JOURNAL OF NATURAL REMEDIES
DOI: 10.18311/jnr/2024/45113
REVIEW ARTICLE

Unlocking Skin Barriers: Applications and Properties of Natural Permeation Enhancers

Sangam Singh[1], Rupa Mazumder[1*], Swarupanjali Padhi[1], Rashmi Mishra[2] and Bimlesh Kumar[3]

[1]Department of Pharmaceutics, Noida Institute of Engineering and Technology (Pharmacy Institute), Gautam Buddha Nagar, Greater Noid – 201306, Uttar Pradesh, India; rupamazumder1@gmail.com

[2]Department of Biotechnology, Noida Institute of Engineering and Technology, Greater Noida – 201310, Uttar Pradesh, India

[3]School of Pharmaceutical Sciences, Lovely Professional University, Phagwara – 144411, Punjab, India

Abstract

Permeation enhancers, also known as sorption promoters, play a crucial role in improving skin permeability for drug delivery by modifying the physical and chemical properties of the Stratum Corneum (SC), the outermost skin layer. Effective permeation enhancers are characterized by their non-toxic, non-irritating nature, rapid action, and chemical compatibility. The skin, as the largest organ, serves as a barrier and absorption site for medications, with various layers contributing to its function. Permeation enhancers act through several mechanisms, including the modification of SC lipids and interaction with cellular proteins, which alter skin barrier properties. Natural Permeation Enhancers (NPEs) such as fatty acid esters, essential oils, and terpenes are emerging as safer and cost-effective alternatives to synthetic enhancers, with studies demonstrating their ability to disrupt keratin patterns and enhance drug flow through the epidermis. Terpenes, in particular, exhibit low irritancy and toxicity while enhancing drug delivery through lipid structure alteration and interaction with intracellular proteins. Key terpenes like menthol and limonene have shown significant efficacy in improving drug absorption. Additionally, fatty acids, especially long-chain unsaturated varieties like oleic acid, enhance skin permeability by increasing fluidity and diffusivity. Their effectiveness is influenced by the characteristics of the permeants, delivery methods, and fatty acid structure. The presence of cosolvents such as ethanol can further boost the permeability effects of fatty acids by facilitating lipid extraction from the skin. Overall, the exploration of both natural and synthetic permeation enhancers offers promising avenues for improving transdermal drug delivery systems.

Keywords: Essential Oils, Fatty Acid, Natural, Permeation Enhancer, Skin, Terpenes

Abbreviations: FTIR = Fourier-Transform Infrared Spectroscopy; DSC = Differential Scanning Calorimetry; GRAS = Generally Recognized As Safe; SC = Stratum Corneum; NPES = Natural Permeation Enhancer; LHRH = Leteinzing Harmone-Releasing Harmone; PDS = Postprandial Distress Syndrome; EPS = Epigastric Pain Syndrome; 5-FU = 5-Fluorouracil

1. Introduction

Permeation enhancers are substances that improve skin permeability[1]. The term "sorption promoter" or "penetration enhancer" refers to substances that regulate drug molecule penetration without harming living cells. The best-known method of penetration enhancers involves reversibly changing the physico-chemical properties of the SC to overcome its resistance to diffusion. The best qualities of a permeation enhancer include nontoxic, non-sensitizing, nonirritating, fast-acting with predictable and repeatable effects, pharmacologically inert, chemically compatible, etc., according to a survey of several literature pieces[2]. The permeation enhancer should have particular absorbable qualities on the surface of the skin rather than removing the natural substance of the skin. The solubility profile of the enhancer and the skin should be identical. After the transdermal systems are removed, it should be fully eliminated. The material should be

*Author for correspondence

Article Received on: 24.07.2024 Revised on: 01.10.2024 Accepted on: 25.10.2024

an appropriate solvent for pharmaceuticals if it is a liquid and employed at large-volume fractions[2]. The solubilization of skin-tissue components, interaction with intracellular lipids that disrupt the lamellar structure, interaction with intracellular proteins that cause issues in the corneocyte layer, increased drug molecule partition coefficient, and use of co-enhancers or cosolvents in the SC are all part of the mechanism of permeation enhancer[3-5].

