Journal of Biomedical and Pharmaceutical Research
Available Online at www.jbpr.in
CODEN: - JBPRAU (Source: - American Chemical Society)
NLM (National Library of Medicine): ID: (101671502)
Index Copernicus Value 2023: 85.86
Volume 14, Issue 5; 2025, 129-137

ISSN (Online): 2279-0594
ISSN (Print): 2589-8752

Review Article

A Comprehensive Review on Transdermal Drug Delivery System

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Article Info: Received: 14-09-2025 / Revised: 22-10-2025 / Accepted: 26-11-2025
Corresponding Author: Ajay Siwach
DOI: https://doi.org/10.32553/jbpr.v14i5.1360
Conflict of interest statement: No conflict of interest

Abstract:

Transdermal Drug Delivery Systems (TDDS) provide a non-invasive and patient-friendly method for delivering drugs directly into systemic circulation through the skin. They offer significant advantages over oral administration by bypassing first-pass metabolism, reducing gastrointestinal irritation, and improving adherence through sustained and controlled drug release. Successful transdermal delivery depends on the skin's structure, the physicochemical properties of the drug, and physiological factors such as skin hydration, temperature, and integrity. Drug permeation occurs through transepidermal (transcellular and intercellular) and transappendageal routes, but is mainly limited by the barrier function of the stratum corneum. To overcome this resistance, various chemical, biological, physical, and natural permeation enhancers are incorporated. TDDS are widely applied in pain management, hormone therapy, cardiovascular treatment, smoking cessation, and neurological disorders, and they continue to expand into areas like vaccination and dermatological care. Advances in microneedles, iontophoresis, and nanoformulations further enhance their therapeutic potential.

Keywords: Transdermal drug delivery, Skin permeation, Stratum corneum barrier, Permeation enhancers, Microneedles, Controlled release systems, physicochemical properties, Transappendageal pathway, Nanoformulation technology.

Introduction

Oral drug delivery is the most common route of administration; however, drawbacks such as hepatic first-pass metabolism, enzymatic degradation, gastrointestinal irritation, and poor patient compliance in chronic therapies necessitate alternative approaches. Transdermal Drug Delivery Systems (TDDS) offer an attractive non-invasive route that bypasses the gastrointestinal tract and delivers drugs directly into systemic circulation [1]. TDDS provide controlled, sustained drug release, reduce dosing frequency, minimize side effects, and improve therapeutic efficiency. The concept dates back to the early 1970s, with the first FDA-approved transdermal patch (scopolamine) introduced in 1979 [2]. The global TDDS market has expanded significantly, driven by increasing demand for painless drug delivery, ease of use, and advancements in materials and nanotechnology. Today, TDDS are used for cardiovascular diseases, hormone therapy, pain management, smoking cessation, and neurological disorders. Despite their benefits, formulation scientists face challenges such as the skin's strong barrier function, drug physicochemical limitations, and inter-subject variability. Innovations like microneedles, iontophoresis, electroporation, nanoemulsions, and lipid nanoparticles have opened new avenues for enhancing transdermal permeation [3]. This review provides a comprehensive overview of transdermal drug delivery, outlining principles, technologies, formulation strategies, evaluation, applications, and emerging trends.

Skin Anatomy and Physiology Relevant to TDDS

The skin is a multilayered organ acting as a protective barrier. It comprises three main layers:

Stratum Corneum (SC): The SC is the outermost layer of the epidermis and the primary barrier to drug permeation. It consists of dead keratinocytes embedded in a lipid matrix ("brick and mortar" model). Its thickness ranges from 10–20 µm and restricts the passage of hydrophilic and large molecules [4].

Epidermis: Avascular layer beneath the SC; contains viable cells and enzymes responsible for metabolic activity.

Dermis: Contains blood vessels, lymphatics, and nerve endings. Once a drug reaches this layer, systemic absorption begins.

Hypodermis: Composed mainly of adipose tissue; supports deeper drug distribution.

Appendages: Hair follicles and sweat glands act as shunt pathways but contribute minimally (<0.1%) to total absorption [5].

