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Review Article

A Review on Role of Essential Oil as Penetration Enhancer in Transdermal Drug Delivery System

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ABSTRACT

The use of essential oils and their constituents as skin penetration enhancers for transdermal drug delivery, as well as the mode of action and potential toxicity. Essential oils and their toxic components have the ability to penetrate the skin and improve the penetration of various drugs from topical formulations into the lower skin layers by various modes of action. (1) disintegration of the highly organised intercellular lipid structure between corneocytes in the Stratum Corneum, (2) association with the intercellular domain of proteins, causing conformational change, and (3) Increase a drug's partitioning essential oils and their components are easily metabolised, do not persist in the body, and are quickly excreted after application to the skin, indicating that they can be used as healthy penetration enhancers. Essential oils and their constituents can be preferable to synthetics as healthy and effective permeation enhancers for promoting the percutaneous absorption of hydrophilic and lipophilic drugs from topical formulations into the lower skin layers. they have been used successfully as secure penetration enhancers. To address these issues, the Transdermal Drug Delivery System (TDDS) was developed, which would increase the clinical effectiveness and safety of medications by allowing for more accurate (i.e., location specific) positioning inside the body, minimising both the size and number of doses. Many medications are now taken orally, but they are not as successful as they can be. This article offers a description of the transdermal drug delivery mechanism and forms of transdermal patches, as well as the use of polymer as a Transdermal Drug Delivery System, preparation processes, and physicochemical assessment methods and the various forms of transdermal systems currently on the market, with an emphasis on recent developments in Transdermal Drug Delivery Systems, which may serve as a forum for prescription drug dosage form research and development for Transdermal Drug Delivery.

Keywords: Transdermal drug delivery system, Transdermal patches, Penetration enhancers, Essential oil, Drugs

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INTRODUCTION

Essential oils are commonly used as antibacterial, antifungal, and antiviral agents in the cosmetics, pharmacy, medical, and food industries (Man A, *et al.*, 2019). They include antioxidant and anti-inflammatory properties (Miguel MG, 2010), anticancer properties (Angelini P, *et al.*, 2018), wound healing properties (Salas-Oropeza J, *et al.*, 2020), will substitute often used preservatives (Pandey AK, *et al.*, 2017), pesticide properties (Isman MB, Machial CM, 2006), and several other biological functions (Mehdizadeh L, Moghaddam M, 2018). Essential oils and their constituents are commonly used to avoid and cure a variety of human diseases due to their many biological activities (Sharifi-Rad J, *et al.*, 2017). As a result, natural agents can be favoured to synthetics as healthy and effective permeation enhancers for promoting the percutaneous absorption of a variety of medications from topical formulations into the lower skin layers (Herman A, Herman AP, 2015). The importance of essential oils and their constituents as a skin permeation enhancer in a transdermal drug delivery mechanism is discussed in this study. The method by which they penetrate the skin and their toxicity were also discussed (Herman A, Herman AP, 2019).

