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HERBAL EXCIPIENTS: AN EMERGING FIELD AS A PENETRATION ENHANCER IN TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

The component obtained from the herbs has been used as excipients in the formulation of pharmaceutical products. The development in the field of the pharmaceutical technology leads to development of different types of formulations. These formulations need the incorporation of few of the chemicals as excipients to modify pharmacokinetic behavior of the drugs of interest and thus, create a whole new field of research to be explored. One such example of the excipients, to be incorporated in the formulation to alter the permeation of the drugs through different membranes. E.g. Ethanol, Dimethyl Sulphoxide, Glycerol, Poly Ethylene Glycol etc. These compounds have been proven to be capable of producing of toxicity, if administered in higher concentration. The factor that really limits the use of synthetic compounds is their ability to alter the anatomical structure of the membrane. A few of the compounds obtained from the herbs have been found to act though some novel pathways, e.g. by altering Permeability Glycoprotein (P- gP) functioning, by altering Cyp – 450 enzymes functioning. The literature compiled here for presentation purpose, with special reference to utilization of herbal permeation enhancers revealed the great research scope in transdermal drug delivery system. The research scope may include development of such herbal excipients and their assessment with respect to toxicity, permeation enhancement potential and their utilization in formulation of Pharmaceutical Products. The aim of this article is to give a comprehensive summary of the results from scientific research conducted on skin penetration enhancers of natural origin.

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INTRODUCTION

Even after wide spread acceptance of modern drug discovery tools such as combinatorial chemistry, High Throughput Screening (HTS), Computer Aided Drug Design the drugs with poor biopharmaceutical properties is yet not reduced. Many of these molecules are very successful and potential therapeutic agents, but suffer from serious drawback of very low bioavailability because of poor permeation across biological barriers[1,2]. Various approaches to reversibly remove the barrier resistance have been investigated. Among these approaches, coadministration of drug with permeation enhancer is widespread accepted and is explored for several drug molecules [3].

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. The worldwide transdermal patch market approaches £ 2 billion, based on only ten drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed[4]. New analysis published in 'U.S. Emerging Transdermal Drug Delivery Technologies Markets', reveals that this market generated revenues worth $1.57 billion in 2002 and is likely to reach a staggering $5.67 billion in 2009[5]. Global Transdermal drug delivery system (TDDS) product sales have been given in segments as shown in Fig 1.

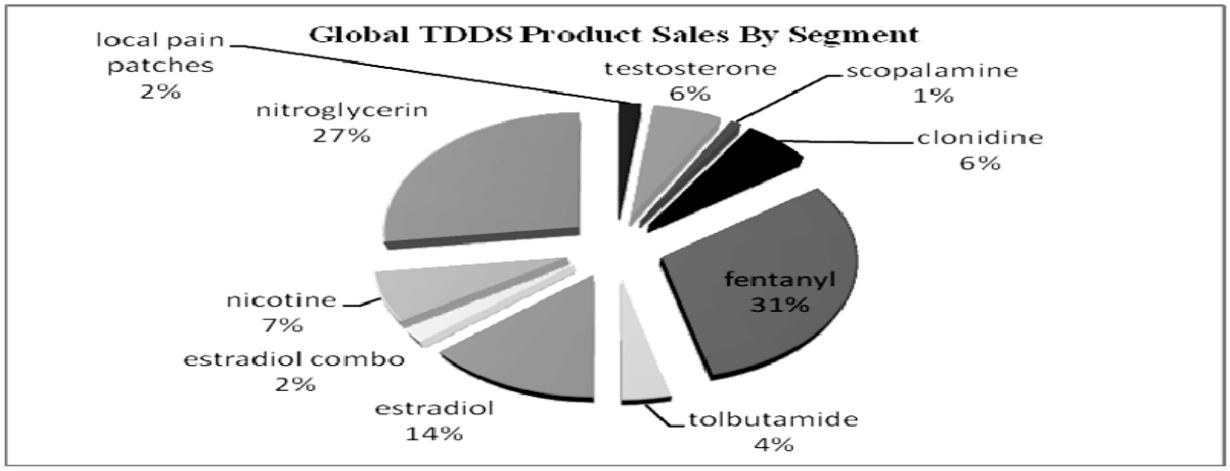


Fig.1: Global TDDS product sales.

Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect. Transdermal drug delivery offers the following advantages over the oral route for controlled drug delivery.

- Avoidance of hepatic first pass metabolism.
- Ability to discontinue administration by removal of the system.
- The ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form.
- The ability to modify the properties of the biological barrier to absorption.
- Less frequent dosing regimens is needed due to the maintenance and longer sustainability of zero-order drug delivery
- Less inter-subject variability occurs [6].

Other advantages listed include aspects such as the accessibility of the skin; a relatively large surface area for absorption and the fact that it is non-invasive make it more patient compliant [7]. A popular approach for improving transdermal drug delivery involves the use of penetration enhancers (sorption promoters or accelerants) which penetrate into skin to reversibly reduce the barrier resistance.

A BRIEF REVIEW OF SKIN STRUCTURE

Drug delivery routes across human skin and skin covers an average body surface area of approximately 2 square meters. Its thickness is approximately 2.97 mm; hair follicles are about 10-70 on every square centimeter and sweat glands 200-250 on every square centimeter. Skin is multilayered tissue consisting of epidermis, dermis and hypodermis. The skin can be considered to have four distinct layers of tissue [8] depicted in figure 2.

1. Non-viable epidermis (stratum corneum)
2. Viable epidermis
3. Viable dermis
4. Subcutaneous connective tissue (hypodermis)

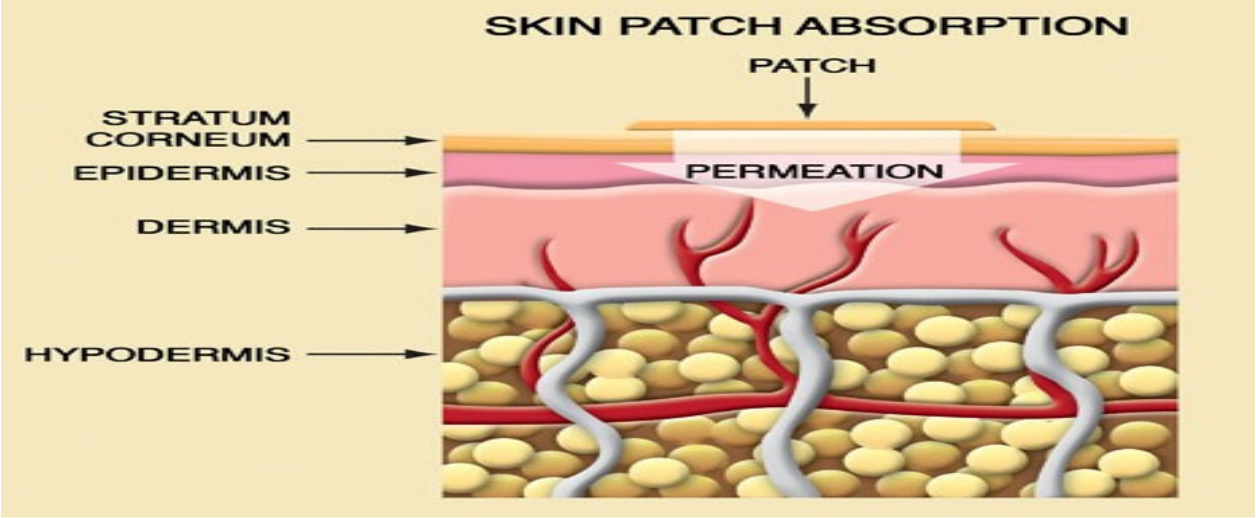


Fig.2: layers of skin

Non-viable Epidermis (stratum corneum)

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate-like structure 34-44 µm long,25 – 36µm wide, 0.5 to 0.20 µm thick - with a surface area of 750 to 1200 µm ^{2} stocked up to each other in brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50-100 µm. The density of this region is not much different than water. The water content is about 90%.

Dermis

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histologically in normal tissue. Dermis thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous.

Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect.

PENETRATION PROCESS

There are following two major routes of penetration [9]

(i) Transcorneal penetration, which includes intra cellular penetration and inter cellular penetration (ii) Transappendegeal penetration.

In intra cellular penetration drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water. Non-polar substances permeate through intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments[10].

