Recent Advances in Transdermal Drug Delivery Systems: Strategies for Controlled Release, Skin Permeation Enhancement, and Targeted Therapeutic Applications in Modern Pharmaceutical Sciences

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Abstract
Transdermal drug delivery systems (TDDS) represent a clinically significant non-invasive route for systemic drug administration, offering distinct pharmacokinetic advantages over conventional oral and parenteral formulations. By delivering active pharmaceutical ingredients across the skin and into the systemic circulation, TDDS circumvents hepatic first-pass metabolism, reduces gastrointestinal adverse effects, and facilitates predictable, sustained plasma drug concentrations. This review aims to provide a concise yet comprehensive appraisal of contemporary advances in transdermal technologies, spanning conventional patch systems, microneedle-based delivery platforms, nanotechnology-driven carriers, and bioresponsive stimuli-sensitive systems. Major technological developments discussed include chemical and physical skin permeation enhancement strategies—such as iontophoresis, sonophoresis, and electroporation—as well as nanocarrier-mediated transport via liposomes, nanostructured lipid carriers (NLCs), transfersomes, and polymeric nanoparticles. Therapeutic applications encompassing pain management, hormonal therapy, cardiovascular pharmacology, neurological conditions, and transdermal vaccine delivery are critically evaluated. The review also identifies persistent clinical and regulatory challenges, including the inherent impermeability of the stratum corneum, constraints on drug physicochemical properties, skin sensitisation risks, and the regulatory complexity surrounding novel enhancement technologies. Emerging innovations such as dissolving microneedles, smart hydrogels, 3D-printed patches, and wearable biosensor-integrated delivery platforms are highlighted as transformative future directions. In conclusion, TDDS hold immense potential for expanding the repertoire of deliverable therapeutics and improving patient-centric outcomes across diverse clinical indications.

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1. Introduction

Transdermal drug delivery systems (TDDS) have emerged as a compelling alternative to traditional routes of drug administration, offering a unique combination of systemic efficacy and patient convenience. Oral delivery, despite its widespread use, is frequently compromised by hepatic first-pass metabolism, gastrointestinal enzymatic degradation, and variable bioavailability. Injectable formulations, while bypassing these barriers, are associated with needle phobia, infection risk, and the requirement for clinical administration [1, 2].

TDDS overcome many of these limitations by exploiting the skin as an accessible, large-surface-area route for drug permeation into the systemic circulation.

The skin, with a total surface area of approximately 1.8 m2 in adults, provides an ideal interface for non-invasive drug delivery [3]. However, its principal barrier function—particularly the outermost stratum corneum—remains the central challenge in transdermal formulation development. The stratum corneum, a 10–20 μm lipid-protein matrix, restricts permeation to predominantly lipophilic, low-molecular-weight compounds (<500 Da), thereby limiting the range of drugs suitable for transdermal delivery without enhancement strategies [4, 5].

Despite these barriers, significant advancements over the past two decades have expanded the clinical applicability of TDDS. The integration of nanotechnology, physical enhancement methodologies, and smart responsive materials has enabled delivery of hydrophilic drugs, macromolecules, and biological therapeutics that were previously incompatible with passive transdermal systems [6, 7]. This review provides a focused analysis of current TDDS technologies, enhancement strategies, controlled release mechanisms, therapeutic applications, and future innovations, aiming to offer pharmaceutical scientists and clinicians a concise yet authoritative reference.

2. Transdermal Drug Delivery Systems

2.1. Transdermal Patches

Transdermal patches represent the most commercially advanced form of TDDS and are broadly classified into reservoir, matrix, and drug-in-adhesive configurations. Reservoir patches contain drug dissolved or suspended in a liquid vehicle, separated from skin by a rate-controlling membrane that governs flux [8]. Matrix patches incorporate drug within a polymer matrix from which release is governed by diffusion. Drug-in-adhesive systems, the most compact design, embed active drug directly within the pressure-sensitive adhesive layer, eliminating membrane complexity [9].