Protecting the body from the outside world, the skin is the largest organ in the human body. It makes up 15% of an adult's total body mass and has an area of about 1.5 to 2.0 m^2 [6]. The human body is also shielded by the skin from Ultraviolet (UV) radiation by the sun[7]. The skin's ability to maintain homeostasis through the thermoregulation system is another crucial function[8]. One such thermoregulation process carried out by human skin is sweating[9]. In addition, the skin is in charge of excreting several chemicals, including urea, uric acid, ammonia, sodium chloride, xenobiotics, and excessive fats[10,11]. Because the dermis has a large number of blood capillaries, researchers have also used the skin as the primary absorption site for a wide range of medication types for both, local and systemic delivery[12]. The epidermis, which varies in thickness from 50 to 100 µm based on the location of the body, is the outermost layer of human skin[13]. In particular, five distinct layers make up the epidermis, which have a part in the skin renewal mechanism. The epidermis's most superficial layer, recognized as the, is composed of 15–30 corneocyte cell layers and has a thickness of 10–20 µm. Every 4 weeks, this layer regenerates[14,15].

The SC is also recognized as the "horny layer" because it is made up of keratin proteins that are created by the cornification process in the deeper layers from dead keratinocyte cells[16]. Stratum lucidum is the thin, transparent layer of skin located beneath the SC. Only the fingers, palms, and soles contain the 2-3 layers of keratinocyte cells that make up the stratum lucidum[17]. The dead corneocytes of the SC are raised from this layer. The next layer is the stratum granulosum the layer that lies beneath the stratum lucidum. Compared to the first two levels, the cells' membranes are thicker in this layer. The granulosum is derived from living cells' granules, which are created when keratohyalin, a protein structure present in granules, accumulates[18]. Eight to ten layers of keratinocytes make up the stratum spinosum, an epidermal layer that lies underneath the stratum granulosum. This layer is known as the "spiny" layer (stratum spinosum) because desmosomes, which connect cells, are present in between the cells[19].

The stratum basale is the innermost layer of the epidermal skin, which is in direct contact with the dermis by interwoven collagen fibres. Cells multiply in the stratum basale and give rise to keratinocytes, which are found in the higher layers of the epidermis[20].

In the Integumentary system, the Dermis are the second layer which is located beneath the epidermis. The papillary and reticular layers are the two layers that make up the dermis. In particular, the dermal papillary layer contains lymphatic capillaries, blood vessels, and adipocytes. Because the dermal layer contains phagocytes, fibroblasts, leucocytes, and mast cells, it is important for immune function[21].

Additionally, there are a lot of sebaceous hair follicles because of their involvement in systems related to sweating and sebum secretion, including skin sweat glands[22] and the deepest layer of skin is the Hypodermis/subcutaneous layer lies beneath the dermis. Or recognized as a superficial fascia — is abundant in glycosaminoglycans and proteoglycans as a connecting tissue between the skin, muscles, and bones[23].

Moreover, The hypodermis's abundance of adipose tissue serves as thermal insulation to maintain the body temperature[24].

2. Natural Permeation Enhancers (Npes)

In the pharmaceutical Industry, Natural permeation enhancers are a relatively new class of penetration enhancers. Owing to its benefits, which include low cost and an improved safety profile, additional study is required in this area to produce stable transdermal formulations with natural permeation enhancers that can be scaled up for transdermal medicinal products for commercially sold.

Since it can be difficult for medications to be absorbed through the skin, appropriate natural and synthetic penetration enhancers are frequently utilized in TDDS. Any type of natural permeation enhancer can be used without risk, however, synthetic enhancers like ionic surfactants, DMF, DMSO, *etc.*, have harmful and unpleasant side effects[25,26].

