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HERBAL DRUG-LOADED TRANSDERMAL DRUG DELIVERY SYSTEMS: A NOVEL APPROACH IN PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

Transdermal drug delivery systems (TDDS) are innovative pharmaceutical dosage forms designed to provide controlled and sustained release of drugs through the skin, offering benefits such as bypassing first-pass metabolism, reducing dosing frequency, and improving patient compliance.. In recent years, the integration of herbal bioactive compounds into TDDS has gained attention due to the increasing demand for natural, safe, and effective therapeutic approaches. Herbal constituents such as andrographolide, curcumin, capsaicin, caffeine, and aloe vera exhibit diverse pharmacological properties, including anti-inflammatory, anti-diabetic, antioxidant, analgesic, and wound-healing activities. Nevertheless, their clinical use is often hindered by challenges like limited skin permeability, low aqueous solubility, and physicochemical instability. Advances in formulation strategies—such as nanocarrier incorporation (liposomes, ethosomes, transfersomes), microneedle-assisted delivery, and penetration enhancers—have been effective in improving dermal absorption and bioavailability of these phytochemicals. Key evaluation parameters, including physicochemical profiling, mechanical strength, drug content uniformity, and in vitro permeation studies, are critical for ensuring safety and therapeutic efficacy. This review highlights current advancements, formulation techniques, evaluation methodologies, challenges, and future directions for herbal drug-loaded TDDS, underscoring their potential to merge traditional herbal medicine with modern drug delivery innovations for optimized patient care.

KEYWORDS: Transdermal Drug Delivery, icroneedle, Liposomes, lithosomes, ethosomes, Nanocarrier.

INTRODUCTION

Transdermal drug delivery systems (TDDS) have emerged as an innovative and patient-friendly approach in pharmaceutical dosage forms, offering controlled and sustained drug release through the skin into systemic circulation.

This route provides distinct advantages, including avoidance of first-pass hepatic metabolism, reduced dosing frequency, improved therapeutic efficacy, and enhanced patient compliance. In recent years, there has been growing interest in utilizing herbal bioactive compounds in TDDS, driven by the rising global preference for natural and safer therapeutic alternatives. Herbal phytoconstituents such as andrographolide, curcumin, capsaicin, caffeine, and aloe vera possess diverse pharmacological properties, including anti-inflammatory, anti-diabetic, analgesic, antioxidant, and wound-healing effects. However, their clinical potential is often limited by poor aqueous solubility, low skin permeation, instability, and batch-to-batch variability. The integration of herbal drugs into advanced TDDS, combined with formulation innovations such as nanocarrier systems (liposomes, ethosomes, transfersomes), microneedle assisted delivery, and penetration enhancers, has demonstrated significant improvements in skin absorption and bioavailability.

- **Advantages of Herbal TDDS**

1. Avoidance of first-pass metabolism for higher bioavailability.
2. Non-invasive administration, improving patient comfort.
3. Sustained and controlled drug release, reducing dosing frequency.
4. Reduced gastrointestinal irritation compared to oral formulations.
5. Feasibility of combining multiple herbal actives for synergistic effects.

- **Limitations & Challenges**

1. Stratum corneum barrier to permeation.
2. Variability in herbal extract quality.
3. Stability issues (light, oxidation, humidity).
4. Risk of skin irritation or allergic reactions.

- **Types of Transdermal Drug Delivery Systems (TDDS)**

1. **Reservoir (Compartmental) TDDS**

A reservoir TDDS contains the drug (solution, suspension, or gel) held in a discrete compartment separated from the skin by a rate-controlling membrane. The membrane regulates drug flux, ideally producing near zero-order release until the reservoir is depleted. A typical transdermal drug delivery system consists of several key components, including an occlusive backing layer, a drug reservoir, a rate-controlling membrane, an adhesive layer, and a protective liner.

Drug diffuses from the reservoir through the rate-controlling membrane and then across the adhesive (if any) and the stratum corneum into systemic circulation. The membrane sets the flux independent of drug concentration in the reservoir (until concentration falls significantly).

