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A COMPREHENSIVE REVIEW ON MICRONEEDLES - AN ARCHETYPE SWING IN TRANSDERMAL DRUG DELIVERY

G. Ravi*, N. Vishal Gupta, M. P. Gowrav

Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Shri Shivarathreeshwara Nagara, Mysuru, Karnataka, India.

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ABSTRACT

Transdermal drug delivery is the non-invasive delivery of medications through the skin surface into the systemic circulation. The advantage of transdermal drug delivery system is that it is painless technique of administration of drugs. The advantage of transdermal drug delivery system is that it is painless technique of administration of drugs. Transdermal drug delivery system can improve the therapeutic efficacy and safety of the drugs because drug delivered through the skin at a predetermined and controlled rate. Due to the various biomedical benefits, it has attracted many researches. The barrier nature of stratumcorneum poses a danger to the drug delivery. By using microneedles, a pathway into the human body can be recognized which allow transportation of macromolecular drugs such as insulin or vaccine. These microneedles only penetrate outer layers of the skin, exterior sufficient not to reach the nerve receptors of the deeper skin. Thus the microneedles supplement is supposed painless and reduces the infection and injuries. Researches from the past few years showed that microneedles have emerged as a novel carrier and considered to be effective for safe and improved delivery of the different drugs. Microneedles development is created a new pathway in the drug delivery field. This review focus on new advances in transdermal drug delivery system using various carriers emphasizing mostly on the potential role of microneedles as transdermal system.

Corresponding author
Dr. G. Ravi
Ph. D Reasearch scholar
Dept. of Pharmaceutics,
JSS College of Pharmacy, Mysore-15.
+91 9986943534
ravigundawar1@gmail.com

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INTRODUCTION

Microneedles:

Microneedles (MNs) are microscopic needles and the size ranges of microneedles from 1-100 microns in length and 1micon in diameter arranged on a transdermal patch that are large and strong enough to painlessly place in to the skin and transport the drugs through the skin [1, 2], but small enough that they do not reach the skin deeper layer to stimulate nerves.

MNs have emerged as one of the most effective means of enhancing transdermal penetration of compounds such as vaccines, proteins, therapeutics into the body in a modestly contained manner and MNs have been fabricated from materials such as metal, polymer and silicone [3].

Drug administration by oral route it remains the favoured method, mainly when compared with parenteral route [4].

These are the microstructure device, consists of a microstructured array projections coated with a vaccine or drug that is applied on the skin to offer intradermal delivery of active agents which otherwise would not cross the stratum corneum [5]. These are considered as a combination of hypodermic needles as well as transdermal patches and effective sufficient to overcome the limitations being possessed by these two systems [6]. In transdermal delivery the microsized needles have been formulated as a novel drug delivery, as these have been developed by fabrication, done by concerning the tools of microelectronics so that the penetration up to hundred microns deep into the skin can be achieved in a painless manner. A basic design of microneedles system is depicted in the following figure 1.

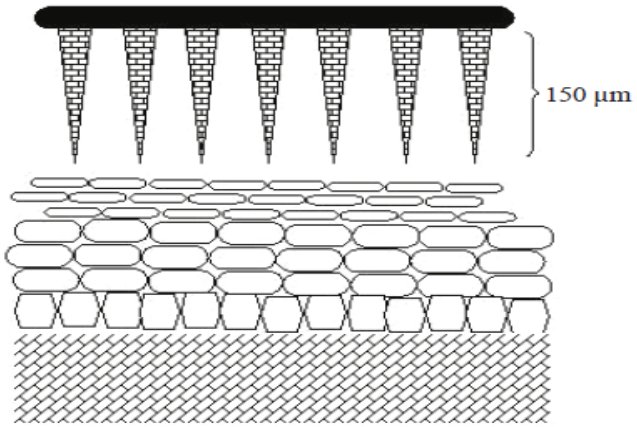

Figure 1: The basic design of microneedle delivery devices [7].

Microneedles are just like conventional needles fabricated only in micro scales. These are mainly arranged in the form of arrays.

Need of using Microneedles:

When oral drug administration is not possible due to enzymatic degradation or poor drug absorption in the liver or gastrointestinal tract, using of injection is a painful hypodermic needle is the most common alternative. An approach that is additional attractive to patients, and deals the possibility of controlled release over time, is drug delivery through the skin using a patch [8-10].

Advantages [11, 12]:

- ✓ Easy to use
- ✓ Reduces chances of pain, infection, or injury
- ✓ Discreetness
- ✓ Controlled release
- ✓ Continuous release
- ✓ Safer handling
- ✓ Self-administration (Compared to surgical implantation)

Disadvantages:

- ✓ Local inflammation
- ✓ Skin irritation
- ✓ Expensive

Requirements of Microneedles

Based on the idea of microneedle base drug delivery, there are a few basic requirements:

Suited to the purpose:

There has been a tendency, particularly in the microfabrication community, to use specialized fabrication methods to prepare microneedles without demonstrating basic feasibility. For the proper function of microneedles, the needles need to have certain sharpness and certain length, and they should be fabricated in a material which can withstand the forces of matter.

Batch compatible:

As a minimally invasive medical device, microneedles for drug delivery will need to be single-use, disposable, devices to increase acceptance in medical practice. Competing with standard needles and syringes at very less cost, microneedles need to be produced in a cost-effective manner. Hence, for general delivery applications of drug such as insulin or vaccination delivery, fabrication methods need to be batch compatible to be commercially competitive [13].

Biocompatible:

Microneedles were designed to be inserted into the human tissue and they required to be well-suited to the local environment, both in terms of toxicity and intended function. The contract duration with the tissue ranges from minutes to days at the most because insulin infusion-sets are typically changed every third day. Hence, the material used should be non toxic [13].

For hollow microneedles there was a risk of blocking the needle bore with a cored tissue during insertion into the skin. Concerning toxicity, bioinert, well-known, materials such as stainless steel, gold or titanium, or biodegradable polymers such as PLGA (poly lactic Co glycolic acid), may be used with confidence as microneedle material. In the scientific literature, it was often questioned whether silicon (the traditional micro engineering material) can be used as microneedle material [14, 15].

MEMS (Micro electro mechanical systems)

MEMS or MST (Micro system Technology) both referred to devices with sub millimetre features. MEMS expanded the fabrication methods developed at the microelectronics industry to add mechanical structures onto micro devices. The MEMS fabrication characteristic attributes are integration, miniaturization and parallelization. Integration referred to monolithic integration of electronics and to packing methods [15, 16]. Miniaturization allowed fabrication of compact, fast responding and energy-efficient devices. Parallelization referred to batch fabrication techniques inherited from the microelectronics industry in which thousands or millions of devices are concurrently produced. The ability to fabricated micro machines or microstructures for biological applications is especially compelling because such devices can be made on the same size scale as the biological entity to be manipulated. Many various types of these devices were being pursued, such as minimally invasive surgical tools, DNA analysis chips, microstructures that assist nerve regeneration, microstructures for studying cell properties and functions, and controlled release of drugs from microchips [17-22].

