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ESSENTIAL OILS AS NOVEL HUMAN SKIN PENETRATION ENHANCER FOR TRANSDERMAL DRUG DELIVERY: A REVIEW

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ABSTRACT

Transdermal drug delivery system established itself as an integral part of a novel drug delivery system because of various factors like high bioavailability, absence of first pass metabolism, steady drug plasma concentration. There are many obstacles that do not allow drug to penetrate deeper into the skin. Now a day's various skin penetration enhancement techniques have been developed to limit this barrier by use of various natural penetration enhancers like essential oils. This review covers the role of essential oils in a transdermal drug delivery system as a skin permeation enhancer because of various factors like natural from its origin, promising penetration enhancement activities and mechanism of action is probably due to its increased skin vehicle partitioning by the oils.

KEY- WORDS: Transdermal, Essential oils, Permeation Enhancers, Skin, Epidermis

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INTRODUCTION

Essential oils was named for the first time as the effective component of a drug"Quinta essential"[1]. An essential oil is a concentrated hydrophobic liquid containing volatile aroma compounds from plants. Essential oils are also known as volatile oils, ethereal oils or aetherolea, or simply as the "oil of" the plant from which they were extracted, such as oil of clove. An oil is "essential" in the sense that it carries a distinctive scent, or essence, of the plant. Essential oils are liquid aroma compounds obtained from natural sources, usually plants. They could be found in different parts of plants like leaves (oregano),seed (almond), flower (jasmine), peel (bergamot),berries (juniper), rhizome (ginger), bark (sassafras),wood (agarwood),resin (frankincense), petals (rose).Essential oils are considered as the "chemical weapons" of the plants world as their compounds may deter insects, or protect the plants against bacterial or fungal attacks[2]. Essential oils are natural, complex, multi-component systems composed mainly of terpenes in addition to some other non-terpene components. Classification of essential oils is shown in Table 1and properties in Table 2.

CHARACTERISTICS

- Essential oils deliver high levels of oxygen and ozone to the cells, creating an oxygen-rich atmosphere in which pathogens cannot survive.
- Essential oils create a negative-ion environment in which pathogens cannot survive.
- Virtually every essential oil is anti-bacterial; many are anti-microbial, anti-fungal, anti-parasitic[3].
- A large number of essential oils such as lemon and mountain savory are immuno-stimulators.
- There are no known viruses or bacteria which have developed an immunity to essential oils through mutation.
- Sesquiterpenes (chemical constituents of some essential oils such as lemon, frankincense and sandalwood) have the rare ability to cross the blood-brain barrier, a critical factor in the healing of many diseases.
- Essential oils can deliver vital nutrients to starving cells by "piggy-backing" them through abnormally thickened cell membranes which have developed due to oxygen deprivation.
- Essential oils, such as helichrysum, are natural chelators, driving toxins/metals out of the cells.
- Essential oils normalize and balance the body's systems.
- Properly produced essential oils are living substances which carry electrical frequency and can help raise the frequency of the human body to levels at which disease cannot exist. Rose essential oil carries the highest frequency.
- Essential oils such as geranium and spruce have the capacity to clear emotional trauma and negative emotional patterns which are at the roots of a vast number of diseases shown in Table 3.
- Essential oils stimulate the release of endorphins, relieving physical and emotional discomfort and promoting a feeling of joy and well-being.
- Essential oils can increase our sense of wholeness and connection with the source of all healing.

SKIN

The human skin is a readily accessible surface for drug delivery. Skin of an average adult body covers a surface of approximately $2m^2$and receives about one third of the blood circulating through the body. An average human skin is known to contain, on the average,40-70 hair follicles and 200-250 sweat ducts on each square centimeter of skin area. The skin is a multilayered organ composed of three major tissue layers:

- The epidermis, which provides waterproofing and serves as a barrier to infection;
- The dermis, which serves as a location for the appendages of skin;
- The hypodermis (subcutaneous adipose layer) shown in Fig. 1.
- The epidermis further divided into five anatomical layers with stratum corneum forming the outer most layer of epidermis[6].