In Transappendegeal penetration (shunt pathway) the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands. The transappendegeal pathway is considered to be of minor importance because of its relatively smaller area (less than 0.1% of total surface). However this route may be of some importance for large polar compounds[11]. The route through which permeation occurs is largely dependent on physico-chemical characteristics of penetrat most important being the relative ability to partition into each skin phase[12].

The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrate molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the Stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, a simple multilayer model can represent the various skin tissue layers (Fig. 3).

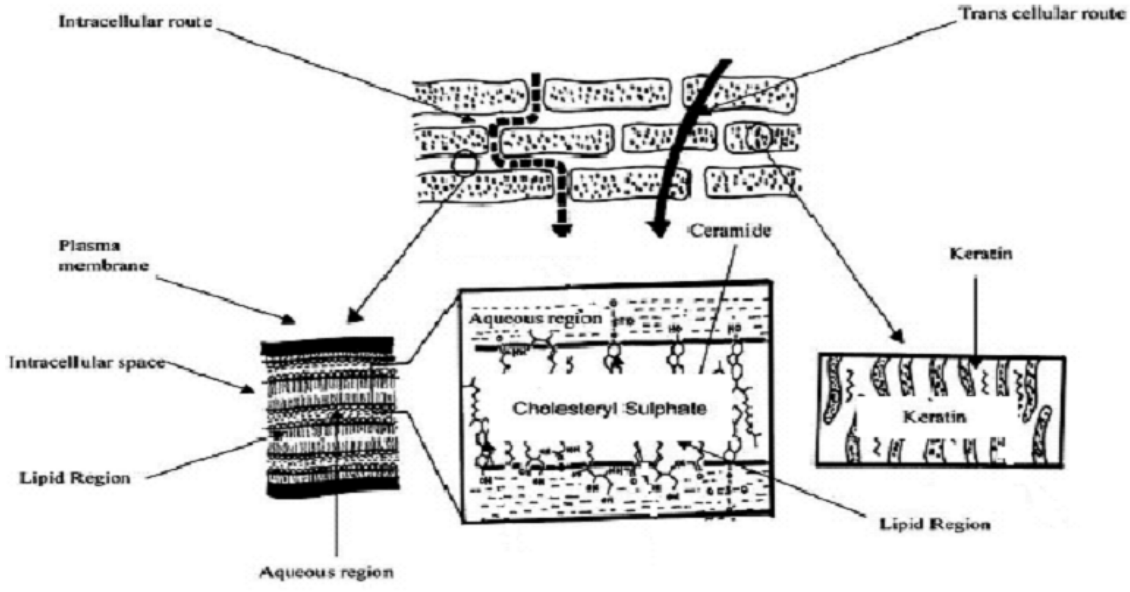


Fig. 3: Structure of skin and mechanism of penetration into skin

NEED OF PENETRATION ENHANCEMENT

Penetration enhancement is the most critical factor in transdermal systems, so as to improve flux. Flux (J) can be defined as the amount (M) of material flowing through unit cross section (S) of a barrier in unit time (t). Flux can be given by: J=dM/S.dt.[13] Each phase of the membrane can be characterized in terms of diffusion resistance(R), which usually is the function of thickness (hs) of the phase, the permeant diffusion coefficient (Ds) within the phase, and the partition

coefficient (Ks) between the membrane phase and external phase.

It can be expressed as: R=hs/Ds.Ks, P= Ds.Ks/hs where P is permeability coefficient. The permeability coefficient is related to membrane flux (J) as given

J=APs (Cp-Cr), where Cp-Cr is the difference in permeant concentration across the membrane and A is the area of application[14].

PENETRATION ENHANCERS

Mechanism of Penetration Enhancers [15]

Penetration enhancers work by one of the many mechanisms.

- They may act by changing mucus rheology that is by reducing the viscosity of the mucus. Mucus forms a viscoelastic layer of varying thickness that affects drug absorption.
- Most penetration enhancer's act by disturbing the intra-cellular lipid packing by interaction with either lipid packing or protein components, thus increasing the fluidity of the lipid bilayer membrane.
- Fluidization of the plasma membrane, loosening of the tight junctions between cells, and inhibition of proteases are a few of the mechanisms.
- The penetration enhancers also act by increasing the thermodynamic activity of peptide drugs. This may be affected by the vehicle com position, which influences Solubility and micellization, and also by ion pair formation between the enhancer and the drug.
- Another way skin penetration enhancers may act by one or more of three potential mechanisms according to the lipid-protein-partitioning theory. Firstly, penetration enhancers can alter the intercellular lipid structure between the corneocytes to increase diffusivity. Secondly, they can modify intracellular protein domains within the horny layer. Thirdly, they may increase the partitioning of the drug into the skin tissue.[16,17]