There are several investigations on the effects of natural permeation enhancers, such as fatty acid esters, essential oils, terpenes, and terpenoids, in the transdermal drug delivery system. Numerous studies have shown that Iontophoresis combined with enhancers (linolenic acid) changed the highly compact SC cells into disrupting the keratin pattern, a looser network of filaments, and causing the SC cell layers of the epidermis to swell. This increased the medication's flow through the human epidermis[27].

2.1 Terpenes

Terpenes act as permeation enhancers at a low concentration (1-5%), where cutaneous irritancy and toxicity are minimal in transdermal preparations facilitating the therapeutic agent to cross the SC and viable epithelium[28-30]. These are essential oil extractions made from combinations of isoprene units that naturally exist in hydrocarbons[29,30]. Terpenoids represent a modified category of terpenes with an oxidized methyl group and unique functional groups that are deleted or repositioned at various locations. Terpenes are simple hydrocarbons. Terpenoids can be categorized as triterpenes, sesquiterpenes, diterpenes, sesquiterpenes, and monoterpenes, based on the number of carbon units. Many diseases are treated worldwide with terpenoids, most of which have different structures but are still physiologically active. A lot of terpenoids, like Taxol and its variants, are used as anti-cancer physic because they inhibit certain human cancer cells. Table 1 Terpenes have oxygen in addition to carbon and hydrogen, as seen in carvone, α-thujone, menthol, and other compounds[31]. Figure 1 shows the structure of terpenes.

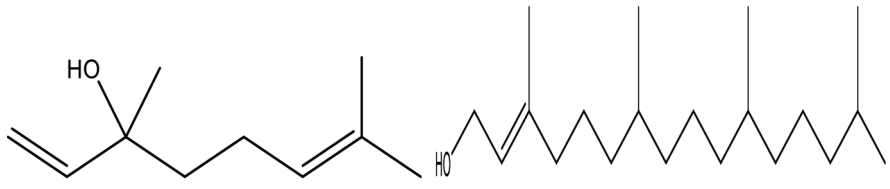
2.2 Classification

Illustration of the classification of terpenes (Figure 2).

2.3 Mechanism of Action of Terpenes

- Alteration of the lipids in the SC
- Interaction between the proteins found inside cells.
- Enhanced drug distribution within the SC.

Terpenes modify the hydrogen bonds which are present at the ceramides (Skin cells contain lipids, or fats, called ceramides. They comprise 30-40 % of the epidermis, the layer of skin on the outside. Ceramides are crucial in keeping your skin hydrated and limiting the spread of bacteria throughout your body. Ceramides are involved in the barrier function of your skin, which acts as your body's first line of protection against pollutants and poisons from the outside world. They also preserve cell function and aid in brain growth) in the lipid bilayer to enhance the drug's penetration[32]. Terpene modulation of skin permeability is assessed by using DSC and FTIR techniques. When the protein and lipid constituents of cell membranes interact with terpenes, their thermotropic activity changes, which are demonstrated by DSC analysis, and Bilayer membrane interactions with terpenes were shown to cause structural and conformational changes, as demonstrated by FTIR[33]. The mechanism examined by Zhao *et al.,*[34] by which ethanol and terpenes (limonene and menthone) improved propranolol hydrochloride's *in vitro* penetration. An *in vitro* penetration evaluation was carried out using Franz diffusion cells and the porcine epidermis skin model. For this experiment, the control group was given a solution of propranolol hydrochloride with ethanol. Propranolol hydrochloride



Linalool Phytol

Monoterpenes Diterpenes
Isoprene unit-2 Isoprene unit -4
Chemical formula-C10H16 Chemical formula -C20H32

Figure 1. Structure of terpenes.



