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MICRO NEEDLES: A NOVEL APPROACH TOWARDS TRANSDERMAL DRUG DELIVERY SYSTEM

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- Micro-needle,
- Transdermal drug delivery system (TDDS)

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ABSTRACT

Transdermal drug delivery offers a number of advantages including improved patient compliance, sustained release, avoidance of gastric irritation, as well as elimination of pre-systemic first-pass effect. Recently, the use of micron-scale needles in increasing skin permeability has been proposed and shown to dramatically increase transdermal delivery, especially for macromolecules. The dosing in microgram quantities can be done by this type of needle. Using the tools of the microelectronics industry, micro needles have been fabricated with a range of sizes, shapes and materials. 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.
INTRODUCTION

Micro-needle, a micro structured transdermal system, consists of an array of micro structured projections coated with a drug or vaccine that is applied to the skin to provide intradermal delivery of active agents, which otherwise would not cross the stratum corneum\(^{(1)}\). Micro-needles are somewhat like traditional needles, but are fabricated on the micro scale. They are generally one micron in diameter and range from 1-100 microns in length. Micro-needles have been fabricated with various materials such as: metals, silicon, silicon dioxide, polymers, glass and other materials. It is smaller than hypodermic needle, the less it hurts when it pierces skin and offer several advantages when compared to conventional needle technologies. The major advantage of micro-needles over traditional needles is, when it is inserted into the skin it does not pass the stratum corneum, which is the outer 10-15 µm of the skin. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for micro-needles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.\(^{(2)}\) These 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.\(^{(3)}\) Most applications of micro-needles studied to date have emphasized drug and vaccine delivery to the skin. Conventional transdermal delivery is limited by the barrier properties of the outermost skin layer, the stratum corneum.\(^{(31)}\)

- Need For Using Transdermal Micro-needle

When oral administration of drugs is not feasible due to poor drug absorption or enzymatic degradation in the gastrointestinal tract or liver, injection using a painful hypodermic needle is the most common alternative. An approach that is more appealing to patients, and offers the possibility of controlled release over time, is drug delivery across the skin using a patch. However, transdermal delivery is severely limited by the inability of the large majority of drugs to cross skin at therapeutic rates due to the great barrier imposed by skin's outer stratum corneum layer.\(^{(33)}\) To increase skin permeability, a number of different approaches has been studied, ranging from chemical/lipid enhancers to electric fields employing iontophoresis and electroporation to pressure waves generated by ultrasound or photoacoustic effects. Although the mechanisms are all different, these methods share the common goal to disrupt stratum corneum structure in order to create “holes” big enough for molecules to pass through. The size of disruptions generated by each of these methods is believed to be of nanometer dimensions, which
is large enough to permit transport of small drugs and, in some cases, macromolecules, but probably small enough to prevent causing damage of clinical significance.\(^6\)

Transdermal drug delivery is a noninvasive, user-friendly delivery method for therapeutics. However, its clinical use has found limited application due to the remarkable barrier properties of the outermost layer of skin, the stratum corneum (SC). Physical and chemical methods have been developed to overcome this barrier and enhance the transdermal delivery of drugs. One of such techniques was the use of microneedles to temporarily compromise the skin barrier layer. This method combines the advantages of conventional injection needles and transdermal patches while minimizing their disadvantages. As compared to hypodermic needle injection, microneedles can provide a minimally invasive means of painless delivery of therapeutic molecules through the skin barrier with precision and convenience. The microneedles seldom cause infection while they can allow drugs or nanoparticles to permeate through the skin. Increased microneedle-assisted transdermal delivery has been demonstrated for a variety of compounds. For instance, the flux of small compounds like calcein, diclofenac methyl nicotinate was increased by microneedle arrays.

In addition, microneedles also have been tested to increase the flux of permeation for large compounds like fluorescein isothiocyanate-labeled Dextran, bovine serum albumin, insulin and plasmid DNA and nanospheres.

**Mechanism of Action**

The mechanism for delivery is not based on diffusion as it is in other transdermal drug delivery products. Instead, it is based on the temporary mechanical disruption of the skin and the placement of the drug or vaccine within the epidermis, where it can more readily reach its site of action. The drug, in the form of biomolecules, is encapsulated within the microneedles, which are then inserted into the skin in the same way a drug like nitroglycerine is released into the bloodstream from a patch. The needles dissolve within minutes, releasing the trapped cargo at the intended delivery site. They do not need to be removed and no dangerous or biohazardous substance is left behind on the skin, as the needles are made of a biodegradable substance. In microneedle devices, a small area (the size of a traditional transdermal patch) is covered by hundreds of microneedles that pierce only the stratum corneum (the uppermost 50 µm of the skin), thus allowing the drug to bypass this important barrier (Figure 1) The tiny needles are constructed in arrays to deliver sufficient amount of drug to the patient for the desired therapeutic response.\(^7\)
Advantages

1. The major advantage of microneedles over traditional needles is, when it is inserted into the skin it does bypass the stratum corneum, which is the outer 10-15 µm of the skin. Conventional needles which do pass this layer of skin may effectively transmit the drug but may lead to infection and pain. As for microneedles they can be fabricated to be long enough to penetrate the stratum corneum, but short enough not to puncture nerve endings. Thus reduces the chances of pain, infection, or injury.

