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REVIEW ARTICLE

MICRONEEDLE TECHNOLOGY FOR TRANSDERMAL DRUG DELIVERY: APPLICATIONS AND COMBINATION WITH OTHER ENHANCING TECHNIQUES

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ABSTRACT

Transdermal delivery system has been extensively employed over the years owing to its advantages over the conventional delivery systems. However, the stratum corneum hinders the penetration of substances through the skin. Microneedle technology is the latest advancement and has gained tremendous attention in transdermal delivery system, overcoming the obstacles of transdermal delivery system and providing advantages over the conventional delivery systems. Numerous studies have been carried out for exploring microneedles. This review article covers the types of microneedles, mechanism of action of microneedles, methodology of drug delivery via microneedles while mainly focusing on the applications of microneedles and their combination with other enhancing techniques in transdermal delivery of drug and other molecules.

Keywords: Transdermal delivery, Microneedles, Stratum corneum, Iontophoresis, Electroporation, Sonophoresis, Vibratory actuation, Immunologicals, Biopharmaceuticals, Phlebotomy, Diagnosis.

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1. INTRODUCTION

Administration of drugs can be achieved through various possible delivery routes available including the 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 has specific merits and demerits. Over the years transdermal drug delivery systems have shown a potential alternative for the oral and parenteral routes of drug delivery systems overcoming their demerits of 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.), in case of oral drug delivery systems [2, 3] and pain associated with the injections, expertise required to deliver the drug, risk of infection and difficulty in obtaining sustained drug delivery in case of parenteral drug delivery systems[4.] . However transdermal technology has limitations due to the inability of a large majority of drugs to cross the skin at the desired therapeutic rates because of the presence of a relatively impermeable thick outer stratum corneum layer. This barrier posed by human skin limits transdermal delivery only to lipophilic, low molecular weight potent drugs [5]. Different strategies, including chemical and physical enhancers have shown, in many cases, a limited impact to overcome this disadvantage. In recent years, great attention has been paid to microneedles, a hybrid between hypodermic needles and transdermal patches to overcome the individual limitations of both the injections as well as patches. These are micron scale needles assembled on a transdermal patch, able to pierce and create micron sized pores in the skin to effectively deliver drugs in a painless manner through the stratum corneum, thus bypassing the most important permeability barrier of the skin. Microneedles have found application in the pharmaceutical field, not only to facilitate the administration of drugs with minimal invasion, but also for the extraction of biological fluids. Numerous studies have found a marked increase in drug transport through the skin when using microneedle arrays alone, in combination with other enhancers (e.g., iontophoresis or electroporation) or even when including more sophisticated devices such as micropumps. Microneedles have shown great

effectiveness in facilitating the passage of macromolecules, hydrophilic substances, and different carriers such as lipid vesicles and nanoparticles.

2. CONCEPT OF MICRONEEDLES

Microneedles are microstructured transdermal systems, consisting of an array of microstructured projections coated with a drug or vaccine that is applied to the skin to provide intradermal delivery of active agents, which otherwise would not cross the stratum corneum [6]. Microneedles are somewhat like traditional needles, but are fabricated on the micro scale. They are smaller than hypodermic needle, generally one micron in diameter and ranges from 1-100 microns in length.

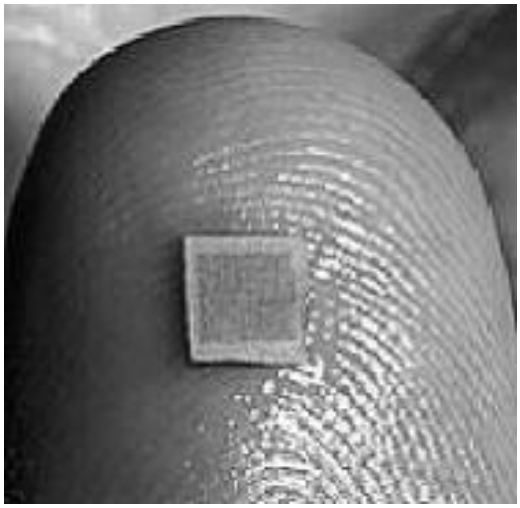

Figure 1: Experimental microneedle array consisting 400 microneedles.

Advantages of Microneedles [7-10]:

- rapid onset of action
- painless administration of the active pharmaceutical ingredient
- Large molecules can be administered
- first-pass metabolism is avoided
- faster healing at injection site than with a hypodermic needle
- patient compliance due to ease of administration
- decreased microbial penetration as compared with a hypodermic needle, the microneedle bypasses the stratum corneum and punctures only the epidermis
- specific skin area can be targeted for desired drug delivery
- Drug can be administered at constant rate for a longer period
- good reproducibility
- good stability and enhanced drug efficacy may result in dose reduction
- good tolerability without long-term oedema or erythema

Disadvantages of Microneedles [7]:

- skin irritation may result because of allergy or sensitive skin
- local inflammation may result if the concentration of drug is high under the skin
- 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
- the thickness of the stratum corneum and other skin layers varies between individuals and so penetration depth of particles could vary too
- external environment, like hydration of the skin, could affect delivery
- tip of the microneedle may break off and remain within the skin on removal of the patch
- Compressed dermal tissue can block hollow microneedles

Selection of the 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. Considering the requirement of microneedle to be long enough to penetrate the stratum corneum and at the same time should be short enough to be painless, they have been manufactured in a variety of shapes and sizes, as required for different applications using different materials as mentioned below [11]. Most microneedle fabrication methods are based on the conventional microfabrication techniques of replicating microstructures using micromoulds, utilizing photolithographic processes, silicon etching, laser cutting, metal electroplating, metal electropolishing etc.

3. MECHANISM OF ACTION

The mechanism of action depends on the type of microneedle design. The general mechanism of delivery via microneedles is based on mechanical disruption of the skin and application of the drug or vaccine within the epidermis, from where it can more readily reach its targeted site of action. The drug is entrapped within the microneedles, which when inserted into the skin and releases the drug into the layers of skin which are highly vascularized. In some cases the needles dissolve within minutes, releasing the entrapped drug at the intended site of delivery from where they reach the target site.

Table 1: Material of construction for microneedles

Material of construction	Example	Type of microneedle produced	Merits	Demerits
Metal	Nickel-iron [11], stainless steel [12], titanium [13],	Hollow/solid/ coated	Good mechanical strength, cost effective	Non-biodegradable, expensive, brittle
Silicon	Silicon dioxide [14]	Solid/hollow	Greater mechanical strength	Expensive, brittle
Glass	-----	Hollow	High drug loading capacity	Non-biodegradable
Biodegradable Polymers	Polylactic acid [15], Polyglycolic acid [15], Polylactide-co-glycolic acid (PLGA) [15], polycarbonate[16], Polyvinylpyrrolidone (PVP) [17]	Solid	Cost effective, good resistance, biocompatible	Thermal instability
Non-biodegradable polymers	Polyvinyl acetate (PVA) [18], Alginic acid [18], Gantrez AN-139, a copolymer of methylvinylether and maleic anhydride (PMVE/MA) [18], Carbopol 971 P-NF [18], Polyetherimide [19]	Solid	Cost effective, good resistance	Non-biodegradable
Polysaccharides	carboxymethylcellulose [20], Amylopectin [20], Maltose [21], Dextran [22], Galactose [22], Chondroitin Sulfate [22], Thermoplastic starch [23]	Solid, dissolving	Rapid drug delivery, biodegradable	Hygroscopic, caramelization

4. TYPES OF MICRONEEDLES

Classification for microneedles usually used in literature is based on the fabrication process: in-plane or out-of-plane microneedles.

Another useful point of distinction is whether the microneedles are solid, hollow, coated or dissolving. The following sections will give an overview of these microneedles.

4.1 Solid microneedles

Solid micro needles are defined as the arrays of projections that are employed for creating holes in stratum corneum and are applied before the application of a drug and then removed afterwards. These can essentially create micron scale holes in the skin, through which drug molecules can easily enter [25]. These needles are inserted into the skin for specified time period. The micro channels developed by the insertion of micro needles promote the drug transport in to the viable epidermis [26].

4.2 Coated microneedles

Coated microneedles are solid microneedles that act as vehicles to carry and deposit drug within the skin or other tissue. This includes coating microneedles with a drug in a formulation suitable for coating and subsequent dissolution. In this way, the desired dose of the drug is delivered into tissue quickly upon insertion of the microneedles. The drug dose that can be administered this way is limited to the amount that can be coated onto the tip and shaft of the microneedles, which is typically less than 1 mg for small microneedle arrays[27]

4.3. Dissolving microneedles

Unlike coated microneedles, dissolving microneedles completely dissolve in the skin and thus leave no bio hazardous waste behind after use. These microneedles typically constitute of water-soluble materials such as polymers and sugars that are safe and inert and will dissolve in the skin after insertion. While dissolving microneedles can be used as a skin pretreatment to increase permeability, drugs are often encapsulated inside the microneedle for release into the skin [28].

4.4 Hollow microneedles

Hollow microneedles contain a hollow bore in the center of the needle. When inserted into the skin, the hollow bore present bypasses the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis [26].These microneedles are mainly employed to inject the drug solutions directly into the skin [29], to carry the drug into the body by diffusion [30]. Similar to hypodermic injection, hollow microneedles enable pressure-driven flow of a liquid formulation. Pressure, and thereby flow rate, can be modulated for a rapid bolus injection, a slow infusion or a time-varying delivery rate. The apparent advantage of this is that a considerably larger amount of drug can be delivered for a given time, thus opening for applications where relatively large amounts are needed to obtain a therapeutic effect. The liquid formulation may simplify use of existing injectable formulations for delivery using microneedles, but misses the opportunity of solid microneedle delivery methods to administer dry-state drug formulations without reconstitution to improve drug stability and the patient convenience of a patch-based delivery method. Hollow microneedles are also used to remove the fluid from the body for analysis [30].

