

Review Article

MICRONEEDLES: AN INNOVATIVE APPROACH TO TRANSDERMAL DELIVERY- A REVIEW

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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. However, various attempts have been made to modify this property of the skin and thus, to improve the transdermal delivery. Delivery of drugs via transdermal route has proved to be the convenient route for various clinical implications. Due to the limitation of oral drug delivery and the pain related with the use of needles in case of injections, drug delivery research has tremendously oriented towards the transdermal route. The objective of the present review is to focus on the recent innovations in transdermal drug delivery systems which can serve as a platform for the research and development of pharmaceutical drug dosage form for efficient transdermal delivery. It also focuses on the delivery of various therapeutic agents effectively via different carriers emphasizing mainly on the potential role of microneedles as transdermal system. Researches in the past few years showed that microneedles have emerged as a novel carrier and considered to be effective for improved and safe delivery of drugs. Thus, it was concluded that the development of microneedles created a new pathway in the field of drug delivery.

Keywords: Drug delivery, Enhanced, Needles, Permeation, Skin, Systemic circulation.

INTRODUCTION

Drug delivery via transdermal route across the skin provides the most convenient route for various clinical implications deep into the systemic circulation [1]. Therapeutic transdermal systems have been developed for controlled drug delivery [2]. Transdermal drug delivery system (TDDS) represents a system which delivers the drug (therapeutically active amount of drug) effectively across the human skin [3]. These are generally describes as the devices, enclosing drug molecules of defined surface area that delivers the predetermined amount of drug to the intact skin surface at a predetermined rate [4]. Transdermal delivery of systemically acting drugs uses the skin as an alternative route [5]. These systems are though designed to deliver the drug through the skin to the systemic circulation [6]. It is defined as a self-contained, innovative delivery system which is considered to deliver the drug upon application onto the skin, at a controlled rate to the systemic circulation [7]. For the transdermal system to be most effective, the drug must penetrate the skin barrier and reach the targeted site in the concentration required to produce systemic action [1]. In the modern therapy, increment of drug delivery across the human skin is very important. In this new era of development, transdermal delivery has gained tremendous achievements as it overcome the numerous problems related with the drug development [8]. Due to the limitation of oral drug delivery and the pain related with the use of needles in case of injections, drug delivery research has tremendously oriented towards the transdermal route [9]. It involves drug transport to the viable epidermis or the dermal tissue layers of the skin to produce local therapeutic action whereas a major portion of the drug is reached to the systemic circulation [10]. 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 [11]. 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 [10]. 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 [11]. About 40 % of the drug candidates employed for clinical evaluation nowadays is related to transdermal or dermal system.

With respect to the USA market of drugs which are under clinical evaluation, among 129 products, 51 % of it corresponds to the transdermal or dermal systems. Across the world, the transdermal patch market has reached to £2 billion, comprises of only ten drugs i.e. Scopolamine (hyoscine), nitro-glycerine, tulobuterol, clonidine, estradiol (with or without norethisterone or levonorgesterol), testosterone, fentanyl and nicotine with a lidocaine patch to be marketed very soon [1]. Transdermal route is one of the most significant routes for drug delivery [12]. The first transdermal system named as "Transderm-SCOP" was approved by FDA in 1979 for the prevention of nausea and vomiting.³ Developments in the field of transdermal research have gain lot of attention in the last few years due to their efficacious advantages over oral delivery system [6]. In the area of research in drug delivery, transdermal delivery is ought to be the most successful and innovative approach [5]. In spite of having so many advantages as discussed below, only few drugs are currently available in the market for transdermal delivery, as variety of drugs has a problem of limited permeability across the stratum corneum [5]. As stratum corneum, the innermost layer of epidermis, being lipophilic creates a barrier which provides resistance to the penetration of variety of drugs. For a drug to be delivered passively across the skin it must be of suitable lipophilicity and of molecular weight < 500 Da. However, where a drug does not possess ideal physicochemical properties, manipulation of the drug or vehicle to enhance diffusion becomes necessary [6]. So, to enhance the penetration across the skin, various methodologies were developed. These are use of various physical and chemical enhancers, development of new physical techniques such as electroporation, sonophoresis, iontophoresis, microneedles etc [6]. The relative importance of these alternatives depends on many factors that include the time-scale of permeation (steady-state vs. transient diffusion), the physicochemical properties of the penetrant (its pKa, molecular size, stability and binding affinity, and its solubility and partition coefficient), integrity and thickness of the stratum corneum, density of sweat glands and follicles, skin hydration, metabolism, and vehicle effects. Stratum corneum forms highly lipophilic membrane and provides the greatest resistance to penetration of drugs [6]. Thus, the major aim behind the development of transdermal systems is to cross the stratum corneum [12]. The related innovations in the field of research of drug delivery systems have not only resulted in the successful implementation of the novel pharmaceuticals, but also leads to the

