How to Cite:
Gulati, P., Pannu, S., Kumar, M., Bhatia, A., Mandal, U. K., & Chopra, S. (2022). Microneedles based drug delivery systems: an updated review. *International Journal of Health Sciences*, *6*(7), 209–242. https://doi.org/10.53730/ijhs.v6n7.10813

Microneedles based drug delivery systems: an updated review

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***Abstract*---**Transdermal drug delivery systems (TDDS) are used to deliver the drug(s) or the therapeutically active substances through topical route primarily through skin. Relatively very small numbers of drugs are administered transdermally because in many cases the physical properties of drugs, including polarity and molecular size,

International Journal of Health Sciences ISSN 2550-6978 E-ISSN 2550-696X © 2022.
Manuscript submitted: 9 March 2022, Manuscript revised: 18 May 2022, Accepted for publication: 27 June 2022

have limited its capacity to deliver the particular dug transdermally. Now a day's transdermal drug delivery techniques are used in various therapeutic areas like motion sickness management, heart disease treatment, hormones replacement, management of pain and smoking cessation etc. TDDS increases the potency of drugs and decreases the relative side effects. We reviewed different approaches used to enhance the drug delivery transdermally (e.g., particulate and vesicle based method, modified stratum corneum method, electrically based method, vehicle interaction method, removed stratum corneum method). As the stratum corneum is the main barrier in transdermal drug delivery, so the approaches can also be classified in three main categories in order to circumventing the barriers related to stratum corneum only (based on drug vehicle, chemical enhancers, physical enhancers). Here we focused mainly on the microneedles (MNs) based approach for transdermal drug delivery. The concept of microneedle based approach is defined by defining the classification of microneedles (i.e., solid microneedle, hollow microneedle , dissolving microneedle , coated microneedle), composition of microneedles (metal materials, inorganic materials, polymer materials), mechanism of drug delivery across the skin via microneedles(poke and flow approach, poke and patch, coat and poke, poke and release), manufacturing of microneedles, *In-vitro* evaluation test for microneedle based drug delivery systems and *in-vivo* study of MNs based drug delivery system on animal model.

***Keywords*---** Microneedle, Transdermal drug delivery, Penetration, *In-vitro-in-vivo,* Stratum corneum

Introduction

Delivery of drug by transdermally is the administration of active substance that has therapeutic application through the skin for the systemic effect. Only small number of products that are administered transdermally because in many cases the physical properties of drugs, including polarity and molecular size, have limited its capacity to deliver the particular dug transdermally. Similarly, insufficient bioavailability and the dermal irritation have been problematic.

Transdermal patch distributes a dose in a time release manner of medication via skin to bloodstream when applied on skin. It is medicated patch with adhesive properties. It can be used in the patients having problem in swallowing capsules, tablets or by the parentral administration of drug and because of these reasons patients sometimes ignores the schedules to take medicine in time. Now a day's transdermal patches are used in various therapeutic areas like motion sickness management, heart disease treatment, hormones replacement, management of pain and smoking cessation etc. On oral administration of drug, it shows numerous side effects like vomiting, nausea, loss of appetite, stomach upset, diarrhoea, weight gain, constipation, damage of liver, pain in upper stomach etc. TDDS increases the potency of drugs and decreases the relative side effects [1].

They can be named as skin patch. The rate of drug passage via skin to bloodstream is controlled by specific membrane. Some drugs are incorporated with substances like alcohol, to enhance the potency/capability of drugs to penetrate through the skin membrane. Skin patches eliminates the pain & fear caused by parentral or other mode of drug administration as they are applied on the skin directly. The first transdermal patch was approved in 1979 by FDA which was used to treat motion sickness. Some examples of drugs which are administered through the transdermal patches are nicotine, estrogen, nitro-glycerine etc. [2].

There are several formulations other then patch which can have given through the transdermal route of drug delivery are ointment, cream, lotion, liniment, gel, matrix formulation, reservoir system, foam based formulations, etc. If these formulations are administered through microneedles, then it may increase the permeation of drug through skin.

1.1. Transdermal drug delivery merits

Transdermal drug delivery has several advantages like it avoid first-pass metabolism, for prolong period of time constant blood level is maintained by this delivery system, the amount of dose administered decreased, side or unwanted effects decreased, GIT side effects decreased, one can remove the patches in case of toxic effects, it increases patient compliances. it can used in unconscious or nauseated patients, to improve the drug absorption from biological barrier one can modify the properties, in comparison with the buccal and nasal cavity large area of application [3], avoids inconvenience caused by parentral administration, frequent dosing is not required [4,5] it is easy to apply & easy to remove. the drugs with narrow therapeutic window can be administered through this route[6,7], painless application, avoid interaction of drug with enzymes, food, drink etc., they are easy to use and easy to remember, this is a better way for delivering the substances which are degraded by stomach or liver, it is suitable for geriatric patients who can't swallow medicine, can be self administration, cost effective, reduce patient variability (intra patient & inter patient) [8–12].

2. Approaches to enhance penetration [13]

In order to increasing penetration of drug and drug molecules through different layers of skin, penetration enhancers are used.

As the stratum corneum is the main barrier in transdermal drug delivery, so the approaches can also be classified in three main categories in order to circumventing the barriers related to stratum corneum only.

2.1 Drug/ prodrug

In order to increase the transdermal drug delivery, approach of prodrug is very suitable. The promoiety is added to the design of prodrug which increases the unsuitable partition coefficient as well as the solubility of drug. It also plays an important role in transportation of drug through stratum corneum. This approach is very useful in increasing the permeability of anti-inflammatory and non-steroidal drugs.

2.2 Eutectic system

A system having a composition of mixture of elements or compounds which changes into solid state when kept at low temperature is called as eutectic system. It is stated in a theory of solution that the solubility is inversely proportional to the melting point of material in any given solution. Eutectic mixtures are used to lower down the melting points of DDS. Example- EMLA cream [13,14].

2.3 Liposomes and vehicles

Liposomes are vesicles which are spherical in shape including the lipid bilayers and have the capability to encapsulate the drug into them. These type of formulations & encapsulations can also be seen in the cosmetics like in humectants, enzymes etc. In order to stabilize the structure and increase the rigidity of liposomes, cholesterol is added to the composition. The mechanism is not cleared about the enhancement of penetration of drug through the stratum corneum by the liposomes. There is a possibility that after penetrating the stratum corneum the liposomes interacts with the lipids in small extent and drug releases [15].

2.4 Nanoparticles

Solid lipid nanoparticles are used as carriers for enhancing penetration in some of cosmetics formulations like sunscreen, in delivery of vitamins (A and E) and glucocorticoids. The occlusive film which is formed on surface of skin is responsible for increasing the hydration of skin, which is the primary reason behind the enhancement of penetration of these formulations [15].

