Review Article

Transdermal Drug Delivery Systems: Mechanistic Insights, Technological Advances And Clinical Applications

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ABSTRACT

Transdermal drug delivery systems (TDDS) provide a non-invasive approach for systemic and localized drug administration through intact skin. They can bypass hepatic first-pass metabolism and gastrointestinal degradation, while providing sustained drug release and improved patient compliance. However, the stratum corneum acts as the principal barrier to drug permeation, limiting the delivery of many therapeutic molecules. Drug transport across the skin occurs through transcellular, intercellular, and appendageal pathways and is influenced by physicochemical properties such as molecular weight, lipophilicity, ionization, and thermodynamic activity, as well as physiological factors including skin hydration, temperature, and application site. Conventional passive TDDS are primarily suitable for small, lipophilic, and potent drugs, whereas active enhancement approaches have expanded their applicability. Recent advances in chemical penetration enhancers, nanocarriers, iontophoresis, sonophoresis, electroporation, and microneedles have improved the delivery of hydrophilic drugs, peptides, proteins, and vaccines. Smart and stimulus-responsive systems further enable controlled drug release in response to physiological signals. Despite these developments, challenges related to manufacturing scalability, regulatory requirements, variability in skin permeability, and long-term safety remain. This review discusses the anatomy and physiology of the skin, drug permeation mechanisms, TDDS design principles, passive and active delivery approaches, formulation factors, evaluation methods, therapeutic applications, and emerging technologies, highlighting current advances and future directions in transdermal drug delivery.

Key words: Transdermal drug delivery systems, Skin permeation, Microneedles, Nanocarriers, Active and passive delivery, Smart transdermal systems.

Transdermal drug delivery systems (TDDS) provide a non-invasive approach for systemic drug administration through intact skin. Compared with oral and injectable routes, TDDS can bypass hepatic first-pass metabolism, provide controlled and sustained drug release, and improve patient compliance [1,2]. The approval of Transderm-Scōp by the U.S. Food and Drug Administration in 1979 marked the beginning of modern transdermal therapy, followed by the development of patches for drugs such as scopolamine, nicotine, nitroglycerin, fentanyl, clonidine, testosterone, and estrogen [2,3]. The effectiveness of TDDS is primarily limited by the stratum corneum, which acts as the major barrier to drug permeation, particularly for hydrophilic and high-molecular-weight molecules [1,2]. Drug transport occurs through transcellular, intercellular, or appendageal pathways and is influenced by physicochemical properties such as molecular weight, lipophilicity, solubility, and ionization [1]. Consequently, conventional passive TDDS are mainly suitable for small, potent molecules with favourable permeability characteristics. To overcome this barrier, various enhancement approaches, including chemical penetration enhancers, iontophoresis, sonophoresis, nanocarriers, and microneedles, have been developed [4,5]. Among these, microneedle-based systems can create temporary microchannels in the stratum corneum, facilitating the delivery of poorly permeable drugs, peptides, proteins, and vaccines. Solid, hollow, coated, dissolving, and hydrogel-forming microneedles have consequently gained considerable attention in transdermal drug delivery [4,5].

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Despite technological advances, challenges including manufacturing scalability, regulatory requirements, variability in skin permeability, cost, and long-term safety continue to influence clinical translation [4]. Therefore, advances in TDDS, particularly the integration of microneedle and nanotechnology-based strategies, are directed toward improving drug permeation, controlled delivery, patient acceptability, and therapeutic performance [2–5].

2. SKIN ANATOMY AND PHYSIOLOGY

The skin is the largest organ of the human body and serves as a protective barrier against mechanical, chemical, microbial, and environmental insults. It also contributes to thermoregulation, fluid balance, sensory perception, and vitamin D synthesis. Its large surface area and accessibility make it an attractive route for drug administration [2,6,7]. Structurally, the skin consists of the epidermis, dermis, and hypodermis [6]. The epidermis contains several layers, of which the stratum corneum is the principal barrier to transdermal drug permeation [2,6]. It comprises non-viable corneocytes embedded in an organized lipid matrix containing ceramides, cholesterol, and free fatty acids. This characteristic "brick-and-mortar" structure provides the skin with high impermeability and limits the penetration of many therapeutic molecules [6,7] (Figure 1).

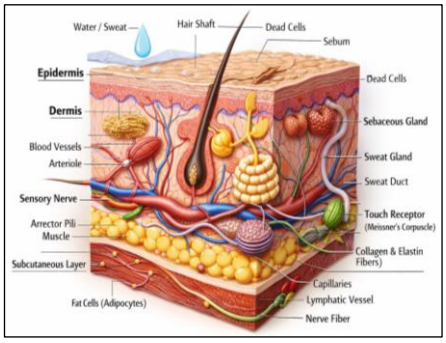


Figure 1. Diagrammatic representation of skin anatomy and physiology.