Figure 2. Classifications of terpenes based on **(a).** chemical groups, **(b).** numbers of carbon atoms.

solutions containing 5% menthone or 5% limonene combined with ethanol significantly increased propranolol hydrochloride's penetration into the pig epidermis. In the case of both terpenes (limonene and Methone), fourier-trans infrared spectroscopy analysis showed a decrease in peak area and peak height for symmetrical and asymmetrical stretching of C–H in comparison to the untreated epidermis layer of the skin[35]. The SC lipid extraction is affected by this decline in peaks and area[34].

Similar research was conducted by Zhao *et al.*,[34] with tamoxifen, wherein they examined the effects of three distinct permeation enhancers, namely menthone, D-limonene, and eugenol on permeability. 50% ethanol was used with each of the three enhancers. The *in vitro* penetration investigation was performed using porcine skin epidermis. FTIR was applied to analyze the impact of enhancers on the biophysical and structural integrity of SC. When the Fourier-trans Infrared Spectroscopy of the porcine epidermis treated with permeation enhancers was compared to the FTIR of the untreated SC, it was shown that the enhancers consistently reduced the areas and height of peaks associated with the symmetric and asymmetric C–H stretching absorbance. This shift in FTIR spectra indicates the extraction of lipids. They also studied the tamoxifen partitioning pattern in an experimental setup. One phase consisted of powdered SC, while the second phase was either a control solution or a drug solution including different penetration enhancers. The results of the tamoxifen solutions containing eugenol and D-limonene are evaluated as the increased drug penetration was caused by the extraction of lipids from the SC and improved drug partitioning into the SC. It was revealed that the extraction of SC's lipids alone was responsible for the increased permeability in the tamoxifen solution including menthone[36].

The effect of terpenes on SC lipids primarily involves interactions with the lipophilic tails of intercellular lipids and the polar head groups, influencing both intercellular lipid and polar transcellular pathways. Recently, more attention has been focused on the intercellular lipid pathway. To understand the mechanism of action, attenuated total reflection-Fourier Transform infrared (ATR-FTIR) spectroscopy is often used to study the biophysical changes in the skin barrier, as it provides information on the conformation of SC lipids and keratins. After terpene application, characteristic stretching peaks around 2850 cm^{-1} (C-H symmetric stretching), 2920 cm^{-1} (C-H asymmetric stretching), 1640 cm^{-1} (Amide I), and 1540 cm^{-1} (Amide II) are commonly observed[36]. A shift to higher

frequencies in the C-H stretching peaks (~2850 and ~2920 cm^{-1}) occurs when the methylene groups of the SC lipid alkyl chains change from a trans to a gauche conformation, signifying disruption in SC lipids. The greater the disruption, the higher the C-H stretching peak position. Additionally, the area and height of the peaks at ~2850 and ~2920 cm^{-1} correlate with the quantity of SC lipids, meaning that terpene-induced lipid extraction leads to a reduction in peak area and height. Both menthol and menthone, commonly used terpenes as Penetration Enhancers (PEs), improve skin permeability by extracting SC lipids[36]. ATR-FTIR studies show that, compared to controls, treatment with menthol or menthone causes a slight shift in the asymmetric and symmetric C-H stretching peaks to higher wave numbers, indicating minor interactions with the lipophilic tails of skin lipids, which could facilitate the transdermal absorption of lipophilic drugs. Notably, menthol and menthone significantly reduce the peak areas of the C-H stretching absorption peaks, suggesting they directly extract some SC lipids, thereby weakening the skin's lipid barrier. However, the positions and areas of the amide bond peaks remain largely unchanged, indicating little to no effect on keratin in the corneocytes. Additionally, menthone demonstrated a greater ability to disrupt and extract lipids compared to menthol and azone. Similar findings were observed with other terpenes, such as 1,8-cineole, 1,4-cineole, rose oxide, safranal, and valencene. FT-IR spectra revealed differences between control and terpene-treated SC samples, with these terpenes enhancing valsartan permeation by directly extracting SC lipids[37], although no peak shift to a higher wave number was observed, indicating that they did not fluidize the lipids[38].

