RESEARCH PAPER

RECENT ADVANCES IN TRANSDERMAL DRUG DELIVERY SYSTEMS: SKIN BARRIER, PERMEATION ENHANCEMENT STRATEGIES, NANOCARRIER-BASED APPROACHES, AND FUTURE PERSPECTIVES

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ABSTRACT
Transdermal drug delivery systems (TDDS) have emerged as an effective alternative to conventional drug administration by providing sustained drug release, improved patient compliance, avoidance of first-pass metabolism, and reduced gastrointestinal adverse effects. However, the highly organized structure of the stratum corneum remains the principal barrier limiting transdermal permeation. Recent advances in pharmaceutical technology have significantly expanded the scope of TDDS through the development of chemical permeation enhancers, physical enhancement techniques, nanocarrier-based formulations, and microneedle-assisted delivery systems. Liposomes, transfersomes, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and nanoemulsions have demonstrated considerable potential in improving drug permeation, stability, and controlled release. Emerging technologies, including iontophoresis, sonophoresis, electroporation, and dissolving microneedles, further facilitate the delivery of macromolecules such as peptides, proteins, vaccines, and nucleic acids. Additionally, smart wearable transdermal patches integrated with biosensors are opening new opportunities for personalized and precision medicine. This review summarizes recent advances in skin physiology relevant to transdermal delivery, mechanisms of drug permeation, formulation strategies, permeation enhancement techniques, nanocarrier-based systems, therapeutic applications, commercially available products, current challenges, and future perspectives. Collectively, these innovations are transforming TDDS into a versatile platform capable of delivering both conventional therapeutics and biologics with improved efficacy, safety, and patient acceptance.

Keywords: Transdermal drug delivery systems; Skin permeation; Stratum corneum; Microneedles; Nanocarriers; Permeation enhancers; Transdermal patches; Controlled drug delivery.
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INTRODUCTION

Transdermal drug delivery systems (TDDS) have become an attractive alternative to conventional oral and parenteral routes because they provide controlled systemic drug delivery while improving patient compliance and minimizing fluctuations in plasma drug concentrations. Unlike oral administration, transdermal delivery bypasses gastrointestinal degradation and hepatic first-pass metabolism, thereby improving the bioavailability of drugs susceptible to extensive presystemic metabolism. In addition, the non-invasive nature of transdermal patches reduces dosing frequency, enhances therapeutic adherence, and allows prompt discontinuation of therapy by simply removing the dosage form, making TDDS particularly suitable for chronic disease management **[1]**.

The human skin, covering approximately 1.8–2.0 m² and accounting for nearly 15% of total body weight, serves as the body's largest protective organ. Although its extensive surface area makes it an attractive route for systemic drug administration, the highly organized structure of the stratum corneum presents a formidable barrier to molecular transport. Often described by the "brick-and-mortar" model, the stratum corneum consists of protein-rich corneocytes embedded within a lipid matrix composed mainly of ceramides, cholesterol, and free fatty acids. This unique architecture effectively restricts the permeation of most hydrophilic compounds, macromolecules, and biologics, representing the principal challenge in transdermal drug delivery **[2–4]**.

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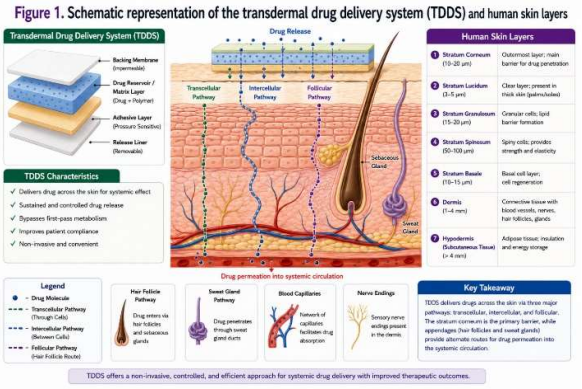
Despite these physiological barriers, several therapeutic agents have been successfully formulated as commercial transdermal products for pain management, cardiovascular diseases, hormone replacement therapy, neurological disorders, and smoking cessation. Conventional first-generation transdermal systems rely primarily on passive diffusion and are generally suitable only for small, lipophilic, and highly potent molecules. Consequently, their clinical applicability remains limited to drugs with favorable physicochemical characteristics **[5]**.

Continuous advances in pharmaceutical sciences, biomaterials, and nanotechnology have substantially expanded the scope of TDDS. Modern strategies employ chemical permeation enhancers, physical enhancement techniques, and nanocarrier-based formulations to improve drug transport across the skin barrier. Technologies such as iontophoresis, sonophoresis, electroporation, thermal ablation, and microneedle-assisted delivery create temporary and reversible modifications in the stratum corneum, enabling efficient delivery of molecules that were previously unsuitable for transdermal administration. Simultaneously, nanocarrier systems including liposomes, transfersomes, ethosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, and nanoemulsions enhance drug solubility, stability, controlled release, and skin penetration while minimizing systemic adverse effects **[6–9]**.

Recent developments have further integrated TDDS with wearable electronics, biosensors, and stimulus-responsive materials, enabling real-time monitoring and personalized drug administration. These smart transdermal platforms have considerable potential for precision medicine by allowing controlled, patient-specific dosing based on physiological feedback. Furthermore, advances in transdermal technologies are facilitating the delivery of complex therapeutics, including peptides, proteins, nucleic acids, vaccines, and gene-based medicines, thereby broadening the clinical applications of this route **[10–12]**.

This review critically summarizes recent advances in transdermal drug delivery systems with particular emphasis on skin barrier physiology, mechanisms of drug permeation, permeation enhancement strategies, nanocarrier-based formulations, therapeutic applications, commercially available products, current challenges, and future perspectives. The review highlights how emerging technologies are transforming TDDS into versatile and patient-friendly platforms for both conventional small-molecule drugs and next-generation biopharmaceuticals.