These devices can be divided into four categories based on their applications:

- Molecular biology and biochemistry tools
- Medical devices
- Biosensors
- Cell biology tools. The microneedles have the potential to affect all four of these categories.

General fabrication techniques

Lithography

The fabrication of both micromachining and microelectronics, starts with lithography, the method used to transfer the master pattern onto the substrate surface (eg. silicon wafer), formerly coated with a photosensitive material, by selective exposure to a radiation source (eg. UV light). The photolithography technique is most widely used type of lithography.

Thin-film deposition on substrate

One of the basic steps in the MEMS process is the deposition of a thin film on the surface of the substrate (eg. silicon wafer). These films can then be patterned using photolithography methods and suitable etching methods. Common materials include silicon nitride (nitride) and silicon dioxide (oxide). Thin-film deposition on the substrate can be also be achieved by using a wide range of materials, including noble metals such as gold. In general, in physical vapour deposition (PVD) based methods; the raw materials (liquid, solid, or vapour) are released from the source (material to be coated) and deposited on the substrate surface.

Etching

The following lithography method, and to create the final functional form of MEMS structure on a substrate, it is necessary to etch the thin-films previously deposited and/or the substrate itself. In general, there are two classes of etching processes: wet etching and dry etching [13,15].

Wet etching:

In this process, the material is removed by immersing the wafer in a liquid bath containing a chemical etchant. The two main wet etching techniques are isotropic and anisotropic etching. Isotropic etchants attack the material, such as oxide, nitride, aluminium, polysilicon, gold, and silicon, at the same rate and in all directions. They remove material horizontally under the etch mask (under-cutting). In contrast, anisotropic etchants attack the material (silicon wafer) at different rates in different directions, to produce more controlled shapes. The crystal planes in silicon limit anisotropic wet etching.

Dry etching:

This form of etching is carried out at low pressure in the presence of inert or reactive gases. Dry etching is categorized into two main types: reactive ion etching (RIE), which involves chemical processes, and ion-beam milling, which involves purely physical processes [22].

Methodology of drug delivery [23]

Over the history, microneedles of different geometries and materials have been developed. Depending on the design of microneedle, microneedles can be applied by four various delivery strategies. A number of delivery strategies have been employed to use the microneedles for transdermal drug delivery. These include

1. Poke with patch approach
2. Coat and poke approach
3. Biodegradable microneedles
4. Hollow microneedles
5. Dip and scrape

Poke with patch approach:

The poke with patch approach was the first microneedle concept to be developed and involves inserting (poking) a solid microneedles array into the skin followed by the drug patch application at the treated site. The drug transport across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied.

Example: Insulin Delivery

Coat and poke approach:

In this approach microneedles were first coated with the drug. The drug coated microneedles inserted into the skin for release of the drug by dissolution. The entire drug to be coated on the microneedle itself to deliver.

Example: Protein Vaccine Delivery

Biodegradable microneedles:

This approach involved within the biodegradable the drug was encapsulated, polymeric microneedles, followed by the insertion into the skin for a controlled release of the drug.

Hollow microneedles:

This approach involved the drug was injected through the needle with a hollow bore. This method of approach was more suggestive of an injection than a patch.

Example: Delivery of Insulin

Dip and scrape:

In this approach, the microneedles were first dipped into a drug solution and then rubbed across the surface of skin to leave behind the drug within the micro abrasions created by the needles. The arrays were dipped into a drug solution and rubbed multiple times across the skin of mice in vivo to create micro abrasions. Unlike microneedles were used before, this study used with blunt-tipped microneedles measuring 50– 200 µm in length over a 1 cm^2 area.

Example: DNA Vaccine Delivery

Types of Microneedles [24]:

The various types of microneedles were fixed by various materials: single-tip microneedles were the first type of microneedles that have a sharp tip. These types of microneedles are 200 µm in length and straight in shape. It contains sharp tip with various angles of 15, 30, 45 and 75 degrees [25, 26].

Quadruplet microneedles were the second type of microneedles, and the hollow microneedles were third types of microneedles.

The Quadruplet and hollow microneedles both were not much expensive and excellent in strength respectively.

The classification for microneedles commonly used in literature was based on the process of the construction: in-plane or out-of-plane microneedles.

In-plane microneedles:

This type of microneedles constructed with the shaft being parallel to substrate surface. The advantage of this plan is that the desired needle length can be exact perfectly completed, useful in analysis of body fluid. The disadvantage is that to fabricate two-dimensional arrays are not possible by this method. A typical In-plane microneedles system is depicted in the following figure 2.

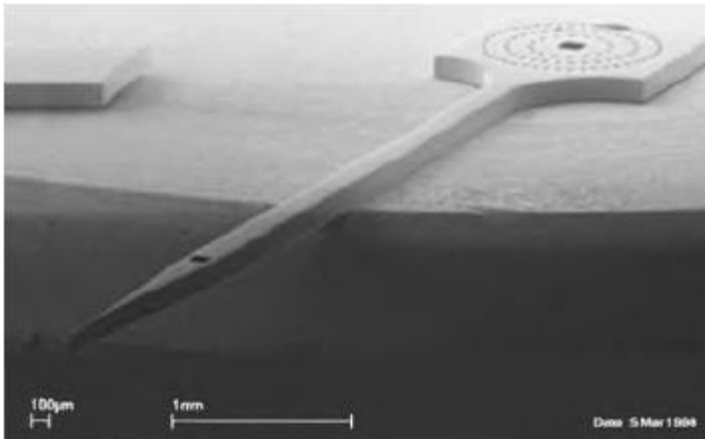

Figure 2: In-plane Microneedles [27].

Out-of-plane Microneedles:

On the other hand, protrude from the substrate and are straight forward to fabricate in arrays. Instead, the high aspect ratios and length become important challenges in these types of microneedles fabrication. Two dimension arrays are possible. A typical Out-of-plane microneedles system is depicted in the following figure 3.

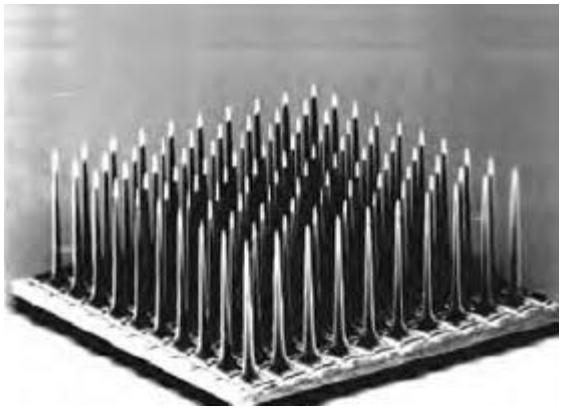

Figure 3: Out of plane Microneedles [27].

1. Hollow Microneedles
2. Other Microneedles

Hollow Microneedles:

The holes created from solid microneedles insertions; by these holes the skin permeability can be dramatically improved. However, it was still required to have extra reproducible and controlled transport pathways to the drug delivery in to the tissue. The hollow microneedles construction that agrees transport through the hollow shaft of the needle was based on this need. The inclusion of a hollow lumen in a structure of microneedles enhances its capabilities dramatically and it can provide the following benefits:

i) The ability to larger particles delivery and molecules delivery,
ii) The material deliver in a convective transport fashion instead of passive diffusion, Ex: Pressure driven flow.
iii) Reduce the cross contamination deliverables and its surroundings.

