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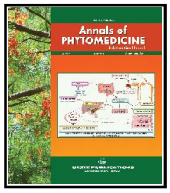

Review Article : Open Access

A review on advancement and usage of microneedle mediated drug delivery over years

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Abstract

One of the novel drug delivery systems is the transdermal drug delivery system. Currently transdermal delivery is one of the most promising methods for drug application. Transdermal drug delivery systems (TDDS) are defined as self-contained, discrete dosage forms which are also known as patches. There are many drawbacks to using conventional transdermal drug delivery techniques, such as needle phobia, which can be overcome by employing a transdermal patch mediated by microneedles, which has a quicker start of action, higher patient compliance, self-administration, and enhanced permeability. The microneedle (MNs) was first described as a novel method of drug delivery in 1998. Researchers have developed a refined technology using microneedles, which allow hydrophilic high molecular weight compounds to enter into the stratum corneum. Several medications, including anticancer medications, oligonucleotides, vaccines, proteins, DNA, and even nanoparticles, are interesting candidates for topical administration using microneedles.

1. Introduction

Delivery of drug refers to either the process or method of giving a pharmaceutical product to a human or animal to have a therapeutic effect, or to a system that serves as a "carrier" or way of delivering an effective medication or drug to the patient's body. Drug delivery systems come in a variety of forms or designs. They are; oral drug delivery, nasal drug delivery, ocular drug delivery, pulmonary drug delivery systems, sublingual drug delivery, transdermal drug delivery, and vaginal/anal administration of medicines (Hannah Blair, 2002). The main internal factors influencing alterations in the structure of the skin include physiological disruptions in the pace of epidermal exfoliation, inhibition of tissue development and differentiation processes, and suppression of tissue regeneration (Nadeem Bari *et al*., 2023).

Transdermal delivery stands out as one of the most promising approaches to medication delivery at present. It lessens the strain that the liver and digestive system often experience when using the oral method. Transdermal patches, also known as medicated adhesive patches that are applied to the skin to deliver a specific dose of medication through the skin and into the bloodstream, are dosage forms intended to deliver a therapeutically effective amount of drug across a patient's skin. Transdermal drug delivery presents an alluring alternative to oral administration and injection (Shanthi Priya *et al.,* 2023). When bioactive chemicals are applied topically, absorption is frequently poor and bioavailability is restricted (Sumedha Saxena *et al.,* 2022). It is useful for transdermally administered medications that require only one weak application, improves patient compliance, and reduces dangerous side effects of a drug produced by an involuntary overdose.

One of the most advanced medication delivery techniques available today is the transdermal system. Transdermal medication delivery devices, sometimes called "patches," are distinct dose forms that are applied separately. Transdermal delivery allows for the continuous administration of medications with short half-lives while preventing pulsed entrance into the systemic circulation, which may cause undesirable side effects. Additionally, it permits the continuous, regulated delivery of medications (Tanwar and Sachdeva, 2016).

1.1 Transdermal routes and prospective routes for drug delivery

In the human body, skin is the most substantial organ, encompassing over two square meters of surface area and receiving just over a third of all blood flow. It functions as a permeability barrier, obstructing the transdermal absorption of various chemical and biological substances. It is one of the easiest organs in the body to reach because it is just a few millimeters thick. The human skin serves as a barrier separating the interior of the body from outside factors. It is a three-layered defensive organ made up of the epidermis, dermis, and hypodermis (Mansood Ali *et al.,* 2022).

- Protects the interior blood circulation network from the external environment. Acts as a defense against biological, chemical, and attacks on the body.

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- Helps regulate body temperature by serving as a thermostat. It plays a role in blood pressure regulation. Blocks UV radiation from invading.
- Epidermis penetration and absorption of medications are two important features of drug administration that are influenced by the skin.

1.2 Advantages of transdermal drug delivery

- Conveniently, this treatment only has to be used once a week. Adherence to medication therapy by patients can be improved with such a basic dose schedule.
- Patients who are intolerant to oral dose forms might be accommodated with an alternate mode of administration: Transdermal medication delivery. Transdermal administration offers an additional means of avoiding first-pass metabolism, which is a constraint associated with oral medication delivery.
- Additionally, the patch allows for continuous dosing as opposed to the peaks and troughs in drug levels that come with taking medication orally. Reduce the amount of unfavorable side effects.