Approved transdermal patch formulations include fentanyl for chronic pain, nitroglycerin for angina pectoris, scopolamine for motion sickness, estradiol and combined hormonal patches for menopausal therapy, nicotine patches for smoking cessation, and rivastigmine for Alzheimer's disease [10]. These systems exemplify the clinical maturity of patch-based TDDS and serve as benchmarks for emerging platform technologies (Table 1).

Table 1: Types of Transdermal Drug Delivery Systems and Their Pharmaceutical Applications

TDDS Type	Examples	Pharmaceutical Applications	Key Drugs Delivered
Transdermal Patches	Matrix, reservoir, drug-in-adhesive	Hormonal therapy, pain, CVD	Fentanyl, nitroglycerin, estradiol
Microneedle Arrays	Solid, hollow, dissolving, coated	Vaccines, insulin, biologics	Insulin, influenza vaccine, parathyroid hormone
Nanoparticle Systems	Liposomes, NLCs, solid lipid NPs	Dermatology, oncology, anti-inflammatory	Diclofenac, minoxidil, tretinoin
Gels and Emulsions	Nanoemulsions, microemulsions, hydrogels	Musculoskeletal, dermatological	Testosterone gel, diclofenac gel
Transfersomes / Ethosomes	Elastic vesicles, ethanol-based carriers	Anti-fungal, anti-viral, anti-aging	Acyclovir, ketoconazole, caffeine
Iontophoretic Systems	Electromotive drug delivery devices	Chronic pain, hyperhidrosis	Lidocaine, fentanyl, pilocarpine

NLCs = Nanostructured Lipid Carriers; CVD = Cardiovascular Disease; NPs = Nanoparticles.

2.2. Microneedle-Based Delivery Systems

Microneedles (MNs) are micro-scale projections (25–2000 μm in height) that create transient aqueous microchannels in the skin, bypassing the stratum corneum without stimulating pain-sensing nerve fibres [11]. Four principal configurations exist: solid MNs (used as pre-treatment to enhance passive flux), hollow MNs (enabling direct drug infusion through the bore), coated MNs (with drug deposited on needle surfaces), and dissolving MNs (fabricated from water-soluble polymers that encapsulate drug and dissolve upon insertion) [12, 13].

Dissolving MNs have attracted particular clinical interest, fabricated from materials such as poly(vinyl alcohol) (PVA), hyaluronic acid, and chitosan, enabling complete transdermal drug deposition without residual sharp waste [14]. Clinical studies have demonstrated effective delivery of insulin, erythropoietin, and influenza vaccines via MN arrays, with bioavailability comparable to subcutaneous injection [15]. The MICRONJET400 and NanoPass devices represent commercially validated MN platforms with demonstrated immunogenicity for vaccine delivery [16].

2.3. Nanotechnology-Based Transdermal Systems

Nanocarrier systems offer versatile platforms to overcome skin permeation limitations by virtue of their nanoscale dimensions, tunable surface chemistry, and capacity to encapsulate both hydrophilic and lipophilic drugs [17]. Liposomes—phospholipid bilayer vesicles—were among the earliest nanocarriers investigated for transdermal delivery; however, conventional liposomes demonstrated limited skin penetration due to vesicle rigidity [18]. Subsequent developments led to elastic vesicles (transfersomes) and ethanol-containing vesicles (ethosomes), which demonstrate substantially enhanced deformability, enabling penetration into deeper skin strata [19].

Nanostructured lipid carriers (NLCs) and solid lipid nanoparticles (SLNs) offer enhanced drug encapsulation efficiency, improved physicochemical stability, and prolonged drug release compared to liposomes [20]. Polymeric nanoparticles fabricated from poly(lactic-co-glycolic acid) (PLGA) and polyethylene glycol (PEG)-based materials provide additional tunability in surface modification and stimuli-responsive release [21].

3. Skin Permeation Enhancement Strategies

3.1. Chemical Permeation Enhancers

Chemical permeation enhancers (CPEs) are compounds that transiently and reversibly disrupt the lipid organisation of the stratum corneum, thereby reducing barrier resistance to drug permeation. Commonly employed CPEs include fatty acids (oleic acid), alcohols (ethanol, propylene glycol), surfactants

(sodium lauryl sulphate), terpenes (menthol, eucalyptol), and bile salts [22]. Oleic acid is particularly well-characterised, intercalating into stratum corneum lipid lamellae and creating fluid domains that enhance drug diffusion [23].