In transdermal drug delivery a variety of hollow microneedles have been successfully constructed and demonstrated. Like a) metal microneedles b) silicon hollow microneedles c) glass microneedles.

Hollow microneedles disadvantage: These are very expensive to prepare and require expensive micro fabrication techniques. A typical Hollow microneedles system is depicted in the following figure 4.

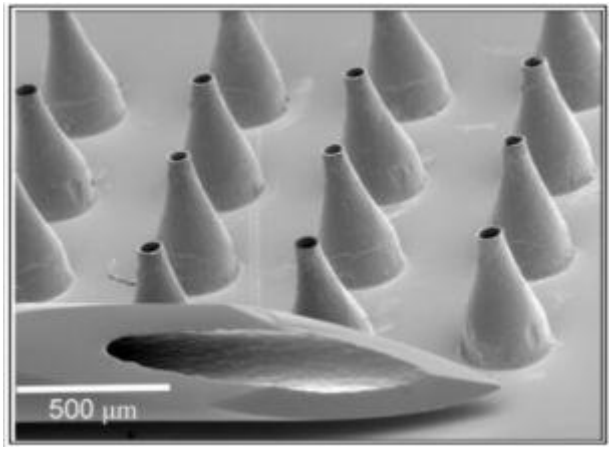

Figure 4: Hollow Microneedles [28].

Other Microneedles:

By using of various materials such as biodegradable polymers, polysilicon and sugar with additional functionalities, the other different types of microneedles were fabricated, besides hollow and solid microneedles. The biodegradable polymer microneedles were developed, because of their biocompatible nature of the tissue. By using lithography based methods these microneedles were fabricated by primarily making master structures, creating inverse structures from the master molds, and finally by melting biodegradable polymer formulations like poly lactic co-glycolic acid (PLGA), poly lactic acid (PLA) into the molds, the replicate microneedles were produced.

The resulting microneedles can be loaded with drugs, molecules, proteins and DNA. A typical Hollow microneedles system is depicted in the following figure 5.

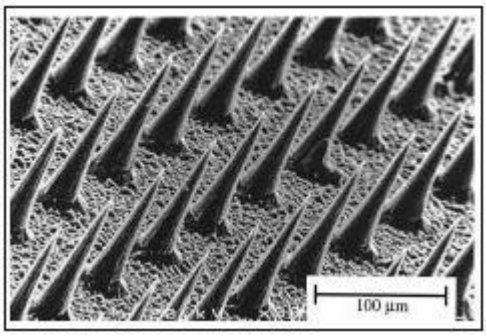

Figure 5: Solid Microneedles [28].

Unlike the solid and hollow microneedles, polymer microneedles themselves serve as the drug implants after insertion into the tissue.

Mechanism of action:

The mechanism for delivery is not based on diffusion process as it is in other transdermal drug delivery products. Instead, it is based on the temporary mechanical disruption of the skin and the placement of the vaccine or drug within the epidermis, where it can more readily reach its site of action.

Microneedles are encapsulated with the drug in the form of bio molecules, which are then injected into the skin in the same way a drug like nitro-glycerine is released into the blood stream from a patch. The needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. They do not need to be removed and no dangerous or bio hazardous substance is left behind on the skin, as the needles are made of a biodegradable substance.

In microneedles devices, a small area (the size of a traditional transdermal patch) is covered by hundreds of microneedles that pierce only the stratum corneum (the upper most 50 µm of the skin), thus allowing the drug to bypass this important barrier.
The tiny needles are constructed in arrays to deliver sufficient amount of drug to the patient for the desired therapeutic response[26].

Characteristics of microneedles:

The characteristics of micro needles are including:

Ruggedness:

Without breaking of the microneedles developed must be capable of insertion deep into the skin. The microneedles should be manufactured by taking optimum size and if they are too long, before penetration the upper portion of the microneedles may not have sufficient rigidity and could undergo breakage. Without delaminating, or fracture they must be able to withstand the insertion force.

Controlled drug release:

At a definite and predetermined rate the micro needles should deliver the controlled amount of drug.

Penetration:

The micro needles should be able to penetrate the drug to the required depth in the body tissues. Painless insertions of micro needles into the skin can be accomplished by gentle pushing, using approximately 10 Newton forces [29].

Microneedles Dimension:

The solid tip microneedles and hollow microneedles both have various dimensions. The arrays of hollow microneedles were fabricated with lumen height of 250 µm and the diameter of 30 µm. The hollow microneedles array center to center the distance is 150 µm. The lumen axis is made-up with the distance of 10 µm to the axis of outside column.

The solid tip microneedles were fabricated in 750-1000 µm in length, 190-300 µm bases area and the tapered tips angle is 15-20^0. The microneedles masks were designed to 400-600 15-20^0 µm triangles length, conduits diameter is 70-100 µm and the arrays density is 25-60 EA/5 mm^2.

Materials used for construction:

The materials required for constructing micro needles include silicone (of brittle nature), glass, and metals such as palladium, stainless steel, solid or gold coat over nickel, cobalt, platinum and biodegradable polymers.

Effect of the Length of microneedles on pain:

The microneedles designing can be such so as to reduce the pain. Various studies exposed that the particular microneedles of about a couple 100 µ in length were reported to be painless. It was reported by various authors that l3-times increase in needle length (i.e., 500-1500 microns) increases the pain by 7 times (i.e., 5-35%caused by hypodermic needle). If the remaining length constant, an increase in number of microneedles (i.e., 620 micron long) 10 fold from 5- 50 also increases the pain by 3 folds [4].

Evaluation Parameters:

***In-Vitro* study of Microneedles:**

In vitro evaluations microneedles are accomplished by using different mediums like methanol and agarose gel to insert the microneedles. In vitro tests are used to determine the characteristics of new test device or compound. The main key objectives of the in vitro testing of microneedles involves optimization of the microneedles, finding out the penetration force and bending force, evaluation of strength of microneedle, determination of the dissolution rate of coating material and the estimation of the efficiency of drug delivery. Various methods employed for conducting in vitro studies are as follows:

Method 1

In vitro methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Para dimethyl siloxane (PDMS) biochip and black ink is injected by the microneedles into the petridish, which contains methanol. The right triangular microneedles with 8.5 and 15 tip taper angles and isosceles triangular microneedles with 9.5 and 30 tip taper angles have been used for this purpose.

Method 2

In this method, the diluted form of Rhodamine B dye is injected through the microneedles into the 1% agarose gel to evaluate the penetration and flow of the solution after penetrating into the 1%agarose gel[30].

Method 3

Inserting microneedles into the porcine cadaver skin and pig cadaver skin for 10s to 20 s and 5 minutes respectively are evaluated by this method. This method is used to test the delivery efficacy, dissolution rate of the coated material, which is coated on the microneedle tip, coated with vitamin B, calcein or sulforhodamine [30].