Factors Affecting Transdermal Drug Delivery System

Molecular Weight of the Drug

The molecular weight of a drug is one of the most critical determinants of its ability to permeate the skin. Generally, drugs with a molecular weight below 500 Daltons are ideal candidates for transdermal delivery because they can more easily diffuse through the tightly packed lipid layers of the stratum corneum. Larger molecules encounter significant resistance, resulting in poor penetration and inadequate therapeutic levels unless assisted by enhancement technologies such as microneedles, iontophoresis, or chemical penetration enhancers.

Lipophilicity (Partition Coefficient)

Lipophilicity, usually expressed as the partition coefficient (log P), influences how effectively a drug can traverse the skin's hydrophobic and hydrophilic domains. An optimal log P between 1 and 3 allows the drug to partition into both the lipid-rich stratum corneum and the aqueous layers beneath it. A drug that is too lipophilic may remain trapped in the stratum corneum, while a highly hydrophilic drug cannot penetrate adequately, making balanced lipophilicity essential for successful transdermal transport [6].

Drug Solubility

Drug solubility in both water and lipids is vital because it directly affects the dissolution of the drug at the skin surface and its subsequent diffusion through the epidermal layers. Poorly soluble drugs often exhibit limited transdermal flux, necessitating the use of solubility-enhancing strategies such as cosolvents, surfactants, nanoemulsions, or lipid-based carriers to improve their permeation characteristics and bioavailability.

Drug Dose Requirement

Drugs suitable for transdermal delivery must have a relatively low daily dose requirement, typically below 10 mg per day. Transdermal patches rely on passive diffusion, and drugs requiring higher doses cannot achieve therapeutic levels through the limited surface area available on the skin. Therefore, only potent drugs with small dose requirements are feasible for transdermal systems without additional enhancement techniques.

Degree of Ionization (pKa and pH)

The degree of ionization of a drug greatly influences its ability to permeate the skin. Only the unionized form of a drug can efficiently dissolve within and diffuse through the lipophilic layers of the stratum corneum. Therefore, the pKa of the drug and the pH of the formulation must be carefully adjusted to ensure a higher proportion of the drug remains in its unionized state when applied to the skin, enhancing permeation and therapeutic efficacy [7,8].

Skin Thickness at Application Site

Skin thickness varies significantly across different anatomical regions of the body and directly impacts drug penetration. Sites such as the scrotum, behind the ear, and inner forearm have relatively thin stratum corneum layers and therefore allow higher drug permeation. Conversely, thicker regions like the palms and soles provide substantial resistance, resulting in minimal absorption. Thus, site selection is a key factor for optimal transdermal delivery.

Skin Hydration Level

Hydration of the stratum corneum increases its permeability by causing swelling of corneocytes and loosening the lipid bilayers, thereby creating more favorable pathways for drug diffusion. Occlusive dressings or backing layers in patches are often used to enhance skin hydration and thereby increase transdermal flux. Excess hydration, however, can lead to irritation or maceration, affecting tolerability [9].

Skin Condition or Integrity

The condition of the skin plays a fundamental role in transdermal absorption. Intact and healthy skin provides the strongest barrier function, while damaged or diseased skin—such as in dermatitis, eczema, psoriasis, wounds, or abrasions—can dramatically increase permeability. Although enhanced permeation may seem advantageous, it can lead to unpredictable absorption and potential systemic toxicity, making application site selection crucial.

Skin Age

Age-related changes in the skin influence transdermal absorption. Infants have thinner skin and higher hydration, resulting in significantly enhanced drug permeability, which can pose toxicity risks. Conversely, elderly individuals often exhibit reduced skin hydration, decreased lipid content, and slower regeneration rates, leading to reduced absorption. Age considerations are therefore essential when designing or prescribing transdermal patches [10].

Skin Temperature

An increase in skin temperature enhances drug permeation by increasing molecular mobility, lipid fluidity, and dermal blood flow. External heat sources, fever, exercise, or hot environments can accelerate drug absorption from transdermal systems, potentially altering therapeutic outcomes. For this reason, patients are often advised to avoid exposing patches to heat to prevent dose dumping.

