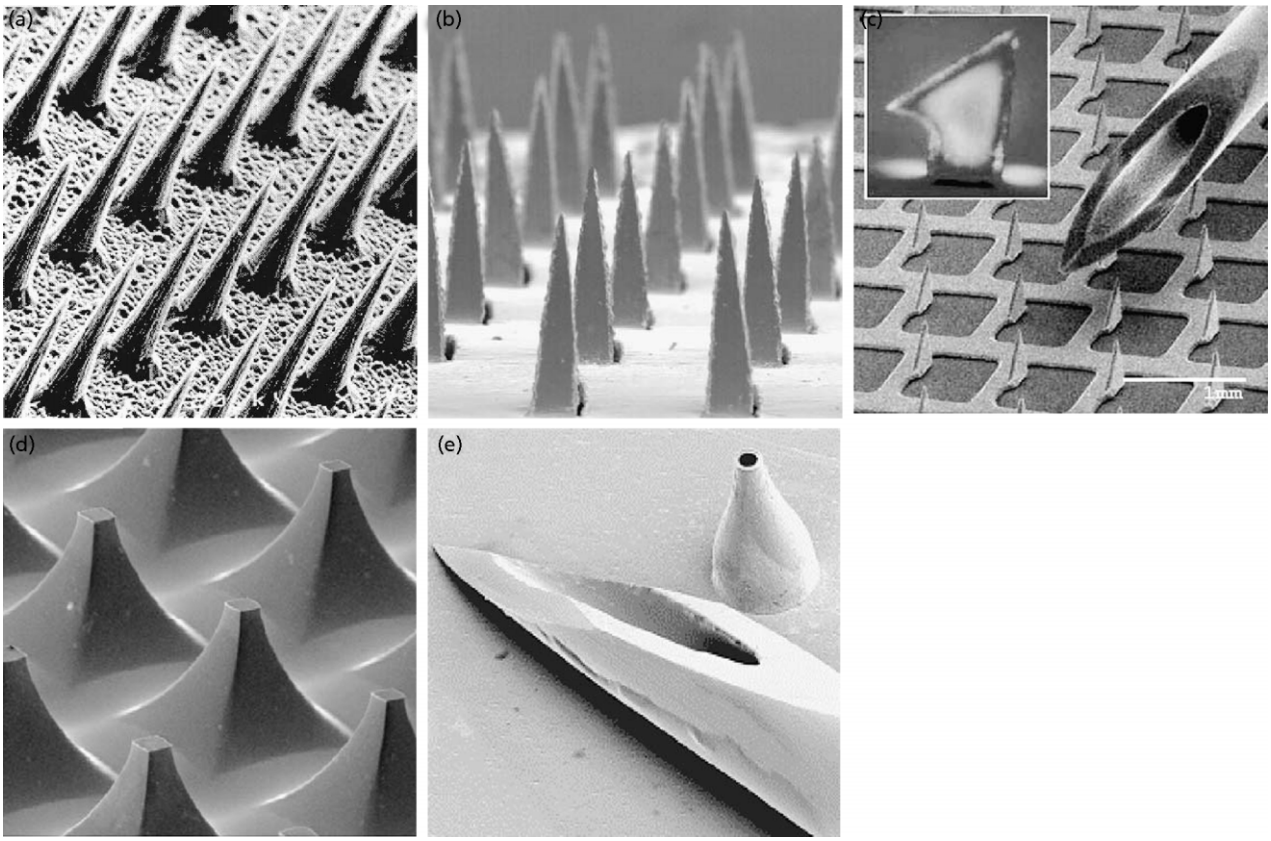

Figure 2 Types of microneedles used for transdermal drug delivery. (a) Solid microneedles ionically etched from silicon wafer, (b) solid microneedles laser cut from stainless steel, (c) solid microneedles acid etched from titanium sheet, (d) solid microneedles chemically etched from silicon wafers and (e) hollow microneedles formed by electrodeposition of metal on to a polymer. Reproduced with permission from Elsevier.[8]

Table 2 List of materials used for preparation of microneedles

	Synthetic polymers		
Metals	Biodegradable	Non-biodegradable	Natural polymers
Silicon[26]	Polylactic acid (PLA)[27]	Polyvinyl acetate (PVA)[18]	Thermoplastic starch[28]
Stainless steel[29]	Polyglycolic acid (PGA)[27]	Alginic acid[18]	Carboxymethylcellulose[30]
Titanium[19]	Polylactide-co-glycolic acid (PLGA)[27]	Gantrez AN-139, a copolymer of methylvinylether and maleic anhydride (PMVE/MA)[18]	Amylopectin[30]
Mesoporous silicon[31]	Polycarbonate[16]	Carbopol 971 P-NF[18]	Dextran, galactose, chondroitin sulfate[32]
	Polyvinylpyrrolidone (PVP)[33]	Polyetherimide[34]	Maltose[35]

material for constitution of the microneedle should be based on criteria such as gentle fabrication without damage to sensitive biomolecules, sufficient mechanical strength for insertion into skin and controlled or rapid drug release as per the requirement. Microneedles have been produced using glass, silicon and metals (Table 2). The use of polymers to constitute microneedles has also been explored; solid microneedles have been produced using plastic or biodegradable polymers.[18] Metallic microneedles are expensive, non-biodegradable and brittle. Polymer microneedles overcome the limitations of silicon and metal microneedles and may provide advantages like low cost, mechanical strength and safety in case of accidental breakage of needle in the skin.[27]

Poly [di(carboxylatophenoxy) phosphagene] (PCPP), having phosphorus-nitrogen backbone and organic side chain, offers potent immunoadjuvant activity. Andrianov *et al.* reported that the thermal stability of protein and its ability to withstand extreme manufacturing conditions were higher when the protein was in a solution of PCPP coated on solid microneedles as compared to aqueous solution.[36] Modulated protein release was observed from microneedles because of the ion-complexing property of PCPP along with salts of multivalent ions, such as calcium chloride and spermine.

