

A Comprehensive Review of Herbal Penetration Enhancers in Transdermal Drug Delivery Systems

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ABSTRACT: Transdermal Drug Delivery Systems (TDDS) are non-invasive platforms designed to deliver therapeutic agents through the skin into systemic circulation while bypassing hepatic first-pass metabolism. TDDS offer controlled and sustained release, improved bioavailability, and enhanced patient compliance. Several systems such as membrane-controlled, matrix-diffusion, drug reservoir, and micro-reservoir patches are utilized depending on drug characteristics and release kinetics. Natural penetration enhancers, including Tulsi, Neem, Turmeric, Ginger, and Peppermint oil, possess antioxidant, anti-inflammatory, and antimicrobial properties that can improve drug permeation across the stratum corneum. These herbal bioactives disrupt lipid packing, increase hydration, enhance blood flow, and stabilize formulations. Herbal-based TDDS show potential in managing chronic pain, inflammation, wound healing, and metabolic disorders. Their biocompatibility and reduced toxicity make them a sustainable alternative to synthetic enhancers. Continuous research is focused on optimizing polymers, improving design, and integrating herbal actives for safer and more effective therapies.

KEYWORDS: Transdermal Drug Delivery System, Herbal Drugs, Permeation Enhancers, Controlled Release, Bioavailability, Herbal Patches, Terpenes, Essential oils.

I. INTRODUCTION

Transdermal Drug Delivery Systems (TDDS) are a new and effective drug delivery system that permits the safe and efficient delivery of therapeutic molecules through the skin⁽¹⁾. TDDS avoids the first-pass metabolism by the liver and gastrointestinal breakdown like traditional oral, injectable or other routes, which results in improved bioavailability and an increase in patient compliance. There is a growing interest in the development of herbal drugs with biocompatibility,

low rates of side effects, and an origin from nature in combination with synthetic drugs. Herbal bioactive molecules have demonstrated therapeutic properties; and possess permeation enhancement properties they can pass through both the stratum corneum and underlying layers of skin⁽²⁾. The review focuses on the overview of the types, mechanisms, benefits, and herbal uses of transdermal systems and highlights the value and potential for achieving improved therapeutic benefit and safety for patients⁽³⁾.

DEFINITION OF TDDS:

TDDS are self-contained, multi-layered therapeutic systems applied to intact skin to deliver drugs at a controlled rate into systemic circulation⁽⁴⁾.

NOVEL DRUG DELIVERY SYSTEM (NDDS):

NDDS include advanced carriers such as nanoparticles, microemulsions, microneedles, lipid vesicles, and herbal-enhanced transdermal systems designed to improve therapeutic efficacy.

CLASSIFICATION:

1. Polymer membrane permeation-controlled.
2. Polymer matrix diffusion-controlled
3. Drug reservoir gradient-controlled
4. Micro reservoir dissolution-controlled

MEMBRANE-MODERATED OR PERMEATION CONTROLLED TDDS (RESERVOIR TYPE):

Drug reservoir is encapsulated within impermeable metallic plastic laminate and rate controlling polymeric membrane. Drug release rate determined by membrane permeability. Adhesive polymer layer secures device on skin⁽⁵⁾. Release rate maintained at a constant rate. TDDS release

rate depends on polymer composition, permeability coefficient, membrane thickness, and adhesive .

Examples:

- Nitroglycerin releasing TDDS (Transderm Nitro / Ciba, USA) for once-a-day medication in angina pectoris
- Scopolamine releasing TDDS (Transderm-Scop/ Ciba, USA) for 72 hrs, prophylaxis of motion sickness

ADHESIVE DISPERSION TYPE SYSTEMS

Drug reservoir is formulated by homogenous dispersion of drug with adhesive polymer poly(isobutylene) or polyacrylate⁽⁶⁾. Then spreading of this medicated adhesive by solvent casting/hot melt on flat sheet of drug impermeable metallic plastic backing to form thin drug reservoir layer. On top of the drug reservoir layer, thin layers of rate controlling adhesive polymer of specific permeability and constant thickness are applied to produce an adhesive dispersion-diffusion controlled TDDS .

Examples:

Isosorbidedinitrate -releasing TDDS for once-a-day medication of angina pectoris.

