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Transdermal Drug Delivery Systems: Principles, Formulation Strategies, Permeation Enhancement and Recent Advances – A Comprehensive Review

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Abstract: *Among the various routes explored for drug administration, the transdermal route has attracted considerable interest over the past few decades, largely because it sidesteps many of the drawbacks inherent to oral and parenteral therapy. Transdermal drug delivery systems (TDDS) make use of the skin as an entry point for drugs intended to act systemically, offering a controlled, non-invasive, and patient-friendly mode of treatment. The present review brings together, in a coherent manner, the key aspects that govern the science and technology of transdermal drug delivery. It begins with the structure and function of skin, with particular attention to the stratum corneum—the layer that, more than any other, dictates how much drug can actually get through. The principles of passive diffusion, including Fick's law and the factors that influence flux, are discussed alongside the physicochemical criteria a drug must ideally meet to be considered a viable transdermal candidate. The review then moves to the formulation side: the components of a transdermal patch, the different patch designs in use, and the laboratory methods commonly employed for their preparation. Evaluation approaches—ranging from basic physical tests to in vitro release and ex vivo permeation studies—are outlined in practical terms. A major portion is devoted to permeation enhancement, covering both chemical approaches such as oleic acid, ethanol, PEG 400, and DMSO, and physical techniques including microneedles, iontophoresis, sonophoresis, and electroporation. Marketed products, therapeutic applications, and recent developments are examined in light of where this field appears to be heading.*

Keywords: Transdermal drug delivery, skin permeation, patch formulation, permeation enhancement, nanocarriers, iontophoresis, controlled release, stratum corneum

I. INTRODUCTION

Getting a drug to work well is not only about the right choice of molecule. It's equally about getting it to the right place, in the right amount, at the right time. For decades the default option has been oral administration but this is not without its well known complications; erratic absorption, hepatic first pass metabolism and gastrointestinal side effects. A Transdermal Drug Delivery System (TDDS) is nothing but a medicated patch applied on the skin to deliver the drug to the blood stream at a controlled rate [1]. This route is appealing since the drug goes directly into the circulation, avoiding the gut and liver altogether. The modern transdermal patch began with scopolamine (Transderm-Scop®), cleared by the US FDA in 1979 for the prevention of motion sickness [2]. What came next was a steady stream of products – nitroglycerin for angina, clonidine for hypertension, nicotine for smoking cessation – that showed the skin could do much more than keep the outside out. TDDS is particularly promising in the Indian context. Non-adherence to multi-dose oral regimens is a common problem, especially in the elderly and in patients with chronic diseases. A patch

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applied once a day or twice a week simplifies treatment. The transdermal route is also a genuinely practical alternative for patients who cannot swallow tablets, such as post-surgical cases, those with dysphagia or children [3]. Another feature to look out for is the ability to stop therapy by removing the patch, especially for drugs with a narrow therapeutic window. Transdermal drug delivery relies on passive diffusion in which the drug moves from a high concentration in the patch to a low concentration in the skin and underlying tissues. Much of transdermal research is focused on understanding this barrier, and finding ways to work around it. The review is organized in a logical sequence of the main aspects of TDDS, including skin anatomy, principles of permeation, formulation design, evaluation, enhancement strategies, marketed products and the direction of the field.

II. ANATOMY AND PHYSIOLOGY OF SKIN

One needs a clear picture of what the drug is actually trying to get through before one can design a transdermal formulation with intelligence. The skin was not evolved as a portal for drug delivery, it was evolved to keep things out [4]. It is the first line of defence for the body against micro-organisms, chemicals and physical injury. The skin covers approximately 1.7 to 2.0 m² in an adult and accounts for approximately 15% of body weight.

2.1. Structure of Skin

2.1.1. Epidermis: The epidermis is the outermost cellular layer of skin, a thin but surprisingly complex structure that varies in thickness from less than 0.1 mm on the eyelids to nearly 1 mm on the soles. It is made up almost entirely of keratinocytes, which originate in the stratum basale and slowly migrate upward, altering their character as they do. By the time they reach the surface, they have lost their nuclei, are stuffed with keratin, and have helped form the tough, flat, overlapping cells of the outermost sublayer. Among them are dispersed melanocytes, Langerhans cells and Merkel cells [5].

2.1.2. Dermis: Under the epidermis is the dermis, a much thicker (normally 1–4 mm) layer of connective tissue, which gives the skin its mechanical strength and flexibility. It is rich in collagen and elastin fibres and has a dense network of blood capillaries, lymphatics, nerve endings, sweat and sebaceous glands and hair follicles. The target is the dermal capillary bed. Once a drug molecule arrives at the dermis and accesses the microcirculation, it is effectively absorbed to the systemic circulation [6].

2.1.3. Hypodermis: The hypodermis or subcutaneous tissue, the deepest layer of the skin, is composed primarily of adipocytes (fat cells) held together by loose connective tissue and traversed by large blood vessels. This layer is not the main target for most applications of transdermal drug delivery, although with very lipophilic drugs the subcutaneous fat can serve as a depot, releasing drug slowly over time.