Dermal Blood Flow

Dermal blood flow affects the rate at which a drug is removed from the application site and transported into systemic circulation. Enhanced blood flow promotes faster absorption by maintaining a strong concentration gradient across the skin. Physical activity, temperature changes, or vasodilators can increase blood flow, whereas conditions reducing circulation may slow transdermal uptake.

Site of Application

Different parts of the body vary in permeability due to differences in skin thickness, hydration, and lipid composition. Drug permeation is highest at highly permeable sites such as the scrotum, behind the ear, and upper arm, while it is lowest at the palms and soles. The choice of application site therefore influences both the rate and extent of drug absorption from transdermal systems.

Use of Chemical Penetration Enhancers

Chemical enhancers play a major role in improving drug permeation by altering the structure of the stratum corneum. They may work by disrupting lipid packing, extracting lipids, modifying protein conformation, or improving drug solubility within the skin. Common enhancers include ethanol, oleic acid, azone, terpenes, and surfactants. These agents must be selected carefully to balance efficacy with safety and avoid irritation [11,12].

Mechanism of Drug Penetration Pathways

The therapeutic effectiveness of a transdermal drug delivery system depends largely on the ability of the drug to permeate through the skin. For any active molecule applied on the skin surface to exert a systemic effect, it must successfully traverse the various skin layers and ultimately reach the systemic circulation. Drug molecules can penetrate the skin through multiple distinct pathways. These routes are broadly classified into transepidermal pathways, which include the intracellular (transcellular) and intercellular routes, and transappendageal or shunt pathways, which involve transport through skin appendages such as hair follicles and sweat glands [13].

Transepidermal Routes

Intracellular / Transcellular Route: In the transcellular or intracellular pathway, drug molecules pass directly through the corneocytes, the principal cells of the stratum corneum. These corneocytes contain hydrated keratin, creating a semi-aqueous environment that facilitates the passage of hydrophilic molecules. However, each corneocyte is surrounded by a lipid envelope, and multiple lipid bilayers separate adjacent corneocytes. Because of this alternating aqueous–lipid architecture, molecules traveling via the transcellular route must repeatedly partition between hydrophilic and lipophilic phases, making this route energetically demanding. After diffusing through the hydrated corneocytes, the drug must continue into the surrounding lipid domains before reaching deeper epidermal layers. Although the physicochemical properties of drugs and penetration enhancers influence the efficiency of this pathway, the transcellular route is particularly relevant for highly hydrophilic drugs under steady-state permeation conditions [14].

Intercellular Route

In the intercellular or paracellular pathway, drug molecules diffuse through the continuous lipid matrix that occupies the spaces between corneocytes. Unlike the more direct transcellular path, the intercellular route is highly tortuous due to the interlocking, "brick-and-mortar" arrangement of corneocytes. This winding pathway forces the drug to travel a much longer distance—estimated to be nearly 50 times the thickness of the stratum corneum—before reaching the viable epidermis. Additionally, the lipid layers in this region are arranged in complex, non-uniform bilayers, requiring the drug to undergo repeated partitioning and diffusion through alternating aqueous and lipid environments. Despite these challenges, the intercellular pathway is considered the predominant route for small, uncharged, and moderately lipophilic molecules to traverse the stratum corneum effectively.

Transappendageal (Shunt) Routes

The transappendageal or shunt pathway involves drug permeation through skin appendages such as hair follicles, sebaceous glands, and sweat ducts. This route offers an alternate means of bypassing the densely packed stratum corneum and allows drugs to enter more permeable regions of the skin. However, appendages collectively occupy only about 0.1% of the total skin surface area, which limits the overall contribution of this pathway to drug absorption. Sweat ducts may either be empty or filled with aqueous sweat, which can dilute or impede drug movement, particularly for lipophilic molecules. Similarly, the sebum produced by sebaceous glands can hinder the penetration of hydrophilic drugs due to its lipid-rich composition. Although the appendageal pathway may dominate drug absorption during the initial period following application, steady-state permeation is typically governed by the transepidermal routes. Nevertheless, this pathway can be particularly useful for delivering large, polar molecules, ions, and nanoparticulate systems, where diffusion through the stratum corneum is otherwise limited [15,16].