Okabe *et al.,*[39] studied the effect of an ethanolic solution of d-limonene on the percutaneous absorption of indomethacin and ketoprofen. They found that limonene plays a key role in increasing the penetration of poorly permeable drugs. However, maintaining enhanced drug permeability can be challenging, as it is difficult to sustain the high activity of enhancers throughout the application period[40,41]. Okabe *et al.,*[39] addressed the challenge of sustaining the activity of penetration enhancers by using a rate-limiting membrane to control the release of ethanol in combination with d-limonene. This cooperative effect between ethanol and d-limonene was shown to be an effective binary enhancer system[39]. The addition of d-limonene enhanced ethanol's effect by altering the adhesive layer structure of the transdermal patch, which had a high affinity for d-limonene. This formulation resulted in a consistent and prolonged steady-state drug permeation. The enhancement was largely due to improved drug diffusivity in the skin, as the lag time for indomethacin permeation was significantly reduced.

Additionally, Ohara *et al.,*[42] investigated the combined influence of d-limonene and temperature on the skin permeation of ketoprofen in rat skin. They found that the apparent penetration rate (Rp) increased sigmoidally with temperature, remaining almost constant at lower temperatures. When the skin was pretreated with 30% ethanol without d-limonene, a linear relationship was observed. However, Arrhenius plots for skin treated with 1.5% d-limonene in 30% ethanol showed a convex curve, suggesting that the skin structure was altered as temperature increased[42].

Krishnaiah *et al.,*[43] reported a significant enhancement in the permeation of nicardipine hydrochloride from gel systems containing menthol (1–12% w/w) through excised rat epidermis. The cumulative permeation of nicardipine hydrochloride over 24 h increased from 1.74±0.13 to 5.03±0.03 mg/cm^2/24 h when hydroxypropyl cellulose gels with menthol were used. However, there was a lag period of 2–3 h before drug permeation began. The flux remained stable at a 2% w/w concentration of menthol, but at concentrations above 5% w/w, there was a rapid increase in flux. The study also showed that the enhancement effect plateaued when the menthol concentration exceeded 8% w/w, with a statistically insignificant decrease ($p>0.05$) in drug permeation at 10% and 12% w/w menthol. Menthol was also found to increase both the moisture uptake and the release rate of propranolol hydrochloride from polymeric films[43]. Additionally, l-menthol (5% w/v) significantly ($p<0.05$) enhanced the pseudo-steady-state flux of zidovudine across human cadaver skin, with an enhancement factor of 53, although it also increased the lag time. Partitioning of l-menthol into the skin was limited, suggesting it may have a lipid fluidizing effect on SC lipids[44].

Chang *et al.,*[45] evaluated various terpenes as enhancers for meloxicam gel and found that menthol

provided the highest flux, attributing its effectiveness to its hydrogen bonding ability[45]. However, a study by Anjos and colleagues showed that l-menthol primarily stabilizes in the central region of SC membranes, interacting with membrane lipids and disrupting hydrogen bonds at the polar membrane interface[46]. The combination of menthol and iontophoresis was also found to enhance the *in vitro* permeation of methotrexate by altering the lipid-protein domains of mouse skin[47].

Some studies have focused on synthesizing o-alkyl and o-acylmenthol derivatives to improve drug permeation through the skin. Among these, o-ethylmenthol (MET) demonstrated the highest drug penetration ability with minimal skin irritation[48]. MET significantly increased ketoprofen flux, suggesting it enhances drug retention on the skin surface[49]. Obata *et al.*,[50] further explored the structure-activity relationship of MET using an artificial neural network, while confocal scanning laser microscopy revealed that MET enhances permeation by perturbing skin lipids, thereby improving drug diffusivity in the lipid layers[50].