1.3 Disadvantages of transdermal drug delivery

- The possibility for localized discomfort when the product is applied. The medication used in the patch formulation, such as the adhesive or other excipients may induce erythema, irritation, or localized edema. It could result in allergic responses. Drugs with high molecular sizes are not prone to development.
- It is unable to administer medication pulsatillously. It might end in an allergic response.
- Adherence over time is challenging (Sonia Dhiman *et al*., 2011).

1.4 Significance of transdermal drug delivery system

Parenteral injection is the method that is most frequently used to provide biopharmaceutical drugs. However, there are certain major drawbacks to this medication delivery route (*i.e.,* needle phobia, sharp waste, disease transmission). Transdermal delivery is an effective replacement that gets over most of the technical problems with hypodermic needles, which increases patient acceptance and compliance. Although, the permeation capacity of the transdermal patches is minimal, a novel approach to microneedle-mediated transdermal patches can be used to enhance the penetration of the drug. Also, this is one of the best choices to deliver the drug directly to the systemic circulation for better therapeutic responses.

So, by using a microneedle-mediated transdermal patch rapid onset of action, greater patient compliance, self-administration, and enhanced permeability can be achieved.

Table 1: A comparison between transdermal route of administration

Product	Topical cream	Transdermal patch	Hypodermic needle	Microneedle
Description	Emulsion, cream, ointments	Adhesive patch to be applied topically	Tiny, hollow tube with a small opening and a sharp point	On a tiny patch's surface, micron-sized needles are positioned.
Onset of action	Slow	Slow	Faster	Faster
Pain	Painless	Painless	Painful	Painless
Bioavailability	Poor	Insufficient	Sufficient	Sufficient
Patient compliance	Less	Better	Less	Better
Self administration	Possible	Possible	Not possible	Possible
Mechanism of drug delivery	Permeation through skin pores	Large molecules diffuse poorly because the medicine must get through the stratum corneum barrier	Drugs placed directly in the dermis	Drugs are injected straight into the dermis or epidermis and bypass the stratum corneum, increasing permeability.

2. Microneedles

In 1998, a new approach to medication delivery using microneedles (MNs) was initially presented. To safely and effectively transfer proteins, deoxyribonucleic acid (DNA), genes, antibodies, and vaccinations to human bodies, drug delivery research has recently undertaken a thorough analysis of several approaches. Oral distribution of medicine may render it inactive due to I-pass metabolism, and hypodermic injection needs specialized staff. These are some of the drawbacks of conventional drug delivery methods. Transdermal medication distribution is an option that is safe, convenient, and patient-friendly for overcoming these disadvantages (Bhuvaneshwaran and Grace Rathnam, 2019).

The stratum corneum can be penetrated by microneedles, which are three-dimensional (3D) microstructures with microscale lengths. They can create temporary microchannels that allow outside molecules to passively permeate into the skin. It is possible to construct microneedles so that their penetration depth is shallow enough to avoid coming into contact with the lower reticular dermal nerve receptors. This leads to a painless delivery of medication. The potential of this microneedle-based transdermal method to provide a self-managing, patient-friendly, and effective medication delivery channel is promising (Valsa Remony Manoj and Hima Manoj, 2019).

Many researchers investigated using microneedles to deliver drugs transdermally to overcome the shortcomings of traditional methods. The device consists of a tiny needle arranged on a small patch, and it was developed as a hybrid of both approaches to address the issue with hypodermic transdermal patches. Using microneedles, researchers have improved a technique that allows hydrophilic high

molecular-weight chemicals to penetrate the stratum corneum (Dugad and Bhattacharya, 2023). There are several therapeutic uses for wearable technology as medical devices. Wearable technologies can aid research on the skin without invasive procedures. This contributes to reliable outcomes both in vivo and in vitro (Vaidya *et al*., 2023).

Microneedle patches prevent the stratum corneum barrier and deliver the medicine directly into the epidermis above the dermis layer which provides 100% of the loaded substance without discomfort. This technology's defining characteristics include a more rapid start of action, increased permeability and effectiveness, higher patient compliance, and self-administration.