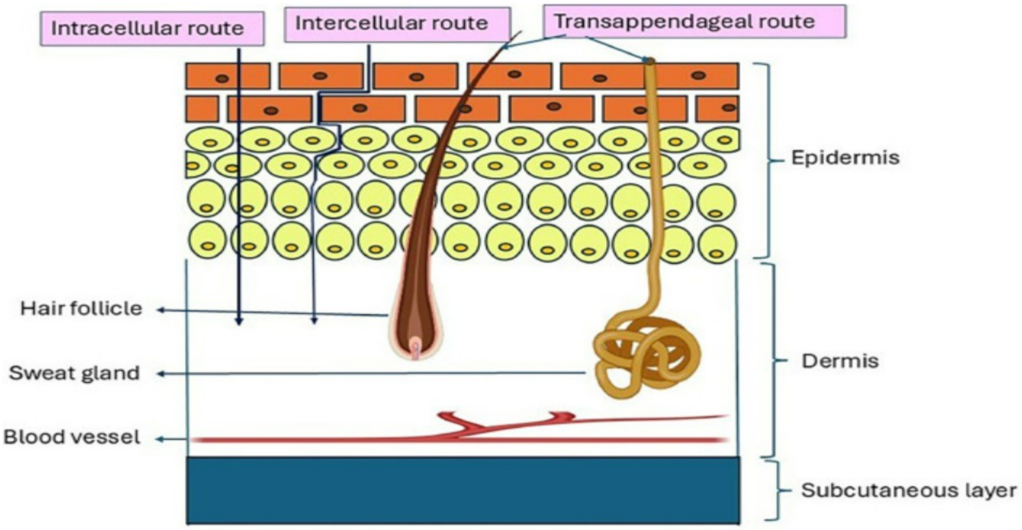

Figure 1: Route of Drug Permeation through Transdermal Drug Delivery System

Permeation Enhancers: Classification and Mechanisms

Permeation enhancers are specialized agents incorporated into transdermal drug delivery systems to temporarily and reversibly increase the permeability of the stratum corneum. They function by altering the tightly packed lipid architecture, modifying keratin structure, improving drug solubility, or enhancing the drug's partitioning into the skin. Depending on their origin, chemical composition, and mechanism of action, permeation enhancers can be classified into chemical, biological, physical, and natural categories, each offering unique advantages for improving transdermal flux [17].

Chemical permeation enhancers

It represents the most commonly used category due to their ability to integrate easily into formulations and reliably improve drug transport. They work primarily by disrupting lipid packing, increasing skin hydration, or enhancing drug solubility. Because they are versatile and compatible with a wide range of drugs, chemical enhancers remain integral to the development of effective transdermal systems.

Alcohols and polyols are frequently used chemical enhancers known for their ability to increase the solubility and thermodynamic activity of drugs. Compounds such as ethanol, isopropyl alcohol, propylene glycol, and glycerol fluidize the stratum corneum lipid layers and act as cosolvents, thereby creating a more permeable environment. These agents can also extract lipids from the skin, further facilitating diffusional transport.

Fatty acids and fatty alcohols enhance transdermal permeation by disrupting the orderly arrangement of the stratum corneum lipids. Agents like oleic acid, linoleic acid, lauric acid, and stearyl alcohol create microcavities within the lipid bilayers, increasing the diffusion pathways available to drug molecules. Fatty acids are particularly effective for lipophilic drugs and are commonly incorporated into modern transdermal patches [18,19].

Surfactants act as permeation enhancers by interacting with both lipids and proteins in the skin to increase its permeability. Examples such as sodium lauryl sulfate, polysorbates, and cetyltrimethylammonium bromide disrupt lipid organization, promote hydration, and induce changes in protein conformation. These effects collectively loosen the barrier structure, enabling easier drug passage.

Terpenes and essential oils are naturally occurring compounds widely recognized for their potent yet relatively safe permeation-enhancing properties. Substances like menthol, limonene, cineole, and thymol disrupt lipid packing and improve drug partitioning into the stratum corneum. Their low irritation potential makes them especially suitable for formulations intended for repeated application [20].