2.2. Stratum Corneum as the Major Barrier

The stratum corneum (SC) is the most important structure in transdermal pharmacology, if one had to say. This is the outermost sublayer of the epidermis, only 10 to 20 µm thick in most areas, but providing the majority of the skin's barrier function. It has been described as a 'bricks and mortar' architecture, where flattened, dead corneocytes (the bricks) are embedded in a matrix of highly organized lipid bilayers (the mortar) [7]. These lipids, mainly ceramides, cholesterol and free fatty acids, form a tortuous hydrophobic pathway that most molecules find very difficult to cross. A water soluble molecule is repelled by the lipid rich matrix and a highly lipophilic molecule may partition readily into the SC but then finds it difficult to move on into the aqueous viable epidermis underneath. This is why most drugs that work well via the transdermal route occupy a rather narrow window of physicochemical properties [8].

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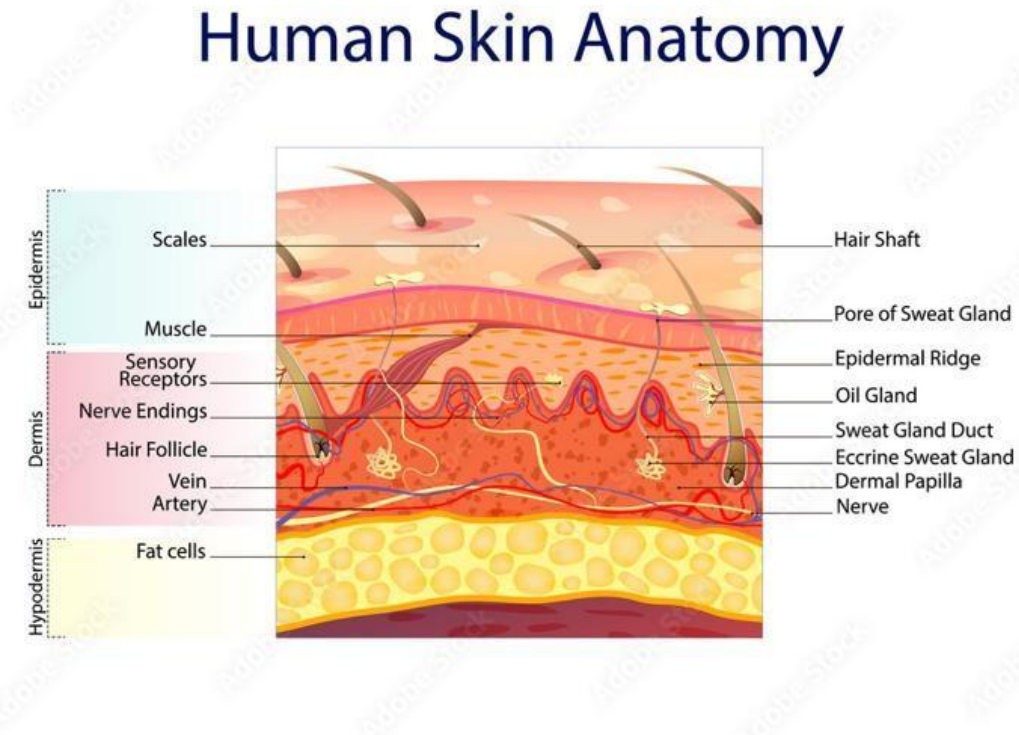

Fig. 1: Anatomy of Human Skin

2.3. Routes of Permeation

Drug molecules can cross the skin by more than one pathway. Three principal routes have been identified:

2.3.1. Transcellular pathway: Molecules traverse the corneocytes directly and then the intercellular lipid regions in an alternating sequence. This is the shortest geometrical path, but the repeated transitions between hydrophilic interiors and lipophilic intercellular spaces are energetically costly for most molecules.

2.3.2. Intercellular pathway: This is generally accepted as the major pathway for passive drug permeation. Molecules can penetrate through the entire lipid matrix surrounding the corneocytes. The pathway is anything but linear, snaking around each corneocyte, and is estimated to be approximately 500-fold longer than the actual thickness of the SC [9].

2.3.3. Appendageal route: Hair follicles and sweat ducts bypass the SC, providing a shunt pathway for hydrophilic drugs, large molecules, and charged species. Appendages cover only about 0.1 to 1.0% of total skin area but become particularly relevant for vaccine delivery and macromolecules [10].