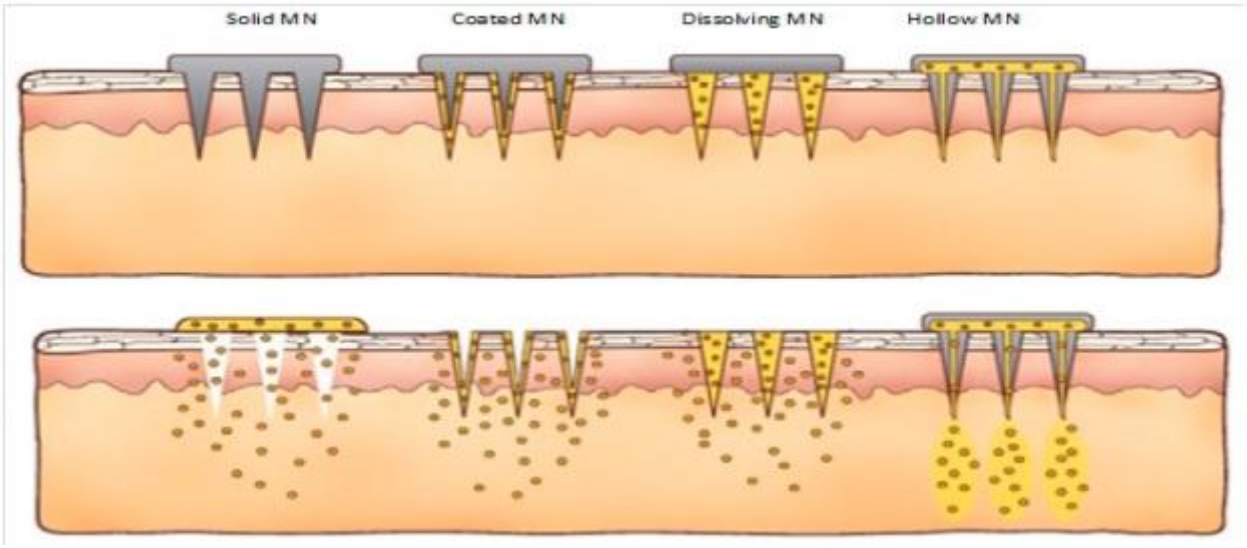

Figure 2: Different types of microneedles: solid, coated, dissolving and hollow.

4.5 Hydrogel-forming microneedles

Hydrogel-forming microneedles are the latest development in microneedle technology. These are arrays of microneedles made up of a swelling material with a drug reservoir attached to the baseplate of the array [31-34]. After insertion into the skin, the array absorbs interstitial fluid and swells to form continuous conduits between the dermal microcirculation and an attached patch-type drug reservoir leading to the diffusion of the drug into the skin [32, 33]. Such microneedles act initially as a tool to penetrate the stratum corneum barrier. Upon swelling, they become a rate controlling membrane. These microneedle arrays are produced mainly using synthetic polymers such as an aqueous polymer gel that can be easily cross-linked by chemical or physical methods [35]. These materials, once swollen, should maintain structural integrity and be reasonably robust during handling [33]. Although hydrogel-forming microneedles are made from polymers, there are distinct differences between these microneedles and the regular dissolving polymer microneedles. Advantages of hydrogel-forming microneedles are that they can be fabricated in a wide range of patch sizes and geometries, can be easily sterilized, resist hole closure while in place and are removed completely intact from the skin [32]. However more effort should be directed at widening the range of materials that can be used to fabricate these useful transdermal drug delivery systems. Hydrogel-forming MN arrays have been employed to deliver a wide range of different molecules from small molecules [32-33, 36-37] to high molecular weight compounds [32-33, 37]. The use of hydrogel-forming microneedle arrays for minimally-invasive extraction and quantification of drug substances and glucose from skin in vitro and in vivo strongly illustrates the potential of hydrogel-forming microneedles in minimally-invasive patient monitoring and diagnosis [38].

5. METHODOLOGY FOR DRUG DELIVERY

A number of delivery strategies have been employed to use the microneedles for transdermal drug delivery.

These include

- Poke and patch
- Coat and poke
- Poke and release
- Poke and flow

5.1 Poke and patch

It involves piercing an array of solid microneedles into the skin followed by application of the drug patch at the treated site. Transport of drug across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied [39]. This technique was also tried to extract the interstitial fluid to measure the glucose level by non-invasive method [40].

5.2 Coat and poke

In this approach needles are first coated with the drug and then inserted into the skin for drug release by dissolution. The entire drug to be delivered is coated on the needle itself [5]. Dip and scrape approach is a variation of this approach, where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the micro abrasions created by the needles [39]. 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.

5.3 Poke and release

It involves release of encapsulated drug into the skin from the microneedles made from polymers and polysaccharides that either slowly dissolves or degrades after administration. 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 [28].

5.4 Poke and flow

In this approach first the skin is pierced (external pressure) and then the drug is allowed to flow through hollow microneedles from the reservoir in the patch [41]. A large amount of drug can be administered by poke and flow method. Additionally, pressure-driven delivery adds the possibility to precisely steer the flow rate and to obtain a more controlled delivery.

All of the above-mentioned approaches can be employed to deliver drugs either systemically or at a restricted site (local action).

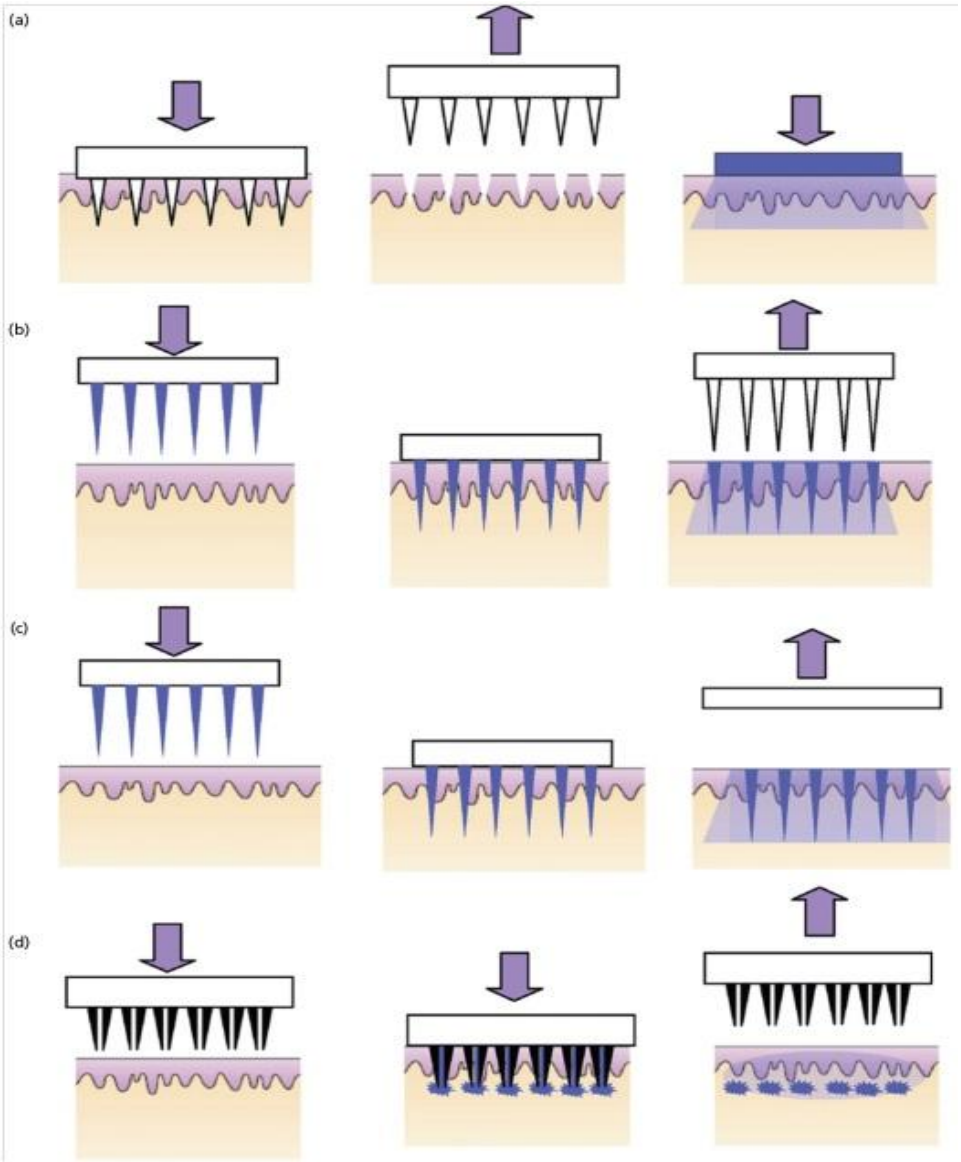

Figure 3 : Methodology for drug delivery by microneedles: (a) 'poke and patch' using solid microneedles, (b) 'coat and poke' using coated solid microneedles, (c) 'poke and release' using polymeric microneedles, (d) 'poke and flow' using hollow microneedles.

6. APPLICATIONS OF MICRONEEDLES

Microneedles have been explored for different applications and are extended to many fields. Owing to benefit of piercing in a minimally invasive manner, apart from being an alternative to conventional hypodermic therapy, they have also been employed for ocular, systemic and intracellular delivery. Microneedles can be used to deliver high molecular weight compounds like proteins and peptides, immunobiologicals like vaccines, antibodies etc. [42], bioactive agents or bio macromolecules like insulin, heparin, albumin, growth hormones [43]. Microneedles have also gained prominent attention in the field of cosmetics and various cosmeceuticals have been used for the treatment of acne, pigmentation, scars and wrinkles as well as for skin toning [42].

6.1 Immunobiologicals

Attributing to the drawbacks of conventional vaccination procedure of needle phobia and the pain

associated with insertion of needle into the skin, recent studies have focused on development of needle-free vaccination like liquid jet injectors, powder injectors, thermal ablation and microneedles for the administration of immunobiologicals via the subcutaneous, intramuscular or intradermal route for prevention of infectious diseases. Microneedles have an edge over the other methods due to lack of pain, self-administration and quick delivery of vaccine [42-43]. Making use of the microneedles allows vaccines to cross the stratum corneum and stimulate a clinical response. In case of dissolving microneedles, controlled and complete penetration is an important parameter to be considered. These are capable of delivering a small dose, less than several milligrams, of peptides, proteins, vaccines, hormones and organic compounds. Numerous studies have been performed and reported on vaccine delivery using microneedles including human IgG [21], tetanus toxoid [23], DNA vaccine [39], influenza vaccine [44], hepatitis B vaccine [45], human papilloma virus vaccine [46], west nile virus vaccine [47], chikungunya virus vaccine [47], herpes simplex virus vaccine [48-49], Bacillus Calmette Guerin vaccine [50], ovalbumin [51], , live attenuated chimeric JE vaccine (ChimeriVax)-JE/flavivirus vaccine [52], diphtheria [53], malaria [53], combination and recombinant protein vaccines for anthrax, botulism, plague and staphylococcal toxic shock [54].

