Emerging Trends and Innovations in Transdermal Drug Delivery Systems

Kiran Sirvi*, Kamal S Rathore
Department of Pharmaceutics, Bhupal Nobles' College of Pharmacy, Udaipur 313001, Rajasthan, India

Abstract

Transdermal Drug Delivery Systems (TDDS) have evolved substantially over recent decades, advancing beyond conventional reservoir and matrix patches to incorporate sophisticated materials, engineering strategies, and responsive delivery technologies. Originally designed to enhance patient compliance and bypass first-pass metabolism, modern TDDS are now engineered to overcome the formidable barrier properties of the stratum corneum while achieving controlled and sustained drug release. Innovations in nanotechnology and material science have enabled the development of nanoparticle-based carriers, including polymeric nanoparticles, lipid-based nanocarriers, and deformable vesicular systems such as liposomes, ethosomes, and transfersomes. These carriers improve drug solubility, stability, and permeation, thereby broadening the applicability of transdermal therapy to poorly soluble drugs and certain macromolecules. Microneedle technologies represent another major breakthrough, offering minimally invasive and painless disruption of the skin barrier to facilitate the delivery of small molecules, proteins, and vaccines. Dissolvable, coated, and biodegradable microneedles provide accurate dosing with enhanced bioavailability and reduced systemic adverse effects. Additionally, physical enhancement approaches such as iontophoresis, sonophoresis, electroporation, and thermal ablation transiently increase skin permeability to further improve drug transport.

Emerging smart transdermal systems integrating biosensors and stimuli-responsive polymers enable on-demand and personalized drug release, marking a shift toward patient-centric and digitally integrated therapies. Despite these advances, challenges related to scalability, regulatory compliance, safety, and cost remain significant. Continued interdisciplinary research and translational development are crucial to fully harness the clinical and commercial potential of next-generation TDDS.

Keywords: TDDS, Patch, skin, transferosome, microneedle.

Introduction

Transdermal drug delivery systems (TDDS) have emerged as a prominent method for non-invasive medication administration via the skin, compared to traditional needle-based injection techniques.[1] The medication Scopolamine was used to treat motion sickness in the first transdermal drug delivery system, Transderm – Scop, which was created in 1980.[2] Transdermal drug delivery has drawn a lot of attention over the past 20 years due to its many benefits over traditional drug delivery methods, such as its ease of use, pre-established dosages, handling convenience, patient self-administration, and rather loose storage conditions. However, the oral route of drug delivery has a number of disadvantages when it comes to therapeutic compounds with limited solubility, permeability, and degradation.[3,4,5] Because most medications taken orally go through first-pass metabolism and face numerous biological and physical obstacles, their oral bioavailability varies widely.[3,6] When administering medications with a limited therapeutic index and low bioavailability, parenteral drug delivery is the most efficient method, especially when patient compliance cannot be assured (e.g., unconscious patients).[7]However, manufacturing and

administering parenteral formulations require specific equipment, sterilization techniques, and skilled personnel.[7,8]Furthermore, the desire for an inexpensive, non-invasive method of vaccination, especially in developing nations, has driven extensive study into the development of simple needle-free alternative systems, such as transdermal drug delivery. TDD is a safe and well-tolerated drug delivery approach with the potential to combine the dosing accuracy and ease of administration associated with oral dosage forms with the metabolism-free delivery of the therapeutic agent to the plasma associated with parenteral drug delivery. However, because of the low skin permeability for some drugs, their application is limited in contemporary clinical practice. The need to overcome the skin as a physiological barrier has given rise to several techniques to enhance the transdermal permeability of drugs.[9] This review aims to summarize recent trends and innovations in TDDS and discuss the advantages and limitations of the various approaches currently being investigated for improving drug permeability across the skin.

Skin Anatomy and Permeation Pathways

The skin is a multilayered and largest organ of the body in surface area and weight. The skin covers about 2 square feet of an average adult body and receives one third of total available blood.[10] Its major functions are; protection of internal organs from the external influences, temperature regulations, control of water output and sensation.[11] The skin is divided into three tissues: Epidermis, Dermis And Hypodermis.