1. Skin Anatomy and Physiology Relevant to Transdermal Drug Delivery



The skin is the largest organ of the human body, covering approximately 1.8–2.0 m² and constituting nearly 15% of total body weight. Besides serving as a physical barrier against environmental hazards, it performs essential physiological functions including thermoregulation, sensory perception, immune surveillance, prevention of transepidermal water loss, and metabolic activities. From a pharmaceutical perspective, the skin offers an attractive route for systemic drug delivery because of its extensive surface area; however, its highly efficient barrier properties significantly limit the permeation of most therapeutic agents **[13,14]**.

Structurally, the skin consists of three major layers: the **epidermis**, **dermis**, and **hypodermis (subcutaneous tissue)**. Among these, the epidermis is the principal barrier to transdermal drug transport. The outermost layer of the epidermis, the **stratum corneum**, is primarily responsible for restricting drug permeation. It consists of terminally differentiated keratinized corneocytes embedded within a continuous lipid matrix composed mainly of ceramides, cholesterol, and free fatty acids. This highly organized arrangement, commonly described as the **"brick-and-mortar" model**, provides remarkable resistance to the diffusion of hydrophilic compounds and high-molecular-weight therapeutics **[15–17]**.

Beneath the epidermis lies the **dermis**, a connective tissue layer rich in collagen, elastin fibers, blood vessels, lymphatics, nerves, hair follicles, sebaceous glands, and sweat glands. Unlike the avascular epidermis, the dermis possesses an extensive vascular network that facilitates systemic absorption once a drug successfully penetrates the epidermal barrier. Consequently, efficient delivery across the stratum corneum followed by rapid uptake into dermal capillaries is essential for achieving therapeutic plasma concentrations **[18]**.

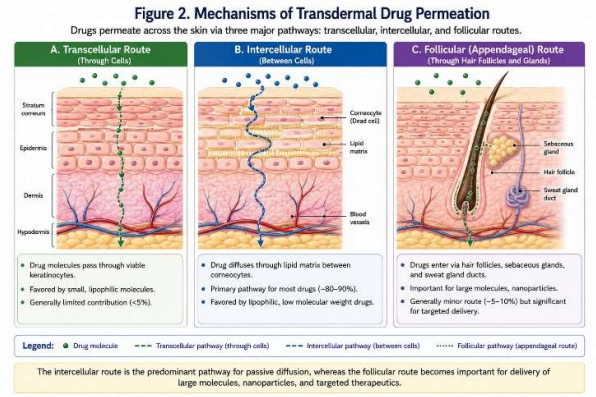
The deepest layer, the **hypodermis**, consists predominantly of adipose tissue and connective tissue that provide thermal

insulation, mechanical protection, and energy storage. Although it contributes minimally to the permeation process, it plays an important role in the systemic distribution of absorbed drugs after they reach the underlying vascular network **[19]**.

In addition to the intercellular lipid matrix, skin appendages such as **hair follicles, sebaceous glands, and sweat glands** provide alternative pathways for drug penetration. Although these appendageal structures occupy less than 1% of the total skin surface area, they can significantly enhance the delivery of nanoparticles, liposomes, peptides, and other macromolecules by bypassing portions of the stratum corneum. Hair follicles also function as localized drug reservoirs, enabling sustained release and prolonged therapeutic action following topical application **[20]**.

Several physiological and physicochemical factors influence transdermal drug permeation, including skin hydration, anatomical site, age, disease condition, skin thickness, blood flow, molecular weight, lipophilicity, ionization, and formulation characteristics. Drugs intended for passive transdermal delivery generally exhibit a molecular weight below 500 Da, balanced hydrophilic–lipophilic properties (Log P approximately 1–4), and sufficient pharmacological potency. A thorough understanding of skin anatomy and barrier function is therefore fundamental for designing effective transdermal formulations and selecting appropriate permeation enhancement strategies **[21–23]**.

2. Mechanisms of Transdermal Drug Permeation

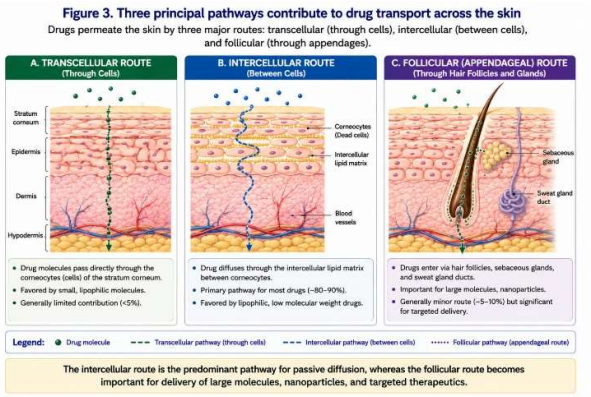


Successful transdermal drug delivery depends on the ability of a therapeutic molecule to penetrate the highly organized skin barrier and reach the systemic circulation at therapeutically effective concentrations. Drug transport across the skin is primarily governed by passive diffusion and is influenced by the physicochemical properties of the drug, formulation characteristics, and physiological conditions of the skin. Since the **stratum corneum** contributes nearly 90% of the skin's barrier resistance, it remains the principal obstacle to efficient transdermal delivery **[24,25]**.

Drug permeation across biological membranes generally follows **Fick's first law of diffusion**, where the diffusion rate is directly proportional to the concentration gradient, diffusion coefficient, and partition coefficient, and inversely proportional to membrane thickness. Consequently, successful transdermal delivery requires optimal drug concentration, balanced lipophilicity, and favorable partitioning into the lipid-rich stratum corneum **[26]**.