The properties of an ideal skin penetration enhancer include the following:

(1) It should be odorless and colorless; (2) It should be specific in its mode of action;

(3) It should be pharmacologically inert; (4) It should be compatible with drugs and other excipients; (5) It should be chemically and physically stable; (6) it should be non-allergenic, non-irritant and non-toxic; (7) Its action should be reversible and (8) It should give a rapid effect for a predictable duration of time [18,19].

Skin penetration enhancers can be mainly classified in two ways: chemicals penetration enhancers and natural penetration enhancers.

Chemical enhancers can be divided into two broad categories: Those that change partitioning into the stratum corneum and those that influence diffusion across the stratum corneum [20]. Examples of chemical penetration enhancers include Sulphoxide (dimethylsulfoxide or DMSO), alcohols (ethanol), polyols (propylene glycol), alkanes, fatty acids (oleic acid), esters, amines and amides (urea, dimethylacetamide, dimethylformamide, pyrrolidones).[21,22].

Natural penetration enhancers include class is terpenes cyclic monoterpenes limonene and cineole hydrocarbons and trans-p-menthane, alcohols, menthol, ketones, menthone, camphor, carvone and alkaloids.

Penetration enhancers from natural origin have become popular as they offer several benefits over their synthetic such as sustainable mass production from a renewable resource, less toxic and lower cost depending on the type of extraction used.

In this article, we review some uses of the more widely investigated natural penetration enhancers like terpenes and alkaloid (piperine) with their possible mechanisms of action and discuss uses.

NATURAL PENETRATION ENHANCERS

1. Terpenes

Terpenes are well recognized penetration enhancers for drug permeation across the human skin and have been receiving considerable interest in the pharmaceutical industry for this application [23, 24]. They are in general clinically acceptable and

relatively safe skin penetration enhancers for both lipophilic and hydrophilic drugs [24]. terpenes a promising group of compounds for transdermal delivery of drugs with a wide range of physico-chemical properties [25].

Terpenes of natural origin have a 'Generally Regarded As Safe' (GRAS) status with the Federal Drug Administration of the United States of America, which offers advantages over other traditional enhancers such as alcohols, fatty acids, Azone®, sulfoxides and pyrrolidones [25]. In general, they have low systemic toxicity and skin irritancy in addition to having good penetration enhancing abilities [26]. Terpenes are present in naturally occurring volatile oils appear to be clinically acceptable enhancer [27]. Moreover, the wide variety of terpenes have been shown to increase the percutaneous absorption of number of drugs.[28] Terpenes, the naturally occurring volatile oils, are considered as clinically acceptable penetration enhancers as indicated by high percutaneous enhancement ability [29,30], reversible effect on the lipids of stratum corneum and low cutaneous irritancy at lower concentrations (1–5%). Moreover, terpenes have been shown to increase the skin permeation of a number of drugs [31]. A number of terpenes are used such as cyclic monoterpenes limonene and cineole hydrocarbons and trans-p-menthane, alcohols, menthol, ketones, menthone, camphor, carvone and piperine are used as permeation enhancers [32].

1.1 Mechanism of action of terpenes:

The effect of permeation enhancers often depends on their applied concentrations [33]. The mechanism of action of permeation enhancers [29] are by (i) disruption of the highly ordered structure of SC lipids, (ii) interactions with intracellular proteins or (iii) improvement in partitioning of the drug, co enhancers or co solvent in to the stratum corneum. It is reported that terpenes enhance diffusion of drugs by extracting lipids from stratum cornea [34], which results in reorganization of lipid domain and barrier disruption [27, 29]. 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 [35]. Mechanism by terpens act on the lipid layer of the stratum corneum is depicted in figure 4.