***In Vivo* Testing of microneedles**

To conduct the *in vivo* preclinical study, generally mice, rabbits, guinea pigs, mouse and monkey etc are used. The main motive of the *in vivo* testing is the determination of safety as well toxicity of the tested compound. The key objectives behind *in vivo* testing of the microneedles includes to perform skin toxicity test, determination of penetration force in different skin, mechanical stability, bending breakage force, to perform various non-clinical safety study and pharmacological study, determination of various parameters like immunogenicity, geno toxicity, skin sensitization and allerginisation, study, developmental toxicity, acute and chronic dermal toxicity, carcinogenicity.

Method 1

This *in vivo* method involves testing of microneedles by pricking the microneedles into vein of the tail of hairless mice. It is used for the determination of the penetration force of the microneedle into theskin [30].

Method 2

This method of *in vivo* testing of the microneedles, Rhodamine B is injected into tail of laboratory mouse-tail and anaesthetized for the determination of penetration force and bending breakage force [30].

Method 3

This method has been performed for the evaluation of vaccine delivery via microneedles. Ovalbumin is used in this method, as a model protein antigen and administered into hairless guinea pig by using solid metal microneedles at the rate of 20 µg ovalbumin in 5sup to 80 µg [31].

Method 4

In this method rabbits have been used to evaluate the vaccine delivery. The anthrax vaccine containing recombinant protective antigen (rPA) of Bacillus anthracis has been administered in the rabbits via solid and hollow microneedles [31].

Microneedle Applications:

The microneedles were first introduced for the application of drug delivery. The major objective was to enhance the permeability of skin through a pretreatment of solid microneedle or to create the hollow microneedles with superior functionality over the conventional hypodermic needles. The present, the microneedle applications have been extended in so many fields, including intracellular, transdermal and ocular delivery.

Transdermal drug delivery

The deliveries of drug into the skin for systemic or local effects are very complicated due to the extreme effective barrier of the outer layer of skin that is the stratum corneum. About 20 drugs with FDA (Food and drug administration) approval transdermal patches all have molecular weights less than 400 Da, are relatively lipophilic nature and need lower doses. The microneedles have been shown significantly enhance the no. of compounds that can be administered across the skin, including drugs which having a low molecular weight, vaccines, bio therapeutics and other materials.

Lidocaine delivery

The drugs which are having a low molecular weight have been administered by using microneedle pretreatment of the skin, the hollow microneedles and coated microneedles each have been used to lidocaine administer for local anesthesia.

In one article, lidocaine was coated in non-dissolving microneedles polymer and administered to pigs. In the skin the lidocaine levels were interpreted as sufficient to cause prolonged local anaesthesia.

In another study, lidocaine was injected into the human subject's skin by using ingle, hollow microneedles and compared to conventional in a transdermal injection of lidocaine. While the delivery of lidocaine for local anaesthesia either by method was same, the human subjects were reported significantly less pain associated microneedles delivery and expressed high preference for that method over intradermal injection with a hypodermic needle [32-35].

- ✓ In one of the study, they demonstrated the pre-treatment with a combination of microneedles and sonophoresis and also determined their combined effects on lidocaine percutaneous delivery of from a polymer hydrogel formulation. Varying ratios of lidocaine were prepared by using carboxy methyl cellulose and gelatin loaded and characterized. This combination has shown increased lidocaine permeation in the skin [36].
- ✓ In another study, the author emphasized on the liquid formulation spreading on microneedle treated skin. They were compared and controlled spreading of solution of lidocaine and hydrogel formulation of lidocaine. Spreadability was attained with the previous one. However the parameters of droplet spreading like droplet height, dynamic contact angle and spreading radius were slightly poorer of Lidocaine than that solution on the skin [37].
- ✓ Local anaesthetics like Lidocaine when given through hypodermic parenteral route cause anxiety or pain to patients and then again in the formulation of ointment leads to slow drug diffusion process. In one paper author addressed these two aims and issues to understand the importance of the 'poke and patch microneedle (MN) treatment of skin in conjunction to the permeation of lidocaine, and in particular, the horizontal (eg. lateral) and vertical (depth averaged) the drug permeation profiles in the skin [38].
- ✓ Similarly, in another study, lidocaine hydrochloride (LidH) was formulated in sodium carboxy methyl cellulose and gelatine hydrogel and method was used for their study was 'poke and patch' microneedle delivery method to improve the permeation flux of LidH. By electrostatic interactions between carboxy methyl cellulose and gelatine the microparticles were formed, macromolecules within a water/oil emulsion in paraffin oil and the covalent crosslinking was by glutaraldehyde. LidH 2.4% w/w LidH sodium carboxy methyl cellulose and gelatine 1:2.3 crossed the minimum therapeutic drug threshold with microneedle permeation of skin in below 70 min [39].
- ✓ In this study the microneedle system was prepared by using biodegradable polymer for the delivery of lidocaine through the skin were evaluated [40].

Biotherapeutics

The biotherapeutic drugs, such as proteins, DNA and RNA, peptides, are large molecules that can't be administered easily by transdermal or orally and therefore they are conventionally by hypodermic injection. The microneedle patch delivery is envisioned as an alternative to hypodermic injection that is less safe, simple and painful for patients to self administration, because the Biotherapeutics doses are often low (i.e., microgram (µg) doses), many biotherapeutics can be administered either encapsulated within dissolving microneedles or coated on microneedles. Because the small size of microneedles, drugs which given on or within the microneedles themselves are usually limited to µg doses, although may be possible of low µg doses.

For the microneedle delivery, insulin has received by far the most attention among the different biotherapeutics was studied, including work with the types of multiple microneedle design and progressing into human trials from animal studies. Dissolving microneedles encapsulating insulin have also been studied comprehensively in dogs, mice and diabetic. This study was shown to enable stable encapsulation of insulin and effective insulin delivery to reduce the glucose level in blood. Newly hollow microneedles have been used for delivery of insulin [41-46].

Vaccine delivery

Vaccination delivery by using microneedles is particularly attractive because it not only gives expected advantages that simplify the distribution of vaccine and get better compliance of patients, but it also allows targeting of vaccine to the skin. It is already known that the skin offers advantages like immunologic over the conventional intramuscular injection so the delivery of vaccine has been extensively investigated the use of microneedles.

Coated microneedles have been the most widely used methods for microneedles vaccination to enable more controlled and efficient delivery. The studies were done on shaved guinea pig by microneedle vaccination employed metal microneedles coated with albumin antigen, which showed a superior immune response and significant dose sparing compared to an equivalent intramuscular or subcutaneous injection. In recent years influenza vaccination with coated microneedles have been widely studied in mice, showed complete protection against lethal viral infection after vaccination using H_1N_1 and H_3N_2 seasonal strains.

Dissolving microneedles were used for influenza vaccination which was made of poly vinylpyrrolidone (PVP) encapsulating lyophilized inactivated influenza vaccine.