2.5 Iontophoresis

For the permeation of drug via skin this method is used by applying an electric current of low level, directly or indirectly (through dosage form) to the skin.
Some parameters which can affect this system are:

- Type of electrodes
- Current intensity
- pH of system [16]

The mechanisms given below can be used in combination or single to increase the permeation by these methods:

- Electro-repulsive- it is used for charged solutes only
- Electro-osmosis- it is used for uncharged solutes only
- Electro-perturbation- it is used for charged as well as uncharged solutes

FDA approved the 1st iontophoretic system in late 1970s named Phoresor™. From last decade the use of iontophoretic devices is continuously increasing, because of its qualities like-

- it increases patient compliance
- it is portable

- it is more effective
- patient friendly [17–19]

2.6 Electroporation

In this system high voltage pulses are applied to the skin to generate the transient pores. The voltage of approx 100V for duration of milliseconds is mainly used in this system. This system increases the permeability of skin for the molecules of different size and different lipophilicity like proteins, peptides etc. It is also applicable for the molecules having weight less than 7Kda [16].

By applying the electric field of high voltage directly to the skin can cause nerve excitation. This system can cause transient erythema and intraepidermal vacuolization [20].

2.7 Ultrasound (sonophoresis & phonophoresis)

In this system the ultrasonic waves of low frequency of approximately 55 kHz are used for about 15 seconds to increase the permeability of skin [21]. In this system ultrasonic energy is used in the methods, sonophoresis and phonophoresis. The ultrasonic energy is used to form gaseous cavities in skin lipids and disrupt the stratum corneum [20]. Generally, the frequencies between 20kHz to 16MHz are used to enhance permeation of skin. The frequencies less then 100kHz are very significant to use in transdermal drug delivery system [20,22].

2.8 Laser radiations

Laser radiations are often used to treat the conditions related to dermatology like acne. In this method laser radiations are exposed to the skin directly or in controlled manner. This exposure of laser to skin is responsible for the excision of stratum corneum without affecting the underlying epidermis [23].

Lasers are used very frequently in clinical therapies for a long time. They are also used in the treatment of facial rejuvenation in which the target cells are destroyed by radiations in very short period of time. Ablation of stratum corneum in this method indicates the enhancing in penetration of both hydrophilic and lipophilic drug [23–25].

The parameters like pulse length, wavelength of pulse, repetition rate of pulse, number of pulse are responsible for controlling the range of disruption of barriers by laser [24].

2.9 Radio frequency

In this method the skin is exposed to alternating current of high frequency to generate micro channels in skin membrane by the action of induced heat. The number of micro channels and the depth of channels generated by the system are responsible to control the drug delivery rate. The duration of treatment is very low i.e.; less than one second [26].

The frequency of current used in this system is approx. 100kHz or more. The drug. The drug delivery rate depends upon the microneedles which are used in this device and mainly on their properties. The micro channels are formed by the electronic device having microneedles array attached to it. After the generation of microchannels the transdermal patch is applied on that area [27].

2.10 Magnetophoresis

This device includes a diamagnetic solute and for the diffusion of that solute across the membrane of skin, an external force in the form of magnetic field is applied. When the skin is exposed to applied magnetic field it may cause the changes in structure of skin and thus the permeability of skin increases by that alteration. The major limitation of this method is that it can't be used without diamagnetic materials [26].

2.11 Microneedle based devices

These devices include a drug reservoir and several projections coming outwards from that reservoir called as microneedles having length approximately 50-110 mm.These microneedles penetrate through the major barrier of transdermal delivery called stratum corneum and releases the drug present in reservoir. The drug in the reservoir may present in any form like solution, gel or in solid form [28–30]

The microneedles are not able to reach the nerve ending because of the estimated length of needles i.e.; 50-200mm. They penetrate the skin to create micropores and channels to allow the diffusion of any drug which is applied topically. The chances of skin erythema in this system are very low [31].

The drugs with small molecular weight, large hydrophilic drugs and vaccines can be delivered by using this method.[32], [33]

2.12 Skin abrasion

This method is significantly used by the dermatologists to treat skin disorders like skin blemishes, acne etc. In order to increase permeability of the compounds applied topically, the upper layers of skin are directly removed or disrupted. In this system the physiochemical properties of drug have not any negative impact on the potential of delivery of drug. This method is used in delivery of drugs which are hydrophilic in nature and vitamin C [25].

When the device is applied it will remove some part of stratum corneum without affecting the remaining layers.
The advantages of this method are:

- Decreasing patient discomfort
- Enhancing patient compliance
- Easy to use
- Risk of infection is low
- Painless
- More convenient then hypodermic needles & cannula.

2.13 Needle less injection

In transdermal system the basic principle of drug delivery is the penetration of drug in the outer layer of skin at extremely fast speed using an acceptable energy source. In this system helium is used as compressed gas which is filled in the device. Drug is incorporated into the compressed gas. With the help of nozzle the gas is released by firing the in jet flow and travelled to penetrate in the skin at sufficient speed [34]. This is painless method of delivering the drug to skin.

The advantages of this method over the hypodermic needles are:

- There is no issue of safety with this method
- This is pain free method
- No issue of fearlessness is associated with this method [35].

The major limitation of this method is high cost of device as well as the dosage development. This system is not appropriate for regular use for drug delivery as the bombardment of particles of drug directly with skin at such high speed may cause problems. Therefore, it is likely to be used for vaccines as no frequent dosing is required.

2.14 Application of pressure

The molecules like caffeine can be easily administered to skin by applying modest pressure of 25kPa. It is simplest, potent and non-invasive method of drug delivery [26]. By increasing the pressure, the solubility of caffeine also increased into the stratum corneum layer of skin.

2.15 Thermophoresis

In human the normal temperature of surface of skin is controlled by homeostasis is 32^0 Celsius. By giving the heat treatment to the skin increases the permeation and diffusion of drugs into vehicles and also the diffusion and permeation of drug in skin which is increased by the increase in lipid fluidity [36]. Homeostasis is very important in delivery of drugs through transdermal route as it cause the vasodilatation of the blood vessels (subcutaneous) and therefore increases the temperature of skin resulting in increasing the delivery of topical material [37, 38].

A heating device is attached to the compounds like testosterone, tertracaine when delivered by the transdermal delivery system (patch) to increase skin temperature at the delivery site. Upper layer of skin can tolerate a maximum of 40-42^0C temperature for a time period of more than one hour. When the heat patch systems are used with high temperature the stability of drug may also considered. This method involves high temperature to disrupt the skin barriers for the delivery of drug [39].

2.16 Skin puncture & perforation

The devices in this system are similar as devices in micro needle system. They generate micro-holes in the skin for the disruptions of barrier in skin by their needle like projections. The length of projections should be of desired

measurement, so that they can't reach the layers beyond epidermis. Various methods of drug delivery like active & passive methods can be used. The needle like projections punctures the skin and the drug present in device penetrates through the micro-holes generated by the system [40].