6.2 Bioactive macromolecules (Biopharmaceuticals)

Owing to the proteolytic degradation and hindered absorption, bioactive macromolecules such as insulin, heparin, and growth hormones are not administered orally. The majority of commercially available biopharmaceuticals are administered via the parenteral route and hence a suitable non-invasive route is desirable. Microneedle arrays have been found to enhance the transport across dermatomed human skin for both low and high molecular weight compounds and also that the length of the microneedles and the depth up to which the microneedles penetrated in the skin had no effect on the transport of either low or high molecular weight compounds[55]. For rapid release as well as controlled release of molecules, an approach of preparing dissolving microneedles constituting water-soluble polysaccharides has been done [20, 22]. Studies performed and reported on administration of biopharmaceuticals using microneedles include delivery of low molecular weight heparin [22], insulin [56], L-Carnitine [57], calcein and bovine serum albumin [58], desmopressin [59], recombinant human growth hormone and desmopressin [60], albumin [61], calcein [62], erythropoietin [63], oligonucleotides [64], porphyrin precursor 5-aminolevulinic acid (ALA) [65], salmon calcitonin [66], daniplestim [67], leuprolide acetate [68], Para thyroid hormone [69], human growth hormone [70] etc.

6.3 Drugs

It is essential for a drug molecule to possess the necessary physicochemical properties to cross the skin barrier. Transport of a drug molecule through the skin and also the rate of transportation are governed by these physico-chemical properties like hydrophilic-lipophilic balance, solubility, molecular weight, etc. The challenges posed in transdermal drug delivery can be overcome by use of microneedles. Use of microneedles enhances the bioavailability of drugs and can exclude the need for penetration enhancers, which may induce irritation. Microneedles may also reduce the side effects and complications associated with systemic administration. Drugs administered via microneedles include L-Ascorbic acid [19], riboflavin [27], galanthamine [71], aspirin [72], docetaxel [73], pilocarpine [74], methotrexate [75], prochlorperazine edisylate [76], lidocaine hydrochloride [77], ropinirole hydrochloride [78], ketoprofen [79], naltrexone with diclofenac sodium [80], phenylephrine [81], naltrexone [82], mannitol [83], glycerol [84] etc.

6.4 Phlebotomy

Phlebotomy refers to the withdrawal of blood samples for analysis of specific blood constituents for diagnosis of a disease. 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. In such case, painless blood sampling using microneedles can be a very good alternative to hypodermic needles [85-86]. Microneedles situated at a distance of 500–2000 mm in the dermis layer beneath the skin can be used to obtain precise body fluids as well as blood samples from the capillaries. Apart from making the procedure painless, microneedles also reduces the blood sample requirements (up to 200 nanolitres). However the most essential requirement is that 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. Painless hollow microneedle-based micro sampling can be used instead of traditional methods for glucose estimation in case of disease diabetes which requires frequent monitoring of blood for estimation of glucose concentration or disease severity [87]. Microneedles can also be used for monitoring of therapeutic drug levels [88]. A jagged-shaped, hollow in-plane silicon microneedle resembling the proboscis of a mosquito has been prepared for collection of blood for testing [89]. Arrays of 350m long, hollow, out-of-plane microneedles demonstrated in-situ analysis biological fluid extraction through capillary action [90].

6.5 Diagnosis

The use of microneedles can also be employed in the field of diagnosis. Hollow microneedles, along with quantum dots, help in medical diagnosis. Quantum dots are Nano scale crystals with a light-emitting property. The multiphoton microscopy method could rapidly diagnose cancers or other medical problems [91]. Recent research focuses on the development of magnetic nanoparticles along with magnetic microneedle tips those safely collect biomarkers that indicate early-stage

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osteoarthritis in knees, hips and other joints [92]. Work has been carried out on development of two sensing device based on hybrid microneedles array for diagnostic and therapeutic applications. Hybrid microneedles having a porous structure were prepared, which can include a variety of biological molecules, as bioprobes or drugs. The first device is an electrochemical sensor where microneedles contain enzymes in their matrix that interact with glucose. The redox reaction with glucose, mediated by ferrocene, creates a charge transfer resulting in a current proportional to the glucose concentration. The second device is a therapeutic tool with optically controlled release of drug. In this case the device includes a porous silicon membrane with a Bragg's mirror, whose reflection wavelength is related to the drug's concentration in the microneedle [93]. Microneedle sensors fabricated at the end of an endoscope using poly caprolactone (PCL) microneedles coated with poly (3, 4-ethylenedioxythiophene) (PEDOT), functionalized with hemin molecules on the surface were employed for both endomicroscopic imaging and biosensing of colon cancer by real-time electrical detection of nitric oxide [94]. Microneedles have also been developed as sensors for hydrogen peroxide, lactate, dissolved oxygen and glutamate [95-97]. Microneedles have been employed as bioelectrical interfaces, especially for neural recording and stimulation [98-106], as well as for electrocardiography (ECG) [107] and electroencephalography (EEG) measurements [108-109].

6.6 Cosmeceuticals

Cosmeceutical industry has shown great interest in microneedle technology, the majority of cosmetic products are lending themselves to microneedle technology for non-surgical and non-ablative treatment of skin conditions such as ageing (wrinkles, lax skin), scarring (acne, surgical), photo damage, hyperpigmentation (age/brown spots) and hair loss (alopecia). The process facilitates and stimulates skin's natural repair without causing permanent epidermal damage. Microneedles can be used for cosmetic applications, mainly for treatment of skin blemishes and the delivery of active cosmetic ingredients [110-111]. Marketed microneedles like Derma rollers® and stamps are available for treatment of skin problems as well as to improve looks. MTS Dermaroller® marketed by Clinical Resolution Laboratory is a cosmetic aid possessing needles that penetrate the skin up to a depth of 0.2–0.3 mm. It contains 200 very fine stainless-steel needles that 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® [112]. A hyaluronic acid based dissolving microneedle patch developed for the intradermal delivery of ascorbic acid and retinyl retinoate displayed improved skin appearance in terms of roughness and wrinkle appearance when tested in human volunteers [113]. An enhancement in the local delivery of eflornithine (used to reduce facial hirsutism) was observed both in vitro and in vivo when the skin was exposed to microneedle pretreatment followed by local administration of an eflornithine cream [114]. Microneedle technology can be used to treat different types of scars by dermabrasion [115-119]. Dermabrasion involves piercing the skin multiple times with microneedles to induce collagen growth. A noticeable improvement was observed in the treatment of patients with dermal scars (striae distensae) using a disc microneedle therapy [116]. However, similar to the treatment of acne, this treatment too is associated with limitations of skin bleeding and painful treatment. An aesthetic improvement in patients with acne scars was reported with a reduction in scar severity in all subjects when treated with Dermaroller® [117]. Similar results were obtained for treatment of atrophic facial scars using Dermarollers® [120]. An alternative approach to the use of Dermarollers® for the treatment of acne scars reported is the fractional radio frequency microneedle system. This system was introduced recently as a new device for facial rejuvenation. It involves creating radiofrequency-induced thermal zones. This causes damage to the reticular dermis followed by the dermal thickening. This system was clinically evaluated and the results suggested that this novel technique is efficacious for the treatment of acne scars, as it reduced the severity of the scars in more than 80% of volunteers [121].

7. MICRONEEDLES IN COMBINATION WITH OTHER ENHANCING TECHNIQUES FOR IMPROVING TRANSDERMAL DRUG DELIVERY

In order to improve the skin permeability, different techniques have been developed and employed such as using permeation enhancers, either chemical or physical. These enhancers may exhibit different mechanisms of action however their sole aim is to modify the structure of stratum corneum which is considered as the main barrier to the permeation of substances. Even though the use of permeation enhancers increases the penetration of drugs through the skin, in many cases it proves to be insufficient in achieving the therapeutic levels. To overcome this, several experiments in which two or even more enhancing techniques are combined have been attempted to obtain a synergistic effect, thus achieving the required effect of enhanced drug delivery and better control of drug delivery across the skin. Following section gives an overview of the enhancing techniques.

7.1 Microneedles in combination with Iontophoresis

The technique of transdermal iontophoresis involves the application of a physiologically acceptable low electric current (<0.5 mA/cm^2) to the skin and works on the principle of "like repels like", in order to promote the transfer of charged and polar substances across the stratum corneum of the skin [122]. The barrier disruption thus caused by employing iontophoresis in combination with microneedles increases the possibility of variety of drugs that can be administered transdermally. It also allows achieving controlled delivery of drug by controlling the current[123].

Iontophoretic transdermal transport mainly involves mechanisms of electromigration and electroosmosis. Electromigration is the movement of ionic species in response to the application of the electric field, and is the most important mechanism for the delivery of ionic drugs. Electroosmosis is the aqueous flow that occurs during the movement of charged species, carrying all the dissolved drugs across the skin. The technique of iontophoresis might be still limited by the molecular size of the drug candidate even though it offers an attractive alternative for the delivery of macromolecules [124].

7.2 Microneedles in combination with Sonophoresis

Sonophoresis involves application of ultrasound (frequency, 20 kHz to 10 MHz; intensity, up to 3 W/cm^2) causing perturbation of lipid bilayer inducing change in the lipid arrangement of the stratum corneum, forming cavitation thus enhancing transportation of drugs across the skin. Drug permeation can be controlled by controlling the frequency of the ultrasound. An increase in the sound frequency from 20 kHz to 1 MHz causes 1000 fold increase in skin perturbation [125]. A synergistic effect on the permeation of molecules through the skin can be achieved by combining sonophoresis with microneedles. Very few studies have been performed on employing this strategy and thus needs to be explored further.

7.3 Microneedles in combination with Electroporation

Electroporation involves application of high voltage short-duration (milliseconds) current (generally 50–1000 V/cm) causing a transitory, localized perturbation of lipid bilayer inducing structural rearrangements of the cell membrane due to the electric fields that are produced during current application. The aqueous pores formed as a result act as the aqueous pathways and provide a local driving force that facilitates the transport of molecules across the stratum corneum. A trans-membrane potential up to 1 kV for 10 ms to 500 ms was used for in-vitro electroporation of stratum corneum [125]. Although this process is useful for delivering large hydrophilic drug species like small molecules, proteins, peptides and oligonucleotides, including biopharmaceuticals with molecular weights greater than 7 kilo Daltons, electroporation was also used for permeation enhancement of larger molecules having molecular weight up to several kilo Daltons [126]. Combining electroporation with microneedles resulted in microneedles that behaved as microelectrodes for electroporation, which eradicated the need for electrodes. This combination provides a synergistic effect on the permeation of molecules through the skin.

7.4 Microneedles in combination with Vibratory actuation

Precise control of insertion force is required for the penetration of a microneedle into the skin and it should not exceed the fracture force of the microneedle. Structure rigidity and miniaturization of microneedles should be well considered and a satisfactory balance between these two should be maintained. Vibration actuation causes tissue damage via fluid cavitation and thermal damage due to frictional interaction. When this mechanism of vibration actuation is combined with microneedles, a reduction in the microneedle insertion force is achieved as a result. A study employing this combination was performed wherein the combination of vibration actuation and microneedles helped in the preparation of microneedles using metals and polymers with low value of Young's Modulus also the effect of vibratory actuation on microneedle insertion force was evaluated and greater than 70% reduction in the insertion force was observed [127].