development of new medical devices with the existing drugs. The designing of transdermal delivery system is one of the most innovative approaches in this aspect, with numerous advantages associated with this [13]. Transdermal drug delivery has made an important contribution to the medical practice, but still more developments are needed to achieve the target of this system as an alternative to oral drug delivery as well the use of hypodermic injections. First generation Transdermal system has gained increment in delivering the low dose of lipophilic drugs for clinical use, whereas second generation delivery systems which used chemical enhancers, non-cavitational ultrasound and iontophoresis have also used in some clinical implications. The third generation delivery systems focussed on targeting the stratum corneum by using microneedles, thermal ablation, electroporation, microderma abrasion etc. Microneedles are one of the recent approaches which are currently designing through clinical trials, in the delivery of macromolecules and vaccines like insulin, parathyroid hormone, and influenza vaccine. 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 [14]. 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 [9].

Advantages of transdermal drug delivery

There are numerous advantages related with the use of transdermal system for the effective delivery of drugs systemically. This includes improved patient compliance, avoids first pass hepatic metabolism in comparison to oral drug delivery systems. this system reduces the adverse effects associated with the drug caused due to overdose and is a convenient route and comprises of simple dosing, especially in case of transdermal patches that require only once in a week application which helps in patient adherence to drug therapy [3]. It also avoids gastrointestinal absorption and enzymatic or pH related deactivation, avoids gastrointestinal irritation and reduces fluctuations in plasma drug profile. Ease of therapy termination [6] and it co-ordinates controlled delivery of the drugs [15]. It enhances the bioavailability [15] as well as high concentrations of drugs delivered via this route can be localized at the site of action, thereby reducing the systemic drug levels and therefore also reducing the systemic side effects associated with the drug [5]. Drug delivery through transdermal route is an attractive method to transport drug or biological compounds due its advantage in reducing the pain and inconvenient intravenous injections [16].

Disadvantages of transdermal drug delivery system

Despite of having the above discussed advantages, it also possessed some limitation such as local irritation, erythema, itching, and local oedema may be produced by the drug or other excipients at the site of application especially in the patch formulation. Limited permeability across the skin may limit the delivery of number of drugs [3]. Systems containing small sized molecules can only easily penetrate the skin. Various attempts have been made to overcome these limitations [15].

Mechanism of transdermal permeation

Transdermal delivery of the systemically acting drugs to the targeted tissues showed that the drugs must possess some physico-chemical properties which act by facilitating the systemic absorption of drug across the skin and also enhance the drug uptake via capillary network into the dermal papillary layer. The rate of permeation as depicted by dQ/dt , across the skin layers can be expressed as

$$dQ/dt = P_s (C_d - C_r)$$

Where

C_d & C_r = concentration of skin penetrate in donor and receptor phase respectively.

P_s = Overall permeability coefficient of the skin.

$$P_s = K_s D_{ss} / h_s$$

Where

K_s = Partition Coefficient of the penetrant.

D_{ss} = Apparent diffusivity of penetrant.

h_s = Thickness of skin [7].

Various approaches for penetration enhancement

To overcome the limitations of transdermal system as well as to circumvent the barrier nature of stratum corneum, various approaches have been made to accomplish the main objective of permeation enhancement across the skin through transdermal route to increase the drug delivery. These are depicted in the figure (Figure 1).

Varieties of drugs have been reported to be delivered via this route using different penetration enhancement approaches as depicted in Table 1.