Rapid-dissolving sugars and polysaccharides have also been explored to prepare dissolvable microneedles.[37] Carbohydrates have addressed many disadvantages of metal microneedles and provide rapid drug delivery. Microneedles of dextrin can be prepared without any special fabrication equipment.[30] However, processing problems such as caramelization and difficulties in handling of molten sugar can be observed. Moreover, sugar microneedles are hygroscopic. The material should have a high Young's modulus so that sufficient mechanical strength can be provided.[38] Microneedles made up of Gantrez AN-139, a mucoadhesive polymer, were able to withstand higher compression than microneedles formed using poly vinyl alcohol (PVA), alginic acid and Carbopol 971.[18]

Drug Delivery through Microneedles

In an earlier phase of research on microneedles, an array of solid microneedles was pierced through the skin to circumvent the barrier effect of the stratum corneum. The needles were made up of silicon wafers and a medicated patch was applied to the treated skin surface thereafter. This approach is known as 'poke and patch' (Figure 3a). This technique was also tried to extract the interstitial fluid to measure the glucose level by non-invasive method.[40]

Subsequent research in microneedle technology focused on development of solid microneedles coated with drug solution using a dip-coating method. The skin was pierced before the release of the drug (Figure 3b). A limited amount of drug could be coated over the microneedles (only about 1 mg) and extensive optimization was required for uniform coating in this 'coat and poke' approach.

Further research resulted in the development of a 'poke and release' approach (Figure 3c). Microneedles were made from polymers and polysaccharides that either slowly dissolved or degraded after administration. The advantage of the 'poke and release' approach was that the drug release could be modulated as per the requirement using a variety of available polymers and polysaccharides. The administration of a large amount of drug was still not feasible with dissolvable or degradable microneedles like other physical approaches, which led to development of hollow microneedles. This approach was known as 'poke and flow' (Figure 3d), where after piercing the skin, drug was allowed to flow through hollow microneedles from the reservoir in the patch.[13]

Wang *et al.* developed hollow microneedle arrays with a drug reservoir.[41] Upon the application of external pressure on the reservoir, the microneedle system penetrates into the skin, followed by the release of the drug solution into the skin. Thus a large amount of drug can be administered by fabrication of hollow microneedles. Generally the pore is kept alongside walls rather than at the centre for easy insertion of the microneedle as well as to prevent blockage of channel. The design of the microneedle is critical for achieving successful drug delivery such that the microneedle neither breaks nor causes pain or irritation. All of the above-mentioned approaches can be employed to deliver drugs either systemically or at a restricted site (local action).

Fabrication of Microneedles

Microneedles can be fabricated employing microelectromechanical systems (MEMS). The basic process can be divided in to three parts: deposition, patterning and etching. Deposition refers to the formation of thin films with a thickness anywhere between a few nanometers to about 100 micrometers. Patterning is the transfer of a pattern onto the film. Lithography is used to transfer a pattern into a photosensitive material by selective exposure to a radiation source such as light. This process can involve photolithography, electron beam lithography, ion beam lithography or X-ray lithography. Diamond patterning is also an option for lithography. Etching is a process of using strong acid or mordant to cut into the unprotected parts of a material's surface to create a design in it and can be divided into two categories: wet etching or dry etching. The selection of any of the above-mentioned methods largely depends on the material of construction and the type of microneedle.

Park *et al.* fabricated biodegradable polymeric microneedles using a micro-molding technique.[27] In this process, moulds or microarray of SU-8 epoxy photoresist or polyurethane were initially made in different shapes, like bevelled-tip, chisel-tip and tapered-cone, using different techniques. Pellets of biodegradable polymer were put on the master structures of different shapes and placed under vacuum at high temperature. Polymeric melt was pulled into the mould by application of vacuum, followed by freezing for separation of the master structure from the mould.

Aoyagi *et al.* studied microfabrication of biodegradable polymers under normal atmospheric conditions.[42] Polylactic acid microneedles were blocked because of formation of hydrolysed intermediate products of polylactic acid. This intermediate product was not formed under vacuum laser microfabrication of needles. Hence application of vacuum during the laser microfabrication process was suggested.