CPE selection requires careful optimisation to balance permeation enhancement against skin irritation potential. Binary and ternary CPE combinations frequently exhibit synergistic effects at lower individual concentrations, reducing toxicity while maintaining efficacy. Computational predictive models and quantitative structure-permeability relationship (QSPR) analyses are increasingly employed to rationally identify and screen candidate CPEs [24].

3.2. Physical Enhancement Techniques

Physical techniques offer mechanistic and spatiotemporally controlled enhancement of transdermal drug permeation. Iontophoresis employs a mild electric current (0.5 mA/cm2) to drive ionised drugs across the skin via electrophoresis and electroosmosis, demonstrating particular efficacy for hydrophilic and charged molecules [25]. Sonophoresis (ultrasound-mediated delivery) uses acoustic cavitation and oscillation to disrupt the stratum corneum bilayer architecture temporarily [26]. Electroporation applies brief, high-voltage electrical pulses to create transient aqueous pores in the lipid bilayer, enabling delivery of macromolecules. Laser ablation and radiofrequency ablation additionally create microchannels in the skin surface, facilitating enhanced permeation of biologics including proteins and oligonucleotides [27].

3.3. Nanocarrier-Mediated Permeation

Nanocarriers enhance transdermal permeation through multiple mechanisms: reduction in particle size to sub-200 nm dimensions favouring follicular penetration, lipid-bilayer fusion with skin lipids (particularly liposomes and NLCs), and the reservoir effect that sustains localised drug concentration gradients. Surface modification with cell-penetrating peptides (CPPs) and hyaluronic acid ligands further promotes receptor-mediated internalisation in keratinocytes and follicular epithelium [28]. These strategies are particularly relevant for macromolecular drugs and biologics that cannot permeate via passive or conventional CPE-assisted pathways.

4. Controlled and Sustained Drug Release Mechanisms

4.1. Diffusion-Controlled Release

Diffusion-controlled release remains the foundational mechanism in reservoir and matrix transdermal systems, governed by Fick's first and second laws of diffusion. In membrane-controlled reservoir systems, the rate-limiting step is drug permeation across the semi-permeable membrane, yielding zero-order kinetics and a constant plasma concentration profile over the patch application period [29]. Matrix systems typically exhibit square-root-of-time (Higuchi) release kinetics, where drug flux declines progressively as the diffusion path length increases.

4.2. Polymer-Based Controlled Delivery

Hydrophilic polymers including hydroxypropyl methylcellulose (HPMC), polyvinyl pyrrolidone (PVP), and Eudragit® copolymers are extensively employed in transdermal matrix formulations to modulate drug release rates. Crosslinked hydrogel networks swell upon hydration, providing sustained drug diffusion and improved mechanical adherence to skin surfaces. Polyurethane and polyacrylate-based pressure-sensitive adhesives serve dual roles as drug vehicles and skin adhesion matrices in modern drug-in-adhesive patch designs [9].

4.3. Smart and Stimuli-Responsive Systems

Stimuli-responsive TDDS represent a paradigm shift toward personalised and on-demand drug delivery. pH-responsive hydrogels trigger drug release in response to local microenvironmental pH changes. Thermoresponsive systems based on poly(N-isopropylacrylamide) (PNIPAM) release drug above their lower critical solution temperature. Photo-responsive azobenzene-conjugated systems and glucose-responsive insulin delivery platforms—employing glucose oxidase enzyme sensors coupled to poly(phenylboronic acid) hydrogels—exemplify the frontiers of intelligent TDDS design for conditions such as diabetes mellitus [30].

5. Therapeutic Applications

5.1. Pain Management and Hormonal Therapy

Pain management represents the largest commercial segment of TDDS, with fentanyl matrix and reservoir patches (Duragesic®) remaining the standard of care for moderate-to-severe chronic pain. Buprenorphine patches (Butrans®, BuTrans®) provide seven-day sustained opioid analgesia. Lidocaine-impregnated patches (Lidoderm®) are FDA-approved for postherpetic neuralgia [10]. In hormonal therapy, estradiol, estradiol-norethisterone, and combined contraceptive patches demonstrate superior pharmacokinetic profiles compared to oral formulations, with significant reductions in peak-to-trough plasma concentration variability [3].