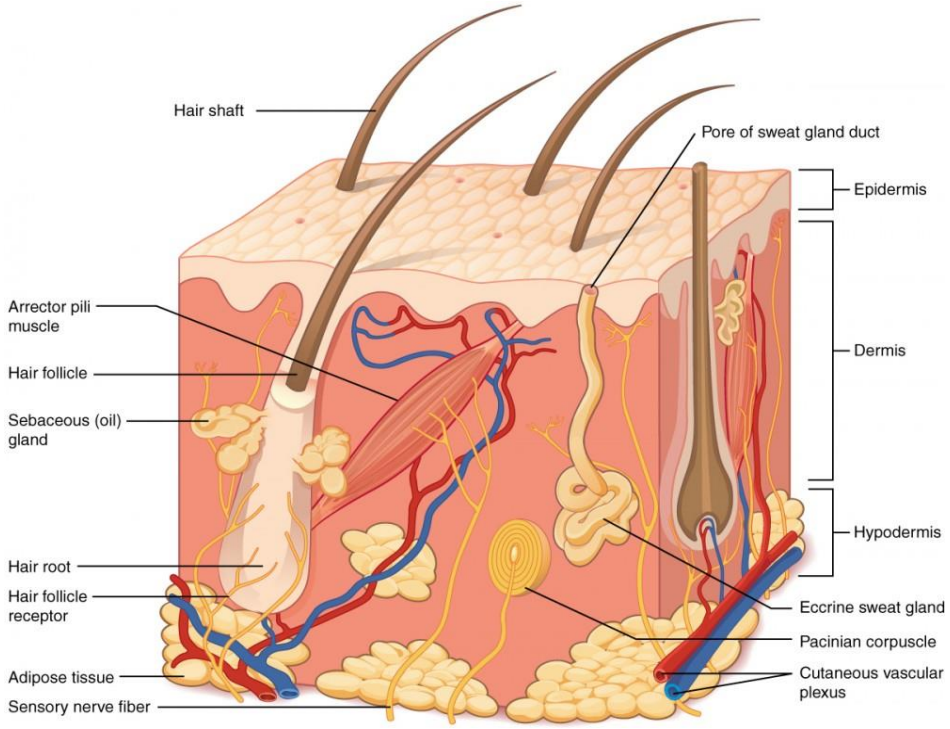

Figure 01: Anatomy of Skin

Epidermis: Epidermis is the primary external coating, which is lined by stratified keratinized squamous epithelium tissue. The width of epidermis sheet is differing throughout body, as it might be thick on the palms of the hand and soles of the foot. The blood vessels or nerve endings fibers are not present in the epidermis. The most superficial layer is stratum corneum (a thick horny coating). Stratum spinosum, stratum lucidum, and stratum germinativum is the deepest layer of epidermis. The structure of cells at the surface of skin is flat, thin and non-nucleated. The dead cells or squames are cells containing fibrous protein keratin. Other appendages of skin are hairs, sebaceous glands and ducts of sweat glands. These ducts pass the sweat or other materials through the epidermis layer on the surface of skin. Other is dermal

layer, it contains dermal papillae and form superficial layer. This layer of skin prepares the passage and allow exchange of nutrients and wastes.[12]

Dermis: The dermis provides ability to stretch and bear stress of pressure from environment. The dermis is composed of connective tissue in addition to the collagen fibers. The elastic fibers could split, while the covering is overstretched throughout work out, and owing to the stretching marks may appear on skin, for instance in case of pregnancy and obesity. [13] The dermis layer has following appendages:

- Blood and lymph vesicular system
- Sensory nerve ending fibers
- Sweat glands ducts
- Hairs etc.

Hypodermis: The hypodermis or subcutaneous fat tissue supports the dermis and epidermis.[14] Sedate is required for transdermal drug delivery. penetrate all three of these layers and enter the underlying flow, but if topical medicine delivery occurs, just entering via the stratum corneum is essential, and then keeping the medication in the skin layers is desired.[15]

Drugs permeate across the skin through three principal pathways: transcellular, intercellular (lipid), and appendageal routes.