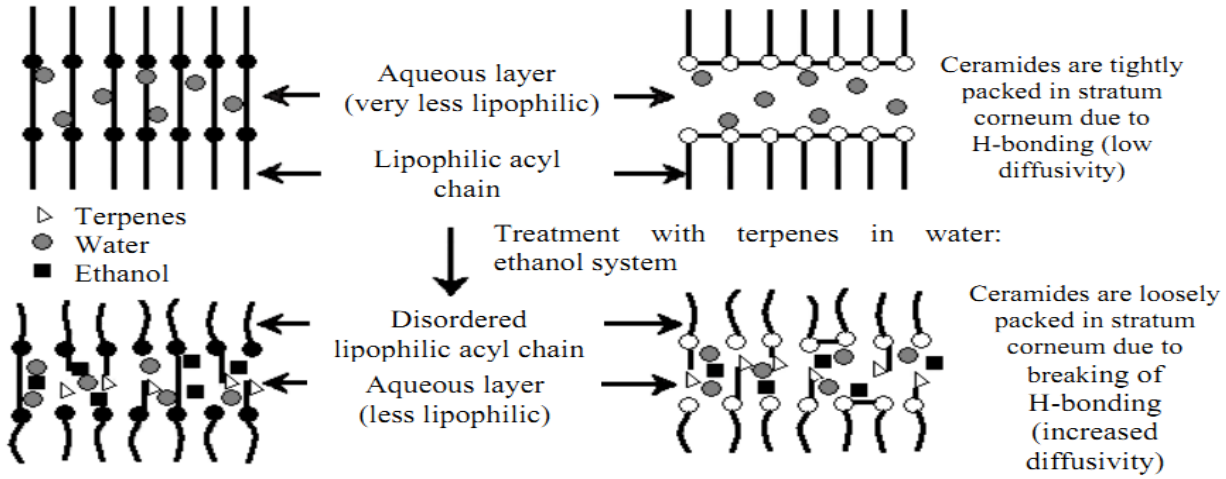


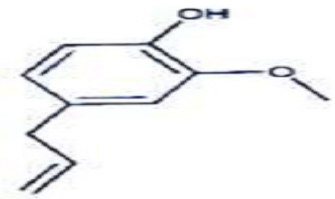
Fig.4: Mechanism by terpnes act on the lipid layer of the stratum corneum.

1.2 Chemical, pharmaceutical and biological aspects of different terpenes:

1.2.1 Camphor:

Camphor is a waxy, white or transparent solid with a strong, aromatic odour. It is a terpenoid with the chemical formula C10H16O. 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

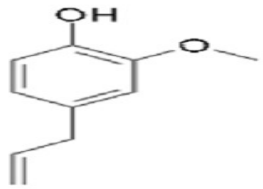


Camphor

From oil of turpentine. It is also used in medicinal purposes. Camphor is readily absorbed through the skin and produces a feeling of cooling [36].

1.2.2 Eugenol:

Eugenol is an allyl chain-substituted guaiacol. Eugenol is a member of the allylbenzene class of chemical compounds. It is a clear to pale yellow oily liquid extracted from certain essential oils especially from clove oil, nutmeg, cinnamon, and bay leaf. It is slightly soluble in water and soluble in organic solvents. It has a pleasant, spicy, clove-like odour. Cloves are the aromatic dried flower buds of a tree in the family Myrtaceae. It is native to Indonesia and used as a spice in cuisines all over the world.



Eugenol

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 effects [37]. FT-IR and partitioning studies reveal that the enhancement in the permeability coefficient of drug by Eugenol is due to lipid extraction and improvement in the partitioning of the drug to the SC [38].

1.2.3 Menthol:

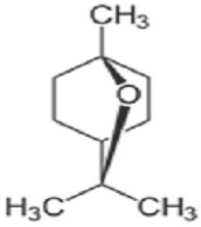
Menthol is an organic compound made synthetically obtained from peppermint or other mint oils. Menthol having the ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin which is responsible for the well known cooling sensation provokes when inhaled, eaten, or applied to the skin. As a topical analgesic to relieve minor aches and pains such as muscle cramps, sprains, headaches and similar conditions, alone or combined with chemicals like camphor or capsaicin. In Europe it tends to appear as a gel or a cream, while in the US patches and body sleeves are very frequently used [39].

Menthol

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 [37].

1.2.4 Cineole:

Eucalyptol is a natural organic compound which is a colorless 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-p-menthane, 1,8-oxido-p-menthane, eucalyptol, eucalyptole, 1,3,3-trimethyl-2-oxabicyclo[2,2,2]octane, cineol, cineole.



