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Microneedles- An Innovative Approach As Skin Permeation Enhancer

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ABSTRACT

Transdermal delivery holds a promising carrier in the transport of drugs to get direct access across the skin deep into the systemic circulation. It has attracted many researchers due to various biomedical advantages. The barrier nature of stratum corneum poses a threat to the drug delivery. Recently, the use of microneedles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. In the microelectronics industry, microneedles have been fabricated with a range of sizes, shapes and materials. Most drug delivery studies have emphasized solid microneedles, which have been shown to increase skin permeability to a broad range of molecules and nanoparticles in vitro Microneedles can be used to enhance transdermal drug delivery. In this review different types of microneedles are described and their methods of fabrication highlighted. There are also hydrogel-forming microneedles. These are innovative microneedles which do not contain drugs but imbibe interstitial fluid to form continuous conduits between dermal microcirculation and an attached patch-type reservoir. Several microneedles approved by regulatory authorities for clinical use are also examined. It also focuses on the delivery of various therapeutic agents effectively different carriers emphasizing mainly on the potential role of microneedles as transdermal system.

Keywords: Transdermal drug delivery, Injection, Needles, Permeation, Skin, Systemic circulation

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INTRODUCTION

When oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. Hypodermic needles are used in clinical practice to deliver medications across the skin into the bloodstream. Injections with hypodermic needles are important from a clinical standpoint, but painful. They may also induce hypersensitivity; bruising, discomfort and bleeding at the site of administration, and in some cases are associated with risks of contamination. There are other concerns linked to their use including accidental needle stick injury and the necessity to train medical staff regarding the proper use of needles [1]. To increase skin permeability, a number of different approaches has been studied, ranging from chemical/ lipid enhancers [2, 3] to electric fields employing iontophoresis and electroporation [4, 5] to pressure waves generated by ultrasound or photoacoustic effects [6, 7]. Although the mechanisms are all different, these methods share the common goal to disrupt stratum corneum structure in order to create ‘‘holes’’ big enough for molecules to pass through. The size of disruptions generated by each of these methods is believed to be of nanometer dimensions, which is large enough to permit transport of small drugs and, in some cases, macromolecules, but probably small enough to prevent causing damage of clinical significance. A variety of drugs has been reported to be delivered transdermally to overcome the limitations being exhibited by the classical oral, injectable, and inhaler systems and about 74% of the drugs taken orally today are not found to be as effective as required [9]. To deliver the therapeutically active amount of drug through the human skin to produce systemic effects, the properties of the skin such as morphological biophysical and physicochemical etc are to be considered [8]. So, to improve such characteristics and also to improve the problems associated with conventional dosage forms, transdermal drug delivery system has emerged as a novel carrier in the new era of research [9]. Although the microneedles concept was proposed in the 1970s [10], it was not demonstrated experimentally until the 1990s when the microelectronics industry provided the microfabrication tools needed to make such small structures. Since the first studies of transdermal drug delivery in 1998 [11], there has been rapidly increasing interest in the field, with most activity in the microfabrication community to develop novel needle fabrication technologies and the drug delivery industry to develop microneedles for pharmaceutical applications. Microneedles are currently being utilized to enhance transdermal delivery of small and large molecules. With the emergence of microfabrication manufacturing technology over the past several decades, Microneedles have been developed by academic laboratories and pharmaceutical companies [12-15].

Transdermal Microneedles create micron sized pores in the skin to enhance delivery of the drug across the skin [13, 15]. Microneedles are ideal for patient adherence as they do not stimulate nerves that are associated with pain. Microneedles improve patient compliance as patient with needle phobia will be more likely to apply the patch because of its painlessness [15.] The present review currently focuses on the use and development of microneedles as an enhancement strategy for transdermal drug delivery which significantly enhance the impact of drug delivery via transdermal route [17]. From the past ten years, microneedles were proposed as a mechanical carrier which pierces through the stratum corneum to create pores for the drug delivery without stimulating the pain nerves. Since then, this system has been emerged as potential carriers for transdermal applications [16.]