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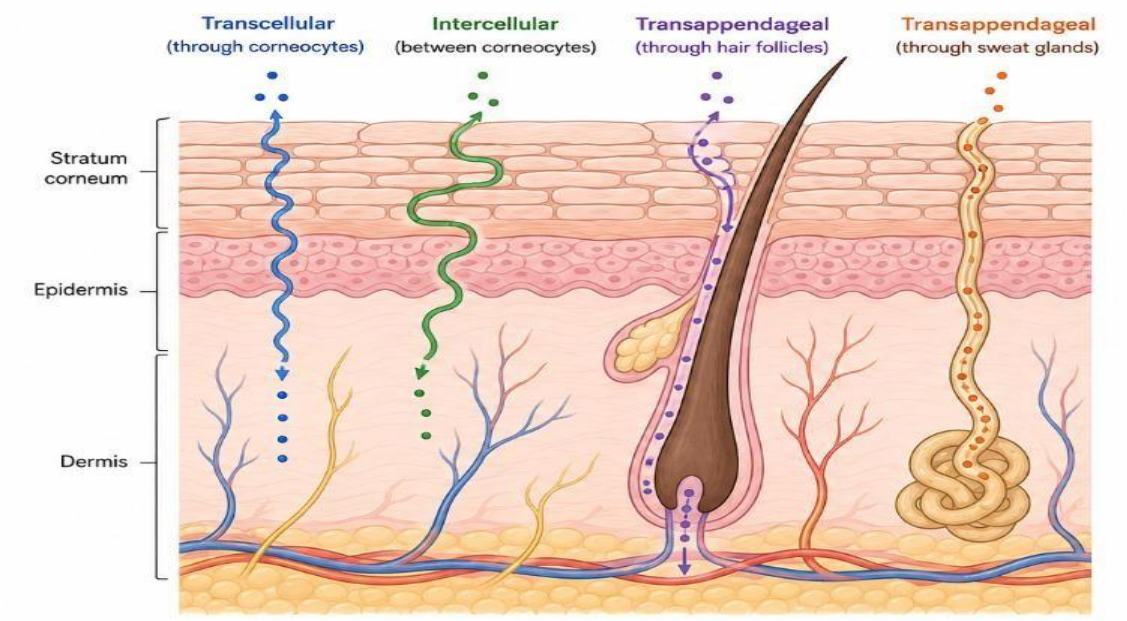

Fig. 2: Drug Permeation Pathways Through the Skin

III. PRINCIPLES OF TRANSDERMAL DRUG DELIVERY

3.1. Mechanism of Drug Transport

A concentration gradient drives the release of drug from a transdermal patch into and through the skin. Drug in the patch (at high concentration) tends to diffuse towards the skin (where drug concentration is initially zero or very low) and provides the driving force for diffusion. The drug first has to partition from the vehicle into the SC, diffuse through the SC, partition into the aqueous viable epidermis and then into the dermal capillaries for systemic circulation. In reservoir-type patches, the rate of drug available for absorption is controlled by a rate-controlling membrane [11].

3.2. Fick's Law of Diffusion

The steady state flux (J) of drug across a membrane is given by Fick's first law:

$$J = D \times Kp \times \Delta C / h \quad (1)$$

Where J = flux (µg/cm²/h), D = diffusion coefficient of the drug in the membrane (cm²/s), Kp = partition coefficient between membrane and donor vehicle, ΔC = concentration gradient across the membrane, and h = membrane thickness (µm). The time taken to reach the steady state is approximated as $h^2/6D$. Higher flux can be achieved by increasing the diffusivity, improving SC partitioning or maximizing the concentration gradient [12].

3.3. Factors Affecting Permeation

3.3.1. Drug-related factors: The most discussed property is probably the molecular weight. The '500 Dalton rule' is often quoted, stating that molecules larger than 500 Da do not permeate intact skin to any clinically meaningful extent. Lipophilicity, expressed as log P, is also important and a log P in the range of 1 to 4 is typically considered favorable. Ionisation state is also important, as unionized molecules permeate much more readily, so formulation pH can greatly affect absorption [13].

3.3.2. Formulation factors: The vehicle can have a significant impact on permeation independent of the drug. Vehicles that increase thermodynamic activity of the drug (e.g. supersaturated systems) maximize the driving force for

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permeation. The polymer concentration, the plasticizer content and the presence of chemical enhancers affect the general permeation profile [14].

3.3.3. Biological factors: Permeability of skin varies greatly with body site, age and disease. Inflamed or eczematous skin is often much more permeable than normal skin. Hydration, temperature and individual genetic variation also affect drug permeation, leading to inter- and intra-individual variability which formulation scientists need to address [15].

IV. IDEAL CHARACTERISTICS OF DRUGS FOR TDDS

Not all drugs are suitable candidates for transdermal delivery. Over the years, a reasonably clear profile has emerged for drugs that tend to work well via this route. The ideal transdermal drug is one potent enough to be effective in low doses, physiochemically balanced enough to cross the skin barrier and pharmacologically well suited to continuous delivery [16].

Key criteria are:

• Molecular weight below 500 Da — larger molecules cannot navigate through the tight lipid matrix of the stratum corneum efficiently
• Log P between 1 and 4 — ensuring adequate SC partitioning without entrapment
• Daily therapeutic dose not exceeding 20–25 mg — since the skin can only deliver drug at relatively modest rates
• Elimination half-life of 2–10 hours — such drugs benefit most from continuous transdermal delivery
• Adequate potency at low plasma concentrations — the flux achievable through skin is inherently limited
• Non-irritating and non-sensitizing — the patch remains in skin contact for hours to days
• Good solubility in both hydrophilic and lipophilic media — to facilitate formulation and permeation
• Chemical stability in the formulation over the intended shelf life
• Low or absent first-pass metabolism — such drugs gain the most from switching to a transdermal route [17]

This profile is met by drugs such as nitroglycerin (MW 227 Da), fentanyl (MW 336 Da), estradiol (MW 272 Da) and nicotine (MW 162 Da) and these drugs have been successfully commercialized as transdermal patches. Most of these criteria are guidelines rather than absolute rules and enhancement techniques have increased the range of candidates considerably.