By using microneedles, drugs may be delivered through the skin as opposed to biological circulatory systems like lymphatic or blood arteries. Because of this, the microneedles should be painless when they pierce the skin and long enough to allow medication delivery to the desired location. Furthermore, the microneedles must possess exceptional physical hardness to pierce the stratum corneum, which has a thickness ranging from 10 to 20 µm (Kai Jun Koh *et al.,* 2018).

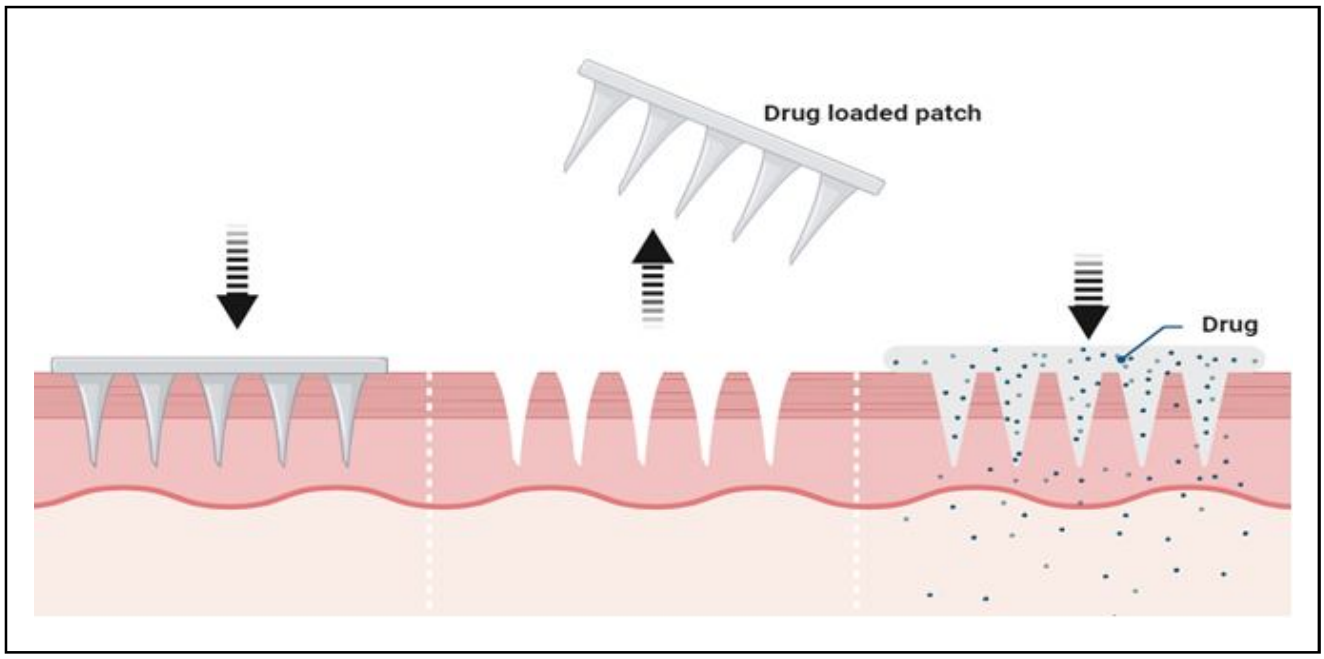

Figure 1: Drug-loaded solid microneedle patch (Drawn by Biorender software).

2.1 Applications of microneedles

The many benefits that microneedles provide have led to their adoption in a variety of health-related applications. Anticancer medications, oligonucleotides, vaccines, proteins, DNA, and even nanoparticles are among the many medications that may be applied topically using microneedles. In the domains of cosmetics, medicine, and pharmacy, microneedles are also widely used. An increasing number of medical operations, like the treatment of glaucoma, have made it possible to administer medication using microneedles. Other significant uses of microneedles have been in diagnostics, such as the tracking of several biomarkers (Tajashree Waghule *et al.,* 2019).

