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Review on: Herbal Drugs Used in Transdermal Drug Delivery System

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Abstract

TDDS also traditionally called as "patches". Due of their remarkable medicinal properties and minimal side effects as compared to synthetic drugs, the usage of herbal bioactive has grown recently on a global scale. In order to improve therapeutic response. The purpose of this review is to give a broad overview of the several innovative techniques that have been developed for the transdermal and dermal delivery of herbal medicines. Drug delivery systems involve the topical administration of medications. Pharmaceutical preparations known as transdermal patches come in a range of sizes and are designed to be applied to intact skin to transfer active ingredients into the bloodstream after they have passed through the skin's barriers and prevented from having a first-pass effect. This review explores the role of various herbal drugs in TDDS, focusing on their bioactive compounds, therapeutic potential and advancements in formulation approaches. Key topics include skin permeability challenges, penetration enhancement strategies and the stability of herbal compounds in transdermal formulations. Novel techniques such as nanotechnology, liposomes and polymer-based carriers are discussed as methods to improve the efficiency of herbal transdermal systems. Herbal drugs hold significant potential in transdermal drug delivery due to their therapeutic benefits and natural origin. It is especially utilised when the liver has a large first-pass effect that can cause medications to be metabolised too soon. A viable and alluring method of administering peptides and proteins is transdermal distribution.

Keywords - Herbal patches, Marketed transdermal patches, Transdermal medicine delivery system, Transdermal patch kind.

INTRODUCTION

A wide range of topical formulations have been produced in the modern period to treat specific local medical issues. For thousands of years, individuals have applied substances to their skin to achieve therapeutic benefits. People are becoming more interested in herbs and herbal medications due to their clinically demonstrated benefits for a variety in of health issues. For many years, skin diseases have been treated with herbal medication therapy.[1]

The most popular drug delivery method is the conventional dose form, such as tablets and capsules. However, the problem of stomach drug/enzyme instability first pass metabolism affects both dose types. Numerous other issues with the oral route include bad taste, odour and colour. Taking tablets is causing a number of other issues, which means that problems are occurring during treatment. Patients can occasionally stop complying. [2]

When designing the dosage for transdermal medicines, the objective is to minimise the drug's retention and metabolism in the skin while simultaneously optimising the amount of drug that

passes through the skin and goes into the bloodstream. [3, 4, 5] One method for delivering drugs through the skin is the transdermal drug delivery system.

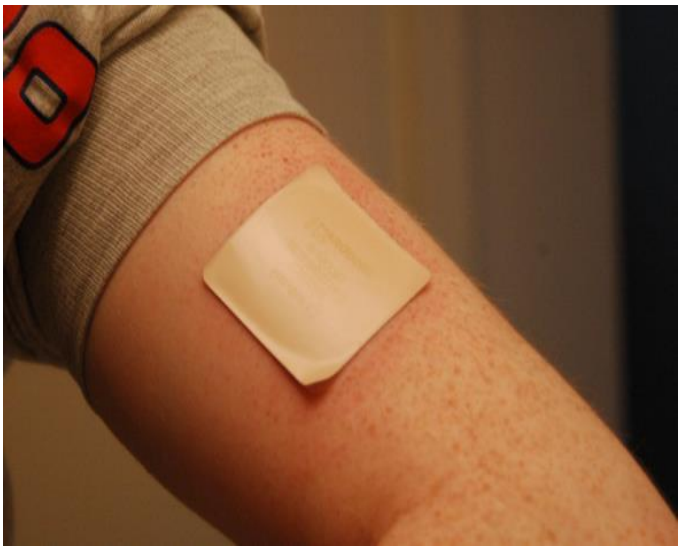

Figure 1*: *Transdermal Patch

There are 3 generations present in TDDS

First generation

The initial TDDS generation started in the late 1970s and early 1980s.This generation's formulations, which include ointments, creams, sprays, gels and patches, need to be lipophilic, have a low molecular weight and work well at low concentrations.

Second generation

The second generation of transdermal drug delivery systems (TDDS) was developed in response to the drawbacks of the first.

Third generation

Targeting the stratum corneum and its effects is the goal of the 3rdgenerations of TDDS methods. Delivery of bigger molecules—such as hydrophilic medications, peptides, proteins and potentially vaccines—is made possible by these method

Figure 2*: *Various Parts of TDDS

Essential component for making the transdermal drug delivery system

Liner

Before using, liner should be removed as it protects the patches during storage.