Hollow microneedles vaccination studies have been conducted mostly with 1.5 mm-long, small-gauge hypodermic needles mounted on a syringe. While these needles are possibly too long to be called microneedles and their mounting on a syringe deviates significantly from the patch-like format of solid microneedle devices, the considerable work in this area is worth including. These small needles allows simplified needle insertion and injection normal to the surface of skin with dependable intradermal targeting, which contrasts with the conventional mantoux method of intradermal injection that requires a precisely controlled, angled insertion and produces unreliable intradermal targeting. For influenza vaccination these prepared microneedles were first tested in rats, which showed that intradermal injection enabled 100 fold doses sparing using inactivated virus vaccine, up to ten fold dose sparing using a split-virion vaccine, and 5 fold doses sparing using a plasmid DNA vaccine when compared to intramuscular delivery.

In other studies using this intradermal microneedle demonstrated an efficient vaccination with a live attenuated vaccine against encephalitis of Japanese in non-human primates, plague F_1-V vaccine in mice, and grouping vaccines including plague, anthrax, botulism and staphylococcal toxic shock in rhesus macaques. A study in the human subjects showed rabies vaccination dose sparing in the skin compared to intramuscular injection.

Influenza vaccination clinical trials:

The above discussed hollow microneedle system was used in a human trial and that showed a decreased dose of the 6 µg vaccine influenza given in to the skin was not significantly dissimilar from intramuscular vaccination at a complete dose of 15 µg influenza vaccine in non-elderly adults (18–60 years old), but showed lesser antibody titers in older patients [41].

Hollow microneedle system further evaluation present in clinical use in several countries around the world for vaccination influenza was performed in clinical studies of elderly people (> 60 years) and healthy adults (18–57 years) [41].

Blood and interstitial fluid extraction:

Microneedles have been used mostly for skin delivery, but a number of studies have investigated the microneedles function as a diagnostic tool to extract analytes from the skin for *ex vivo* analysis or by integrating a sensor into the microneedle for *in situ* sensing in the skin. In one approach, up to a few micro liters of interstitial fluid were extracted under suction from skin pretreated with microneedles; measured concentrations of glucose in the extracted interstitial fluid showed excellent correlation with corresponding blood glucose levels in rats and human subjects. A microneedle for micro dialysis has also been developed to selectively collect analytes below a molecular weight cut off to prevent biosensor fouling with high molecular weight compounds Rather than extracting fluid containing biomarkers, microneedles have been surface-modified to specifically bind biomarkers of interest and, in that way, selectively extract those compounds for analysis. Other approaches have involved building sensors into the microneedle itself. For example, microneedles have been developed as sensors for hydrogen peroxide, lactate, dissolved oxygen and glutamate. Microneedles have also been used as bioelectrical interfaces, especially for neural recording and stimulation, as well as for electrocardiography (ECG) and electroencephalography (EEG) measurements [47, 48].

Combination of microneedles and other methods:

Microneedle technology has been combined with electroporation, iontophoresis and other methods to give synergistic effects. In one paper delivery of drug using microneedles, first the skin was pretreated with microneedles then oligo nucleotides were driven through the permeabilized skin by iontophoresis method in hairless guinea pigs.

By using microneedles this approach decreases, the skin barrier and then it provides a driving force for improved transport by iontophoresis. In further studies, this approach was efficient for dextrans delivery *in vitro* with a molecular weight up to 200 kDa and for delivery of 13 kDa protein daniplestim *in vitro* and *in vivo*. By iontophoresis insulin nanovesicles were delivered across microneedle pre-treated skin of diabetic rats, which were having low blood-glucose level. For dental applications the combination of pretreatment with iontophoreis has been proposed for deliveries of local anaesthetics across the oral mucosa.

Occular drug delivery

The micro needle concept for transdermal drug delivery has found acceptance, and studies have shown the potential of using microneedles to improve delivery of drug across the skin. In addition to applications in the skin, microneedles have also been used for delivery of the drug to the eye. Using microneedles as the recent tool in delivery of ocular drugs can offer the following advantages:

1) They may reduce tissue damage and pain relative to hypodermic injections because they are small enough to avoid significant tissue trauma and stimulating nerves.
2) They should be well tolerated and thereby enhance patient compliance since a single application might be suitable for long term use; and
3) They will offer a localized and target delivery of the drug to the back of the eye.

Ocular drug delivery may be used to treat diseases such as glaucoma, macular degeneration and diabetic retinopathy. Microneedles are durable enough to deliver drugs to the eye by penetrating the sclera for targeted drug delivery. Animal data show that the microneedle delivery approach is more effective than topical application. Safety have shown hole in the cornea caused by microneedle piercing healed after 3 hours [49-51].

Delivery into cells

Single, hollow microneedles has been used for intracellular injection for decades, facilitating applications in the clinical medicine, animal cloning and bioscience laboratory (eg. *In vitro* fertilization). This highly lower-throughput approach uses pulled glass micropipettes that are carefully inserted into individual cells under a microscope for intra nuclear or intra cytoplasmic injection of DNA, ermatozoa, proteins or other materials. As an alternative approach, modified AFM (Atomic Force Microscopy) tips have been developed into nanoneedles of diameter 200–300 mm and length 6–8 μm for intracellular penetration and delivery. Nanoneedles have also been made from multi walled carbon nanotubes (MWCNT) mounted on AFM tips, microscopic needles and glass micropipettes. Nanoparticles and fluids were also delivered through the MWCNT bore. Microneedle arrays have been adapted to facilitate higher-throughput delivery into cells, in contrast to the single-cell approaches described on top [48-52].

Other applications

For medical applications, the solid microneedles have been developed for delivery of drugs in blood vessel walls (example to treat restenosis). Such type of microneedles was shown to puncture across the internal elastic lamina in rabbit arteries *ex vivo.*

For biofuels applications, the gold-plated microneedle electrodes were fictionalized to electrochemically detect p-cresol for high-throughput analysis of biochemical species in of plants for biofuels research.

Applications in drug delivery

By the using of hypodermic needles, the maximum vaccines and bio therapeutic agents are injected. Benefit of injection possesses the advantage of providing a rapid, inexpensive and delivers directly almost all types of molecules in the body.

However, there is a problem associated with the use of hypodermic needles that they cannot be easily used by patients themselves. Though oral delivery can overcome this problem, but by this route different drug cannot be given due to drug degradation and poor absorption in the liver and gastrointestinal tract. Thus, an attempt has been made to modify the needles, by shrinking it to micron size in order to make it efficient for drug delivery and also enhancing the patient safety and compliance. As a micron-scale device, a microneedle should be capable enough to drug delivery as well as to avoid fear, pain and the need for expert training to administer. Most microneedles applications studied till now have emphasized mostly to vaccine and drug delivery to the skin. Conventional drug delivery of transdermal system was limited due to the nature of the barrier stratum corneum. Different physical, biochemical and chemical methods have been studied to enhance the permeability of the skin.

