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Review Article

Review on Transdermal drug delivery focus on Recent trend of Microneedle in transdermal patch its current and future advancement

Ashwini Karnakoti[1]*, Ruchita Badekar[2], Vishal Bodke[3], Mangesh Dagale[4], Swapnil Phalak[5], Amol Borade[6]

Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat.

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ABSTRACT

Transdermal drug delivery offers an appealing option to oral administration and has the potential to serve as a substitute for hypodermic injection as well. For centuries, individuals have applied substances onto the skin to achieve medicinal benefits, and in the present day, a range of topical formulations have been created to address local medical issues. Transdermal drug delivery has significantly influenced medical practice; however, it has not yet reached its full potential as a substitute for oral administration and hypodermic injections. First-generation transdermal systems have seen a consistent rise in clinical applications for the administration of small, lipophilic, low-dose medications. Meanwhile, second-generation systems that incorporate chemical enhancers, nonactivational ultrasound, and iontophoresis have also led to the development of clinical products, with iontophoresis offering the advantage of real-time control over delivery rates. Third-generation systems focus on the skin's barrier layer, the stratum corneum, employing techniques such as microneedles, thermal ablation, microdermabrasion, electroporation, and cavitational ultrasound. Currently, microneedles are advancing through clinical trials aimed at delivering macromolecules and vaccines, including insulin, parathyroid hormone, and the influenza vaccine. With the implementation of these innovative second- and third-generation enhancement methods, transdermal delivery is set to greatly enhance its role in the field of medicine. In present we discussed the transdermal drug review and mainly focus on recent developed microneedle for transdermal delivery.

INTRODUCTION

Transdermal patches facilitate the controlled release of active ingredients through the skin into systemic circulation. Drugs delivered via these systems bypass first-pass metabolism, maintaining a steady state akin to a continuous intravenous

***Corresponding Author:** Ashwini karnakoti
Address: *Department of Pharmaceutics, Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat*
Email : ashukarnakoti2001@gmail.com

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infusion for several days. Controlled release forms of drugs, including microcapsules, nanoparticles, liposomes, chitosan and vancomycin microspheres, and encapsulated biopolymers, have gained significant importance in therapy due to their numerous advantages [1]. These forms enable the gradual release of active substances over an extended period following a single administration, offering considerable convenience for patients. For example, in rheumatism, numerous preparations are available on the market; however, the development of drugs with controlled release has enabled the creation of transdermal pharmaceutical forms that utilize piperine and capsaicin as active substances [2]. with favorable outcomes for the patient. Since 1980, this area has experienced remarkable growth, marked by significant commercial success. This progress is founded on an enhanced understanding of skin barrier function, along with the physicochemical, pharmacokinetic, and physiological factors that facilitate the feasibility of transdermal administration. One of the key areas of nanotechnology is nano-formulations. Considering their smaller particle size, nano formulations enhance drug retention, specificity, and targeting, establishing them as optimal transdermal drug delivery systems (TDDS) [3]. The skin is the body's largest organ, serving as a barrier that is largely impermeable to various external chemicals, microbes, and particulate matter, including colloidal substances. It has a schematic structure that includes major pathways for transdermal drug transport, such as appendageal, transcellular, and intracellular routes. The stratum corneum (SC), the outermost layer of the skin, is rich in lipids, allowing only drugs with moderate lipid solubility to penetrate it [4]. Although there are some hydrophilic channels and pores from sweat ducts and hair follicles, only compounds with both moderate aqueous and lipid solubility can effectively pass through the skin for topical and transdermal delivery. The skin's barrier properties can vary significantly depending on the body area, influenced by the thickness of the SC, the distribution of pores and hair follicles, and the patient's age. Consequently, transdermal products are designed for application on specific body sites, such as the chest, thighs, under the ears, underarms, or scrotum [5]. Currently, in addition to traditional oral medication forms, alternative drug administration methods are becoming increasingly important, particularly through topical (or dermal) and transdermal delivery systems for active pharmaceutical ingredients (APIs). Topical and dermal formulations are mainly intended to produce localized effects on the skin's surface and its upper layers, such as the epidermis, or to target deeper tissues, including the dermis, muscles, or joints [6]. In contrast, transdermal formulations are designed to enable APIs to enter systemic circulation, allowing for wider therapeutic impacts. Therefore, the skin and transdermal route play a vital role not only in dermatological treatments but also in addressing various other organs, such as joints, the central nervous system, and for uses in hormone therapy and pain relief. Additionally, many cosmetic products are formulated for application on the skin or related structures, such as hair and nails [7]. However, due to the unique structural properties of human skin, which serves as a robust mechanical barrier, many active ingredients find it challenging to penetrate effectively. Thus, successful skin delivery typically depends on specially designed formulations combined with methods that enhance penetration [8,9]. Over the past few years, significant progress has been made in the field of microneedles. This encompasses not only microneedle compositions and morphologies but also various applications, including drug delivery, vaccination, patient fluid collection (point-of-care diagnostics), and bio signal acquisition, among others [10].