TRANSDERMAL DRUG DELIVERY USING MICRONEEDLES

Most work has focused on making microscopic holes in the skin by inserting solid microneedles made of silicon or metal. The ‘‘poke with patch’’ approach uses microneedles to make holes and then apply a transdermal patch (or some prototype) to the skin surface. Transport can occur by diffusion or possibly iontophoresis if an electric field is applied. Another approach is ‘‘coat and poke,’’ where the needles are first coated with drug and then inserted into the skin. There is no drug reservoir on the skin surface; all the drug to be delivered is on the needle itself. A variation on this second approach is ‘‘dip and scrape,’’ where microneedles are first dipped into a drug solution and then scraped across the skin surface to leave behind drug within microabrasions created by the needles. Hollow microneedle designs and methods have also been studied using an approach more reminiscent of an injection than a patch. Although harder to make and use, hollow needles facilitate active fluid flow through the needle bore and into the skin, which can lead to much faster rates of delivery that can be modulated over time. Following is a summary of the literature on the use of microneedles for transdermal delivery of drugs.

TYPES OF MICRONEEDLES

Microneedles can be divided into four categories (Figure 1): hollow, solid, coated and polymer [18]. Hollow Microneedles are like regular hypodermic needles but shorter in length. A liquid formulation of the drug is infused through bores in the Microneedles. Solid Microneedles are used to create holes in the skin. Subsequently a patch is then applied. Coated MN are MN coated with the drug while polymer Microneedles are made from polymers that can be dissolving, nondissolving or hydrogel-forming.

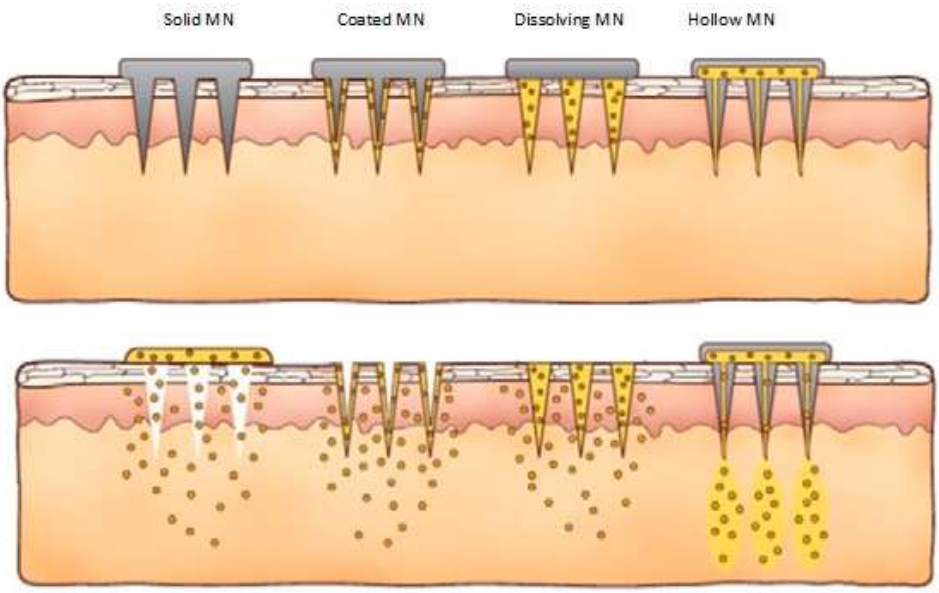

Figure 1: Different types of microneedles: solid, coated, dissolving and hollow from [19]

Hollow microneedles

Hollow microneedles contain a hollow bore in the centre 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. These microneedles are mainly employed to inject the drug solutions directly into the skin [21]. These are very expensive to prepare and require expensive micro fabrication techniques [20]. These micro needles contains hollow bore which offers possibility of transporting drugs through the interior of well defined needles by diffusion or for more rapid rates of delivery by pressure driven flow microneedles containing a hollow bore offer the possibility of transporting drugs through the interior of well-defined needles by diffusion or, for more rapid rates of delivery, by pressure-driven flow. A variety of hollow microneedles have been fabricated, but only limited work has been published on their possible use to deliver compounds into skin. These needles were fabricated using a micropipette puller and beveler with a tip radius of 60 Am and were inserted into the skin to a depth of 500– 800 Am. This study demonstrates microneedle-based drug injection into the skin. Hollow microneedles can be fabricated from a commercially available 30 gauge hypodermic needles [23]. Pressure, and thereby flow rate, can be changed in HM for a rapid bolus injection, a slow infusion or a varied delivery rate [22]. HM can also be used to administer a larger dose of drug solution [14]. Fabricated Hollow microneedles from 30G stainless steel needles [23]. The 4 × 4 pattern of holes was drilled in a polyetheretherketone mold (diameter 9 mm). Then, the needles were placed through the holes at a predetermined length of 300, 550, 700 and 900 μm. Hollow microneedles can also be fabricated

