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Review on Transdermal Drug Delivery System and Herbal Transdermal Patches

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Abstract: Transdermal drug delivery system (TDDS) has emerged as one of the most reliable non-invasive routes of drug administration, offering an alternative to oral and parenteral dosage forms. By delivering therapeutic agents across intact skin directly into the systemic circulation, transdermal patches bypass hepatic first-pass metabolism, minimize gastrointestinal degradation, sustain plasma drug concentrations, reduce dosing frequency and improve patient compliance. This review presents a detailed account of the anatomy of skin as a delivery portal, the historical evolution of transdermal technology, the rationale, advantages and limitations of TDDS, the mechanisms and pathways of percutaneous absorption, the physicochemical and physiological factors that govern permeation, the essential components of a patch, the various design approaches (reservoir, matrix, drug-in-adhesive and micro-reservoir systems), chemical and physical permeation-enhancement strategies, methods of fabrication, pharmacopeial evaluation parameters and currently marketed transdermal products.

The second half of the review focuses specifically on herbal transdermal patches, an emerging green alternative in which standardized plant extracts and phytoconstituents are incorporated into a polymeric matrix instead of, or in combination with, synthetic drugs. Herbal transdermal systems combine the traditional therapeutic wisdom of medicinal plants with the controlled-release engineering of modern TDDS, offering reduced toxicity, wider patient acceptance and lower manufacturing cost. The review discusses commonly employed herbal drugs, natural polymers and permeation enhancers, formulation strategies unique to phytopharmaceuticals, evaluation protocols, current challenges such as standardization and stability, and recent advances including nanocarrier-based herbal patches. The review concludes that although considerable technological progress has been made, systematic pharmacokinetic and clinical validation of herbal transdermal systems remains an important area for future research.

Keywords: *Transdermal drug delivery system; transdermal patch; permeation enhancer; herbal patch; polyherbal formulation; skin permeation; controlled release; phytoconstituents.*

1. INTRODUCTION

Delivery of a drug via the skin is a highly effective approach to drug administration. The transdermal drug delivery system (TDDS) is an innovative approach in the pharmaceutical field for the administration of drugs because it has several advantages over other routes of drug administration. Conventional formulations of drug delivery systems require larger doses and larger regimens to achieve therapeutic effects, and long-term regimens may produce major side effects and ultimately low patient compliance [1]. The oral route is generally the most suitable, convenient, and ideal route of drug administration because of the many advantages associated with it. Despite these advantages, there are several disadvantages associated with this route for drug delivery, including enzymatic degradation in the gastrointestinal tract, gastrointestinal irritation, low absorption and low bioavailability, etc. Some drugs are also unsafe via this route. In cases of drugs that are administered parenterally, needle phobia is a common psychological problem associated with children and adults, as is at a risk of infection while drug is being administered [2]. To overcome such challenges, TDDS is the ideal approach for such drugs.The skin is considered the first line of defense in an organism, which prevents direct exposure of the organism to toxins, antagonistic pathogens, and environmental viruses. There are several layers of lipid matrix along with encircled keratinocytes within the upper strata (15 µm) of the skin, which act as a barrier. The skin is also the main barrier that restricts the entrance of most drugs. Many permeation enhancers have been developed to overcome the problems associated with skin permeation. In TDDS, several approaches have been developed to enhance drug permeation via several mechanisms through the skin layer of the stratum corneum. While hydrophilic drugs partition within the intracellular area of the stratum corneum and lipophilic drugs pass through an intercellular route, most molecules cross the stratum corneum via intracellular and intercellular routes. Several factors may affect the activity of drug formulation, such as molecular weight, polarity, drug dose, and drug solubility. As drug formulation is considered an important factor for the development of the dosage form that ultimately reaches the target site, the physiochemical properties of the drug entity are important for the development of formulations that can reach the systemic circulation across the stratum Basic Principles of Drug Permeation Through Skin

Fig 1: Transdermal Patch

Drug permeation is the process by which a drug moves from a transdermal formulation across the skin and, when intended, reaches the systemic circulation. The stratum corneum is the main barrier controlling this process.

BASIC PRINCIPLE OF DRUG PERMEATION

1. Drug Release

After application of a transdermal patch, the drug or herbal active constituent is released from the polymer matrix or reservoir.

2. Partitioning into the Skin

The drug must move from the formulation into the outer skin layer, mainly the stratum corneum. The ability of the drug to partition into the skin depends on its physicochemical properties.

3. Diffusion Through the Stratum Corneum

The drug then diffuses across the stratum corneum from an area of higher concentration toward an area of lower concentration. This is generally described by Fick's law of diffusion.

A simplified relationship is:

- Drug flux (J) ∝ concentration gradient
- Factors such as drug concentration, diffusion coefficient, and skin permeability influence the rate.

4. Movement Through the Viable Epidermis and Dermis

After crossing the stratum corneum, the drug passes through the viable epidermis and dermis. From the dermis, a drug intended for systemic delivery can enter the cutaneous microcirculation.

5. Routes of Skin Permeation

Drugs can potentially cross the skin through:

- Intercellular route – between skin cells.
- Transcellular route – directly through skin cells.
- Appendageal route – through hair follicles and sweat glands.

The stratum corneum usually provides the greatest resistance to permeation

Advantages of TDDS

- To prevent first-pass metabolism, transdermal delivery ensures a sustained and continuous permeation of a substance over an extended period.[4]
- Increase Patient compliance.
- It does not interfere the liquid of the stomach and intestines.[5]
- Sustains stable and constant blood levels, providing control over an extended period.[6], [7]
- Reduced plasma concentration levels of drugs.
- Reduce fluctuations of drug in plasma levels, Utilize drug candidates with short half-life and Low therapeutic index.[8]
- In case of toxicity drug delivery is easy eliminated.
- Reduce of dosing frequency an enhance Patients compliance.[2]
- Transdermal delivery enhances the effectiveness of numerous drugs by circumventing certain issues related to the medication, such as poor absorption and gastrointestinal irritation.
- The streamlined medication schedule results in decreased differences in drug response both within and among patients.