V. COMPONENTS OF TRANSDERMAL PATCH

The transdermal patch is a sophisticated multi-layer system with each layer having a specific and well-defined purpose. The choice and quality of each component are directly related to drug release, adhesion, patient comfort and shelf life.

5.1. Drug: The active pharmaceutical ingredient may be dissolved in a liquid reservoir, dispersed in a polymer matrix or directly incorporated in an adhesive layer. The drug should be physically and chemically compatible with all the surrounding materials and should remain stable during the shelf life of the product.

5.2. Polymer Matrix: The matrix type patches have a polymer matrix that serves as a structural backbone for diffusion of drug to the surface of the skin. Commonly used polymers are ethylene-vinyl acetate copolymers, polyurethane, hydroxypropyl methylcellulose, ethyl cellulose and polyvinyl alcohol. Polymer selection influences release kinetics and mechanical properties [18].

5.3. Plasticizer: Plasticisers reduce the glass transition temperature of the polymer, and therefore impart flexibility. Examples include dibutyl sebacate, triethyl citrate and propylene glycol. They can also affect the mobility of the drugs in the matrix by changing the free volume.

5.4. Permeation Enhancer: Chemical permeation enhancers are added to transiently and reversibly reduce the SC barrier resistance. Mechanisms of action may include disruption of organized lipid bilayers, increasing drug solubility in the SC or changing keratin structure.

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5.5. Adhesive: The pressure sensitive adhesive (PSA) secures the patch in place during the wearing period. Common types of PSA include silicone, acrylic and polyisobutylene based systems. The adhesive must have enough tack, peel strength and cohesive integrity and be nonirritating [19].

5.6. Backing Membrane: The outermost layer provides structural support, prevents the drug from escaping in the wrong direction and protects the formulation from environmental exposure. Materials include polyester films, polyethylene and metallised foil laminates.

5.7. Release Liner: The release liner covers the adhesive side of the patch, which is removed immediately before application of the patch. Silicone coated polyester films and fluoropolymer coated papers are frequently used.

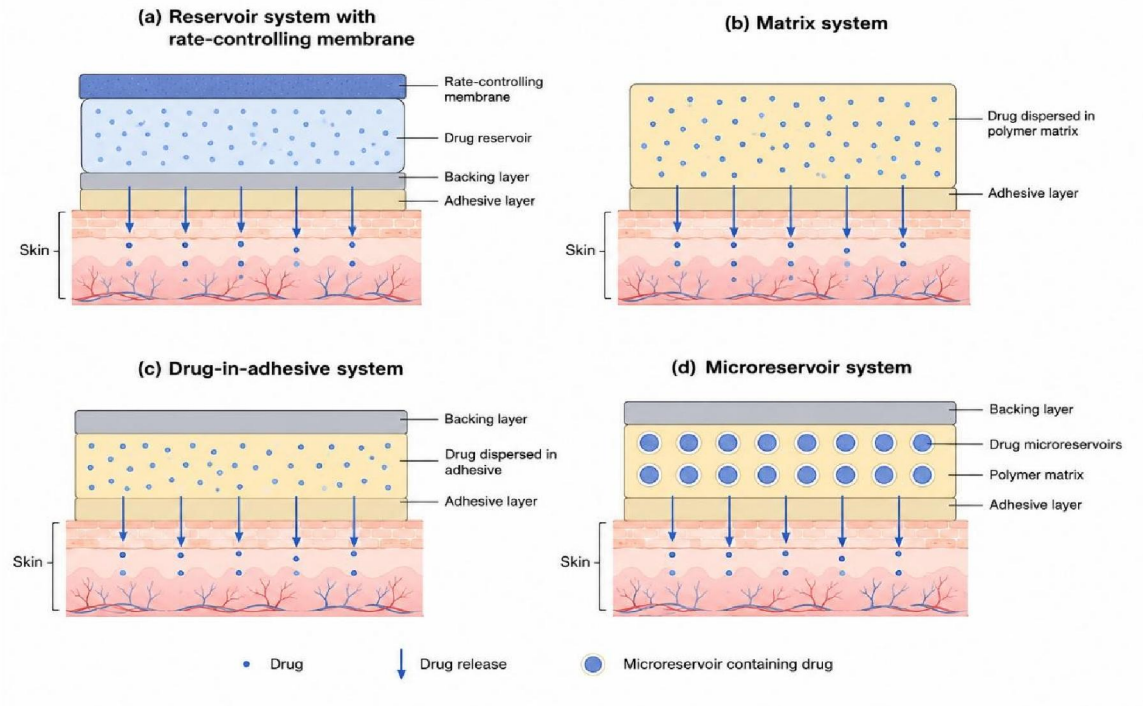

Fig. 3: Types of Transdermal Patch Systems

VI. TYPES OF TRANSDERMAL PATCHES

6.1. Reservoir System: Drug is contained in a separate compartment between a backing membrane and a rate controlling membrane. Thus, release is roughly zero-order, with the reservoir remaining saturated for most of the wearing period. The trade off is increased manufacturing process complexity and potential risk of dose dumping if membrane is breached [20].