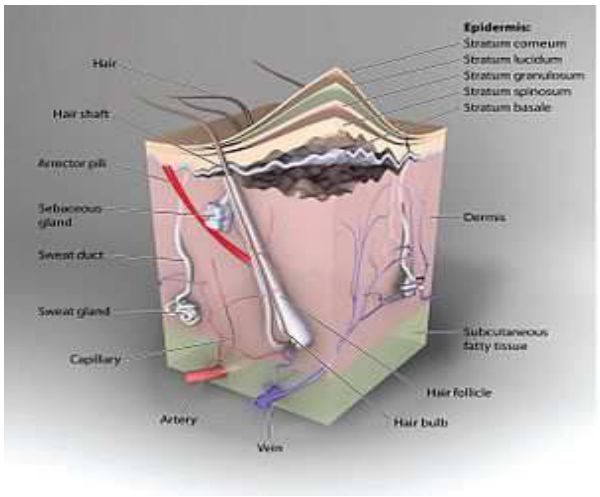


Figure 1
A cross section of human skin, showing various skin tissue layers and appendages.

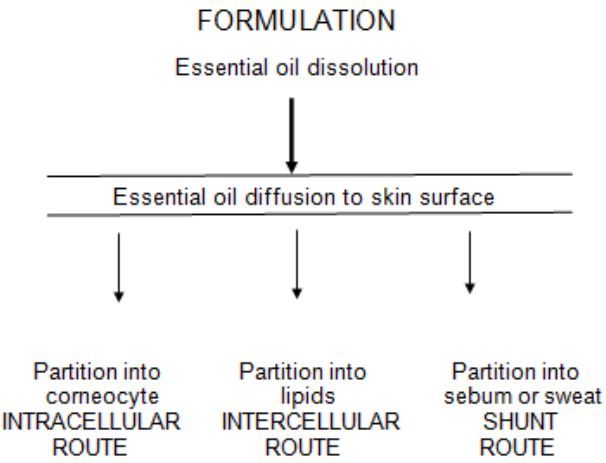


Figure 2
Routes through the stratum corneum

TRANSDERMAL DRUG DELIVERY SYSTEM *[7,20]*

Transdermal drug delivery system is the system in which the delivery of the active ingredients of the drug occurs by the means of skin. Various types of transdermal patches are used to incorporate the active ingredients into the circulatory system via skin. The patches have been proved effective because of its large advantages over other controlled drug delivery systems. A transdermal patch or skin patch is a medicated adhesive patch that is placed on the

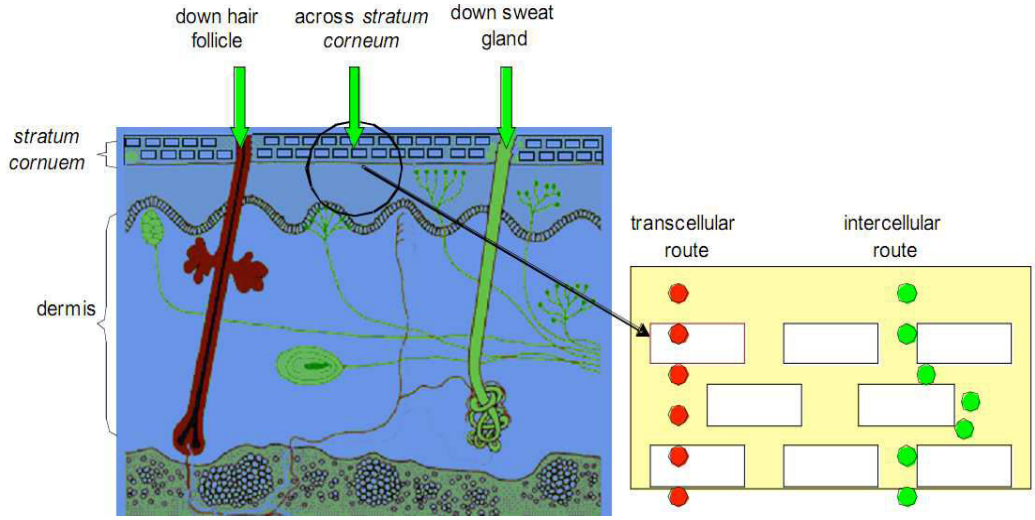
skin to deliver a specific dose of medication through the skin and into the bloodstream[8] .The first commercially available prescription patch was approved by the U.S. Food and Drug Administration in December 1979, which administered scopolamine for motion sickness.