However, chemical and biochemical methods developed so far do not find to be largely effective for bio therapeutics delivery and vaccine delivery across the skin. While physical methods have the superior promise of macromolecule delivery, they normally involve the use of sophisticated devices that are relatively expensive, large and need training to use. Microneedles, in comparison to all the methods, low-cost patch can be prepared and that is simple for patients to apply for bio macromolecule delivery [52], macromolecules like growth insulin, hormones, proteins, peptides and immune biological [53].

Other microneedles applications have also been such undergo development like delivery of the drug to the eye, particularly via the suprachoroidal space, has received current attention. As a micropipette technique extension, microneedles have been used for molecules deliver into cells and their nuclei, along with other laboratory applications[55]. Microneedles have also gained prominent attention in the field of cosmetics and various cosmeceuticals have been used for the treatment of pigmentation, scars, wrinkles and acne as well as for toning of the skin [53].

Microneedles have been employed a delivery system of vaccine, the micron scale fabricated needles can deliver the vaccine into the skin by the simple self-administering method [54].

Table 1 simplifies the various microneedles applications as a carrier system for improved transdermal delivery.

APPROVED MICRONEEDLE PRODUCTS

There are a number of approved cosmetic and medical products using microneedles that are sold around the world.

The first approved microneedle product was the Dermaroller®, which was a cylindrical roller covered on its surface with metallic, solid microneedles that measure 0.2–2.5 mm in length. The smaller needles were designed particularly for patients, they can use at home to enhance the texture of the skin and the longer ones are used in clinics to treat hyperpigmentation and scars. In 1999 the product was first sold in Europe, the Dermarolleris present sold around the world. Many numbers of companies sell similar products as flat microneedle patches as well as microneedle rollers.

- ✓ The Micro Hyala® product was introduced in 2008 to treat wrinkles; it was developed as a patch covered with dissolving microneedles containing hyaluronic acid that was released into the skin. It is currently sold in Japan.
- ✓ Recently LiteClear® was introduced in China for treatment of acne and worldwide for cosmetic blemish treatment. This family of products uses solid silicon microneedles as a skin pretreatment followed by application of the active agents topically.
- ✓ Soluvia® is a single hollow microneedle that is 1.5 mm long and is attached to a syringe. It is marketed worldwide prefilled with influenza vaccine for intradermal vaccination as IDflu®, Intanza® and Fluzone Intradermal®.
- ✓ MicronJet® recently received FDA clearance. This device contains a row of four hollow, silicon microneedles mounted on a plastic adapter compatible with standard syringes. Table 1 summarizes the various patents of microneedles for drug delivery.
- ✓ Finally Raphas® beauty patch product consists of dissolving microstructures. These are much less painful than the standard needle and syringe. They are easy to use (in the form of a patch), comfortable and ecofriendly. A technology currently being used at Raphas for production of microstructures is called Droplet-born Air Blowing (DAB). Patch microstructure products overcome the disadvantages of existing transdermal drug delivery systems, while combining the effective aspects of needle and syringe delivery methods [55].

Exendin-4 tip loaded micro needle arrays were evaluated for characteristics and their acute efficacy was compared with subcutaneous injections in type 2 diabetic GK/SLC rats. These novel tip loaded microneedle arrays were found useful in the clinical applications of exendin-4 [56].

Novel self dissolving micro needle arrays from hyaluronic acid (HC) was fabricated, which contained a drug with relatively high molecular weight. The skin disruption caused by microneedle (MN) arrays was reversible, which indicated the safety of MN arrays. This study indicated that self dissolving hyaluronic acid microneedle arrays were an alternative to improve the transdermal delivery of drugs [57].

In one study, they developed novel insulin loaded Microneedle arrays fabricated from hyaluronic acid (HA). It demonstrated that these microneedles were found to be safe and possessed self dissolving properties, suitable hygroscopicity, dissolution properties, stability and drug releasing profiles [58].

In another study new transdermal drug delivery system alendronate using a self dissolving microneedle array was developed. It was found that absorption of Alendronate after the application of Alendronate –loaded microneedle arrays was almost equivalent to that after subcutaneous administration. Bioavailability of drug was apporimately 90% in rats. These findings indicated that these Alendronate-loaded Microneedle array has been a promising Transdermal Delivery formulation for the treatment of osteoporosis [59].

In the present review named “Microneedles - An archetype swing in transdermal drug delivery: A comprehensive review” new advances in transdermal drug delivery system (TDDS) using various carriers was discussed mostly emphasizing on the potential role of microneedles as transdermal drug delivery system. General fabrication technologies like lithography, thin film deposition on substrate, etching were discussed in brief whereas in the review “Microneedles for drug delivery: Trends and progress”, main emphasize was made on various technologies developed in microneedle research and showed the rapidly grown numbers of research papers and patent publications since the first invention of microneedles. This article provided research and industrial communities a valuable synopsis of the trends and progress that has been made in this field [60].

While comparing with the other review named A review on “Potential of combined ultrasound and microneedles for enhanced transdermal drug permeation” the former review differs few aspects. In the latter one, it was mainly focused on discussing the potential of microneedles and Ultraviolet combinational technique. Possible rays to achieve this combination and how this combination would enhance the permeability were discussed [61].

Patents on microneedles

Prausnitz *et al.* (2012) [62] have developed methods and devices for targeted drug administration to a patient's eye using microneedles. In one embodiment, the method included inserting a hollow microneedle into the eye sclera at an insertion site and infusing a fluid formulation of drug through the inserted microneedle and into the eye suprachoroidal space, wherein the infused fluid drug formulation flows within the suprachoroidal space away from the insertion site during the infusion. The fluid drug formulation may flow circumferentially toward the retinochoroidal tissue, macula and optic nerve in the posterior segment of the eye.

Lee *et al.* (2011) [63] have invented an drug delivery system of microneedle comprising of a housing that has an opening formed in the bottom wall and a microneedle device including a substrate along with a microneedle array formed protruding downward from the bottom surface of the substrate so as to pierce the skin. One or more capsule-disrupting micro-projections formed upwardly from the top surface of the substrate, and one or more drug delivery channels are formed so as to allowed the drug to be delivered from the top surface of the substrate to the bottom surface of the substrate through the microneedle device which is seated in the opening of the housing in such a fashion as to be hermetically sealed with the housing bottom wall and a drug-containing capsule was mounted in the housing in such a fashion so as to be spaced apart from the microneedle device, and adapted to be moved to a position where the drug-containing capsule can come into contact with the micro-projections to allow the drug-containing capsule to be disrupted by the micro-projections.

Prausnitz*et al.* (2011) [64] have patented methods and devices for drug administering to the eye of the patient's. The methods include (a) the hollow microneedles inserted into the sclera or corneal stroma without penetrating across the sclera or corneal stroma; and (b) infusing a fluid drug formulation through the microneedle and into the sclera or cornea. It further may include partially retracting the microneedle before infusion to enhance delivery. Alternatively, the methods may include (a) inserting a solid microneedle into the sclera or corneal stroma without penetrating across the sclera or corneal stroma, wherein the solid microneedle comprises a first quantity of a drug formulation and inserting causes the solid microneedle to form a pocket in the sclera or corneal stroma; and (b) releasing the drug formulation into the pocket to form a drug depot, whereby a drug is released from the depot. The methods and devices may include an array of multiple microneedles.