Following application of a transdermal formulation, drug absorption occurs through a sequence of events including release of the drug from the dosage form, partitioning into the stratum corneum, diffusion through the viable epidermis, migration across the dermis, and eventual uptake into the dermal capillary network for systemic distribution. Among these processes, diffusion through the stratum corneum is generally considered the rate-limiting step **[27]**.

3. Three principal pathways contribute to drug transport across the skin



Transcellular pathway: Drug molecules pass directly through corneocytes by repeatedly partitioning between intracellular aqueous domains and surrounding lipid bilayers. Although this route provides the shortest diffusion distance, repeated transitions between hydrophilic and lipophilic environments make it energetically unfavorable for many compounds **[28]**.

Intercellular pathway: This is the predominant pathway for passive transdermal delivery. Drug molecules diffuse through the continuous lipid matrix surrounding corneocytes. The highly ordered lamellar arrangement of ceramides, cholesterol, and free fatty acids creates a tortuous diffusion pathway that favors moderately lipophilic molecules while limiting the transport of highly hydrophilic or large molecular weight drugs **[29]**.

Appendageal (follicular) pathway: Hair follicles, sebaceous glands, and sweat glands provide alternative shunt pathways that partially bypass the stratum corneum. Although these appendages occupy less than 1% of the total skin surface, they play an important role in the delivery of nanoparticles, peptides, proteins, vaccines, and other macromolecules. Hair follicles also function as localized drug reservoirs, enabling sustained release and enhanced local retention following topical administration **[30]**.

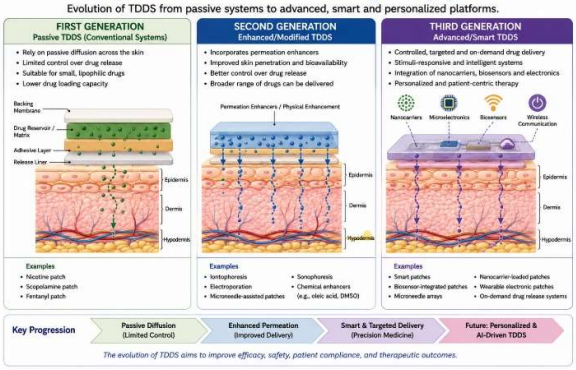
The efficiency of transdermal permeation is further influenced by multiple factors, including molecular weight, lipophilicity, aqueous solubility, degree of ionization, skin hydration, formulation composition, and anatomical site of application. Passive diffusion is generally most effective for drugs with a molecular weight below 500 Da, balanced hydrophilic–lipophilic properties (Log P 1–4), and adequate pharmacological potency. To overcome the intrinsic barrier properties of the skin, modern TDDS frequently incorporate chemical permeation enhancers, physical enhancement techniques, and nanocarrier-based delivery systems that transiently and reversibly improve skin permeability without causing permanent tissue damage **[31–34]**.

A comprehensive understanding of these permeation mechanisms provides the scientific basis for designing advanced transdermal formulations capable of delivering both conventional small molecules and emerging biopharmaceuticals with improved therapeutic efficacy and safety.

4. Generations of Transdermal Drug Delivery Systems

Figure 4. Generations of Transdermal Drug Delivery Systems

Evolution of TDDS from passive systems to advanced, smart and personalized platforms.



The evolution of transdermal drug delivery systems (TDDS) has significantly expanded the range of therapeutic agents that can be administered through the skin. Early transdermal formulations were restricted to a limited number of potent, low-molecular-weight, lipophilic drugs capable of passive diffusion across the intact stratum corneum. Advances in pharmaceutical technology, biomedical engineering, and nanotechnology have progressively overcome these limitations, leading to the development of sophisticated delivery platforms capable of transporting peptides, proteins, vaccines, and nucleic acid therapeutics. Based on technological progression and barrier-modulation strategies, TDDS are broadly classified into first-, second-, and third-generation systems **[35,36]**.

5.1 First-Generation TDDS

First-generation transdermal systems rely exclusively on **passive diffusion** through intact skin without altering the barrier properties of the stratum corneum. These systems are suitable only for drugs possessing favorable physicochemical characteristics, including molecular weight below 500 Da, balanced lipophilicity (Log P 1–4), adequate potency, and sufficient skin permeability. Commercial products such as **nitroglycerin, nicotine, fentanyl, clonidine, and scopolamine patches** have demonstrated the clinical success of this approach. However, passive diffusion limits drug loading capacity and excludes most hydrophilic compounds and macromolecules **[37,38]**.

5.2 Second-Generation TDDS

To overcome the limitations of passive delivery, second-generation TDDS employ **reversible permeation enhancement techniques** that transiently modify the stratum corneum while preserving deeper tissues. Chemical permeation enhancers, including alcohols, fatty acids, terpenes, surfactants, and sulfoxides, improve drug transport by disrupting lipid organization, increasing skin hydration, and enhancing drug partitioning. Device-assisted approaches such as **iontophoresis** and **low-frequency sonophoresis** further facilitate transdermal delivery by increasing skin permeability and promoting the transport of charged or hydrophilic molecules. Although these methods improve drug flux, their effectiveness for large biomolecules remains limited, and skin irritation may occur with prolonged application **[39–41]**.