6.2. Matrix System: Drug evenly distributed or dissolved in a solid polymer matrix. Controls drug diffusion to skin surface. Matrix patches are cheaper and easier to manufacture. Their release rate is usually decreasing with time, i.e. a first order process, but polymer combinations can approach zero order behaviour. Matrix patches are thinner and more comfortable to wear.

6.3. Drug-in-Adhesive System: Drug is directly dispersed in the pressure-sensitive adhesive layer that acts as the drug reservoir and skin anchor. This removes the need for an additional matrix, resulting in a thinner, more elegant patch. This design is utilised in many commercially successful transdermal products [21].

6.4. Microreservoir System: The drug is entrapped in small aqueous compartments which are uniformly distributed throughout the polymer matrix. Each compartment is a local source of drug and the overall release is controlled by the matrix surrounding it. This hybrid approach can provide a more reproducible release than simple matrix systems.

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VII. METHODS OF PREPARATION

7.1. Solvent Casting Method: In this method, the selected polymer is dissolved in a suitable volatile solvent. The drug, along with required excipients such as plasticizers and permeation enhancers, is then added to form a homogeneous solution. This solution is poured into a flat casting surface (like a glass plate or Petri dish) and allowed to dry under controlled conditions to evaporate the solvent. After drying, the film is carefully peeled off and cut into desired size patches for further evaluation [25].

7.2. Mercury Substrate Method: In this method drug is dissolved in polymer solution along with plasticizer. The above solution is to be stirred for 10–15 minutes to produce a homogenous dispersion and poured in to a levelled mercury surface, covered with inverted funnel to control solvent evaporation.

7.3. Asymmetric TPX Membrane Method: Heat sealable polyester film with a concave of 1 cm dia is used as the backing membrane to fabricate patch in this method. Drug sample is dispensed into the concave membrane, covered by a TPX {poly (4-methyl-1-pentene)} asymmetric membrane, and sealed by an adhesive [26].

VIII. EVALUATION PARAMETERS

A transdermal patch must meet a range of quality standards before it can be considered fit for use. Evaluation is carried out at multiple levels—physical, physicochemical, in vitro, ex vivo, and stability—and each test provides information about a different aspect of product quality and performance.

8.1. Physical Evaluation

8.1.1. Physical appearance: Prepared transdermal patches were inspected visually for clarity, uniformity, flexibility and smoothness.

8.1.2. Thickness: Patch thickness is measured at five or more points using a micrometer. Variation is generally required to remain within ±5% of the mean value.

8.1.3. Weight variation: Individual patches are weighed and the values compared; acceptable variation is typically within ±5% of the mean batch weight.

8.1.4. Folding endurance: Folding endurance of prepared patches was determined by repeatedly folding a selected patch from the same place until it breaks. The number of times a film could be folded from the same place without breaking gives the value of folding endurance.

8.1.5. Flatness: Strips cut from different positions are measured for length before and after conditioning; zero percentage change indicates that the patch lies flat without tendency to curl or contract.

8.1.6. Tensile strength and elongation at break: Using a texture analyser, the patch is stretched until it breaks. These parameters confirm mechanical strength sufficient to resist tearing during handling and application.

8.2. Physicochemical Evaluation

8.2.1. Drug content uniformity: Drug content study was performed in triplicate for each formulation. Drug content uniformity was determined by dissolving the patch (2 cm square in diameter) from each batch by homogenization in 100 ml of an isotonic phosphate buffer (pH 7.4) under stirring. The 2 ml solution was taken and diluted with isotonic phosphate buffer pH

7.4 up to 10 ml, and the resulting solution was filtered through a 0.45 µm Whatman filter paper. The drug content was then determined after proper dilution using UV spectrophotometer.

8.2.2. Moisture content and moisture uptake: Moisture content is determined by drying over a desiccant and recording weight loss. Moisture uptake is assessed by exposing patches to 84% RH for a fixed period. Excessive moisture can promote microbial growth, weaken the film, and accelerate drug degradation [28].

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8.3. In vitro Drug Release

In vitro release testing is conducted using Franz diffusion cells. The patch is fixed on a synthetic membrane between donor and receptor compartments and aliquots are taken at regular intervals. To characterize the release mechanism, the data are fitted to kinetic models (zero-order, first-order, Higuchi, Korsmeyer-Peppas). In vitro release is not a good predictor of in vivo performance but it is indispensable for quality control and batch to batch comparison [29].