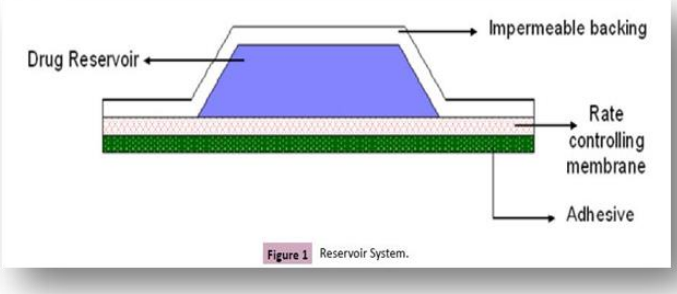


Figure 1 Reservoir System.

Advantages

Predictable, near zero-order release; easier control of release rate by membrane selection; suitable for potent actives requiring low daily doses.

Limitations

Complex manufacturing; risk of dose dumping if membrane fails; not flexible (thicker) and less conformable; higher cost.

Herbal examples / applicability

Small-molecule phytoactives (e.g., potent terpenes, low-dose alkaloids) that require controlled constant delivery can be formulated as reservoir systems when stability in a liquid/gel reservoir is possible.

2. Matrix (Drug-in-Polymer) TDDS

Matrix systems (also called monolithic systems) embed the drug uniformly within a polymeric matrix (hydrophilic or hydrophobic). The drug moves from the matrix to the skin's surface and subsequently enters the systemic circulation. Common components include a backing film, a drug-containing matrix (which may also serve as the adhesive), and a release liner.

Mechanism

Release is governed by diffusion through the polymer network and is concentration-dependent (Higuchi kinetics for many systems). When the matrix is also the adhesive (drug-in-adhesive), the patch is thin and conforms well to skin.

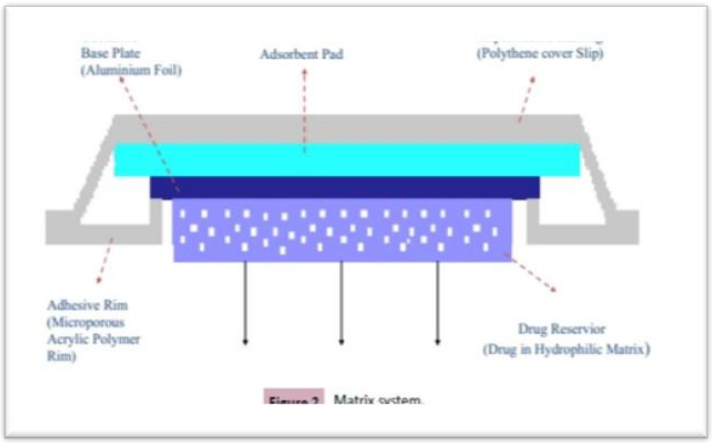


Figure 2: Matrix system.

Advantages

Simple manufacturing (solvent casting or hot-melt); thin, comfortable, and easy to scale; good for moderate dose delivery. Drug-in-adhesive designs minimize components.

Limitations

Release rate typically declines with time; achieving zero-order release is harder; limited high-dose loading.

Herbal examples / applicability

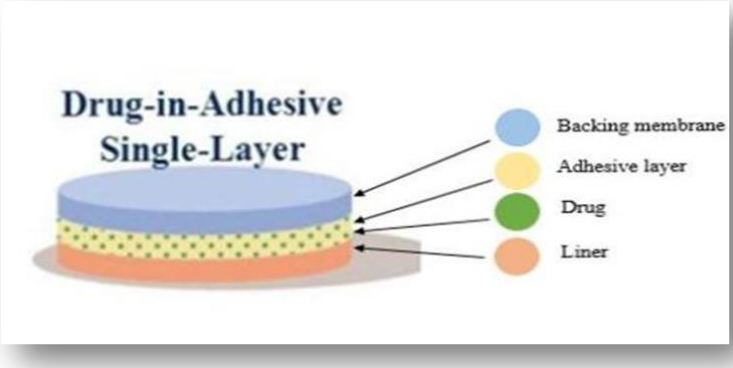
Curcumin, andrographolide, menthol, and other moderately potent phytochemicals have been successfully loaded into matrix patches using polymer blends and permeation enhancers.