MATRIX DIFFUSION – CONTROLLED SYSTEMS:

The drug reservoir, consisting of a homogenous dispersion of the active pharmaceutical ingredient with either hydrophilic or basophilic polymers, is meticulously prepared using one of the following methodologies⁽⁷⁾. A homogenous dispersion of finely milled drug particles is achieved by incorporating a liquid polymer or a highly viscous polymer base, subsequently followed by the cross-linking of polymer chains . A solid drug and rubbery polymer are amalgamated at elevated temperature for uniformity. They are dissolved in a common solvent and evaporated in a mold at elevated temperatures or vacuum conditions. The medicated polymer is carefully molded into a disc with the requisite surface area and controlled thickness. This disc is affixed to an opaque baseplate with impermeable plastic backing. An adhesive polymer is applied around the circumference to create a cohesive adhesive rim encircling the disc. This TDDS prevents dose dumping, as the polymer cannot rupture⁽⁸⁾.

Examples:

Clonidine patches

MICRO RESERVOIR TYPE/ MICRO SEALED DISSOLUTION-CONTROLLED SYSTEMS.

Microreservoir systems contain drugs in aqueous emulsion or soluble polymer . Drug particles form microscopic spheres in basophilic polymer⁽⁹⁾. Spheres are stabilized by cross-linking. The drug disc shape is coated based on drug characteristics. The disc is attached to an opaque plate with an adhesive rim. This process aids in developing sustained drug release systems. Various polymers and coatings can modulate drug release kinetics for precise treatment. Microreservoir systems enable targeted drug delivery⁽¹⁰⁾.

Examples:

Nitro glycerin releasing TDDS (Nitrodisc, searle, USA) deliver daily dose of 0.5mg/cm² for once a day therapy of angina pectoris .

HERBAL PATCHES :

A transdermal patch is a treated tenacious patch that's placed on the skin to deliver a specific cure of drug through the skin and into the bloodstream⁽¹¹⁾.

TRANSDERMAL:

Transdermal is a route of administration wherein active constituents are delivered across the skin for systemic distribution. exemplifications include transdermal patches used for drug delivery⁽¹²⁾. The medicine is administered in the form of a patch or ointment that delivers the medicine into the rotation for systemic effect⁽¹³⁾.

METHODS OF PREPARATION OF HERBAL PATCHES:

STEPS IN PREPARATION:

- 1.Selection of herbal extract
- 2.Selection of polymer (HPMC, PVP, Eudragit)
- 3.Plasticizer addition
- 4.Solvent casting
- 5.Drying
- 6.Backing layer attachment
- 7.Evaluation (thickness, folding endurance, drug content, diffusion etc.)

ADVANTAGES :

- TDDS is a drug delivery system using a patch on the skin for systemic drug delivery at a constant concentration.

- Useful for nauseated or unconscious patients, and those with gastrointestinal issues.
- Like IV infusion, it maintains constant plasma levels.

DISADVANTAGES :

- Hydrophilic drugs struggle to penetrate skin, affecting their metabolism.
- Patches may cause problems like itching, edema, and erythema.
- Skin barrier function varies between individuals, with age, and by location.
- Transdermal drug delivery system incompatible with ionic drugs.
- Risk of dose dumping.

APPLICATIONS OF TRANSDERMAL PATCHES :

- Nicotine patch is the top-selling transdermal patch in the US for smoking cessation.
- Fentanyl (Duragesic) and Buprenorphine (BuTrans) are opioid patches for severe pain.
- Estrogen patches treat menopausal symptoms and osteoporosis.
- Nitroglycerin patches are used for angina.
- Clonidine is an anti-hypertensive patch.

IDEAL PROPERTIES OF TDDS :

- Maximum durability of two years.
- Patch of small size (less than 40 cm²).
- Easy dosage scheduling (e.g., once daily to once weekly).
- Acceptable in terms of appearance (i.e., a clear, white colour)
- Easy organizing.

THE HERBAL DRUGS USED IN TDDS:**1. TULSI:**

SYNONYMS: Ocimum sanctum, Ocimumtomentosum

BIOLOGICAL SOURCE: leaves, seeds, and whole plant of the Ocimum species, such as O. Sanctum L. And O. Basilicum L.

FAMILY: Lamiaceae

CHEMICAL CONSTITUENTS: Eugenol, Oleanolic acid, Linalol⁽¹⁴⁾

USES:**PENETRATION IMPROVEMENT:**

The natural penetration enhancers in Tulsi are the essential canvases, especially eugenol. These substances have the capability to alter the lipid composition of the remotest subcaste of skin, called the stratum corneum, adding the

permeability of the skin. As a result, specifics are suitable to enter the skin more successfully, enhancing the transdermal distribution of active medicinal factors⁽¹⁵⁾.