Amines and amides, such as azone, urea, and pyrrolidones, are powerful synthetic enhancers that significantly increase skin permeability. These agents insert themselves into lipid lamellae and increase their fluidity, creating more accessible diffusion channels for drug molecules. Their strong lipid-disrupting action makes them effective for challenging drugs that show poor permeation.

Sulfoxides and other solvents function as highly potent permeation enhancers capable of transporting both hydrophilic and lipophilic drugs. Compounds like dimethyl sulfoxide (DMSO) and dimethylformamide (DMF) exhibit strong solvent properties, allowing them to extract lipids, denature proteins, and open permeation pathways. They are used carefully due to their powerful biological effects.

Biological and biochemical enhancers

These exert their permeation-enhancing effects through interactions with skin components at a molecular level. These enhancers typically modify or partially degrade specific constituents of the stratum corneum, such as proteins or lipids, thereby reducing its barrier resistance. Their targeted and often reversible actions make them suitable for enhancing the permeation of macromolecules.

Enzymes represent an important subgroup of biological enhancers capable of weakening the structural components of the stratum corneum. Proteases, lipases, and hyaluronidases degrade proteins or lipids within the skin, making the barrier more permeable.

This controlled disruption can facilitate increased drug diffusion while minimizing irritation when used appropriately [21].

Peptides and short-chain amino acids facilitate transdermal transport by interacting with lipid domains or forming temporary pores that allow drug movement. Cell-penetrating peptides (CPPs) and arginine-rich peptides improve the transport of hydrophilic drugs and macromolecules, which otherwise have limited permeation through intact skin. Their specificity and efficiency have made them promising tools in advanced transdermal systems.

Physical permeation enhancers

They utilize mechanical or energy-based techniques to alter the barrier properties of the skin. These methods create microchannels, apply external forces, or disrupt lipid structures, thereby allowing drugs that would not normally permeate the skin to enter more efficiently. Physical enhancers are especially valuable for large, ionic, or hydrophilic molecules. [18,19]

Microneedles offer a minimally invasive way to enhance drug penetration by forming microscopic, reversible channels in the skin. These channels bypass the stratum corneum, allowing direct access to the viable epidermis and dermis. This method enables efficient delivery of peptides, vaccines, and other molecules that cannot passively permeate.

Iontophoresis enhances drug permeation by applying a low-level electric current across the skin. This current facilitates the movement of charged drug molecules through electromigration and electroosmosis. Iontophoresis is particularly effective for ionic drugs and allows precise control over the rate of drug delivery.

Sonophoresis, or ultrasound-enhanced delivery, increases drug permeation by disrupting lipid structures through cavitation and mild thermal effects.

The oscillation of ultrasound waves temporarily modifies the skin barrier, making it more permeable to various drugs. This method is advantageous for both small molecules and larger macromolecules.

Electroporation works by applying short, high-voltage pulses that form transient aqueous pores in the stratum corneum. These microchannels significantly increase permeability and allow rapid entry of drugs into deeper skin layers. Electroporation is effective for delivering hydrophilic molecules and genetic materials [22].

Natural permeation enhancers

These are gaining attention due to their favorable safety profile, low irritation potential, and biocompatibility. These enhancers are typically derived from plant oils, essential oils, or herbal extracts and provide effective permeation enhancement with minimal adverse effects.

Plant oils such as olive oil, coconut oil, jojoba oil, and almond oil contain fatty acids and terpenes that can fluidize lipid structures and improve skin hydration. These changes enhance drug permeation while maintaining skin health, making plant oils popular choices for long-term or patient-friendly formulations.

Essential oils and herbal extracts offer additional advantages due to their potent yet gentle permeation-enhancing properties. Oils such as eucalyptus, peppermint, and clove oil modify lipid domains and improve drug partitioning into the skin. Their natural origin and sensory benefits also increase patient acceptability [24].

