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Pharmacy Practice and Research
Volume 2 Issue 2, 2022

Microneedles: Novel and Futuristic Approach in Transdermal Drug Delivery System- A Review

Manmeet Kaur, Simran Sharma, Sachin Saggar*
**Principal, Amritsar Pharmacy College (Pharmacy), 12 km stone, Amritsar Jalandhar, GT road, Amritsar, Punjab, India*
****Corresponding Author***
Email Id: sachinsaggar25@gmail.com

ABSTRACT

Transdermal drug delivery system is a system which uses skin as the site of administration of drug. The administered drug is absorbed into the systemic circulation via blood vessels in the skin and then circulates around the body. Transdermal drug delivery systems offer some advantages for patients, such as being less invasive (some methods are entirely noninvasive), first-pass metabolism avoidance, ease of application and administration. The elect of most of the therapeutic agents is limited due to the stratum corneum layer of the skin, which serves as a barrier for the molecules and thus only a few molecules are able to reach the site of action. A new form of delivery system called the microneedles helps to enhance the delivery of the drug through this route and overcoming the various problems associated with the conventional formulations. The basic principle of microneedle delivery is disruption of the skin layer which creates micron size pathways that lead the drug directly to the epidermis or upper dermis region from where the drug can directly go into the systemic circulation without facing the barrier. In this review various advancements in transdermal drug delivery system are discussed. This review focuses on the microneedles (MN) as transdermal drug delivery system. This review provides an overview on the mechanism and type of needles, design (consideration, material, fabrication, and coating), Microneedle aided drug administration, application and safety and marketed preparations of microneedles.

Keywords – *Transdermal Drug Delivery system (TDDS), microneedles, fabrication,coating techniques.*

INTRODUCTION

Transdermal drug delivery systems is an attractive alternative to the oral and parenteral drug delivery system and include a wide range of non-invasive or minimum invasive techniques for drug delivery across the skin[1].

The main advantage of Transdermal drug delivery systems is economical, self-administered, better patient compliance, avoids first pass metabolism, increased bioavailability, no palpability issues and no hepatotoxicity concerns [2]. Microneedles (MNs) only puncture the epidermal skin layer hence large active pharmaceutical molecules can be administered easily without causing pain using [3].

The epidermis consists of five different layers that function in the mechanism of skin regeneration. The stratum corneum (SC) is the most superficial layer of the epidermis (thickness of 10–20 μm), consisting of 15–30 corneocyte cell layers. The SC is made up of keratin proteins that comes from dead keratinocyte cells in the deeper layers, in a process termed cornification and, hence it is also known as a ‘horny layer’. [4].

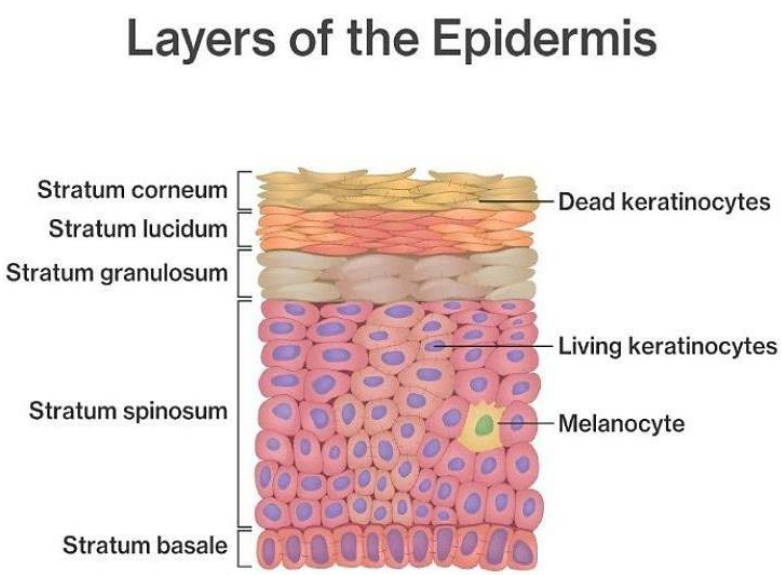


Fig 1: Diagrammatic representation of layers of epidermis [4].

Furthermore, SC is also composed of lipids, such as ceramides (30–40%) [5, 6], cholesterols, cholesterols esters, free fatty acids. However due to the nature of the skin (stratum corneum) which acts as the main barrier to the delivery of the drug, the choice of the drug is limited to only few molecules which are small in size or molecular weight, are lipophilic in nature and have low therapeutic dose.