Transcellular route: The transcellular route involves the direct passage of drug molecules through the corneocytes of the stratum corneum. In this pathway, the permeant partitions sequentially into the keratin-rich intracellular domains and the surrounding lipid bilayers. Because the drug must traverse alternating hydrophilic and lipophilic environments, this pathway generally favors small molecules with balanced solubility characteristics. [16,17]

Intercellular (lipid) route: The intercellular (lipid) route is considered the predominant pathway for passive percutaneous absorption. Here, drug molecules diffuse between corneocytes through the continuous extracellular lipid matrix composed primarily of ceramides, cholesterol, and free fatty acids. Lipophilic drugs preferentially partition into this lipid domain, making it the major determinant of transdermal flux for most small-molecule therapeutics. [18,19]

Appendageal route: The appendageal route involves transport through skin appendages such as hair follicles, sweat glands, and sebaceous glands. Although these appendages represent a small fraction of the total skin surface area, they can act as shunt pathways, particularly for hydrophilic molecules, macromolecules, ions, and nanoparticulate systems. This pathway is especially relevant during the early stages of permeation and in follicular-targeted delivery approaches. [20]

Challenges in Transdermal Delivery

- The limitations of transdermal drug delivery are mainly associated with barrier function of skin, so it is limited to potent drug molecules.
- Chances to allergic reaction.
- High molecular drug level cannot attain therapeutic level.
- It is delivered to ionic drug.
- It requires significant lag time
- Transdermal drug delivery system cannot deliver ionic drugs

- It cannot achieve high drug levels in blood.
- It cannot develop for drugs of large molecular size
- It cannot deliver drugs in a pulsatile fashion.
- It cannot develop if drug or formulation causes irritation to skin. [21,11]

Approaches for enhancing drug transport across the skin

The stratum corneum**,** the outermost layer of the skin, acts as the primary barrier to drug permeation, limiting the effectiveness of transdermal drug delivery systems (TDDS). To overcome this barrier, various enhancement strategies have been developed. These approaches can be broadly classified into passive and active techniques.[23]

1. Passive Enhancement Techniques

Passive methods improve drug permeation without external energy by modifying the formulation or skin barrier properties.

1.1 Chemical penetration enhancers

Chemical penetration enhancers (CPEs) are widely used in transdermal drug delivery systems to improve drug permeation across the stratum corneum by temporarily altering its barrier properties. They act through mechanisms such as disruption of intercellular lipid structure, interaction with keratin, and enhancement of drug partitioning into the skin. Common CPEs include fatty acids (oleic acid), alcohols (ethanol), surfactants, and terpenes (menthol), which increase skin permeability without causing permanent damage. Despite their effectiveness, issues such as skin irritation and toxicity limit their use, necessitating careful selection and optimization in formulations.[17]

1.2 Vesicular Drug Delivery Systems

Vesicular drug delivery systems are advanced carrier-based approaches widely employed to enhance drug permeation across the skin in transdermal drug delivery systems. These systems consist of lipid-based vesicles that encapsulate drugs, improving their stability, bioavailability, and controlled release.[25] Common vesicular carriers include liposomes, niosomes, transfersomes, and ethosomes, each differing in composition and flexibility. Liposomes are phospholipid vesicles that can fuse with skin lipids, facilitating drug deposition in deeper layers, while niosomes, composed of non-ionic surfactants, offer greater stability and cost-effectiveness. Transfersomes are ultra-deformable vesicles capable of penetrating through narrow intercellular spaces, and ethosomes contain high concentrations of ethanol, which enhances lipid fluidization and improves skin permeation. [26,27]