PERMEATION ENHANCERS

Permeation enhancers are the substances that reduce the skin ability to perform its barrier function and makes skin more permeable and they allow drug molecules to cross the skin at a faster rate[10].These substances can increase the drug diffusivity in the stratum corneum (SC) by dissolving the skin lipids or by denaturing skin proteins.The mechanism of action of permeation enhancers are 1)disruption of the highly ordered structure of SC lipids 2) interactions with intracellular proteins 3)improvement in partitioning of the drug, co-enhancers or co solvent in to the stratum corneum[9 b].

ROLE OF ESSENTIAL OILS AS PERMEATION ENHANCER

Dermal application provides the principal route for essential oil administration and it is axiomatic that it is the primary route for dermatological care. Transdermal permeation of essential oil molecules is complex, involving many possible steps from initial application to their arrival in the systemic circulation. However, they have been shown to penetrate into and through the skin where they exert local therapeutic effects. The stratum corneum for most molecules is the rate-limiting barrier to further permeation. There are three ways that intact stratum corneum can be crossed as shown in Fig.2



1) intercellular ± via lipid domains
2) transcellular ± diffusion through the corneocyte
3) shunt routes ± via hair follicles and sweat glands.

Figure 3
Intracellular and Intercellular routes of essential oil absorption

Intercellular permeation

The intercellular pathway involves drug diffusing through the continuous lipid matrix. The intercellular domain is a region of alternating structured bilayers. Consequently, a drug must sequentially partition into, and diffuse through repeated aqueous and lipid domains[8]. Lipophilic substances such as essential oil components are absorbed more readily as the stratum corneum provides a formidable barrier for hydrophilic compounds, which penetrate more slowly Fig. 3.