2. ANATOMY AND PHYSIOLOGY OF THE SKIN LAYER

Understanding the anatomy and physiology of the skin can lead to the ideal design and development of robust approaches for drug delivery systems. In humans, the skin is the largest body part. The total area of human skin is 20 square feet, and the entire area consists of approximately one-third of the blood traveling through the body [4]. The function of the skin is represented in Fig. 1. Anatomy of the skin is a heterogeneous medium composed of multiple composite layers with specific functions. It consists of several layers, such as the epidermis (the outer layer), dermis, and subcutaneous layer. The absorption of chemical and outer entities occurs through the different layers of the skin. Intercellular or transcellular mechanisms involve drug delivery into systemic circulation through the stratum corneum. Several factors affect drug delivery through the skin, i.e., the physiology and environmental nature of the skin, the origin (human or animal), and the physicochemical properties of the drug and the compatibility of the excipient, should be considered [5].

The epidermis, dermis, and subcutaneous tissue, together with sebum and sweat glands, make up human skin. The stratum corneum is formed by the stratified epithelium known as the epidermis, which has layers of spinous and basal granular cells. Compacted with metabolically dormant cells, the stratum corneum is around 15–20 layers deep and contains a complex interlocking structure with proteins and

lipids that resembles bricks and mortar. Fatty acids, cholesterol, and ceramides are among the important lipids found in it; ceramides comprise around half of the lipids. Free fatty acids (10–15 %) are saturated and have a very long chain. The function of the stratum corneum barrier depends on these lipids [6]. About 75–80 % protein, 5–15 % lipids, and 5–10 % unidentified substances make up the stratum corneum. Corneocytes, according to the brick and mortar model, are flat, elongated, and polygonal cells that are 0.2–1.5 µm thick and 34.0–46.0 µm in diameter. They are encased in a lipid matrix that consists of crystalline or gel lipid bilayers and lamellar structures [7]. Importantly, mortar is not just a homogenous matrix; rather, lipids are fairly connected with the lamellar part (corresponding layers of lipid bilayers and water), together with other lipid bilayers found to be in the crystalline or gel form. A review on transdermal drug delivery through patches

A transdermal drug delivery system (TDDS) falls under the controlled drug delivery category, aiming to administer drugs through the skin at a predetermined and controlled rate. This approach presents numerous benefits, such as extended therapeutic impact, reduced adverse effects, increased bioavailability, enhanced patient adherence, and convenient discontinuation of medication.

3. SKIN STRUCTURE

Indeed, the Skin is the body's largest organ, acting as a crucial protective barrier safeguarding the body from a range of external factors and potential threats. Its large surface area, approximately 1.7 square meters in an average person, allows it to effectively shield the body from microorganisms, ultraviolet (UV) radiation, chemicals, allergens, and water loss. This protective function is vital for maintaining overall health and well-being. [12], [8], [13] Additionally, the skin also plays a role in regulating body temperature, sensation, and the synthesis of vitamin D through exposure to sunlight. Taking care of the skin is essential to support its functions and maintain good health.

The skin is commonly categorized into three primary layers: The outermost layer, known as the epidermis; (b) The middle layer, referred to as the dermis; and (c) The innermost layer, called the hypodermis.

3.1 Structure of the skin

Fig 2: Basic structure of skin

1. Epidermis

The epidermis constitutes the skin’s outermost layer. It provides a waterproof barrier and contains no blood vessels. The cells in the epidermis include keratinocytes, which produce the protein keratin and help make the skin tough and protective. The epidermis includes melanocytes, responsible for skin color, and Langerhans cells, integral components of the immune system.

The epidermis has several sub- layers, including:

- Stratum corneum
- Stratum granulosum
- Stratum spinosum
- Stratum basale

It's different thickness in different parts of our body, about 0.8 mm thick on our palms and the soles of our feet.[13] The epidermis is made up of layers of skin cells. Most of these cells are called keratinocytes. They make up about 95% of the cells in the epidermis. The epidermis houses various cell types, including melanocytes, Langerhans cells, and Merkel cells. [14]

On top of the epidermis, there's a super thin layer called the stratum corneum. It's the very surface of our skin and touches everything around us. This layer is special because it keeps our body safe. Its thickness and how much water it has are important. The stratum corneum is made mainly of tough proteins (70% keratin) and some fats (20% lipid). [15] Water in this layer is connected to these proteins. [16]

1. Dermis

The dermis is located beneath the epidermis which is 3 to 5 mm and is thicker than the epidermis. The dermis is responsible for providing nutrients to the epidermis and housing the skin's appendages and sensory receptors.

It comprises diverse structures, such as:

- Blood vessels
- Hair follicles
- Sweat glands
- Sebaceous glands
- Nerve endings
- Collagen and elastin fibers

Tiny blood vessels called capillaries are absolutely close to the skin surface, about 0.2 mm away. These capillaries act like drains, pulling away most of the stuff that tries to get through the skin. This is essential because it keeps the concentration of substances that enter the skin very low. This difference in concentration between the inside and outside of the skin helps push things through it.

When it comes to delivering medicines through the skin, this layer is like a gel made Mostly of water. For most medicines that dissolve in water, this layer doesn't offer much resistance, making it easier for the medicines to pass through. However, if a Medicine is oily (like some lotions or creams), this layer can create more of a challenge for it to get through. [17]

2. Subcutaneous tissue (Hypodermis)

The subcutaneous tissue, also known as the hypodermis, constitutes the deepest layer of the skin, consisting of adipocytes (fat cells) and connective tissue. This layer serves as an insulator, helping to regulate body temperature and serves as a protective cushion, shielding the body's organs and bones from impacts.

When medicines are applied to the skin, like creams or patches, they have to go through these three layers to get into our bloodstream. For some medicines, they need to go even deeper, reaching our body's circulation. But for most skin treatments, they just need to get through the outermost layer, the stratum corneum, and stay in the skin layers to work effectively.