2.1.1 Vaccine therapy

Immunization is a biological treatment. It offers acquired immunity that is active against a specific illness. It has been discovered that vaccination treatment benefits from the microneedle technique. Using a microneedle, the DNA vaccine was administered. Compared to standard injections, the observed immune responses were significantly better.

2.1.2 Peptide delivery

When peptides are taken orally, they are broken down by enzymes. Although transdermal administration eliminates this, less peptide can get through the skin. Insufficient peptide penetration through the skin can be addressed by peptide administration using microneedles. A study on the administration of desmopressin by microneedles revealed that this method was safer and more effective than previous approaches.

2.1.3 Hormone delivery

One type of peptide hormone is insulin. To decrease the elevated blood sugar levels, the medicine is administered. More effective blood glucose lowering was seen when insulin was administered using a microneedle. Solid microneedles were created to investigate how insulin delivery was impacted by the blood glucose levels of diabetes mice. By employing microneedles to increase the permeability of insulin to the skin, the results showed that the blood glucose level was lowered to 29% of the original level at 5 h (Tajashree Waghule *et al.,* 2019).

2.1.4 Cosmetics

The application of microneedles in cosmetics is becoming more and more popular, particularly for treating scars and blemishes on the skin and enhancing its look. Using the microneedle method, an effort was made to administer various active compounds for cosmetics, such as retinyl retinoate, eflornithine, and ascorbic acid.

2.2 Advantages of microneedle drug delivery

- It is possible to administer large molecules. The active therapeutic component is administered painlessly, and first-pass metabolism is prevented.
- Better injection site healing compared to using a hypodermic needle. Replacement of needles for pediatric patients. It is simple to administer.
- Lower doses could be indicated due to enhanced drug efficacy (Shital Bariya *et al.,* 2012).

2.3 Disadvantages of microneedle drug delivery

- There could be less dosage preciseness than with hypodermic needles for injections. The delivery may be impacted by outside factors, such as moisture in the skin. Numerous administrations may cause the veins to rupture.
- When the patch is removed, the microneedle tip might break off and persist in the skin (Shital Bariya *et al.,* 2012).

3. Development of microneedle molds

Microneedle molds and patches can be prepared by various methods;

3.1 Microneedle molds using resins

A 3M microneedle mold with a combination of unsaturated polyester resin and peroxide can be used to create microneedle molds. The resin and hardener (1:100) mixture has to be thoroughly and correctly mixed. After that, a 3M microneedle tip punctured to the size of a micron is used to get an array mold. Mold arrays should be prepared and then dried at room temperature for 24 h to allow for the production of firm, solid molds (Mogusala *et al.,* 2015).

3.2 Microneedle molds using beeswax

Beeswax is melted and then poured into a circular vessel to solidify to create microneedle molds. After that, an array mold was obtained by puncturing it with a needle tip the size of a micron. The mold arrays were prepared and then allowed to dry at room temperature for a day to make firm, solid molds (Gittard *et al.,* 2009).

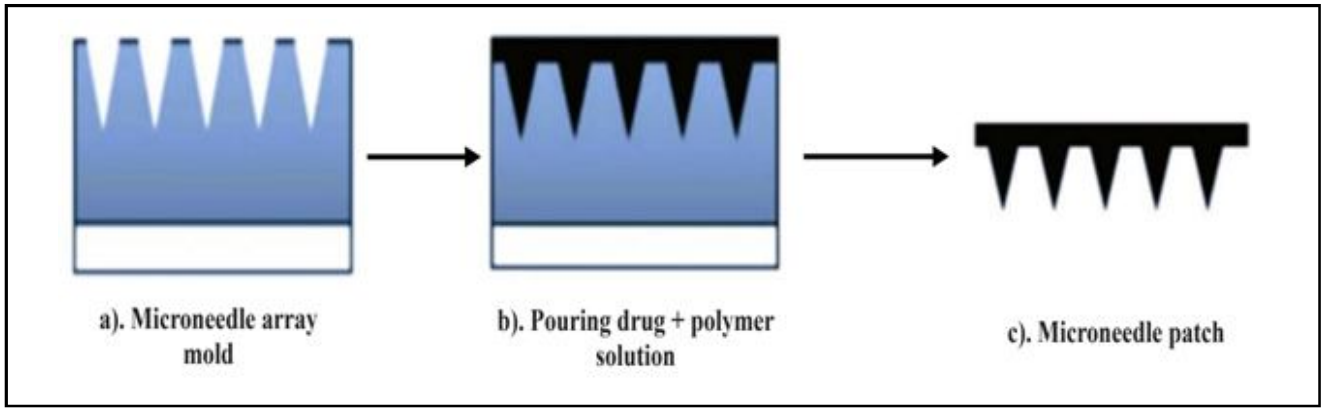

Figure 2: Fabrication of microneedle mold and patch.

