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TRANSDERMAL DRUG DELIVERY SYSTEMS: A CONCISE REVIEW OF DESIGN, COMPONENTS, EVALUATION AND EMERGING TECHNOLOGIES

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ABSTRACT

A proven, non-invasive method of delivering pharmaceuticals through the skin and into the bloodstream is provided by transdermal drug delivery devices (TDDS). In addition to vesicular carriers (liposomes, niosomes, and transfersomes) created to increase the permeability of hydrophilic medications and macromolecules, patch design has evolved to reservoir, matrix, drug-in-adhesive, and micro-reservoir kinds since the first patch (scopolamine) was approved in 1979. The fundamental obstacle is still the lipoidal "bricks-and-mortar" structure of the stratum corneum, which typically prevents passive delivery of strong, lipophilic medications below about 500 Da. The range of deliverable pharmaceuticals has been expanded by the use of both active physical tactics (iontophoresis, electroporation, sonophoresis, microneedles, thermal/radiofrequency ablation, needle-free injection) and passive strategies (chemical enhancers, prodrugs, vesicular carriers). The patch adheres to the skin equally

crucial because adhesive failure jeopardizes safety and effectiveness. The anatomy of the skin and the permeation pathway, the justification for transdermal distribution, patch components and architectures, preparation and assessment techniques, adhesion testing, commercial products, and future prospects for active delivery systems are all summarized in this review.

KEYWORDS: Transdermal drug delivery system; stratum corneum; permeation enhancer; pressure-sensitive adhesive; transfersomes; iontophoresis; microneedles; patch adhesion.

1. INTRODUCTION

Approximately 70% of medications are taken orally, although this method involves gastrointestinal breakdown, first-pass hepatic metabolism, and blood level fluctuations that may result in toxicity or undertreatment. The skin provides an alternative location of administration because it is the largest accessible organ. An adhesive device known as a transdermal drug delivery system (TDDS) or "patch" allows a medication to be released through the skin at a regulated pace and dosage.

In 1979, the FDA approved the first transdermal patch for motion sickness, called Transderm-SCOP (scopolamine). In 1981, nitroglycerin was approved for angina. With billions of dollars in yearly sales, TDDSs are being sold for clonidine, estradiol, testosterone, nicotine, fentanyl, lidocaine, oxybutynin, and hormone combinations. Avoiding first-pass metabolism, stable plasma levels, simple patch removal for cessation, and increased compliance with infrequent dosage are some benefits. However, only a limited variety of medications can be used because of the stratum corneum's physicochemical limitations. Skin biology, patch technology, design and assessment, adhesion, and permeation-enhancing technologies that continue to broaden the spectrum of transdermally delivered medications are all included in this review.

2. Anatomy and Physiology of Human Skin

Human skin covers 1.5-2.0 m^2 in an adult and receives roughly one-third of total blood supply. It comprises three layers: the avascular epidermis (stratified keratinizing epithelium including keratinocytes, melanocytes, Langerhans and Merkel cells), the vascularised dermis (collagen and elastin fibres, blood vessels, nerves, follicles and glands), and the hypodermis (fatty insulating and cushioning layer). The outermost epidermal layer, the stratum corneum (SC), is a 10-20 µm non-viable layer of 15-25 layers of anucleate corneocytes embedded in a continuous lipid bilayer of ceramides, cholesterol and free fatty acids. This "bricks-and-mortar" arrangement — proteinaceous corneocytes (bricks) within multilamellar lipid bilayers (mortar) — is the rate-limiting barrier to transdermal permeation. Drug molecules that traverse the SC and viable epidermis enter systemic circulation via the dermal vasculature.