7.5 Microneedles in combination with Vesicles

Several studies have been performed and reported on employing lipid vesicles for the transdermal drug delivery. However these systems are surrounded with controversy related to their delivery mechanism which is reported to be associated with the accumulation of the vesicle and the encapsulated drug in the stratum corneum because of their inability to penetrate the skin deep enough rendering them with little value as carriers for transdermal drug delivery. This paved the way for employing other vesicular systems which are able to penetrate into deeper skin layers, such as niosomes (vesicles composed of nonionic surfactants), ethosomes (vesicles with high alcohol content), transferosomes (vesicles composed of phospholipids as their main ingredient, with 10-25% surfactant and 3-10% ethanol), invasomes (vesicles formed by phospholipids, ethanol and terpenes as penetration enhancers) etc. Combining microneedles with these vesicular systems holds potential for enhanced transdermal drug delivery. Depending on the diameter and height of microneedles, liposomes can be located in different parts of the skin. Results may vary according to the needle geometries. Microneedles of short height render vesicles on the surface of the stratum corneum, while longer microneedles lead vesicles into deeper skin layers.

7.6 Microneedles in combination with Microparticles and Nanoparticles

The versatility of microparticles and nanoparticles for the effective and targeted release of different therapeutic agents to different anatomical regions makes them a good candidate as drug carriers or vehicles for topical and transdermal drug delivery for enhanced drug permeation [128]. Microparticles and nanoparticles are distinct with respect to their size (micrometric and nanometric, respectively), biopharmaceutical properties and their therapeutic applications. These carriers can be constituted of biodegradable polymers or lipid materials. Penetration of nanoparticles through human skin depends on the nanoparticle size and shape, material properties etc. Nanospheres or nanocapsules of different sizes can be obtained by varying the materials employed and the method of preparation. A dramatic increase in cellular uptake can be achieved by reducing the size of nanoparticles. Few nanoparticle systems have a characteristic capability of diffusing into the cells, which makes them candidates to reach the drug target

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in a specific cellular compartment. Combining microneedles with these nanoparticulate systems may significantly enhance the transdermal drug delivery wherein microchannels created by the microneedles may prove to be large enough to deliver drug-loaded nanostructures into the skin. Delivery of microparticles into the skin sets a challenge. In such case combining microneedles with these solid particles could facilitate the delivery of the later into the skin. By making use of appropriate microneedle design and insertion methods, even relatively large microparticles can be delivered into the skin. Perhaps the greatest shortcoming of controlled-release microneedles is that limited dose can be administered. Since the drug is encapsulated within microneedles and microneedles are, of course, very small, the maximum total dose that can be administered is likely to be less than 1 mg [58].

7.7 Microneedles in combination with Micro pumps

Conjunction of microneedles with micro pumps provide precise delivery of drug as the pumps control the flow rate and pressure for delivery of concentrated drug solution as required. This combination was employed in preparing an integrated system, with micro valves and micro-pumps, which was capable of controlling fluid withdrawal for medical analysis and delivering the drug in response to metabolites levels [129].

7.8 Pocketed and Grooved Microneedles

Modification of the microneedle surface can be employed for targeted drug delivery to a specific depth in the skin and for loading greater amount of drug onto the microneedle. This can be achieved by applying the protective coat or second drug coat on the same microneedles after filling the first part in the pockets. Such microneedles are known as pocketed microneedles. These can also be obtained by fabricating microneedles with one or more holes cut through the center [130]. Also grooved microneedles that capable of loading greater amount of drug onto the microneedle can be employed for enhanced drug delivery [131].

Table 2: Summary of few results of the delivery of drugs to the skin via microneedles in combination with carriers and/or enhancers

S.N.	Type of microneedle	Enhancer	Carrier	Drug	Model	Result
1	Coated microneedles [2]	---------	1-µm diameter barium sulfate particles and 10-µm diameter latex particles	--------	Porcine cadaver skin, in vitro	Relatively large microparticles can be delivered into the skin for controlled drug release using appropriate microneedle design and insertion methods
2	Solid stainless microneedle arrays [12]	Iontophoresis (0.2 mA/cm^2)	Nanovesicles	Insulin	Pig skin, in vitro Rats, in vivo	Combination approach of microneedles and iontophoresis showed significant increase in the permeation of charged nanovesicles. Comparable levels to subcutaneous injection of insulin was achieved
3	Beveled-tip and tapered-cone biodegradable polymeric microneedles[58]	----------	carboxymethylcellulose or poly-L: -lactide microparticles	Calcein and bovine serum albumin	Human cadaver skin and test in saline, in vitro	Microneedles capable of encapsulating drug and providing controlled-release delivery in skin for hours to months.
4	Macroflux® titanium or stainless Steel microprojection Array [64]	Iontophoresis (100 µA/cm^2)	------	Oligodeoxynucleotide ISIS 2302 (ODNs)	Hairless guinea pigs, in vivo	Delivering ODNs into and through the skin in therapeutically relevant amounts
5	Maltose microneedles[66]	Iontophoresis (0.2 mA/cm^2 for 1 hr)	--------	Salmon Calcitonin (SCT)	Hairless rat skin, in vivo	Transdermal delivery of SCT was achieved with highest delivery

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						flux.
6	Maltose Microneedles[67]	Iontophoresis (0.5 mA/cm^2)	-------	Daniplestim	Hairless rat skin, in vivo	The combination approach yielded much higher flux values of daniplestim compared to iontophoresis alone
7	Maltose microneedles[68]	Iontophoresis (0.1 mA/cm^2 for 4 hrs)	------	Leuprolide acetate	Hairless rats, in vivo	The combination approach yielded much faster and higher flux values of leuprolide acetate compared to iontophoresis and microneedles alone respectively
8	Microneedle Array [73]	-------	Elastic liposomes	Docetaxel (DTX)	Rat skin, in vitro Porcine skin, in vitro	Microneedle treatment led to increased steady-state flux of DTX from all formulations and shorter lag time when applying elastic liposomes through microneedle
9	Maltose Microneedles [75]	Iontophoresis (0.4 mA/cm^2 for 1 hr)	--------	Methotrexate	Hairless rat skin, in vitro and in vivo	Enhanced transdermal delivery of methotrexate both in vitro and in vivo.
10	Dermaroller® [76]	Iontophoresis (0.4 mA/cm^2)	------	prochlorperazine edisylate	dermatomed human skin, in vitro	Significantly enhanced the transdermal delivery of prochlorperazine edisylate
11	AdminPatch®[78]	Iontophoresis	-------	Ropinirole hydrochloride	Porcine ear skin, in vitro	Continuous iontophoresis in combination with microneedles showed enhanced reflux of Ropinirole hydrochloride
12	Dermarollers®[83]	----------	Invasomes	Mannitol	Human abdominal skin, in vitro	Enhanced penetration and permeation of hydrophilic model drugs due to skin perforation by Dermarollers® particularly when combined with invasosome formulation.
13	Microneedle roller [85]	Sonophoresis	-------	Glycerol	Porcine skin, in vitro	The combination method effectively enhanced transdermal delivery of glycerol by accelerating the diffusion rate through the skin barrier.
14	Silicon microneedleelectrode array[126]	Electroporation	-------	Fluorescein isothiocyanate (FITC)-dextran	Male hairless rats, in vivo	Enhanced permeation of FITC-dextran observed as a synergistic effect of the

						combination approach
15	Hollow microneedles[127]	Vibratory actuation	-------	-------	Excised animal skin, in vitro	Greater than 70% reduction in microneedle insertion force by using vibratory actuation
16	Pocketed solid stainless steel microneedle[130]	----------	---------	Sulforhodamine, sodium fluorescein, luciferase plasmid DNA, vit B2	Abdominal porcine cadaver skin, in vitro	Rapid release of the model drugs at a targeted depth in the skin.
17	Grooves-embedded microneedle arrays of poly-L-lactic acid [131]	----------	-------	Ovalbumin	Mice, in vivo	Microneedles coated with ovalbumin render higher antibody response as the number and depth of grooves increase
18	Maltose Microneedles[132]	Iontophoresis (0.5 mA/cm^2)	------	Low mol. wt heparin (LMWH)	Hairless rat skin, in vitro	Increased skin permeation of LMWH
19	Microneedle Array [133]	Iontophoresis (0.3 mA/cm^2)	------	FITC-dextrans	Hairless rat skin, in vitro	Enhanced transdermal delivery of dextrans
20	Silicon and glass hollow microneedle array [134]	Sonophoresis	--------	Calcein and bovine serum albumin (BSA)	Pig skin, in vitro	In vitro results showed a significant improvement in the delivery rate even when large molecular weight compounds were used.
21	Stainless steel & silicon solid microneedles[135]	Sonophoresis	--------	FITC-dextrans	excised porcine skin, in vitro	Significantly increased skin permeation of FITC-dextrans.
22	Stainless steel solid microneedles [136]	Sonophoresis	Cross-linked hydrogelof NaCMC and gel emulsion	Lidocaine	Porcine skin, in vitro	Slight increase in the permeability of lidocaine due to the combination approach.
23	Dissolving microneedles[137]	Electroporation	-------	p2CMVmIL-12	Mice, in vivo	in-situ cutaneous transfer of p2CMVmIL-12 to successfully treat B16F10 subcutaneous tumors
24	Silicon microneedle electrode arrays [138]	Electroporation	-------	-------	--------	A uniform drug release through hollow microneedle electrodes into tissue is expected to be achieved during electroporation.
25	Coated microneedle array [139]	Electroporation	-------	Plasmid DNA	Mice, in vivo	Robust antibody responses.
26	Solid microneedles[140]	--------	L595 vesicles (composed of sucrose-laurate ester & octaoxyethylene -laurate ester) and sPC	hepatitis B surface antigen (HBsAg)	Mice, in vivo	Successful transcutaneous immunization (TCI) of hepatitis B surface antigen (HBsAg)