3. Drug-in-Adhesive (DIA) TDDS

A subtype of matrix systems where the adhesive layer itself contains the drug. The adhesive in such systems serves a dual purpose, functioning both to release the drug and to adhere the patch to the skin, while a backing layer and a release liner are typically included.

Mechanism

Drug diffuses through the adhesive into the skin. Release kinetics depend on adhesive composition, drug-polymer interactions, and adhesive thickness.



Advantages

Thin, flexible patches with good adhesion; simplified design and manufacturing.

Limitations

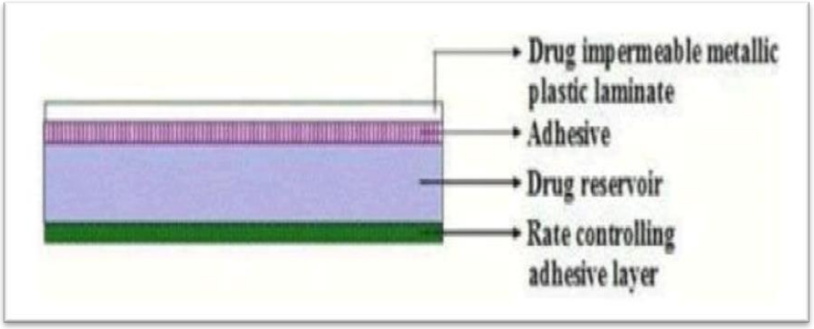
Adhesive chemistry can limit drug loading & stability; risk of skin irritation from adhesive components or herbal constituents.

4. Micro-Reservoir TDDS (Microsuspended)

Micro-reservoir systems integrate the characteristics of both reservoir and matrix designs, in which the drug exists as tiny droplets or solid particles dispersed within a polymer matrix. The microscale reservoirs give more controlled release and improved stability for certain actives.

Mechanism

Drug diffuses from the micro-reservoirs through surrounding polymer and then into the skin. Release can approximate controlled profiles while maintaining matrix flexibility.



Advantages

Improved stability and modulated release compared with simple matrices; retains flexibility.

Limitations

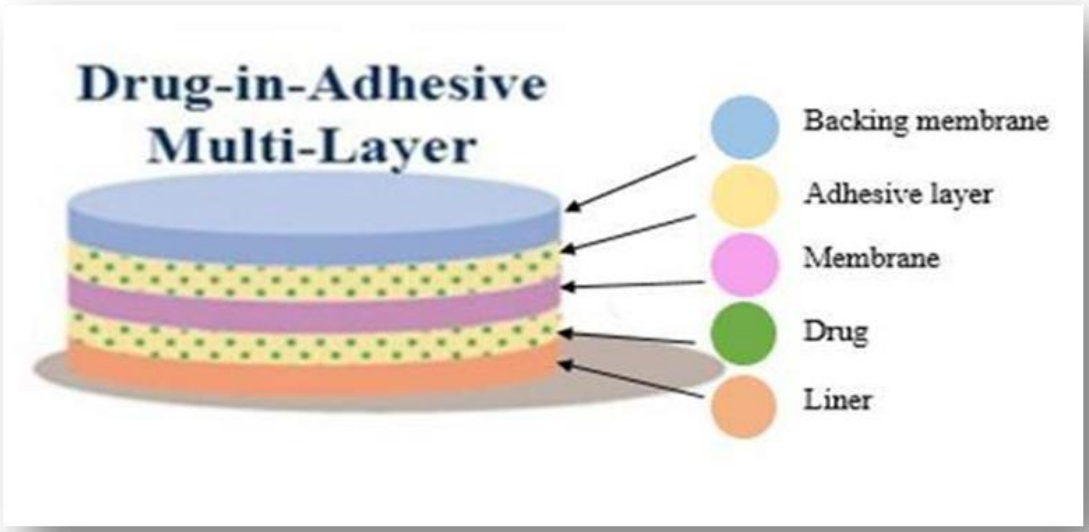
More complex formulation and manufacturing control required.

5. Multilayer / Multilaminate TDDS

Multilayer patches contain two or more functional layers — for example, an immediate-release layer and a sustained-release layer, or separate layers for different actives. Layers may differ in polymer type or drug loading to achieve complex release profiles.