Adhesive

It was used to both bind the patch's components together and secure it to the skin.

Membrane of cell

It using several layers, the membrane controls the medication release from the patches.

Drug

The drug reservoir and the release line are in direct touch.

Backing

Shields the patches from the outside world. [6, 7]

Transdermal Patch

The body receives a specific quantity of medication via the skin and into the bloodstream at a predetermined rate of release thanks to a transdermal patch and an adhesive medicament put above the skin. [8, 9, 10, 11]

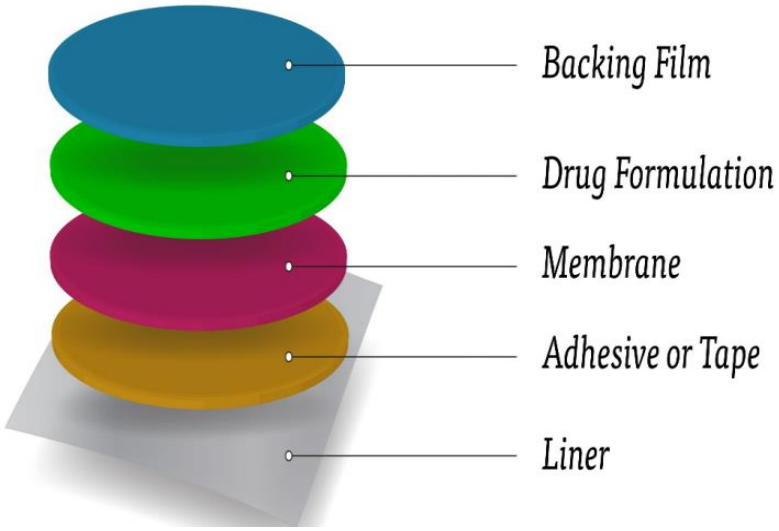

Figure 3*: *Layers of Transdermal Patches

Transdermal Pathway Type

Adhesive patches with a single layer of medication

Adhesive patches with multiple layers of medication

Sections of the type of reservoir

Matrix type

Patches with vapour

Advantages of TDDS

Transdermal drug delivery technologies offer several important advantages over more traditional techniques, benefits, such as being safe, efficacious and easily withdrawable at the patient's discretion.

The following are the main benefits of TDDS

It avoids the liver's first pass metabolism.

Delivery that is steady and regulated over an extended length of time.

Easy access to the intended or afflicted area.

Variances across and within patients.

It's simple to stop therapy at any moment.

Variability resulting from elements that significantly alter the bioavailability of medications administered orally, such as pH, intestinal motility, food consumption, etc.
Easy to administer and appropriate in pain.
Expected and unlimited duration of activity.
Sustain the plasma concentration of powerful medications.
Preventing gastrointestinal incompatibility. [12,13,14,15]

Drawbacks of TDDS

Only rather powerful medications make good candidates.
Can only be applied to medications whose actions depend on extremely low plasma concentrations.
The function of the skin's barrier changes with age and between sites on the same individuals
Variance in the effectiveness of absorption at various skin locations.
Transdermal distribution will provide significant challenges if the medication dose needed for therapeutic purposes exceeds 10 mg/day.
The fact that skin is another major drawback of transdermal medication administration acts as a barrier to prevent foreign particles from penetrating, it is less permeable.
Transdermal patches require an excess of active medication to ensure continuous release states. [16,17,18,19]

Restrictions of TDDS

The skin permeability of transdermal medication delivery systems is restricted.
Limited to strong medications and long lag times.
Large quantities of medication must be delivered through the skin, and transdermal distribution is neither practicable nor economical in this situation.
Another aspect that needs to be carefully considered before deciding to manufacture a transdermal medicine is clinical need.
The skin’s barrier function varies with age, from person to person and from one location on the same body to another.
TDDS is unable to deliver ionic medication.
Blood or plasma cannot contain high drug concentrations via TDDS.
TDDS is unable to provide medication in a pulsatile manner.
If a medication or formulation irritates the skin, TDDS cannot form. [20,21,22]

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.
For young patients and the elderly, the release liner can be easily removed [23]

The Herbal Drugs Used in TDDS

Tulsi

Synonyms: Ocimum sanctum, Ocimum tomentosum
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[24]

Figure 4*: *Tulsi

Mechanism of Action

Tulsi used in TDDS the following mechanism of action can be observed:

Penetration Enhancement

The natural penetration enhancers in Tulsi are the essential oils, especially eugenol. These substances have the ability to alter the lipid composition of the outermost layer of skin, called the stratum corneum, increasing the permeability of the skin. As a result, medications are able to enter the skin more successfully, enhancing the transdermal distribution of active medicinal components.