SKIN: a site for transdermal delivery

Skin is the multilayered organ of the human body, comprising of number of histological layers. It is one of the most extensive and readily accessible organs of the human body, exhibiting an extremely good barrier to the penetration of drugs. The skin of an average adult covers an area of about two square meters [7]. Its prominent characters include elasticity, ruggedness, and self-regenerating and have a thickness of 2.97 ± 0.28 mm [32]. It consists of 40-70 hair follicles and on an average of 200-250 sweat ducts on each centimetre square of the skin [7]. It acts as a medium of contact between the human body and the existing environment [33]. Skin is mainly acting as a protective layer providing protection against heat, light, injury and infection, inspite of performing a protective action, it also serves these purposes such as it regulates the temperature of the body, prevents loss of water and also inhibits the bacterial entry. It is considered as a site of drug application both for local and systemic effects [32]. It acts as an optimum interface for the systemic drug delivery [34]. The human skin consists of mainly three major layer i.e. epidermis, dermis, subcutaneous fat layer [35]. The stratum corneum also known as horny layer is ought to be the outermost layer of the skin and has been identified as the principal barrier for penetration of most of the drugs. The outermost layer of the skin represents the final stage of epidermal cell differentiation. The thickness of this layer is about 10 μ m, but a number of factors like the degree of hydration and skin location affect this thickness. The stratum corneum comprises of 10-25 rows of dead corneocytes embedded in a lipid matrix and the cells are joined together by desmosomes, which maintains the cohesiveness of this layer. The structure of the stratum corneum is comprised of approximately 75-80% protein, 5-15% lipid and 5-10% unidentified on a dry weight basis. The main lipids present in the stratum corneum include ceramides, fatty acids, cholesterol, and cholesterol sulphate and sterol/wax esters. These lipids are arranged in the form of multiple bilayers to form lipid lamellae. The brick and mortar model of the stratum corneum was first depicted by Michaels et al. [36]. The bricks correspond to dead keratinised corneocytes arranged in parallel plates, and the mortar represents the continuous interstitial lipid matrix. The mortar is not a homogenous matrix and lipids are arranged in the lamellar phase including some of the lipid bilayers in the gel or crystalline state. The extracellular matrix is further composed of intrinsic and extrinsic proteins such as enzymes. The barrier nature of the stratum corneum is studied to be due to the presence of multiple lipid bilayers located in the intercellular space. This bilayer prevents desiccation of the underlying tissues by inhibiting water loss and limits the penetration of substances from the external environment. As stratum corneum is considered to be the principal barrier to the permeation of various drugs across the skin, lots of efforts have been made effort in this aspect to investigate and develop the novel strategies to maximize the amount of drug permeated across this barrier. Thus, the invention of innovative approaches which focussed on changing the drug-vehicle interaction to enhance partitioning into the stratum corneum, or modifying the structure of the stratum corneum to make it less

resistance to drug diffusion have been made [5]. During the last few years the number of drugs incorporated in patches, has hardly gain any interest and only a little modification has been observed in the development of patches.

The changes were remaining confined only up to the refinement of the materials used [37]. So, various skin permeation enhancement techniques have been developed by various researchers in this new

world of research field of transdermal delivery for enhanced bioavailability [7]. All these techniques were designed to enhance the bioavailability and to explore the range of various drugs for which transdermal delivery is a viable option [38].

Use of microneedles is a recently developed novel approach for transdermal drug delivery [39] and it was shown to dramatically enhance the transdermal delivery of macromolecules [40].

Table1: Delivery of various drugs through different transdermal carriers.