8.4. Ex vivo Permeation Studies

Ex vivo permeation studies employ excised animal or cadaveric human skin. In Indian research institutions, porcine ear or abdominal skin is most commonly used, as it closely resembles human skin in its lipid composition and thickness. The patch is applied to skin mounted on a Franz diffusion cell and drug permeating through is measured as a function of time. Flux, permeability coefficient and lag time are calculated. Quantification of drug penetration in skin layers by tape-stripping and confocal microscopy [27].

8.5. Skin Irritation Study

Primary irritation studies are usually performed in rabbits (Draize test) with scoring of erythema and oedema at 24 and 72 hours. The sensitization potential can also be assessed by human volunteer patch testing and by repeated insult patch testing (RIPT).

8.6. Stability Studies

Stability study is carried out according to ICH Q1A(R2) guidelines at accelerated (40°C/75% RH) and long term (25°C/60% RH) storage conditions of patches. Drug content, in vitro release, appearance and adhesive properties are measured at specified time intervals to determine shelf life [30].

IX. PERMEATION ENHANCEMENT TECHNIQUES

The SC barrier is formidable and passive diffusion alone is often not sufficient to achieve therapeutically meaningful flux, especially for hydrophilic, large or high dose drugs. Many methods have been developed to improve skin permeability, which can be broadly divided into chemical and physical methods.

9.1. Chemical Methods

Chemical penetration enhancers (CPEs) are compounds added to the formulation that can temporarily and reversibly reduce the barrier resistance of the skin. An ideal CPE should be pharmacologically inert, non-toxic, non-irritating, reversible in its action in a short time and compatible with other components of the formulation [31].

9.1.1. Oleic acid: One of the most studied CPEs is oleic acid, an 18-carbon unsaturated fatty acid. It penetrates the ordered lipid bilayers of the SC, disrupting their crystalline organization and generating fluid, disordered microdomains through which drug molecules can diffuse more easily. The effect is particularly dramatic in a propylene glycol vehicle [32].

9.1.2. PEG 400: Polyethylene glycol 400 is a solvent and penetration enhancer. It primarily acts by reducing the affinity of the drug for the vehicle, effectively "pushing" the drug to the skin, and also by hydrating the SC and reducing diffusional resistance.

9.1.3. Ethanol: Many commercial transdermal formulations use ethanol. The enhancement effect is multi-faceted, including extraction of some SC lipids, acting as a co-solvent to increase drug solubility and carrying drug molecules into the SC. Ethanol-based supersaturated systems gain from the high thermodynamic driving force by ethanol evaporation from the skin surface [33].

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9.2. Physical Methods

9.2.1. Microneedles:

Microneedles are made up of microscopic needles in an array, usually 25 to 2000 µm long, which penetrate the SC to create transient microchannels without touching nerve endings, thus making the process essentially painless. Microneedles are broadly of four types i.e. solid, coated, dissolving and hollow microneedles. Indian researchers have been active contributors to microneedle research particularly from Karnataka and Maharashtra [34].

9.2.2. Iontophoresis:

Iontophoresis is the application of a mild electric current, of the order of 0.5 mA/cm², to move charged drug molecules through the skin by electrophoresis (the migration of ionized drug) and electroosmosis (bulk solvent flow carrying neutral molecules). It is well suited for hydrophilic, ionized drugs which cannot cross the SC passively and allows on demand dosing by controlling the current [35].

9.2.3. Sonophoresis:

The use of ultrasound energy to increase skin permeability. More effective than higher frequencies is low frequency ultrasound (around 20 kHz). The main mechanism is the acoustic cavitation, i.e. the formation and collapse of microbubbles in the SC lipid bilayers. Low-frequency sonophoresis has been shown to enhance skin permeability to macromolecules such as insulin by orders of magnitude.

9.2.4. Electroporation:

Electroporation uses very short, high-voltage electrical pulses on the skin, which transiently create aqueous pores in the lipid bilayers of the SC. It physically creates new pathways through the skin unlike iontophoresis. It can dramatically increase permeability for large, charged molecules and has been used for delivery of nucleic acids and macromolecular drugs [37].

X. ADVANTAGES OF TDDS

The clinical and pharmaceutical attractiveness of transdermal drug delivery is based on a set of advantages that can hardly be matched by any other route of administration:

• Avoid first-pass metabolism, which can dramatically improve bioavailability—nitroglycerin achieves near-complete systemic availability via the transdermal route compared to about 1–2% after oral dosing

• Controlled, sustained drug delivery results in relatively constant plasma concentrations, reducing peak-trough fluctuations, which contribute to side effects and inadequate therapeutic coverage

• Patches usually have better patient compliance than multiple daily tablets, especially in elderly patients, patients with chronic conditions, or children who resist oral medication

• Removable patches allow for easy withdrawal of therapy, which is important for drugs with narrow therapeutic windows or when adverse effects occur

• It bypasses the gastrointestinal environment and is useful for drugs that are unstable in the gut or cause gastric irritation when taken orally

• No needles are used, making TDDS suitable for patients with needle phobia and eliminating infection risks associated with injections

• Reduced dependence on healthcare facilities, simplified self-administration. This is a major benefit in the Indian scenario where access to clinical facilities is skewed [38]

XI. LIMITATIONS AND CHALLENGES

Transdermal drug delivery has many attractions but there are significant limitations that need to be taken into account in considering whether this route is appropriate:

• The skin barrier is an effective barrier to transdermal delivery of large (generally above 500 Da), poorly lipophilic and high-dose molecules. The number of drugs in commercial transdermal products is still quite small

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• Inflammatory or allergic reactions can occur as a result of adhesives, enhancers and the drug itself – skin irritation and contact sensitization are real concerns particularly with long term or repeated patch use
• Skin permeability varies considerably between individuals and body sites and is influenced by age, disease, ethnicity and environment; this variability makes it difficult to predict plasma concentrations accurately
• Adhesion failures, such as patches that peel off during physical activity, in hot and humid weather or from elderly skin, remain a practical problem that affects therapy reliability
• The maximum drug delivery rate is limited by the aesthetic and practical acceptability of the patch size and high-dose drugs are excluded
• Drugs which bind irreversibly to skin proteins or are extensively metabolized within skin layers may not enter systemic circulation in adequate amounts
• Once the dose rate is applied it is not easy to change, whereas an intravenous infusion can be altered in real time [39]

XII. MARKETED TRANSDERMAL PRODUCTS

For almost five decades, transdermal patches have been used commercially, and the range of drugs delivered by this route has been steadily increasing. Table 1 summarizes representative products available across the globe, many of which are available in India as well. Several of these products have been manufactured by Indian pharmaceutical companies as generics with approval of DCGI.

Table 1. Representative Marketed Transdermal Drug Delivery Systems

Brand Name	Active Drug	Indication	Dose / Duration
Nitro-Dur®	Nitroglycerin	Angina pectoris	0.1–0.8 mg/h / 24 h
Catapres-TTS®	Clonidine	Hypertension	0.1–0.3 mg/day / 7 days
Nicoderm CQ®	Nicotine	Smoking cessation	7–21 mg/day / 24 h
Duragesic®	Fentanyl	Chronic pain	12–100 µg/h / 72 h
Estraderm®	Estradiol	HRT / Menopause	0.05–0.1 mg/day /3–4 days
Transderm-Scop®	Scopolamine	Motion sickness	1 mg / 72 h
Lidoderm®	Lidocaine	Post-herpetic neuralgia	700 mg / 12 h on
Exelon Patch®	Rivastigmine	Alzheimer's disease	4.6–13.3 mg / 24 h
Ortho Evra®	Norelgestromin/EE	Contraception	Weekly patch
Ionsys®	Fentanyl HCl	Acute post-op pain	40 µg/activation

In the Indian context, rivastigmine patch (Exelon Patch®) deserves special mention due to increasing burden of Alzheimer's disease and documented improvement in gastrointestinal tolerability of patch as compared to oral capsule. The advent of fentanyl patches has transformed palliative care for cancer pain from requiring hospital-based intravenous analgesia to allowing ambulatory patients at home.

XIII. RECENT ADVANCES IN TDDS

13.1. Nanocarrier-Loaded Patches

The convergence of nanotechnology with transdermal delivery has created opportunities that are not attainable by conventional patch systems. To improve skin permeation, patches can be formulated with nanocarriers such as transfersomes, ethosomes, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs) and nanoemulsions. The flexible phospholipid bilayers of transfersomes can pass through the intercellular lipid channels in ways that rigid conventional liposomes cannot. Ethosomes utilise the fluidising effect of ethanol to enhance both vesicle deformability and SC lipid disruption simultaneously. Studies in India have shown that NLCs have been used for drugs like simvastatin and tretinoin with promising results, improving drug solubility, protecting labile molecules and providing sustained release at the same time [40].

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13.2. Smart Patches

The idea of a smart transdermal patch, one that can sense a physiological parameter and modulate drug delivery in response, has moved closer to clinical reality. These devices combine a biosensor for glucose, cortisol, uric acid or other analytes in sweat or interstitial fluid, with a responsive drug delivery system in a flexible device that can conform to the skin. Proof-of-concept systems have been demonstrated for glucose-responsive insulin delivery, and for patches that monitor inflammatory markers. The Indian engineering and pharmaceutical sciences groups have begun to contribute in this area especially in the development of low-cost flexible sensor platforms [41].

13.3. 3D Printed Patches

3D printing has provided geometric and compositional flexibility that is not easily achieved by traditional manufacturing. Now it is possible to manufacture patches with spatially controlled drug distribution, layer thickness and patch geometry using fused deposition modelling, inkjet printing or semi-solid extrusion. This is especially true for personalized medicine, where, theoretically, a patch could be made to spec for an individual patient based on body weight, skin characteristics and pharmacogenomic profile. 3D printing of microneedle arrays allows the production of complex tip geometries which maximize the efficiency of skin penetration while minimizing pain [34].

13.4. Stimuli-Responsive Systems

Stimuli-responsive transdermal systems release drug in response to specific triggers, either physiological signals or external stimuli. pH-sensitive polymers can respond to changes in the pH of the skin surface or to local changes associated with infection. Poly(N-isopropylacrylamide)-based thermoresponsive systems exhibit reversible phase transitions within certain temperature ranges. Photo responsive patches deliver drug when exposed to near-infrared light. Hyperthermic activation of alternating magnetic field exposes drug release from magnetic nanoparticle-loaded patches [42].