The dermis is a connective-tissue layer containing collagen and elastin fibres that provide structural support and elasticity. It also contains blood and lymphatic vessels, nerves, hair follicles, sweat glands, and sebaceous glands. Its rich capillary network facilitates systemic uptake after drugs cross the epidermal barrier. Beneath it, the hypodermis consists mainly of adipose and connective tissue and contributes to drug storage, insulation, and skin permeability [2,6,7].

The stratum corneum is the major rate-limiting barrier to transdermal absorption. Drugs can cross the skin through transcellular, intercellular, and appendageal pathways, with the intercellular lipid pathway generally predominating during passive diffusion [6,7]. Permeation is influenced by drug molecular weight, lipophilicity, ionization, skin hydration, temperature, and application site; drugs with a molecular weight below approximately 500 Da and moderate lipophilicity generally show more favourable transdermal permeability [2,6].

TDDS deliver drugs across intact skin to achieve systemic effects and are particularly useful for sustained or controlled drug administration [2,7]. Their advantages include avoidance of first-pass metabolism, reduced gastrointestinal exposure, improved adherence, and the ability to discontinue drug delivery by removing the dosage form [2,7]. However, transdermal delivery remains largely dependent on favourable drug properties, including low molecular weight, adequate lipophilicity, and sufficient potency, making an understanding of skin structure and permeability essential for TDDS development.

3. PRINCIPLES OF TRANSDERMAL DRUG DELIVERY

Drug delivery systems are designed to provide controlled and efficient drug administration while achieving the desired therapeutic effect with minimal adverse reactions [8–10]. Controlled drug release helps maintain therapeutic plasma concentrations and reduce dosing frequency, while targeted delivery can direct drugs toward specific sites of action and potentially limit unwanted systemic effects [8–10].

The design of TDDS depends on drug properties such as molecular weight, solubility, stability, and lipid affinity, which influence drug absorption and distribution [9,10]. The formulation must facilitate drug passage across the stratum corneum without causing skin damage or irritation [9,11]. Bypassing hepatic first-pass metabolism can further improve systemic drug availability [8,9]. Advanced approaches, including microneedles, chemical penetration enhancers, and electrically assisted techniques, can enhance drug transport across the skin and improve delivery efficiency [10,11] (Figures 2 and 3).

4. ADVANTAGES OF TDDS

4.1 Avoidance of First-Pass Hepatic Metabolism

Transdermal delivery transports the drug directly into the systemic circulation across the skin, bypassing hepatic first-pass metabolism. This enhances the bioavailability of drugs that are extensively metabolized after oral administration and permits use of lower doses to achieve the desired therapeutic effect [12].

4.2 Controlled and Sustained Drug Release

TDDS deliver drugs at a predetermined, near-constant rate over an extended period, maintaining plasma concentrations within the therapeutic window. This profile minimizes fluctuations in drug levels, improves therapeutic efficacy, and reduces dose-related adverse effects [12].

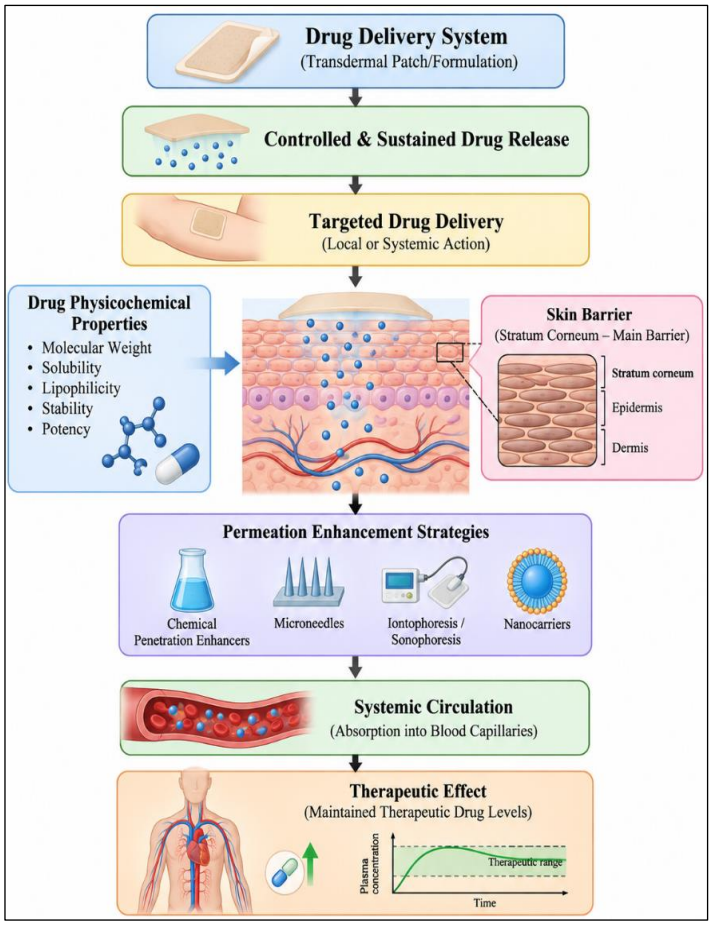


Figure 2. Schematic representation of the fundamental principles governing TDDS.