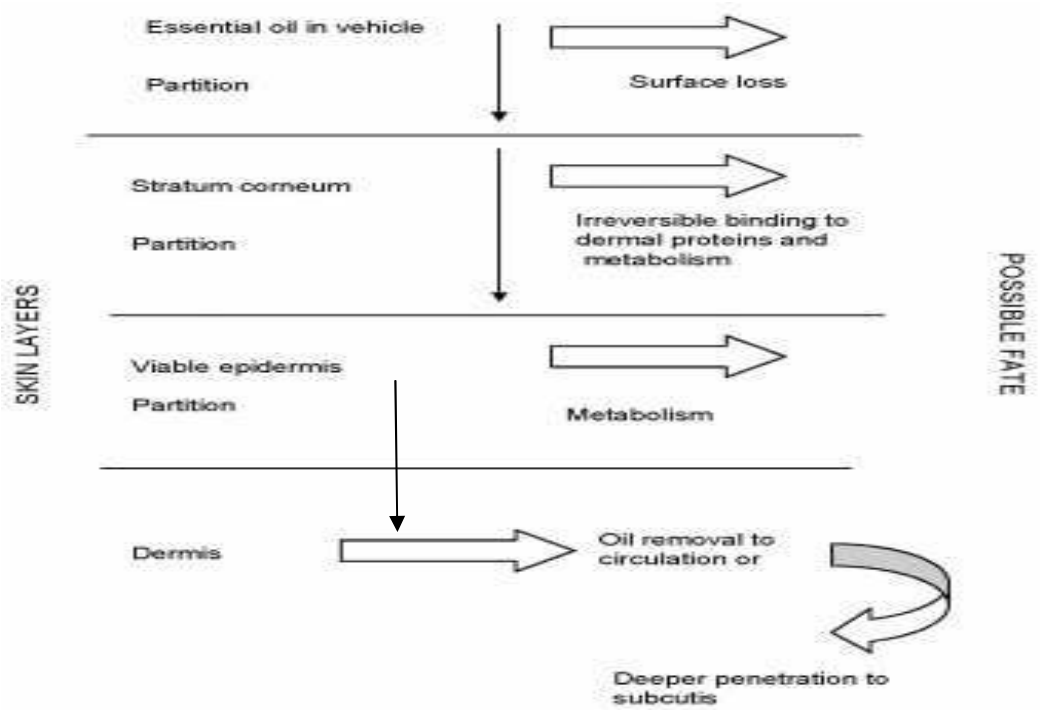


Figure 4
Potential fate of essential oil components when applied to skin

Intracellular permeation

Drugs entering the skin *via* the transcellular route pass through corneocytes. After partitioning into and diffusing through the relatively aqueous corneocytes, the permeant must partition into the surrounding lipid envelope, and subsequently partition in and out of the multiple lipid bilayers separating corneocytes [11]. The transcellular pathway is, however, thought to be the predominant pathway for highly hydrophilic drugs during steady-state flux [12]. The intracellular route is usually regarded as a pathway for polar (hydrophilic) molecules, since cellular components are predominantly aqueous in nature.

Shunt routes

Skin appendages provide a continuous channel directly across the stratum corneum barrier and has little influence on flux, it has been proposed that this route may be important for large polar molecules and ions[13].

ESSENTIAL OILS AS SKIN PENETRATION ENHANCERS

Penetration enhancers partition into the stratum corneum and interact with tissue components to reduce the barrier properties of this membrane without causing damage to the underlying skin cells. D-limonene and 1,8 cineole have both been shown to disrupt stratum corneum lipid bilayers thereby modifying permeant diffusivity through the stratum corneum.

Effects of mediums on essential oil permeation

Due to their lipophilicity essential oil molecules will partition into the stratum corneum lipids from an aqueous formulation such as a lotion or cream more readily than from an oily vehicle or ointment. Only essential oil molecules adjacent to the skin can partition from the vehicle into the tissue, thus movement through the vehicle to the skin surface is important. Diffusion through the vehicle depends on the

nature of the formulation such as its viscosity.

Other permeation variables

Transdermal essential oil permeation is influenced by many variables which includes:

- Warmth of the skin
- Increasing the dose applied
- Extending the duration of contact
- Humidity
- Occlusion
- Skin hydration.

The fate of essential oil molecules

At the stratum corneum/viable epidermis junction essential oil molecules must partition into the viable tissue before further diffusion to the dermoepidermal junction. Partitioning occurs once more at this site, followed by diffusion through the dermal tissue to the vascular capillaries Fig. 4. In addition to these partitioning and diffusion processes there are other potential fates for essential oil molecules entering the skin which include:

- Irreversible binding to cutaneous proteins such as keratin
- Degradation or biotransformation by cutaneous enzymes
- Partitioning into and forming a reservoir in the subcutis.

TABLE 1
CLASSIFICATION OF ESSENTIAL OIL COMPOUNDS[4]

COMPOUND CLASSIFICATION	
Hydrocarbon	Contain only carbon and hydrogen atoms.
Alcohol	Contains a hydroxyl group (OH) attached to the terpene structure.
Aldehyde	Terpenoids with a carbonyl group (C=O) and hydrogen bonded to a carbon.
Cyclic aldehydes	Aldehyde group attached to a benzene ring
Ketone	Contains a carbonyl group bonded to two carbon atoms.
Phenol	Hydroxyl group attached to a benzene ring
Phenolic ether	Contains an O between C and benzene ring
Oxide	Has an O bridging 2 or more carbons
Ester	Condensation product of acid and alcohol