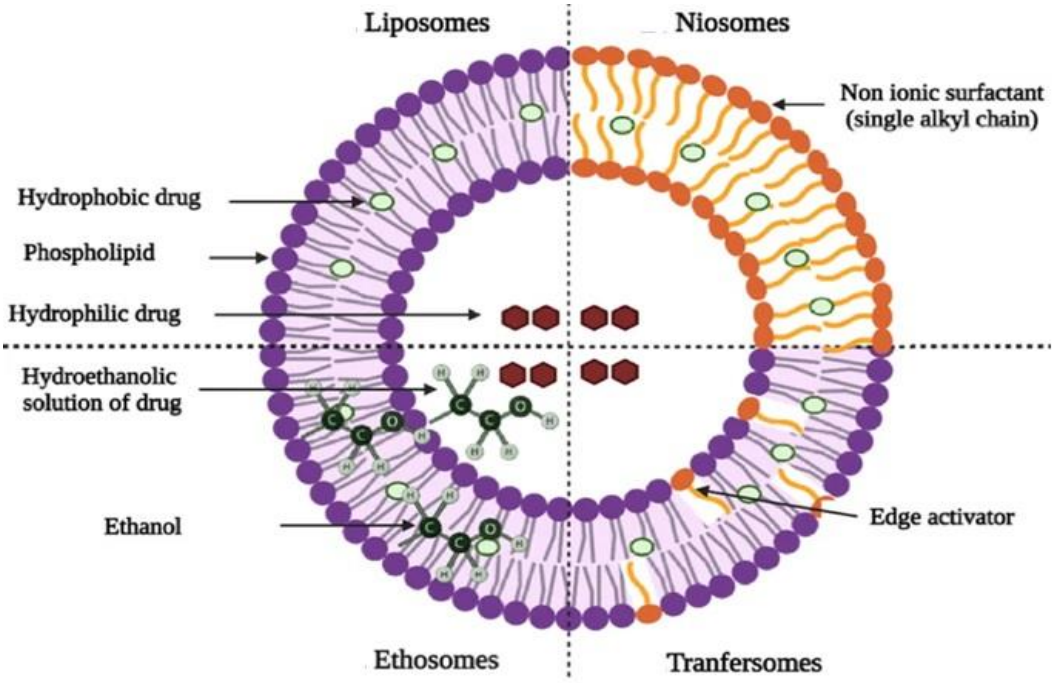

Figure 02: Vesicular Drug Delivery Systems

The primary mechanism of vesicular systems involves interaction and fusion with the stratum corneum lipids, leading to enhanced drug partitioning and diffusion. Additionally, these carriers can act as drug reservoirs, providing sustained and controlled drug release. Vesicular systems are particularly advantageous for delivering both hydrophilic and lipophilic drugs and have shown significant potential in improving the transdermal delivery of anti-inflammatory, analgesic, and antihypertensive agents. However, limitations such as vesicle instability, high production cost, and scalability challenges must be addressed for widespread application. Overall, vesicular drug delivery systems represent a promising and versatile strategy for overcoming the barrier properties of the skin. [28,29]

1.3 Nanocarrier systems

Nanocarrier systems have emerged as a promising strategy to enhance drug transport across the skin in transdermal drug delivery systems (TDDS). These systems include polymeric nanoparticles, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, and dendrimers, which are designed to improve drug solubility, stability, and controlled release. Due to their nanoscale size, these carriers can closely interact with the stratum corneum, enhancing drug penetration by increasing surface contact and facilitating diffusion through intercellular lipid pathways. Lipid-based nanocarriers such as SLNs and NLCs also form an occlusive film on the skin surface, increasing hydration and thereby improving permeability. Additionally, nanocarriers can act as reservoirs, enabling sustained drug release and reducing dosing frequency. [30,31] They are particularly effective for delivering poorly soluble drugs and bioactive molecules with limited skin permeability. Despite their advantages, challenges such as formulation complexity, potential toxicity, and large-scale manufacturing issues remain. Nevertheless, nanocarrier systems represent a versatile and efficient approach for improving transdermal drug delivery and are an active area of pharmaceutical research. [32,33]

2. Active Enhancement Techniques

Active methods use external energy to enhance drug transport.

2.1 Iontophoresis

Iontophoresis is a technique used in transdermal drug delivery to improve the movement of drugs across the skin using a small electric current.[34] It is especially useful for drugs that do not easily pass through the skin on their own. In this method, a low electrical current is applied, which helps push charged drug molecules through the skin. Positively charged drugs are delivered from the positive electrode, while negatively charged drugs are delivered from the negative electrode. Another mechanism, called electroosmosis, helps move neutral molecules along with the flow of water in the skin. Iontophoresis allows better control over the amount of drug delivered by adjusting the current and time of application. [35,36]

It is commonly used for delivering pain relievers, anti-inflammatory drugs, and local anaesthetics. The method also avoids first-pass metabolism and reduces side effects. However, it may cause mild skin irritation, redness, or discomfort, and requires special equipment. Overall, iontophoresis is a safe and effective method to enhance drug delivery through the skin when used properly.[37]