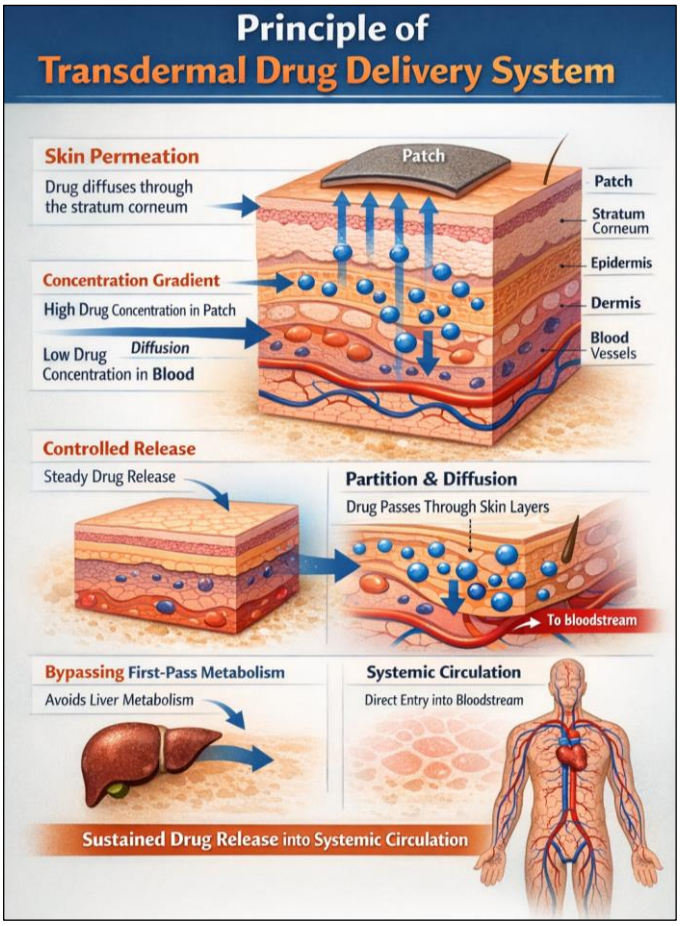


Figure 3. Illustration of the principle of TDDS.

4.3 Improved Patient Compliance

Because transdermal patches are typically designed for once-daily or once-weekly application, dosing frequency is markedly reduced. This simplicity improves adherence, particularly among elderly patients and those requiring long-term medication [12].

4.4 Non-Invasive and Painless Administration

By delivering drugs through the skin without breaching deeper tissues, TDDS eliminate the pain, discomfort, and risk associated with injections, making them especially acceptable to paediatric, geriatric, and needle-phobic patients [12].

4.5 Reduction of Gastrointestinal and Systemic Side Effects

By avoiding gastrointestinal exposure and hepatic metabolism, TDDS reduce gastrointestinal irritation, food–drug interactions, and the formation of toxic metabolites, thereby improving overall tolerability [12].

4.6 Rapid Termination of Therapy

Drug input can be discontinued immediately by simply removing the patch, allowing prompt cessation of delivery in cases of toxicity, hypersensitivity, or overdose and thereby enhancing the safety profile of therapy [12].

4.7 Suitability for Self-Administration

Transdermal systems can be applied and removed by patients without professional assistance, making them well suited to home-based therapy and reducing dependence on healthcare providers [12].

4.8 Suitability for Long-Term and Chronic Therapy

TDDS are especially appropriate for chronic disorders such as cardiovascular disease, hormonal deficiencies, and chronic pain, where continuous drug delivery is required; the stable plasma levels they achieve improve therapeutic consistency and quality of life [12].

5. DISADVANTAGES OF TDDS

5.1 Limited Range of Suitable Drug Candidates

Only drugs with favourable physicochemical properties, low molecular weight (generally <500 Da), moderate lipophilicity, and high pharmacological potency, are suitable for transdermal delivery; many therapeutic agents fail to meet these criteria and

cannot achieve therapeutically effective plasma concentrations by this route [13,14].

5.2 Inability to Deliver High Drug Doses Rapidly

TDDS are unsuitable for drugs requiring high systemic concentrations or rapid onset of action, since the rate and extent of transdermal absorption are inherently limited; consequently, this route is inappropriate for emergency therapies or large-dose drugs [13,14].

5.3 Skin as a Formidable Biological Barrier

The stratum corneum presents the principal barrier to drug permeation because of its dense cellular structure and lipid-rich composition. Drugs lacking balanced lipid and aqueous solubility often exhibit poor skin penetration and inadequate systemic exposure [13,14].