using other micro-electro-mechanical systems (MEMS) technologies such as laser micromachining, deep reactive ion etching, integrated lithographic molding technique, wet chemical etching and X-ray photolithography [22]. Hollow microneedles can deposit a compound directly into the viable epidermis or the dermis avoiding the stratum corneum. This is especially useful for the delivery of high molecular weight compounds such as proteins, oligonucleotides and vaccines. Transdermal delivery of insulin continues to represent a significant scientific challenge. It is desirable that hollow microneedles possess adequate mechanical strength and that the bores are not clogged during transdermal drug delivery. Even though, a number of fabrication techniques have been highlighted earlier, there is a need to continue research that will lead to a "gold standard" hollow microneedle drug delivery system.

Solid microneedles

These needles were inserted into cells and nematodes to increase molecular uptake and gene transfection. Shortly after this work was published, microneedles were developed for transdermal delivery applications, which have been shown to insert into skin. 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 enters [20]. These can be used by inserting the needles 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. Solid micro needles can be prepare by coating with the drug and then inserted into the skin. After removal of the micro needle containing device, drug will remain deposited within the skin membranes. Erodible micro needles when inserted into the skin, dissolves and the drug can easily be loaded into the soluble needles [24]. These microneedles can pierce through the superficial skin layers then followed by the delivery of drugs. It also suffers from some limitations such as in solid microneedle arrays, the drug delivered cannot easily flow via the holes present in the skin because it remains plugged by the microneedles. An application of a thick layer of drug formulation was not found to be the desirable because it reduces the sharpness of the microneedles and therefore made insertion more difficult and painful. These microneedles have the potential for reduced drug leakage resulting in improvement of drug delivery efficiency and the possibility of introducing multiple drugs [29]. The fabricated solid MN with rectangular cup shaped tip are 200 μm in height [28]. The cup shaped tips have dimensions of 60 × 60 μm (length × breadth) with a depth of 60 μm. The cups are filled with drug using a novel drop coating system [27]. Gupta fabricated stainless steel solid MN by laser cutting stainless steel sheets [26]. The desired microneedle shape and dimensions were

first drafted in AutoCAD software [28]. Stainless steel microneedles can also be made by wet-etching photolithographically defined needle structures from stainless steel sheets [29].

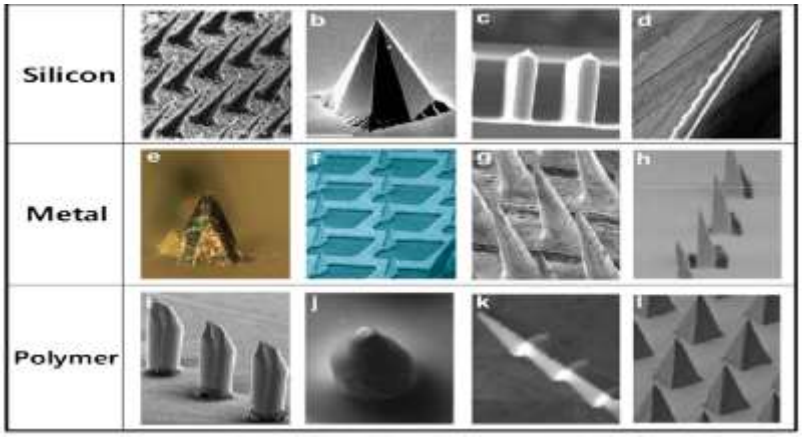

Figure 2:Solid microneedles fabricated from silicon, metal and polymer

The microneedles were successfully inserted into porcine skin and were shown to dissolve gradually at 0, 60, 120 and 180 s after insertion [30]. The microneedles contained methylene blue as model drug and successfully pierced porcine skin [30]. The microneedles were successfully inserted into porcine skin and were shown to dissolve gradually at 0, 60, 120 and 180 s after insertion 30. The microneedles contained methylene blue as model drug and successfully pierced porcine skin [30]. A microneedle roller is a device that contains MN mounted on cylindrical surface that rolls over the skin [18]. In this scenario, microneedles are mounted on a cylindrical surface and can be rolled across the skin. In vitro studies were performed with microneedle-treated porcine ear skin using vertical static Franz diffusion cells. Passive diffusion across untreated porcine skin served as control. Aliquots were taken every two hours for 12 h and analyzed by liquid chromatography–mass spectrometry. We used stainless steel microneedle arrays (750 μm) made by Microneedle Systems to facilitate the delivery of captopril and metoprolol tartrate across porcine skin. We studied the influence of microneedles rollers on the diffusion of these drugs [31]. Solid microneedles are also promising for the delivery of vaccines. Microneedle-mediated delivery of vaccines can lead to longer-lasting and more-robust antibody responses in comparison with intramuscular delivery [12].