2.17 Suction ablation

In this system negative pressure or vacuum is applied on the skin for removal of epidermis in order to generate the suction blister without affecting the basal membranes [41]. This device may cause skin erosion. The major limitation of this method is the time required to generate blister which is about 2.5 hours. This time can be minimize by heating the skin surface to 38^0C [42,43]. This system avoids the risk associated with the systemic infection. The side effects of this system are not so serious except infections of epidermal layer [44].

2.18 Skin stretching

These devices include the holding of skin under stress in uni or multi directional way. For the generation of micro pathways, the stress/tension of about 0.01-10 mPa is required. The stretching of skin in bidirectional manner helps in opening the pathways with delayed closure and therefore enhances the permeation of drug. After stretching of skin the pathways open and microneedle can easily penetrate into the skin. Some methods like pressure, electro transport, passive mechanism and osmotic mechanism uses the skin stretching along with the devices used in transdermal delivery of drug [45].

3. Microneedle drug delivery system

The field of microelectronics and micro machinery is ending up being increasingly material to clinical purposes, since at present it is conceivable to build precisely Nano-scaled structures by strategies created for the PC business. These procedures are used for the creation of microneedles for transdermal and dermal medication on conveyance, which implies transport of medication into and through the skin separately [46].

Back in 1976, microneedles were first discovered and till 2000s the innovation employed to produce needles of micron measurements was not comprehensively accessible. The microneedles are empty needle like structure having a size ranging from microns and length measures up to 1micrometer that is adequate to permit going of a liquid and solid medication through the microneedle. The empty shafts can be straight, for example extended from base to tip, and having atleast one or more opening on the sides from the lateral side of the needle instead of having only opening at the tip.

Microneedles can be installed inside transdermal drug delivery. Microneedles are invented to pass through the epidermis layer till a profundity of 70–200 micrometer. Because of short and thin structure of the microneedle they are not able to pass to nerves through the dermis layer that's gives the painless delivery of active pharmaceutical ingredients (APIs) of small and higher molecular weight

[47]. In comparison of other transdermal drug delivery microneedles are more capable in delivering accurate amount drug at site of action [48].

The microneedles classification shown in **(Fig. 1)**

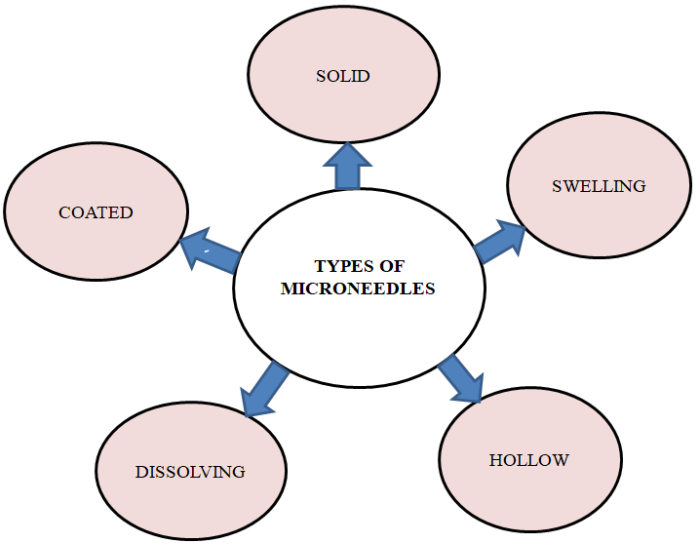


Fig. 1. Types of microneedles.

Depending upon the requirement of drug delivery, microneedles are further classified into various types like solid microneedle, hollow microneedles and biodegradable microneedle which are explained below:

3.1.1. Solid Microneedle

As the name suggests, it is entirely solid and work by creating the hole in Stratum Corneum of the skin. As the drug are coated on the upper surface of solid microneedle, it delivered at the site of action by puncturing the stratum corneum layer of skin and would be removed after the delivery and whole process of drug delivery is shown in (Fig. 2). It also increases the permeability of skin by creating hole on skin layer so that applied drug can easily reach the site of action with minimal loss and less amount of time. The size of solid microneedle varies between 750-1000µm in length and comparison with hypodermic needle is shown in (Fig. 3). Li et al. formulated a PLA composed microneedle of size of 600 micrometre to increase the delivery of small molecule drugs across the skin [49].

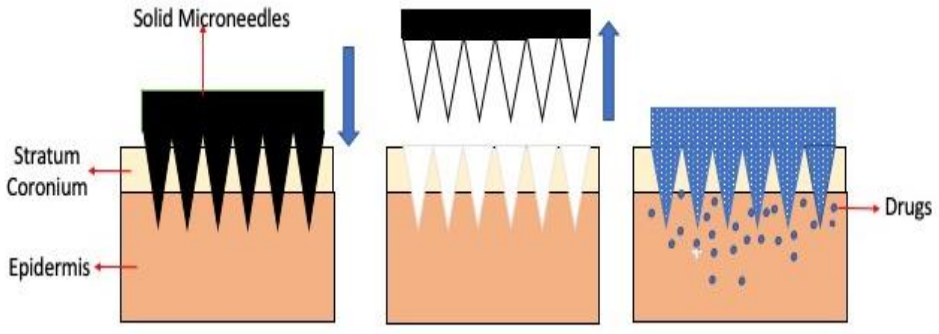


Fig. 2. Drug delivery across the Stratum Corneum by using solid microneedles.

3.1.1.1. Materials used for the formulation of Solid Microneedle

- Silicon: Manufacturing solid microneedle using silicon is costly and has disadvantage of being brittle and have possibility of breaking down in skin [50].
- Metal: Microneedle formulated using metals are generally having good mechanical strength and manufacturing cost is also low. Various metal involved during the formulation of solid microneedle are stainless steel, gold, platinum, titanium, nickel, iron, etc.

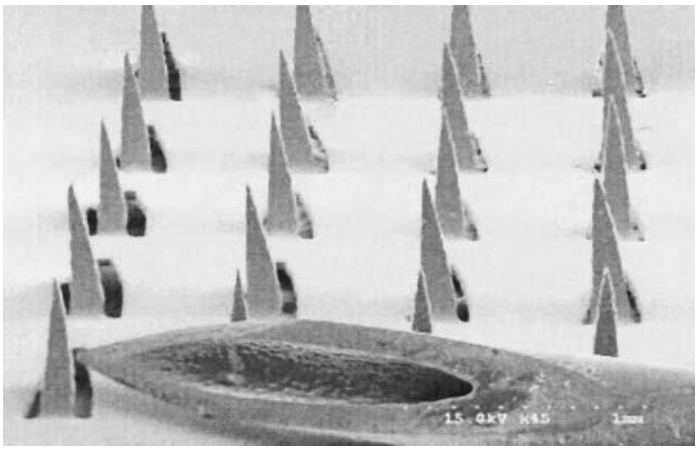


Fig. 3. Figure illustrating relative comparison of solid microneedle with hypodermic injection [51].

Biodegradable materials such as PCCP [Poly di(carboxylatophenoxy) phosphagene)] consisting of phosphorus-Nitrogen provides potent adjuvant activity and also overcomes the limitation of metal and silicon made solid microneedles [51].