5.4 Risk of Skin Irritation and Sensitization

Prolonged contact between transdermal formulations and the skin may cause local adverse reactions such as erythema, itching, oedema, contact dermatitis, or allergic responses, which may arise from the drug itself, the adhesive layer, or the penetration enhancers used [13].

5.5 Inter- and Intra-Individual Variability in Drug Absorption

Drug absorption through the skin varies considerably between individuals and even between anatomical sites within the same individual. Age, skin hydration, stratum corneum thickness, local blood flow, and application site all influence permeation and may lead to unpredictable plasma concentrations [13].

5.6 Adhesion and Patient Comfort Issues

Patch performance may be compromised by sweating, body movement, and anatomical contours, leading to partial detachment; prolonged wear may also cause discomfort, reducing patient acceptance and adherence [13].

5.7 Unsuitability for Pulsatile or On-Demand Drug Delivery

Because TDDS are designed primarily for continuous, sustained release, they are poorly suited to therapies requiring rapid drug input or precisely timed, pulsatile dosing, such as those needed for acute or episodic pain [13,14] (Figure 4).

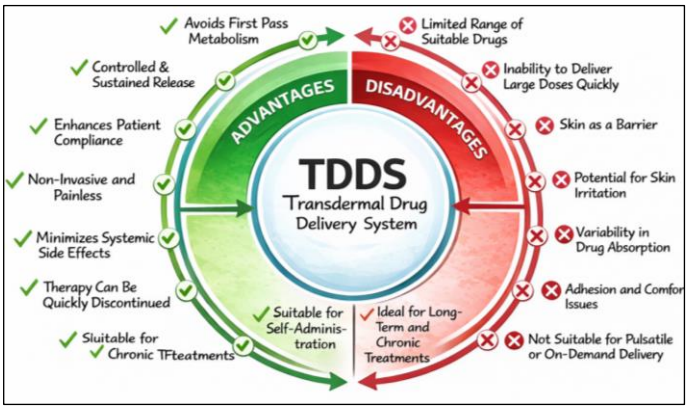


Figure 4. Illustration of the advantages and disadvantages of TDDS

6. PROPERTIES OF TDDS

The key physicochemical and design-related properties of TDDS are summarized in **Table 1** [12,15-17].

Table 1. Fundamental Properties of Transdermal Drug Delivery Systems

S.No	Property	Scientific Description
1	Controlled and predictable drug release	TDDS deliver drugs at a controlled, predetermined rate, sustaining plasma levels and reducing dosing frequency.
2	Non-invasive administration	Drugs are delivered across intact skin without needles, offering a painless, patient-friendly route.
3	Avoidance of first-pass metabolism	Drugs enter the systemic circulation directly, bypassing gastrointestinal degradation and hepatic first-pass metabolism, thereby improving bioavailability.
4	Improved patient compliance	Extended dosing intervals (daily or weekly) reduce pill burden and improve adherence, especially in chronic therapy.
5	Maintenance of stable plasma levels	Continuous drug input reduces peak–trough fluctuations associated with conventional dosage forms, improving efficacy and safety.
6	Multilayered, self-contained design	TDDS patches comprise a drug reservoir or matrix, adhesive layer, backing membrane, and release liner, ensuring uniform and reliable delivery.
7	Utilization of a large skin surface area	The skin provides a broad, accessible surface for application, facilitating uniform absorption of suitable drugs.
8	Dependence on drug physicochemical properties	Permeability depends on molecular weight (<500 Da), lipophilicity, solubility, and partition coefficient.
9	Multiple permeation pathways	Drugs permeate the skin via transcellular, intercellular, or appendageal routes depending on drug and formulation characteristics.
10	Stratum corneum as the primary barrier	The dense lipid–protein structure of the stratum corneum restricts penetration, often necessitating enhancers or physical techniques.

7. MECHANISM OF DRUG PERMEATION

Transdermal drug delivery involves controlled movement of a drug across intact skin to achieve systemic therapeutic effects [1,18]. The process begins with drug release from the formulation and partitioning into the stratum corneum, the principal barrier to percutaneous absorption [1,11,14].

Drug permeation occurs through intercellular, transcellular, and appendageal pathways, with the intercellular route generally predominating for lipophilic drugs [1,11,14]. After crossing the stratum corneum, the drug passes through the viable epidermis and dermis before entering the dermal microcirculation and systemic circulation [1,11,14]. Drug flux is primarily governed by the concentration gradient and depends on the drug's diffusion and partition coefficients and the thickness of the diffusion pathway [1,11,14].

Permeation is influenced by drug properties such as molecular weight, lipophilicity, ionization, and solubility, as well as physiological factors including skin hydration, temperature, and application site [1,18,19]. To overcome the stratum corneum barrier, chemical penetration enhancers, iontophoresis, sonophoresis, electroporation, and microneedles can be employed to increase skin permeability and facilitate the delivery of poorly permeable drugs, peptides, proteins, and vaccines [2,11,18] (Figure 5).