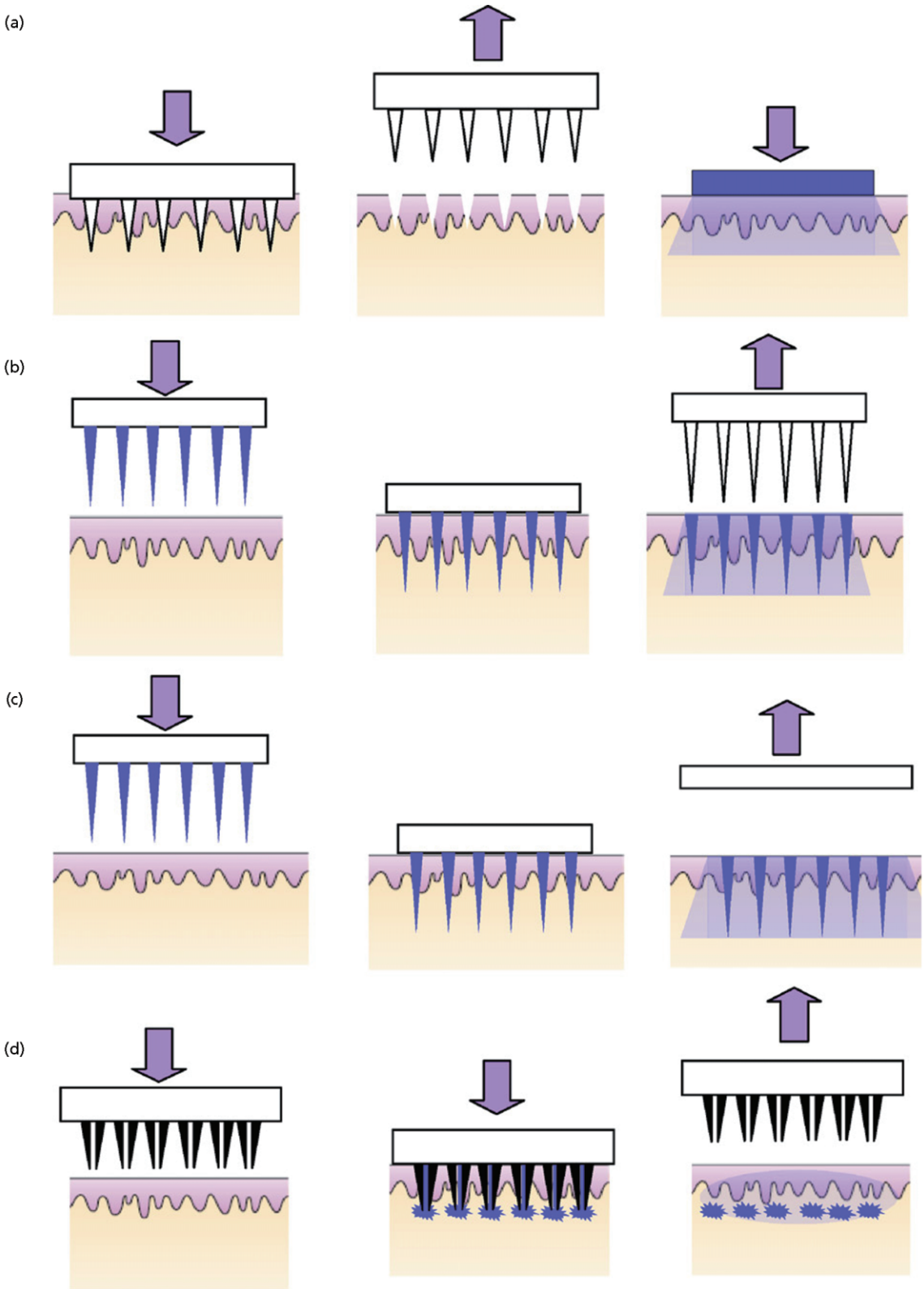

Figure 3 Approaches for drug delivery by different designs of microneedles: (a) 'poke and patch' using solid microneedles, (b) 'coat and poke' using coated solid microneedles, (c) 'poke and release' using polymeric microneedles, (d) 'poke and flow' using hollow microneedles. Reproduced with permission from Elsevier.[39]

Donnelly *et al.* used laser micromachining technology for preparation of microneedle moulds of silicon.[18] An aqueous polymeric blend was filled in the moulds to fabricate microneedles. Polymeric microneedles can also be fabricated using casting,[36] injection moulding and hot embossing.[18] Chen *et al.* presented a robust Gas-jet coating method to achieve uniform coating of a range of immunotherapeutics, like antigens, DNA and proteins, on microneedles.[43]

Evaluation of Microneedles

Characterization of microneedle geometry

Scanning electron microscopy can be used to determine the base radius, tip radius and wall thickness of the microneedles. Interfacial area (i.e. the effective area of contact between the needle and the skin) can be calculated in two ways: (1) the annular surface area, A_a; at the needle tip

$$A_a = \pi(r_t t - t^2/4) \quad (1)$$

and (2) the full cross-sectional area, A_f; at the needle tip

$$A_f = \pi r_t^2 \quad (2)$$

Needle wall angle, α, is calculated as

$$\alpha = \tan^{-1}(r_b - r_t/h) \quad (3)$$

where r_t is the outer radius of the microneedle tip, r_b is the outer radius at the needle base, t is the wall thickness and h is the height.[44]

Functional capacity test

Wang *et al.* evaluated the functional capacity of microfluidic lumens using a custom fluidic test setup.[41] The test setup consisted of a syringe pump system with a dye-filled syringe, a polymer tube and microneedle array. This syringe pump system was used to examine the formation of the microneedle lumens by allowing dye to flow from the syringe to the microneedle orifice. Microscopic inspection of the microneedle tips and the base plate during the microfluidic characterization can be used to detect cracks in the base plate and passage continuity.

Measurement of insertion force into human skin

A displacement–force test station was used by Shawgo *et al.* to measure the force applied to a needle, needle position and skin resistance during the sequence of the needle's translation, deflection of tissue around the needle and insertion into the skin of human subjects.[22] A drop in electrical resistance of the skin was used to identify needle penetration since visual observation of needle insertion was extremely difficult. The electrical resistance of skin's outermost layer, the stratum corneum, is much greater than deeper tissues, therefore the resistance of the skin drops dramatically as soon as a needle penetrates.

Margin of safety

Forvi *et al.* defined the margin of safety as the ratio between the force required for piercing the stratum corneum and the force at which microneedles broke.[45] They hypothesized that if the ratio is <1 then microneedle array can be used in biomedical application. They checked margin of safety for silicon microneedles using computerized apparatus. For compressive failure force measurement, Enduratec station was used in which microneedles were placed between punch and load cell. An appropriate margin of safety was found for sample silicon microneedle arrays.

Measurement of fracture force

The force required for mechanical fracture of a microneedle was tested by Davis *et al.*, employing an axial load test station that drove the microneedle against a flat block of aluminium at a rate of 0.01 mm/s until a preset displacement of 500 μm was reached.[44] Microneedles were attached to the testing surface using adhesive tape around the base of the needle. Microneedle fracture was observed through an attached microscope to evaluate the mode of failure. The force and displacement data were used to quantitatively determine the fracture force.

Penetration/diffusion test

In-vitro and ex-vivo test

In-vitro/ex-vivo tests are performed on isolated animal/human dermatomed skin to study penetration or diffusion of drug from a dosage form to its site of application. These tests can also be used to compare the depth of penetration of the molecule. Wu *et al.* used confocal laser scanning microscopy (CLSM) to demonstrate the depth of penetration of Rhodamine B in human dermatomed skin using microneedles of 150 μm length.[46] They reported the concentration of the dye to be very weak below 80 μm depth. They also evaluated the penetration of model drug using Franz diffusion cell across the microneedle-treated and untreated skin and reported enhancement in penetration by 10^4 to 10^5 times with use of microneedles. Similar observations were also reported by other researchers.[12,47]

On the other hand You *et al.* reported that penetration of L-ascorbic acid was not significantly increased through microneedle-treated skin as compared with untreated skin.[34] They punctured the skin more than once to demonstrate the effect of application frequency of microneedles.

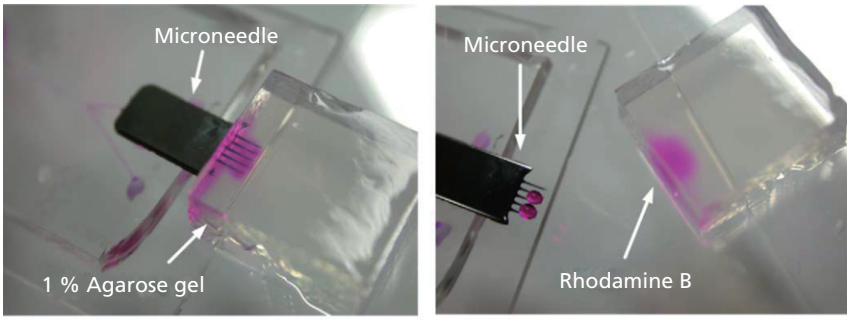

Figure 4 Injection of Rhodamine B dye in to 1% agarose gel using microneedles. Reproduced with permission from Elsevier.[48]

They concluded that permeation of L-ascorbic acid was increased by 10.54-fold only after insertion of microneedles in four directions nine times.