Coated microneedles

Coated microneedles refer to microneedles which are coated with the drug-containing dispersion. A plethora of techniques has been used in the literature to prepare coated microneedles. An approach using electrohydrodynamic atomisation (EHDA) principles in the preparation of smart microneedle coatings was reported in the literature [32]. Stainless steel (600–900 μm in height)

microneedles were coupled to a ground electrode (in the EHDA coating set-up) with the deposition distance and collecting methodology varied for an ethanol:methanol (50:50) vehicle system. The authors used this technique to prepare nano- and micrometer-scaled pharmaceutical coatings [32]. Fluorescein dye (serving as potential drug, sensory materials or disease state markers) and polyvinylpyrrolidone (PVP, polymer matrix system) formed the remaining components of the coating formulation. Based on these excipients and by varying the coating process, particles (100 nm to 3 μm) and fibres (400 nm to 1 μm) were deposited directly on microneedles in controlled and selectable fashion [32]. Ma and Gill used a polyethylene glycol matrix containing a water insoluble drug lidocaine to coat solid microneedles [33]. Uniform coatings were obtained on microneedle surfaces.

Dissolving microneedles

These include the one-step application process which is convenient for patients. Dissolving microneedles are fabricated on the basis of the "poke and release" principle. They are made from polysaccharides or other polymers. These microneedles release encapsulated drug into the skin following application and dissolution. Micromoulding is the preferred fabrication method for making dissolving microneedles. Certain drugs and vaccines are thermolabile so moulds are often filled with solutions of drugs and excipients and then dried under mild conditions. The fabrication process involves pouring the polymer solution into female molds, filling the microcavities of the mould under vacuum or pressure, drying under ambient conditions, centrifugation or pressure [34–36].

MECHANICSM OF MICRONEEDLE INSERTION INTO SKIN 37

The mechanics of microneedle insertion have received only limited attention, but are critically important to practical applications. Only microneedles with the correct geometry and physical properties are able to insert into skin. Some needle designs require only insertion by hand, whereas others benefit from high-velocity insertion, as mentioned above. When the force required for insertion is too large, needles can break or bend before insertion occurs. To determine the effect of microneedle geometry on the force of insertion, individual microneedles were inserted into the skin of human subjects while recording the force and displacement of the needle, as well as monitoring skin resistance (which was used to indicate needle insertion into the skin). Forces of insertion varied from 0.1 to 3.0 N (i.e. 10–300 g) and showed an approximately linear dependence on the area of the needle tip. Insertion force was found to be independent of wall thickness; thin-walled hollow needles and solid needles with the same outer tip radii required the same force of insertion. Almost all needles tested had margins of safety greater than one and some were greater

than ten. The largest margin of safety was achieved using needles with small tip radius (to facilitate insertion) and large wall thickness (to provide strength).

LACK OF PAIN CAUSED BY MICRONEEDLES 38

Microneedles are of interest primarily because they offer the promise of painless drug delivery. Because the skin's stratum corneum barrier has no nerves, skin anatomy provides the opportunity to pierce needles across the stratum corneum without stimulating nerves. In current practice, there is no evidence of microneedles penetrating just 10–20 Am across stratum corneum without entering the viable epidermis, where nerves are found. Instead, microneedles are inserted at least into the epidermis and sometimes into the superficial dermis, as discussed above. Nevertheless, microneedles are still reported as painless, probably because their small size reduces the odds of encountering a nerve or of stimulating it to produce a painful sensation.

FORMULATION DESIGN PARAMETERS [39]

The general design parameters that are to be considered in the development of microneedles are that these should be capable enough to insert into skin without breakage. Polymers should be selected to have sufficient mechanical strength and should be biocompatible. They should not produce any pain. The geometry of the micro needle is also very important, where sharpness of tip strongly effects the microneedles insertion into skin.

CONTROLLED DRUG RELEASE

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

Penetration

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

Ruggedness

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

DIMENSIONS OF MICRONEEDLES

The dimensions of micro needles can vary depending on the types of micro needles. Typical microneedle geometries may ranges from 150-1500 microns in length, 50-250 microns in base width, and 1-25 microns in tip diameter. The tips of microneedles are of different shapes like

triangular, rounded or arrow shaped. The hollow microneedle arrays are fabricated with lumen diameter of 30 micro meters and height 250 micro meters. Centre to centre hollow micro needle array 150µm and the axis of lumen is fabricated with the distance of 10 micro meters to the axis of outside column.