8. COMPARISON OF PASSIVE AND ACTIVE TDDS

Passive transdermal delivery depends on the natural permeability of the skin and concentration gradient to drive drug diffusion across the stratum corneum. The permeation rate is influenced by the drug's diffusion and partition coefficients and the thickness of the diffusion pathway [20]. Because the stratum corneum remains intact, passive TDDS are mainly suitable for small, potent, moderately lipophilic drugs with favourable physicochemical properties, generally providing sustained but relatively low drug flux. In contrast, active transdermal delivery uses physical or physicochemical methods to temporarily overcome the stratum corneum barrier [20]. Iontophoresis uses a low-intensity electric current, sonophoresis uses ultrasound, electroporation creates transient aqueous pores, and microneedles form microchannels through the stratum corneum to facilitate drug transport [21–24]. These approaches can expand transdermal delivery to hydrophilic drugs, peptides, proteins, and vaccines while allowing greater control over drug flux.

Thus, passive systems are limited by the intrinsic barrier properties of the stratum corneum, whereas active technologies enhance permeability and broaden the range of deliverable drugs. Combining passive delivery with active enhancement approaches can improve drug flux and enable sustained delivery of both conventional drugs and macromolecular therapeutics [24] (Figure 6).

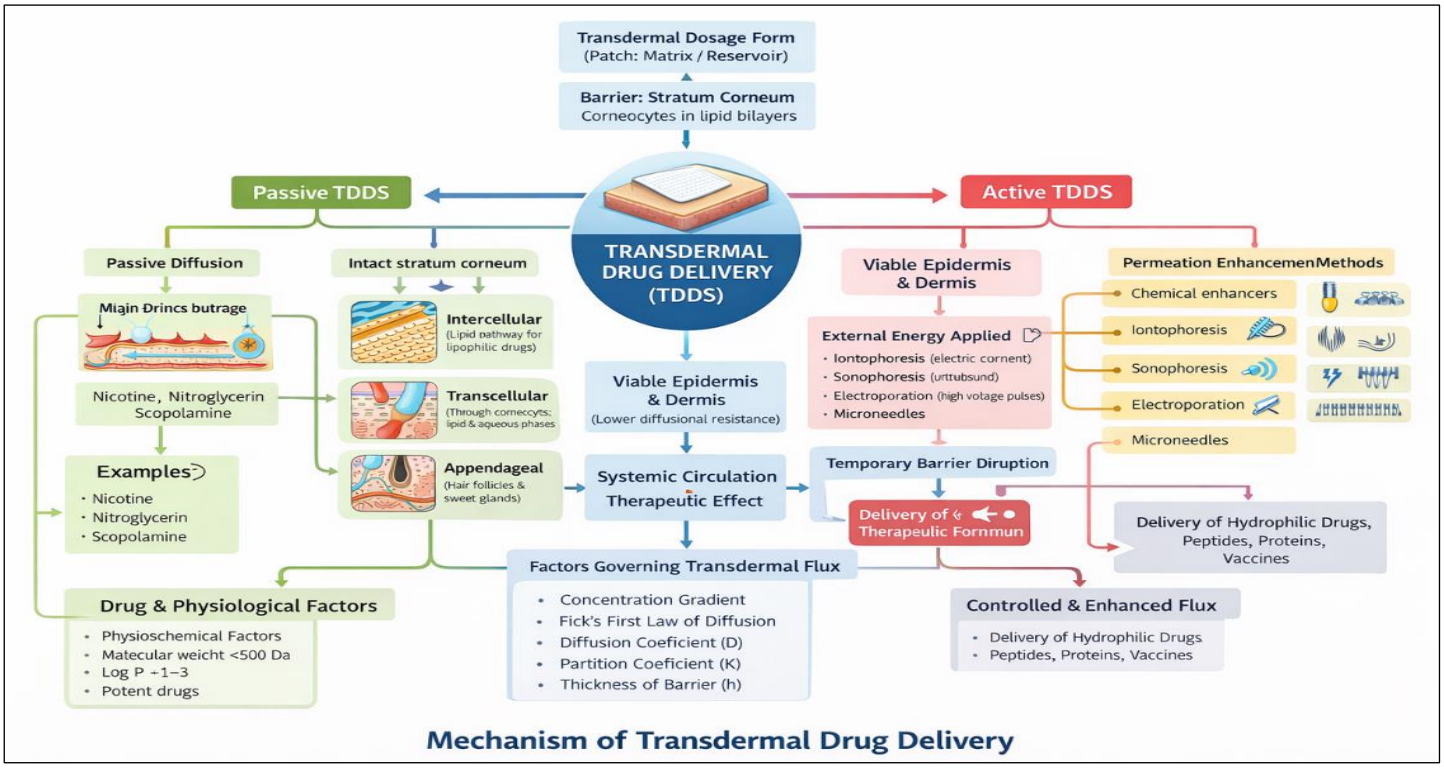


Figure 5. Mechanism of TDDS.