5.2. Cardiovascular and Neurological Drugs

Nitroglycerin transdermal patches for angina pectoris were among the first approved TDDS products and retain clinical utility. Clonidine patches provide once-weekly antihypertensive therapy with improved compliance in hypertensive patients. In neurology, rivastigmine (Exelon® patch) delivers consistent cholinesterase inhibition for Alzheimer's and Parkinson's disease dementia, with a substantially lower incidence of gastrointestinal adverse effects compared to oral capsules [7]. Rotigotine patches (Neupro®) provide continuous dopaminergic stimulation for Parkinson's disease management, highlighting the therapeutic advantage of uninterrupted systemic delivery.

5.3. Vaccines and Biologics Delivery

Transdermal vaccine delivery via microneedle platforms has gained substantial momentum, driven by the desire for needle-free immunisation programmes that improve coverage and cold-chain independence. Dissolving MN patches loaded with influenza, measles, and hepatitis B antigens have demonstrated immunogenicity comparable to intramuscular injection in murine and human clinical studies [15, 16]. The dermal immune cell population—rich in Langerhans cells and dermal dendritic cells—confers immunological advantages for cutaneous antigen presentation. Peptide-based and mRNA-loaded lipid nanoparticle systems for transdermal vaccine delivery are currently under preclinical evaluation, representing a convergence of nanotechnology and transdermal immunology [21].

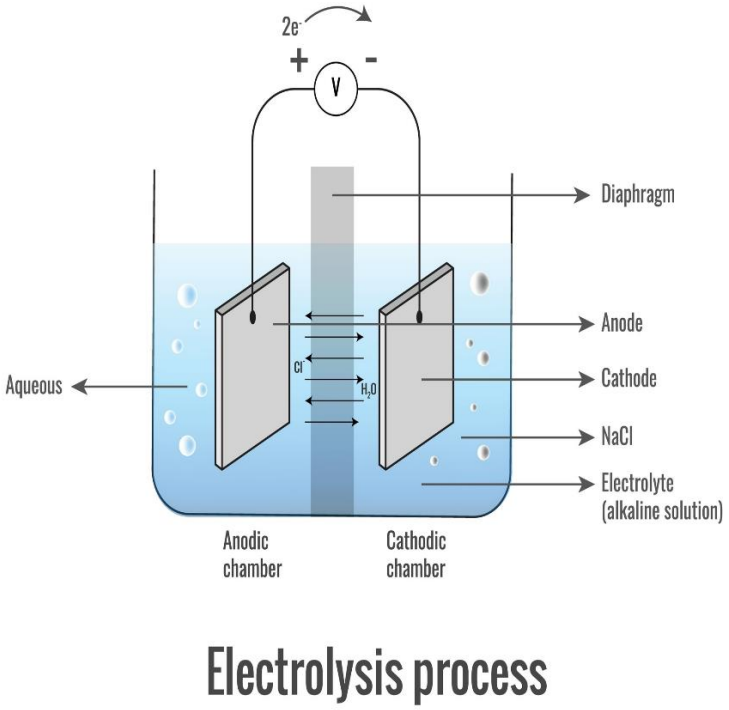

Fig 1: Overview of Transdermal Drug Delivery Technologies and Enhancement Strategies

Table 2: Advantages and Limitations of Transdermal Drug Delivery Systems

Advantages	Limitations
Avoids first-pass hepatic metabolism	Stratum corneum acts as major permeation barrier
Non-invasive and painless administration	Limited to potent, low-molecular-weight drugs (<500 Da)
Sustained and controlled drug release	Potential skin irritation or sensitisation
Improved patient compliance and adherence	Drug loading capacity is relatively low
Predictable and steady plasma drug levels	Inter-individual variability in skin permeability
Reduced GI side effects	Slow onset of action compared to IV/oral routes
Termination of therapy possible by patch removal	Regulatory complexity for novel enhancement technologies

GI = Gastrointestinal; IV = Intravenous; Da = Daltons.