TABLE 2
PROPERTIES OF ESSENTIAL OIL FAMILIES

COMPOUND	PROPERTIES
Hydrocarbons	Stimulant, decongestant, antiviral, antitumour
Alcohols	Antimicrobial, antiseptic, tonifying, spasmolytic
Sesquiterpene alcohols	Anti-inflammatory, anti-allergenic
Phenols	Antimicrobial, irritant, immune stimulating
Aldehydes	Spasmolytic, sedative, antiviral
Cyclic aldehydes	Spasmolytic,
Ketones	Mucolytic, cell-regenerating, neurotoxic
Esters	Spasmolytic, sedative, antifungal
Oxides	Expectorant, stimulant
Coumarins	UV sensitising, antimicrobial
Sesquiterpenes	Anti-inflammatory, antiviral
Phenylpropanes	Carminative, anaesthetic
Sesquiterpene	Lactones Mucolytic, immune stimulating

TABLE 3
APPLICATIONS OF ESSENTIAL OILS

Condition	Essential Oil	Application
Acne	Tea Tree, Lavender [b]	Topical
Allergies	Wintergreen, Lavender, Chamomile	Inhalation, Topical (Asthmatics should not inhale - put on soles of feet.)
Alzheimers	Cedarwood, Myrrh, Sandalwood, Frankincense	Topical
Apnea	Valor, Clarity	Inhalation, Topical
Arthritis	Wintergreen, PanAway, Peppermint, Idaho Balsam Fir	Topical
Backache	Deep Relief, Wintergreen, Peppermint, Aroma Siez	Topical
Blisters	German Chamomile, Tea Tree, Melrose, Lavender, Purification	Topical
Bronchitis	RC, Thieves, Myrtle, Pine, Eucalyptus, Idaho Balsam Fir	Topical, Inhalation
Burns	Lavender	Topical
Clogged Pores	Ta Tree, Lemon, Purification	Topical
Colds	Thieves, Eucalyptus Radiata, RC, Raven, Peppermint	Topical, Inhalation, Ingestion
Dandruff	Tea Tree, Cedarwood	Topical
Dizziness	Peppermint, Frankincense, Cedarwood	Inhalation, Topical
Dry, Chapped, or Cracked Skin	Myrrh, Sandalwood, Lavender	Topical
Fever	Wintergreen, Peppermint, Copaiba	Topical,Inhalation
Infection	Thieves, Oregano, Thyme, Mountain Savory, Lemongrass	Inhalation, Topical, Ingestion
Insect Bites (Bee Stings)	Peppermint, Purification, Melrose, Citronella, Lavender, Teatree	Topical
Itching	Peppermint, Lavender	Topical
Joint Pain	PanAway, Wintergreen, Idaho Balsam Fir	Topical
Menstrual Cramps	Dragon Time, Lavender, Clary Sage, Peppermint, Deep Relief	Topical
Motion Sickness	Ginger, Peppermint	Topical
Muscle Spasms (Charley Horses)	Wintergreen	Topical
Nausea	Patchouli, Peppermint, Ginger	Topical, Inhalation, Ingestion
Snoring	Thyme	Topical (4-6 drops diluted on soles of feet at bedtime)
Sprain	Idaho Balsam Fir, Pine, Cypress, Spruce, Peppermint,Wintergreen	Topical
Strep Throat	Oregano, Thyme, Thieves	Inhalation, Ingestion, Topical
Toothache	Clove, PanAway, Wintergreen, Deep Relief	Topical, Oral
Wounds, Scrapes, Cuts	Lavender, Thieves, Melrose	Topical

TABLE 4
NATURAL SOURCES OF TERPENES

S.No	Source	Botanical name	Major Terpenes
1	Apti fructus	Apium graveolens	Limonene
2	Cardamom	Elettaria cardamomum	1,8-Cineole,α-terpineol,α-terpinyl acetate
3	Fennel	Foeniculum vulgare	Trans-anethol,terpene hydrocarbons(α-pinene,α-phellandrene)
4	Melissa	Melissa officinalis	Geranial,neral
5	Orange	Citrus aurantium	d-Limonene
6	Eucalyptus	Eucalyptus globulus	1,8-Cineole,eucalyptol,moderate amounts of monoterpenes(α-pinene)