Several techniques have been developed to improve transdermal transportation of the drug. These techniques can be categorized as passive and active method depending upon whether an external source is used to enhance skin permeation. Passive methods particularly chemical methods are easy to incorporate in the transdermal patches but they have the distinct disadvantage of lag time of hours and hence cannot be used where rapid onset is required. These methods include use of chemical enhancers, emulsions and lipid assemblies [7].

The active methods for improving the transport of drug across the skin include iontophoresis, ultrasound, electroporation, jet injectors, ablation, tape striping, micro needles, etc. [8]. The active method increases the skin permeation by physically disrupting the skin barrier or by using an added driving force for drug transport. This facilitates the movement of the drug towards the blood supply in the skin. This is advantageous as many hydrophilic drugs and macromolecules can be administered moreover active method offer more control over delivery profile thus resulting in shorter lag time as compared to passive method [9]. The disadvantage is that of complexity of fabrication and integration of the devices used in active method.

Though hypodermal needles can be used to avoid the skin barrier but they are painful and are generally not well accepted by the patients. Alternatively microneedles (MN) can be employed for precise delivery of the drug through the skin with minimum pain. MN offer an advantage of rapid penetration of drug in the blood circulation system, with fast healing at site of injection and low risk of microbial infection [10]. The challenges with MNs is that their use is limited due to their size and material, MN tip can break and may embed in the skin, allergic and sensitive skin may be affected and improper application can lead to skin inflammation [10].

MICRONEEDLES

Microneedles are micron sized needles that are used for transdermal vaccination and drug delivery [11]. The concept of the drug delivery across the stratum corneum using small needles was proposed in 1970s but it could not be progressed due to lack of fabrication techniques at that time. The first work on use of microneedles for transdermal drug delivery was first reported in 1990s [12]. Initial microneedles were fabricated from silicon, current design use metal and polymeric material [12].

Mechanism and Types of Microneedles

The mechanism of action of the microneedles depends upon its design. All types of microneedles are fabricated as an array of up to hundreds of microneedles over a base substrate. Solid microneedles can either be pressed onto the skin or scrapped on the skin for creating microholes; hence the skin permeability is increased by up to four orders of magnitude [13]. Thereafter drugs or vaccines are applied from patch or formulation. The holes left after the removal of microneedle measure micron in size, these holes have a lifetime of more than a day if kept covered by an occlusion but less than 2 hours when left uncovered[14].

The second approach is to encapsulate the solid microneedles made of insoluble metal or polymer microneedles with a dry coating of vaccines and drugs [15]. This coating dissolves within one minute after insertion in skin after which the microneedles can be withdrawn and discarded. Alternatively microneedles have been fabricated using biodegradable or water soluble polymers instead of insoluble material; the drug is encapsulated within the microneedles. Microneedles have been fabricated using polylactic-co-glycolic acid (PLGA) polymer, water soluble carboxymethyl cellulose, polyvinyl-pyrrolidone and maltose [16]. These polymers degrade safely in the skin providing both sustained and rapid response depending upon the polymer used.

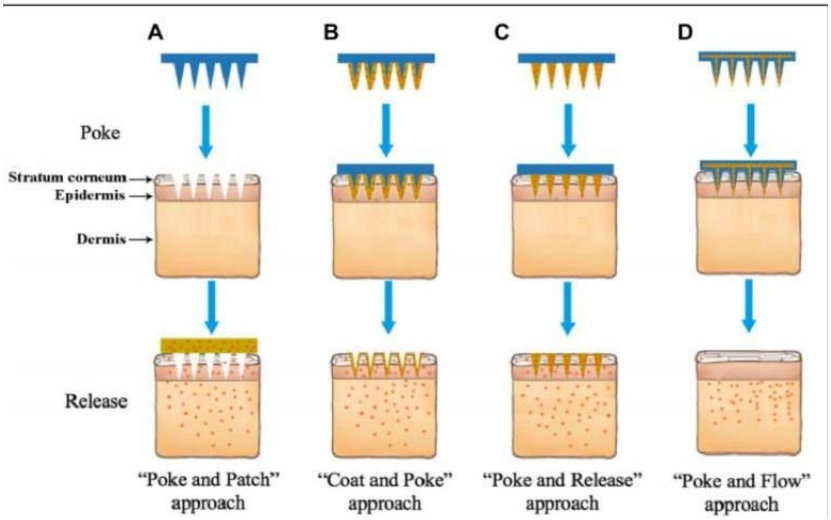


Fig 2: different approaches of microneedles drug deliverysystem

Another approach consists of using hollow microneedles to puncture the skin followed by infusion of liquid formulation through the needle bores in the same manner as hypodermic injection [17, 18] though they are less painful than theinjection.