- **Mechanism**

Layered diffusion and/or sequential drug release from distinct layers, offering biphasic kinetics.



Advantages

Customizable release profiles; co-delivery of incompatible actives by physical separation.

Limitations

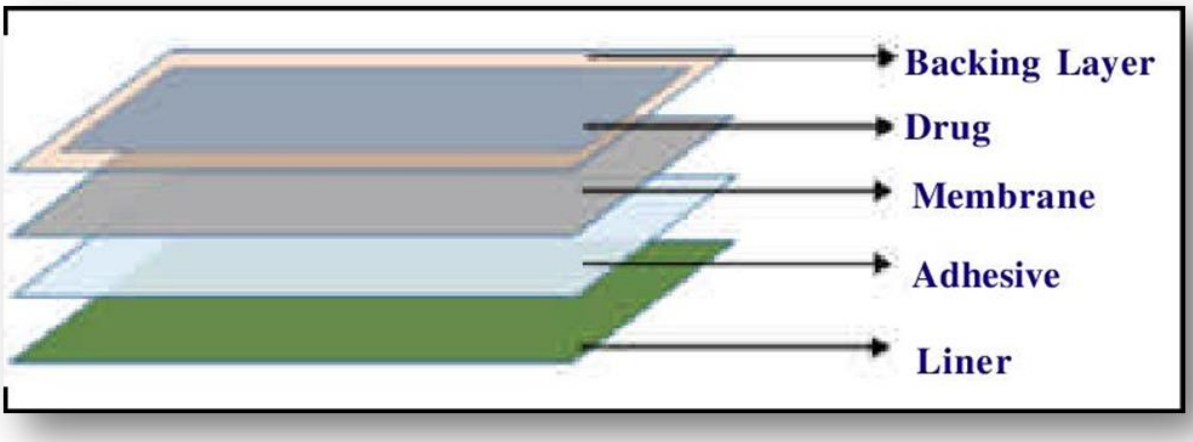
Thicker patch, more complex manufacturing and quality-control.

6. Vapour (Volatile Active) Patches

Vapour patches are designed to release volatile or semi-volatile actives (e.g., essential oils) as vapour that is inhaled near the nasal/oral region or acts locally on skin. Often used for aromatherapy or symptomatic relief (decongestion).

Mechanism

Controlled evaporation of volatile constituents through a semi-permeable backing or porous matrix. Release may be influenced by temperature and airflow.



Advantages

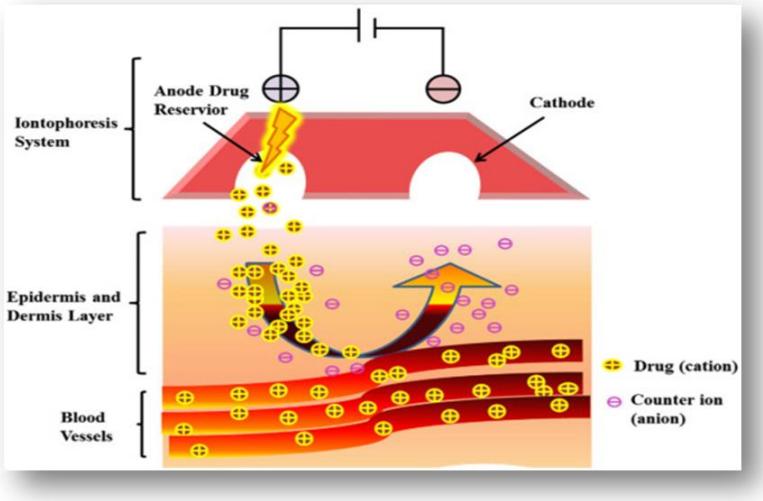
Non-systemic action useful for topical or inhalational benefit; simple design.

Limitations

Dosing is less precise; long-term systemic delivery is not feasible; risk of skin sensitization.

7. Iontophoretic TDDS (Electrically Assisted)

Iontophoresis is a technique that employs a low-intensity electrical current to facilitate the movement of ionized drug molecules through the skin barrier. The device comprises electrodes, a drug reservoir (often gel), and a controller. Iontophoretic patches are active systems requiring power.