AN ANTIOXIDANT AND ANTI-ALLERGIC PARCELS:

Flavonoid, which have antioxidants located in tulsi, guard the skin from oxidative stress and inflammation. This promotes skin integrity and lessens vexation or inflammation that may else help specifics from being absorbed transdermally⁽¹⁶⁾.

2. NEEM :

SYNONYM:Neem

BIOLOGICAL SOURCE: The natural source of the substance is the leaves of Azadirachtaindica.

FAMILY: Meliaceae

CHEMICAL CONSTITUENTS: Nimbinin, Nimbinbdin, and Nimbin⁽¹⁷⁾

USES:**SKIN PERMEATION ENHANCEMENT:**

Neem oil, as well as other terpenoids it contains, act as natural permeation enhancers by disrupting lipid bilayer within the stratum corneum (the outermost skin layer), which improves skin permeability and transdermal drug absorption⁽¹⁸⁾.

ANTI-INFLAMMATORY AND ANTIOXIDANT EFFECTS:

Antioxidants present in neem - including quercetin and nimbolide - have been shown to reduce oxidative damage to skin and can decrease skin irritation⁽¹⁹⁾. As it decreases inflammation and oxidative damage, neem in turn improves overall skin health and can facilitate drug transport through the skin.

ANTIMICROBIAL ACTION:

The antimicrobial properties of neem will also serve as an effective defense against bacterial or fungal infections created at the skin surface upon transdermal drug administration, which can hinder drug absorption. Nimbin and azadirachtin are compounds that provide neem various antibacterial properties. and lead to additional complications at the skin surface⁽²⁰⁾.

3. TURMERIC:

SYNONYM: Curcuma, Haldi (Hindi), Indian saffron, Curcuma longa, etc.

BIOLOGICAL SOURCE: It is the source of Curcuma longa.

FAMILY:Zingiberaceae.

CHEMICAL CONSTITUENTS: Curcumin, Zingiberene, Proteins, Resins, etc⁽²¹⁾.

USES:

1.ANTI-INFLAMMATORY EFFECTS:

Strong anti-inflammatory qualities of curcumin are advantageous when applied topically. In localised locations like joints or skin diseases, it reduces inflammation by inhibiting enzymes like COX-2 and the transcription factor NF-κB⁽²²⁾.

2.ANTI OXIDANT ACTIVITY :

Curcumin protects the skin and aids in healing by through the elimination of free radicals and enhancement of the function of naturally occurring antioxidant enzymes such as superoxide dismutase and glutathione peroxidase⁽²³⁾.

3.PERMEATION ENHANCER:

Turmeric's volatile oils, particularly turmerone, can interact with skin lipids to improve skin penetration⁽²⁴⁾. This improves the stratum corneum's permeability, which helps curcumin and other medications absorb more effectively into the skin's deeper layers.

4.ANTIMICROBIAL ACTION:

Applying curcumintransdermally can help prevent infections because of its antibacterial qualities. It breaks down bacterial

membranes and prevents pathogens like Escherichia coli and Staphylococcus aureus from growing⁽²⁵⁾.

4. GINGER:

SYNONYM:Zingiber, Root ginger, Fresh ginger etc.

BIOLOGICAL SOURCE: ginger is the plant Zingiberofficinale.

FAMILY:Zingiberaceae

CHEMICAL CONSTITUENTS:Gingerols, Zingerone, Zingiberene, Phenolic Compounds, Terpenes, Vitamins and Minerals⁽²⁶⁾.

USES:

1.ENHANCING SKIN PERMEABILITY:

Natural penetration enhancers include essential oils like β-bisabolene, citral, and zingiberene. By interfering with the lipid bilayer and relaxing the densely packed cells in the outer layer of the skin, these oils facilitate easier passage of medicines through the skin⁽²⁷⁾.

2.VASODILATORY EFFECTS:

Vasodilation, or the widening of blood vessels, is stimulated by ginger, which improves

blood flow where it is applied. Drug distribution and absorption into the bloodstream are increased as a result⁽²⁸⁾.

3.ANTIOXIDANT PROTECTION:

Strong antioxidants like zingerone and gingerols are found in ginger. By preventing oxidative damage to the skin and the drug formulation, these antioxidants preserve the stability and efficacy of the medication both during and after application⁽²⁹⁾.

4.ANALGESIC AND SENSORY EFFECTS:

When transdermal systems are administered for extended periods of time, ginger's analgesic qualities can improve patient compliance by reducing pain at the application site⁽³⁰⁾.