5.3 Third-Generation TDDS

Third-generation transdermal systems intentionally create **controlled and localized disruption of the stratum corneum**, enabling efficient delivery of biologics while minimizing damage to viable tissues. Technologies such as **microneedles, electroporation, thermal ablation, laser-assisted delivery, and nanocarrier-based formulations** have transformed TDDS into advanced platforms capable of delivering peptides, proteins, vaccines, monoclonal antibodies, and nucleic acids. Microneedle systems have received particular attention because they provide painless administration, high patient compliance, and effective transport of large therapeutic molecules. Simultaneously, nanocarrier-based systems including liposomes, transfersomes, ethosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric

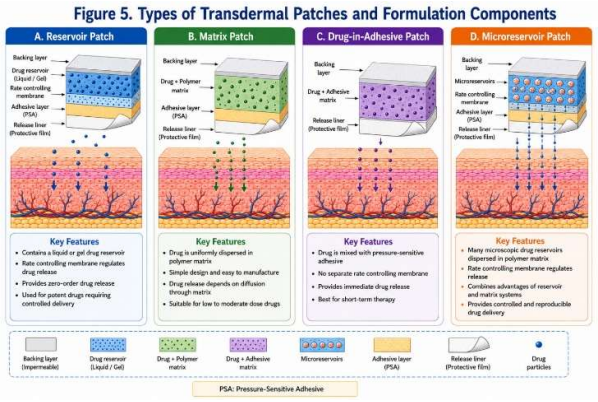
nanoparticles, and nanoemulsions enhance drug stability, skin penetration, and controlled release, thereby expanding the therapeutic potential of transdermal delivery **[42–45]**.

The continuous integration of nanotechnology, wearable electronics, biosensors, and artificial intelligence is driving the development of **next-generation smart transdermal systems** capable of real-time physiological monitoring and personalized drug administration. These intelligent platforms are expected to play an increasingly important role in precision medicine, chronic disease management, and self-administered therapeutics **[46]**.

Table 1. Comparison of Generations of Transdermal Drug Delivery Systems

Feature	First Generation	Second Generation	Third Generation
Drug transport mechanism	Passive diffusion	Chemical/physical enhancement	Controlled barrier disruption
Suitable molecules	Small lipophilic drugs	Small and moderately hydrophilic drugs	Small molecules, peptides, proteins, vaccines, nucleic acids
Barrier modification	None	Reversible	Controlled and localized
Major technologies	Conventional patches	Chemical enhancers, iontophoresis, sonophoresis	Microneedles, electroporation, nanocarriers, thermal ablation
Advantages	Simple, safe, economical	Improved permeation	Broad drug applicability, targeted delivery
Limitations	Limited drug candidates	Variable enhancement, possible irritation	Higher complexity and manufacturing cost

6. Types of Transdermal Patches and Formulation Components



The therapeutic performance of a transdermal drug delivery system (TDDS) depends not only on the physicochemical properties of the active pharmaceutical ingredient (API) but also on the design of the patch and the selection of formulation components. Appropriate patch architecture ensures controlled drug release, adequate skin adhesion, formulation stability, and patient comfort. Modern transdermal patches are multilayered systems composed of polymers, pressure-sensitive adhesives, permeation enhancers, plasticizers, backing membranes, release liners, and the drug substance, all of which collectively influence drug release kinetics and transdermal permeation **[47,48]**.

6.1 Types of Transdermal Patches

Based on drug incorporation and release characteristics, transdermal patches are classified into four major types.

Reservoir-type patches consist of a drug reservoir enclosed by a rate-controlling membrane that regulates drug diffusion to the skin. These systems provide near zero-order drug release but require complex manufacturing and may present a risk of dose dumping if the membrane is compromised **[49]**.

Matrix-type patches contain the drug uniformly dispersed within a polymer matrix from which drug release occurs by diffusion. Owing to their simple design, improved stability, and lower production cost, matrix systems are among the most widely used commercial transdermal formulations **[50]**.

Drug-in-adhesive patches incorporate the drug directly into the pressure-sensitive adhesive layer, thereby combining the functions of adhesion and drug delivery. Their thin profile, flexibility, ease of manufacturing, and superior patient comfort have made them the predominant

design for many currently marketed transdermal products **[51]**.

Microreservoir systems combine characteristics of reservoir and matrix technologies by dispersing microscopic drug reservoirs within a polymer matrix, thereby improving release control and drug loading capacity. Although less frequently employed commercially, these systems offer advantages for sustained drug delivery **[52]**.

6.2 Formulation Components of TDDS

The **active pharmaceutical ingredient (API)** should possess appropriate physicochemical properties for transdermal delivery, including low molecular weight, balanced lipophilicity, adequate potency, and chemical stability. Drug candidates with molecular weights below 500 Da and moderate partition coefficients generally exhibit optimal passive skin permeation **[53]**.

Polymers form the structural framework of transdermal patches and regulate drug release. Commonly employed polymers include natural polymers (chitosan, alginate), semi-synthetic polymers (hydroxypropyl methylcellulose and ethyl cellulose), and synthetic polymers such as polyvinyl alcohol, polyvinylpyrrolidone, polyethylene glycol, and Eudragit derivatives **[54]**.

Pressure-sensitive adhesives (PSAs) ensure intimate contact between the patch and the skin throughout the application period. Acrylic, silicone, and polyisobutylene adhesives are widely used because of their excellent adhesion, biocompatibility, and compatibility with a broad range of pharmaceutical agents **[55]**.

Plasticizers, including propylene glycol, glycerol, polyethylene glycol 400, and triethyl citrate, improve flexibility, mechanical strength, and film-forming properties while facilitating drug diffusion through the polymer matrix **[56]**.

Chemical permeation enhancers, such as ethanol, oleic acid, menthol, dimethyl sulfoxide, and surfactants, transiently modify the lipid organization of the stratum corneum, thereby increasing drug permeation without causing irreversible skin damage **[57]**.

Additional structural components include the **backing membrane**, which protects the formulation from environmental factors and prevents drug loss, the **release liner**, which safeguards the adhesive surface before application, and, in reservoir systems, a **rate-controlling membrane** that regulates drug release. Together, these components ensure formulation stability, reproducible drug delivery, and patient acceptability **[58]**.

Recent advances in polymer science and nanotechnology have enabled the development of hydrogel patches, nanocarrier-loaded transdermal systems, and smart wearable patches capable of controlled and stimulus-responsive drug delivery, thereby expanding the clinical applications of TDDS **[59]**.