DRUG	THERAPEUTIC CATEGORY	CARRIER	CONCLUSION
Ketoconazole	Anti-fungal	Ethosomes	Enhanced transdermal permeation [17]
Methotrexate	Anticancer	Iontophoretic	Effective drug release [18]
Clotrimazole	Anti-fungal	Ethosomes	Enhanced dermal delivery with better efficiency [19]
Ciclopirox olamine	Anti-fungal	Ethosomes	Enhanced accumulation [20]
Diclofenac Acid	NSAIDs	Patches	Effect drug release with enhanced permeation [21]
Fentanyl	Opioid Analgesic	Electroporation	Enhanced transdermal delivery [22]
Metoprolol	Cardiovascular agent	Electroporation	Enhanced transdermal delivery [23]
Ketoconazole	Anti-fungal	Ethosomes	Treatment of dermal infections with better efficiency [24]
Bleomycin	Anticancer	Electroporation	Effective delivery of electrical pulses to the tumour [25]
Betamethasone-17-benzoate	Anti-inflammatory	Chemical enhancer	Enhanced in vivo bioavailability [26]
6-Mercaptopurine	Antineoplastic	Prodrug	240 times enhanced permeability [27]
Hydrocortisone	Anti-inflammatory	Phonophoresis	Enhanced delivery for the effective treatment of polyarthritis [28]
5-fluorouracil	Antineoplastic	Prodrug approach	25 times enhanced permeability [26]
Diclofenac	NSAID	Iontophoretic	Effective plasma concentration within 1 hr.[29]
Timolol maleate	β -Adrenergic blocker	Iontophoretic	Increased transport in human skin [30]
Salbutamol	Bronchodilator	Iontophoretic	Increased transdermal flux [31]

Microneedles

Microneedles are one of the recently developed systems for drug delivery which is similar to traditional needles but the difference is these are fabricated on the micron scale and the size ranges from 1-100 microns in length and 1 micron in diameter. These are defined as micro-scale needles, arranged on a transdermal patch [41]. These are the microstructure system composed of micro sized array projection coated with a drug or vaccine [39]. These are considered as a combination of hypodermic needles as well as transdermal patches and effective enough to overcome the limitations being possessed by these two systems. Micro needles have been formulated as a novel drug delivery carrier for effective transdermal delivery, as these have been developed by fabrication, done by involving the tools of micro electronics so that the penetration up to hundred microns deep into the skin (Figure 2.) can be achieved in a painless manner [41].

Stratum corneum is the limiting barriers for the transport of several drugs and it will be bypassed by the use of microneedles [42]. These are tiny and sleek devices manufactured by silicon etching technology and micro-mechanical system manufacturing (MEMS) technique [43]. Microneedles are just like conventional needles fabricated only in micro scales [39]. These are mainly arranged in the form of arrays [42]. Micro needle arrays have been developed based on etching method used by microelectronics industry to

develop arrays of micron-sized needles. Various reports have shown to prepare silicon or metal micro needles, and also by using dextrin, maltose, glass. It is also a patch system which will be used for transdermal delivery [44]. As the success of transdermal delivery is limited by the fact that most of the drugs are insufficient in reaching the layers of the skin at the desired therapeutic rate. Thereby, the use of micro needle patches to enhance the skin permeability has been put forward and was found to be efficient in increasing transdermal delivery specifically for macromolecules [41].

The first report related to the development of micro needles for topical delivery was published in late 1990s, where the use of micro needles was emphasized in puncturing the skin for the enhanced permeability of the drug "calcein" (molecular weight 623 Da) across the human skin by four folds *in vitro*. Since then, a lot interest has been developed in this field both in terms of micro needle fabrication and drug delivery [44]. The first micro needle system comprises of a drug reservoir and projections which are extending from the reservoir to penetrate the stratum corneum and epidermis to deliver the drug [45]. The benefit of microneedles is that it provides pain free injection of large as well as small molecular weight pharmaceuticals [44]. This technique has been observed to improve the transdermal delivery of a variety of molecules like anthrax vaccine, β -galactosidase, calcein, bovine serum albumin, desmopressin, diclofenac, erythropoietin, methyl nicotinate, ovalbumin, plasmid DNA, insulin [44]. The micro needles are capable

to deliver the drug deep into the epidermis and dermis, which subsequently resulted in the uptake by capillaries into the systemic circulation without disturbing the nerves. Silicon is used for the fabrication of micro needles. It contains very sharp tips which are meant for piercing the skin [45]. Micro grams quantity of drugs can be delivered via micro needles. They act by temporary mechanical disruption of the skin. Drug in the form of bio molecules is enclosed within the micro needles which then undergo insertion within the skin in the similar way as drug is released from the patches into the blood stream. Needles undergo dissolution within a minute and released the drug at the desired targeted site [39]. Microneedles painlessly disrupt the barrier layer of the skin and create pores which results in an increased penetration. The First, microneedle systems were described in 1976 consisting of a drug reservoir and a plurality of projections (microneedles 50 to 100 mm long) extending from the reservoir, which penetrated the stratum corneum and epidermis to deliver the drug into the systemic circulation. Recently, as an outcome of the rapid innovations in micro fabrication technology in the last ten years, various cost-effective methods of producing microneedle devices have been came into existence. More recently, The ALZA Corp. has commercialized a microneedle technology named Macroflux which can either be used in combination with a drug reservoir or by dry coating the drug on the microprojection array. The dry coating method is being employed for better intracutaneous immunization [46]. Micro needle array devices have been undergo tremendous advancements delivery the drug in a controlled manner in a more convenient and lesser invasion method [16].