3.1.2. Hollow Microneedle

As the solid microneedle dramatically increases the skin permeability, still there is need of some more controlled and reproducible drug delivery system. In this

scenario, Hollow Microneedle found its application as it provides more accurate and controlled drug delivery. Hollow microneedles are hollow inside their shaft and have various advantages such as option of delivering both high and low molecular weight drug in according to need of body, possibility of pressure driven movement of drug instead of passive movement and reduces the chance of cross contamination of surrounding with deliverables. Fig.4. shows the delivery of drugs across stratum coronium by using the hollow microneedles. Various type of hollow microneedles are fabricated for delivery of drug transdermal like as Metal Hollow Microneedles made of metal, Silicon hollow microneedle made up of silicon and of glass microneedle [49].

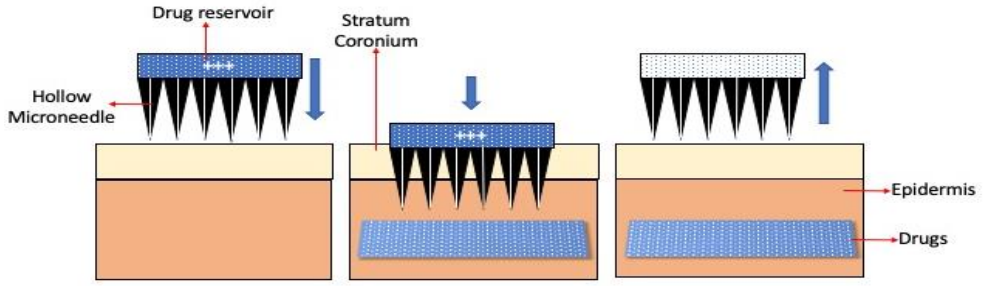


Fig. 4. Drug delivery across the Stratum Corneum by hollow solid microneedles.

De Groot *et al.* formulated hollow shaft microneedle for the delivery of ovalbumin loaded PLGA nanoparticles transdermally [52]. In another Li et al described the manufacturing method of hollow microneedle which is good enough for the extraction of blood [53].

3.1.3. Dissolving or Degradable Microneedle

Dissolving or degradable microneedle patch is manufactured with the help of soluble/degradable polymer materials with drug / molecules with tangled in polymeric matrices. Drug is released through the dissolving or biodegradable of the polymer & rate of drug release is controlled by the dissolving or degradable rate of polymer matrices of microneedle. Dissolving or degradable microneedle patch can be employed for alter delivery of protein [54].

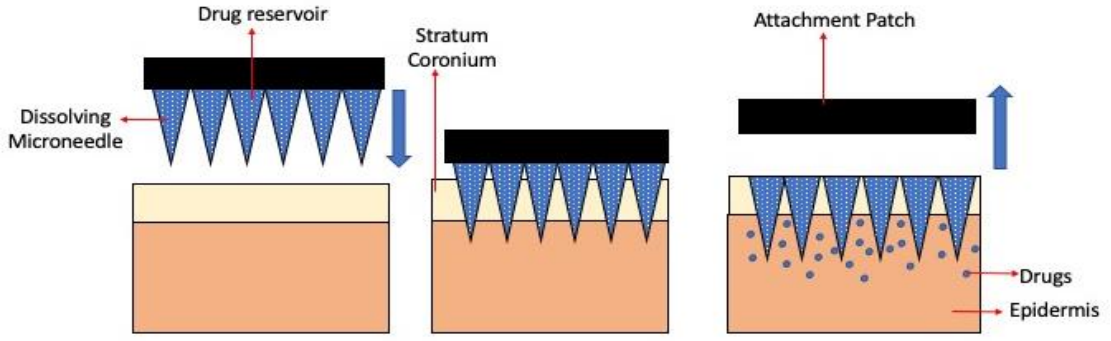


Fig. 5. Drug delivery across the Stratum Corneum by dissolving microneedles.

Material used: Polycarbonate, PVP, PLA, PLGA, PGA, PVP etc. Other materials like fast-dissolving sugars and also various polysaccharides have been searched to prepare the dissolvable microneedles. Another mucoadhesive polymer such as Gantrez AN-139 can also be used due to advantage of withstanding higher compression pressure. Ito et al. formulated bi-layered dissolving transdermal microneedle containing the intermediate-acting insulin and these needles shows near about same release as the type of subcutaneous injection [55].

3.1.4 Coated Microneedle patch

Coated Microneedle are those which consists of coating of drug on its surface. This microneedle allows the diffusion of drug from surface to deep epidermal layer of skin. But due to coating it increases the thickness of the microneedle and can influence the penetrating ability of microneedle. Despite this limitation, the coated microneedle found great utility in vaccine delivery across the skin.

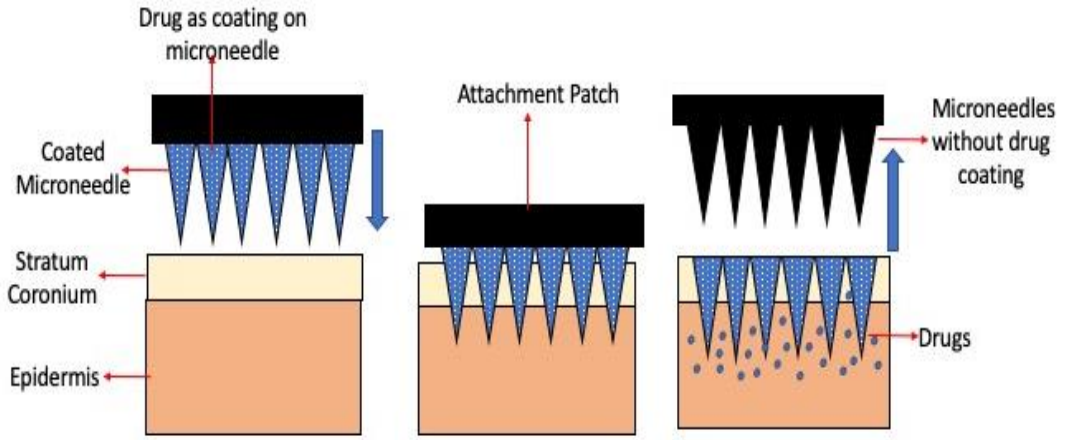


Fig. 6. Drug delivery across the Stratum Corneum by drug coated microneedles.

Zhang *et al.* formulated microneedle coated with lidocaine for analgesic action. When compared with commercially solution for treatment coated microneedles showed promising result [56]. DeMuth et al formulated vaccine coated microneedle for quick delivery of vaccine [57].

4. Composition of Microneedle

Microneedles can be produced using various materials, each contribute in different attributes. As reported in literature, the materials used for the formulation of microneedles can be isolated into three sorts: metal materials, inorganic materials, and polymer materials. These materials can be utilized to produce different types of microneedles by means of various techniques (Table 1). Each sort of material is discussed in detail in the following sections [54].