3. HISTORICAL EVOLUTION OF TRANSDERMAL DRUG DELIVERY

The concept of applying medicinal substances to the skin for systemic effect is not new; poultices and plasters were used in ancient Egyptian, Greek and Ayurvedic medicine long before the pharmacological basis of skin permeation was understood. The modern era of TDDS began in the twentieth century with systematic studies on percutaneous absorption kinetics. The landmark event in commercial transdermal

technology was the 1979 approval of the scopolamine patch (Transderm-Scop) for motion sickness, followed by nitroglycerin patches for angina in 1981, clonidine patches for hypertension, and subsequently a wide range of hormonal, analgesic and smoking-cessation patches [7]. Over the past four decades, patch design has evolved from simple reservoir systems to sophisticated matrix, drug-in-adhesive, microneedle and iontophoretic systems, reflecting continuous refinement of polymer science, adhesive technology and permeation-enhancement strategies [10].

4. RATIONALE, ADVANTAGES AND LIMITATIONS OF TDDS

4.1 Advantages

- Avoidance of hepatic first-pass metabolism and gastrointestinal degradation, thereby improving systemic bioavailability of susceptible drugs [1,3].
- Maintenance of steady, sustained plasma drug concentrations over an extended period, avoiding the peak-and-trough fluctuations typical of oral dosing [2,4].
- Reduced dosing frequency and improved patient compliance, particularly beneficial for chronic conditions and paediatric or geriatric patients [1,6].
- Non-invasive and painless mode of administration compared with parenteral routes [4,9].
- Ability to terminate drug input rapidly simply by removing the patch, which is valuable in the event of adverse effects [4].
- Suitability for drugs with short biological half-life or narrow therapeutic index that require constant plasma levels [7].
- Self-administration is simple, improving convenience and reducing dependence on healthcare personnel [9].

5. MECHANISMS AND PATHWAYS OF PERCUTANEOUS DRUG PERMEATION

Drug molecules applied to the skin surface may traverse the stratum corneum through three principal microscopic routes: the intercellular route, the transcellular route and the appendageal (shunt) route [5,9].

5.1 Intercellular Route

In this pathway, the drug diffuses through the lipid matrix that surrounds the corneocytes, following a tortuous path around the cells rather than through them. Because the actual diffusional path length is many times greater than the physical thickness of the stratum corneum, this route is generally slow but is the predominant pathway for most lipophilic drug molecules [5].

5.2 Transcellular Route

Here the drug passes directly through the corneocytes and the intervening lipid lamellae in a sequential fashion. Since the drug must partition repeatedly between the hydrophilic keratin-rich corneocyte interior and the lipophilic intercellular domains, this pathway offers greater resistance and is less favored for highly lipophilic drugs, although it remains relevant for smaller polar molecules [5,9].

5.3 Appendageal (Shunt) Route

This route utilizes hair follicles, sebaceous glands and sweat ducts, which effectively bypass the stratum corneum. Although appendages occupy a very small fraction of total skin surface area, this pathway can dominate during the initial, non-steady-state phase of absorption and is particularly relevant for ionic species, macromolecules and nanoparticulate carriers that cannot easily cross the continuous stratum corneum barrier [5,10].

Drug transport across the skin is generally described by Fick's first law of diffusion, according to which the steady-state flux of drug across a membrane is directly proportional to the concentration gradient across that membrane and the diffusion coefficient of the drug within it, and inversely proportional to the thickness of the diffusional pathway. This relationship forms the theoretical basis for designing rate-

controlling membranes and for the selection of permeation enhancers that increase either drug diffusivity or its partition coefficient into the stratum corneum [9,10].

6. FACTORS AFFECTING TRANSDERMAL PERMEATION

6.1 Physicochemical Factors

- Molecular weight and size: molecules below roughly 500 Da permeate more readily than larger molecules.
- Partition coefficient (log P): moderate lipophilicity (log P 1–3) favours partitioning into the lipid-rich stratum corneum while retaining sufficient aqueous solubility for partition into the viable epidermis.
- Degree of ionisation: unionised drug species cross the lipid membrane far more readily than ionised species, making pH of the vehicle an important formulation variable.
- Drug concentration and dose: a steep concentration gradient favours passive diffusion; the daily dose must be compatible with the finite patch surface area.
- Melting point: lower-melting-point compounds generally exhibit greater membrane solubility and permeability.

6.2 Physiological and Biological Factors

- Skin condition, thickness and site of application: palms and soles have a thick stratum corneum, whereas post-auricular and scrotal skin are considerably more permeable.
- Skin hydration: occlusive patches increase local hydration of the stratum corneum, which loosens the packing of corneocytes and lipid lamellae and enhances permeability.
- Skin temperature and blood flow: increased cutaneous blood flow (for example after exercise or in febrile states) maintains a steeper concentration gradient and can enhance absorption.
- Age, sex and race: neonatal and aged skin, as well as certain ethnic variations in stratum corneum lipid composition, can alter barrier function.
- Skin metabolism: cutaneous enzymes may metabolize certain drugs during permeation (a 'skin first-pass effect').

6.3 Formulation Factors

- Nature and concentration of permeation enhancers included in the patch matrix.
- Type and grade of rate-controlling polymer or membrane.
- Vehicle pH and solvent system, which influence the ionisation state and thermodynamic activity of the drug.
- Patch surface area and drug loading, which together determine the maximum deliverable dose.

7. BASIC COMPONENTS OF A TRANSDERMAL PATCH

Regardless of design, most transdermal patches share a common set of functional components, each contributing to the safety, stability and performance of the delivery system [6,9].

7.1 Backing Membrane

The backing layer is the outermost component, providing structural support and protecting the formulation from the external environment, including moisture, dust and mechanical damage. It is typically occlusive,

flexible, chemically inert and impermeable to the drug and to water vapor. Common materials include polyester, aluminium-vinyl laminates and metallised plastic films.