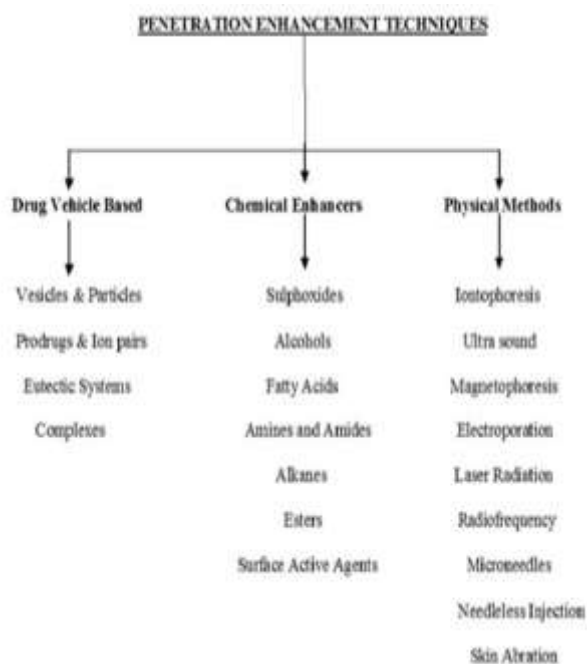


Fig. 1: Various penetration enhancement techniques for improved transdermal drug delivery[1].

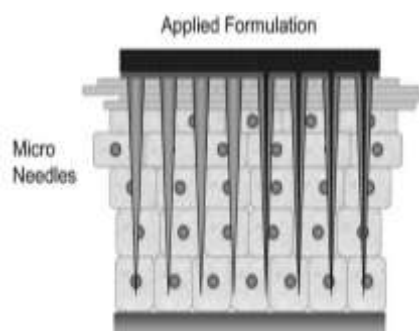


Fig. 2: Penetration of applied formulation via microneedles across the skin [25].

Types of microneedles

Micro needles are broadly classified into two types mainly. These are Solid micro needles and Hollow micro needles.

Solid microneedles

Solid micro needles are defined as the arrays of projections that are employed for creating holes in stratum corneum and are applied before the application of a drug and then removed afterwards. These can essentially create micron scale holes in the skin, through which drug molecules can easily enters [41]. 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 [44]. 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.

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. ⁴⁴ These microneedles are mainly employed to inject the drug solutions directly into the skin [42]. These are very expensive to prepare and require expensive micro fabrication techniques [41]. 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.

Formulation design parameters

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.

Characteristics of microneedles

The characteristics of micro needles include

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.

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.

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 150 μ m 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.

Effect of the Length of microneedle on pain

The designing of microneedles can be such so as to minimize the pain. Various studies revealed that specific micro needles of about a couple hundred microns length were reported to be painless. It was reported by various authors that 13-times increment in needle length (i.e., 500-1500 microns) increases the pain by 7 times (i.e., 5-35% caused by hypodermic needle). If the length remains constant, an increase in number of microneedles (i.e., 620 micron long) 10 fold from 5- 50 also increases the pain by 3 folds [41].

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].

Mechanism of permeation

The mechanism of delivery via microneedles is based on mechanical disruption of the skin and application of the drug or vaccine within the epidermis, from where it can more readily reach its targeted site of action. The drug such as biomolecules is entrapped within the microneedles, which are then further inserted into the skin and released the drug into the blood stream. The needles dissolve within minutes, released the entrapped drug at the intended site of delivery.

Evaluation Parameters

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. 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 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 [48].

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 [48].

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 [48].

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, 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 the skin [48].

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 [48].