ESSENTIAL OILS AND THEIR COMPOUNDS CAN PENETRATE THE SKIN

The origin (human, animal) and condition of skin, as well as the physicochemical properties of the studied compound and distribution mechanisms, as well as potential skin pretreatment and environmental conditions, all influence dermal absorption (Zsikó S, *et al.*, 2019). However, it is not widely available. As a result, animal skin is often used in penetration tests (Dayan N, 2005). A variety of animal models (primates, porcines, mice, rats, guinea pigs, and snakes) have been proposed as ideal substitutes for human skin (Günther C, *et al.*, 2020). Unfortunately, human and animal skin have different anatomical structures (thickness, composition of intercellular Stratum Corneum (SC) lipids, number of skin shafts, density of hair follicles, vascular morphology, and collagen fibre arrangement) (Herman A, Herman AP, 2019; Mauldin EA, Peters-Kennedy J, 2016). The volume, tape, and ease of penetration of the investigated substances through the skin are all affected by variations in skin structure. Rodent skin, with the exception of pig and rat skin, has greater permeation rates than human skin (Andrews SN, *et al.*, 2013). As a result, researchers are still struggling to find a connection between animal and human models for predicting percutaneous absorption in humans. The composition of the skin is another factor that influences transepidermal penetration (Zsikó S, *et al.*, 2019). Overcoming the most outer layer of the non-viable epidermis-SC-is a significant barrier to active compound penetration through the skin. SC acts as a rate-limiting lipophilic filter to prevent the absorption of chemical and biological toxins, as well as water loss through the skin (Haque T, Talukder MM, 2018). Transcellular (intracellular) permeation through the corneocytes of the SC, penetration across the intercellular spaces of the SC, and appendage penetration through hair follicles, sebaceous, and/or sweat glands are the only potential routes for active compounds to penetrate the epidermis (Desai P, *et al.*, 2010). The intercellular pathway, on the other hand, is generally regarded as the primary route and main barrier to opioid permeation. Polarity, molecular weight (500 Da), concentration of active compounds in formulation, molecule solubility in oil and water, and preparation structure all have an effect on skin penetration (N'Da DD, *et al.*, 2014; Homayun B, *et al.*, 2019). As a result, only a small number of molecules with unique physicochemical properties can adequately cross the skin and, in the case of drugs that target subdermal tissue, only a small number of molecules with specific physicochemical properties can cross the skin. The ac-

tive constituents of essential oils are among them (Alkilani AZ, *et al.*, 2015; Dhifi W, *et al.*, 2016).