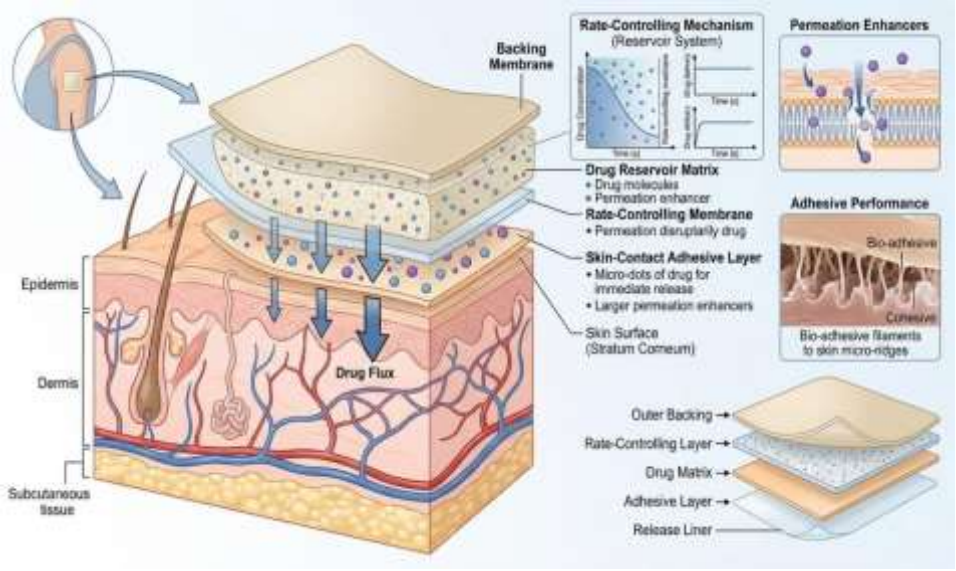


Fig 3: Basic Components of Transdermal Patches

7.2 Drug Reservoir / Matrix

This is the core of the patch containing the active pharmaceutical ingredient, either dissolved or dispersed within a polymeric matrix, gel or liquid reservoir. Selection of an appropriate polymer determines the rate and duration of drug release.

7.3 Rate-Controlling Membrane

Present in reservoir-type systems, this semi-permeable membrane governs the release rate of drug from the reservoir into the adhesive layer and then to the skin, allowing zero-order release kinetics to be engineered independent of the skin's own permeability.

7.4 Pressure-Sensitive Adhesive (PSA)

The adhesive layer ensures intimate and sustained contact between the patch and the skin surface throughout the wear period. Ideal adhesives should adhere readily with light pressure, be removable without residue or skin trauma, and be non-irritating, non-sensitising and compatible with the drug and other excipients. Commonly used adhesive classes include polyisobutylene, acrylics and silicone-based adhesives.

7.5 Permeation Enhancers

These are chemical or natural agents incorporated into the formulation to reversibly reduce the barrier resistance of the stratum corneum and thereby increase drug flux [14].

7.6 Release Liner

A protective liner covers the adhesive surface prior to use and is peeled away immediately before application; it is generally made of a siliconised polyester film.

7.7 Other Excipients

Plasticisers (glycerol, propylene glycol, dibutyl phthalate) impart flexibility to polymer films; humectants prevent drying; and preservatives, antioxidants and stabilisers protect the formulation from microbial and oxidative degradation during shelf life.

8. TYPES AND DESIGN APPROACHES OF TDDS

8.1 Reservoir-Type System

The drug is held as a solution or suspension in a liquid, gel or semisolid reservoir separated from the skin by a rate-controlling microporous or non-porous polymeric membrane, with an adhesive rim ensuring skin contact. This design permits precise, predictable zero-order drug release but carries a risk of dose dumping if the membrane ruptures [6,7].

8.2 Matrix-Type (Monolithic) System

The drug is homogeneously dispersed throughout a hydrophilic or lipophilic polymer matrix, which is then moulded into a medicated disc and mounted onto an occlusive backing. Release generally follows Higuchi (square-root-of-time) kinetics. Matrix systems are simpler and cheaper to manufacture and eliminate the dose-dumping risk associated with reservoir systems [6,9].

8.3 Drug-in-Adhesive System

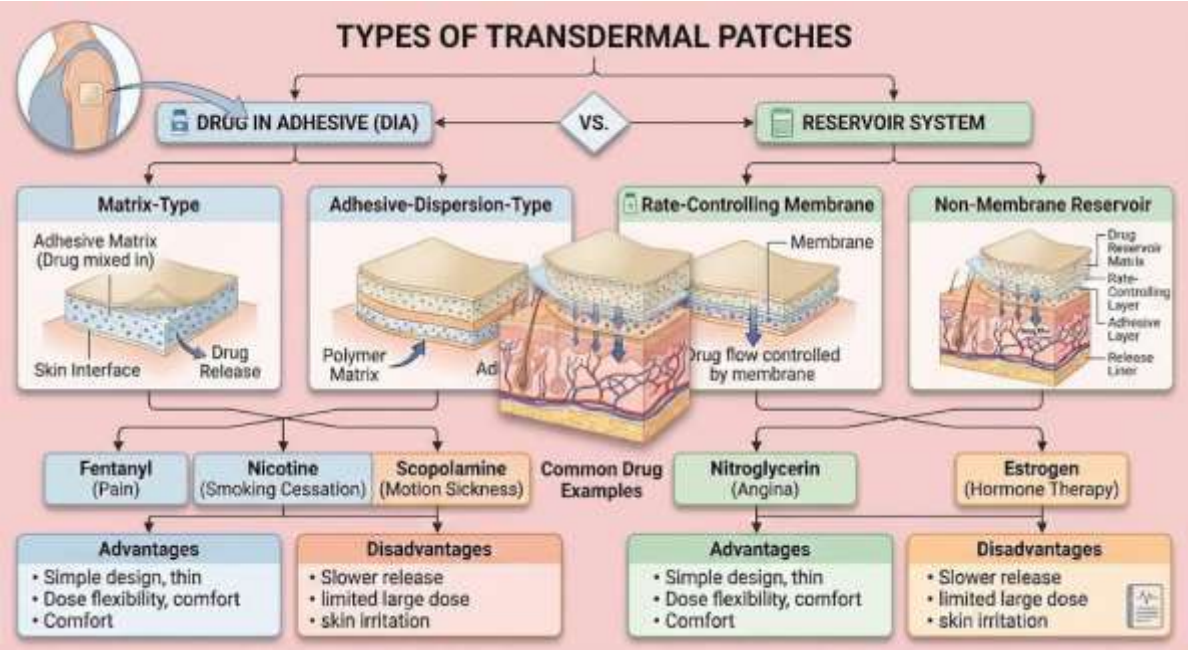
The drug is incorporated directly into the pressure-sensitive adhesive polymer, which itself serves as the drug reservoir and the means of skin contact. This design allows thinner, more comfortable and more cosmetically acceptable patches, and is the design most frequently used commercially today [6].