Table 2. Types of Transdermal Patches

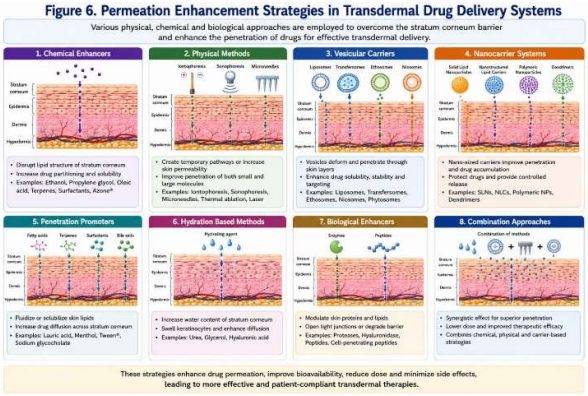
Patch Type	Drug Location	Release Mechanism	Advantages	Limitations
Reservoir	Drug reservoir	Membrane-controlled diffusion	Zero-order release	Dose dumping risk
Matrix	Polymer matrix	Diffusion through polymer	Simple, stable, economical	Limited drug loading
Drug-in-Adhesive	Adhesive layer	Diffusion from adhesive	Thin, flexible, patient-friendly	Drug compatibility issues
Microreservoir	Drug microdroplets in polymer	Controlled diffusion	Better release control	Complex manufacturing

Table 3. Major Components of a Transdermal Patch

Component	Function	Representative Materials
Active Pharmaceutical Ingredient	Therapeutic action	Nicotine, Fentanyl, Rivastigmine
Polymer	Drug matrix and release control	HPMC, PVA, PVP, Chitosan
Pressure-Sensitive Adhesive	Patch adhesion	Acrylic, Silicone, Polyisobutylene
Plasticizer	Flexibility and mechanical strength	PEG-400, Glycerol, Propylene glycol
Permeation Enhancer	Improve skin permeability	Ethanol, Oleic acid, Menthol
Backing Membrane	Protect formulation	Polyester, Polyethylene
Release Liner	Protect adhesive before use	Silicone-coated polyester
Rate-Controlling Membrane	Control drug release	Ethylene-vinyl acetate (EVA)

	(reservoir systems)	

7. Permeation Enhancement Strategies in Transdermal Drug Delivery Systems



The **stratum corneum** is the principal barrier to transdermal drug delivery, limiting the permeation of most therapeutic agents, particularly hydrophilic compounds, peptides, proteins, and other macromolecules. Although passive diffusion is adequate for a limited number of lipophilic drugs, most molecules require permeation enhancement techniques to achieve therapeutically effective transdermal flux. Modern enhancement strategies are designed to temporarily and reversibly modify skin barrier properties without causing irreversible tissue damage, thereby improving drug transport while maintaining patient safety **[60,61]**.

Permeation enhancement approaches are broadly classified into **chemical, physical, and nanotechnology-based methods**, each employing distinct mechanisms to facilitate drug transport across the skin barrier.

7.1 Chemical Permeation Enhancement

Chemical permeation enhancers improve drug penetration by interacting with the lipid and protein components of the stratum corneum. Their primary mechanisms include disruption of intercellular lipid organization, increased lipid fluidity, enhanced skin hydration, and improved drug partitioning into the epidermis. Commonly used enhancers include alcohols (ethanol and isopropanol), fatty acids (oleic acid and linoleic acid), terpenes (menthol and limonene), sulfoxides such as dimethyl sulfoxide (DMSO), and non-ionic surfactants including Tween 80 and Span 80. These compounds have been widely incorporated into transdermal formulations because they are relatively simple to formulate and cost-effective. However, excessive concentrations may cause skin irritation, dryness, or erythema, necessitating careful optimization of formulation composition **[62–64]**.

7.2 Physical Enhancement Techniques

Physical enhancement techniques transiently disrupt the skin barrier or provide external energy to facilitate drug transport without permanently damaging viable tissues.

Iontophoresis employs a low-intensity electrical current to drive charged drug molecules across the skin through electrorepulsion and electroosmosis. It enables controlled, on-demand drug delivery and is particularly useful for ionizable compounds and local anesthetics **[65]**.

Sonophoresis (phonophoresis) utilizes low-frequency ultrasound to enhance skin permeability through cavitation, thermal effects, and disruption of lipid organization. This technique has demonstrated improved delivery of anti-inflammatory drugs, analgesics, peptides, and other hydrophilic molecules **[66]**.

Electroporation involves the application of short-duration high-voltage electrical pulses that generate transient aqueous pores within the stratum corneum. This approach significantly enhances the transport of large biomolecules, including proteins, nucleic acids, and DNA vaccines **[67]**.

Among all physical techniques, **microneedle technology** has emerged as one of the most promising strategies. Microneedles create microscopic channels that bypass the stratum corneum while avoiding pain and significant tissue injury. Solid, coated, dissolving, and hollow microneedles have been successfully investigated for the delivery of insulin, vaccines, peptides, monoclonal antibodies, and other biologics, demonstrating excellent patient acceptance and therapeutic efficacy **[68]**.

Additional technologies, including **thermal ablation, laser-assisted delivery, and magnetophoresis**, further increase skin permeability by creating controlled microchannels or enhancing molecular diffusion. Although these approaches are highly effective, their clinical application is often limited by specialized equipment, increased treatment costs, and technical complexity **[69]**.

7.3 Nanotechnology-Based Enhancement

Nanotechnology has substantially expanded the scope of transdermal drug delivery by overcoming limitations associated with conventional formulations. Nanocarriers such as liposomes, transfersomes, ethosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), polymeric nanoparticles, and nanoemulsions enhance drug solubility, improve skin adhesion, facilitate follicular targeting, and provide sustained drug release. Their nanoscale dimensions and large surface area promote closer interaction with the skin surface, resulting in improved

penetration and enhanced therapeutic efficacy while reducing systemic toxicity **[70,71]**.