Paik *et al*. investigated penetration of microneedles both *in vitro* and *ex vivo* by injecting Rhodamine B dye.[48] For in-vitro testing 1% agarose gel was used and for ex-vivo testing, chicken breast flesh, laboratory mouse and an anaesthetized rabbit were used. The Rhodamine B easily penetrated across the 1% agarose gel and chicken breast flesh; the penetration in 1% agarose gel can clearly be viewed in Figure 4.

In-vivo test

For a transdermal drug delivery system, it is practically impossible to predict the skin permeability of formulations using in-vitro experiments alone. Significantly different results might be observed while performing in-vivo study. This is reflected by a study conducted by Teo *et al*.[12] They reported that the transport of insulin through rat skin was found to increase by 10–20 times in an in-vitro study, while during their in-vivo study, microneedles failed to deliver drug systemically. Thus, along with in-vitro/ex-vivo testing, in-vivo tests should always be performed. If correlation is established between ex-vivo and in-vivo models, the drug development process could be made more economic and shorter.

Bal *et al*. reported penetration of fluorescent dye through human skin after microneedle application with the help of confocal laser scanning microscopy (CLSM).[49] Further, Enfield *et al*. used optical coherence tomography (OCT) for imaging of tissue structure.[50] Both these methods provide tissue imaging without the need for tissue pre-treatment or removal.

Burton *et al*. studied penetration of methylene blue dye at the microneedle treated application site in domestic swine after removal of array.[25] A hilltop chamber was attached to the application site. After a 10-min staining period, the chamber was removed followed by washing with distilled water and observed for penetration.

Analysis of plasma concentrations was also adopted by a few scientists to compare the microneedle technique with other TDDS. Shivamani *et al*. measured the maximum blood fluxes and time taken to reach maximum flux in healthy human volunteers for comparison of pointed microneedle, hollow microneedle and topical application.[51] They found that the time required to reach maximum blood flux was significantly decreased after administration of methyl nicotinate by pointed and hollow microneedles as compared with topical administration. Similarly So *et al*. also reported that a higher plasma concentration of ketoprofen was achieved in rats with microneedles in comparison with a topical gel formulation alone.[52] They found increment in both C_{max} and AUC of ketoprofen after application with microneedles.

Martanto *et al*. studied in-vivo delivery of insulin using microneedles in rats and examined the resultant blood glucose level.[5] This was decreased by 80% with the use of microneedles. Hafeli *et al*. administered radiolabelled albumin intradermally in mice using a microneedle-based miniature syringe.[53] They found a significant amount of radioactivity in mouse skin even after wiping off the site of application with wet tissue, which was indicative of successful delivery of protein (albumin).

Transepidermal water loss (TEWL)

DermaLab TEWL probe and Tewameter TM 210 probe were used by researchers during their investigation on microneedles.[24,54] TEWL can be determined by employing a diffusion cell and intact animal skin. Probes were held in a clamp to prevent any interference above the application site and readings were taken over three minutes at various time intervals before and after application of microneedle array. The researchers concluded that there was an increase in skin permeability after the use of microneedle.

Biological safety test

Wu *et al.* determined extractable chemicals from microneedles according to ISO 10993-12:2002 standard: 'Sample Preparation and Reference Materials'.[46] Extraction of chemicals from microneedles was done by immersing microneedles in physiological saline at 37°C for 72 h. The extract was then directly applied on shaved intact human skin for checking dermal irritation. Negative result of the test revealed the biological safety of the microneedles.

Applications of Microneedles

Skin is suitable for gene and oligonucleotide delivery because it is well characterized at the cellular as well as the molecular level. The microneedle delivery system can be used for treatment of various genetic diseases related to skin, various types of malignancies and infectious diseases, and for immunization. A dense array of very sharp pyramidal microneedles were used to deliver gene into cells.[55] Microneedle delivery of gene is better than a microinjection technique because many cells can be treated at once. Thus microneedles can be used to deliver bioactive agents systematically as well as locally. Research could focus on antiviral, antidiabetic, genetic, oncological, anti-osteoporosis, vaccine, dermatological, etc., areas for bioavailability improvement by developing microneedle-based transdermal drug delivery systems.

Immunobiologicals

Conventionally immunobiologicals are administered through a needle via the subcutaneous, intramuscular or intradermal route for prevention of infectious diseases. However the conventional vaccination procedure suffers from drawbacks like needle phobia and the pain associated with insertion of needle into the skin. Research has focused on development of needle-free vaccination like liquid jet injectors, powder injectors, thermal ablation and microneedles. Microneedles have an edge over the other methods due to lack of pain, self administration and quick delivery of vaccine.[56,57]

Combination vaccination is one of the ways to reduce the number of injections to be administered; 'DPT' is a well-known example, used to prevent infection of diphtheria, pertussis and tetanus. However to develop such a formulation is a challenge as the physical, chemical and biological interactions between the vaccine components may have a detrimental effect on vaccine safety or efficacy. Physical and chemical interaction as well as adverse effect on the biological activity of each component was not observed by researchers.[62]

Conventional liquid vaccines require cold conditions during transportation and tend to have a short shelf life. The stability of vaccines at high temperature as well as maintenance of antigenicity was reported by Hirschberg *et al.* in coated microneedles.[61]

Microneedles form transient conduits and enhance passage of the vaccine molecule across the skin barrier. Using microneedles, vaccines are able to cross the stratum corneum and stimulate a clinical response. An increase in haemagglutination inhibition (HI) and IgG subtype titres was observed when influenza vaccine and cholera toxoid were co-administered employing microneedles.[76] The clinical response was much higher than that obtained after intramuscular injection of plain vaccine.

High purity subunit vaccines are safer than live attenuated or whole inactivated vaccines. The use of pure vaccines results in decreased immunogenicity.[77] Several studies have been carried out to achieve effective immunization of vaccines via microneedle delivery along with adjuvant (Table 3).