2.2 Sonophoresis

Sonophoresis, also known as ultrasound-enhanced transdermal drug delivery, is an effective physical method used to increase drug permeation across the skin. It involves the application of ultrasound waves, typically in the low-frequency range (20–100 kHz), to temporarily disrupt the structure of the stratum corneum.[38] The primary mechanism of sonophoresis is acoustic cavitation, where the formation and oscillation of microbubbles within the skin lead to disruption of lipid bilayers, thereby enhancing skin permeability. This process creates microscopic channels that facilitate the transport of both hydrophilic and lipophilic drugs. [39,40] Additionally, thermal effects generated by ultrasound can increase skin temperature, improving drug diffusion and blood flow in the treated area.[39] Sonophoresis has been successfully used to enhance the delivery of various therapeutic agents, including analgesics, anti-inflammatory drugs, and macromolecules such as proteins and peptides. It offers advantages such as non-invasive application, improved drug penetration, and controlled delivery. Furthermore, it can be combined with other enhancement techniques like chemical penetration enhancers or nanocarriers for synergistic effects. [41,42]

2.3 Electroporation

Electroporation is an advanced physical technique used in transdermal drug delivery to enhance the permeation of drugs across the skin by applying short, high-voltage electrical pulses. These electrical pulses create temporary pores or aqueous channels in the lipid bilayers of the stratum corneum, thereby reducing its barrier resistance and allowing drugs to pass through more easily.[43] The process is rapid and reversible, as the skin typically regains its normal structure after the removal of the electrical stimulus. Electroporation is particularly useful for delivering large and hydrophilic molecules, such as peptides, proteins, and nucleic acids, which cannot penetrate the skin through passive diffusion. The mechanism of electroporation involves the reorganization of lipid molecules under the influence of an electric field, resulting in increased membrane permeability. This technique can significantly enhance drug flux and improve bioavailability. Additionally, electroporation can be combined with other methods such as iontophoresis or chemical enhancers to further increase drug delivery efficiency. [44,45] Despite its advantages, electroporation has some limitations, including possible skin irritation, discomfort due to

electrical pulses, and the requirement for specialized equipment. Careful optimization of voltage, pulse duration, and frequency is essential to ensure safety and effectiveness. Overall, electroporation is a promising and powerful approach for transdermal delivery of a wide range of therapeutic agents. [46,47]

2.3 Microneedles

Microneedles are a minimally invasive and highly effective approach used to enhance transdermal drug delivery by creating microscopic channels in the skin. These micron-sized needles penetrate the stratum corneum without reaching deeper nerve endings, making the process virtually painless and well-tolerated.[48] Microneedles are classified into different types, including solid, coated, hollow, dissolving, and hydrogel-forming microneedles, each designed for specific drug delivery purposes.[49] Solid microneedles are used to create microchannels followed by drug application, while coated and dissolving microneedles deliver the drug directly into the skin. Hollow microneedles allow liquid formulations to be injected, and hydrogel-forming microneedles enable controlled and sustained drug release.

The primary mechanism of microneedles involves bypassing the barrier function of the stratum corneum, thereby enhancing drug permeation for a wide range of molecules, including small drugs, peptides, proteins, and vaccines. This technique improves bioavailability, provides controlled drug release, and reduces first-pass metabolism. Microneedles have been widely explored for applications such as vaccination, insulin delivery, and pain management. Despite their advantages, challenges such as manufacturing complexity, cost, and ensuring mechanical strength and sterility remain. Overall, microneedles represent a promising and patient-friendly strategy for transdermal drug delivery with significant potential in modern therapeutics.[50]

Conclusion

Transdermal drug delivery systems (TDDS) have improved greatly in recent years with the help of new technologies and innovative approaches. Modern systems such as nanocarriers, microneedles, iontophoresis, and ultrasound-based methods have made it easier for drugs to pass through the skin and work more effectively. These advancements allow not only small drug molecules but also larger molecules like proteins and vaccines to be delivered through the skin. In addition, the use of smart and wearable devices helps in controlling drug release and improves patient comfort and convenience.

However, some challenges still exist, such as skin irritation, high cost, and difficulty in large-scale production. Researchers are continuously working to overcome these issues and make these systems safer and more affordable. Overall, TDDS offers a promising, painless, and patient-friendly alternative to traditional drug delivery methods, and its future looks very bright in modern healthcare.

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