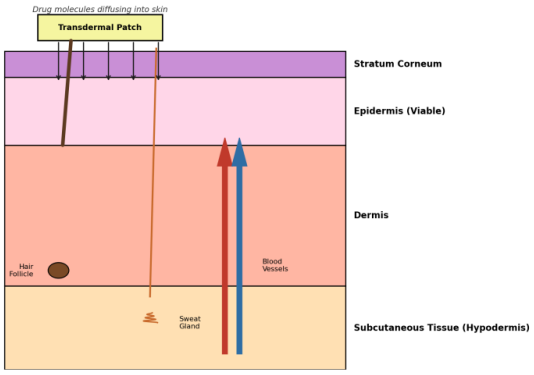


Figure 1. Layered barrier of human skin (stratum corneum, viable epidermis, dermis, subcutaneous tissue) and appendages relevant to transdermal delivery (original drawing).

3. Routes of Drug Penetration Across the Skin

- Transcellular — direct diffusion through corneocytes into hydrated keratin and lipid layers; used by small, moderately polar molecules.
- Intercellular — diffusion through the tortuous lipid matrix between corneocytes (path length 20-50× SC thickness); the primary route for most small, uncharged molecules.
- Appendageal (shunt) — bypass of the SC via hair follicles, sebaceous glands and sweat ducts; despite occupying only ~0.1% of skin area, this route is important for rapid penetration of ionic and large polar molecules.

4. Rationale, Advantages and Limitations

Transdermal delivery combines the non-invasiveness of topical application with the sustained input of injectable therapy, avoiding the peaks/troughs of oral dosing and the invasiveness of injections. Key trade-offs are summarised in Table 1.

Advantages	Limitations
Avoids hepatic first-pass metabolism and GI degradation/irritation	Suitable mainly for potent, low-dose drugs (<20 mg/day) owing to limited flux through a practical patch area
Provides sustained, often zero-order input, avoiding peak-trough fluctuations	Restricted largely to molecules of moderate lipophilicity and MW below ~500 Da
Improves compliance via infrequent (daily-weekly) dosing; therapy stopped by removal	Onset may be delayed by the lag time needed to cross the skin; adhesion can vary with site and conditions
Self-administered, painless, needs no sterile technique; useful when oral intake is not possible	Skin irritation/sensitisation and inter-patient variability in barrier properties can occur

5. Basic Components of a Transdermal Patch

Most transdermal patches share the same functional components: a polymer matrix/drug reservoir, an optional rate-limiting membrane, the drug substance, a permeation enhancer, a pressure-sensitive adhesive (PSA), an impermeable backing laminate and a release liner.

5.1 Polymer Matrix and Rate-Controlling Membrane

Polymers govern mechanical stability and drug-release rate and should be inert, drug-compatible, stable and film-forming. Natural polymers (cellulose derivatives, gelatin, chitosan), synthetic elastomers (polyisobutylene, silicone rubber) and synthetic film-forming polymers (Eudragits, HPMC, PVP, polyurethane) are all used. For reservoir systems, a microporous or non-porous membrane — commonly ethylene vinyl acetate (EVA), silicone rubber or polyurethane — sits between reservoir and skin to control release independent of skin permeability; higher vinyl-acetate content in EVA increases its amorphous phase and permeability.

5.2 Drug Substance and Permeation Enhancers

An "ideal" transdermal drug typically has a low daily dose (<20 mg), MW <400-500 Da, log P of 1.0-4.0, melting point <200 °C, a short plasma half-life, low oral bioavailability/therapeutic index, and low irritation potential — properties met by scopolamine, nitroglycerin, clonidine, oestradiol, testosterone, nicotine, fentanyl, lidocaine, oxybutynin, rivastigmine, rotigotine and selegiline. Because the SC limits most drugs to sub-therapeutic flux, chemical enhancers (sulphoxides, fatty acids/esters, alcohols, azone, terpenes, pyrrolidones, surfactants) are used to increase drug solubility, fluidise SC lipids or alter keratin conformation, while physical/active enhancers are discussed in Section 9.

5.3 Adhesive, Backing and Release Liner

The pressure-sensitive adhesive maintains continuous skin contact throughout wear; common chemistries include polyisobutylene, acrylate and silicone adhesives, applied either as a continuous layer or a peripheral ring. The backing laminate (polyester, polyethylene, polyolefin or aluminised film) is the outer, drug-impermeable protective layer, ideally flexible with adequate moisture-vapour transmission. The release liner (siliconised or fluoropolymer-coated polyester) protects the adhesive face before use and must be inert and drug-impermeable.