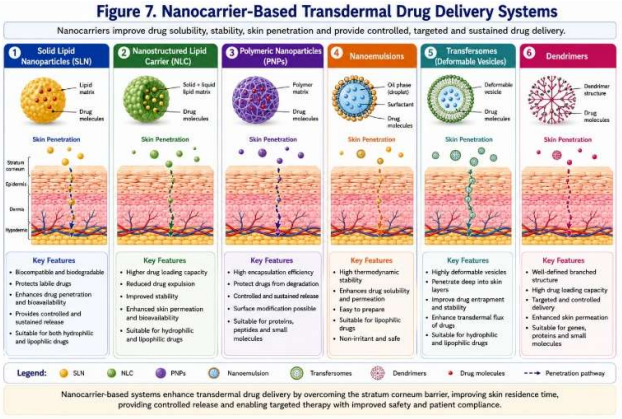
Recent research has focused on **combination approaches**, including microneedles integrated with nanoparticles, iontophoresis-assisted nanocarriers, and ultrasound-responsive drug delivery systems. These hybrid technologies combine the advantages of multiple enhancement strategies and are increasingly being explored for personalized medicine, vaccine delivery, and targeted treatment of chronic diseases **[72]**.

Overall, permeation enhancement technologies have transformed TDDS from systems suitable only for small lipophilic molecules into versatile platforms capable of delivering complex biologics and advanced therapeutics. Continued integration of nanotechnology, biomedical engineering, and smart wearable devices is expected to further improve transdermal drug delivery, enabling safer, more effective, and patient-centered therapies **[73]**.

Table 4. Comparison of Major Permeation Enhancement Strategies

Strategy	Mechanism	Advantages	Limitations	Representative Applications
Chemical Enhancers	Lipid disruption, hydration, partition enhancement	Simple, economical	Skin irritation	NSAIDs, hormones
Iontophoresis	Electrical current	Controlled delivery	Device required	Lidocaine, peptides
Sonophoresis	Ultrasound-induced cavitation	Non-invasive	Equipment cost	Analgesics, anti-inflammatory drugs
Electroporation	Transient aqueous pores	Large molecule delivery	Patient discomfort	DNA vaccines, proteins
Microneedles	Microchannel formation	Painless, highly efficient	Manufacturing complexity	Vaccines, insulin, biologics
Nanocarriers	Enhanced	Improved	Formulation	Hydrophobic and
	penetration and controlled release	stability and targeting	complexity	macromolecular drugs

8. Nanocarrier-Based Transdermal Drug Delivery Systems



Nanotechnology has revolutionized transdermal drug delivery by overcoming the limitations of conventional formulations, particularly poor skin permeability, low drug loading, instability of bioactive molecules, and restricted delivery of hydrophilic compounds and macromolecules. Nanocarriers, typically ranging from **10–1000 nm**, possess a high surface-area-to-volume ratio, tunable physicochemical properties, and the ability to interact closely with the skin barrier, thereby improving drug permeation, controlled release, and therapeutic efficacy. In addition, these systems enhance drug stability, reduce systemic toxicity, and facilitate targeted delivery, making them attractive platforms for both topical and systemic drug administration **[74,75]**.

8.1 Liposomes

Liposomes are phospholipid vesicles composed of one or more lipid bilayers surrounding an aqueous core. Their amphiphilic structure enables encapsulation of both hydrophilic and lipophilic drugs. Liposomes improve transdermal delivery primarily by hydrating the stratum corneum, interacting with epidermal lipids, and enhancing drug partitioning into the skin. Although conventional liposomes generally exhibit limited penetration into deeper skin layers, they remain valuable carriers for topical and localized drug delivery because of their excellent biocompatibility and low toxicity **[76]**.

8.2 Transfersomes and Ethosomes

Transfersomes are highly deformable lipid vesicles containing phospholipids and edge activators that enable them to squeeze through narrow intercellular spaces significantly smaller than their own diameter. This unique deformability results in superior skin penetration and efficient delivery of peptides, proteins, and anti-inflammatory drugs **[77]**.

Ethosomes are ethanol-rich phospholipid vesicles in which ethanol fluidizes both vesicular and skin lipids, markedly enhancing drug permeation. Their superior penetration capability has made ethosomes particularly useful for dermal and transdermal delivery of antifungal, antiviral, anti-inflammatory, and cosmetic agents **[78]**.

8.3 Lipid Nanocarriers

Solid lipid nanoparticles (SLNs) consist of physiological solid lipids that remain solid at body temperature. They provide controlled drug release, protection of unstable drugs, enhanced skin hydration, and improved biocompatibility. However, their highly ordered crystalline structure may restrict drug loading and promote drug expulsion during storage **[79]**.

To overcome these limitations, **nanostructured lipid carriers (NLCs)** combine solid and liquid lipids, creating an imperfect lipid matrix that accommodates greater amounts of drug while reducing drug leakage. Consequently, NLCs exhibit higher encapsulation efficiency, improved stability, prolonged release, and enhanced skin penetration compared with SLNs **[80]**.

8.4 Polymeric Nanoparticles

Polymeric nanoparticles prepared from biodegradable polymers such as PLGA, chitosan, polycaprolactone, and alginate provide sustained drug release, improved protection of labile molecules, and opportunities for surface modification and targeted delivery. Their versatility has facilitated the transdermal administration of anti-inflammatory agents, anticancer drugs, antimicrobial compounds, peptides, and gene therapeutics. Surface functionalization with ligands or stimuli-responsive polymers further enhances therapeutic specificity and controlled drug release **[81]**.