The mechanism of action or approaches can be generalized as of fourtypes:[17]

A. Poke and patch
B. Coat and poke
C. Poke and release
D. Poke and flow

Types of Microneedles

Currently four different types of microneedles are available depending on the mechanism of action or approach

1) Solid microneedles used to pretreat the skin prior to administration of drug orvaccine
2) Drug-coated solid microneedles for drug dissolution inskin
3) Hollow microneedles forinjection
4) Dissolving microneedles prepared from biodegradable or water soluble polymers in which the drug or vaccine is embedded [19,20].

Design Consideration

Microneedles have the same advantages as that of the hypodermic needles and transdermal patches of delivering the drug through the skin and by passing the first pass metabolism but at the same time the microneedles are able to overcome the various disadvantages associated with hypodermic needle (pain and risk) and transdermal patches (limited by transport barrier provided by skin) [21,22].

The basic design of Microneedles patches consists of ordered array of Microneedles ranging from a few to few hundred in number and they differ from hypodermic needles on basis of their length and the pore size it generate on applying. Microneedles are prepared from variety of materials such as polymer, glass, and metal, ceramic and are available in number of shapes and sizes depending on its application [21].

Gill et al. investigated the influence of Microneedles geometry on pain compared to 26 gauge hypodermal needles. The Microneedles geometry with variation in length, thickness, width, tip angle and number of Microneedles on a patch were investigated. The results indicated that all the Microneedles were 5 to 40 % less painful as compared to the selected hypodermic needle. The variation in thickness, width and tip angle did not have any significant impact on the pain but the pain decreased considerably by reducing the number and length of the Microneedles. They concluded that a 10 fold increase in the number of Microneedles resulted in only two fold increase in pain and threefold increase in length of Microneedles resulted in seven fold increase in pain[22].

Design Parameters

1) Microneedles must be easily inserted into skin without breaking. While metals are typically strong enough, polymers must be selected to have sufficient mechanical strength.
2) Geometry of MNs is also an important parameter for designing microneedles, where sharpness of tip strongly affects the force required for microneedle insertion into skin. Other parameters, including microneedle length, width and shape all influence force required for microneedle fracture [23]. Microneedle geometries vary from 150 to 1500 µm in length, 50 to 250 µm in base width and 1 to 25µm in tip diameter. Microneedles can also be designed to minimize pain. Initial studies showed that specific microneedles of a couple hundred microns length were reported painless[24].
3) Recent studies has shown that microneedle length strongly affects pain, where a 3-fold increase in needle length (i.e. 500–1500 µm) increased pain 7-fold (i.e. from 5% to 35%

of the pain caused by a hypodermic needle) [25]. Increasing the number of microneedles (620 µm long) 10-fold from 5 to 50 increased pain by a factor of three. Other geometrical parameters did not influence pain significantly.

4) Fabrication methods for microneedles need to be designed appropriately. As single-use, disposable devices, manufacturing costs should be kept low. Lithographic etching and micro-molding methods are most cost effective and economical and best suited for mass production. Fabrication methods also need to avoid denaturing of vaccines and drugs and have therefore emphasized room temperature. Controlled release in the skin, (d) hollow microneedles for injection of drug solution[26].

Material and Technologies in Fabrication of Microneeedles

The first microneedles were fabricated from silicone by lithography technique followed by wet and dry etching but now a days the various materials including polymers such as carboxymethyl cellulose, ceramic, glass and metals like titanium, stainless steel etc. are also being used to fabricate microneedles of different shapes and sizes, using divergent technologies [27].

The designing of microneedles are limited and restricted due to various variables involved:

1) The microneedles should be able to insert into the skin withoutbreaking.
2) The microneedles should cause minimalpain.
3) Economicconsiderations.