An Antioxidant and Anti-allergic properties

Flavonoids, which have antioxidants located in tulsi, shield the skin from oxidative stress and inflammation. This promotes skin integrity and lessens irritation or inflammation that may otherwise prevent medications from being absorbed transdermally.

Uses

It is used to promote wound healing by stimulating fibroblast activity, increasing collagen deposition and reducing inflammation.

Protect the skin from UV-induced damage and environmental pollutants.

Preventing infections in minor wounds or surgical sites.

Neem

Synonym: Neem

Biological Source: The natural source of the substance is the leaves of Azadirachta indica.

Family: Meliaceae

Chemical constituents: Nimbinin, Nimbinbdin, and Nimbina [25]

Figure 5*: *Neem

Mechanism of Action

Skin Permeation Enhancement

Natural permeation enhancers are neem oil and its active ingredients, terpenoids. These substances cause the stratum corneum (outer skin layer) lipid bilayers to break, increasing skin permeability and aiding in medication absorption via the skin.

Anti-inflammatory and Antioxidant effects

Antioxidants like quercetin and nimbolide, which are found in neem, can lessen oxidative stress and skin irritation. Neem can enhance skin health and facilitate effective drug transport through the skin by reducing local inflammation and oxidative damage prevention.

Antimicrobial Action

Nimbin and azadirachtin are two of the chemicals that give neem its strong antibacterial qualities. These characteristics guard against bacterial or fungal infections at the transdermal drug application site, which could otherwise hinder drug absorption and result in problems at the skin's surface.

Anti-aging and Skin Condition

Neem's fatty acid and vitamin E concentration are responsible for its moisturising and anti-aging qualities, which enhance skin moisture and suppleness. This improves the conditions for transdermal drug diffusion, particularly in systems of extended drug delivery.

Uses

Neem has natural antibacterial and antifungal Properties, making it beneficial in the management of numerous skin diseases, cuts, and infections [(25)]

Preventing infections in wounds, surgical sites, or burns.

Antipyretic [26]

Peppermint Oil

Synonym: Peppermint Oil, Sweet Balm

Biological Source: The leaves of the fragrant plant Mentha piperata,

Family: Lamiaceae

Chemical constituent: Menthol, Menthone, cineol

Figure 6*: *Peppermint oil

Mechanism of Action

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.

Additionally, menthol has an impact on skin hydration, which enhances the skin's lipids' fluidity and increases the skin's susceptibility to drug absorption.

Vasodilation

The blood vessels beneath the skin may enlarge due to the modest vasodilatory impact of peppermint oil. A faster and more effective systemic absorption of the medicine is made possible by this improved blood flow to the application site.

Because peppermint oil contains menthol, which increases permeability, improves blood flow, and has local analgesic and anti-inflammatory properties, it improves drug delivery via the skin. It is therefore an important part of transdermal medication delivery systems.

Uses

It increasing skin permeability and allowing drugs to pass through more easily.

It is often used in TDDS for conditions like arthritis or neuralgia.

Peppermint oil has antimicrobial activity, which can protect TDDS from microbial contamination.

Peppermint oil is widely used in TDDS for its role as a penetration enhancer, therapeutic properties, and added sensory benefits.

Aloe Vera

Synonyms: Aloe, Kummarimussabar

Biological Source: Aloe, Aloe barbadensis, Aloe perryi, Aloe Ferox is the dried fruit juice obtained from the leaves of Aloe Spicata.

Family: Liliaceae [27]

Figure 7*: *Aloe vera

Mechanism of Action

Skin Permeation Enhancement

Aloe vera facilitates more drug penetration through the epidermal barrier, including hydrophilic and lipophilic medicines, by altering the lipid structure in the stratum corneum.

Hydration and Softening of the Stratum Corneum

Aloe vera facilitates easier drug diffusion between the skin's outer layers by moisturising skin and creating microchannels in the lipid matrix of the skin.

Natural Penetration Enhancers

The lignin and saponins in Aloe vera can mix with the skin lipids and increase their fluidity, allowing medication molecules to penetrate more easily.

