IASR J. Med. Pharm. Sci.
ISSN: 2582-9343
Website: https://ijmps.com/
Open Access Journal
Country: India

IASR Journal of
Medical and
Pharmaceutical Science

REVIEW ARTICLE OPEN ACCESS

Advances and Challenges in Transdermal Drug Delivery: A Comprehensive Review

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Received: 05 March 2026
Accepted: 08- April 2026
Available online: 28 April 2026

A B S T R A C T

The delivery of transdermal drugs (TDDs) has been a successful and non-invasive substitute for oral and parenteral administration, preventing liver metabolism and gastrointestinal decomposition and increasing bioavailability. This review follows the development of TDD over four generations, ranging from basic passive diffusion to complex bioelectronic integration. We investigate the physiological difficulties posed by the structure of the "cement and mortar" layer of the corneum and by the intercellular, transcellular and appendage micropaths used for molecular transport. The thermodynamic foundations of the Fick law and the use of computational QSPR models are discussed in the prediction of drug permeability. We also emphasize the revolutionary effect of high-resolution 3D printed microneedles for pain-free delivery and new developments in nanomedicine such as solid lipid nanoparticles and ethosomes. The analysis concluded by examining the latest technologies, including a "Smart" closed loop system for autonomous dosage and the use of microneedles to deliver and stabilize mRNA vaccines. Modern TDD systems combine material sciences, computational physics, and bioelectronics and can transform personalized and non-invasive treatments.

Key Words: *Stratum corneum, microneedles, nanomedicine, bioelectronics, closed-loop systems, mRNA therapies, and transdermal drug delivery.*

1. Introduction and Generational Evolution

Direct distribution of medications across the epidermal barrier is a highly effective alternative to oral ingestion and hypodermic injections. The cutaneous route preserves medicine bioavailability and lessens gastrointestinal discomfort by avoiding hepatic first-pass metabolism and the harmful acidic conditions of the stomach.[1] Over the past few decades, transdermal drug delivery (TDD) has progressed through four distinct developmental generations.[2]

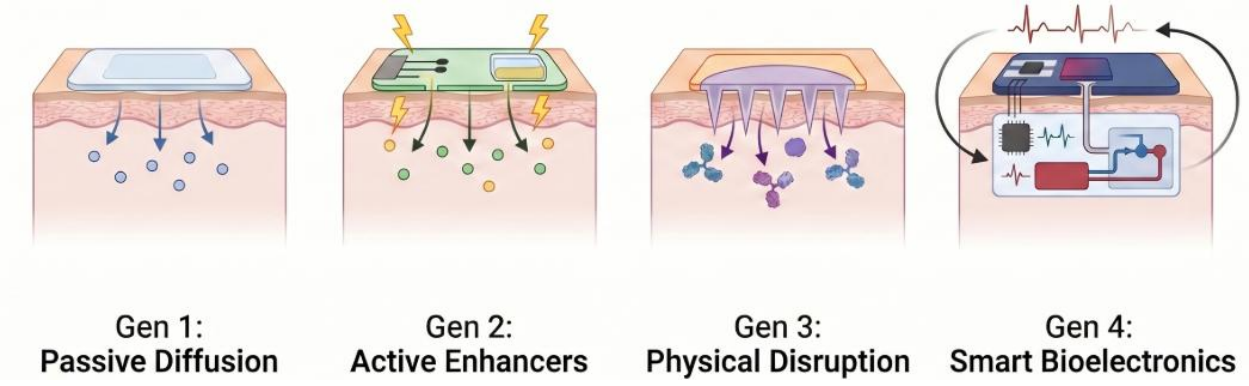

Figure. 1; The Generational Evolution of Transdermal Drug Delivery (TDD) Systems.

Prospective drugs were mostly restricted to low-molecular-weight, highly lipophilic chemicals since the initial generation relied heavily on passive diffusion mechanisms.[3] In order to expand this limited repertory, second-generation platforms used focused electrical currents and chemical penetration enhancers to momentarily fluidise the skin's lipid structures.[4] The third generation represented a paradigm shift by physically breaking the barrier and enabling the delivery of massive biologics by mechanical disruption techniques like as electroporation and microneedle arrays.[5] The industry is presently moving toward a fourth generation with wearable bioelectronics and sophisticated, closed-loop biosensors that provide dynamic, patient-specific dosing.[6]

2. Anatomical Barriers and Transport Pathways

The primary physiological barrier in transdermal research is the stratum corneum (SC), the outermost layer of the epidermis. In dermatological models, the SC is sometimes described to a "brick and mortar" wall, with the "bricks" being stiff, anucleate corneocytes neatly embedded in a highly organised "mortar" of extracellular lipids.[7] The biochemical composition of this lipid matrix, which is made up of almost equimolar ratios of free fatty acids, cholesterol, and ceramides, is crucial to the skin's barrier function.[8] Pathological alterations in these ceramide subtypes are strongly associated with chronic inflammatory disorders, such as atopic dermatitis and increased trans epidermal water loss.[9]

A medication often takes one of three micro-routes when trying to get beyond this barrier:

Intercellular channel: This is the thermodynamically preferable channel for most lipophilic compounds, where the permeant diffuses entirely through the winding lipid matrix.[10]

Transcellular Pathway: The molecule often splits between the lipophilic matrix and the hydrophilic core of corneocytes, an energy barrier that only highly specialised permeants encounter.[11]