PENETRATION-ENHANCING MECHANISM

Penetration enhancers are substances that improve drug diffusivity across the skin by lowering the SC's membrane tolerance without harming viable cells (Lizelle T, *et al.*, 2011). Enhancers should ideally have the following characteristics: pharmacologically inert, non-irritating, non-toxic, non-allergenic, compliant with medications, have strong solvent properties, odourless, tasteless, colourless, cheap, do not cause loss of body fluids, electrolytes, or other endogenous materials, simple removal from the skin and rapid re-establishment of the skin's natural barrier (Roy N, *et al.*, 2017; Moiseev RV, *et al.*, 2019). Various chemical groups have been established as possible skin penetration enhancers by rigorous sampling and testing over the years. Sulphoxides (dimethyl sulphoxide, dimethylacetamide), azone (1-dodecylazacycloheptan2-one, laurocapran), and pyrrolidones (2-pyrrolidone, laurocapran) are the most extensively studied penetration enhancers. Basic oils and their constituents (terpenes, terpenoids) as well as chelating agents (EDTA, citric acid) (Dragicevic N, Maibach HI, 2016). These natural agents can transport drugs through skin through a variety of mechanisms: (1) In SC, the strongly organised intercellular lipid arrangement between corneocytes is disrupted, allowing drugs to pass through this membrane. (2) contact with the protein's intercellular domain, which causes conformational changes in the protein and increases SC permeability. Promotional partitioning (3) many solvents modify the properties of the SC, increasing drug partitioning; and (4) enhancers that operate on desmosomal interactions between corneocytes or alter metabolic activity within the skin (Haque T, Talukder MM, 2018). Changing the polar pathway with a general enhancer causes protein conformational changes or solvent swelling, while changing the polar pathway with a fatty enhancer causes protein conformational changes or solvent swelling. Acid enhancers make the lipid part of the SC more elastic. By modifying the multilaminate pathway for penetration, some enhancers function on both polar and non-polar pathways (Kim B, *et al.*, 2020). Essential oils and their constituents have been extensively studied as healthy and effective skin penetration enhancers for both hydrophilic and hydrophobic products, but the mechanism of action remains unknown (Herman A, Herman AP, 2019). In a dose-dependent way, eucalyptus, tea tree, and peppermint oil added topically decreased skin integrity, according to Nielsen (Nielsen JB, 2006). Peppermint oil in low concentrations lowered benzoic acid percutaneous penetration and acted as a buffer against it, while higher concentrations weakened the dermal barrier. Turpentine, eucalyptus, and peppermint oils strengthened ketoconazole permeation by altering the skin layer without altering their composition (Nielsen JB, 2006). Alpinia oxyphylla oil had a higher affinity for the lipophilic SC and likely decreased its polarity, allowing more lipophilic indomethacin to permeate into the rat's dorsal skin (Lizelle T, *et al.*, 2011). Furthermore, in-vivo experiments revealed that transepidermal water loss improvements were insignificant, suggesting that the intercellular routes were not disrupted and that these drug permeation enhancers caused no irritancy or toxicity. Finally, the authors concluded that the key mechanism of A. oxyphylla essential oils' skin penetration enhancement effect is attributed to an improvement in skin-vehicle partitioning (Lizelle T, *et al.*, 2011). Turpentine oil, at a concentration of 5% (v/v), was found to be an important enhancer for flurbiprofen permeation by Charoo NA, *et al.* (Charoo NA, *et al.*, 2008). This was likely attributed to increased disturbance of the SC and mild skin irritation. Black cumin essential oil was found to remove lipids from SC and trigger -keratin denaturation, which changed the skin protein composition by 5% (v/v) in isopropyl alcohol (Chouhan S, *et al.*, 2017). The active compounds obtained from essential oils work primarily by altering the structure of the SC barrier and interacting with intercellular SC lipids to improve drug diffusivity (Sharifi-Rad J, *et al.*, 2017; Haque T, Talukder MM, 2018). It was proposed that d-limonene penetrated into the skin in the presence of ethanol and may alter indomethacin diffusivity by altering the composition of the SC membrane, as a potential mechanism for enhanced activity of d-limonene and ethanol via rat skin (Herman A, Herman AP, 2019; Lizelle T, *et al.*, 2011; Sapra B, *et al.*, 2008). Williams and Barry demonstrated that the main mechanism of action of the tested cyclic terpenes (-pinene, -terpineol, carvone, 1,8-cineole, and ascaridole) is dependent on their association with intercellular SC lipids, which increases diffusivity for hydrophilic permeant 5-fluorouracil (5-FU) across human epidermal membranes (Herman A, Herman AP, 2019; Williams AC, *et al.*, 2006). After terpene therapy, however, no important protein interactions or large partitioning changes were found (Xing S, *et al.*, 2016). L-mechanism menthols of action in the transdermal delivery of propranolol hydrochloride through excised hairless mouse skin entails its diffusion preferentially into the intercellular spaces of SC and the potential reversible degradation of the intercellular lipid domain (Kang L, *et al.*, 2013). By partially extracting lipids in the SC, menthol increased the percutaneous flux of nicardipine hydrochloride from a 2% w/w hydroxypropyl cellulose gel system from the excised rat epidermis. Thymol and menthol improved tamoxifen partitioning into the SC, while carvone and 1-8-cineole disrupt SC lipids (Krishnaiah YS, *et al.*, 2002). The chemical composition of essential oil constituents that function as enhancers has an effect on drug penetration through the skin. In most cases, transdermal absorption of terpenes with polar functional groups increases the absorption of hydrophilic drugs, while hydrocarbon terpenes improve the absorption of lipophilic drugs. However, the hydrocarbon terpene was found to be more powerful than the ketones and oxide terpene in the gels, which can be attributed to the ketones' lower thermodynamic behaviour (Lizelle T, *et al.*, 2011). Since geraniol and nerolidol contain definitive hydrocarbon tail groups in addition to a polar head group, their structures are ideal for disrupting the lipid packing of the SC, allowing diclofenac sodium to penetrate full-thickness abdominal male rat skin (Herman A, Herman AP, 2019; Lizelle T, *et al.*, 2011). Essential oil terpenes have an alcoholic group, allowing them to compete more competitively with the amide groups of skin ceramides than terpenes with a carbonyl group (Herman A, Herman AP, 2019; Lizelle T, *et al.*, 2011; Jain R, *et al.*, 2008). The formation of hydrogen bonds between terpenes and skin ceramides loosens the close junctions of lipid layers, allowing for new molecular permeation pathways (Lizelle T, *et al.*, 2011; Chen J, *et al.*, 2006). In comparison to these effects, geraniol thymol and clove oil were found to have a lower enhancement ratio than camphor, considering the fact that these oils contain more alcoholic oxygen atoms (Lizelle T, *et al.*, 2011; Jain R, *et al.*, 2008). The disruption of the hydrogen bond network at the heads of the ceramides was suggested to be the mechanism for imipramine hydrochloride permeation enhancement through the dorsal rat skin by terpenes (menthol, terpineol). Only hydrogen bond accepting moieties (carbonyl or ether groups) are found in menthone, pulegone, carvone, and cineole, resulting in less degradation of the hydrogen bond network between the ceramide heads (Herman A, Herman AP, 2019; Lizelle T, *et al.*, 2011; Jain R, *et al.*, 2008). The physico-chemical properties of the permeant molecules, as well as those of the enhancer molecules, greatly change the permeation of a molecule through the skin and establish various modes of action, according to studies on the mechanism of essential oils and their active compounds penetration enhancement action (Haque T, Talukder MM, 2018).