2. By fabricating these needles on a silicon substrate because of their small size, thousands of needles can be fabricated on single wafer. This leads to high accuracy, good reproducibility, and a moderate fabrication cost.

3. Hollow like hypodermic needle; solid— increase permeability by poking holes in skin, rub drug over area, or coat needles with drug

4. Arrays of hollow needles could be used to continuously carry drugs into the body using simple diffusion or a pump system.

5. Hollow microneedles could be used to remove fluid from the body for analysis – such as blood glucose measurements – and to then supply microliter volumes of insulin or other drug as required.\(^8\)

6. Immunization programs in developing countries, or mass vaccination or administration of antidotes in bioterrorism incidents, could be applied with minimal medical training.

7. Very small microneedles could provide highly targeted drug administration to individual cells.

8. These 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.
Disadvantages
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.\(^{(9)}\) Limited permeability across the skin may limit the delivery of number of drugs. Systems containing small sized molecules can only easily penetrate the skin. Various attempts have been made to overcome these limitation.\(^{(10)}\)

➢ Methodology of Drug Delivery
A number of delivery strategies have been employed to use the micro-needles for transdermal drug delivery.
These include:-
• Poke with patch approach
• Coat and poke approach
• Biodegradable micro-needles
• Hollow micro-needles
• Dip and scrape
  • Poke with patch approach:-
It involves piercing an array of solid micro-needles into the skin followed by application of the drug patch at the treated site. Transport of drug across skin can occur by diffusion or possibly by iontophoresis if an electric field is applied.
  • Coat and poke approach :-
In this approach needles are first coated with the drug and then inserted into the skin for drug release by dissolution. The entire drug to be delivered is coated on the needle itself.
  • Biodegradable micro-needles :-
It involves encapsulating the drug within the biodegradable, polymeric micro-needles, followed by the insertion into the skin for a controlled drug release.
  • Hollow micro-needles :-It involves injecting the drug through the needle with a hollow bore. This approach is more reminiscent (suggestive of) of an injection than a patch.
  • Dip and scrape :-
Dip and scrape approach, where micro-needles are first dipped into a drug solution and then scraped across the skin surface to leave behind the drug within the microabrasions created by the needles. The arrays were dipped into a solution of drug and scraped multiple times across the skin of mice in vivo to create microabrasions. Unlike micro-needles used previously, this study used blunt-tipped micro-needles measuring 50– 200 µm in length over a 1 cm\(^2\) area.\(^{(11)}\)
Types of micro-needles

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

1. Solid micro-needles: 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. 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 into 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.

These micro-needles can pierce through the superficial skin layers then followed by the delivery of drugs. It also suffers from some limitations such as in solid micro-needle arrays, the drug delivered cannot easily flow via the holes present in the skin because it remains plugged by the micro-needles. An application of a thick layer of drug formulation was not found to be the desirable because it reduces the sharpness of the micro-needles and therefore made insertion more difficult and painful.

2. Hollow micro-needles: Hollow micro-needles contain a hollow bore in the centre of the needle. When inserted into the skin, the hollow bore present bypasses the stratum corneum layer of the skin and produces a direct channel into the other lower layers of the epidermis. These micro-needles are mainly employed to inject the drug solutions directly into the skin. These are very expensive to prepare and require expensive micro fabrication techniques. 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.

Characteristics of micro-needles

The characteristics of micro needles include,

1) 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.

2) Controlled drug release:- The micro needles should deliver the controlled amount of drug at a definite and predetermined rate.

3) 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.

4) Dimensions of micro-needles: - The dimensions of micro needles can vary depending on the types of micro needles. Typical micro-needle geometries may range from 150-1500 microns in length, 50-250 microns in base width, and 1-25 microns in tip diameter. The tips of micro-needles are of different shapes like triangular, rounded or arrow shaped. The hollow micro-needle arrays are fabricated with lumen diameter of 30 micrometers and height 250 micro meters. Centre to centre hollow micro needle array 150μm and the axis of lumen is fabricated with the distance of 10 micro meters to the axis of outside column.\(^{(14)}\)

**Evaluation Parameters**

1) **In-Vitro study of Micro-needles**: - In vitro evaluation micro-needles are accomplished by using various mediums like agarose gel and methanol to insert the micro-needles. 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 micro-needles involves optimization of the micro-needles, finding out the penetration force and bending force, evaluation of strength of micro-needle, 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 micro-needles. In this test, the micro-needles are integrated with Paradimethylsiloxane (PDMS) biochip and black ink is injected by the micro-needles into the petridish, which contains methanol. The right triangular micro-needles with 8.5 and 15 tip taper angles and isosceles triangular micro-needles with 9.5 and 30 tip taper angles have been used for this purpose.