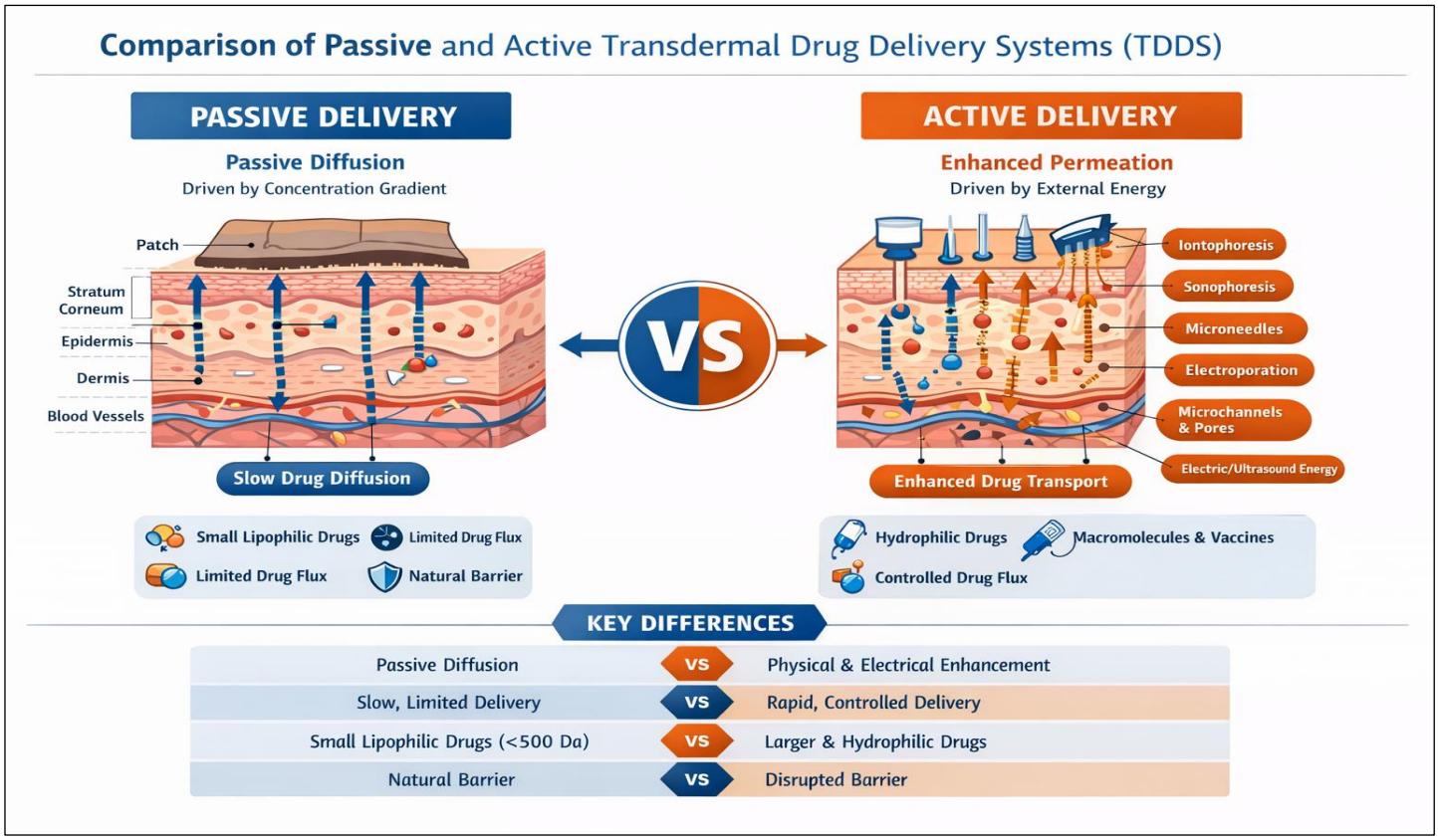


Figure 6. Illustration of the comparison between active and passive delivery.

9. FACTORS AFFECTING TDDS PERFORMANCE

The performance of transdermal drug delivery depends on several interrelated biological, physicochemical, formulation, and environmental factors that influence drug permeation and systemic absorption [19,20]. Biological factors include skin integrity, age, dermal blood flow, skin metabolism, anatomical site, and inter-individual variability, as changes in skin thickness, hydration, lipid composition, blood circulation, and barrier function can alter drug permeation [21]. Drug-related factors such as molecular size, lipophilicity, partition coefficient, degree of ionization, concentration, solubility, and pH strongly influence the ability of a drug to cross the stratum corneum; an appropriate balance between lipid and aqueous solubility is particularly important [22]. Formulation and device characteristics, including penetration enhancers, patch architecture, adhesives, rate-controlling membranes, viscosity, moisture content, and matrix structure, also affect drug release and permeation and should be optimized to maintain consistent delivery while minimizing skin irritation [23]. Environmental and external factors, particularly skin hydration, temperature, humidity, and application site, can further modify skin permeability and drug absorption [24].