Microneedle

For administering drugs through the skin, topical creams and hypodermic needles are the most commonly used methods. Patients are less likely to accept needles due to the pain they cause, and topical creams have lower bioavailability [11,12]. The main obstacle to delivering drugs topically is the skin itself. Skin consists of three main layers - the middle epidermis, the thicker dermis, and the outermost stratum corneum. The stratum corneum acts as a key barrier, filtering out certain compounds like lipophilic and low molecular weight drugs. This relatively low permeability of the stratum corneum poses challenges when formulating topical products. To address the drawbacks of traditional methods, researchers have explored using microneedles (MNs) for transdermal drug delivery [13,14]. A microneedle device is composed of tiny needles arranged on a small patch. The microneedle drug delivery approach was developed to overcome the issues with both transdermal patches and hypodermic needles, combining features of the two [15]. The main limitation of transdermal technology is that many drugs cannot penetrate the skin quickly enough to achieve a therapeutic effect. By using microneedles, researchers have improved a technique that allows hydrophilic high molecular weight substances to permeate the stratum corneum [16-18].

Table 1. Comparison between topical cream, transdermal patch, hypodermic needle, and microneedle drug delivery systems [19].

	Topical cream	Transdermal patch	Hypodermic needle	Microneedle
Description	Emulsion/ emulgel/ cream/ ointments	Adhesive patch to be placed on the skin	Fine, hollow tube having a sharp tip with small opening at the end	Micron size needles are aligned on the surface of a small patch
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.	Drug has to cross stratum corneum barrier, thus poor diffusion of large molecules	Drug placed directly in the dermis	Bypass stratum corneum and drug placed directly into epidermis or dermis hence enhanced permeability

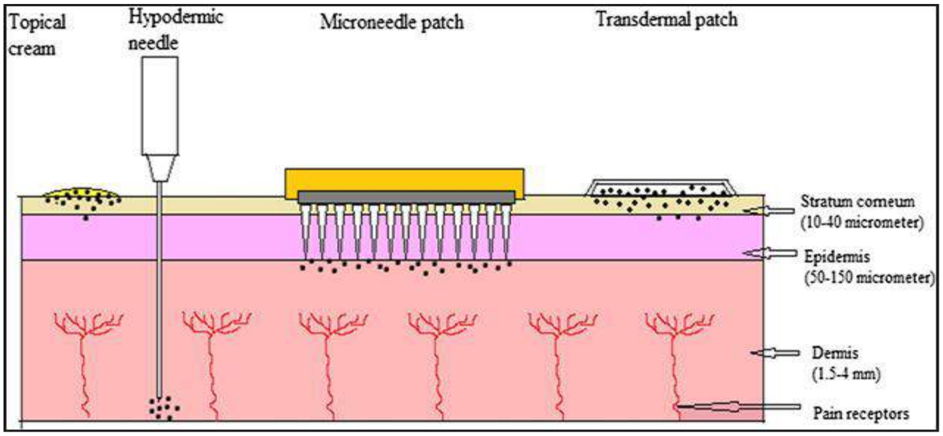

Figure 1. Comparison of topical cream, hypodermic needle, microneedle patch and transdermal patch. [20]

Table 2. Advantages of microneedles as a transdermal delivery

Improve drug delivery	(1) Drugs are delivered directly into the body through the stratum corneum (2) Onset of drug action is rapid (since there are capillary bed and associated lymphatic vessels in the superficial dermis) (3) Accurate drug dose is delivered by controlling microneedle formulations (4) Microneedles avoid the first-pass metabolism (5) Microneedles enable high drug bioavailability (6) It is effective for vaccine delivery because of the abundance of immune cells in the dermis.
Improve safety and patient compliance	(1) Microneedles are painless and safe because of their small length and size (2) The need for expertise is reduced for the patch application (3) Microneedle patches reduce or eliminate biohazardous sharps waste.
Improve manufacturing process and cost-saving	(1) The optimized solid-state formulation of the microneedle does not need the cold-chain system (2) Microneedle patches, which encompass the functionality of the drug, needle, and syringe, reduce the overall size of the drug package (3) Microneedle patches save cost in terms of dose sparing, manufacturing, and logistics [21].