Controlled and complete penetration is an important parameter to be considered at the time of development of dissolving microneedles. Li *et al.* developed microneedles for rapid delivery of monoclonal antibodies.[35] They covered the skin with cardboard and observed that microneedles dissolved in a minute and micro channels remained open for 24 h. BioserenTach developed dissolving microneedles that are under clinical trial. Dissolving microneedles are capable of delivering a small dose, less than several milligrams, of peptides, proteins, vaccines, hormones and organic compounds.[78]

Sullivan *et al.* compared the immune response to influenza vaccination delivered via polymeric dissolvable microneedles, coated solid microneedles and intramuscular injection of influenza vaccine at the same dose.[33] These investigators found that lung virus clearance was 1000 times more efficient when the vaccine was delivered via polymeric microneedles than via intramuscular injection. During a comparative study between metallic and polymeric microneedles, the authors found no significant difference in humoral immune response, while increased cellular response was observed, when vaccine was given via polymeric microneedles. The researchers finally concluded that polymeric microneedles were a better means of vaccination delivery than either intramuscular injection or coated metallic microneedles.

Table 3 shows a few examples of immunobiologicals administered via microneedles.

Bioactive macromolecules (biopharmaceuticals)

Insulin, heparin, and growth hormones are not administered orally due to proteolytic degradation and hindered absorption. The majority of commercially available biopharmaceuticals are administered via the parenteral route and hence a suitable non-invasive route is desirable.

Verbaan *et al.* administered macromolecules with varying molecular weight across human dermatomed skin using microneedles.[79] They revealed that microneedle arrays enhanced the transport across dermatomed human skin for

Table 3 Applications of microneedles

	Active constituent/product	Delivery approach	Description
Immunobiologicals	Influenza vaccine[58–60]	Coat and poke	Adjuvant increases cellular immunogenicity, safety and self life.
	Hepatitis B vaccine[61]	Poke and release	Antigenicity was maintained at high temperature.
	Human IgG[35]	Poke and release	Transportation of macromolecules through skin was enhanced.
	Anthrax, botulism, plague and staphylococcal toxins[62]	Poke and flow	To avoid physical and chemical incompatibility of such multiple/combination vaccine.
	Tetanus toxoid[28]	Poke and release	Due to enhanced immunogenicity dose can be reduced by four times.
	Ovalbumin[18,63]	Coat and poke	Antigenicity was increased.
	Flavivirus vaccine[64]	Poke and flow	Vaccination was safer and well tolerated.
Biopharmaceuticals	L-Carnitine[65]	Poke and patch	Bioavailability of L-carnitine was increased and controlled delivery could be achieved.
	Recombinant human growth hormone and desmopressin[66]	Poke and release	Absorption, bioavailability and stability were increased.
	Albumin[53]	Poke and flow	MEMS syringe were used to successfully delivery of macromolecules.
	Low molecular weight heparin, calcein, erythropoietin[32,67,68]	Poke and release	Bioavailability and stability were increased.
	Insulin[30]	Poke and release	Increased in bioavailability and rapid onset of action.
	Calcein and bovine serum albumin[69]	Poke and release	Controlled release in skin for hours to month.
	Insulin[5]	Poke and patch	Insulin was successfully delivered in animal with 80% reduction in blood glucose.
	Desmopressin[70]	Coat and poke	Efficient, controlled and less variable delivery of desmopressin was achieved.
Drugs	L-Ascorbic acid[34]	Poke and release	Faster hair growth due to 10.54 fold increased in penetration.
	Galanthamine[71]	Poke and patch	Enhanced drug delivery.
	Aspirin[72]	Poke and patch	Polymeric microneedle rollers were fabricated.
	Docetaxel[73]	Poke and patch	Administration in form of liposomes increases the bioavailability and reduces lag time.
	Pilocarpine[74]	Coat and poke	Rapid and extensive pupil constriction with higher bioavailability.
	Riboflavin[75]	Coat and poke	Studied various parameters of coating of riboflavin on microneedles.

both low and high molecular weight compounds. Their study also revealed that the length of the microneedles and the length up to which the microneedles penetrated in the skin had no effect on the transport of either low or high molecular weight compounds.

Parathyroid hormone is used in the treatment of advanced osteoporosis in men and post-menopausal women. Forteo (a once-daily subcutaneous injection of human parathyroid hormone) is the only US-approved anabolic therapy for the treatment of osteoporosis. The use of Forteo is limited due to the requirement of product refrigeration. Zosano Pharma has developed a parathyroid hormone coated microneedle patch system that is now under phase-3 clinical trial. These patches show an ideal plasma profile, indicative of efficient parathyroid hormone therapy in osteoporosis using microneedles.[80]

Dissolving microneedles can be developed for rapid release as well as controlled release of molecules. Microneedles prepared with water-soluble polysaccharides dissolve within a minute in the body. Ito *et al*. prepared self-dissolving microneedles for rapid delivery of low-molecular-weight heparin using dextrose, dextran and chondroitin sulfate.[32] Lee *et al*. prepared matrix dissolving microneedles by encapsulation using amylopectin/carboxy methyl cellulose polymers.[30] They found that the microneedles dissolved in a minute followed by bolus delivery of biotherapeutics and proteins due to micro encapsulation. Likewise, formation of microneedles of calcein, insulin, erythropoietin and L-carnitine showed good bioavailability and stability (Table 3).[32,65,67,68]

Drugs

Very few drug molecules possess the necessary physico-chemical properties to cross the skin barrier and even if the drug can cross the barrier, drug delivery rate via the transdermal route is very low. Physico-chemical properties like hydrophilic-lipophilic balance, solubility, molecular weight, etc., govern the transport of a drug through the skin and also the rate of transportation. These challenges can be overcome by use of microneedles. Highly hydrophilic drug formulations like PEGylated naltrexone or hydrophobic formulations of drugs like ketoprofen, show a many-fold increase in area under the curve (AUC) and maximum drug concentration

(C_{max}) as compared with conventional cream or gel formulations. The need for penetration enhancers, which may induce irritation, can be eliminated by the use of microneedles.[12,52]

In photodynamic therapy for cancer, a combination of photosensitive drug and light is used to destroy the selected cells via generation of highly cytotoxic singlet oxygen. Topical administration of such high-molecular-weight photosensitizer drugs results in poor bioavailability. Their accumulation in normal cells precludes their intravenous administration. Donnelly *et al.* worked on microneedle-mediated intradermal delivery of 5-aminolevulinic acid and transdermal delivery of meso-tetra (*N*-methyl-4-pyridyl) porphine tetra tosylate using silicon microneedles.[81,82]

Ashraf *et al.* designed a microfluidic drug delivery device with an electronic module, sensor for blood pressure and flow, and drug delivery device as its main components.[26] The system automatically injected the desired drug dose through microneedles at a controlled rate on sensing an increase in blood pressure.