Appendageal (Shunt) Pathway: The drug totally bypasses the SC by going through hair follicles and eccrine sweat ducts. Cutaneous appendages are becoming recognised as crucial entrance routes for high-molecular-weight nanocarriers, while accounting for just 0.1% of the epidermal surface.[12]

3. Kinetic Constraints and Computational Predictions

Passive drug diffusion is rigorously governed by the thermodynamic forces of concentration gradients, which are mathematically governed by Fick's First Law of Diffusion. $J = -D(dC/dx)$, where J is the diffusion flux, D is the permeant's specific diffusion coefficient, dC/dx is the concentration gradient, and x is the barrier thickness or route length, depicts the steady-state flow over the skin.[13]

Ideal passive transdermal candidates must have a molecular weight precisely below 500 Daltons, an octanol-water partition coefficient (log P) between 1.0 and 3.0, and strong pharmacological efficacy needing daily systemic dosages of fewer than 20 milligrams due to the rigorous requirements of the SC.[14] Researchers use Quantitative Structure-Permeability Relationship (QSPR) models to expedite drug development. The Potts and Guy model and other seminal frameworks only consider a molecule's spatial volume and lipophilicity when assessing skin permeability.[15] By mapping intricate, non-linear thermodynamic interactions using sophisticated machine learning algorithms, modern QSPR techniques significantly reduce the requirement for drawn-out animal testing.[16]

4. Nanomedicine and Green Solvents

Certain nanoscale vehicles that purposefully get over earlier mass and solubility restrictions have been developed by formulators. Solid lipid nanoparticles (SLNs) are unusual because of their exceptional biocompatibility. When applied, they combine with the skin's surface to create an occlusive barrier that stops water loss, hydrating the SC and widening the intercellular gaps.[17] Ethosomes are an example of another sophisticated carrier system. Because they include large quantities of ethanol in addition to typical phospholipids, ethosomes have very elastic and flexible membranes.[18] This "ethosomal effect" aggressively fluidizes the native SC lipids while allowing the soft vesicle to penetrate further into the dermal layers.[19]

Nanocarriers are developing alongside Ionic Liquids (ILs), which are organic salts that stay liquid at room temperature.[20] Crucially, in vitro cytotoxicity experiments confirm that the formation of these fluidic channels does not result in significant cellular toxicity or irreversible epidermal damage.[21] Some choline-based ILs temporarily disrupt the tight lipid packing of the SC while simultaneously maximising the water solubility of resistant medications.[22]

5. Microneedles and High-Resolution 3D Printing

Microneedles (MNs) provide a seamless transition between non-invasive patches and traditional hypodermic syringes. These microscopic projections, which are between 50 and 1000 micrometres long, easily penetrate the SC but are too short to activate deep dermal pain receptors, ensuring painless delivery.[23]

Before applying a standard formulation, solid MNs use a physical pre-treatment to create micro-channels, which are mostly used to improve epidermal penetration for big molecules.[24] Coated MNs allow for the rapid bolus delivery of antigens and sensitive proteins by immersing solid matrices in highly concentrated immunisation or drug solutions.[24] To enable continuous liquid injections based on volume, hollow MNs include a central lumen that serves as a miniature hypodermic needle.[24] Dissolving MNs are composed of biodegradable polymers that dissolve without damage as they absorb interstitial fluid, allowing for long-term biotherapeutic release free of biohazardous waste.[25]

The manufacture of these intricate arrays is rapidly being replaced by additive manufacturing. High-resolution vat photopolymerization techniques, especially Stereolithography (SLA) and Digital Light Processing (DLP), far surpass traditional moulding procedures.[26] SLA uses concentrated UV lasers to cure liquid photopolymer resins layer by layer, achieving remarkable precision.[27] This enables the creation of complex, channel-shaped needles that greatly reduce the

physical insertion force required to penetrate the skin while increasing the inner volume accessible for massive medicine loading.[28]

6. Bioelectronic Integration and mRNA Therapeutics

The pinnacle of contemporary transdermal research is "smart" response systems. By fusing soft wearable bioelectronics with active medications, researchers have successfully developed closed-loop delivery systems.[29] For example, modern glucose-responsive hydrogel patches utilise immobilised glucose oxidase or phenylboronic acid (PBA) networks to continuously monitor ambient blood sugar.[30] When a hyperglycaemic shift occurs, the polymer matrix undergoes a targeted chemical phase change that releases calculated insulin doses on its own and stops delivery once physiological baselines are restored.[30]

Third and fourth generation MNs are also revolutionising immunisation procedures worldwide. Scientists have effectively enclosed fragile messenger RNA (mRNA) lipid nanoparticles in totally water-soluble polymer microneedles.[31] Because the epidermal environment is especially rich in antigen-presenting Langerhans cells, transdermal mRNA administration results in greater, superior systemic antibody responses compared to intramuscular injections.[32] It also prevents expensive cold-chain storage by stabilising the fragile mRNA constructs at room temperature.[33]

7. Conclusion

Transdermal medication delivery has undoubtedly developed into a highly engineered intersection of bioelectronics, computational physics, and materials science from its basic origins of passive diffusion. By using accurate 3D printing, flexible nanovesicles, and closed-loop biosensors, modern therapies can successfully overcome the skin's inherent defences. As these advanced, customised systems continue to show their efficacy and safety in clinical trials, transdermal delivery will inevitably become a crucial part of individualised, non-invasive therapy in the future.

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