10. ENHANCEMENT TECHNIQUES IN TDDS

Various chemical, physical, mechanical, and carrier-based approaches have been developed to overcome the skin barrier and enhance transdermal drug flux [25]. Chemical penetration enhancers, such as ethanol, oleic acid, dimethyl sulfoxide, propylene glycol, fatty acids, and surfactants, improve permeation by altering stratum corneum lipids and proteins or enhancing drug partitioning into the skin [26].

Physical methods include iontophoresis, which uses low-intensity electrical current; sonophoresis, which uses ultrasound to modify lipid organization and hydration; electroporation, which creates transient aqueous pores; and thermal ablation, which generates micropores to facilitate drug transport [21–23,27]. Microneedle-assisted delivery creates temporary microchannels through the stratum corneum, enabling the delivery of poorly permeable drugs, peptides, proteins, and vaccines into viable skin layers; these systems offer minimally invasive and controlled delivery [24,28,29].

Nanocarrier-based systems, including liposomes, ethosomes, transfersomes, and niosomes, can improve drug solubilization and skin permeation. In particular, the deformability and lipid-fluidizing properties of ethosomes and transfersomes can enhance transdermal flux compared with conventional liposomes for suitable drugs [30,31].

11. COMPONENTS OF TDDS FORMULATION

A typical transdermal patch is a multilayered assembly whose components and functions are summarized in **Table 2** [12].

Table 2 Components of Transdermal Drug Delivery Systems (TDDS) and Their Functions

Component	Function
Drug (API)	Provides the therapeutic effect; must possess suitable molecular size, lipophilicity, and potency.
Adhesive	Maintains skin contact and ensures uniform drug delivery.
Polymer matrix / reservoir	Stores the drug and controls its release.
Rate-controlling membrane	Regulates drug diffusion.
Backing layer	Provides support and protects against environmental factors.
Release liner	Protects the patch prior to use.
Penetration enhancer	Improves drug permeability through the skin.

12. CLINICAL APPLICATIONS OF TDDS

Transdermal drug delivery systems (TDDS) are used for both systemic and localized therapy because they can provide sustained drug release, bypass first-pass metabolism, and reduce dosing frequency [9,25]. Clinically, TDDS are used in pain management, including fentanyl and buprenorphine for chronic pain; hormone replacement therapy, using estrogen, progesterone, and testosterone; and smoking cessation, through controlled nicotine delivery [32–34]. They are also employed in cardiovascular disorders, particularly with nitroglycerin and clonidine, and in neurological disorders, such as Parkinson's and Alzheimer's disease, where transdermal rivastigmine provides sustained drug exposure [33–35]. Other applications include dermatological disorders and contraception, while microneedle-based systems are being investigated for vaccines and immunotherapy [35,36]. Emerging applications include transdermal delivery of insulin and other metabolic therapies, glucose-responsive microneedle systems, local anaesthetics such as lidocaine and prilocaine, and potential applications in anti-obesity therapy [37,38]. TDDS are also used in cosmetic and cosmeceutical applications for the delivery of agents such as antioxidants, moisturizers, and anti-ageing compounds.

13. EVALUATION OF TDDS

Evaluation of TDDS is essential to establish their quality, safety, efficacy, and reproducibility. A comprehensive evaluation includes physical, mechanical, drug-content, release, permeation, irritation, stability, and in vivo assessments [19,20,25,39–41]. Physical and mechanical evaluation includes thickness, weight variation, folding endurance, flatness, moisture content, surface pH, tensile strength, percentage elongation, Young's modulus, and adhesive properties to assess patch uniformity, flexibility, strength, stability, and skin adhesion [19,20,25,39–41]. Drug content uniformity is determined using analytical methods such as UV spectroscopy or HPLC to ensure consistent drug loading [25,39]. In-vitro drug release studies, commonly performed using USP paddle-over-disk apparatus or Franz diffusion cells, characterize release behaviour and can be fitted to zero-order, first-order, Higuchi, and Korsmeyer–Peppas models [20,39,42,43].

Ex vivo skin permeation studies using suitable animal or human skin evaluate parameters such as steady-state flux (Jss), permeability coefficient (Kp), and lag time [44]. Skin irritation and sensitization studies assess dermatological safety, while stability studies monitor drug content, physical characteristics, and release behaviour under long-term and accelerated conditions [20,40,41]. In-vivo and pharmacokinetic evaluation determines plasma concentration–time profiles and parameters such as Cmax, Tmax, AUC, and bioavailability [20]. For active and microneedle-based TDDS, additional evaluation includes needle geometry, insertion force, drug-loading capacity, pore formation and closure, and release efficiency [45] (Figure 7).