The bioavailability of drugs can be increased, with reduced side effects and complications associated with intraocular injection and systemic administration, by the use of coated microneedles. Chronic ocular diseases, like glaucoma, age-related macular degeneration, diabetic retinopathy, retinitis pigmentosa, etc., require long-term medication to stop the progression of the disease. Conventional treatment of such diseases by both non-invasive and invasive drug delivery systems has many drawbacks. Drug delivery via a novel refillable MEMS demonstrates advantages such as manually actuated, accurate and targeted dosing. Lo *et al.* prepared a refillable MEMS using polydimethylsiloxane, which consisted of a drug reservoir, flexible cannula, check valve and suture tables.[83]

Microfabrication technology can be used in the delivery of drugs for the treatment of restenosis and late thrombosis. Various medical devices, such as stents, embolic grafts, stent grafts, catheters, etc., of micron size can be used as minimally invasive surgical treatments. Drugs like riboflavin, galanthamine, aspirin, etc. have also been evaluated for administration through microneedles (Table 3).

Phlebotomy

Phlebotomy is the withdrawal of blood for diagnostic purpose. Analysis of blood samples for specific blood constituents helps in the diagnosis of a disease. Some diseases like diabetes require frequent monitoring of blood for estimation of glucose concentration or disease severity. Painless hollow microneedle-based micro sampling can be used instead of traditional methods for glucose estimation.[84]

Microneedles can be used to obtain precise body fluids as well as blood samples from the capillaries, which are situated at a distance of 500–2000 μm in the dermis layer beneath the skin. This method has many advantages like reduction in blood sample requirements (up to 200 nanolitres) while making the procedure painless. The microneedle must penetrate to sufficient depth, hence care should be taken in the design, material selection and dimensions of the microneedle, to ensure penetration at low pressure without breakage. During a study on the geometrical effects in mechanical characteristics of microneedles, Aggarwal and Johnston reported the following order for withstanding strain in various designs of microneedles: circular > rectangular > square. However, fabrication of circular microneedles is difficult and a rectangular shape was preferred for the preparation of microneedles for phlebotomy.[85] Oka *et al.* prepared jagged-shaped microneedles of silicon similar to the mosquito needle for blood testing.[86] The jagged shape provided less contact area between the microneedle and the dermis of the skin during insertion, which resulted in easy insertion. Mukerjee *et al.* prepared two-dimensional microneedle arrays for biological fluid extraction and in-situ analysis.[87] They resolved problems in microneedles, like bending and clogging, by a combination of design and fabrication processing to achieve optimal tip shape, opening size, needle height and needle area density.

Blood samples are generally collected from capillaries by pricking the skin or from veins using evacuated collection tube, depending on the volume of blood required for analysis. These methods are associated with disadvantages such as excessive bleeding, infection, scarring, fainting or feeling light-headed. People may hesitate to give blood due to fear of needles and the moderate pain associated with the procedure. Hence painless blood sampling using microneedles can be a very good alternative to hypodermic needles.[88,89]

It can be concluded that the design and dimensions of microneedles used for blood sampling are the most important parameters to be precisely selected for easy penetration to a particular depth in the skin without bending, damage to nerves situated deep inside dermis, and tissue trauma. The device can be used anywhere on the skin for sampling, therefore there is the need to place it on a large visible vein or on the finger tip. This approach can be used for monitoring of therapeutic drug levels too.[90,91]

Diagnosis

Hollow microneedles can be used to withdraw fluid from tissue or blood which can be subsequently analysed to check the status of diseases like cancer, diabetes and many more. Hollow microneedles, along with quantum dots, help in medical diagnosis. Quantum dots are nanoscale crystals with a light-emitting property. The multiphoton microscopy method could rapidly diagnose cancers or other medical problems.[92]

Mukerjee *et al*. evaluated the influence of geometry and design of microneedles on the piercing ability (through the skin) and capillary movement of interstitial fluid.[87] They investigated three designs of microneedle tip shape on the basis of shifting the borehole away from the centre of the column: a 'volcano-like' design (centre), a 'micro-hypodermic' design (25 μm from centre), and 'snake-fang' design (50 μm from centre). The snake-fang design proved to be superior among the three designs for extraction of interstitial fluid from the skin.

Cosmetic products

Generally, only minor fractions (maximum 0.3%) of the active substance present in a cream, gel or lotion can penetrate deeply into the skin. This means that the majority of an active ingredient, about 99.7%, is wasted. Derma rollers and stamps are available on the market for treatment of skin problems as well as to improve looks. Clinical Resolution Laboratory markets MTS Dermaroller, a cosmetic aid possessing needles that penetrate the skin up to a depth of 0.2–0.3 mm. The product contains 200 very fine stainless-steel needles to pierce the epidermis, creating a micro-channel effect. Clinical studies from various countries have proven that therapeutic serum absorption is increased by as much as 1000 times when applied using the MTS Dermaroller.[93]

The majority of cosmetic products lending themselves to microneedle technology are for non-surgical and non-ablative treatment of skin conditions such as ageing (wrinkles, lax skin), scarring (acne, surgical), photodamage, hyperpigmentation (age/brown spots) and hair loss (alopecia). The process facilitates and stimulates skin's natural repair without causing permanent epidermal damage.

Advances in Drug Delivery by Microneedles

Application of physical methods such as iontophoresis, sonophoresis and electroporation have been explored in conjunction with microneedles to provide enhanced drug delivery and better control of delivery of drug across the skin.

Combination of iontophoresis and microneedles

In iontophoresis a small electrical current is used for transportation of drug across the stratum corneum of the skin. The main advantage of using iontophoresis along with microneedles is to control delivery of drug by controlling the current. The current may be turned on and off by the patient, and can deliver small drug molecules and biomolecules having a molecular weight up to a few thousand Daltons.[94] Chen *et al*. studied the administration of insulin unilamellar nanovesicles through microneedles along with iontophoresis.[29] The positive zeta-potential and small diameter of the nanovesicles enhanced the penetration of insulin with the help of iontophoresis and microneedles.