The microneedles should be capable of insertion into the skin without breaking, microneedle made of metals has sufficient strength but selection of polymers should depend on the mechanical strength of the material employed for fabrication. The other factor that affects the force required for insertion of microneedle into the skin are sharpness of tip, length width and shape. Generally microneedle varies from 150 to 1500 µm in length, 50 to 250 µm in base width and 1 to 25 µm in tip diameter. Lithography as well as wet and dry etching techniques are adapted from microelectro mechanical systems (MEMS) technology. Microfabrication using silicon, glass and metal and microscale polymeric drug delivery devices have become available [28].

These techniques comprise three Categories divided by the manner in which the polymeric material is processed:

1) Photolithography: this involves polymerization of a substance and constructs the desiredstructures.
2) Replica moulding: a polymer is injected into or cast onto a hard or soft master mould which is fabricated using MEMS micro-fabricationtechniques.
3) Polymer micromachining: In this technique micromilling or ablation is used to modify a material to achieve the definite structure[29].

The most commonly used techniques in microneedle manufacture are:

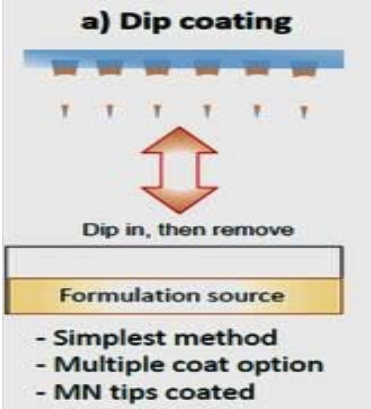
1) Micromoulding
2) Lasercutting
3) Lithography
4) Wet and dry etching [30,31]

Microneedle (MNS) Coating Methods

Previously, MNs coating resulted in drug wastage and loss, variable coating thickness of

active ingredient onto MNs and thus inaccuracy in drug dosage. At that time coating was done by simply immersing patches in a liquid solution for several hours to ensure a full coat onto their surface. This resulted in uneven coating and inaccuracy in drug dosage [32]. Now, development of new different coating techniques has improves the coating process and also reduces the inaccuracy in coating of MNs. These techniques, including dip coating, gas-jet drying, spray-coating, EHDA based processes and piezoelectric ink-jet printing.

Dip Coating



The dip coating method is the simplest method for coating MNs. In this process microneedles are first dipped into the formulation and then are removed from it, this will produce a liquid film on MNs. The liquid layer is then allowed to dry to form a solid film coating. The dip coating method is used to deliver hydrophilic and hydrophobic drugs. Several biomolecules have been coated onto MNs using this technique, e.g., proteins, viruses and DNA, for rapid transdermal delivery [33].

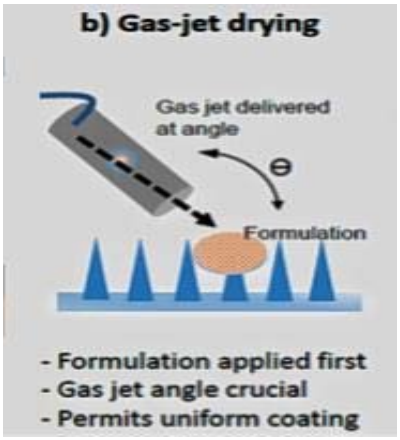
The dip coating method works by submerging MNs into a drug solution and result in a non-uniform coating [33]. Surface tension is a main reason due to which coating of MN is non-uniform, as they are closely spaced [34]. To prevent non-uniform coating of MNs, Gill and Prausnitz developed a micron scale dip coating process. This process is based on coating MN shafts with a thick layer of coating and not the base substrate using a highly viscous formulation which decrease surface tension [32]. This dip coating design used dip holes with similar dimensions of MNs instead of large open coating surfaces to avoid rising of the meniscus subsequently masking the base substrate within the spaced MNs.

The first attempt of coating MNs was performed by Ma and Gill, on a hydrophobic drug coating onto MNs using molten dip coating. They select Lidocaine (MW = 270.8 Da), which is a hydrophobic drug used as a local anesthetic agent to perform dip molten technique on MNs. Usually, the administration of lidocaine to the patient is either topically (i.e., cream) or parentally (i.e., injection). The molten dip coating process was performed to develop uniform lidocaine coated MNs for transdermal delivery. Polyethylene glycol (PEG) was used as a hydrophilic matrix with a lidocaine base to create the solid dispersion. Drug stability was attained at elevated temperatures of ~130 °C. The mass fraction of lidocaine in the drug dispersion had an impact on the PEG-lidocaine molten solution, as decreasing the mass fraction of lidocaine increased the solution viscosity. Compared to the conventional 1 h application of topical cream (0.15 g EMLA®, a 5% emulsion of equal quantities of 2.5% lidocaine and 2.5% prilocaine), the in vitro dissolution studies of PEG-lidocaine coated MNs

in porcine skin demonstrated a significant increase in lidocaine delivery within 3 minute[35].