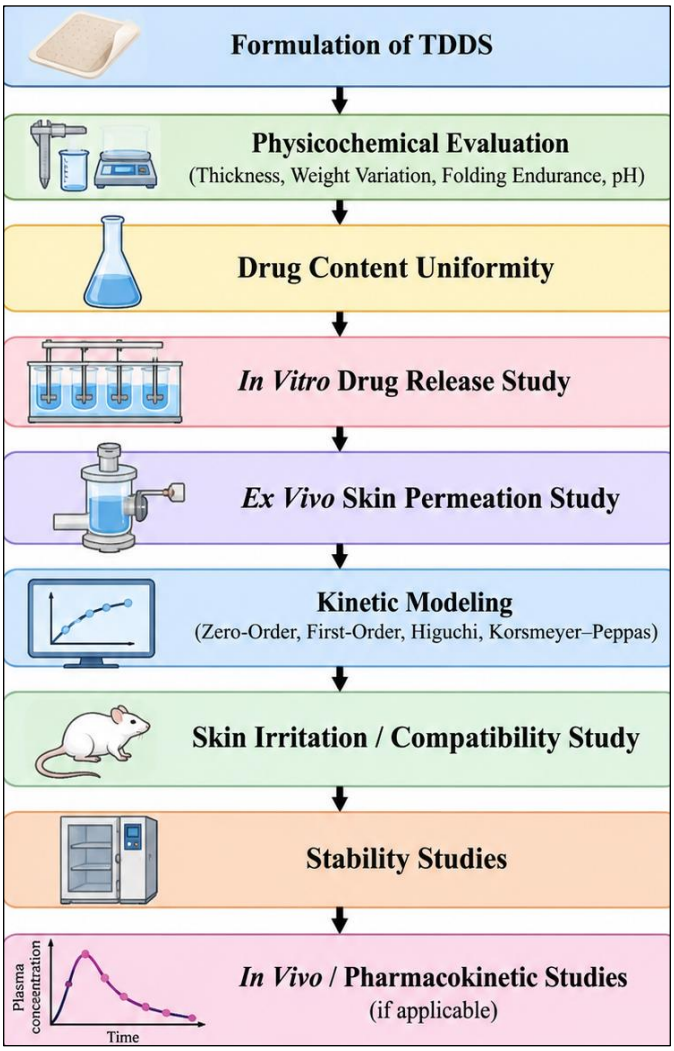


Figure 7. Schematic workflow for the evaluation of TDDS.

14. FUTURE SCOPE AND RECENT DEVELOPMENTS

Recent advances in materials science, nanotechnology, and microfabrication have expanded TDDS beyond conventional delivery of small, lipophilic drugs toward macromolecules and complex therapeutics [46,47]. Microneedle-based systems, particularly dissolving and hydrogel-forming microneedles, create transient microchannels in the stratum corneum and enable delivery of peptides, proteins, vaccines, and nucleic acids [48–51]. Integration of nanocarriers, including liposomes, niosomes, ethosomes, transfersomes, and polymeric nanoparticles, can improve drug solubilization, stability, skin penetration, and controlled release [46,47].

Advances in iontophoresis and electroporation have enabled greater control over drug flux and programmable delivery [46]. Stimulus-responsive TDDS can modulate drug release in response to physiological signals such as temperature, pH, or glucose, while wearable systems integrated with biosensors may support personalized and adaptive drug delivery [38,47,52,53]. Future development is expected to focus on transdermal delivery of biologics, vaccines, and gene-based therapeutics, alongside applications in metabolic disorders, oncology, immunotherapy, and neurological diseases [46,48,54]. However, scalable manufacturing, regulatory harmonization, cost, and long-term safety remain important considerations for clinical translation and commercialization [46,48,54].

CONCLUSION

Transdermal drug delivery systems (TDDS) provide a non-invasive approach for controlled systemic and localized drug administration, offering advantages such as avoidance of first-pass metabolism, sustained drug release, and improved patient convenience. Successful TDDS development depends on understanding skin structure, drug physicochemical properties, and formulation characteristics.

The stratum corneum remains the major barrier limiting passive transdermal delivery. However, chemical penetration enhancers, nanocarriers, electrically assisted methods, and particularly microneedle-based systems have expanded the potential of TDDS for peptides, proteins, vaccines, and other poorly permeable therapeutics. Emerging smart, responsive, and wearable systems further support controlled and personalized drug delivery. Despite these advances, challenges involving manufacturing scalability, regulatory requirements, variability in skin permeability, cost, and long-term safety require continued attention.

Overall, ongoing advances in pharmaceutical technology, materials science, nanotechnology, and biomedical engineering are expected to broaden the therapeutic applications of TDDS and improve their clinical translation and patient acceptability.

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