Lin *et al*. investigated the delivery of antisense oligonucleotide (ODN) by using Macroflux microprojection patch technology.[95] They used hairless guinea-pigs for comparative transdermal delivery of ODN via passive diffusion, Macroflux patch and Integrated Macroflux patch with iontophoresis. They found an increase in the concentration of ODN from the stratum corneum to the dermis in the following order: Integrated Macroflux patch with iontophoresis > Macroflux patch > passive diffusion. Macroflux patch technology was found capable of delivering a therapeutically relevant amount of ODN into and through the skin.

Combination of sonophoresis and microneedles

Sonophoresis uses ultrasound (frequency, 20 kHz to 10 MHz; intensity, up to 3 W/cm^2) for enhancing transportation of drugs by forming cavitation and change in the lipid arrangement of the stratum corneum. Drug permeation can be controlled by controlling the frequency of the ultrasound. As the sound frequency increases from 20 kHz to ≈1 MHz, skin perturbation increases 1000 fold.[96] Chen *et al*. found that an increase in the rate and extent of delivery of calcein (623 Da) and bovine serum albumin (66.430 kDa) could be achieved by using a combination of sonophoresis and microneedles.[97]

Combination of electroporation and microneedles

Electroporation causes localized perturbation by forming aqueous pathways in the lipid bilayer of skin using high-voltage short-duration current. A *trans*-membrane potential up to 1 kV for 10 μs to 500 ms was used for in-vitro electroporation of stratum corneum.[96] Longer pulse width and higher voltage was required to increase skin perturbation. This technique was also used for permeation enhancement of larger molecules having molecular weight up to several kiloDaltons.[98] Furthermore, each microneedle behaved as a microelectrode for electroporation, which eradicated the need for electrodes.

Electroporation can be used in concert with chemotherapy (electrochemotherapy) for effective tumour treatment. Wilke *et al*. designed a silicon microneedle electrode array with integrated temperature and fluidic system for drug delivery specifically to tumour cells.[99]

Combination of vibratory actuation and microneedles

Penetration of a microneedle into the skin requires precise control of insertion force, which should not exceed the fracture force of the microneedle. A satisfactory balance between

structure rigidity and miniaturization should be kept in mind. Yang and Zahn studied the effect of vibratory actuation on microneedle insertion force and found there to be a reduction in insertion force by greater than 70%.[100] Vibration caused tissue damage via fluid cavitation and thermal damage due to frictional interaction, which reduced microneedle insertion force. This combination helped in the preparation of microneedles using metals and polymers with low value of Young's Modulus.

Pocketed and grooved microneedles

Microneedles with modified surface can be used for the targeting of drugs to a specific depth in the skin and to load a greater amount of drug onto the microneedles. The protective coat, or second drug coat, can also be applied on same microneedles after filling the first part in the pockets. Gill and Prausnitz made pocketed microneedles by fabricating microneedles with one or more holes cut through the centre.[101] They worked on parameters like controlled coating of pockets, their filling capacity, possibility of multi-layered coating and targeting drug to specific depths in the skin. Grooved microneedles were prepared by Han *et al.* for improvement of antigen delivery.[102] They prepared 3D polymeric microneedles having groove-embedded shafts, sharp tips and a large base and determined drug loading capability. A higher antibody response was observed with more antigen being loaded in comparison with smooth microneedles.

Combination of micro-pumps and microneedles

Micro-pumps, when associated with microneedles, provide precise delivery of drug. Pumps control flow rate and pressure for delivery of concentrated drug solution as per specifications. Zahn *et al.* prepared an integrated system, with microvalves and micro-pumps, which was capable of controlling fluid withdrawal for medical analysis and delivering the drug in response to metabolites levels.[103]

Safety Issues of Microneedles

Microneedles have been used for the safe and efficient delivery of drugs and vaccines by creating reversible microchannels in the skin. Disruption of the stratum corneum by using conventional needles for the delivery of drugs and vaccines may cause pain, bleeding, skin irritation, skin redness and infection. The use of microneedles is considered safe owing to their small size and observed lack of significant damage to sensory neurons and blood vessels situated in the dermis layer beneath the skin, which means negligible pain and bleeding. But as microneedles disrupt the stratum corneum, safety concerns should be taken into account. Many studies related to the safety of microneedles have been conducted and these have proved their safety.

Microchannels created by needles may cause chances of infection at the injection site because of permeation of pathogenic microbes or any toxic substances. Faster resealing of the microchannels is essential to prevent infection. In a study of the kinetics of skin resealing after insertion of microneedles, Gupta *et al.* compared the time taken for skin resealing after application of microneedle and hypodermic needle (26 Gauge).[23] They found faster resealing of skin after application of microneedles than after the hypodermic needle, which imparts an inherent safety feature to the microneedles.

Jiang *et al.* examined the presence of microchannels or inflammation, after insertion of microneedles into the cornea of a rabbit, using a slit lamp.[74] They found that microchannels disappeared within 3 h and there was no evidence of an inflammatory response. This study suggests that microneedles can be explored for delivery of drugs to the eye for the treatment of ocular diseases.

Damme *et al.* administered influenza vaccine intradermally using microneedles and intramuscularly using conventional hypodermic needle.[104] They found that pain associated with needle insertion was significantly less with microneedles. Some transient reactions occurring on the skin at the site of microneedle application were found to be tolerable. They concluded that efficacious vaccination could be achieved using microneedles as compared with conventional intramuscular delivery of influenza vaccine. A similar study was conducted by Laurent *et al.* in which the safety and efficacy of rabies vaccination administered using a microneedle-based drug delivery system was proved.[105] They also found tolerability with efficacious vaccination using microneedles as compared with conventional vaccination.

Gupta *et al.* and Gill *et al.* studied the effect of microneedle length and number of microneedles on pain.[23,106] They reported that a small increase in length of microneedles resulted in an increase in pain while little increase in pain was observed with increasing the number of microneedles. On the basis of their experiment, it can be concluded that to administer higher dose or to increase permeability, it might be better to increase the number of microneedles in spite of increasing length of microneedles.

Bal *et al.* and Kaushik *et al.* studied the safety of microneedles and reported that drug could be delivered without adverse reactions and pain using microneedles.[107,108] Overall, we can conclude that microneedles are safe but a few challenges remain to be faced for their development and commercialization as successful transdermal drug delivery technology.