Table 1
Different approaches used to enhance penetration of drug[13].

Sr. No.	Approaches to enhance penetration of drug	Examples
1	Modified stratum corneum methods	Hydration
		Chemical Enhancers
2	Removed/bypassed stratum corneum methods	Microneedles
		Ablation
		Follicular
		Needle less injections
3	Electrically based methods	Iontophoresis
		Phonophoresis
		Electroporation
		Photochemical Wave
		Magnetophoresis
4	Particles and vesicles based methods	Microemulsions
		Lipid Nanoparticles
		Liposomes and its Analogues
		High Velocity Particles
5	Active or vehicle interaction methods	Eutectic System
		Chemical Potential
		Drug or Prodrug
		Ion Pairs or Coacervates

4.1 Metal Materials

Metal materials are broadly utilized in transdermal medication conveyance frameworks to the upside of mechanical quality and durability. Metal materials can be utilized to make strong microneedles [58], covered microneedles [59], and hollow shaft microneedles [60]. Moreover, limitations include the breakage of the microneedles inside the skin may prompt safety issues, so some new materials should be created. Various metal involved during the formulation of solid microneedle are stainless steel, gold, platinum, titanium, nickel, iron, etc.[50]. Chen *et al.* fabricated solid needles for the transdermal delivery of insulin [61].

4.2 Inorganic Materials

The most widely recognized inorganic materials for manufacturing microneedles includes silicon, glass, and ceramic. The qualities and properties of the microneedles manufactured by inorganic materials are like those of metal materials, and in this manner inorganic materials can be used for formulation of reliable strong microneedles, drug coated microneedles and hollow microneedles. However, non-compatibility with biological membranes and broken pieces' silicon are the principle concerns influencing the utilization of inorganic microneedles. Zhang *et al.* formulated solid microneedle made up of silicon of length about 150 m for the efficient delivery of hydrophilic peptides [62].

4.3 Polymer Materials

In contrast with metal materials and inorganic materials, polymer materials are viewed as the most encouraging materials for microneedle manufacture. They can be utilized to get ready strong microneedles, covered microneedles, dissolving microneedles, and empty microneedles as shown in (Table 2) [54].

Variety of polymer materials have been utilized to manufacture microneedles, including polylactide-co-glycolide corrosive (PLGA) [63–65], poly-L-lactic corrosive (PLA) [66,67], polycaprolactone (PCL) [68–70], poly-glycolic corrosive (PGA) [71,72], hyaluronic corrosive (HA) [73–76], polyvinyl pyrrolidone (PVP) [77],[78],etc. Of these, HA, sodium alginate, CMC and PVP are frequently used to manufacture dissolving microneedles which can disperse in the skin barriers quickly. For increment of mechanical strength/ reliability of the microneedles, some edifices, as carboxymethyl cellulose-trehalose, polyvinyl pyrrolidine-cyclodextrin (PVP-CD) [79], and polyvinylpyrrolehyaluronic corrosive (PVP-HA)[80], are additionally used to set up the microneedles. Polymer materials have ideal biocompatibility and could limit intrusive gadgets for transdermal medication delivery.

Table 2
The different types of materials used for the formulation of microneedle.

Types of Microneedles	Metal Material	Inorganic Material	Polymer Material
Solid Microneedle	√	√	√
Coated Microneedle	√	√	√
Dissolving Microneedle	X	X	√
Hollow Microneedle	√	√	√

5. Mechanism of Drug delivery across skin through Microneedle.

There are generally four different methods through which drug delivery through microneedle. Approaches for drug delivery are generally classified as “poke and flow”, “poke and patch”, “poke and release” and “coat and poke” approach which are explained below. Approaches generally classified as on the basis of types of microneedle employed for the delivery of drug transdermally like as hollow and solid microneedle. As mentioned in the figure, approach generally followed in the hollow microneedle is “poke and flow” whereas “poke and patch”, “poke and release” and “coat and poke” approaches are generally followed using solid microneedle.Fig.11. Different approaches of drug delivery across skin with help of microneedle [81].

5.1 Hollow microneedles

5.1.1 “Poke and Flow” approach

Hollow microneedle generally transports across the skin by mechanism known as “poke and flow “. In this approach the drugs are generally delivered by the passive diffusion via the bore of hollow microneedle. Advantage of using this approach

generally include a force driven drug delivery same as like of syringe that particularly increases the delivery rate of drug [81]. Further flow of drug delivery across the skin can be controlled through this approach. This is the most encouraging framework for the market since it is genuinely simple and generally cheap in the production [82,83].

But low infusion rate (50–300 nL/min) is one of the common drawbacks of this method but it can be controlled by partial addition of hyaluronidase in the infusion solution that increases the infusion rate to 18.8 μL/min by breaking hyaluronic acid in the skin collagen fibers.[84] The microneedle based on hyaluronic acid has been approved by FDA and clinically trailled for transdermal delivery for insulin [85].

5.2 Solid microneedles

Generally, there are three approaches by which drug delivery across skin by using solid microneedle took place which includes, “poke and patch”, the “coat and poke” and “poke and release”.

5.2.1 Poke and patch

This is the one of the first approach that were used by solid microneedle for the delivery of drug across the skin. In this approach of drug delivery, solid microneedles were employed on skin for creating micropores [81], [86]. After creating micropores the solid microneedles are removed from the site of action and transdermal patches or layer of drug are applied on the treated place where micropores are created by needles [87]. Drug transportation across the skin generally occurs by diffusion or by applying electric field (Iontophoresis) [87]. One of the most important parameters or limitation in this approach that affect the delivery of drug through this approach is the time of opening of micropore created by needles. Nonetheless, micropores close soon after the microneedle application when the micropores are not blocked or after the fix expulsion [88]. Moreover, it has been indicated that micropore opening can be increased out as long as 7 days when the diclofenac is added to fix plan in transdermal patches applied on target area [89]. However long opening of micropore causes skin irritation and increase the chance of infection limits the application of this approach [90].

5.2.2 Coat and poke

Another approach for utilizing solid microneedles to upgrade the delivery of target drugs across the skin is “Coat and Poke” approach where the coated microneedles are used as single-unit-drug delivery method [91]. Needles are covered/coated with wide variety of drugs like low molecular drugs, hydrophobic and hydrophilic drugs, RNA, Protein, Inactivated pathogen (Vaccines) [56,82,92–96]. Microneedle needle coating are generally done in suitable conditions and dry covering generally more stable and steadier in comparison of liquid formulation. Nonetheless, disadvantage of this method is that strong microneedles must be covered with small amounts of the medications because thick coatings leads to a lower amount of drug delivery across the skin because of small availability of surface area on microneedle [95]. Therefore, coated microneedles are generally

employed for delivery of very potent drugs which are generally required in small amount such as vaccines, peptides, etc.[82,97,98]. High loss of medication during the process of coating is one of the problem that are generally faced with these approach of “Coat and Poke”.