- **Method 2**
  
  In this method, the diluted form of Rhodamine B dye is injected through the micro-needles into the 1% agarose gel to evaluate the penetration and flow of the solution after penetrating into the 1% agarose gel.
Method 3
Inserting micro-needles 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 micro-needle tip, coated with vitamin B, calcein or sulforhodamine.\(^{(15)}\)

2) **In Vivo Testing of micro-needles**:- 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 micro-needles 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 micro-needles by pricking the micro-needles into vein of the tail of hairless mice. It is used for the determination of the penetration force of the micro-needle into the skin.

   ➢ Method 2
This method of in vivo testing of the micro-needles, Rhodamine B is injected into tail of laboratory mouse-tail and anaesthetized for the determination of penetration force and bending breakage force.

   ➢ Method 3
This method has been performed for the evaluation of vaccine delivery via micro-needles. Ovalbumin is used in this method, as a model protein antigen and administered into hairless guinea pig by using solid metal micro-needles at the rate of 20 \(\mu\)g ovalbumin in 5s up to 80 \(\mu\)g.\(^{(32)}\)

   ➢ 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 micro-needles.

**APPLICATIONS**
Micro-needle technology has been developed as a platform technology for delivery of high molecular weight and hydrophilic compounds through the skin. The first ever study of transdermal drug delivery by microarray technology was conducted by Henry et al who demonstrated an increase in the permeability of skin to a model compound calcein using microarray technology. In a follow up study, McAllister et al found a change in the permeability of cadaver skin to insulin, latex nanoparticles and bovine serum albumin after treatment with micro-needles, and unleashed the mechanism of transport as simple diffusion.

- **Oligonucleotide delivery**: Lin and co-workers extended the in vitro findings of microarray drug delivery to in vivo environment. An oligonucleotide, 20merphosphorothioated oligodeoxynucleotide was delivered across the skin of hairless guinea pig either alone or in combination with iontophoresis. Lin and co-workers used solid micro-needles etched from stainless steel or titanium sheet prepared with the poke with patch approach. This delivery system increased the absorption of the molecules relative to the intact skin. Iontophoresis combined with microneedles was able to increase the transdermal flux by 100 fold compared to the iontophoresis alone.

- **DNA vaccine delivery**: The cells of Langerhans present in the skin serve as the first level of immune defence of the body to the pathogens invading from the environment. These cells locate the antigens from the pathogens and present them to Tlymphocytes, which in turn stimulate the production of antibodies. Mikszta et al reported the delivery of a DNA vaccine using micro-needle technology prepared with the dip and scrape approach. The arrays were dipped into a solution of DNA and scrapped multiple times across the skin of mice in vivo. Expression of luciferase reporter gene was increased by 2800 fold using micro-enhancer arrays. In addition, micro-needle delivery induced immune responses were stronger and less variable compared to that induced by the hypodermic injections.

- **Desmopressin delivery**: M. Cormier et al (Alza Corporation, USA) examined the use of micro-needles to deliver desmopressin, a potent peptide hormone used in the treatment of nocturnal enuresis in young children, as well as for the treatment of diabetes insipidus and haemophilia A. Micro-needles were coated by an aqueous film coating of desmopressin acetate on titanium micro-needles of length 200 µm, a maximal width of 170 µm and a thickness of 35 µm. Micro-needle patch was inserted into the skin with the help of an impact applicator. A target dose of 20 µg of desmopressin was delivered to hairless guinea pig from 2 cm2 micro-needle array within 15 minutes.
Insulin delivery: Insulin is one of the most challenging drug of all times for the drug delivery technologists. Martano et al.10, used microarrays for the delivery of insulin to diabetic hairless rats. Solid micro-needles of stainless steel having 1mm length and tip width of 75 µm were inserted into the rat skin and delivered insulin using poke with patch approach. Over a period of 4 hours, blood glucose level steadily decreased by as much as 80% with the decrease in glucose level being dependent on the insulin concentration.

Delivery of various drugs through different transdermal carriers

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<td>5-fluorouracil</td>
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Marketed formulations based on microneedles as a transdermal system

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<th>Market product</th>
<th>Description</th>
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CONCLUSION
Micro-channel based Transdermal Delivery System by using Micro-needles is a Novel Approach for Drug delivery system. It is a convenient, painless, and less invasive alternative to injection & it can be used a common method for administering large proteins and peptides, antibiotics, vaccines in low manufacturing cost. In contrast to oral delivery, micro-needles avoid first pass effect and offer the benefit of immediate cessation of drug administration in case of an adverse effect or overdose. In contrast to passive delivery, this allow for the delivery of watersoluble drugs. In contrast to iontophoresis, this is use for long time. There is also no molecular size limitation, no molecular electrical charge requirement, and no specific formulation pH constraint. In contrast to conventional TDDS, this is use for potent & less potent the drug, the more extended release the delivery system.

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