Shaari *et al.* (2011) [65] have invented a nasal delivery device comprising one or more microneedles. In certain embodiments, the nasal delivery device comprises a substrate for administration of a composition to the nasal and/or sinus mucosa, wherein the substrate is non-absorbent and comprises one or more microneedles. In some embodiments, the nasal delivery device comprises a reservoir comprising one or more therapeutic agents, wherein the reservoir is in fluid communication with one or more microneedles.

Moore *et al.* (2011) [66] have developed a novel method of vaccination using microneedle arrays which, when applied to the skin of a subject, create a defined total pore volume. Arrays may be chosen of varying total microneedle volumes (small, intermediate or large) for use in immunisation regimes to induce different T-cell and antibody responses in the subject. This invention also provides kits for use in such vaccination method(s) comprising the appropriate microneedle array(s).

Kaspar *et al.* (2011) [67] have come up with an invention which relates to microneedle arrays and related systems. Particularly, microneedle arrays that are configured to deliver active agents, including nucleic acids and vaccines, are provided. Additional related methods of vaccinating and minimizing the amount of vaccine necessary for effective inoculation are also provided.

Yuzhakov*et al.* (2010) [68] have developed methods for use of microneedle arrays on a flexible or contoured surface of tissue. In one embodiment, the microneedle array included a plurality of microneedles, each was having a base portion, a tip end portion distal to the base portion, and body portion there between and a flexible substrate which comprised a plurality of apertures, each of which were defined by (i) a plurality of substrate elements which were integral with the microneedles base portions, and (ii) at least one spring element was connected to two of the substrate elements. The spring element may include a curved element, such as a U-shaped, S-shaped, or C-shaped element. Apertures may be defined, for example, by two substrate elements, which connected to three or four spring elements. A skin patch was provided for diagnostic or therapeutic applications, which included the microneedle array and an adhesive material.

A novel method of immunogenicity enhancement using a microneedle device has been developed by Nozaki *et al.* (2010) [69], which can enhance the immunogenicity of an influenza vaccine. In the immunogenicity enhancement method by using a microneedle device, a microneedle device comprised microneedles composed of a poly (lactic acid) coated with an influenza vaccine was put on the skin so as to administered the influenza vaccine transdermally, wherein the influenza vaccine comprised an antigen comprising a type-A strain (H1N1), a type-A strain (H3N2) and a type-B strain as active ingredients. After the transdermal administration, lauryl alcohol was applied to a part on the skin on which the microneedle device has been put.

Pettis *et al.* (2009) [70] have invented an injectable substance delivery pen comprising of a microneedle hub assembly removable engaged with a pen device body which included a cartridge, a plunger, and a drive mechanism. The hub assembly included at least one microneedle for intradermal or shallow subcutaneous injection of the contents of the cartridge. The cartridge, plunger and drive mechanism components of the pen body were fabricated of non-compressible and non-compliant materials to allow effective communication of the cartridge contents via the microneedle patient interface.

Eriksson *et al.* (2008) [71] have patented an apparatus to enabled the direct gene transfer of genetic material into a target cell site ("microseeding"), as a means of obtained long term expression of non-native or native polypeptides in a host. The apparatus included a matrix of microneedles that oscillate at a predetermined frequency and received the genetic material from a delivery system that wss integrated with the apparatus.

Prausnitz *et al.* (2007) [72] have developed simple microneedle devices for drug delivery across or into biological tissue, which permitted delivery of drug at clinically relevant rates into or across skin or other barriers of tissues, with minimal or no pain, irritation or damage to the tissue. The devices included a substrate to which a plurality of hollow microneedles were attached or integrated, and at least one reservoir, containing the drug, selectably in communication with the microneedles, wherein the volume or amount of drug to be delivered can be selectively altered. The reservoir can be formed of a deformable, preferably elastic, material. The device typically includes a means, such as a plunger, for compressing the reservoir to drive the drug from the reservoir through the microneedles. In one embodiment, the reservoir was a syringe or pump connected to the substrate.

Kirby *et al.* (2006)[73] have patented a device for transport of material across or into a biological barrier , with the help of a puncturing projection associated with first portion of a substrate, the first portion of the substrate being movable between a first substrate position in which, in use, the puncturing projection was in puncturing contact with the biological barrier so as to form a flow path for said material across or into said biological barrier and a second substrate position in which, in use, the puncturing projection was at least partially retracted from said first position, wherein the substrate was resiliently deformable or displaceable from the first to the second substrate position by a biasing means associated with said substrate.

Eriksson *et al.* (2003) [74] have developed a method for direct gene transfer of genetic material into an internal or external target cell site ("microseeding"), in optional combination with a wound treatment chamber, which was particularly effective as a means of obtaining long term expression of native or non-native polypeptides in a host. A wide variety of proteins and materials can be expressed, either for secretion into the general blood and lymphatic system, or to alter the properties of the protein, for example, to not express proteins eliciting an immune response. The use of the optional wound chamber system for gene transfer to skin target sites also allowed non-invasive assessment of the success of transfered by assaying for the presence of the expressed protein in wound fluid, in contrast to the prior art used of invasive techniques, such as biopsies, in order to achieve the same assessment of early expression.

Prausnitz*et al.* (2003) [75] have invented microneedle devices for transport of therapeutic and diagnostic materials and/or energy across tissue barriers, and methods for manufacturing the devices. The microneedles are hollow and/or porous and have diameters between about 10 nm and 1 mm. The microneedle devices permit drug delivery (or removal or sensing of body fluids) at clinically relevant rates across skin or other tissue barriers, without damage, pain, or irritation to the tissue. Micro fabrication techniques are used to cost-effectively produce arrays of microneedles from metals, silicon, silicon dioxide, ceramic, and polymeric materials. Methods are provided for making porous or hollow microneedles.

A method for directly delivering the drug into intradermal space within mammalian skin has been developed by Pettis*et al.* (2002) [76] which involved administering the substance through at least one small gauge hollow needle having an outlet with an exposed height between 0 and 1 mm. The outlet is inserted into the skin to a depth of between .3 mm and 2 mm such that the delivery of the substance occurs at a depth between .3 mm and 2 mm. Various on drug delivery system based on microneedles are quoted in Table 3.

Various applications of microneedles in efficient drug delivery are quoted in Table 1

Table 1: Applications of microneedles in efficient transdermal drug delivery.