XIV. APPLICATIONS OF TDDS

14.1. Hypertension: The clonidine transdermal patch (Catapres-TTS®) solved the compliance problem of many oral antihypertensive regimens by providing a week of therapy with a single application. Nitroglycerin patches provide sustained prophylactic antianginal coverage without the tolerance problems noted with continuous oral or intravenous nitroglycerin.

14.2. Pain management: Fentanyl patches (Duragesic®) have become the standard of care for moderate to severe chronic pain, including cancer pain. This is a disease burden that India bears heavily, with access to oral opioids often restricted. Lidocaine patches for the topical delivery of local anaesthetic concentrations to painful skin in post-herpetic neuralgia with minimal systemic absorption [38].

14.3. Hormone therapy: For women at higher thromboembolic risk, many clinicians favour transdermal oestrogen over oral oestrogen for hormone replacement therapy as it bypasses the hepatic first-pass synthesis of clotting factors stimulated by oral oestrogen. Transdermal testosterone preparations are the treatment of choice for male hypogonadism.

14.4. Smoking cessation: Nicotine replacement therapy with transdermal patches is one of the most evidence-based pharmacological aids to smoking cessation. The patches provide steady-state nicotine levels that blunt withdrawal symptoms without the cardiovascular risks of continued smoking.

14.5. Neurological conditions: Rivastigmine patches (Exelon Patch®) are as effective as the oral capsule, but with a significantly lower incidence of nausea and vomiting. Rotigotine patches (Neupro®) deliver continuous dopaminergic stimulation for Parkinson's disease in the setting of motor fluctuations associated with intermittent oral levodopa dosing.

14.6. Antifungal applications: An important application is the transdermal delivery of antifungals like clotrimazole, miconazole and terbinafine for dermatophyte infections, ensuring sustained drug concentrations in the local region of

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infection, with minimal systemic adverse effects. This is even more relevant as superficial fungal infections are on the rise in the warm, humid climate of many parts of India [43].

XV. FUTURE PROSPECTS

15.1. Personalized medicine: The vision of personalized transdermal therapy, where a patch is designed for an individual patient based on skin characteristics, genetic profile, body weight and disease status, is becoming more feasible. Single-patient SC information can be obtained by non-invasive optical techniques like confocal Raman spectroscopy. This, combined with pharmacogenomic data and AI-assisted formulation design, could guide the choice of patch type, enhancer and drug loading for each patient [44].

15.2. Biosensor-integrated patches: Flexible electrochemical sensors embedded into patch materials can measure biomarkers in sweat or interstitial fluid continuously and transmit the data wirelessly. In closed-loop systems, this sensor signal would be the direct triggering signal for the drug delivery module, the paradigmatic example of which is the wearable artificial pancreas. The main remaining technical challenges are the miniaturization of power sources, the long-term sensor stability and regulatory framework for adaptive delivery devices [41].

15.3. AI-assisted formulation design: Machine learning models trained on large databases of drug properties, excipient combinations and permeation outcomes can be used to predict skin permeability coefficients, suggest potential enhancer combinations and identify possible irritation risks before any laboratory work. This is a feasible direction even in the absence of enormous resources, provided Indian institutions have access to open source machine learning tools and permeation databases available to the public [44].

15.4. Delivery of biologics: Microneedle arrays that dissolve have been used to deliver influenza vaccines, hepatitis B antigens, and insulin with results similar to subcutaneous injection. If this technology is translated into clinical practice, it could revolutionize vaccination programs in resource-limited settings by removing the cold chain requirements and the need for trained injection personnel, both major barriers to vaccination in rural India [27].

XVI. CONCLUSION

Transdermal drug delivery has come a long way since the first days of the nicotine patch. Once a niche route for a few small, lipophilic, low-dose drugs, decades of research have turned it into a platform with genuine versatility, and increasing clinical relevance. The stratum corneum, once considered only as a barrier, is now sufficiently well understood as to be manipulated, bypassed or worked around with a sophisticated toolkit of chemical enhancers, physical techniques and nanotechnology-based methods. The result is a route of administration that overcomes many of the limitations of oral and parenteral therapy while also providing controlled release, easy termination and improved compliance. Today's marketed products include those for cardiovascular disease, pain management, neurology, hormone replacement and smoking cessation. Many more products are in various stages of clinical evaluation. TDDS is especially promising in India, where compliance with complex oral regimens is a well-recognized challenge and the burden of chronic disease is increasing rapidly. What's most exciting looking forward is the convergence of a number of technologies. Smart patches that can monitor and respond to physiology, 3D-printed personalized formulations, dissolving microneedle arrays for vaccine delivery and AI-assisted design are no longer purely speculative, but the subject of active research with demonstrable early results. The extent to which these innovations will become affordable and accessible clinical products depends not only on continued scientific progress, but also on regulatory adaptation, manufacturing scale-up and on the ability of the health system to make use of them where they are most needed.

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