Another dip coating technique was performed on Human growth hormone (191 amino acids).It is a peptide which is important for growth, cell regeneration and reproduction in humans. Recombinant human growth hormone (rhGH) was successfully dip coated onto titanium MNs for transdermal delivery (200 mg/mL; 20% w/w).Different studies suggest that rhGH MN patches were stable for 6 months at 40 °C. Comparing to commercial subcutaneous Norditropin injection (rhGH), rhGH coated MNs were found to provide a similar absolute bioavailability. This suggests that rhGH MN patches have potential to replace rhGH injections in the pharmaceutical market due to reduced pain benefits and ease of administration [36].

Gas-Jet Drying



The gas jet drying technique of microneedle coating was introduced by Chen et al [37]. Problems arises during coating process like coating material remains wet on surface of MNs, thick multi-layer coating (of solution) accumulates and dries at the base substrate. [38] These problems were overcome with gas jet drying technique, especially for very small (<90 micron length) and very closely (~20.000 cm−2) spaced MNs.

Solid silicon microprojections were spray coated with a thin layer of gold. To improve the surface tension and viscosity, whole length of the microprojections was coated with a (6–8 µL) solution. The coating solution consists of:

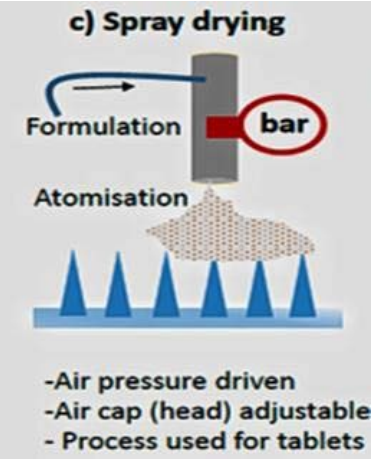
1) Methylcellulose which increases the viscosity and decreases the surface tension of the coating solution at the sametime.
2) Quil-A is a component of saponin, derived from the plant *Quillaja saponaria* and used as a surfactant to reduce the surface tension and works as a vaccine immune-stimulatory adjuvant.
3) Selected concentrations of model active drugs (vaccines or fluorescentdyes).
4) Formulations were applied and were modified using (6–8 m/s) a gas jet. The viscosity of the coated layer (5 µm thick) onto the microprojections increased rapidly, allowing the coated material to dry rather than relocate on the base substrate. This was followed by a fast gas jet (10 m/s) at an incident angle of 20° to remove all excess coating solution. The uniformly dried coating remained intact during skin penetration and the model drugs were released in 3 min. within wet skin[37].

Vaccine delivery using MNs are found to be better than diffusion delivery and

electroporation delivery methods. Transdermal delivery enhances the penetration of small drug molecules (<500 Da) through the stratum corneum [39].

Chen et al. resolve many coating problems and improves vaccine delivery efficiency by using gas jet coated MNs, by focusing on depositing actives on MN tips rather than whole MNs. This was achieved by increasing the gas jet incident angle to 70°, removing the patch edge and rotating the patches during the coating process to ensure uniformity. With the help of gas jet spraying technique the delivery efficiency of vaccines was increased from 7.3% ± 1.1% to 17.8% ± 1.5% (for incident angle 20°) simply by removing the patch edge. Delivery efficiency increased from17.8% ± 1.5% (for incident angle 20°) to 32.5% ± 3.9% (for incident angle 70°) based on the incident angle with continuous rotating of patches [39].

Spray Drying



The spray coating process was first introduced by McGrath et al. [40]. Spraying drying system comprises 0.5 mm spraying nozzle connected to a compressed air pump and a coating solution. Under the nozzle, silicon MNs was placed on the platform stage using double sided tape. The coating solution was injected into the nozzle for atomization with the help of peristaltic pump or a syringe driver. Optimization of spray process parameters (e.g., atomization air pressure, gun to-surface distance and air cap setting) is necessary for uniform film coating on the MN substrate. The film coat formation depends on the coating solutions physio–chemical properties and the spray process parameters [40]. The spray coating method is similar to conventional coating methods like coating of tablets to produce millimetre thicknesses. Spray coating of micro particles onto MNs is followed by three steps.