6. Challenges and Future Perspectives

Despite remarkable technological progress, several challenges continue to constrain the broader clinical application of TDDS. The stratum corneum remains the primary pharmacokinetic bottleneck, fundamentally restricting passive transdermal delivery to highly lipophilic, low-molecular-weight drugs with a favourable partition coefficient (log P 1–3) and melting point below 200°C [4]. The molecular weight threshold of approximately 500 Da excludes the vast majority of proteins, peptides, oligonucleotides, and large-molecule biologics from conventional passive delivery. Additionally, drug loading capacity in patches remains limited relative to oral or parenteral formulations, restricting TDDS to pharmacologically potent drugs.

Skin irritation, sensitisation, and contact dermatitis—particularly associated with chemical permeation enhancers and pressure-sensitive adhesives—represent clinically significant safety concerns requiring comprehensive dermatotoxicological evaluation [24]. Inter-individual variability in skin permeability, arising from differences in skin age, hydration status, disease states (psoriasis, eczema), and anatomical site, introduces pharmacokinetic variability that complicates dose standardisation.

Regulatory pathways for novel TDDS technologies—particularly MN arrays, active physical enhancement devices, and biologics-loaded nanocarriers—remain complex and jurisdiction-specific, with limited harmonised international guidance [13]. The convergence of TDDS with wearable biosensors, closed-loop feedback systems, and additive manufacturing (3D printing) offers transformative future potential. Three-dimensionally printed personalised transdermal patches with patient-specific drug loading, dissolving MN systems for painless insulin delivery in diabetes, and biodegradable polymer-based smart hydrogel patches responsive to glucose or cortisol represent near-future clinical innovations [30]. These developments necessitate continued interdisciplinary collaboration between pharmaceutical scientists, biomedical engineers, clinicians, and regulatory bodies.

7. Conclusion

Transdermal drug delivery systems represent a scientifically rich and clinically impactful domain within pharmaceutical sciences, offering significant advantages in terms of non-invasive systemic drug delivery, controlled pharmacokinetics, and enhanced patient compliance. Advances in microneedle fabrication, nanocarrier engineering, stimuli-responsive polymer design, and physical enhancement technologies have substantially expanded the therapeutic scope of TDDS beyond the classical small-molecule patch paradigm. Contemporary research demonstrates the feasibility of delivering biologics, vaccines, and macromolecular drugs via the skin—a frontier that was

conceptually beyond reach two decades ago. Addressing the outstanding challenges of the stratum corneum barrier, drug loading constraints, skin biocompatibility, and regulatory harmonisation will be decisive for the continued evolution and clinical translation of next-generation TDDS. The integration of intelligent delivery platforms with digital health technologies and personalised medicine approaches heralds a new era of precision transdermal therapeutics with far-reaching implications for global healthcare.