6. Types (Architectures) of Transdermal Patches

●Reservoir system: medication in solution, suspension, or gel with near zero-order kinetics, surrounded by an impermeable backing and a rate-controlling membrane (e.g., Transderm-Scop, Catapres-TTS).

- Drug-in-adhesive matrix — drug dissolved/dispersed directly in the adhesive layer (e.g., Nitro-Dur, many oestradiol/fentanyl patches); simpler than membrane-controlled systems.
- Matrix-dispersion system — drug dispersed in a hydrophilic/lipophilic polymer disc with peripheral adhesive, minimising dose-dumping from tearing.
- Microreservoir system — combines reservoir and matrix approaches; drug dispersed as microscopic droplets within a lipophilic polymer, stabilised by in-situ cross-linking.
- Vapour patch — releases a volatile substance (e.g., essential oils) through the adhesive; rarely used for conventional drugs.

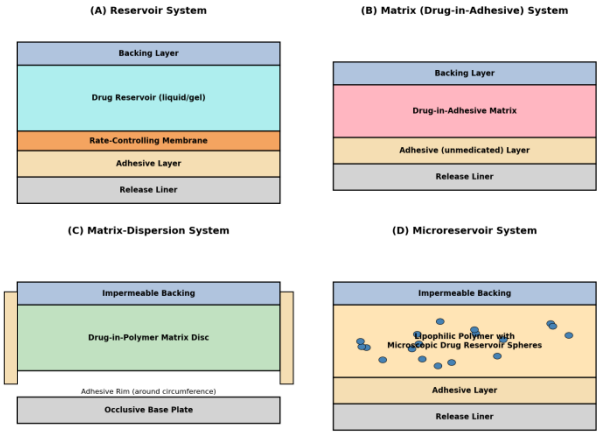


Figure 2. Major transdermal patch architectures: (A) reservoir, (B) drug-in-adhesive matrix, (C) matrix-dispersion with peripheral adhesive ring, (D) microreservoir system (illustration original).

7. Novel Vesicular Carriers

Vesicular carriers were developed to deliver hydrophilic, high-molecular-weight drugs that cannot diffuse effectively through the SC. Conventional liposomes and niosomes are limited by the rigidity of their bilayers, which restricts migration through the SC. Transfersomes, first described by Cevc in 1991, are ultra-deformable vesicles of phospholipids and edge-activator surfactants (sodium cholate, Tween-80, Span-80) that squeeze through pores 5-10 times smaller than their own diameter, driven by the transepidermal osmotic (hydration) gradient. Compared with conventional liposomes, transfersomes show high entrapment efficiency (up to ~90%) for lipophilic drugs and have been used to deliver analgesics, hormones, anticancer agents, insulin, interferon-α and proteins for transcutaneous immunisation, though they suffer from oxidative instability and higher production cost. Related lipid-based carriers include ethosomes (ethanol-rich liposomes), niosomes (non-ionic surfactant vesicles), elastic liposomes and polymeric/lipid nanoparticles.

8. Methods of Fabrication

Laboratory-scale TDDS are usually prepared by solvent/film-casting, in which drug, polymer, plasticiser and enhancer are dissolved or dispersed in a common solvent and cast on glass, Teflon or mercury substrates. Common techniques include the circular Teflon-mould method (controlled solvent evaporation under an inverted funnel), the mercury-substrate technique, the asymmetric TPX membrane technique (dry/wet phase inversion for reservoir patches), IPM/EVAC membrane lamination, aluminium-backed adhesive films (for higher drug loading), and proliposome/free-film techniques for vesicular carriers.

9. Active (Physical) Skin-Permeation Enhancement

Passive techniques are largely ineffective for solutes above ~500 Da, prompting development of active methods that apply an external energy source to overcome the SC barrier (Table 2).