FIRST

the generation of formulated microdroplets from the

SEC

the deposition and adherence of droplets onto the

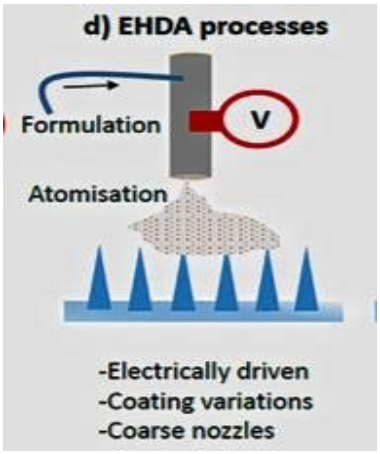
THI

the aggregation of droplets on the substrate to form an intact

Hydroxypropylmethylcellulose(HPMC) and carboxymethylcellulose(CMC) were introduced as two coating materials for MNs. The addition of a surfactant (Tween 80) along with CMC solutions was necessary to assist coalescence of the sprayed droplets onto the silicon surface [40].

Spray coated solid MN patches were also used for transcutaneous delivery of live recombinant adenovirus (rADV) and modified vaccinia virus Ankara (MVA) vectors as vaccines. The potency of recombinant virus vaccine coated onto MNs patches to induce antibody response, transcutaneous infection and induced antibody (or CD8+ T cell) response was equivalent to the response induced by transdermal injection of the same vaccine [41].

EHDA Processes



EHDA stands for Electrohydrodynamic Atomisation.

1) This process was described by Grace and Marijnissen (1994) and has been developed to generate near uniform micro- and Nano-meter scaled architectures in one step. In this process atomized droplets are produced by an electrically imposed moving liquid (the electrical field generates charge inside droplets) that jet through a capillary nozzle exit and are subsequently collected over a ground electrode positioned below the nozzle tip [42]. The liquid used is a polymeric solution, or formulation, containing three main components .i.e. a solvent, polymer and active drug and other excipients.
2) This technique has been widely used by researchers for various drug delivery therapies like insulin[43], folic acid [44], titanium dioxide antimicrobial agent [45], gold used in gene delivery etc.[46].
3) The EHDA system can generate both particles (electro-spraying) and fibres (electrospinning).
4) Using the EHDA process, controlled particle and fibre coating thickness is achievable [38]. This is especially important for sensitive biomolecules such as peptides and protein drugs which are stable during EHDA processes but unstable for delivery via oral route of administration[38, 43 ,46]. In comparison to dip coating, the electrical spray-coating system (e.g., EHDA system) can be optimized to coat MN tips only and avoid coating the base substrate (by using surface insulating polymeric masks).
5) There are three main types of EHDA processes:

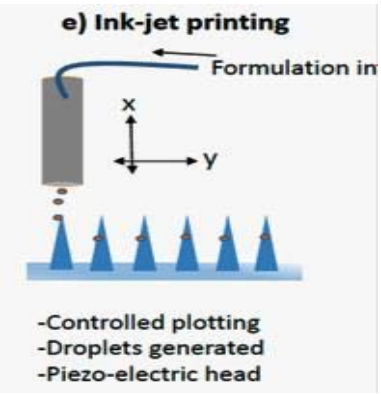
1) **Single needle:** this is the process in which the formulation is injected into a single nozzle by a single precision syringe pump.
2) **Coaxial EHDA:** this system uses two or more immiscible liquids which are fed through separately enveloped nozzles. One of the benefits of EHDA using a coaxial system is protection of the sensitive drug from direct exposure to the biological environment [47]. The coaxial EHDA system is preferred as it can produce therapeutic particles with sustained and controlled release.
3) **Multiplexed EHDA:** liquid formulation fed through a single or coaxial nozzle array.

Some parameters need to be considered when using EHDA process:
1) Flow rate applied voltage
2) The distance between the nozzle
3) The collecting platform[48].