S.NO	Drug	Transdermal system	Application
1	Anti restenosis	Micro needle patches	Targeted drug delivery in atherosclerosis [77]
2	Bovine serum albumin	Chitosan microneedles patches	Promising device for sustained delivery of macriolecules [78]
3	Bovine serum albumin	Polymeric Microneedles	Potentially deliver bovine serum albumin [79]
4	Desmopressin	Microneedles	Enhanced bioavailability, in the treatment of enuresis [80]
5	Immunization (Antigen)	Microneedle array patch system	Effective immunization [81]
6	Insulin	Micro needle patches	Reduced glycerol level up to 80% within 4 hrs [4]
7	Insulin	Fabricated arrays of solid microneedles	Increases insulin transdermal delivery to lower the blood glucose level by 80% [82]
8	Insulin	Microneedles	Increased percutaneous administration of insulin [83]
9	Lidocaine Hydrochloride	Microneedle array	Repeatable and robust penetration across stratumcorneum and epidermis [84]
10	Naltrexone	Microneedles	Enhanced transdermal delivery [85]
11	Naltrexone with Diclofenac	Microneedle array	Effective transdermal delivery [86]
12	Vaccination(Influenza vaccine)	Microneedle patches	Enhanced immune response as compared to intramuscular injection [4]
13	5-amino levulinic acid	Microneedle array	Enhanced production of photo sensitizer protoporphyrin IX [87]

Delivery of vaccine via solid as well as hollow microneedles can occur through various pathways such as by piercing the skin and then followed by the application of vaccine formulation over the skin or by entrapping or coating the vaccine over or within the microneedles for frequent release of drug into the skin. Use of modified syringe or pump can also be used to be injected into the skin. These can also deliver inactivated viruses, trivalent split antigen vaccine; DNA Plasmids encoded with influenza hemagglutinin. Microneedle patches are also gaining increasing focus as an alternative method to deliver vaccine [88]. Use of hollow microneedles in influenza vaccination has widespread clinical utility worldwide. Despite of having all the applications, microneedles are also utilized nowadays for the ocular delivery of bioactives and other ocular drugs. Inspite of drug delivery, microneedles are also used in bio-sampling, local cell treatment etc [89]. Application of microneedles relies mainly on the function of the device that accelerate insertion of microneedles, its sufficient infusion into the skin, followed by skin recovery, drug delivery, stability and storage in addition to lack of skin irritation, infection and pain and also included drug safety and efficacy. Various formulations based on microneedles have also come into the market due to its effectivity in the treatment via transdermal route. Marketed formulations based on microneedles as a transdermal system are quoted in Table 2.

Table 2: Marketed formulations based on microneedles as a transdermal system.

Market product	Description	Manufacturer
AdminPen™	Microneedle array-based pen-injector device	AdminMed [90]
AdminPatch™	Microneedle array	AdminMed [90]
Macroflux®	Microneedle array	MacrofluxR Corporation Inc [91]
Microcore®	Dissolvable peptide microneedle patch	Corium [92]
Microjet®	Intradermal microneedle injection system	NanoPass [92]

Table 3: Patents on drug delivery system based on microneedles.

Title	Patent number	Inventors	Year	Reference
Methods and devices for delivery of the drug to ocular tissue using microneedle	US8197435	Prausnitz et al.	2012	[62]
Drug delivery system of microneedles including movable drug-containing capsule	WIPO016615	Lee et al.	2011	[63]
Method for delivery of drug to ocular tissue using microneedle	US7918814	Prausnitz et al.	2011	[64]
Microneedle nasal delivery device	WIPO112713	Shaari et al.	2011	[65]
Vaccination method using microneedle arrays	WIPO135309	Moore et al.	2011	[66]
Microneddle arrays for delivery of active agent	WIPO156641	Kasparet al.	2011	[67]
Tissue conforming microneedle array and transdermal patch drug delivery or biological fluid collection	US7785301	Yuzhakov et al.	2010	[68]
Microneedle device, and method for increasing the efficacy of influenza vaccine	WIPO001671	Nozaki et al.	2010	[69]
Microneedle-based pen device for delivery of drugs	US7556615	Pettis et al.	2009	[70]
Microseeding device for delivery of gene by microneedle injection	US7422574	Eriksson et al.	2008	[71]
Microneedle drug delivery device	US7226439	Prausnitz et al.	2007	[72]
Microneedle device for transdermal transport of fluid	WIPO064271	Kirby et al.	2006	[73]
Delivery of gene to periosteal cells by microneedle injection	US6525030	Eriksson et al.	2003	[74]
Microneedle device for transport of molecules across tissue	US6503231	Prausnitzet al.	2003	[75]
Microneedle for delivering a substance into the dermis	WIPO002179	Pettiset al.	2002	[76]

Combinational approaches:

Tao H, Diganta BD., studied the effect of permeability enhancement for transdermal delivery of large molecule using low frequency sonophoresis combined with microneedles. They found that the transdermal drug delivery was limited by high resistance of skin towards diffusion of high-molecular-weight drugs. This was mainly because of the fact that the outer layer of the skin, that is the stratum corneum, can prevent diffusion of molecules whose molecular weight is greater than 500 Da. Sonophoresis can be used to enhance the permeability of the skin. However, in the delivery of large molecules, ultrasound alone cannot provide sufficient permeability enhancement. In addressing this issue, they proposed optimized ultrasound combined with microneedles to further increase the permeation rates. In this paper, they used porcine ear skin to simulate human skin and treat the skin samples with both ultrasound and microneedles. Further, bovine serum albumin (BSA) was used as a model of larger molecular weight molecule. Our results show that the permeability of BSA is increased to 1 μm/s with the combination of 1.5 mm microneedles patch and 15-W ultrasound output which was about 10 times higher than the permeability obtained in passive diffusion. Diffusion with only microneedles or ultrasound pre-treatment was also tested. The maximum permeability from microneedles and ultrasound treatment reached 0.43 and 0.4 μm/s, respectively [93].

Dongwei Z, Diganta BD, Chris DR. performed the experimental study of microneedle-assisted microparticle delivery. They said a set of well-defined experiments has been carried out to explore whether microneedles (MNs) can enhance the penetration depths of microparticles moving at high velocity such as those expected in gene guns for delivery of gene-loaded microparticles into target tissues. These experiments were based on applying solid MNs that were used to reduce the effect of mechanical barrier function of the target so as to allow delivery of microparticles at less imposed pressure as compared with most typical gene guns. Further, a low-cost material, namely, biomedical-grade stainless steel microparticle with size ranging between 1 and 20 m, had been used in this study. The microparticles were compressed and bound in the form of a cylindrical pellet and mounted on a ground slide, which were then accelerated together by compressed air through a barrel. When the ground slide reached the end of the barrel, the pellet was separated from the ground slide and was broken down into particle form by a mesh that was placed at the end of the barrel. Subsequently, these particles penetrate into the target. This paper investigated the implications of velocity of the pellet along with various other important factors that affected the particle delivery into the target. Their results suggested that the particle passage increased with an increased in pressure, mesh pore size, and decreased with increased in polyvinylpyrrolidone concentration. Most importantly, it was shown that MNs increased the penetration depths of the particles [94].

CONCLUSION

Microneedles have been observed as a potential carrier in the form of array or a patch for the delivery of numerous macromolecular drugs for the effective transdermal delivery. Various research reports studied confirmed that microneedles are must to be the prominent carriers for enhancing the permeation deep into the systemic circulation and providing an effective, safe and painless route for the drug delivery. These simple systems are gaining slowly, superior position and would qualify to be one of the important devices for controlled release of drug in future. Thus, it was concluded that, these systems represented it to be a sufficient and greater carriers as compared to other needle based formulation for the transdermal delivery.

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