Mechanism

Electrorepulsion and electroosmosis increase flux of ionic and some neutral molecules; flux is controllable by current magnitude and duration.

Advantages

On-demand, controllable transdermal delivery; enhanced permeability for molecules that otherwise permeate poorly.

Limitations

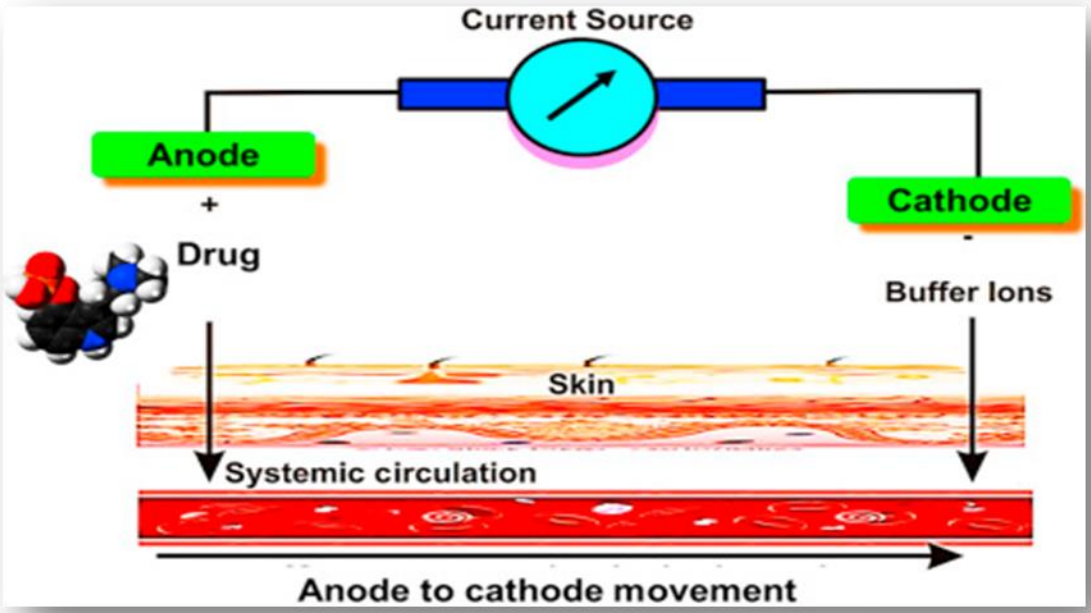
Requires device/electrical power; potential for skin irritation under electrodes; not suitable for all actives.

8. Sonophoresis / Phonophoresis (Ultrasound-Assisted)

Ultrasound (low-frequency) enhances skin permeability by cavitation and mechanical effects. It is generally a clinic/device-assisted method rather than a passive patch, but hybrid devices combining patches and ultrasound applicators exist.

Mechanism

Ultrasound temporarily disrupts lipid bilayers and increases drug diffusion; can be pulsed for safety.



Advantages

Significant permeation enhancement without chemical enhancers; potential for localized, targeted delivery.

Limitations

Requires external device; safety and standardization considerations.

9. Microneedle-Assisted TDDS

Microneedles (solid, coated, dissolving, hollow, or hydrogel) create microchannels through the stratum corneum, permitting transport of large or hydrophilic molecules. Microneedle arrays can be integrated with patches or used as pre-treatment.

Mechanism

Microneedles overcome the stratum corneum, the primary skin barrier, enabling both convective and diffusive transport of drugs. Dissolving microneedles can release payload directly into epidermis/dermis.

Advantages

Dramatic permeability enhancement; potential for vaccine-like delivery and controlled depot release.