DISADVANTAGES

1. Drug dose is limited due to the small size of the microneedle
2. Temporary inflammation and allergy can be caused
3. Sophisticated technologies are needed for manufacturing a microneedle patch with reproducibility
4. Microneedle patches need a storage container for holding the microneedle patches hygienically without damage during distribution from the manufacturers to the patients
5. When the solid microneedles are applied, some part of the microneedles can be broken or left in the skin [22].

Types of microneedles

The design of microneedles is influenced by various factors, including the specific medication intended for delivery, the type of microneedle employed, and the mechanism of delivery. However, many microneedle patches exhibit common characteristics [23]. A standard microneedle typically features a tapered sharp tip, with dimensions ranging from 150 to 1500 µm in length, 50 to 250 µm in width, and a tip thickness of 1 to 25 µm [24]. Materials commonly used in the fabrication of microneedles include metal, silicon, polymer, glass, or ceramic. The medication is generally placed into or onto the tip of the microneedle, which is then anchored to a substrate beneath to form an array. For ease of use, the microneedle array is attached to a patch backing that includes a skin adhesive to improve adherence to the skin [25]. Microneedles, as innovative devices, provide several advantages, including effectiveness, portability, and precision. It is important to highlight that the selection of materials, microneedle design, and manufacturing process are critical factors for the device's success in any application. A transdermal delivery system provides a painless method of drug administration through intact skin [26].

Solid Microneedles: These are microscopic needles that physically penetrate the outer layers of the skin, creating tiny channels for drug delivery. Solid microneedles can be made from materials like silicon, metal, or polymers [27]. **Coated Microneedles:** Coated microneedles have a drug coating on their surface that dissolves or releases upon insertion into the skin, delivering the medication directly into the bloodstream [28]. **Dissolving Microneedles**: These microneedles are made from biodegradable materials and dissolve after penetrating the skin, releasing drugs into the underlying tissue. **Hollow Microneedle Arrays:** Hollow microneedle arrays have channels or conduits through their centers that allow for direct injection of drugs or vaccines into deeper layers of skin tissue.

Hydrogel-forming Microneedle Patches: These consist of water-soluble polymers that form a hydrogel upon insertion into the skin, facilitating sustained drug release over time [29]. These different types of microneedles offer various advantages in terms of drug delivery efficiency, patient comfort during application, and stability during storage and transportation. They continue to be researched and developed for various applications in transdermal drug delivery systems due to their potential to improve therapeutic outcomes while minimizing side effects.

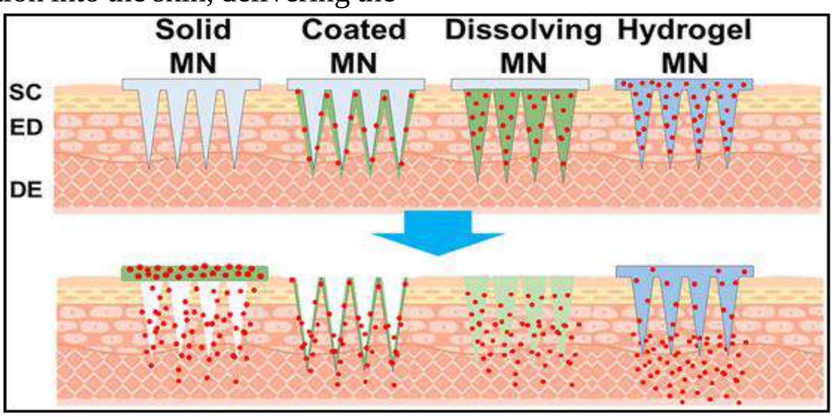

Figure 2. Types of Microneedles [30].

CONCLUSION

Transdermal drug delivery presents numerous advantages, including diminished side effects, enhanced in vivo bioavailability, increased patient convenience, and streamlined dosing schedules. Ongoing advancements in transdermal technology are continually improving the efficacy and applicability of transdermal patches, positioning them as a viable option in contemporary pharmaceutical treatment. These patches hold the promise of effectively delivering medication for various conditions; however, several challenges remain, such as the risk of self-induced toxicity from incorrect dosing, inadequate adhesion, insufficient drug penetration, potential skin irritation, and the possibility of patch malfunction. It is crucial to carefully evaluate drug characteristics and formulation elements to address the limitations encountered in the development and commercial production of these patches. The area of microneedles has advanced significantly in the last few years. This applies to a variety of applications, such as drug delivery, vaccinations, patient fluid collection (for point-of-care diagnostics), and biosignal acquisition, in addition to microneedle compositions and morphologies. The novel devices known as microneedles have a number of benefits, including precision, efficacy, and portability. It is important to remember that the manufacturing process, material choice, and microneedle design are crucial components of any device's success in its intended use.

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