ESSENTIAL OILS AS PENETRATION ENHANCERS

5-FU, ibuprofen, aminophylline, p-aminobenzoic acid, and other drugs have been shown to be effective in delivering across the skin with essential oils (Herman A, Herman AP, 2019). Drugs like Estradiol, ketoconazole, chlorhexidine digluconate, nitrendipine, diclofenac sodium, indomethacin, benzoic acid, and carvedilol also good delivered into the skin. Few experiments have compared the efficacy of essential oils versus chemical penetration enhancers for opioid penetration through the skin. The effect of Rhizoma Et Radix Notopterygii essential oil (5%) on palmatine hydrochloride permeation was greater than that of azone. When fructus cnidii essential oil and azone were used individually, metronidazole absorption was similar, but when they were combined, metronidazole penetration through the skin was increased. The enhancing effect of eucalyptus, peppermint, and turpentine oils was found to be less than that of azone, but all of the oils studied improved 5-FU permeation via excised rat tissue. The enhancement ratios were 89.45 for azone, 59.63 for eucalyptus oil, 45.2 for peppermint oil, and 27.16 for turpentine oil. Some examples of drugs with essential oil as penetration enhancer are in *Table 1*.

Table 1: Drugs with Essential oil as penetration enhancer

Drug	Essential oil	Place where applied	Characterization
5-fluorouracil (Williams AC, Barry BW, 1989)	Eucalyptus, anise, chenopodium, ylang ylang oils	Excised human skin	The most powerful 5-FU permeation enhancers were eucalyptus and chenopodium oils, which showed a 30-fold improvement in drug permeability coefficient. The medication permeability coefficients of ylang ylang and anise oils increased eight-fold and three-fold, respectively.
5-fluorouracil (Abdullah D, *et al.*, 1996)	Eucalyptus, peppermint, turpentine oils	Rat skin	Eucalyptus, peppermint, and turpentine, respectively, caused a 60-fold, 46-fold, and 28-fold rise in opioid permeability coefficient.
Ibuprofen (Sebastiani P,*et al.*, 2005)	turpentine oil	Cellulose membrane, excised rabbit abdominal skin	A median flux of 10.87 mg/cm^2/h was observed across artificial skin and 17.26 mg/cm^2/h was observed across rabbit abdominal skin using a hydrogel containing 1% ibuprofen and 3% turpentine oil.
Aminophylline (Wang LH, *et al.*, 2007)	Rosemary, ylang, lilacin, peppermint oils	Human skin	All oils increased aminophylline permeation, but their effects were less than those of ethanol as an enhancer.
Flurbiprofen (Charoo NA, *et al.*, 2008)	Tulsi, turpentine oils	Rat abdominal skin	Transdermal patch increased flurbiprofen bioavailability in rats by 2.97, 3.80, and 5.56 times as compared to orally administered flurbiprofen. tulsi and turpentine oil formulations of 5% (v/v) tulsi and turpentine oil, respectively
Abetolol hydrochloride (Jain R, *et al.*, 2008)	Basil oil	Rat abdominal skin	Basil oil has been suggested as a potential penetration enhancer for improving labetolol hydrochloride transdermal drug delivery.
p-aminobenzoic acid (Wang LH, Chen JX, 2010)	Ylang, lavender, orange, nutmeg, chamomile, sage, eucalyptus, ginger, peppermint oils	Human skin	The levels of p-aminobenzoic acid and its metabolites in the urine of those who were given essential oils were higher than in the urine of those who were not.
Estradiol (Monti D, *et al.*, 2006)	Niaouli oil	Hairless mouse skin	As opposed to the control group of propylene glycol and estradiol, Niaouli oils (10 percent (w/w) raised the transdermal flux of estradiol from 41.50 to 84.63 times, correspondingly
Ketoconazole (Rajan R, Vasudevan DT, 2012)	Turpentine, eucalyptus, peppermint oils	Pig skin	Ketoconazole permeation was higher in formulations containing eucalyptus oil as a permeation enhancer than in formulations containing other essential oils.
Indomethacin, diclofenac, piroxicam (Huang YB, *et al.*, 1995)	Cardamom oil	Rabbit abdominal skin	The effectiveness of cardamom oil was dependent on its concentration; a concentration of 1% (v/v) was more effective than a concentration of 0.5 percent (v/v) essential oil. Cardamom oil has an improving effect that is dependent on the pH of the solvent; piroxicam had the highest penetration index at both pH 5.8 and pH 7.4 with 1 percent cardamom oil, followed by indomethacin, and then diclofenac.
Benzoic acid (Nielsen JB, 2006)	Peppermint, tea tree, eucalyptus oils	Human breast or abdominal skin	Peppermint oil in concentrations of 0.1 percent and 1.0 percent (v/v) has the greatest impact on benzoic acid skin penetration.