ROLE OF TERPENES IN TRANSDERMAL DELIVERY

Terpenes and terpenoids are usually the constituents of volatile oil. Several natural sources and their major terpene contents are summarized in Table 4.The basic chemical structure consists of a number of repeated isoprene (C_5H_5)units, which is used to classify terpenes.Thus monoterpens have two isoprene units(C_{10}) sesquiterpenes have three(C_{15}),and diterpenes have four (C_{20}),etc. Terpenes may be classified as acyclic/linear, monocyclic and bicyclic. Numerous terpenes have long been used as medicines as well as flavouring and fragrance agents.The essential oils of eucalyptus,chenopodium and ylang ylang has been found to be effective penetration enhancer for 5-flourouracil transfusing human skin in vivo[14].The mechanism by which this agents operates is to modify the solvent nature of stratum corneum, thus improving drug partitioning into tissues.

Mechanism of action of terpenes

Terpenes enhance diffusion of drugs by extracting lipids from stratum cornea which results in reorganization of lipid domain and barrier disruption .The mechanism of barrier disruption may be due to the competitive hydrogen bonding of oxygen containing monoterpenes with ceramide head groups, thereby breaking the interlamellar hydrogen bonding network of lipid bilayer of stratum corneum and new polar pathways or channels are formed[15].

Pharmaceutical and biological aspects of different terpenes

Camphor

It is found in wood of the camphor laurel (Cinnamomum camphora). It also occurs in some other related trees in the laurel family, notably Ocotea usambarensis. It can also be synthetically produced from oil of turpentine. It is also used in medicinal purposes. Camphor is readily absorbed through the skin and produces a feeling of cooling**.**

Eugenol

It is a clear to pale yellow oily liquid extracted from certain essential oils especially from clove oil, nutmeg, cinnamon, and bay leaf. Eugenol, a component of clove, may reduce the ability to feel and react to painful stimulation. Therefore, use of clove products on the skin with other numbing or pain-reducing products such as lidocaine / prilocaine cream, theoretically it may increase the effects. Eugenol is due to lipid extraction and improvement in the partitioning of the drug to the SC.

Menthol

Menthol is an organic compound made synthetically obtained from peppermint or other mint oils. Menthol having the ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin which is responsible for the well known cooling sensation provokes when inhaled, eaten, or applied to the skin. In Europe it tends to appear as a gel or a cream, while in the US patches and body sleeves are

very frequently used A study has been made to elucidate the mechanism of skin permeation enhancement is, it increase in skin flux, to eight times the base line, could be attributed to the effect of menthol on the skin barrier properties.

Cineole

Eucalyptol is a natural organic compound which is a colourless liquid. It is cyclic ether and a monoterpenoid. Eucalyptol is also known by a variety of synonyms: 1,8-cineol, 1,8-cineole, limonene oxide, cajeputol, 1,8-epoxy-pmenthane, 1,8-oxido-p-menthane, eucalyptol, eucalyptole, 1,3,3-trimethyl-2oxabicyclo[2,2,2]octane, cineol, cineole. Cineole has been used to promote the percutaneous absorption of several lipophilic drugs through hairless mouse skin[10,15].

D-Limonene

D-Limonene is obtained as a by-product of the citrus juice industry. It is the major component of the oil extracted from the rinds of citrus fruits. There are two main grades of dLimonene which are called food grade and technical grade. When citrus fruits are juiced, the oil is extracted out of the rind. The juice is separated from the oil and the oil is distilled to recover certain flavour and fragrance compounds[10].