8.4 Micro-Reservoir (Combination) System

This design combines features of reservoir and matrix systems: the drug suspension is dispersed as microscopic spheres in a biocompatible polymer, which is then cross-linked in situ, giving a large number of tiny drug reservoirs distributed through a matrix, thereby achieving both a controlled release profile and improved patch stability [7].

8.5 Vapour Patch

A relatively newer category in which the adhesive layer contains volatile active ingredients (for example essential oils or menthol) that are released for local or inhalational rather than strictly systemic effect, illustrating the flexibility of transdermal patch technology for non-conventional applications [9].



9. PERMEATION ENHANCEMENT STRATEGIES

9.1 Chemical Permeation Enhancers

Chemical enhancers act by disrupting the ordered arrangement of stratum corneum lipids, extracting lipid components, increasing lipid fluidity, altering keratin conformation within corneocytes, or improving drug partitioning into the skin. Commonly used classes include alcohols and glycols (ethanol, propylene glycol),

fatty acids and esters (oleic acid, isopropyl myristate), sulphoxides (dimethyl sulphoxide), pyrrolidones (N-methyl-2-pyrrolidone), surfactants (sodium lauryl sulphate, polysorbates), terpenes (menthol, limonene) and urea derivatives. Although effective, many synthetic enhancers can cause skin irritation, erythema or sensitisation at concentrations required for meaningful enhancement, which has stimulated growing interest in naturally derived alternatives [14].

9.2 Herbal / Natural Permeation Enhancers

Naturally derived permeation enhancers, including essential oils (eucalyptus oil, clove oil, peppermint oil, cineole), terpenes, fatty acid esters from plant sources, and certain saponins, have gained attention because they are generally regarded as pharmacologically compatible, biodegradable, less irritating and non-sensitising compared with many synthetic agents, while still being capable of transiently loosening the intercellular lipid packing of the stratum corneum [14,15]. Menthol, camphor, clove oil and eucalyptus oil are among the most extensively studied herbal enhancers and are frequently incorporated into both conventional and herbal transdermal patches.

9.3 Physical Enhancement Techniques

Beyond chemical strategies, several physical methods have been developed to transiently and reversibly increase skin permeability, including iontophoresis (application of a small electric current to drive ionised drug molecules across the skin), electroporation (application of short high-voltage pulses that create transient aqueous pores in the lipid bilayer), sonophoresis or phonophoresis (use of low-frequency ultrasound to disrupt stratum corneum lipid organisation), microneedle arrays (which create microscopic channels through the stratum corneum while avoiding pain receptors in the dermis), and needle-free/jet injection and thermal ablation techniques [5]. These physical methods extend the range of deliverable molecules to include larger, hydrophilic and even macromolecular drugs such as peptides and vaccines, which are otherwise poor candidates for passive transdermal delivery.

10. METHODS OF PREPARATION OF TRANSDERMAL PATCHES

10.1 Solvent Casting / Solvent Evaporation Technique

This is the most widely used laboratory-scale method. The drug, polymer(s) and other excipients are dissolved or dispersed in a common organic or aqueous solvent system, the resulting homogeneous solution or dispersion is poured into a levelled mould or Petri dish (often lined with a backing membrane or mercury/silicone surface), and the solvent is allowed to evaporate slowly, typically at room temperature or under mild heat, over several hours to yield a uniform, dry polymeric film that is subsequently cut into patches of the desired dimensions [17,22,23].

10.2 Hot-Melt Extrusion / Direct Milling

The drug and polymers are blended in the molten state and extruded through a die to obtain a continuous uniform film without the use of solvents, which is advantageous for heat-stable drugs and eliminates residual solvent concerns.

10.3 Circular Teflon Mould / Mercury Substrate Method

A polymer solution containing the drug is poured over a mercury surface or a Teflon mould, covered to control the rate of solvent evaporation, and dried to form a film that is then cut into patches; this method is common for laboratory-scale matrix patch preparation.

10.4 Proprietary Membrane Lamination

Used for commercial reservoir-type systems in which a preformed rate-controlling membrane is laminated together with the drug reservoir layer, adhesive layer, and backing membrane using continuous roll processing.

10.5 Asymmetric TPX Membrane Method

A polymeric solution is cast on a glass mould and dried under controlled humidity and temperature conditions to create an asymmetric membrane with graded porosity, offering a reservoir-type patch with improved control over drug release rate.

11. EVALUATION PARAMETERS OF TRANSDERMAL PATCHES

Comprehensive physicochemical and biopharmaceutical evaluation is essential to ensure the quality, safety and performance of transdermal patches. Standard evaluation parameters, as widely reported in formulation studies, are summarised in Table 1 [16,17,18,19,20,21,22,23].