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			vesicles (composed of soybean–phosphatidylcholine and Span-80)			
27	Solid microneedles[141]	-------	anionic surfactant-based vesicles	diphtheria toxoid	BALB/c mice, in vivo	Enhancement in the immunogenicity of topically applied diphtheria toxin due to microneedle pretreatment
28	Dermaroller® [142]	--------	liposomes	--------	Human skin, iv vitro	Evaluation of potential of Dermaroller®, with different needle geometries, to deliver a lipophilic fluorescent compound encapsulated in liposomes across the human skin
29	Nanopore turbo roller [143]	--------	nanoliposomes	sepia melanin	Human skin, iv vitro	Accelerates the delivery of melanin into hair structures allowing an even absorption, larger pigment deposits, and deeper penetration of the formulation into the hair.
30	Silicon microneedle arrays [144]	--------	Polystyrene nanospheres	-------	Human skin, iv vitro	Potential for significant enhancement the intra/transdermal delivery of nanoparticle formulations.
31	Solid silicon microneedle arrays [145]	---------	poly(d,l-lactic-co-glycolic acid) (PLGA) nanoparticles	-------	Human skin, iv vitro	Permeation of nanoparticles into the skin was enhanced by microneedles
32	Microneedle arrays [146]	--------	Microparticles	Gene	--------	Microneedles increase the penetration depths of the particles.
33	Hollow microneedle [147]	--------	nanoparticle and microparticle suspensions	-------	whole rabbit, pig, and human eyes ex vivo	Microneedles were shown for the first time to deliver nanoparticle and microparticle suspensions into the suprachoroidal space of rabbit, pig and human eyes.
34	Solid silicon microneedle Arrays [148]	----------	Polystyrene latex nanospheres	---------	Human cadaver epidermis, in vitro	A significant number of latex nanoparticles cross the skin.
35	Silicon microneedle arrays [149]	----------	Fluorescent latex nanospheres	----------	Human skin, in vitro	Topical application of nanospheres followed by the microneedle treatment resulted in the migration of the

						charged fluorescent particles into the microchannels, & to the cells of the viable epidermis
36	Silicon-based Microneedles[150]	----------	Fluorescent polystyrene nanospheres	Lipid: polycation : pDNA (LPD) nonviral gene therapy vectors.	Heat-separated human epidermal sheets, in vitro	Microneedle membrane treatment resulted in enhanced diffusion of fluorescent polystyrene nanospheres
37	Silicon Microneedles[151]	----------	Hydrogel / Fluorescent Nanoparticle Loaded	---------	Human skin, in vitro	Microneedle treatment resulted in successful targeting of nanoparticles within the viable epidermis
38	Hollow Microneedles[152]	----------	Nanospheres of PLA with Nile red and latex fluorescein labeled microspheres	---------	Human corpse sclera, in vitro	Successful delivery of soluble molecules and nanoparticle Suspensions into the sclera.
39	Pocketed stainless steel microneedles[153]	----------	---------	Botulinum toxin A (BT)	Excised human skin, in vitro	Microneedles provide less invasive alternative that is suited to delivery of large proteins such as BT. Microneedles were not only able to accommodate therapeutic doses of a model protein but they were also able to deliver an inactivated form of the toxin into human skin.
40	Coated microneedles[154]	----------	Poly(lactic-co-glycolic) acid (PLGA) nanoparticles	Doxorubicin	porcine cadaver buccal tissues, in vitro	Coated microneedles provide uniform and effective delivery of drugs to localized oral cancers.
41	Silicon microneedles[155]	----------	Hypoxia-sensitive hyaluronic acid-based vesicles	Insulin	Mice, in vivo	Glucose responsive vesicles loaded microneedles provided convenient, painless, and continuous administration of insulin. They were found to be responsive to glucose challenge and also efficiently minimized the risk of hypoglycemia in the in vivo glucose tolerance test.

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42	Silicon microneedles[156]	----------	Lipid microparticles	Quercetin	Pig skin, in vitro	Compared to intact skin, a marked increase in quercetin levels permeated into the stratum corneum and viable epidermis was achieved when skin was treated with the flavonoid-loaded LMs in combination with microneedle arrays
43	Solid silicon microneedles[157]	----------	Poly-D, L-lactic acid (PDLLA) nanoparticles	Ketoprofen	Porcine skin, in vitro	An enhanced flux of ketoprofen was observed in the skin treated with silicon microneedles over a prolonged period of time.

CONCLUSION

Various research studies carried out on microneedles are evident enough to state that microneedles are the efficient and potential transdermal delivery systems. They have been gaining a lot of importance due to their key advantages over the conventional delivery systems of being safe, convenient and painless. Microneedles have proved to be the solution for overcoming the barrier imposed by the stratum corneum, thus broadening the number of drugs and other molecules to be administered by this route. Extensive work has been carried out to create advances and to explore the wide applications of microneedles. Apart from playing the vital role in transportation of numerous drug molecules including poorly permeable ones, macromolecules and biopharmaceuticals, microneedles have also been applied in phlebotomy, diagnosis and cosmeceuticals. Numerous studies have been performed and reported on the synergistic effect of combining microneedles with other techniques for enhanced drug delivery such as sonophoresis, electroporation, iontophoresis, vibratory actuation etc. and have turn out to be beneficial in efficient transportation of drug and other macromolecules across the skin. Conjugating microneedles with carriers such as vesicles, nanoparticles, microparticles etc. allows achieving a controlled delivery of drug molecules. Precise drug delivery has been possible by employing microneedles in combination of micro pumps while greater amount of drug can be delivered by loading into the pocketed and grooved microneedles. Thus it was concluded that microneedles are more efficient as compared to the hypodermic needles and the other conventional delivery systems.

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REFERENCES

1. Langer R, Drug delivery. Drugs on target, Science, 2001, 293(5527), 58–59.
2. Gill HS, Prausnitz MR, Coated microneedles for transdermal delivery, Journal of Control Release, 2007, 117(2), 227–237.
3. Xie Y, Xu B, Gao Y, Controlled transdermal delivery of model drug compounds by MEMS microneedle array, Nanomedicine, 2005, 1(2), 184– 190.
4. Avis KE Lieberman HA, Lachman L. Pharmaceutical Dosage Forms: Parenteral Modifications. 2nd ed. New York: Marcel Dekker Inc; 1992.
5. Bora P, Kumar L, Arvind K, Bansal AK, Microneedle technology for advanced drug delivery: Evolving vistas, Current Research & Information on Pharmaceutical Sciences (CRIPS), 2008, 9(1), 7-10.
6. Henry S, McAllister D, Allen MG, Prausnitz MR, Microfabricated microneedles, Journal of Pharmaceutical Sciences, 1998, 87(8), 922–925.
7. Bonilla MD, Molina TE, Microneedle: A valuable physical enhancer to increase transdermal drug delivery, Journal of Clinical Pharmacology, 2011, 51(7), 964-977.
8. Gupta J, Gill HS, Andrews SN, Prausnitz MR, Kinetics of skin resealing after insertion of microneedles in human subjects, Journal of Control Release, 2011, 154(2), 148–155.
9. Haq MI, Smith E, John DN, Kalavala M, Edwards C, Anstey A, Morrissey A, Birchall JC, Clinical administration of microneedles: skin puncture, pain and sensation, Biomedical Microdevices, 2009, 11(1), 35–47.
10. Burton SA, , Ng CY, Simmers R, Moeckly C, Brandwein D, Gilbert T, Johnson N, Brown K, Alston T, Prochnow G, Siebenaler K, Hansen K, Rapid intradermal delivery of liquid formulations using a hollow microstructured array, Pharmaceutical Research, 2011, 28(1), 31–40.
11. Arora A, Prausnitz MR, Mitragotri S, Micro-scale devices for transdermal drug delivery, International Journal of Pharmaceutics, 2008, 364(2), 227-236.