Anti-inflammatory and Antioxidant Effects

Aloe vera minimises the skin's defence reaction, which could otherwise prevent drugs from penetrating the epidermis, by minimising localised skin irritation and inflammation.

Aloe vera improves transdermal drug delivery systems' efficacy and efficiency by leveraging these pathways, which leads to superior therapeutic outcomes.

Uses

Aloe vera contains polysaccharides like acemannan that improve the permeability of skin, allowing drugs to penetrate the outermost layer of skin) more effectively.

Aloe vera acts as a natural penetration enhancer, this enhances the bioavailability of drugs when applied transdermally.

Aloe vera has well-known anti-inflammatory properties, this makes it suitable for use in TDDS for delivering anti-inflammatory drugs.

Bitter Melon

Synonym: Momordica indica, Momordica chinensis

Biological source: Is the plant of Momordica charantia.

Family: Cucurbitaceae

Chem. constituents: Charantin, Polypeptide-p, Momordicosides, Cucurbitacins ,Saponins, Flavonoids , Phenolic acids

Figure 8*: *Bitter Melon

Mechanism of Action

Permeation Enhancement

Saponins, flavonoids, and triterpenoids found in bitter melon have the ability to improve skin penetration. By interacting with lipids and proteins, these substances break down the tight structure of stratum corneum, for outer layer of the skin, increasing permeability of skin. This makes it possible for more bioactive components of bitter melon and any concurrently delivered medication molecules to be absorbed.

Lipophilic Nature of Active Compounds

The lipid-rich environment of the skin is more easily penetrated by the triterpenoids and other lipid-soluble chemicals found in bitter melon, which facilitates medication administration via the transdermal route.

Anti-Inflammatory and Antioxidant Actions

The bioactive substances in bitter melon, particularly flavonoids and triterpenoids, have anti-inflammatory properties that lessen inflammation and skin irritation. This characteristic helps to treat skin disorders and improves drug absorption by preserving skin integrity and lowering localised immune reactions.

Local and Systemic Effects

Bitter melon extracts can be applied topically to the skin to provide localised antioxidant and anti-inflammatory properties that are beneficial for skin disorders such as psoriasis, eczema, and wound healing. The penetration and release of bitter melon's active ingredients, which are known for their hypoglycemics, anti-inflammatory, and antioxidant properties, are major factors influencing its molecular oxygen content (MOA) in transdermal drug delivery systems. Steady absorption and localised or systemic therapeutic results are made possible by the system.

Uses

Bitter melon extracts potentially beneficial in TDDS for managing inflammatory skin conditions (like psoriasis or dermatitis) or healing wounds.

The antimicrobial and wound-healing properties of bitter melon extracts could be applied to transdermal or topical systems.

Bitter melon extracts can enhance the permeability of the skin to other drugs. This makes it a potential component of TDDS formulations designed to deliver other therapeutic agents more efficiently.

Some research has explored the role of bitter melon in regulating lipid metabolism, making it a candidate for TDDS aimed at managing obesity.

Turmeric

Synonym: Curcuma, Haldi (Hindi), Indian saffron, Curcuma longa, etc.
Biological source: It is the source of Curcuma longa.
Family: Zingiberaceae.
Chem. Constituents: Curcumin, Zingiberene, Proteins, Resins, etc.

Figure 9*: *Turmeric

Mechanism of Action

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.

Antioxidant 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.

Permeation Enhancer

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

Antimicrobial Action:

Applying curcumin transdermally 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.

Modulation of Skin Proteins

When administered via TDDS, curcumin can alter proteins associated in inflammation, apoptosis, and cell proliferation, which makes it advantageous in disorders like dermatitis and psoriasis.
Hence, localised therapeutic effects can be achieved using turmeric-based TDDS, especially in the treatment of infections, pain alleviation, inflammatory skin disorders, and wound healing.

Uses

When turmeric used in transdermal systems, it can directly target inflamed tissues or skin injuries, bypassing gastrointestinal degradation and improving its Transdermal delivery helps overcome these challenges by allowing curcumin to enter the bloodstream directly through the skin, thus bypassing the liver's first-pass metabolism.

Curcumin's antibacterial, antifungal and anti-inflammatory properties make it useful in treating skin wounds. It can be incorporated into transdermal patches.

By applying curcumin directly to the skin, it can potentially target skin cancers and other localized cancers without systemic side effects that occur with oral or intravenous administration.

Turmeric and curcumin are also used in treating psoriasis, eczema, and acne when delivered transdermally.