Category	Representative Techniques
Electrical methods	Iontophoresis; electroporation
Mechanical methods	Microneedle arrays; microdermabrasion; needle-free (jet) injection; suction ablation; skin stretching
Energy-based/other	Sonophoresis (ultrasound); radiofrequency thermal microporation; laser ablation and photomechanical waves; magnetophoresis; controlled thermal delivery

Iontophoresis uses weak currents (up to 0.5 mA/cm2) to drive uncharged solutes by electroosmosis and charged solutes by electrorepulsion; commercial and clinical examples include the GlucoWatch Biographer and the ALZA E-TRANS fentanyl system. It works best with strong, medium-sized molecules (<7 kDa). In order to transport macromolecules (>7 kDa) like heparin, insulin, and DNA vaccines, electroporation uses brief high-voltage pulses to produce transitory aqueous micropores in SC lipid bilayers. This process frequently works in concert with iontophoresis.

Microneedles (50-900 µm; silicon, metal or biodegradable polymer) create painless microchannels for passive or active diffusion, as used in the ALZA Macroflux® array, and have shown efficacy for vaccines, insulin and other macromolecules in pre-clinical/clinical studies. Sonophoresis (20 kHz-16 MHz, with low-frequency ultrasound generally more efficient) enhances permeability via cavitation; the SonoPrep® device reduces anaesthetic onset from ~60 minutes to 5-15 minutes. Other techniques include radiofrequency thermal microporation (Transpharma ViaDerm), laser/photomechanical ablation, needle-free jet injection (PowderJect®, PMED®), suction-ablation (CellPatch®), magnetophoresis and heat-assisted (CHADD®) delivery, which increases flux 2-3-fold per 7-8 °C rise in skin temperature.

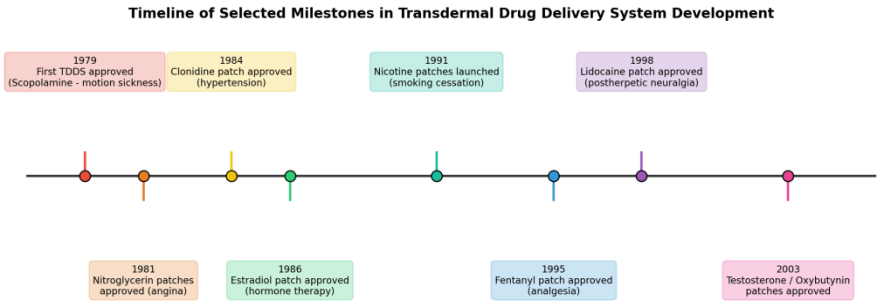


Figure 3. Timeline of key regulatory milestones in TDDS development (author's illustration).

10. Patch Adhesion

Sustained, uniform adhesion is a critical safety, efficacy and quality attribute of TDDS. Loss of contact area impairs delivery and can cause treatment failure, while a detached patch — particularly one containing potent opioids — poses a serious secondary-exposure risk, especially to children. Adhesive failure is classified as Case I (adhesive stays entirely on the patch — the desirable outcome), Case II (adhesive fully transfers to the skin), Case III (adhesive and cohesive failure, residue on both surfaces) or Case IV (a combination); only Case I is considered acceptable.

In vitro assessment adapts pressure-sensitive-tape methods (PSTC/ASTM): the peel-adhesion test measures peel force at a set angle and speed (complicated by the surface-energy mismatch between stainless steel, ~500 dyn/cm, and skin, ~27 dyn/cm); tack tests (probe-tack, rolling-ball, quick-stick, or the subjective "thumb tack" test) measure the force to break temporary bonds; and creep tests assess cohesive strength, since excessive creep compliance causes "cold flow" beyond the patch edge. Because skin is rough, flexible and variable, in vitro results do not fully predict in vivo performance, so clinical adhesion scoring (0 = no lift-off to 4 = complete detachment) remains essential, accounting for bathing, sweating and activity.