Evaluation Parameter	Purpose / Typical Method
Physical appearance	Visual inspection for colour, clarity, smoothness and flexibility of the film
Thickness	Measured at several points using a digital micrometer or screw gauge to confirm uniformity
Weight variation	Individual patches weighed and compared with the average to check formulation consistency
Folding endurance	Number of times a patch can be folded at the same point before it breaks, reflecting film flexibility and mechanical strength
Drug content uniformity	Assay of drug in patches by UV spectrophotometry or HPLC to confirm homogeneous distribution
Moisture content and moisture uptake	Determines film stability, brittleness and susceptibility to microbial growth under storage conditions
Water vapour transmission rate (WVTR)	Assessed to evaluate the occlusive/breathable nature of the backing membrane
Tensile strength / % elongation	Mechanical testing to evaluate durability during handling and wear
Flatness	Measurement of any shrinkage after drying, expressed as percentage constriction
Surface Ph	Measured using a pH electrode on a swollen patch to rule out skin irritation potential
Swelling index	Extent of water uptake by the polymer matrix, related to drug release behaviour
In vitro drug release	Franz diffusion cell or USP dissolution apparatus (paddle-over-disc) used to generate cumulative release profiles
Ex vivo / in vitro skin permeation study	Permeation across excised animal or synthetic membrane to determine flux, permeability coefficient and lag time
Drug–excipient compatibility	FTIR, DSC and XRD studies to rule out chemical interaction between drug and polymer/excipients
Skin irritation / sensitisation study	In vivo or reconstructed skin model testing to confirm dermal safety
Stability studies	Storage under ICH-recommended conditions to evaluate shelf life and packaging suitability

In vitro release data are typically fitted to kinetic models such as zero-order, first-order, Higuchi and Korsmeyer–Peppas equations to elucidate the mechanism of drug release, whether diffusion-controlled, erosion-controlled, or a combination (anomalous, non-Fickian transport) [20,22]. Folding endurance values exceeding roughly 200 folds without cracking, and drug content values within pharmacopoeial limits of ninety to one hundred ten percent of the labelled amount, are generally regarded as indicative of a robust formulation [17,18].

12. MARKETED TRANSDERMAL PRODUCTS

Several transdermal products have achieved sustained commercial and clinical success worldwide, validating the technology across diverse therapeutic categories, as illustrated in Table 2 [7,10].

Drug / Brand (representative)	Therapeutic Category	Design Type
Nitroglycerin (Nitro-Dur, Transderm-Nitro)	Angina pectoris / anti-anginal	Matrix / reservoir
Scopolamine (Transderm-Scop)	Motion sickness (antiemetic)	Reservoir
Clonidine (Catapres-TTS)	Hypertension	Reservoir
Fentanyl (Duragesic)	Chronic pain management	Reservoir / matrix
Nicotine (Nicoderm, Habitrol)	Smoking cessation	Matrix / drug-in-adhesive
Estradiol (Estraderm, Climara)	Hormone replacement therapy	Reservoir / matrix
Rivastigmine (Exelon patch)	Alzheimer's / Parkinson's dementia	Matrix
Rotigotine (Neupro)	Parkinson's disease / restless legs syndrome	Drug-in-adhesive
Buprenorphine (Butrans)	Chronic pain management	Matrix
Methylphenidate (Daytrana)	Attention-deficit hyperactivity disorder	Drug-in-adhesive
Diclofenac epolamine (Flector patch)	Local analgesic / anti-inflammatory	Matrix
Lidocaine (Lidoderm)	Post-herpetic neuralgia (local analgesia)	Matrix

13. HERBAL TRANSDERMAL PATCHES: INTRODUCTION AND RATIONALE

Herbal medicine continues to occupy a central place in global healthcare, particularly in countries such as India where traditional systems including Ayurveda, Siddha and Unani have been practiced for centuries. Despite their long history of use and generally favourable safety profile, most herbal formulations are administered orally as decoctions, tablets, capsules or syrups, formats that expose the active phytoconstituents to harsh gastric pH, hepatic first-pass metabolism and enzymatic degradation, resulting in low and inconsistent systemic bioavailability [11,12]. A herbal transdermal patch is a controlled-release dosage form in which a standardized plant extract, an isolated phytoconstituent, or a combination of several herbal actives (a polyherbal formulation) is incorporated into a polymeric film or matrix designed for topical application, allowing sustained percutaneous absorption of the active constituents directly into the systemic circulation [11,13].

The rationale for herbal TDDS mirrors that of conventional TDDS but carries additional advantages specific to phytopharmaceuticals: avoidance of gastrointestinal instability of labile constituents such as flavonoids and glycosides, avoidance of extensive hepatic metabolism that can inactivate many plant-derived molecules, provision of a steady and prolonged release profile suited to chronic conditions such as arthritis, diabetes and hypertension for which many herbal drugs are traditionally used, and the ability to combine several synergistic herbal actives within a single small, patient-friendly dosage form [12,13].

14. ADVANTAGES OF HERBAL / POLYHERBAL TRANSDERMAL SYSTEMS

- Natural origin generally translates into a lower incidence of severe adverse effects and better patient acceptance compared with synthetic drugs [13].
- Avoidance of first-pass hepatic metabolism preserves labile phytoconstituents that would otherwise be extensively degraded after oral administration [11,12].
- Polyherbal combinations allow multiple therapeutic actions (for example anti-inflammatory, analgesic and antimicrobial) to be delivered from a single patch, exploiting pharmacological synergy among plant actives [13].
- Sustained release from the patch matrix reduces dosing frequency, which is valuable for chronic disease conditions traditionally managed with herbal therapy such as osteoarthritis and diabetes [12].
- Generally lower manufacturing cost of many plant extracts compared with certain synthetic drugs or biologics [14].

- Biodegradable natural polymers and enhancers used in herbal patches are often more environmentally sustainable than purely synthetic systems [15].
- Non-invasive, self-administrable format improves compliance in long-term herbal therapy regimens [11].