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 μ g ovalbumin in 5s up to 80 μ g [49].

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 [48].

Drug transport via microneedles

Drug delivery through microneedles can occur via two main pathways i.e. poke with patch or coat and poke method. 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 [50]. 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. Encapsulation of drugs within the polymeric core has an advantage of a higher drug loading as compared to other systems developed so far. Hence encapsulation of drugs within the microneedles has received most attention from transdermal drug delivery scientists in the past few years [48]. 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 [41]. Microneedles having the specific geometric pattern and required physical properties can only be capable for insertion into the skin. Some needles can easily be

inserted by hand whereas other needles required high velocity insertion force [52].

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.

However, chemical and biochemical methods developed so far do not found to be broadly effective for delivery of bio therapeutics and vaccines across the skin. While physical methods have greater promise for delivery of macromolecules, they typically involve the use of sophisticated devices that are relatively large, costly and require training to use. 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 [53], macromolecules like insulin, growth hormones, immunobiologicals, proteins and peptides [54]. 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 [53]. 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 [54]. Microneedles have been employed as vaccine delivery system, as micron scale fabricated needles can deliver the vaccine into the skin by the simple self-administering method [55]. Table 2 implies the various applications of microneedles as a carrier system for improved transdermal delivery.

Table 2: Applications of microneedles in efficient transdermal drug delivery

Drug	Transdermal system	Application
Anti restenosis	Micro needle patches	Targeted drug delivery in atherosclerosis [56]
Insulin	Micro needle patches	Reduced glycerol level up to 80% within 4 hrs.[41]
Desmopressin	Microneedles	Enhanced bioavailability, in the treatment of enuresis [57]
Immunization (Antigen)	Microneedle array patch system	Effective immunization [58]
Vaccination (Influenza vaccine)	Microneedle patches	Enhanced immune response as compared to intramuscular injection [41]
Insulin	Fabricated arrays of solid microneedles	Increases insulin transdermal delivery to lower the blood glucose level by 80% [59]
Lidocaine Hydrochloride	Microneedle array	Repeatable and robust penetration across stratum corneum and epidermis [60]
Naltrexone with diclofenac	Microneedle array	Effective transdermal delivery [61]
5-amino levulinic acid	Microneedle array	Enhanced production of photosensitizer protoporphyrin IX [62]
Phenylephrine	Microneedle	Enhanced mean resting anal sphincter pressure in rats to treat faecal incontinence [63]
Bovine serum albumin	Polymeric Microneedles	Potentially deliver bovine serum albumin [51]
Recombinant Human Insulin	Microneedles hydrogel patch	Sustained release of insulin [64]
Bovine serum albumin	Chitosan microneedles patches	Promising device for sustained delivery of macromolecules [65]
Naltrexone	Microneedles	Enhanced transdermal delivery [66]
Insulin	Microneedles	Increased percutaneous administration of insulin [67]

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 coating or entrapping 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 [55]. Microneedle patches are also gaining increasing focus as an alternative method to deliver vaccine [68]. 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 [53]. In spite of drug delivery, microneedles are also used in bio-sampling, local cell treatment etc [69]. Application of microneedles relies mainly on the function of the device that accelerate insertion of microneedles, its efficient infusion into the skin, followed by skin recovery, drug delivery, stability and storage in addition to lack of pain, skin infection and irritation, and also including drug safety and efficacy [53]. Various formulations based on microneedles have also come into the market due to its effectivity in the treatment via transdermal route (Table 3).

Table 3: Marketed formulations based on microneedles as a transdermal system

Market product	Description	Manufacturer
AdminPen™	Microneedle array-based pen-injector device	AdminMed [70]
AdminPatch™	Microneedle array	AdminMed [70]
Macroflux ^R	Microneedle array	Macroflux ^R Corporation Inc.[71]
Microcore ^R	Dissolvable peptide microneedle patch	Corium [72]
Microjet ^R	Intradermal microneedle injection system	NanoPass [72]

Microneedles have also undergoing further research to have use in clinical implications to make them a better system to be effective in therapies, vaccinations and other useful applications in the field of pharmaceuticals [53].

CONCLUSION

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.

DECLARATION OF INTEREST

The authors declare no conflict of interest.

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