5.2.3 Poke and Release

The third approach for transdermal delivery of drug includes the “Poke and Release”. This method includes the controlled delivery of medication across the skin by utilization of materials for formulation of microneedles as drug depot [81]. This infers, not as like “Poke and Patch” methodology the microneedles must stick on the skin after application on skin until the medication is completely discharged [99,100]. This strategy utilizes either biodegradable, permeable, or dissolving microneedles from which the medication is slowly discharged into the skin. However, there is provision of formulation of hybrid solid microneedles consisting of body made up of non-biodegradable materials such as stainless steel with biodegradable or dissolvable tip. Recently biodegradable microneedles are employed for the delivery of insulin in porcine cadaver skin in very short period of time [93,94,101–103].

6. Fabrication / Manufacturing of Microneedle

Microneedles can be created utilizing microelectromechanical frameworks (MEMS). The fundamental procedure can be isolated in to three sections: Deposition, Patterning and Itching. Furthermore, the manufacturing of particular type of microneedle i.e. Solid, hollow and dissolvable as shown in (Fig 6).

6.1 Deposition

Deposition alludes to the development of thin films on any surface (e.g. silicon water) with a thickness anyplace between nanometres to around 100 micrometres. Common methods employed for deposition of thin films that include chemical vapour deposition and physical vapour deposition. It can be achieved by employing varieties of materials such as noble metals (e.g. gold, silver) [104].

Physical vapour affidavit (PVD) based procedures, the crude materials (i.e. strong, fluid, or fume) are discharged from the source (i.e. material to be covered) and then put on the substrate surface. Example, in warm dissipation, the silicon water is put inside a vacuum chamber and source (for example aluminium) is warmed by beam of electron or radio-recurrence. Warming produced by above sources created vapour. Vapour were further condensed on the surface to produce the thin film. In the faltering method, substrate and source is put in a chamber which contains idle gas (for example argon or Xe) at low weight.[104] Thin film deposition produced by the method of chemical vapor deposition (CVD) includes the chemical reaction in chamber between the warm substrate and inert carrier gases [105,106].

6.2 Patterning

Patterning is defined as the exchange of a pattern onto the developed film. The Lithography is a method utilized to move a pattern into photosensitive material by particular introduction to radiation source, for example, light. This procedure can include photolithography, particle pillar lithography, X-beam lithography, electron bar lithography, etc.[107]

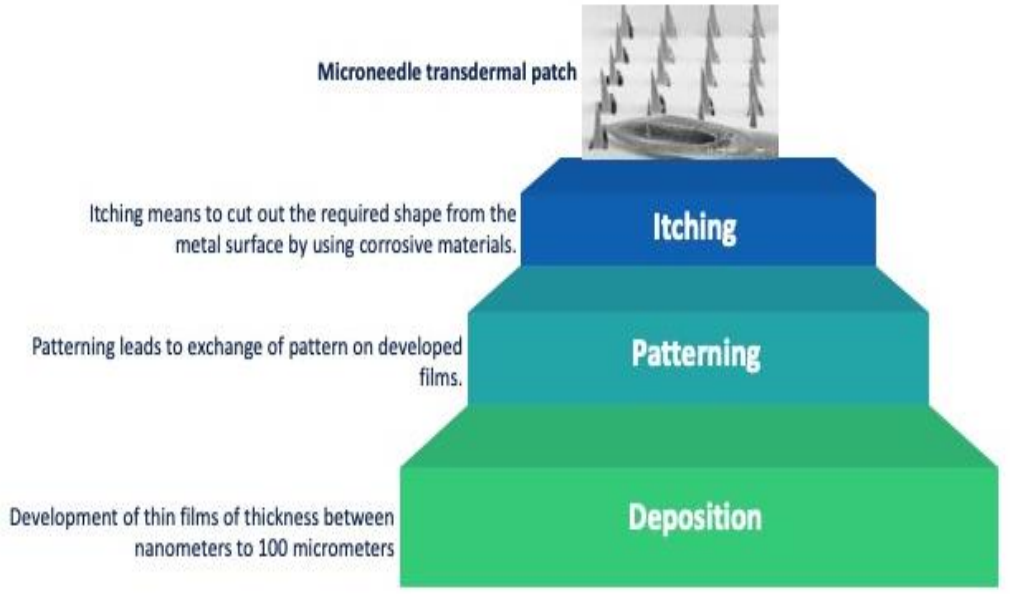


Fig. 6. Different processes involved in fabrication of microneedle [48]

6.3 Itching

Itching is a procedure of utilizing solid corrosive/ strong acid or severe to slit into various unprotected pieces of the surface material to make a structure in it and it can be separated into two classifications: wet itching and dry itching. The choice of some of the previously introduced techniques to a great extent relies upon the material of development and the sort of different types of micro needles.

Various literatures are documented regarding the formulation like Park *et al.* created biodegradable polymeric microneedles utilizing a micro-moldingscale forming technique.[83] In this procedure, molds or microarray made up of SU-8 epoxy photo resist or polyurethane were at first made in various shapes like slanted tip, etch tip and tightened cone, utilizing various methods. Parts of biodegradable polymer were put on the ace structures of various structures and put under vacuum at high temperature. Polymeric soften was maneuvered into the form by use of vacuum, followed by freezing for division of the ace structure from the shape. Aoyagi *et al.* considered formulation of biodegradable polymers under typical barometrical conditions [108]. Chen et al. introduced a strong Gas-stream covering technique to accomplish uniform covering of a scope of immune-therapeutics, similar to antigens, DNA and proteins, on microneedles [95].

7. Manufacturing of different types of microneedles

7.1 Solid Microneedle

Solid Microneedle can be manufactured by the plates of metal by employing electrical discharge or infrared laser to move out the needle structure from the metal plates and manoeuvring to bend the needle at angle of 90^0 from the plane of the metal sheet. Metal like stainless steel, tungsten [51], titanium [109] is generally employed for the formulation of the solid microneedle.

For manufacturing silicon solid microneedle, photolithography followed by with deep reactive itching and wet etched method is employed. Other method employed for the formulation of solid microneedle are dry etching, two stage etching and electrochemical itching for formulation of spherical shapes. Equation 1 shows that process of the silicon wet etching.

$$3Si+4HNO_3+18HF \rightarrow 3H_2SiF_6+4NO+8H_2O$$ …. Equation 1 [110]

Solid microneedle consisted of Poly (lactic-co-glycolic acid) can be made by employing method of drawing lithography[111]. In the method of drawing lithography polymer is heated till its temperature reaches above the transition temperature, after which they are drawn in desired shape and size and cool at room temperature. Various other methods are employed for formulation of Solid microneedle that includes Infrared laser cutting, Wire electrical discharge machining[112], Ion sputtering deposition[113], Deep reactive ion etching[109], Twisted light with spin[114], Two stage etching[115], One stage KOH etching[116], etc.