Limitations

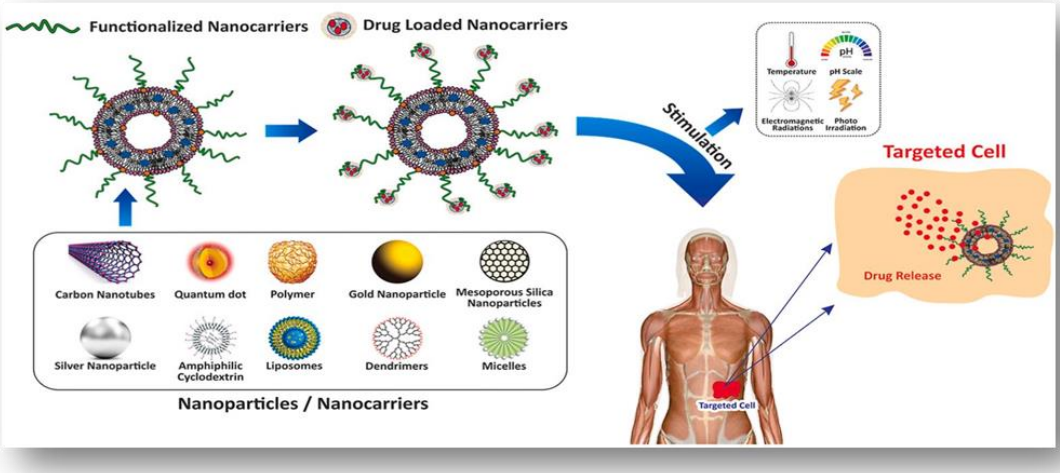
Device complexity, sterility requirements, regulatory pathway more involved; possible pain/skin damage if misused.

10. Nanocarrier-Based Patches (Nanoparticles, Liposomes, Nanoemulsions)

Nanocarriers (solid lipid nanoparticles, polymeric nanoparticles, liposomes, nanoemulsions) are incorporated into a patch matrix or reservoir to enhance solubility, stability, and skin penetration of herbal actives.

Mechanism

Nanocarriers protect labile phytoconstituents, increase thermodynamic activity at skin surface, and may interact with skin lipids to enhance permeation. Some carriers also provide controlled release.



Advantages

Improved solubility, stability, controlled release, and often enhanced permeation without harsh chemical enhancers.

Limitations

Added formulation complexity, potential regulatory scrutiny, and scale-up challenges.

11. Biodegradable / Dissolving Films & Patches

Degradable or dissolvable patches (including dissolving microneedles) are made of water-soluble or biodegradable polymers that gradually dissolve/release actives on application, leaving no patch residue.

Mechanism

Polymer matrix dissolves in interstitial fluid, releasing herbal actives in a controlled fashion; in microneedle form, needles dissolve delivering cargo intradermally.

Advantages

No patch removal required; reduced environmental waste; potential for depot formation.

Limitations

Dose limitations, stability during storage (moisture sensitivity), and potential for variable dissolution in different skin conditions.

Fundamental Elements of Transdermal Drug Delivery Systems

The components of Transdermal devices include:

1. Polymer matrix or matrices
2. The drug
3. Permeation enhancers
4. Other excipients

1. PolymerMatrix

The polymer serves as the backbone of the patch and regulates the rate at which the drug is released.

- Natural polymers: cellulose derivatives, starch, zein, gelatin, shellac, waxes, gums, proteins, natural rubber, etc.
- Synthetic elastomers: polybutadiene, polysiloxane, silicone rubber, hydrin rubber, acrylonitrile, nitrile, butyl rubber, styrene–butadiene rubber, neoprene, etc.
- Synthetic polymers: polyethylene, polypropylene, polyvinyl alcohol, polyvinyl chloride, polyacrylates, polyamides, polymethyl methacrylate, polyurea, polyvinylpyrrolidone, epoxy resins, etc.

2. Drug

The active pharmaceutical ingredient (API) are also beneficial for transdermal delivery. The ideal drug should possess properties such as low molecular weight, adequate lipophilicity, and effective potency at low doses, ensuring it can permeate the skin and achieve systemic activity.

Physicochemical properties

1. Molecular size: Ideally, the molecular weight should be below 1000 Daltons to facilitate skin permeation.
2. Partitioning behavior: The compound must possess balanced lipophilic and hydrophilic characteristics; drugs that are excessively hydrophilic or highly lipophilic show poor transdermal absorption.
3. Melting point: A relatively low melting point is desirable, as it generally correlates with better solubility and diffusivity.
4. Pharmacological properties: The drug should be potent enough to be effective at low doses, have a short biological half-life, and should not cause skin irritation or sensitization.