8.5 Nanoemulsions and Dendrimers

Nanoemulsions are kinetically stable colloidal systems composed of nanosized oil droplets dispersed within an aqueous phase using surfactants. Their large interfacial surface area increases drug solubilization, enhances skin hydration, and promotes rapid drug permeation, making them particularly suitable for poorly water-soluble drugs **[82]**.

Dendrimers are highly branched, monodisperse polymeric macromolecules with multiple surface functional groups that facilitate high drug loading, controlled release, and targeted delivery. Their well-defined architecture and ease of chemical modification make them promising carriers for transdermal gene delivery and advanced therapeutic applications, although concerns regarding synthesis complexity and potential toxicity remain under investigation **[83]**.

8.6 Recent Advances and Future Prospects

Current research increasingly focuses on **hybrid nanocarrier systems**, including nanoparticle-loaded microneedles, nanogels, stimuli-responsive nanocarriers, and biosensor-integrated smart transdermal patches. These platforms enable site-specific delivery, real-time therapeutic monitoring, and personalized drug administration. Advances in nanomedicine, artificial intelligence, and wearable biomedical devices are expected to further enhance the clinical utility of nanocarrier-based TDDS, particularly for chronic diseases, vaccination, precision medicine, and biologic therapeutics **[84,85]**.

Overall, nanocarrier-based formulations have significantly expanded the capabilities of transdermal drug delivery by improving drug permeation, stability, controlled release, and therapeutic targeting. Continued optimization of carrier composition, manufacturing methods, and regulatory standardization will facilitate their successful translation from laboratory research to routine clinical practice.

Table 5. Comparison of Major Nanocarrier Systems Used in TDDS

Nanocarrier	Major Composition	Principal Advantages	Limitations	Representative Applications
Liposomes	Phospholipid bilayers	Biocompatible, dual drug loading	Limited deep penetration	Topical anti-inflammatory drugs
Transfersomes	Phospholipids + edge activators	Excellent deformability and penetration	Higher formulation cost	Peptides, insulin
Ethosomes	Phospholipids	Superior skin	Ethanol-related irritation	Antifungal,

	+ ethanol	permeation		antiviral drugs
SLNs	Solid lipids	Controlled release, high stability	Limited drug loading	NSAIDs, corticosteroids
NLCs	Solid + liquid lipids	High encapsulation efficiency	Complex formulation	Curcumin, ketoprofen
Polymeric nanoparticles	PLGA, chitosan, PCL	Sustained release, targeted delivery	Polymer processing complexity	Anticancer and peptide drugs
Nanoemulsions	Oil, surfactant, water	Improved solubility and rapid penetration	Thermodynamic instability	Hydrophobic drugs
Dendrimers	Branched polymers	High drug loading, surface modification	High synthesis cost	Gene and peptide delivery

9. Therapeutic Applications of Transdermal Drug Delivery Systems

Transdermal drug delivery systems (TDDS) have evolved from simple patch-based formulations to advanced therapeutic platforms capable of delivering a wide range of pharmaceuticals. Their ability to provide sustained drug release, avoid hepatic first-pass metabolism, improve patient compliance, and maintain stable plasma drug concentrations has resulted in successful clinical applications across several therapeutic areas **[86]**.

Pain management remains one of the most established applications of TDDS. Transdermal formulations of fentanyl, buprenorphine, diclofenac, ketoprofen, and lidocaine provide prolonged analgesic effects while reducing gastrointestinal adverse events associated with oral non-steroidal anti-inflammatory drugs (NSAIDs). Controlled drug release also minimizes dosing frequency and improves treatment adherence in patients with chronic pain **[87]**.

In cardiovascular therapy, transdermal patches containing nitroglycerin and clonidine are routinely employed for the management of angina pectoris and hypertension, respectively. These formulations maintain consistent plasma concentrations and reduce fluctuations commonly associated with conventional dosage forms **[88]**.

Hormonal therapies constitute another major application of TDDS. Transdermal delivery of estradiol, testosterone, and contraceptive hormones improves bioavailability while reducing hepatic metabolism and gastrointestinal intolerance. Similarly, nicotine patches remain one of the most successful examples of transdermal therapy for smoking cessation because they provide sustained nicotine release and reduce withdrawal symptoms **[89]**.

Recent technological advances have considerably expanded the scope of TDDS for neurological disorders. Rivastigmine and rotigotine transdermal patches have demonstrated clinical effectiveness in Alzheimer's disease and Parkinson's disease by providing continuous drug delivery and reducing dosing frequency. In addition, nanocarrier-based and microneedle-assisted systems are being investigated for the transdermal administration of peptides, proteins, insulin, vaccines, monoclonal antibodies, and nucleic acid therapeutics, thereby overcoming the limitations of conventional passive diffusion **[90,91]**.

Transdermal formulations are also increasingly explored in dermatology, oncology, diabetes management, vaccination, and localized anti-inflammatory therapy. Integration of nanotechnology, biosensors, and wearable electronics has further enabled stimulus-responsive drug release and personalized treatment approaches. These advances are expected to broaden the therapeutic applications of TDDS in precision medicine and chronic disease management **[92]**.

Overall, the combination of improved patient compliance, controlled drug release, enhanced safety, and continuous technological innovation has established TDDS as one of the most versatile and rapidly expanding drug delivery platforms in modern pharmaceutical research.