5. PEPPERMINT OIL:

SYNONYM: Peppermint Oil, Sweet Balm

BIOLOGICAL SOURCE: The leaves of the fragrant plant Menthapiperata

FAMILY:Lamiaceae

CHEMICAL CONSTITUENT: Menthol, Menthone, cineol⁽³¹⁾

USES:

1.SKIN PENETRATION ENHANCEMENT:

In peppermint oil, menthol enhances permeation. It changes the by disrupting the stratum corneum, the outermost layer of the skin, lipid structure and enhances skin permeability. This facilitates skin-to-drug penetration of other medications in the formulation⁽³²⁾.

2.VASODILATION :

Because of its vasodilatory properties, peppermint oil causes blood vessels to dilate below the skin surface and enhances the absorption of the medicinal or drug delivery across the skin. Peppermint oil, as it contain menthol, increases skin permeability and blood flow, and has analgesic and anti-inflammatory effects, so it should play an important role in transdermal drug delivery systems. It can improve skin permeability and promote the passage of drugs⁽³³⁾.

II. DISCUSSION

Herbal-based penetration enhancers have emerged as promising alternatives to synthetic agents in Transdermal Drug Delivery Systems (TDDS) due to their improved safety profile, biocompatibility, and additional therapeutic benefits⁽³⁴⁾. This review highlights that while

synthetic enhancers such as dimethyl sulfoxide (DMSO), azone, and alcohol-based compounds provide strong and rapid permeation enhancement, they are often associated with skin irritation, cytotoxicity, and long-term safety concerns. In contrast, herbal enhancers like menthol, eugenol, limonene, camphor, and curcumin offer moderate enhancement of drug permeation with significantly lower risks of skin damage and systemic toxicity⁽³⁵⁾.

A major advantage of herbal TDDS is their multifunctional nature. Many plant-derived compounds exhibit anti-inflammatory, antioxidant, antimicrobial, and wound-healing properties, which further support skin health during transdermal therapy⁽³⁶⁾. This makes herbal-based systems particularly suitable for long-term and chronic treatments. However, the discussion also reveals critical limitations, including variability in phytochemical composition, lack of standardization, limited stability, and relatively lower permeation efficiency for high-molecular-weight drugs.

Safety considerations remain central to the development of herbal TDDS. Although generally safer than synthetic counterparts, herbal formulations are not entirely risk-free. Allergic reactions, contact dermatitis, and potential contamination with heavy metals or pesticides have been reported in poorly standardized products. These concerns emphasize the need for strict quality control, toxicological screening, and dermatological testing⁽³⁷⁾.

Future research directions should prioritize improving the standardization, stability, and efficacy of herbal formulations⁽³⁸⁾. The integration of herbal enhancers with advanced technologies such as nanoparticles, liposomes, microneedles, and bioresponsive polymers offers a promising approach to overcome current limitations. More *in vivo* studies and clinical trials are required to establish long-term safety, therapeutic efficacy, and regulatory acceptance of these systems⁽³⁹⁾.

Overall, the findings of this review support the growing scientific interest in herbal TDDS as a safer and more sustainable drug delivery approach, while also highlighting the need for technological advancements and regulatory clarity⁽⁴⁰⁾.

III. CONCLUSION

Transdermal drug delivery systems (TDDS) offer a highly effective, non-invasive

platform for controlled and sustained drug release while improving patient compliance and avoiding gastrointestinal and hepatic first-pass metabolism. This review highlights the growing role of herbal drugs in TDDS, emphasizing their natural origin, safety, biocompatibility, and additional pharmacological benefits such as anti-inflammatory, antioxidant, and antimicrobial activities. Herbal penetration enhancers and plant-based bioactives have demonstrated promising potential in improving skin permeation while maintaining skin integrity, making them suitable for long-term and chronic therapeutic applications. The reviewed studies indicate that herbal-based TDDS provide a balanced therapeutic approach by combining the advantages of medicinal plants with the technological strengths of modern transdermal patches. Nevertheless, challenges such as variability in herbal composition, lack of standardization, stability issues, and limited clinical validation remain significant barriers to large-scale clinical use. Recent advances in nanotechnology, polymer science, and smart patch systems have shown strong potential to overcome these limitations and enhance the reproducibility and efficacy of herbal formulations. Overall, the integration of herbal drugs with TDDS represents a promising and patient-friendly strategy that bridges traditional medicine with modern pharmaceutical technology and may offer safer, more effective, and targeted therapeutic options in the future.

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