Transdermal Drug Delivery Systems (TDDS), also called "patches," are dosage formulations that distribute a therapeutically beneficial volume of drug through the skin of a patient. The transdermal drug delivery mechanism has been around for quite some time. In the past, the most widely used systems for dermatological conditions were topically applied creams and ointments (Tanwar H, Sachdeva R, 2016). The fact that any of these formulations cause systemic side effects indicates that they are absorbed by the skin. For systemic therapy, a variety of medications have been added to the skin. The expression "transdermal delivery device" refers to any topically applied drug formulation that is meant to inject the active ingredient into the bloodstream. Transdermal therapeutic systems are engineered to distribute medicines to the systemic circulation in a regulated and continuous manner through the skin (Duan D, *et al.*, 2011).

TRANSDERMAL PERMEATION: FACTORS AFFECTING IT THE INFILTRATE MOLECULES' PHYSICOCHEMICAL PROPERTIES

Penetrate concentration, partition coefficient, and pH conditions (Kim B, *et al.*, 2020).

Physiological variables

1. The skin's Stratum Corneum plate.

2. The body's anatomical application site.

3. Skin problems and diseases. The patient's age.

4. The metabolism of the skin. Desquamation is the peeling or flaking of the skin's surface.

5. Irritation and sensitization of the skin (Ramadon D, *et al.*, 2021; Monika B, *et al.*, 2012).

Transdermal Drug Delivery System components

• The drug comes into touch with the release liner. The physicochemical properties of the drug are used to pick it for TDDS. The transdermal drug delivery mechanism is ideal for drugs with a long half-life. Backing membrane protects the patch from the elements, is impervious to the transdermal patch materials, and allows the patch to move. It is preferably nonbreathable and made of elastomers (polyolefin oils, polyester, polyethylene, polyvinylidene chloride, and polyurethane) (Bird D, Ravindra NM, 2020; Isaac M, Holvey C, 2012).

• Membrane controls how much of the medication is released. It's made of natural or plastic polymer or synthetic elastomers, and it comes in thicknesses ranging from 2 to 7 mm (Bird D, Ravindra NM, 2020; Isaac M, Holvey C, 2012).

• Adhesive connects the patch's components together as well as the patch to the skin. Depending on the skin adhesion properties required, it is made of silicone, rubber, polyvinyl acetate, or polyisobutylene. It may contain permeation enhancers (solvents, surfactants, or other chemicals) that change the structure of the skin to increase permeability (Rajan R, Vasudevan DT, 2012; Bird D, Ravindra NM, 2020; Isaac M, Holvey C, 2012).