12. Chen H, Zhu H, Zheng J, Mou D, Wan J, Zhang J, Shi T, Zhao Y, Xu H, Yang X, Iontophoresis-driven penetration of nanovesicles through microneedle-induced skin microchannels for enhancing transdermal delivery of insulin, Journal of Control Release, 2009, 139(1), 63-72.
13. Widera G, Johnson J, Kim L, Libiran L, Nyam K, Daddona PE, Cormier M, Effect of delivery parameters on immunization to ovalbumin following intracutaneous administration by a coated microneedle array patch system, Vaccine, 2006, 24(10), 1653–1664.
14. Ashraf MW Tayyaba S, Nisar A, Afzulpurkar N, Bodhale DW, Lomas T, Poyai A, Tuantranont A, Design, fabrication and analysis of silicon hollow microneedles for transdermal drug delivery system for treatment of hemodynamic dysfunctions, Cardiovascular Engineering, 2010, 10(3), 91–108.
15. Park JH, Allen MG, Prausnitz MR, Biodegradable polymer microneedles: fabrication, mechanics and transdermal drug delivery, Journal of Control Release 2005, 104(1), 51–66.
16. Jin CY, Han MH, Lee SS, Choi YH, Mass producible and biocompatible microneedle patch and functional verification of its usefulness for transdermal drug delivery, Biomedical Microdevices, 2009, 11(6), 1195–1203.
17. Ji J, Tay FEH, Miao J, Iliescu C, Microfabricated microneedle with porous tip for drug delivery, Journal of Micromechanics and Microengineering, 2005, 16(5), 958–964.
18. Donnelly RF, Majithiya R, Singh TR, Morrow DI, Garland MJ, Demir YK, Migalska K, Ryan E, Gillen D, Scott CJ, Woolfson AD, Design, optimization and characterisation of polymeric microneedle arrays prepared by a novel laser-based micromoulding technique, Pharmaceutical Research, 2011, 28(1), 41–57.
19. You SK, Noh YW, Park HH, Han M, Lee SS, Shin SC, Cho CW, Effect of applying modes of the polymer microneedle roller on the permeation of L-ascorbic acid in rats, Journal of Drug Targeting, 2010, 18(1), 15–20.
20. Lee JW, Park JH, Prausnitz MR, Dissolving microneedles for transdermal drug delivery, Biomaterials, 2008, 29(13), 2113–2124.
21. Li G Badkar A, Nema S, Kolli CS, Banga AK, In vitro transdermal delivery of therapeutic antibodies using maltose microneedles. International Journal of Pharmaceutics, 2009, 368(1-2), 109–115.
22. Ito Y, Murakami A, Maeda T, Sugioka N, Takada K, Evaluation of selfdissolving needles containing low molecular weight heparin (LMWH) in rats. International Journal of Pharmaceutics, 2008, 349(1-2), 124-129.
23. Hirschberg HJ, Van de Wijdeven GG, Kelder AB, Van den Dobbelsteen GP, Kersten GF, Bioneedles as vaccine carriers, Vaccine, 2008, 26(19), 2389–2397.
24. Bagga M, Kumar R, Silpi C, Microneedle in transdermal drug delivery: An unique painless option, International Journal of Pharmaceutics, 2011, 2(4), 72-78
25. Kumar SL, Singh V, Nanoemulsification-a novel targeted drug delivery tool, Journal of Drug Delivery and Therapeutics' 2012; 2(4):40-45
26. Morrow DIJ, McCarron PA, Woolfron AD, Donnelly RF, Innovative strategies for enhancing topical and transdermal drug delivery, Open Drug Delivery Journal, 2007, 1, 36-59.
27. Gill HS, Prausnitz MR, Coating formulations for microneedles, Pharmaceutical Research, 2007, 24(7), 1369–1380.
28. Kumar V, Kulkarni P, Raut R, Microneedle: Promising technique for transdermal drug delivery, International Journal of Pharma and Biosciences, 2011, 2(1), 684-708.
29. Vandervoort J, Ludig A, Microneedles for transdermal drug delivery: a mini review, Frontiers in Bioscience, 2008, 1(13), 1711-1715.
30. Suner S, Fellows MR, Vargas-Irwin C, Nakata GK, Donoghue JP, Reliability of signals from a chronically implanted, silicon-based electrode array in non-human primate primary motor cortex, IEEE Transactions on Neural Systems and Rehabilitation Engineering, 2005, 13(4), 524–541.
31. Donnelly RF, Singh TR, Alkilani AZ, McCrudden MT, O'Neill S, O'Mahony C, Armstrong K, McLoone N, Kole P, Woolfson AD, Hydrogel-forming microneedle arrays exhibit antimicrobial properties: potential for enhanced patient safety, International Journal of Pharmaceutics, 2013, 451(1–2), 76–91.
32. Donnelly RF, Singh TRR, Garland MJ, Migalska K, Majithiya R, McCrudden CM, Kole PL, Mahmood TM, McCarthy HO, Woolfson AD, Hydrogel-forming microneedle arrays for enhanced transdermal drug delivery, Advanced Functional Materials, 2012, 22(23), 4879–4890.
33. Donnelly RF, McCrudden MTC, Zaid Alkilani A, Larrañeta E, McAlister E, Courtenay AJ, Kearney MC, Singh TR, McCarthy HO, Kett VL, Caffarel-Salvador E, Al-Zahrani S, Woolfson AD, Hydrogel-forming microneedles prepared from "Super Swelling" polymers combined with lyophilised wafers for transdermal drug delivery, PLoS One, 2014, 9(10), e111547.
34. Larrañeta E, Lutton REM, Brady AJ, Vicente-Pérez EM, Woolfson AD, Thakur RRS, Donnelly RF, Microwave-assisted preparation of hydrogel-forming microneedle arrays for transdermal drug delivery applications, Macromolecular Materials and Engineering, 2015, 300(6), 586–595.
35. Kumar S, Proniosomal gel of flurbiprofen: formulation and evaluation, Journal of Drug Delivery and Therapeutics, 2012; 2(1):1-5
36. Donnelly RF, Morrow DI, McCrudden MT, Alkilani AZ, Vicente-Pérez EM, O'Mahony C, González-Vázquez P, McCarron PA, Woolfson AD, Hydrogel-forming and dissolving microneedles for enhanced delivery of photosensitizers and precursors, Photochemistry and Photobiology, 2014, 90(3), 641–647.
37. Tripathy S, Patel DK, Barob L, Naira SK, A review on phytosomes, their characterization, advancement & potential for transdermal application, Journal of Drug Delivery and Therapeutics, 2013; 3(3):147-152
38. Caffarel-Salvador E, Brady AJ , Eltayib E, Meng T, Alonso-Vicente A, Gonzalez-Vazquez P, Torrisi BM, Vicente-Perez EM, Mooney K, Jones DS, Bell SEJ, McCoy CP, McCarthy H, McElnay JC, Donnelly RF, Hydrogel-forming microneedle arrays allow detection of drugs and glucose in vivo: potential for use in diagnosis and therapeutic drug monitoring, 2015, PLoS ONE 10(12): e0145644.
39. Prausnitz MR, Microneedles for transdermal drug delivery, Advanced Drug Delivery Reviews, 2004, 56(5), 581-587.
40. Wang PM, Cornwell M, Prausnitz MR, Minimally invasive extraction of dermal interstitial fluid for glucose monitoring using microneedles, Diabetes Technol Ther, 2005, 7(1), 131–141.
41. Milewski M, Brogden NK, Stinchcomb AL, Current aspects of formulation efforts and pore lifetime related to microneedle treatment of skin, Expert Opinion on Drug Delivery, 2010, 7(5), 617–629.
42. Jagannathan S, Dawood CS, Rajesh K, Ayyappan SR, A novel approach in delivering immunobiologicals : a glimpse, Advanced Biotech, 2009, 5, 22–31.
43. Carstens MG, Opportunities and challenges in vaccine delivery, European Journal of Pharmaceutical Sciences, 2009, 36(4-5), 605–608.
44. Kim YC, Quan FS, Compans RW, Kang SM, Prausnitz MR, Formulation and coating of microneedles with inactivated influenza virus to improve vaccine stability and immunogenicity, Journal of Control Release, 2010, 142(2), 187–195.
45. Hirschberg HJ, van de Wijdeven GG, Kraan H, Amorij JP, Kersten GF, Bioneedles as alternative delivery system for hepatitis B vaccine, Journal of Control Release, 2010, 147(2), 211–217.
46. Corbett HJ, Fernando GJP, Chen XF, Frazer IH, Kendall MAF, Skin vaccination against cervical cancer associated human papillomavirus with a novel micro-projection array in a mouse model, PLoS One, 2010, 5(10): e13460.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

47. Prow TW, Chen X, Prow NA, Fernando GJ, Tan CS, Raphael AP, Chang D, Ruutu MP, Jenkins DW, Pyke A, Crichton ML, Raphaelli K, Goh LY, Frazer IH, Roberts MS, Gardner J, Khromykh AA, Suhrbier A, Hall RA, Kendall MA, Nanopatch-targeted skin vaccination against West Nile virus and Chikungunya virus in mice, Small, 2010, 6(16), 1776–1784.
48. Chen XF, Kask AS, Crichton ML, McNeilly C, Yukiko S, Dong LC, Marshak JO, Jarrahian C, Fernando GJP, Chen DX, Koelle DM, Kendall MAF, Improved DNA vaccination by skin targeted delivery using dry-coated densely-packed microprojection arrays, Journal of Control Release, 2010 148(3), 327–333.
49. Kask AS, Chen X, Marshak JO, Dong L, Saracino M, Chen D, Jarrahian C, Kendall MA, Koelle DM, DNA vaccine delivery by densely-packed and short microprojection arrays to skin protects against vaginal HSV-2 challenge, Vaccine, 2010, 28(47), 7483–7491.
50. Hiraishi Y, Nandakumar S, Choi SO, Lee JW, Kim YC, Posey JE, Sable SB, Prausnitz MR, Bacillus Calmette-Guerin vaccination using a microneedle patch, Vaccine, 2011. 29(14), 2626–2636.
51. Matriano JA, Macroflux® microprojection array patch technology: a new and efficient approach for intracutaneous immunization, Pharmaceutical Research, 2002, 19, 63–70.
52. Dean C, Alarcon HJ, Waterston BA, Draper MK, Early R, Guirakhoo F, Monath T, Mikszta PJA, Cutaneous delivery of a live, attenuated chimeric flavivirus vaccine against Japanese encephalitis (ChimeriVax)-JE) in non-human primates, Human vaccines, 2005, 1(3), 106–111.
53. Matsuo K, Hirobe S, Yokota Y , Ayabe Y, Seto M, Quan Ying-Shu, Kamiyama F, Tougan T, Horii T, Mukai Y ,Okada N, Nakagawa S, Transcutaneous immunization using a dissolving microneedle array protects against tetanus, diphtheria, malaria, and influenza, Journal of Control Release, 2012, 160(3), 495–501.
54. Morefield GL, Tammariello RF, Purcell BK, Worsham PL, Chapman J, Smith LA, Alarcon JB, Mikszta JA, Ulrich RG, An alternative approach to combination vaccines: intradermal administration of isolated components for control of anthrax, botulism, plague and staphylococcal toxic shock, Journal of Immune Based Therapies and Vaccines, 2008, 6(5), 1–11.
55. Verbaan FJ, Bal SM, van den Berg DJ, Groenink WH, Verpoorten H, Lüttge R, Bouwstra JA, Assembled microneedle arrays enhance the transport of compounds varying over a large range of molecular weight across human dermatomed skin, Journal of Control Release, 2007, 117(2), 238–245.
56. Martanto W, Davis SP, Holiday NR, Wang J, Gill HS, Prausnitz MR, Transdermal delivery of insulin using microneedles in vivo, Pharmaceutical Research, 2004, 21(6), 947–952.
57. Zhang S, Qin G, Wu Y, Gao Y, Qiu Y, Li F, Xu B, Enhanced bioavailability of L-carnitine after painless intradermal delivery vs. Oral administration in rats, Pharmaceutical Research, 2011, 28(1), 117–123.
58. Park JH, Allen MG, Prausnitz MR, Polymer microneedles for controlled-release drug delivery, Pharmaceutical Research, 2006, 23(5), 1008–1019.
59. Cormier M, Johnson B, Ameri M, Nyam K, Libiran L, Zhang DD, Daddona P, Transdermal delivery of desmopressin using a coated microneedle array patch system, Journal of Control Release, 2004, 97(3), 503–511.
60. Fukushima K, Ise A, Morita H, Hasegawa R, Ito Y, Sugioka N, Takada K, Two-layered dissolving microneedles for percutaneous delivery of peptide/protein drugs in rats, Pharmaceutical Research, 2011, 28(1), 7–21.
61. Häfeli UO, Mokhtari A, Liepmann D, Stoeber B, In vivo evaluation of a microneedle-based miniature syringe for intradermal drug delivery, Biomedical Microdevices, 2009, 11(5), 943–950.
62. Oh J, Park H, Do K, Han M, Hyun D, Kim CG, Kim CH, Lee S, Hwang S, Shin S, Cho C , Influence of the delivery systems using a microneedle array on the permeation of a hydrophilic molecule, calcein, European Journal of Pharmaceutics and Biopharmaceutics, 2008, 69(3), 1040–1045.
63. Ito Y, Yoshimitsu J, Shiroyama K, Sugioka N, Takada K, Self-dissolving microneedles for the percutaneous absorption of EPO in mice, Journal of Drug Targeting, 2006, 14(5), 255–261.
64. Lin W, Cornier M, Samiee A, Griffin A, Johnson B, Teng C, Hardee GE, Daddona P, Transdermal delivery of antisense oligonucleotides with microprojection patch (Macroflux) technology, Pharmaceutical Research, 2001, 18(2), 1789-1793.
65. Donnelly RF, Morrow DIJ, McCarron PA, Woolfson AD, Morrissey A, Juzenas P, Juzeniene A, Lani V, McCarthy HO, Moan J, Microneedle-mediated intradermal delivery of 5-aminolevulinic acid: Potential for enhanced topical photodynamic therapy, Journal of Control Release, 2008, 129(3), 154-162.
66. Vemulapalli V, Bai Y, Kalluri H, Herwadkar A, Kim H, Davis SP, Friden PM, Banga AK, In vivo iontophoretic delivery of salmon calcitonin across microporated skin, Journal of Pharmaceutical Sciences, 2012, 101(8), 2861-2869.
67. Katikaneni S, Badkar A, Nema S, Bang, AK, Molecular charge mediated transport of a 13 kD protein across microporated skin, International Journal of Pharmaceutics, 2009, 378(1-2), 93-100.
68. Sachdeva V, Zhou Y, Banga AK, In vivo Transdermal delivery of leuprolide using Microneedles and Iontophoresis, Current pharmaceutical Biotechnology, 2012, 14(2), 180-193.
69. Ameri M, Fan SC, Maa YF, Parathyroid hormone PTH(1-34) formulation that enables uniform coating on a novel transdermal microprojection delivery system, Pharmaceutical Research, 2010, 27(2), 303–313.
70. Cormier M, Daddona PE, Macroflux technology for transdermal delivery of therapeutic proteins and vaccines. In Rathbone MJ, Hadgraft J, Roberts MS editors, Modified-Release Drug Delivery Technology. New York: Marcel Dekker; 2003.
71. Li WZ, Huo MR, Zhou JP, Zhou YQ, Hao BH, Liu T, Zhang Y, Super-short solid microneedles for transdermal drug delivery application, International Journal of Pharmaceutics, 2010, 389(1-2), 122–129.
72. Park JH, Choi SO, Seo S, Choy YB, Prausnitz MR, A microneedle roller for transdermal drug delivery. European Journal of Pharmaceutics and Biopharmaceutics, 2010, 76, 282–289.
73. Qiu Y, Gao Y, Hu K, Li F, Enhancement of skin permeation of docetaxel: a novel approach combining microneedle and elastic liposomes, Journal of Control Release, 2008, 129(2), 144–150.
74. Jiang J Jiang J, Gill HS, Ghate D, McCarey BE, Patel SR, Edelhauser HF, Prausnitz MR, Coated microneedles for drug delivery to the eye, Investigative Ophthalmology and Visual Science, 2007, 48(9), 4038–4043.
75. Vemulapalli V, Yang Y, Friden PM, Banga AK, Synergistic effect of iontophoresis and soluble microneedles for transdermal delivery of methotrexate, Journal of Pharmacy and Pharmacology, 2008, 60(1), 27–33.
76. Kolli CS, Xiao J, Parsons DL, Jayachandra BR, Microneedle assisted Iontophoretic transdermal delivery of prochlorperazine edisylate, Drug development and Industrial pharmacy, 201, 38(5), 571-576.
77. Duan D, Moeckly C, Gysbers J, Novak C, Prochnow G, Siebender K, Albers L, Hansen K, Enhanced delivery of topically-applied formulations following skin pre treatment with a hand-applied, plastic microneedle array, Current Drug Delivery, 2013, 8(5), 557-565.
78. Singh ND, Banga AK, Controlled delivery of ropinirole hydrochloride through skin using modulated iontophoresis and microneedles, Journal of Drug and Targeting, 2013, 21(4), 354-366.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