Applications of Transdermal Drug Delivery Systems (TDDS)

Management of Chronic Pain

One of the most significant applications of transdermal drug delivery systems is in the long-term management of chronic and severe pain. Patches containing analgesics such as fentanyl, buprenorphine, and lidocaine provide controlled and sustained drug release over several hours or days. This steady delivery minimizes fluctuations in plasma concentration that are commonly seen with oral medications, thereby improving therapeutic outcomes. Transdermal systems are especially beneficial for patients with chronic pain conditions such as cancer pain or neuropathic pain, as they offer a non-invasive method with improved compliance and reduced gastrointestinal side effects [23].

Hormone Replacement Therapy

TDDS are widely used for hormone replacement therapy (HRT), particularly in menopausal women and individuals with hormonal imbalances. Estradiol, progesterone, and testosterone patches provide continuous hormone delivery while bypassing hepatic first-pass metabolism, which reduces risks associated with oral hormone administration. Transdermal patches offer a more consistent hormone profile, fewer systemic side effects, and increased patient comfort. This makes them a preferred option for long-term hormonal regulation, menstrual disorders, and menopausal symptom management [24].

Cardiovascular Disease Management

Transdermal systems play a crucial role in the treatment of cardiovascular disorders, where maintaining steady plasma concentrations is essential. Nitroglycerin patches are commonly used for the prevention of angina pectoris, providing prolonged vasodilation and reducing the frequency of angina attacks. Clonidine patches are used to manage hypertension by offering sustained antihypertensive effects and improving compliance in patients who struggle with frequent oral dosing. The ability of TDDS to bypass first-pass metabolism further enhances the therapeutic efficacy of cardiovascular drugs.

Smoking Cessation Therapy

Nicotine patches are among the earliest and most successful examples of transdermal drug delivery. These patches deliver nicotine at a controlled rate, reducing cravings and withdrawal symptoms associated with smoking cessation. The non-invasive nature, ease of use, and ability to maintain stable nicotine levels make TDDS a widely accepted method in smoking cessation programs. Nicotine patches have significantly contributed to reducing tobacco dependence worldwide [25].

Neurological and Psychiatric Disorders

TDDS have demonstrated substantial benefits in the treatment of neurological and psychiatric conditions. Rivastigmine patches, used in Alzheimer's disease management, improve cognitive symptoms with fewer gastrointestinal side effects compared to oral formulations. Transdermal systems are also being explored for delivering antidepressants and antipsychotics, offering advantages such as improved adherence, reduced peak-related side effects, and greater patient convenience. These characteristics make TDDS a promising approach in long-term neurological care.

Vaccination and Macromolecule Delivery

Emerging technologies such as microneedle-based patches have expanded the application of TDDS into vaccine and macromolecule delivery. These systems enable painless administration of proteins, peptides, and vaccines, overcoming limitations associated with injectable routes. Microneedles can target immune cells within the skin, enhancing vaccine efficacy while reducing the need for trained personnel. This approach is particularly beneficial for large-scale immunization programs and developing biologic-based therapeutics.

Dermatological and Cosmeceutical Applications

Transdermal and topical delivery systems are widely used in dermatology and cosmetology for targeted skin treatment. Active compounds such as retinoids, corticosteroids, antioxidants, and depigmenting agents can be delivered directly to affected skin regions, providing localized therapeutic effects. These systems help manage conditions such as acne, psoriasis, hyperpigmentation, and skin aging. In cosmeceutical applications, TDDS enhance the penetration of skincare actives, offering improved anti-aging and skin rejuvenation effects [26].

Conclusion

Transdermal Drug Delivery Systems offer a reliable and convenient route for drug administration, providing controlled release, improved patient compliance, and avoidance of first-pass metabolism. Although the skin's barrier properties restrict drug entry, advances in permeation enhancers and modern technologies have significantly improved transdermal efficiency. Chemical enhancers, microneedles, iontophoresis, electroporation, and nano-based carriers have broadened the range of drugs suitable for transdermal application, including macromolecules and vaccines. TDDS continue to gain importance in managing chronic diseases, hormonal disorders, cardiovascular conditions, and dermatological problems. With ongoing research and innovation, transdermal systems are expected to become even more versatile, effective, and widely used in future pharmaceutical applications.

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