MATERIALS USED FOR CONSTRUCTION

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

ADVANTAGES OF MICRONEEDLES

The major advantages associated with the use of microneedles over traditional needles are when it is inserted into the skin it bypasses the stratum corneum, can be fabricated, and easily penetrated across the stratum corneum. Thus, reduces the chances of pain, infection, or injury. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system. These systems could provide highly targeted drug administration to individual cells and are capable of very accurate dosing, complex release patterns, local delivery and biological drug stability enhancement by storing in a micro volume that can be precisely controlled [47].

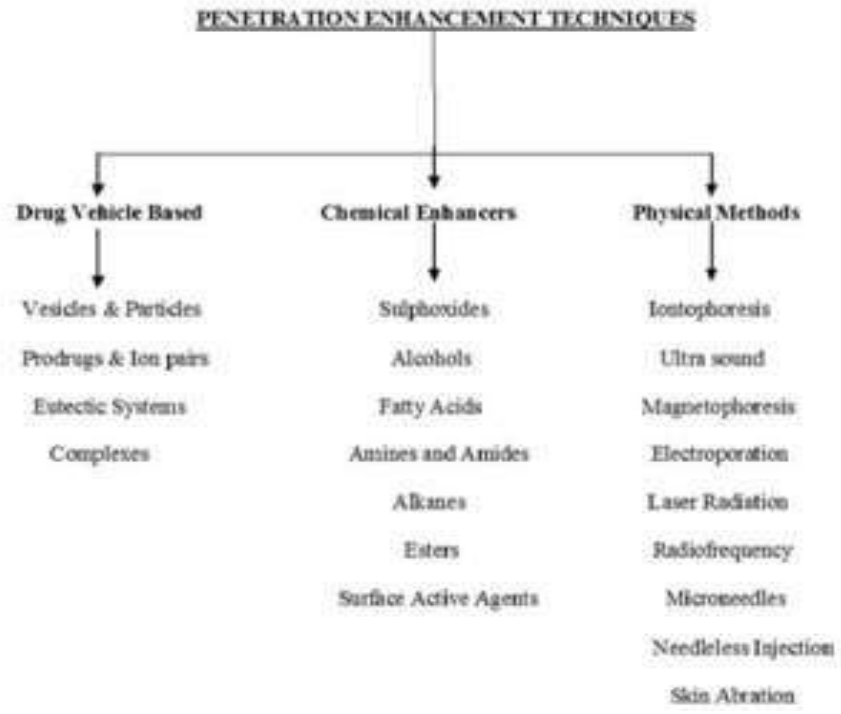

Figure 3: Various Penetration Enhancement Techniques for Improved Transdermal Drug Delivery [40]

EVALUATION PARAMETERS FOR MICRO NEEDLES

In-vitro study of microneedles

In vitro evaluation microneedles are accomplished by using various mediums like agarose gel and methanol 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.

Method 1

In vitro methods tested the delivery efficacy of the microneedles. In this test, the microneedles are integrated with Paradimethylsiloxane (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 [41].

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 [41].

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 [41].

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, genotoxicity, skin sensitization and allerginisation.

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 the skin [41].

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 [41].

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 5s up to 80 μg [42].

DRUG TRANSPORT VIA MICRONEEDLES

Drug delivery through microneedles can occur via two main pathways i.e. poke with patch or coat and poke method. Microneedles were prepared with a dry-film coating of antigen and then inserted into the skin of hairless guinea pigs in vivo using a high-velocity injector. Insertion depth was shown to average 100 Am, with 300 Am as the maximum depth. A range of doses was given by varying the antigen solution concentration coated onto the needles and the number of needles used. In case of poke with patch technique pores are firstly made on the skin by microneedles and then after the removal of micro needles drug is applied on the skin. Where as in case in coat and poke method the microneedle surface is coated with the drug and then these microneedles is applied on the skin. So, drug transfer will occur via the needles surface [43]. With the development of polymeric microneedles, a third approach was further developed in which drugs can be encapsulated in the polymeric matrix and released from the polymer upon application on the skin. Among all these approaches, coated microneedles are the most attractive mode for the delivering a rapid bolus consisting of high molecular weight molecules into the skin and can be considered similar to a simple band- aid like system for self administration. Further, this mode may also enhance their long term stability even at room temperature. Among variety of coating techniques like dip coating, roll coating and spray coating, dip coating is particularly appealing for coating micro needles because of its simplicity and ability to coat complex shapes. Dip coating has been developed to coat macroscopic objects mostly by submerging them completely within the coating solution because surface tension becomes dominant on the micron scale [20]. Some needles can easily beinserted by hand whereas other needles required high velocity insertion force [44].