These factors have a high impact on the controlled particle size, size distribution, porosity, shape and surface charge. Applied voltage is the most important factor in controlling the jet mode and the size of resulting particles/fibres, increase in applied voltage will lead to the formation of smaller particles/fibred [42]. Moreover, as the applied voltage is increased significantly the morphology of particles has the potential to transition from spherical to elongate. An optimum voltage is determined to overcome the surface tension on the initially atomized droplets. Flow rate has a direct relation to the particle size and the size distribution of the produced architectures as the size reduces with decreasing flow rate. The distance between the tip of the needle and the ground platform has an impact on resulting morphologies. This is due to the relaxation time required for solidifying droplets to reach the deposition substrate, which can be increased by increasing the distance between the two points [42, 49]. In addition to processing parameters, material properties also impact resulting particles/fibres as they significantly affect the jet stability. The viscosity, surface tension, electrical conductivity and density are all major factors to be considered before processing [50].

The most important parameter is:-
The electric conductivity of the vehicle (solvent), as liquid with low electrical conductivity (e.g., heptane) cannot be used for single needle EHDA systems. The addition of antistatic additives or their coupling with an electrically conductive liquid improves process ability (e.g., through coaxial EHDA) [51]. Atomised particle size is directly related to solution viscosity and surface tension, while the reverse is true with regard to liquid density [42].

Ink-Jet Printing



Piezoelectric (piezo) inkjet printing technology is the most acknowledged industrial inkjet printing process. In this approach, a piezoelectric crystal (ceramic actuator) undergoes distortion by theeffect of an electric field that creates a pressure pulse in the ink chamber forcing drops to eject from the nozzle. The droplet size is correlated with the nozzle dimensions.

The inkjet printing approach is a valuable engineering apparatus that enables controlled distribution and accurate arrangement of fine liquid droplets (1–100 picolitres) onto a substrate (e.g., MNs) before solidification [49, 50]. Unlike the dip coating method, inkjet printing technology requires formulations with low viscosity to avoid blockage of the jetting nozzle (which possess small dimensions) for a continuous MN coating process [52].

The concept of Piezoelectric Inkjet Printing involves dissolving of selected excipients in a liquid to form an ink. The mechanism of drop formation and ejecting from the nozzle occurs by either:-

1) Inducing vibrations on the material by using a voltage supply connected to a piezoelectric transducer (piezoelectric inkjet printing).
2) Increasing the temperature of the formulation (to slightly higher than its boiling point) which leads to thermal inkjet printing [50,51].

Boehm et al. fabricated biodegradable polyglycolic acid MNs coated with voriconazole (antifungal agent) using piezoelectric inkjet printing. This system was compared with unmodified and vehicle modified MNs against different micro-organisms (*Candida albicans, Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus*). Voriconazole-polyglycolic acid MNs showed antifungal activity against *Candida albicans* while other devices were ineffective. The method was identified as a useful application of piezoelectric inkjet printing for drug loading onto MNs for poorly soluble pharmacological agents [51].

Miconazole (antifungal agent) was also printed onto MNs created from Gantrez® AN 169 BF (polymethyl vinyl ether-co-maleic anhydride) using piezoelectric inkjet printing technology. Dimethyl sulfoxide was used as a solvent to enhance the antifungal drug penetration. Miconazole-loaded Gantrez® AN 169 BF MNs exhibited antifungal activity against *Candida albicans*[51].

Three anticancer agents with varying solubilities 5-fluororacil (5-FU), curcumin (CRC) and cisplatin (CPT) were utilized for transdermal delivery using MNs. At various drug-polymer ratios, anticancer agents with sol plus® coatings (a copolymer used to increase the solubility of water insoluble drugs, hence dissolution rates) were uniform, reproducible and printable onto metallic MNs using the piezoelectric inkjet printing approach. The release profile depended on drug solubility[52].

Hydrophilic 5-FU showed a rapid release profile compared to water insoluble CRC and CPT. However, varying antiproliferative action was observed for the three anticancer agents. Antiproliferative activity was concentration dependent, and at low concentrations (15µg/mL) no antiproliferative activity was observed but observation increased with drug dose. This was dependent on drug potency as 7% and 9.4% viability was observed for 7 µg/mL (CRC) and 200µg/ml (CPT), respectively, sufficient to trigger antiproliferative activity. 5-FU was least potent with 20% cell viability at400 µg/ml[52].

Various drugs are delivered through microneedles based drug delivery system and they have various applications which are listed in table 1[55].