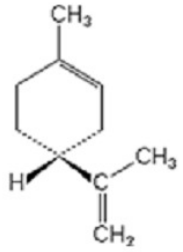
cineol

Eucalyptol suppository is used for the treatment of some respiratory ailments. Because of its pleasant spicy aroma and taste, eucalyptol is used in flavourings, fragrances, and cosmetics. It

is also an ingredient in many brands of mouthwash and coughsuppressant. 1, 8-Cineole has been used to promote the percutaneous absorption of several lipophilic drugs through hairless mouse skin [36].

1.2.5 D-Limonene:

D-Limonene [40] 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 d-Limonene 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 flavor and fragrance compounds. This is called food grade d-limonene which is 96% to 97% pure and has a mild orange aroma. After the juicing process, the peels are taken to a steam extractor. More oil is extracted from the peel. When the steam is condensed, a layer of oil floats on the surface of the condensed water, this is called technical grade d-Limonene which is 95% pure and has a strong orange

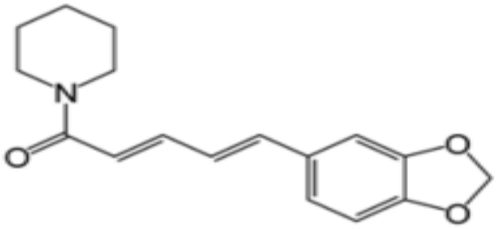


d-limonene

Both products are called orange terpenes. Food grade d-Limonene is usually used for consumer products and technical grade is used for industrial products. D-Limonene is also a possible candidate for a variety of medical applications including cancer and aids research, and has been noted to have insecticidal properties.

2. Alkaloids (piperine)

Piperine is a major alkaloid of Piper nigrum Linn. and Piper longum Linn., which are widespread consumed as a spice and medicinal compound since ages.[41] In addition, piperine is also known to improve the oral bioavailability of several drug and nutraceutical molecules. The study presented here confirms that piperine induces alteration in membrane dynamics and permeation characteristic of SC by lipid extraction and interaction with keratin and thereby increased permeation of drug across human epidermal membrane



Piperine (1-Piperoyl piperidine) is a major alkaloid of Piper nigrum Linn. And Piper longum Linn. It is shown to possess bioavailability-enhancing activity with various structurally and therapeutically diverse drugs. The mechanism of enhancing the bioavailability, is, however, not understood. We hypothesize that piperine's bioavailability-enhancing property may be attributed to increased absorption, which may due to alteration in membrane lipid dynamics. piperine significantly reduces percentage of secondary structures of keratin at amide I band. These results indicate that piperine enhances transdermal permeation of drug by biphasic mechanism involving partial extraction of stratum corneum (SC) lipid and interaction with SC keratin.

This suggests that piperine could modulate the membrane dynamics due to it's a polar nature by interacting with surrounding lipids and hydrophobic portions in the protein vicinity, which may decrease the tendency of membrane lipids to act as stearic constrains to enzyme proteins and thus modify enzyme conformation. Ultra structural studies with piperine showed an increase in microvillus length with a prominent increase in free ribosome and ribosomes on the endoplasmic reticulum in entrecotes, suggesting that synthesis or turnover of cytoskeletal components or membrane proteins may be involved in the observed effect. In conclusion, it is suggested that piperine may be inducing alterations in membrane dynamics and permeation

characteristics, thus assisting efficient permeation through the epithelial barrier.[42]

CONCLUSIONS

The fact that the transdermal drug administration route offers so many advantages over oral administration of drugs has stimulated research to find ways to overcome the barrier function of the skin. One of the approaches to enhance drug permeation across the skin includes the incorporation of skin penetration enhancers into drug formulations. Unfortunately some skin penetration enhancers are toxic and a need therefore exists for discovery of safe and effective skin penetration enhancers which led to screening of natural compounds for this purpose. The aim of this review article was to summaries research done on skin penetration enhancers of natural origin. The study presented here confirms that terpens and piperine induces alteration in membrane dynamics and permeation characteristic of SC by lipid extraction and interaction with keratin and thereby increased permeation of drug across human epidermal membrane. Thus, easy availability, inexpensive, relatively safe, effective at lower concentration and biphasic mode of permeation enhancement make it attractive natural molecule. It can be concluded from the literature that natural penetration enhancers will play a major role in developing effective transdermal products in future.

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