Table 6. Representative Therapeutic Applications of TDDS

Therapeutic Area	Representative Drugs	Clinical Benefits
Pain management	Fentanyl, Buprenorphine, Lidocaine	Sustained analgesia, reduced GI toxicity
Cardiovascular disorders	Nitroglycerin, Clonidine	Stable plasma concentrations
Hormone replacement	Estradiol, Testosterone	Improved bioavailability

Smoking cessation	Nicotine	Reduced withdrawal symptoms
Neurological disorders	Rivastigmine, Rotigotine	Continuous drug delivery
Diabetes & Biologics	Insulin (investigational)	Improved patient compliance
Vaccination	Peptide and DNA vaccines	Needle-free administration
Dermatology	Diclofenac, Corticosteroids	Localized therapy with fewer systemic effects

10. Commercially Available Transdermal Products

The commercial success of transdermal drug delivery systems (TDDS) demonstrates their clinical utility and patient acceptability. Since the approval of the first transdermal scopolamine patch in 1979, numerous products have been developed for the management of chronic diseases requiring sustained and controlled drug delivery. Commercial transdermal formulations provide several therapeutic advantages, including maintenance of consistent plasma drug concentrations, reduced dosing frequency, improved patient compliance, avoidance of first-pass metabolism, and rapid termination of therapy by patch removal **[93]**.

Currently marketed transdermal products are primarily used for pain management, cardiovascular disorders, hormone replacement therapy, smoking cessation, neurological diseases, and contraception. Continuous advancements in formulation technology, adhesive materials, and permeation enhancement strategies have further improved their safety, efficacy, and patient convenience. More recently, microneedle-assisted systems and nanocarrier-based formulations have entered clinical evaluation, with several products progressing through late-stage clinical trials for biologics, vaccines, and peptide therapeutics **[94,95]**.

The continued expansion of commercial TDDS reflects increasing confidence in transdermal delivery as a reliable alternative to oral and injectable dosage forms. Future commercialization is expected to focus on smart wearable systems capable of integrating biosensors, controlled drug release, and real-time therapeutic monitoring to support personalized medicine **[96]**.

Table 7. Representative Commercially Available Transdermal Products

Drug	Brand/Example	Therapeutic Indication
Scopolamine	Transderm Scōp®	Motion sickness
Nitroglycerin	Nitro-Dur®	Angina pectoris
Clonidine	Catapres-TTS®	Hypertension
Fentanyl	Duragesic®	Chronic pain
Buprenorphine	Butrans®	Chronic pain
Nicotine	Nicoderm CQ®	Smoking cessation
Estradiol	Climara®	Hormone replacement therapy
Rivastigmine	Exelon Patch®	Alzheimer's disease
Rotigotine	Neupro®	Parkinson's disease

11. Challenges, Regulatory Considerations and Future Perspectives

Despite remarkable progress in transdermal drug delivery systems (TDDS), several scientific, technological, and regulatory challenges continue to limit their broader clinical application. The highly organized structure of the stratum corneum remains the principal obstacle to efficient drug permeation, restricting passive delivery primarily to potent, low-molecular-weight, moderately lipophilic compounds. Delivery of peptides, proteins, nucleic acids, and other biologics still requires advanced permeation enhancement techniques or specialized carrier systems **[97]**.

From a formulation perspective, achieving adequate drug loading, long-term physicochemical stability, controlled release, and reproducible manufacturing remains challenging, particularly for nanocarrier-based and microneedle-assisted systems. Large-scale manufacturing, sterilization, storage stability, and cost-effectiveness are additional factors influencing successful commercialization. Furthermore, variability in skin physiology due to age, disease, anatomical site, ethnicity, and environmental conditions may result in inconsistent drug absorption and therapeutic response **[98]**.

Safety remains a major consideration for advanced TDDS. Chemical permeation enhancers may cause irritation or sensitization following prolonged exposure, whereas physical enhancement techniques require careful optimization to avoid excessive barrier disruption or patient discomfort. Comprehensive evaluation of skin irritation, sensitization, systemic toxicity, and long-term biocompatibility is therefore essential during product development **[99]**.

Regulatory agencies require extensive evidence of pharmaceutical quality, safety, efficacy, manufacturing consistency, and clinical performance before approval of

transdermal formulations. Standardized characterization methods, validated in vitro–in vivo correlation models, and harmonized regulatory guidelines will facilitate the translation of emerging nanotechnology-based systems into routine clinical practice **[100]**.

Future research is expected to focus on multifunctional transdermal platforms integrating nanotechnology, microneedles, biosensors, artificial intelligence, and wearable electronics. These technologies will enable real-time physiological monitoring, stimulus-responsive drug release, and individualized dosing, thereby supporting precision medicine. Hybrid systems combining nanocarriers with physical enhancement techniques are also expected to improve the delivery of vaccines, gene therapeutics, monoclonal antibodies, and other complex biological agents. Continued collaboration among pharmaceutical scientists, biomedical engineers, clinicians, and regulatory authorities will be essential for overcoming current limitations and accelerating the clinical translation of next-generation TDDS **[101,102]**.

12. Conclusion:

Transdermal drug delivery systems (TDDS) have evolved into versatile pharmaceutical platforms capable of overcoming several limitations associated with conventional oral and parenteral drug administration. Advances in skin permeation enhancement, biomaterials, nanotechnology, and biomedical engineering have significantly broadened the range of therapeutic agents that can be delivered through the skin. Modern approaches, including chemical and physical enhancement techniques, microneedles, lipid-based nanocarriers, polymeric nanoparticles, and smart wearable devices, have improved drug permeation, controlled release, therapeutic efficacy, and patient compliance. These innovations have also facilitated the transdermal delivery of biologics, peptides, vaccines, and nucleic acid therapeutics that were previously unsuitable for this route.

Despite these advances, challenges related to skin barrier variability, formulation stability, large-scale manufacturing, regulatory approval, and long-term safety remain important considerations for successful clinical translation. Continued interdisciplinary research integrating pharmaceutical sciences, nanomedicine, biomaterials, wearable electronics, and artificial intelligence is expected to accelerate the development of next-generation personalized transdermal therapies. Overall, TDDS represents a rapidly advancing drug delivery platform with considerable potential to improve therapeutic outcomes, enhance patient adherence, and contribute significantly to the future of precision medicine and advanced healthcare **[103–105]**.

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