79. So JW, Park HH, Lee SS, Kim DC, Shin SC, Cho CW, Effect of microneedle on the pharmacokinetics of ketoprofen from its transdermal formulations, Drug Delivery, 2009, 16(1), 52–56.
80. Ghosh P, Pinninti RR, Hammell DC, Paudel KS, Stinchcomb AL, Development of a co drug approach for sustained drug delivery across microneedles-treatment skin, Journal of Pharmaceutical Sciences, 2013, 102(5), 1458-1467.
81. Back C, Han M, Min J, Prausnitz MR, Park JH Local transdermal delivery of phenylephrine to the anal sphincter muscle using microneedles Journal of Control Release, 2011, 154(2), 138-147.
82. Wermeling DP, Banks SL, Hudson DA, Gupta J, Prausnitz MR, Stinchcomb AL. Microneedles permit transdermal delivery of a skin-impermeant medication to humans, Proceedings of National Academy of Sciences, USA 2008, 105(6), 2058-2063.
83. Badran MM, Kuntsche J, Fahr A, Skin penetration enhancement by a microneedle device (Dermaroller®) in vitro: Dependency on needle size and applied formulation, European Journal of Pharmaceutics and Biopharmaceutics, 2009, 36(4-5), 511–523.
84. Yoon J, Park D, Son J, Seo J, Stuart J, Jung NB, A physical method to enhance transdermal delivery of a tissue optical clearing agent: Combination of microneedling and sonophoresis, Lasers in Surgery and Medicines, 2010, 42(5), 412-417.
85. Phlebotomy, The Internet Pathology Laboratory for Medical Education, Mercer University School of Medi- cine, USA. http://library.med.utah.edu/WebPath/TUTORIAL/PHLEB/PHLEB.html (accessed 11 July 2011).
86. Capillary sample, Mediline Plus, National Institute of Health. http:// www.nlm.nih.gov/medlineplus/ency/ article/003427.htm (accessed 11 July 2011).
87. Smart WH, Subramanian K, The use of silicon microfabrication technology in painless blood glucose monitoring, Diabetes Technology and Therapeutics, 2000, 2(4), 549–559.
88. Yuzhakov VV, Tissue conforming microneedle array and patch for transdermal drug delivery and biological fluid collection, United States Patent, 2010, US7, 785, 301 B2.
89. Oka K, Aoyagi S, Arai Y, Isono Y, Hashiguchi G, Fujita H, Fabrication of a micro needle for a trace blood test, Sensors and Actuators A: Physical, 2002, 97-98, 478–485.
90. Mukerjee EV, Collins SD, Isseroff RR, Smith RL, Microneedle array for transdermal biological fluid extraction and in situ analysis, Sensors and Actuators A: Physical, 2004, 114(2-3), 267–275.
91. Microneedle, quantum dot study opens door to new clinical cancer tools, North Carolina State University, USA, 2010. http://www.physorg.com/ news201950905.html (accessed 30 August 2010).
92. Magnetic nanoparticles and microneedle tip that collect biomarkers for safe early- stage arthritis diagnosis and monitoring, Office of technology licensing, University of Florida, http://technologylicensing.research.ufl.edu/technologies/14237_magnetic-nanoparticles-and-microneedle-tip-that-collect-biomarkers-for-safe-early-stage-arthritis-diagnosis-and-monitoring
93. Dardano P, Calio A, Politi J, Stefano L, Hybrid microneedles devices for diagnostic and therapeutic applications: Fabrication & preliminary results, Proceedings of SPIE, Bio-MEMS and Medical Microdevices, 9518, 2015, doi: 10.1117/12.2178919
94. Keum DH, Jung HS, Wang T, Shin MH, Kim Y, Kim K, Ahn G, Hahn SK, Microneedle Biosensor for Real-time Electrical detection of nitric oxide for insitu Cancer diagnosis During Endomicroscopy, Advanced Healthcare Materials, 2015, 4, 1153-1158.
95. Windmiller JR, Zhou ND, Chuang MC, Valdes-Ramirez G, Santhosh P, Miller PR, Narayan R, Wang J, Microneedle array-based carbon paste amperometric sensors and biosensors, Analyst, 2011, 136(9), 1846–1851.
96. Lee JH, Seo Y, Lim TS, Bishop PL, Papautsky I, MEMS needle-type sensor array for in situ measurements of dissolved oxygen and redox potential, Environmental Science and Technology, 2007, 41(22), 7857–7863.
97. Wassum KM, Tolosa VM, Wang J, Walker E, Monbouquette HG, Maidment NT, Silicon wafer based platinum microelectrode array biosensor for near real-time measurement of glutamate in vivo, Sensors, 2008, 8(8), 5023–5036.
98. Bai Q, Wise KD, Anderson DJ, A high-yield microassembly structure for three-dimensional microelectrode arrays, IEEE Transactions on Biomedical Engineering, 2000, 47(3), 281–289.
99. Chen CH, Yao DJ, Tseng SH, Lu SW, Chiao CC, Yeh SR, Micro-multi-probe electrode array to measure neural signals, Biosensors and Bioelectronics, 2009, 24(7), 1911–1917.
100. Hoogerwerf AC, Wise KD, A three-dimensional microelectrode array for chronic neural recording, IEEE Transactions on Biomedical Engineering, 1994, 41(12), 1136–1146.
101. Normann RA, Maynard EM, Rousche PJ, Warren DJ, A neural interface for acortical vision prosthesis, Vision Research, 1999, 39(15), 2577–2587.
102. Rajaraman S, Bragg JA, Ross JD, Allen MG, Micromachined three-dimensional electrode arrays for transcutaneous nerve tracking, Journal of Micromechanics and Microengineering, 2011, 21(8), 085014.
103. Rajaraman S, Choi S-O, McClain MA, Ross JD, LaPlaca MC, Allen MG, Metal-Transfer- Micromolded Three-Dimensional Microelectrode Arrays for in-vitro Brain-Slice Recordings, Journal of Microelectromechanical Systems, 2011, 20(2), 396–409.
104. Rousche PJ, Pellinen DS, Pivin DP, Williams JC, Vetter RJ, Kipke DR, Flexible polyimide-based intracortical electrode arrays with bioactive capability, IEEE Trans Biomedical Engineering, 2001, 48(3), 361–371.
105. Vetter RJ, Williams JC, Hetke JF, Nunamaker EA, Kipke DR, Chronic neural recording using silicon-substrate microelectrode arrays implanted in cerebral cortex, IEEE Transactions on Biomedical Engineering, 2004, 51(6), 896–904.
106. Wise KD, Sodagar AM, Yao Y, Gulari MN, Perlin GE, Najafi K, Microelectrodes, microelectronics, and implantable neural microsystems, Proceedings of the IEEE, 2008, 96(7), 1184–1202.
107. Yu LM, Tay FEH, Guo DG, Xu L, Yap KL, A microfabricated electrode with hollow microneedles for ECG measurement, Sensors and Actuators A: Physical, 2009, 151(1), 17–22.
108. Griss P, Tolvanen-Laakso HK, Merilainen P, Stemme G, Characterization of micromachined spiked biopotential electrodes, IEEE Transactions on Biomedical Engineering, 2002, 49(6), 597–604.
109. Griss P, Enoksson P, Tolvanen-Laakso H, Merilainen P, Ollmar S, and Stemme G, Micromachined electrodes for biopotential measurements, IEEE ASME Journal of Microelectromechanical Systems, 2001, 10(1), 6-10.
110. Doddaballapur S, Microneedling with Dermaroller, Journal of Cutaneous and Aesthetic Surgery, 2009, 2(2), 110–111.
111. Park Y, Park J, Chu GS, Kim KS, Sung JH, Kim B, Transdermal delivery of cosmetic ingredients using dissolving polymer microneedle arrays, Biotechnology and Bioprocess Engineering, 2015, 20(3), 543-549.
112. How does 'Microneedle Therapy System' work? Clinical Resolution Laboratory, Inc., USA. http://www. microneedle.com/main/whatismts. Html
113. Kim M, Yang H, Kim H, Jung H, Jung H, Novel cosmetic patches for wrinkle improvement: retinyl retinoate- and ascorbic acid-loaded dissolving microneedles, International Journal of Cosmetic Science, 2014, 36(3), 207-212.
114. Kumar A, Naguib YW, Shi YC, Cui Z, A method to improve the efficacy of topical eflornithine hydrochloride cream, Drug Delivery, 2016, 23(5), 1495-1501.