To improve the penetration of curcumin through the skin, it is often formulated in nanoparticle, liposomal, or micellar forms in transdermal patches or gels.

Turmeric, particularly curcumin, is a promising candidate for use in transdermal drug delivery systems, offering enhanced bioavailability, targeted delivery and therapeutic benefits in the treatment of various inflammatory, skin and cancerous conditions.

Ginger

Synonym: Zingiber, Root ginger, Fresh ginger etc.

Biological source: ginger is the plant Zingiber officinale.

Family: Zingiberaceae [28]

Chem. Constituents: Gingerols, Zingerone, Zingiberene, Phenolic Compounds, Terpenes, Vitamins and Minerals

Figure 10*: *Ginger

Mechanism of Action

In transdermal drug delivery systems (TDDS), ginger exhibits several mechanisms of action (MOA) that enhance the efficacy of the system.

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.

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.

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.

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.

Carrier Role for Lipophilic Drugs

This is particularly useful in TDDS developed for delivering medications with poor water solubility.When used in transdermal drug delivery systems, ginger mainly improves drug absorption through inducing vasodilation, decreasing inflammation, increasing skin permeability, and acting as an antioxidant. Its natural bioactive components boost the effectiveness of medicine administration and patient comfort.

Uses

Ginger's essential oil serves as a natural alternative to synthetic penetration enhancers, reducing the risk of skin irritation.

Ginger's anti-inflammatory properties make it valuable for transdermal patches designed to relieve localized pain and inflammation, such as in conditions like arthritis, muscle soreness, or joint pain.

Ginger is used in TDDS for its natural analgesic (pain-relieving) properties.

Ginger's antiemetic properties (ability to prevent nausea and vomiting) make it useful in TDDS formulations designed to alleviate symptoms of motion sickness, pregnancy-related nausea, or chemotherapy-induced nausea.

Ginger is known to improve blood circulation, making it beneficial in TDDS for localized conditions where increased blood flow is desirable, such as muscle pain, joint disorders.

Jojoba oil

Synonym: Jojoba Seed Oil, Simmondsia chinensis oil , Sorafine Cremogel , etc.

Biological source: Jojoba oil is the seeds of the jojoba plant (Simmondsia chinensis).

Family: Simmondsiaceae

Chem. constituents: Eicosenoic acid, Docosenoic acid, Oleic acid, Palmitic acid, Sterols.

Figure 11*: *Jojoba oil

Mechanism of Action

Skin Penetration Enhancement

As a penetration enhancer, jojoba oil helps to make the uppermost layer more permeable by: disturbing the stratum corneum's lipid composition.

Lipophilic Nature

Due to its high lipophilicity, or love of fat, jojoba oil blends very nicely with the skin's other lipid constituents. As a result, lipophilic medications are absorbed and transported through the epidermal barrier more effectively.

Moisturization and Hydration

Jojoba oil helps the skin maintain moisture by leaving a thin, non-greasy layer on the skin's surface. By limiting water loss, it keeps the skin moist, which can promote medication diffusion since wet skin is more porous.

Jojoba oil is an important ingredient in TDDS formulations because it can improve skin compatibility, increase medication absorption, and stabilise the formulation.

Uses

Jojoba oil helps in increasing the permeability of skin, allowing drugs to enter through outermost layer more easily.

Due to its lipophilic nature, jojoba oil can dissolve and carry fat-soluble drugs through the skin. This helps in improving the bioavailability of certain upon drugs when delivered transdermally.

Jojoba oil is an effective emollient, which softens and moisturizes the skin. This property helps maintain the integrity of the skin during prolonged drug application, reducing irritation and enhancing patient compliance.

Jojoba oil can act as a stabilizing agent in transdermal patches and creams.

Jojoba oil is often used in TDDS because it does not block pores (non-comedogenic) and is unlikely to cause allergic reactions.

The oil is a powerful emollient that helps to keep skin hydrated because it closely mimics the skin's natural sebum.[29]

CONCLUSION

As concluded in the last lines of the review article, now pharmaceutical scientists are more instigated to prepare new dosage forms for drugs already known since they can be formulated in them. New dosage forms are also needed for other drugs to enhance their efficacy in terms of reducing dosing, enhancing absorption, etc., or reaching the desired site, etc. These are the objectives of the patented advancements in transdermal medication delivery. However, successful in vivo performance represents the final challenge that any new technique has to pass as a test.

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