Challenges in the Development of Microneedles

Many applications of microneedles have been discussed but very few products have been marketed to date. There is a need

to consider safety and efficacy while developing microneedles for delivery of both small and large molecules. With metallic microneedles, traces of metal are retained beneath the skin which may lead to irritation, erythema, swelling, discoloration or other side effects.[18] Frequent application of the microneedle at the same site may result in the aforementioned problems. Application at different sites every time or variation in skin thickness in individuals may result in variation in bioavailability, which needs to be considered while developing microneedles.[109] Today, research is more focused in the development of new technologies for administration of existing molecules, which are already proven as safe, thus reducing development time and assuring a higher rate of success. This is the main reason why many workers in the pharmaceutical industry strive for successful development of microneedles as transdermal drug delivery systems.

Development of different types of microneedles faces varied challenges. Use of solid metallic microneedles may result in irritation or retention of metallic particle in the skin. Furthermore, they may leave behind biohazardous sharp waste after use and destruction needs to be done carefully.[110] Dissolving microneedles are made of polysaccharides and dissolve in the skin with no waste left after use. Complete dissolution, proper insertion into the skin and loading of drug extensively at the tip only are the foremost challenges to be faced during their development.[68,79] The use of hollow microneedles is another approach gaining the attention of researchers due to the capacity of the hollow microneedle to administer a larger variety of molecules as compared with other devices. However, this type of microneedle does not possess enough strength, an issue which needs to be focused on by the researcher.[37]

Commercial and Regulatory Status

Microneedles were developed as a technology for administration of proteins, peptides, immunobiological, drugs and cosmetics as well as for biofluidic analysis. Intanza/IDflu is the first intradermal influenza vaccine marketed in Europe, Australia and Canada.[111] Recently it was approved by the USFDA for marketing in the USA. ZP-PTH is a product developed by Zosano Pharma for the treatment of severe osteoporosis, which demonstrated excellent safety and efficacy in Phase II clinical trials and now is ready for Phase III study.[112] Table 4 shows examples of marketed products based on microneedle technology, together with their possible use. It would appear that many of the currently marketed applicators are utilized for improving the efficacy of cosmetic products. Thus it can be concluded that though many pharmaceuticals are involved in development of microneedle-based transdermal products, only a few are successfully marketed. Guidelines for the development of transdermal drug delivery systems are followed right now.

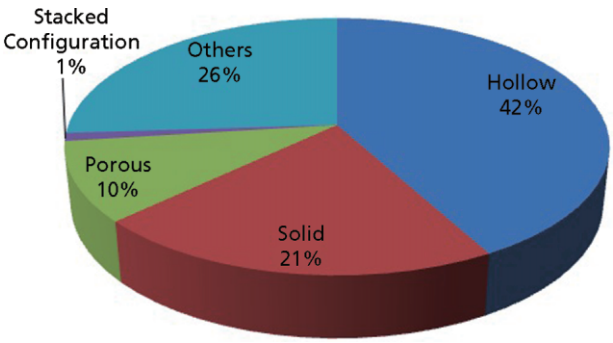

Figure 5 Division of patents filed based on type of microneedles.[134]

However, there is strong need to draft specific regulatory guidelines for development of microneedles.

Recent Patents on Microneedles

Microneedle application is an emerging technique for transdermal drug delivery and this is reflected by the large number of patent applications filed.[125–133] The majority of these patent applications are focused around design of, and delivery through, hollow microneedles since a higher amount of drug can be delivered from such microneedles as compared with other microneedles. Many of the patents based on hollow microneedle technology are also because of its major merit of administration of a larger volume compared with other microneedles. Figure 5 shows patent distributions of microneedles based on type.

Conclusions

Transdermal drug delivery system is an emerging area for systemic as well as local delivery of macromolecules. The biggest drawback of TDDS is poor permeability through stratum corneum and it can be overcome by using microneedles. Hence, researchers focused their attention on development of different types of microneedles for delivery of macromolecules, immunobiologicals and drugs as well as to withdraw the tissue fluids. Physical approaches have also been combined with microneedles to enhance drug delivery through skin. In conclusion, microneedles have been tried by many scientists as a novel means to administer the molecules. Many patents have been filed to cover the invention and this reflects the scope of development of microneedle as a means to administer the problematic macromolecules. Improved therapeutic response can be obtained using microneedles.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Table 4 Commercial status of microneedle-based transdermal products

Brand name	Manufactured by	Applications
VaxMat	TheraJect Inc., USA	It is dissolvable microneedles and can deliver hundreds of micrograms of drug rapidly through the stratum corneum into the epidermal tissue.[113]
Micro-Trans	Valeritas Inc., USA	It can deliver the drug into dermis without limitations of drug size, structure, charge or the patient's skin characteristics.[114]
Nanoject	Debiotech, Switzerland	Useful for intradermal and hypodermic drug delivery and for interstitial fluid diagnostics.[115]
Janisys	Janisys, Ireland	Actively delivers drugs from transdermal patches and multiple drugs can be administered via one patch.[116]
BD Soluvia	Becton Dickinson, USA	It is a prefillable microinjection system for accurate intradermal delivery of drugs and vaccines.[117]
Onvax	Becton Dickinson, USA	It is a skin micro abrader having plastic microneedles for disruption of stratum corneum for the delivery of vaccines.[105]
MicronJet	NanoPass Inc., Israel	It can be used with any standard syringe for painless delivery of drugs, protein and vaccines approved for this delivery route.[118]
Macroflux	Zosano Pharma Inc., USA	Metallic microneedles for the delivery of peptides and vaccines.[119]
MicroCor	Corium International Inc., USA	It can be used to deliver small as well as large molecules like proteins, peptides and vaccines.[120]
Microstructured transdermal system technology (MTS)	3 M Corp., USA	The technology can be used to administer drugs including monoclonal antibodies in solid or liquid dosage form.[121]
AdminPen	AdminMed, USA	Liquid pharmaceutical formulation or cosmetics can be conveniently injected in to the skin.[122]
NanoCare	NanoPass Inc., Israel	It is a small hand-held device for rejuvenation of skin and to boosts the cosmetic effect of topical applications.[123]
MTS-Rollers	Clinical Resolution Laboratory Inc., USA	It is used for transdermal delivery of cosmetics in deeper skin layers.[124]

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