References

1. Prausnitz MR, Langer R. Transdermal drug delivery. Nat Biotechnol. 2008;26(11):1261–8.
2. Paudel KS, Milewski M, Swadley CL, Brogden NK, Ghosh P, Stinchcomb AL. Challenges and opportunities in dermal/transdermal delivery. Ther Deliv. 2010;1(1):109–31.
3. Wiedersberg S, Guy RH. Transdermal drug delivery: 30+ years of war and still fighting! J Control Release. 2014;190:150–6.
4. Bos JD, Meinardi MM. The 500 Dalton rule for the skin penetration of chemical compounds and drugs. Exp Dermatol. 2000;9(3):165–9.
5. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2004;56(5):603–18.
6. Karande P, Mitragotri S. Enhancement of transdermal drug delivery via synergistic action of chemicals. Biochim Biophys Acta. 2009;1788(11):2362–73.
7. Benson HAE, Watkinson AC, editors. Transdermal and Topical Drug Delivery: Principles and Practice. Hoboken: Wiley; 2012.
8. Hadgraft J, Lane ME. Passive transdermal drug delivery systems: new advances and opportunities. Int J Pharm. 2016;514(1):52–7.
9. Wokovich AM, Prodduturi S, Doub WH, Hussain AS, Buhse LF. Transdermal drug delivery system (TDDS) adhesion as a critical safety, efficacy and quality attribute. Eur J Pharm Biopharm. 2006;64(1):1–8.
10. Pastore MN, Kalia YN, Horstmann M, Roberts MS. Transdermal patches: history, development and pharmacology. Br J Pharmacol. 2015;172(9):2179–209.
11. Prausnitz MR. Microneedles for transdermal drug delivery. Adv Drug Deliv Rev. 2004;56(5):581–7.
12. Ita K. Dissolving microneedles for transdermal drug delivery: advances and challenges. Biomed Pharmacother. 2017;93:1116–27.
13. Larrañeta E, Lutton REM, Woolfson AD, Donnelly RF. Microneedle arrays as transdermal and intradermal drug delivery systems: materials science, manufacture and commercial development. Mater Sci Eng R Rep. 2016;104:1–32.
14. Donnelly RF, Singh TR, Woolfson AD. Microneedle-based drug delivery systems: microfabrication, drug delivery, and safety. Drug Deliv. 2010;17(4):187–207.
15. Sullivan SP, Koutsonanos DG, Del Pilar Martin M, Lee JW, Zarnitsyn V, Choi SO, *et al*. Dissolving polymer microneedle patches for influenza vaccination. Nat Med. 2010;16(8):915–20.
16. Kim YC, Park JH, Prausnitz MR. Microneedles for drug and vaccine delivery. Adv Drug Deliv Rev. 2012;64(14):1547–68.
17. Prow TW, Grice JE, Lin LL, Faye R, Butler M, Becker W, *et al*. Nanoparticles and microparticles for skin drug delivery. Adv Drug Deliv Rev. 2011;63(6):470–91.
18. Elsayed MM, Abdallah OY, Naggar VF, Khalafallah NM. Lipid vesicles for skin delivery of drugs: reviewing three decades of research. Int J Pharm. 2007;332(1–2):1–16.
19. Cevc G. Transfersomes, liposomes and other lipid suspensions on the skin: permeation enhancement, vesicle penetration and transdermal drug delivery. Crit Rev Ther Drug Carrier Syst. 1996;13(3–4):257–388.
20. Müller RH, Radtke M, Wissing SA. Solid lipid nanoparticles (SLN) and nanostructured lipid carriers (NLC) in cosmetic and dermatological preparations. Adv Drug Deliv Rev. 2002;54(Suppl 1):S131–55.
21. Patel A, Cholkar K, Agrahari V, Mitra AK. Ocular drug delivery systems: an overview. World J Pharmacol. 2013;2(2):47–64.
22. Barry BW. Novel mechanisms and devices to enable successful transdermal drug delivery. Eur J Pharm Sci. 2001;14(2):101–14.
23. Ghosh TK, Pfister WR, Yum SI, editors. Transdermal and Topical Drug Delivery Systems. Buffalo Grove: Interpharm Press; 1997.
24. Magnusson BM, Walters KA, Roberts MS. Veterinary drug delivery: potential for skin penetration enhancement. Adv Drug Deliv Rev. 2001;50(3):205–27.
25. Kalia YN, Naik A, Garrison J, Guy RH. Iontophoretic drug delivery. Adv Drug Deliv Rev. 2004;56(5):619–58.
26. Mitragotri S, Blankschtein D, Langer R. Ultrasound-mediated transdermal protein delivery. Science. 1995;269(5225):850–3.
27. Denet AR, Vanbever R, Préat V. Skin electroporation for transdermal and topical delivery. Adv Drug Deliv Rev. 2004;56(5):659–74.
28. Nasrollahi SA, Taghibiglou C, Azizi E, Farboud ES. Cell-penetrating peptides as a novel transdermal drug delivery system. Chem Biol Drug Des. 2012;80(5):639–46.
29. Guy RH, Hadgraft J. Transdermal Drug Delivery. 2nd ed. New York: Marcel Dekker; 2003.
30. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nat Mater. 2013;12(11):991–1003.