7.2 Hollow microneedles

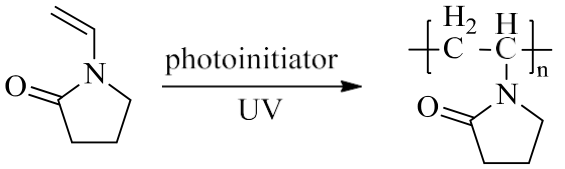
Hollow Microneedle can be made from metal by using metal electrodeposition which are joined with the master mold [117–121]. Additionally, Hollow Microneedle can be designed by using two-phase electrodeposition in which the hollow shaft is produced by twice electrodeposition [122,123].

Hollow microneedle made up of silicon can be manufactured through dry etching or a blend of wet and dry etching. Photolithography is generally used for creation of SU-8 hollow microneedle [124,125]. Additionally, materials like polyimide, agarose, polymethyl methacrylate (PMMA) and polyformaldehyde (POM) plastic could likewise be utilized to create hollow microneedles by employing different techniques, for example, dissolvable casting [126], polymerization casting [127] and microinjection shaping [128].

7.3 Dissolving / biodegradable microneedles

Dissolving / biodegradable microneedles are mainly manufactured by employing dissolvable casting methods [54] and using solvents polymers as core ingredient. Methods of Centrifugation [129], pressure [130] and vacuum [131] are generally used to make the dissolvable polymers in the shape of microneedle. Additionally, dissolving microneedles can also be manufactured by using the method of melt casting. As melt casting method employs the involvement of high temperature which in some case can be harmful for the drugs having lower melting point

[132,133]. Polyvinylpyrrolidone is a material which has high water dissolvability and can be utilized for formulation of dissolvable microneedles by involving the method of photopolymerization. Equation 2 shows the method of photo polymerization [133].



Various other methods involved in the formulation of biodegradable microneedle includes Molding combines with photopolymerization, Solvent casting combines with centrifugation [129], Solvent casting combines with vacuum, molding combines with photo polymerization [133] etc. Some of microneedles based delivery of drug shown in (Table 3).

Table.3
Microneedles based drug delivery through transdermal route.

Drug Incorporated	Type of Microneedle used	Composition of microneedle	Pharmacokinetic Parameters	Model	References
Vitamin B12	Dissolving Bilayer MNs arrays	silicon, non-degradable polymers, copolymers, biodegradable polymers	$AUC_{0\text{-}30}$n(µg/ml.h)- 0.81 C_{max}(µg/ml)- 0.37±0.04 T_{max}(min)- 30	Rat	[134]
Levonorgestrel	Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	AUC(h*ng/ml)- 136.46±26.41 C_{max}(ng/ml)- 189.27±57.46 T_{max}(h)- 0.5 MRTC(h)- 1.14±0.34 T1/2(h)- 0.70±0.17 CL(ml/h)- 381.13±92.83 Vd(ml)- 381.17±112.19	Female Rat	[135]
Insulin	Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	AUC (µv h/ml)- 100.6±13.1 T_{max}(h)- 1.00±0.00 C_{max}(µv/ml)- 62.6±12.4 RBA(%)- 96.1±12.5	Rat	[136]
Doxycycline Monohydrate	Two Layered Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	C_{max}- 0.17±0.3µg/g T_{max}- 4h Relative Bioavailability- 639.51±98.43%	Rat	[137]
AlbandazoleSalfone	Two Layered Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	C_{max}-0.07±0.03µg/g T_{max}- 4h RB- 1304.42±226.65%		[137]

Diethyl Carbamazine	Two Layered Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	C_{max}- 0.15±0.06µg/g T_{max}- 4h RB- 654.46±1032.43%	NA	[137]
Bevacizumab	Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	AUC(ng*h/ml)- 44354±4540 C_{max}(ng/ml)-358.2±100.4 T_{max}(h)- 48h C_{xx}(ng/ml)- 924±95	Female Sprague Dawley Rats	[138]
Naltrexol	Dissolving MNs Array	silicon, non-degradable polymers, copolymers, biodegradable polymers	AUC(ng*h/ml)- 193.2±103.4 C_{max}(ng/ml)- 9.7±1.5 T_{max}(h)- 1.0±0.9 C_{ss}(ng/ml)- 505±1.9 T_{log}(h)- 0.8±0.2	Guinea Pig	[139]
Nicotine	Dissolving MNs Array	silicon, non-degradable polymers, copolymers, biodegradable polymers	C_{max}(ng/ml)- 70.10±3.55 T_{max}- 0.875±0.25h AUC(h*ng/ml)- 339.31±15.97	Rat	[140]
Rhodamine B	Dissolving MNs	silicon, non-degradable polymers, copolymers, biodegradable polymers	T_{max}(h)- 120 $C_{max}\|10^6$(Photon/mg)- 28±0.7 AUC$\|10^8$- 2.13	Mice	[141]
Sulfurhodamine B	Single hollow glass MN	Silicon, metal, polymer and glass	NA	NA	[129]
Radio labeled mannitol and carboxyfluroescein	Solid micro - needles	Titanium and stainless steel	NA	NA	[47]
5-aminolevulinic acid	Solid silicon MN arrays	Silicon, titanium, stainless steel and polymers	N/A	Human	[142]
Methotrexate	PLGA Microneedle	Stainless steel, Silicon	NA	NA	[143]
Rizatriptan	AdminPatch® arrays (ADM) and laboratory-fabricated polymeric MN arrays (PM)	Polymers like hyaluronic acid (HA), polyvinylpyrrolidone (PVP),sodium alginate,carboxymethylcellulose (CMC), dextran, hydroxypropyl methylcellulose (HPMC),hydroxyl propyl cellulose poly-l-glutamic acid (γ-PGA), sodium chondroitin sulfate, gelatin	NA	NA	[144]

Dyclonine	Functional microarray(FMA)	silicon, stainless steel, polymers and titanium	NA	NA	[145]
Naltraxone	Solid microneedles	Titanium, stainless steel, silicon and polymers	NA	NA	[146]
Ibuprofen Sodium	Dissolving polymeric microneedle	Polymers like hyaluronic acid (HA), sodium alginate, hydroxypropyl cellulose (HPC), carboxymethylcellulose sodium chondroitin sulfate, gelatin, polyvinylpyrrolidone (PVP), dextran, hydroxypropyl methylcellulose (HPMC), (CMC), poly-l-glutamic acid (γ-PGA),	Cmax- 263μgml^{-1} Tmax- 24hrs.	male Sprague dawley rat	[147]
Ovalbumin	Dissolving microneedle array (dMNA)	silicon, non-degradable polymers, copolymers, biodegradable polymers, chondroitin sulfate	NA	NA	[148]
Nadroparin calcium	Dissolving microneedle (DMN) arrays	silicon, non-degradable polymers, copolymers, biodegradable polymers, Aluminium	NA	NA	[149]

8. *In-vitro* evaluation test for Microneedle drug delivery system

There has been significant increase of demand of microneedle for controlled drug delivery due to of its various advantages including painless administration of drug form. As the demand increases there are more chances of approval of these kinds of dosage form from regulatory bodies like USFDA, European agencies, etc. *In-vitro* studies are one of the important parameter for passing of particular dosage form from regulatory bodies. *In-vitro* studies are performed with cells, microbes or any biological molecules outside their biological entity. *In-vitro* studies of solid, hollow or dissolvable microneedle can be done through various methods including *In-vitro* skin permeation study, Franz Diffusion Cells, In-vitro drug release study in saline condition etc.