4. Quality control of microneedles

4.1 Preformulation study (Compatibility studies)

To look at incompatibilities between drug polymers and excipients used in the preparation patches, an ATR-FTIR analysis can be conducted. The formulated patch and the pure drug's ATR-FTIR spectra are compared. A total of 32 scans are used to evaluate each spectra, with resolutions varying from 4000 to 600 cm^{-1}.

4.2 Physical appearance

Examine the microneedle patches by sight to ensure that the needles are sharp and the color is regular.

4.3 Thickness of the microneedles

By using a digital micrometer screw gauge that is electronic, take three separate measurements of the microneedle's thickness. Determine the prepared microneedle readings three average and standard deviation (SD) values (Chen *et al.,* 2016).

4.4 Optical microscopy

A stage micrometer can be used in optical microscopy to analyze the surface morphology of the microneedle patch. After placing the stage and microneedle for needle visualization projections, place the sample under examination on the glass slide.

4.5 Sem analysis

SEM analysis may be used to identify the shape and surface properties of a microneedle. To examine the size and form of the beads, digital microscopy (Nikon digital sight, DS-Fi20) was used. A calibrated eye-piece micrometer was used to measure the beads' size. Scanning electron microscopy (SEM) was used to examine the surface morphology of the prepared beads. Following the attachment of the beads on a shaft with a dual-sided tape for adhesion, they were vacuum-encrusted in an ion sputter for 75 sec to produce a thin layer of three to five nm gold. An acceleration voltage of 30 kV was used for the SEM photos (Norman *et al.,* 2013).

4.6 Drug content

Methanol was used to dissolve the whole microneedle patch and the drug was extracted by continuous stirring for 24 h to determine the drug concentration. Following the proper dilution, the drug content was measured using Spectrophotometry of UV visible light at 296 nm (Pablo Castaneda *et al.,* 2018).

4.7 *In vitro* permeation studies

Drug release studies were conducted in vitro utilizing a Franz diffusion cell equipped with a receptor compartment. After the microneedle film was ready, it was inserted between the donor compartment and

the receptor and wrapped in aluminum foil. Phosphate buffer, pH 7.4, was put within the diffusion cell's receptor compartment. The entire assembly was mounted on a hot plate magnetic stirrer, and since human skin temperature normally ranges from 32°C to 36°C, the fluid in the receptor-containing chamber was continually and systematically swirled using magnetic beads. The samples were taken out at various intervals of 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 h and subjected to a drug content spectrophotometer analysis at 296 nm. At each sample withdrawal, the phase of the receptor was refilled with the same amount of phosphate buffer (McGrath *et al.,* 2014). *In vitro* permeation studies for microneedle patches can also be determined by several standard methods which are used to determine transdermal patches.

5. Conclusion

The present review briefly summarizes the mechanism of delivering drugs and systems especially the transdermal drug delivery system with its advantages and disadvantages. Also, the significance of transdermal drug delivery regarding microneedle-mediated transdermal patches has been discussed. Compared to traditional drug delivery of transdermal drug delivery systems, microneedle patches have their pros and cons that as the quicker start of the action, increased patient compliance, self-administration, and enhanced permeability. Currently, microneedle-mediated drugs can emerge as the most promising and improvising drug delivery for their advantages and significance over the other drug delivery methods. Microneedle patch preparation from technical to cost-effective and easiest method has also been discussed including quality control. Therefore, further study should take place concerning microneedle drug delivery in several other fields such as oncology, and immunology to improvise this delivery method in the future.

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Conflict of interest

The authors declare no conflict of interest relevant to this article.

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