Table1: Delivery of various drugs through different transdermal carriers

Drug	Therapeutic category	Carrier	Conclusion
Ketoconazole	Anti-fungal	Ethosomes	Enhanced transdermal permeation [17]
Clotrimazole	Anti-fungal	Ethosomes	Enhanced dermal delivery with better efficiency [19]
Ketoconazole	Anti-fungal	Ethosomes	Treatment of dermal infections with better efficiency [24]
Bleomycin	Anticancer	Electroporation	Effective delivery of electrical pulses to the tumour [25]
5-fluorouracil	Antineoplastic	Prodrug	approach 25 times enhanced permeability [26]
Diclofenac	NSAID	Iontophoretic	Effective plasma concentration within 1 hr.[29]
Salbutamol	Bronchodilator	Iontophoretic	Increased transdermal flux [31]
Betamethasone-17-benzoate	Anti-inflammatory	Chemical enhancer	Enhanced in vivo bioavailability [26]

APPLICATIONS IN DRUG DELIVERY

Most bio therapeutic agents and vaccines are injected by the use of hypodermic needle. Use of injection possesses the advantage of providing a low-cost, rapid and direct way to deliver almost all types of molecules into 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 various drugs cannot be given by this route due to poor absorption and drug degradation in the gastrointestinal tract and liver. 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 improving the patient compliance and safety. As a micron-scale device, a microneedle should be capable enough to deliver the drug as well as to avoid pain, fear and the need for expert training to administer. In addition to this, a microneedle allows precise tissue localization of delivery, such as within the skin, the suprachoroidal space of the eye, and the cell nucleus. Most applications of microneedles studied till now have emphasized mostly to drug and vaccine delivery to the skin. Conventional transdermal drug delivery system is limited by the barrier nature of the stratum corneum. Various chemical, biochemical and physical methods have been studied to enhance the skin permeability. Microneedles, in comparison to all the methods, can be prepared as

a low-cost patch that is simple for patients to apply for delivery of bio macromolecules [22], macromolecules like insulin, growth hormones, immunobiologicals, proteins and peptides [45]. Microneedles can also be employed for targeted vaccine delivery to antigen-presenting cells in the skin and is of keen interest nowadays. Other applications of microneedles have also been such undergo development like drug delivery to the eye, especially via the suprachoroidal space, has received recent attention. As an extension of micropipette techniques, microneedles have been used to deliver molecules into cells and their nuclei, among other laboratory applications [22]. Microneedles have also gain 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 [45].

Table 2: Applications of microneedles in efficient transdermal drug delivery [56, 58]

Drug	Transdermal system	Application
Anti restenosis	Micro needle patches	Targeted drug delivery in atherosclerosis
Insulin	Microneedles	Increased percutaneous administration of insulin
Immunization (Antigen)	Microneedle array patch system	Effective immunization
Lidocaine Hydrochloride	Microneedle array	Repeatable and robust penetration across stratum corneum and epidermis
Recombinant Human Insulin	Microneedles hydrogel patch	Sustained release of insulin

A review of the literature shows that microneedles can be fabricated by a number of different methods to yield a variety of needle sizes, shapes and materials. Solid microneedles have been shown to increase transdermal delivery by ‘‘poke with patch,’’ ‘‘coat and poke,’’ and ‘‘dip and scrape’’ methods, and hollow Microneedles either in the form of patch or an array have been observed as a potential carrier for the delivery of numerous macromolecular drugs for the effective transdermal delivery. Various research reports studied confirmed that microneedles are ought to be the prominent carriers for enhancing the permeation deep into the systemic circulation and providing a painless, effective and safe route for the drug delivery. These painless systems are slowly gaining importance and would qualify to be one of the important devices for controlled drug release in future. Thus, it was concluded that, these systems represented it to be an efficient and superior carriers as compared to other needle based formulation for the transdermal delivery microneedles have been shown to microinject into skin. It is known that as microneedles length

increases, there is a high probability that pain receptors located in the dermis may be stimulated. In spite of the above-mentioned limitations, the outlook for the use of these devices is promising even as more work needs to be done for microneedles to become routine drug delivery systems in clinical practice.

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