Guo *et. al.* performed *In-vitro* study of polymer microneedle by two ways. First, he conducted *In-vitro* study in porcine cadaver skin. Microneedle loaded with sulfohodamine B was firmly inserted in porcine cadaver skin. Skin was stored in optimum environment for maintaining the humid condition of skin and distribution of sulfohodamine B in skin was measured by fluorescence microscope at regular interval. In another way, he conducted *In-vitro* drug release study in saline condition. For this sulfohodamine B loaded polymeric microneedles were packed in dialysis bag. The microneedle containing dialysis

bag was completely submerged in phosphate buffer solution of pH 6.2 (0.01M). Release of sulfohodamine B from dialysis bag in buffer solution was determined through calibration graph [151].

Das *et. al.* performed *In-vitro* study of rizatriptan loaded microneedle through Franz diffusion cell. Pig ear skin was used for this permeation study and saline fluid employed as receptor fluid. Receptor fluid was fixed at 600 RPM during the experiment and care should be taken for preventing the entrapment of air bubbles in pig ear skin and receptor solution. 500 µL of receptor solutions containing the excess amount of rizatriptan on skin. Samples were drowned at regular interval of 6 hr till 48 hr and analysed by HPLC. Same process were repeated by applying rizatriptan containing microneedle and result were compared to determine permeation rate of drug in microneedle [144].

Skin pore created by microneedle is very important parameter that determines the permeation rate of drug through skin. So it is necessary to monitor the time of opening of pore for more optimized delivery of drug by using microneedle. Banga et al. performed *Invitro* pore monitoring studies by using Franz Diffusion Cells. Porcine ear skin was used in this process. However, it is worthwhile to mention that skin regeneration is absent in dead skin but whole process of pore healing through skin regeneration was hypothesized by skin hydration due to absorption of water from receptor solution. Porcine skin was treated with receptor fluid and clamped carefully in Franz Diffusion Cells. Electric resistance and TEWL were determined at regular interval of time. After that skin was stained with FluoSpheres® and digital camera was used for recording the time of pore closing. Author also performed *In-vitro* drug release study of drug containing microneedle by using Franz Diffusion cells employing porcine ear skin or cadaver human skin [143].

Table 4
In-vivo Success of MNs Based Formulations

Types of MNs	Drug Incorporated	Pharmacokinetic Parameters	In-Vivo Model	References
Dissolving Bilayers MNs Array	Vitamin B	$AUC_{0\text{-}30}$n(µg/ml.h)- 0.81 C_{max}(µg/ml)- 0.37±0.04 T_{max}(min)- 30	Rat	[134]
Dissolving MNs	Levonorgestrel	AUC(h*ng/ml)- 136.46±26.41 C_{max}(ng/ml)- 189.27±57.46 T_{max}(h)- 0.5 MRTC(h)- 1.14±0.34 T1/2(h)- 0.70±0.17 CL(ml/h)- 381.13±92.83 Vd(ml)- 381.17±112.19	Female Rat	[135]
Dissolving MNs	Insulin	AUC (µv h/ml)- 100.6±13.1	Rat	[136]

		T_{max}(h)- 1.00±0.00 C_{max}(µv/ml)- 62.6±12.4 RBA(%)- 96.1±12.5		
Two Layered Dissolving MNs	Doxycycline Monohydrate	C_{max}- 0.17±0.3µg/g T_{max}- 4h Relative Bioavailability- 639.51±98.43%	Rat	[137]
	AlbandazoleSalfone	C_{max}-0.07±0.03µg/g T_{max}- 4h RB- 1304.42±226.65%		
	Diethyl-Carbamazine	C_{max}- 0.15±0.06µg/g T_{max}- 4h RB- 654.46±1032.43%		
Dissolving MNs	Bevacizumab	AUC(ng*h/ml)- 44354±4540 C_{max}(ng/ml)- 358.2±100.4 T_{max}(h)- 48h C_{xx}(ng/ml)- 924±95	Female Sprague Dawley Rats	[138]
Dissolving Microneedle Array	Naltrexol	AUC(ng*h/ml)- 193.2±103.4 C_{max}(ng/ml)- 9.7±1.5 T_{max}(h)- 1.0±0.9 C_{ss}(ng/ml)- 505±1.9 T_{log}(h)- 0.8±0.2	Guinea Pig	[139]
Dissolving MNs Array	Nicotine	C_{max}(ng/ml)- 27.47±10.49(%CV 38.2) PamolAUC[a](h*ng/ml)- 62.44±18.79(03.1)% Total AUC[b](h*nh/ml)- 173.8±54.10(31.1)%	Human	[150]
Dissolving MNs	Rhodamine B	T_{max}(h)- 120 C_{max}|10^{b}(Photon/mg)- 28±0.7 AUC|10^{8}- 2.13	Mice	[141]
Dissolving Microneedle	Nicotine	C_{max}(ng/ml)- 70.10±3.55 T_{max}- 0.875±0.25h AUC(h*ng/ml)- 339.31±15.97	Rat	[140]

Conclusion

Conclusion & future perspectives

With the present study we have concluded that drug delivery through microneedles is a better approach for drug delivery through transdermal route. Needleless system is not appropriate for regular use for drug delivery as the bombardment of particles of drug directly with skin at such high speed may cause problems. Therefore, these are likely to be used for vaccines as no frequent dosing is required. Microneedle based devices includes a drug reservoir and several projections coming outwards from that reservoir called as microneedles having length approximately 50-110mm. These microneedles penetrate through the major barrier of transdermal delivery called stratum corneum and releases the drug present in reservoir. The drug in the reservoir may present in any form like solution, gel or in solid form. The drugs with small molecular weight, large hydrophilic drugs and vaccines can be delivered by using this method. By using microneedle based devices the skin barriers can by passed easily and it will have resulted in the increased permeability of drug through skin. Various dosage forms like nanoemulsions, nanoparticles etc. can be effectively delivered through microneedles based delivery system.

Acknowledgement

The authors would like to express their gratitude to the Maharaja Ranjit Singh Punjab Technical University (MRSPTU), Bathinda, India, for providing the essential facilities for this work. Authors would also like to specially acknowledge the support of Indian Council of Medical Research, New Delhi, India and department of Pharmaceutical Sciences and research University, Delhi in the completion of this article.

Funding

Research grant (5/8-4/5/Env/2020-NCD-II Dated 22/12/2021) Under Indian Council of Medical Research (ICMR), New Delhi, India.
Declarations of interest
None

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