PENETRATION EFFECTS OF VARIOUS ESSENTIAL OILS

Niaouli Oil

Niaouli oil is extracted through steam distillation from the leaves and twigs of Melaleuca quinquenervia, which is part of the Myrtaceae (Myrtle) family . Its key constituents is 55–70% 1,8-cineole (oxide) and limonene (monoterpene), 7–15% a-pinene (monoterpene), 2–6% ß-pinene (monoterpene) and 2–6% viridiflorol (sesquiterpene). In vitro studies were performed using hairless mouse skin to determine the penetration enhancement effect of different essential oils at a 10% (w/w) concentration in propylene glycol on estradiol as model drug. Niaouli essential oil proved to be more effective than cajuput-, cardamom-, melissa-, myrtle- and orange essential oils for enhancing the transdermal penetration of estradiol. The results therefore showed that undefined phytoconstituents present at low concentrations in the whole Niaouli essential oil may considerably increase its penetration enhancing activity [16].

Eucalyptus Oil

Eucalyptus oil can be obtained from numerous species of the Myrtaceae family, which includes Eucalyptus citriodora, Eucalyptus dives, Eucalyptus globules, Eucalyptus polybractea and Eucalyptus radiata. The oil is extracted by steam distillation from the leaves.Penetration study on full-thickness human skin showed that eucalyptus oil enhanced the penetration of chlorhexidine (2% (w/v)) into the dermis and lower layers of the epidermis. When chlorhexidine was combined with 70% (v/v) isopropyl alcohol and 10% (v/v) eucalyptus oil, the skin penetration of the drug was significantly enhanced 2 min after application compared to a solution of chlorhexidine/isopropyl alcohol alone [17].

Black Cumin Oil

Black cumin essential oil is obtained with steam distillation from the seeds of Cuminum cyminum of the Apiaceae or Umbelliferae family. Black cumin oil was found to be a better penetration enhancer with an enhancement factor of 6.40 for the model lipophilic drug, carvedilol, when compared to clove oil, eucalyptus oil, tulsi oil, oleic acid and Tween 80. Fourier Transform Infrared Spectroscopy (FTIR) studies confirmed that black cumin oil alters the permeability of the skin by extracting lipids and by hydrogen bonding which affect other hydrogen bonds between the ceramides [18].

Fennel Oil

Fennel oil is obtained from steam distillation of the crushed seeds of Foeniculum vulgare, which is part of the Apiaceae or Umbelliferae family.Fennel oil was found to be the most effective enhancer for the percutaneous penetration of trazodone hydrochloride, which

was followed by eucalyptus oil, citronella oil and mentha oil. Propylene glycol pre-treatment itself also significantly enhanced the permeation of trazodone hydrochloride; nevertheless pre-treatment with 10% fennel oil in propylene glycol showed an enhancement ratio of 9.25 compared to the control. The phytochemicals with variable physicochemical properties and molecular weights present in the different essential oils may be the cause of differences in the permeation enhancement ratios between the oils. Trans-anethole and 1,8-cineole have low boiling points and molecular weights which may contribute to the higher enhancement ratio of fennel oil and eucalyptus oil [19].

CONCLUSION

Skin permeation enhancement technology is a rapidly developing field which would significantly increase the number of drugs suitable for transdermal drug delivery, with the result that skin will become one of major routes of drug administration in the next decade. Transdermal drug administration route offers so many advantages over oral administration of drugs and has stimulated research to find ways to overcome the barrier function of the skin by use of essential oils as natural permeation enhancers. The aim of this review article was to summarise that essential oils can be used as good penetration enhancer for transdermal drug delivery system because of their origin from natural origin, good penetrating power on skin, no toxic side effects and low cost. It was further observed that the effectiveness of the penetration enhancers depends not only on their concentration in the formulation, but also on the physico-chemical characteristics of the drug to be transported through/into the skin layers. Terpenes the naturally occurring volatile oils are considered to be clinically acceptable penetration enhancers as indicated by high percutaneus enhancement ability, reversible effects on the lipids of SC, good evidence of freedom from toxicity. It can be concluded that research is desirable in order to scale up natural permeation enhancer system and implement manufacturing of final dosage form on commercial scale so that natural penetration enhancers will play a major role in developing effective transdermal products in future.

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