3. Permeation Enhancers

These may be classified into three types;

a) Solvents

Solvents act as permeation enhancers by either disrupting the polar pathways of the skin or by fluidizing the lipid layers, thereby facilitating drug movement. Common examples include alcohols (such as methanol and ethanol), dimethyl sulfoxide and its homologs (dimethyl acetamide, dimethyl formamide), pyrrolidones (like 2-pyrrolidone and N-methyl-2-pyrrolidone), laurocapram (Azone), and other miscellaneous agents such as propylene glycol, glycerol, silicone oils, and isopropyl palmitate.

b) Surfactants

Surfactants enhance drug penetration primarily by modifying the polar transport pathways, which is especially beneficial for hydrophilic drugs. Their effectiveness depends on the chemical nature of the polar head group and the length of the hydrocarbon chain, which together influence the extent of skin barrier alteration.

- Anionic Surfactants: e.g. Dioctyl sulphosuccinate, Sodium lauryl sulphate, Decodecylmethyl sulphoxide etc.
- Non-ionic Surfactants: e.g. PluronicF127, Pluronic F68, etc
- Bile Salts:e.g. Sodium taurocholate, Sodium deoxycholate, Sodium tauroglycocholate.
- Binary Systems
- These systems enhance drug permeation by simultaneously affecting both the heterogeneous multi-lamellar pathways and the continuous transport routes within the skin. Typical examples include combinations such as propylene glycol with oleic acid, and 1,4-butanediol with linoleic acid.

c) Miscellaneous chemicals

These include urea, a hydrating and keratolytic agent; N, N-dimetyl-m-touamide; calcium thioglycolate; anticholinergic agents.

"A number of new permeation enhancers have been reported in recent studies; however, the evidence regarding their actual efficacy remains limited." These include eucalyptol, di-o-methyl-ß-cyclodextrin and soybean casein.

4. Other Excipients

a) Adhesives

In transdermal delivery systems, attachment to the skin is generally achieved using pressure-sensitive adhesives. These may be applied either on the surface of the patch that comes in contact with the skin or on the backing layer, extending towards the edges. Regardless of the type, an ideal adhesive should meet the following requirements:

1. Provide strong adhesion to the skin while allowing easy removal.
2. Leave no persistent or difficult-to-clean residue on the skin surface.
3. Be non-irritant and non-sensitizing to the skin.

In addition, face adhesives are expected to satisfy some specific conditions:

1. Exhibit both physical and chemical compatibility with the drug, excipients, and penetration enhancers incorporated in the formulation.
2. Ensure that drug permeation across the skin remains unaffected.
3. Support the effective delivery of single or combined permeation enhancers without interference.

b) Backing membrane

The backing layer in a transdermal system is designed to be flexible while ensuring a strong seal with the drug reservoir. Its main functions are to prevent drug loss through the upper surface of the patch, provide protection to the formulation during application, and allow printing if required. Typically, this layer is made of impermeable materials such as metallic–plastic laminates, plastic films combined with absorbent pads, or occlusive base plates like aluminum foil. Other examples include adhesive foam pads (e.g., polyurethane) paired with aluminum foil discs to enhance flexibility and protection.

❖ **Evaluation & Development Considerations for Herbal TDDS**

1. Phytochemical standardization

Consistency of active phytoconstituents across different batches should be maintained by using appropriate marker compounds.

2. Compatibility assessment

Possible interactions between herbal actives, polymers, adhesives, and backing membranes must be thoroughly examined.

3. Permeation enhancement approach

Selection of suitable enhancers—chemical agents, physical techniques such as microneedles or iontophoresis, or nanocarrier-based systems—should be guided by the properties of the herbal drug.

4. Safety and irritation evaluation

Since many plant extracts may cause dermal sensitivity, both in vitro and in vivo skin toxicity studies are essential.

5. Storage stability

Herbal formulations should be protected from oxidative degradation, light exposure, and moisture. Stabilizers such as antioxidants, UV protectants, and desiccant-based packaging can be incorporated.

6. Regulatory considerations

As herbal TDDS fall under both herbal medicinal product and medical device categories, early interaction with regulatory authorities is crucial.

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