• Liner is peeled off before use and serves to protect the patch during storage (Bird D, Ravindra NM, 2020; Isaac M, Holvey C, 2012).

Advantages

Transdermal Drug Delivery Systems have a number of advantages. Since transdermal delivery is easy and discreet, it's an intriguing choice. The below are some of the advantages of delivering medications across the skin for systemic effects: First-pass metabolism should be avoided if at all possible. In order to avoid stomach-intestinal incompatibility, you should eat foods that are compatible with your digestive system. Event that is predictable and lasts a long time. Allows for the use of medications with brief biochemical half-lives and a limited treatment window. Improve the clinical effectiveness. With the elimination of the patch, the drug administration comes to an end. Patients who are reluctant to take oral drugs will take this alternative path. Noninvasive, painless, and easy implementation improved patient compliance and comfort (Tanwar H, Sachdeva R, 2016; Kandil LS, *et al.*, 2020).

Disadvantages

Currently, only tiny, lipophilic drugs can be administered via this method. Since the patch size limits the volume of medication, the drug molecule must be potent. Drugs with a low or high partition coefficient should not penetrate the bloodstream. In the event of overdose, drug distribution can be easily stopped. Owing to their poor solubility in both water and fat, this path can be used to administer strongly melting drugs. The medication, the adhesive, or other excipients in the patch formulation can cause erythema, scratching, and local edoema (Tanwar H, Sachdeva R, 2016; Kandil LS, *et al.*, 2020).

Physicochemical properties

The medication should be soluble in both oil and water to some extent (ideally greater than 1 mg/ml). The melting point of the material should be less than 200°F. Low molecular weight hydrogen bonding groups can be smaller than 2.8 (less than 500 Daltons) (Rajan R, Vasudevan DT, 2012; Tanwar H, Sachdeva R, 2016; Ramadon D, *et al.*, 2021; Petrilli R, Lopez RF, 2018).

Biological properties

The drug should be extremely active, meaning it should be available in just a few milligrams per day (ideally less than 25 milligrams a day). Tolerance to drugs does not grow if the dose is kept low order transdermal distribution profile of release. In the subcutaneous tissue, the substance does not become irreversibly bound. The compound cannot be metabolised thoroughly in the skin. Therapeutic window is limited (Tanwar H, Sachdeva R, 2016; Ramadon D, *et al.*, 2021; Bird D, Ravindra NM, 2020; Jan Su, *et al.*, 2020).

CONCLUSION

Transdermal Drug Delivery Systems have been shown to be both safe and reliable. The promise of their role in supervised release is being explored all over the world. Scientists who have a high degree of success. Transdermal delivery is a remarkable successful route of administration if a drug has the perfect combination of physical chemistry and pharmacology. Delivery is a very efficient method of administration. Because of the TDDS's many benefits, several new studies are currently being conducted to bring newer medications into the scheme. Chemical enhancers have a number of drawbacks, including their efficacy and protection. They have low permeation in the SC, and their presence is restricted to just the top few layers. Their focus, as well as their behaviours, declines as they progress further through the SC. Chemical enhancers with a higher concentration in the formulation improve drug transport through the skin, but this is equal to their tendency to irritate the skin. As a result, maintaining an ideal balance between the protection and efficacy of chemical enhancers in drug permeation is difficult. As healthy and appropriate permeation enhancers, essential oils and their constituents can be favoured to the traditionally used synthetic materials. encourage the percutaneous absorption of a variety of medications from topical formulations into the deeper layers of the skin Essential oils help hydrophilic and lipophilic drugs permeate more easily and with less cytotoxicity. Many organisations, such as the Research Institute for Fragrance Materials, the International Flavor and Fragrance Association, have well-documented their toxicity. The National Toxicology Program, the Fragrance Association, and the Flavor Essence Manufacturers Association Basic oils and their constituents have been shown to have a low toxicity as compared to the majority of synthetic penetration enhancers. As a result, essential oils and their

components are significant, can be used to improve the prevention of drug permeation across the skin.

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