 ISSN: 2250-1177 CODEN (USA): JDDTAO

115. Chandrashekar BS, Nandini AS, Acne Scar Subcision, Journal of Cutaneous and Aesthetic Surgery, 2010, 3(2), 125–126.
116. Park KY, Kim HK, Kim SE, Kim BJ, Kim MN, Treatment of striae distensae using needling therapy: a pilot study, Dermatologic Surgery, 2012, 38(11), 1823-1828.
117. Fabbrocini G, Fardella N, Monfrecola A, Proietti I, Innocenzi D, Acne scarring treatment using skin needling, Journal of Clinical and Experimental Dermatology, 2009, 34(8), 874-879.
118. Shingade G, Review on: recent trend on transdermal drug delivery system, Journal of Drug Delivery and Therapeutics, 2012; 2(1):66-75
119. McCrudden MTC, McAlister E, Courtenay AJ, Gonza´ lez-Va´ zquez P, Raj Singh TR, Donnelly RF, Microneedle applications in improving skin appearance, Experimental Dermatology, 2015, 24(8), 561–566.
120. Majid I, Microneedling Therapy in Atrophic Facial Scars: An Objective Assessment, Journal of Cutaneous and Aesthetic Surgery, 2009, 2(1), 26–30.
121. Chandrashekar BS, Sriram R, Mysore R, Bhaskar S, Shetty A, Evaluation of microneedling fractional radiofrequency device for treatment of acne scars, Journal of Cutaneous and Aesthetic Surgery, 2014, 7(2), 93–97.
122. Kalia YN, Naik A, Garrison J, Guy RH, Iontophoretic drug delivery, Advanced Drug Delivery Reviews, 2004, 56(5), 619–658.
123. Prausnitz MR, Langer R, Transdermal drug delivery, Nature Biotechnology, 2008, 26(11), 1261–1268.
124. Cazares-Delgadillo J, Naik A, Ganem-Rondero A, Quintanar-Guerrero D, Kalia YN, Transdermal delivery of cytochrome C-A 12.4 kDa protein –across intact skin by constant – current iontophoresis, Pharmaceutical Research, 2007, 24, 1360-1368.
125. Naik A, Kalia YN, Guy RH, Transdermal drug delivery: overcoming the skin's barrier function, Pharmaceutical Science and Technology Today, 2000; 3(9): 318–326.
126. Yan K, Todo H, Sugibayashi K, Transdermal drug delivery by in-skin electroporation using a microneedle array, International Journal of Pharmaceutics, 2010, 397(1-2), 77-83.
127. Yang M, Zahn JD, Microneedle Insertion Force Reduction using Vibratory Actuation, Biomedical Micro devices, Communication and Therapeutic Micro and Nanotechnology section, 2004, 6(3), 177-182.
128. Orive G, Gascón AR, Hernández RM, Domínguez-Gil A, Edraz JL, Techniques: New approaches to the delivery of biopharmaceuticals. Trends in Pharmacological Sciences, 2004, 25(7), 382-387.
129. Zahn JD, Deshmukh A, Pisano AP, Liepmann D, Continuous on-chip micropumping for Microneedle enhanced drug delivery, Biomedical Microdevices, 2004, 6(3), 183–190.
130. Gill HS, Prausnitz MR, Pocketed microneedles for drug delivery to the skin. Journal of Physics and Chemistry of Solids, 2008, 69(5-6), 1537-1541.
131. Han M, Kim DK, Kang SH, Yoon HR, Kim BY, Lee SS, Kim KD, Lee HG, Improvement in antigen-delivery using fabrication of a grooves-embedded microneedle array. Sensors and Actuators.B, 2009, 137(1), 274-280.
132. Lanke SS, Kolli CS, Strom JG, Banga AK, Enhanced transdermal delivery of low molecular weight heparin by barrier perturbation, International Journal of Pharmaceutics, 2009, 365(1-2), 26-33.
133. Wu XM, Todo H, Sugibayashi K, Enhancement of skin permeation of high molecular compounds by a combination of microneedle pretreatment and iontophoresis, Journal of Control Release, 2007, 118(2), 189–195
134. Chen BT, Wei JS, Iliescu C, Sonophoretic enhanced microneedles array (SEMA)- Improving the efficiency of transdermal drug delivery, Sensors and Actuators B: Chemical, 2010, 145(1), 54-60.
135. Pamornpathomkul B, Duangjit S, Laohapatarapant S, Rojanarata T, Opanasopit P, Ngawhirunpat T, Transdermal delivery of fluorescein isothiocynate-dextrans using the combination of microneedles and low frequency sonophoresis, Asian journal of Pharmaceutical Sciences, 2015, 10(5), 415-424.
136. Nayak A, Babla H, Han T, Bhusandas DB, Lidocaine carboxymethylcellulose with gelatin co-polymer hydrogel delivery by combined microneedle and ultrasound, Drug Delivery, 2016, 23(2), 658-669.
137. Lee K, Kim JD, Yoel Lee CY, Her S, Jung H, A high-capacity, hybrid electro-microneedle for in-situ cutaneous gene transfer, Biomaterials, 2011, 32(30), 7705-7710.
138. Wilke N, Hibert C, O'Brien J, Morrissey A, Silicon microneedle electrode array with temperature monitoring for electroporation. Sensors and Actuators A: Physical, 2005, 123-124, 319-325.
139. Hooper JW, Golden JW, Ferro AM, King AD, Smallpox DNA vaccine delivered by novel skin electroporation device protects mice against intranasal poxvirus challenge, Vaccine, 2007, 25(10), 1814–1823.
140. Hirschberg H, Kuijk S, Loch J, Jiskoot W, Bouwstra J, Kersten G, Amorji JP, A combined approach of vesicle formation and microneedle arrays for transcutaneous immunization against hepatitis B virus, European Journal of Pharmaceutical Sciences, 2012, 46(1-2), 1-7.
141. Ding Z, Bal SM, Romeijn S, Kersten GFA, Jiskoot W, Bouwstra JA, Transcutaneous immunization studies in mice using Diphtheria Toxoid-loaded vesicle formulation and a microneedle array, Pharmaceutical Research, 201, 28(1), 145-158.
142. Verma DD, Fahr A, Investigation on the efficacy of a new device for substance deposition into deeper layers of the skin: Dermaroller®, Institut für Pharmazeutische Technologie und Biophar mazie, Philipps-Universität Marburg, www.beautyroller.se/pdf/needelbeautyroller.pdf
143. Serrano G, Almudever P, Serrano JM, Cortijo J, Faus C, Reyes M, Exposito I, Torrens A, Millan F, Microneedling dilates the follicular infundibulum and increases transfollicular absorption of liposomal sepia melanin, Clinical, Cosmetic & Investigational Dermatology, 2015, 8, 313-318.
144. Coulman SA, Anstey A, Gateley C, Morrissey A, McLoughlin P, Allender C, Birchall JC, Microneedle mediated delivery of nanoparticles into human skin, International Journal of Pharmaceutics, 2009, 366(1–2), 190–200.
145. Zhang W, Gao J, Zhu Q, Zhang M, Ding X, Wang X, et al, Penetration and distribution of PLGA nanoparticles in the human skin treated with microneedles, International Journal of Pharmaceutics, 2010, (1–2), 205–212.
146. Zhang D, Das DB, Rielly CD, An experimental study of microneedle-assisted microparticle delivery, Journal of Pharmaceutical Sciences, 2013, 102(10), 3632–3644.
147. Patel SR, Lin AS, Edelhauser HF, Prausnitz MR, Suprachoroidal drug delivery to the back of the eye using hollow microneedles, Pharmaceutical Research, 2011, 28(1), 166–176.
148. McAllister DV, Wang PM, Davis SP, Park JH, Canatella PJ, Allen MG, Prausnitz MR, Microfabricated needles for transdermal delivery of macromolecules and nanoparticles: Fabrication methods and transport studies, Proceedings of the National Academy of Sciences, 2003, 100(24), 13755–13760.
149. Coulman SA, Barrow D, Anstey A, Gateley C, Morrissey A, Willke N, Allender C, Brain K, Birchall JC, Minimally invasive cutaneous delivery of macromolecules and plasmid DNA via microneedles, Current Drug Delivery, 2006, 3(1), 65-75.
150. Chabri F, Bouris K, Jones T, Barrow D, Hann A, Allender C, Brain K, Birchall J, Microfabricated silicon microneedles for nonviral cutaneous gene delivery, British Journal of Dermatology, 2004, 150(5), 869–877.
151. Pearton M, Allender C, Brain K, Anstey A, Gateley C, Wilke N, Morrissey A, Birchall J, Gene delivery to the epidermal cells of human skin explants using microfabricated

 ISSN: 2250-1177 CODEN (USA): JDDTAO

microneedles and hydrogel formulations, Pharmaceutical Research, 2008, 25(2), 407-416.
152. Jiang J, Moore JS, Edelhauser HF, Prausnitz MR, Intrascleral drug delivery to the eye using hollow microneedles, Pharmaceutical Research, 2009, 26(2), 395-403.
153. Torrisi BM, Zarnitsyn V, Prausnitz MR, Anstey A, Gateley C, Birchall JC, Coulman SA, Pocketed microneedle for rapid delivery of a liquid state botulinum toxin A formulation into human skin, Journal of Contro Release, 2013, 165(2), 146-152.
154. Ma Y, Boese SE, Luo Z, Nitin N, Gill HS, Drug coated microneedles for minimally invasive treatment of oral carcinomas: development and in vitro evaluation, Biomedical Microdevices, 2015, 17(2), 44.
155. Yu J, Zhang Y, Ye Y, Disanto R, Sun W, Ranson D, Liger FS, Buse JB, Gu Z, Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery, Applied Biological Sciences, 2015, 112(27), 8260-8265.
156. Paleco R, Vucen SR, Crean AM, Moore A, Scalia S, Enhancement of the in vitro penetration of quercetin through pig skin by combined microneedles and lipid microparticles, International Journal of Pharmaceutics, 2014, 472(1-2). 206-213.
157. Vucen SR, Vuleta G, Crean AM, Moore AC, Ignjatovic N, Uskokovic D, Improved percutaneous delivery of ketoprofen using combined application of nanocarriers and silicon microneedles, Journal of Pharmacy and Pharmacology, 2013, 65(10), 1451-1462.

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