15. COMMONLY USED HERBAL DRUGS/EXTRACTS IN TRANSDERMAL PATCHES

A wide range of medicinal plants and their extracts have been explored in matrix and polyherbal transdermal patch formulations, targeting anti-inflammatory, analgesic, antimicrobial, wound-healing and antidiabetic applications, as summarized in Table 3 [11,12,13].

Plant / Extract	**Reported Bioactive(s)**	**Principal Therapeutic Use in TDDS**
Curcuma longa (Turmeric)	Curcumin	Anti-inflammatory, wound healing, antimicrobial [11]
Azadirachta indica (Neem)	Nimbin, azadirachtin	Antimicrobial, wound healing [11]
Tridax procumbens	Flavonoids, tannins	Wound healing, anti-inflammatory [11]
Aloe vera	Aloin, polysaccharides	Skin soothing, wound healing, moisturising [13]
Zingiber officinale (Ginger)	Gingerol, shogaol	Analgesic, anti-inflammatory [13]
Matricaria chamomilla (Chamomile)	Apigenin, bisabolol	Anti-inflammatory, soothing [13]
Arnica montana	Helenalin, sesquiterpene lactones	Analgesic, anti-inflammatory (musculoskeletal pain) [13]
Lavandula angustifolia (Lavender)	Linalool, linalyl acetate	Analgesic, relaxant, penetration enhancement [13]
Boswellia serrata	Boswellic acids	Anti-inflammatory (joint disorders)
Plant / Extract	Reported Bioactive(s)	Principal Therapeutic Use in TDDS
Cissus quadrangularis	Ketosterone, triterpenoids	Anti-inflammatory, bone/joint support

16. FORMULATION APPROACHES SPECIFIC TO HERBAL PATCHES

Formulating herbal transdermal patches introduces additional considerations beyond those relevant to single synthetic drug molecules, primarily because plant extracts are complex multi-component mixtures rather than single chemical entities.

16.1 Extract Standardization and Selection

Prior to formulation, crude plant material is typically processed by maceration, Soxhlet extraction, or hydro-alcoholic extraction to yield a concentrated extract, which is then standardized against a marker phytoconstituent (for example curcumin content in turmeric extract) using validated analytical methods such as HPLC or UV spectrophotometry, so that batch-to-batch consistency of the active content in the final patch can be assured [11,12].

16.2 Matrix-Type Herbal Patches

The standardized extract is uniformly dispersed within a hydrophilic or hydrophobic polymer matrix (such as HPMC, ethyl cellulose, chitosan or sodium alginate), cast into a film and dried; this is the most common approach reported for polyherbal patches owing to its simplicity and cost-effectiveness [12,13].

16.3 Reservoir and Nanocarrier-Based Herbal Systems

More advanced formulations encapsulate herbal actives within liposomes, ethosomes, nano emulsions, or polymeric nanoparticles prior to their incorporation into the patch matrix, aiming to protect labile phytoconstituents, improve their solubility and enhance their permeation across the stratum corneum [12].

16.4 Incorporation of Natural Permeation Enhancers

Essential oils and terpenes derived from plants (eucalyptus oil, menthol, clove oil, camphor) are frequently incorporated into herbal patches both for their intrinsic pharmacological activity and their capacity to reversibly enhance stratum corneum permeability, maintaining formulation consistency with the 'all-natural' positioning of the product [14,15].

17. NATURAL POLYMERS AND EXCIPIENTS USED IN HERBAL TDDS

Natural and semi-synthetic polymers are preferred in herbal transdermal formulations because they are biocompatible, biodegradable and consistent with the overall philosophy of a plant-based product, as summarised in Table 4 [12,13].

Polymer / Excipient	Origin	Function in Herbal Patch
Chitosan	Deacetylated chitin (crustacean shells)	Film-forming matrix polymer with intrinsic mucoadhesive and antimicrobial properties
Sodium alginate	Brown seaweed	Gel-forming matrix polymer, controls drug release
Guar gum / Xanthan gum	Plant / microbial fermentation	Viscosity modifier and matrix-forming agent
Hydroxypropyl methylcellulose (HPMC)	Semi-synthetic cellulose derivative	Film-forming, rate-controlling matrix polymer
Ethyl cellulose	Semi-synthetic cellulose derivative	Backbone polymer providing mechanical strength, often blended with HPMC
Gelatin	Animal collagen hydrolysate	Film former, occasionally used as a matrix base
Glycerin / Propylene glycol	Plant/petrochemical-derived	Plasticiser and co-solvent
Vitamin E oil (tocopherol)	Plant oil extract	Antioxidant preservative for extract stability

18. EVALUATION OF HERBAL TRANSDERMAL PATCHES

Herbal transdermal patches are evaluated using largely the same physicochemical and biopharmaceutical parameters applied to conventional patches (thickness, folding endurance, weight variation, moisture content, WVTR, tensile strength, surface pH, in vitro drug release and ex vivo skin permeation), described in Section 11 [16,17,18,19,22]. In addition, herbal formulations require certain extract-specific evaluations:

- Phytochemical screening of the incorporated extract, to confirm the presence of expected classes of secondary metabolites (alkaloids, flavonoids, tannins, saponins, terpenoids) prior to formulation.
- Estimation of marker compound content (for example total curcuminoid or total phenolic content) in the finished patch by validated spectrophotometric or chromatographic methods, in place of single-drug assay.
- Antimicrobial, antioxidant or anti-inflammatory activity testing (in vitro assays such as DPPH radical scavenging or zone-of-inhibition studies) to confirm retention of the extract's pharmacological activity after formulation processing.
- Accelerated and long-term stability studies with particular attention to oxidative degradation of sensitive phytoconstituents, since plant extracts are often more prone to color change, odor change and potency loss than single synthetic molecules.
- Skin irritation and sensitization testing, which is especially important for essential-oil-containing herbal enhancers that, despite being 'natural', can still cause contact sensitization in susceptible individuals.