11. Evaluation of Transdermal Patches

Category	Representative Parameters/Methods
Physicochemical	Drug-excipient interaction (FT-IR, DSC, HPLC); film thickness; weight uniformity; folding endurance; moisture content/uptake; flatness; % elongation at break
Adhesive properties	Shear, 180° peel and tack (thumb, rolling-ball, probe, quick-stick) tests
Drug content/uniformity	UV/HPLC assay per patch or unit area; batch content uniformity; polariscopic examination of crystalline vs. amorphous state
In vitro release	USP Apparatus V or VI dissolution in phosphate buffer at 32 ± 0.5 °C
In vitro permeation	Franz diffusion cell studies (excised animal or human skin); steady-state flux and permeability coefficient
Irritation/stability/in vivo	Draize-type or human patch testing; ICH stability storage (e.g., 40 ± 0.5 °C/75 ± 5% RH); PK/PD studies in animal models followed by Phase I-IV trials

Water-vapour permeability (WVP) of the backing/adhesive is measured via the foam-dressing method: too-low WVP allows moisture accumulation and skin maceration with loss of adhesion, while too-high WVP can destabilise the formulation.

12. Selected Marketed Products

Brand (Active Drug)	System / Wear Duration / Indication
Transderm-Scop (scopolamine)	Reservoir; 3 days; motion sickness
Transderm-Nitro/Nitro-Dur (nitroglycerin)	Reservoir/Matrix; 12-24 h; angina pectoris
Catapres-TTS (clonidine)	Reservoir; 7 days; hypertension
Estraderm/Climara/Vivelle-Dot (estradiol)	Reservoir/Matrix; 3-7 days; hormone replacement
Androderm/Testoderm (testosterone)	Reservoir/Matrix; 24 h; male hypogonadism
Nicoderm/Habitrol/Nicotrol (nicotine)	Reservoir/Matrix; 16-24 h; smoking cessation
Duragesic (fentanyl)	Reservoir; 72 h; chronic pain
Lidoderm (lidocaine)	Matrix; 12 h; postherpetic neuralgia
Oxytrol (oxybutynin)	Matrix; 3-4 days; overactive bladder
Ortho-Evra (norelgestromin/ethinyl oestradiol)	Matrix; 7 days; contraception

13. Clinical Applications

- Cardiovascular: nitroglycerin (angina), clonidine (hypertension).
- Hormonal therapy/contraception: oestradiol, testosterone, combination patches.
- Analgesia: fentanyl, lidocaine, NSAID and anaesthetic patches.
- Smoking cessation: nicotine patches.
- CNS/neurodegenerative disease: selegiline, rotigotine.
- Urology: oxybutynin; Motion sickness: scopolamine.

● Emerging areas: transcutaneous vaccination, peptide/protein/oligonucleotide delivery, ADHD (methylphenidate patch).

14. Future Perspectives

Growth in transdermal delivery continues to outpace oral and inhaled routes, driven by advances in microfabrication, materials science and bioengineering ("third-generation" active technologies). Microneedle arrays are moving toward clinical and commercial use for vaccines and macromolecules, while radiofrequency, sonophoresis and thermal devices are in clinical evaluation. New technologies must satisfy regulatory demands for safety (reversibility of SC disruption), efficacy, convenience and cost. Continued development of adhesive formulations, biodegradable microneedle materials and "smart", physiologically responsive patches is expected to broaden transdermal delivery to biologics without the use of needles.

15. CONCLUSION

A proven, non-invasive method of achieving consistent blood medication levels without first-pass metabolism or GI adverse effects is through transdermal drug delivery devices. The drug's physicochemical characteristics, polymers, membranes, enhancers, adhesives, and overall design (reservoir, matrix, drug-in-adhesive, or microreservoir) all affect performance; adherence is just as crucial as drug release and needs to be evaluated both in vitro and in vivo. The range of passively deliverable molecules has been somewhat expanded by ultradeformable transfersomes, but the most promising approaches for macromolecules and biologics are still iontophoresis, electroporation, microneedles, sonophoresis, and thermal/radiofrequency ablation. It is anticipated that further developments in bioengineering, materials science, and pharmaceutics would increase the therapeutic applicability of TDDS.

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