Table 1: **Marketed Microneedle-Based Transdermal Products Table 1**

Brand name	Manufacturer	Description	Applications
Darmaroller ®	Dermaspark, Canada	Metallic microneedle	Used to treat acne, stretch mark, hair loss. Able to enhance drug absorption (Minoxidil, hyaluronic acid, etc.).
MicroHyala ®	CosMEDPharm aceuticalCo. Ltd.,Japan	Dissolvable microneedle patch	It contains hyaluronic acid that is released in the skin to treat wrinkle.
VaxMat®	TheraJectInc., USA	Dissolvable microneedle patch	It is used to deliver macromolecules, like proteins, peptides, and vaccines.
Micro-Trans®	ValeritasInc., USA	Microneedle patch	It delivers the drug into the dermis without limitations of drug size, structure, charge, or the patient's skin characteristics.
Drugmat®	TheraJectInc., USA	Dissolvable microneedle patch	It delivers hundreds of micrograms of drug rapidly through the stratum corneum into the epidermal tissue.
Soluvia®	Becton Dickinson, USA	Hollow microneedle array	It is a prefillable microinjection system for accurate intradermal delivery of drugs and vaccines.
Macroflux®	Zosano Pharma Inc., USA	Metallic microneedle array	Delivery of peptides and vaccines
Micronjet® Intradermal	NanoPassInc., Israel	microneedle injection	It is used with any standard syringe for painless delivery of drugs, protein, and vaccines.
IDflu®/ Intanza®	Sanofi Pasteur, Lyon, France	Intradermal microneedle injection	Prefilled with influenza vaccine for intradermal influenza vaccination

Applications of Microneedle

1) In humans and in animals microneedles have been studied in vitro for variety of applications. Microneedle piercing has shown to increase skin permeability by orders of magnitude to a variety of compounds that ranges from low molecular weight tracers to proteins, DNA and even nanoparticles[56].
2) Drugs that are been delivered through microneedles has considerable attention. For example: influenza vaccine which is administered through microneedle elicits the immune responses comparable to or better than the intramuscular injection in the mouse model. Human clinical flu trials vaccination using hollowmicroneedleshavecompletedPhaseIIIandhavebeensubmittedasthebasisforregistrationinEurope through collaboration between Becton Dickenson (Franklin Lakes, NJ, and USA) and Sanofi Pasteur (Lyon, France) [57].
3) Solid microneedles have also been coated with a number of different compounds,

including low molecular weight drugs, proteins, DNA, virus particles and micro-particles. According to recent studies, it is reported that naltrexone can be delivered into normal human by using microneedle technique at therapeutic levels to treat alcohol and opioid addiction[58].

4) Hollow microneedles have been shown to deliver insulin to rodent models and modulate blood glucose levels. Recent work in human subjects has demonstrated insulin delivery to control blood glucose levels in diabetic human subjects and lidocaine delivery to induce local anaesthesia in normal human subjects. Dissolving polymer microneedles have similarly encapsulated various compounds, including erythropoietin and enzymes that were shown to retain activity after encapsulation and even after at least 2 months of storage at roomtemperature.
5) Studies also demonstrated dose sparing ability of microneedles, where lower antigen dosage via microneedles elicited immune response comparable to higher antigen doses via alternate routes, i.e. subcutaneous and intramuscular injections. Other studies of vaccines include administration of following ChimeriVaxTM-JE for yellow fever[59].
6) Plasmid DNA encoding hepatitis B surface antigen, and recombinant protective antigen of Bacillus anthraces.
7) In all these studies mentioned above, microneedles generated immune responses at least as strong as those generated by subcutaneous or intramuscular injections.

CONCLUSION

Microneedles are a transdermal drug delivery system that is painless, less invasive, and easy to self- administer, with a high drug bioavailability. MN approach is applied to a number of drugs and a lot of studies have to be conducted to get it clinically approved. Researchers have focused their attention on the development of different types of MN for delivery of macromolecules, immunobiologicals and drugs as well as withdraw the tissue fluids. A proper material has to be selected for fabrication of these needles which has adequate mechanical strength and insertion force. The main objective is to increase the permeation without causing pain.

This emerging technology is flexible enough and can be used to administer number of proteins which directly go into systemic circulation.

In conclusion, a microneedle device is made by arranging hundreds of microneedles in arrays on a tiny patch in order to deliver sufficient amount of drug to give a required therapeutic response. It pierces the stratum corneum thus bypassing the barrier layer and these techniques hold a potential as a novel means of transdermal drugs delivery in future.

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