19. CHALLENGES IN HERBAL TRANSDERMAL DRUG DELIVERY

- Standardization difficulty: plant extracts are complex mixtures whose composition varies with plant source, geography, season of collection and extraction method, making batch-to-batch reproducibility more difficult than with single synthetic drugs [12].
- Limited pharmacokinetic data: unlike well-characterised synthetic drugs, the permeation coefficients, flux values and systemic bioavailability of most phytoconstituents through skin are not well documented, complicating rational formulation design.
- Large molecular size and polarity of many phytoconstituents (glycosides, tannins, polysaccharides) restrict their passive diffusion across the stratum corneum, often necessitating nanocarrier or physical enhancement strategies [12].
- Stability concerns: several bioactive phytoconstituents (curcumin, many flavonoids) are prone to photodegradation, oxidation and hydrolysis, requiring careful selection of antioxidants, opaque packaging and storage conditions.
- Regulatory ambiguity: herbal transdermal products often fall into a regulatory grey zone between conventional pharmaceuticals and cosmeceuticals/nutraceuticals, and pharmacopoeial standards specific to herbal patches are still evolving in most jurisdictions.
- Limited clinical validation: comparatively few herbal transdermal formulations have undergone rigorous randomized controlled clinical trials, so most reported evidence remains at the preclinical or exploratory in vitro/ex vivo stage.

20. RECENT ADVANCES AND NANOTECHNOLOGY IN TDDS

Recent research in both conventional and herbal transdermal delivery has increasingly turned to nanotechnology-based carriers to overcome the intrinsic limitation of stratum corneum impermeability toward large or hydrophilic molecules. Liposomes and ethosomes (ethanol-containing flexible vesicles) have been used to encapsulate both synthetic drugs and herbal actives, improving their solubility, protecting them from degradation, and enhancing their penetration into deeper skin layers via fusion with intercellular lipids [2,10,12]. Solid lipid nanoparticles and nanostructured lipid carriers offer controlled release with good biocompatibility and are increasingly explored for lipophilic phytoconstituents such as curcumin and Boswellia acids [2].

Microneedle-based transdermal systems, which create transient microchannels through the stratum corneum using arrays of micron-scale needles, are being investigated for both synthetic macromolecules (peptides, vaccines) and herbal extracts that would otherwise permeate poorly, offering the prospect of painless, self-administered delivery of large or polar actives [5]. Nano emulsion- and nanocrystal-based transdermal patches have also been reported to significantly increase drug flux compared with conventional matrix patches by improving thermodynamic activity and reducing particle size below one hundred nanometers [19]. Iontophoretic and electroporation-assisted patches, combined with feedback-controlled electronic dosing units, represent another active area of translational research aimed at achieving patient-specific, on-demand dosing [5,10].

21. REGULATORY CONSIDERATIONS

Conventional transdermal patches containing approved synthetic drugs are regulated as pharmaceutical dosage forms and must satisfy the same pharmacopoeial (USP/BP/IP) requirements applicable to controlled-release products, including content uniformity, in vitro release testing, skin irritation/sensitization studies and stability testing under ICH guidelines, in addition to bioequivalence data where a generic patch is being developed against an innovator product. Herbal transdermal products, by contrast, are frequently classified under traditional/complementary medicine regulations (for example the AYUSH framework in India) or as cosmetic/wellness products, which typically impose less stringent requirements for systemic pharmacokinetic and clinical data than those applied to new chemical entities. This regulatory divergence, combined with the analytical complexity of standardizing multi-component plant extracts, remains an important barrier to the wider clinical adoption and international harmonization of herbal transdermal patches, and is an area where future pharmacopeial guidance is needed [12,13].

22. FUTURE PROSPECTS:

- Integration of nanocarrier technology (liposomes, ethosomes, solid lipid nanoparticles) with herbal extracts to overcome permeability limitations of large phytoconstituents.
- Development of standardized analytical protocols and pharmacopeial monographs specific to herbal transdermal patches, to support regulatory harmonization.
- Greater emphasis on ex vivo and in vivo pharmacokinetic studies of phytoconstituents delivered transdermal, to build a stronger evidence base comparable to that available for synthetic TDDS.
- Exploration of 'smart' and stimuli-responsive patches (temperature-, pH-, or enzyme-triggered release) combining natural polymers with programmable release behavior.
- Wider use of microneedle and physical enhancement technologies to extend herbal transdermal delivery to larger, more polar phytoconstituents such as glycosides and polysaccharides.
- Increased application of polyherbal synergy studies to rationally design multi-extract patches with optimized therapeutic combinations for chronic conditions such as osteoarthritis, diabetes and hypertension.

23. CONCLUSION

Transdermal drug delivery system has established itself as a clinically validated and commercially successful alternative to oral and parenteral routes, offering sustained plasma drug levels, improved patient compliance and avoidance of first-pass hepatic metabolism, while being constrained by the inherent barrier properties of the stratum corneum to a relatively narrow range of potent, moderately lipophilic, low-molecular-weight drugs [1,4,9]. Continuous innovation in polymer science, adhesive technology, and chemical and physical permeation-enhancement strategies has progressively expanded the range of therapeutic categories addressed by marketed transdermal products, from cardiovascular and hormonal agents to central nervous system and analgesic drugs [7,10].

Herbal transdermal patches extend this technology platform to standardized plant extracts and phytoconstituents, offering a rational solution to the poor oral bioavailability that limits many traditional herbal medicines, while capitalizing on the perceived safety and holistic therapeutic action associated with natural products [11,12,13]. Nevertheless, challenges relating to extract standardization, limited pharmacokinetic characterization, stability of labile phytoconstituents and an evolving regulatory framework must be addressed before herbal transdermal patches can achieve the same level of clinical validation as their synthetic counterparts. With continued advances in nanocarrier technology, natural permeation enhancers and analytical standardization, herbal transdermal patches hold considerable promise as a safe, patient-friendly and scientifically robust drug delivery platform for the future [14,15].

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