The physical characteristics of the SC, which block the medication delivery through human skin, have been studied using DSC. Thermal analysis has also been used to study structural changes to this barrier caused by PEs, compounds that reversibly decrease the skin's barrier. In this study, we examine how DSC can be utilized to forecast penetration improvement of terpenes with varying activities towards the polar medication 5-fluorouracil (5-FU) by predictive modelling. Samples of human SC were produced using the Kligman and Christophers procedure. To get rid of surface contaminants, the tissues were washed in ice-cold acetone for ten seconds. 5 mg samples (R.H. 96%) were weighed and hydrated over saturated potassium sulfate. After reweighing and soaking in terpene for Ih, the tissues were hermetically sealed in a pan made of stainless steel, and any extra terpene was blotted out. The samples were heated with a Perkin-Elmer 7 Series Thermal Analysis System between 10 and 140˚C at 10˚C/min. Three main endotherms are visible in a typical DSC trace of the human SC across the temperature range of 40 to 120˚C. T4 is linked to protein denaturation, while the first two, designated T2 and T3, are related to SC lipids. In the same way, cineole and limonene have a significant impact on the lipid structure of the human SC. But although limonene simply causes the drug permeability coefficient to double, cineole effectively accelerates the polar drug, causing a nearly 100-fold increase in drug penetration. Lipid peak locations were similarly affected by pinene, which has no discernible effect on 5-FU, as well as by limonene and cineole. While T and T3 shifts differ in Carveol and Pulegone, their accelerant actions are identical. Not seen terpene activity. Numerous variables,

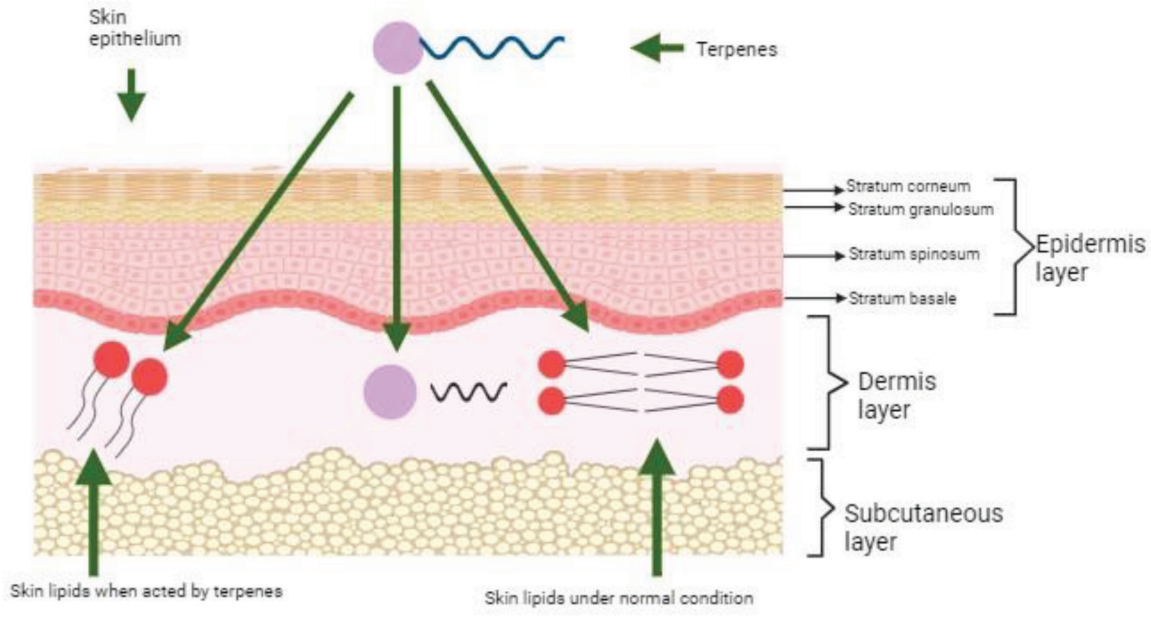


Figure 3. Mechanism of action of terpenes.

such as treatment duration, hydration, and the used scanning parameters, affect the peak locations, forms, sizes, and resolution. As a result, DSC might not be able to discern between accelerants that are somewhat good and ineffective. The primary benefit of this technique is that, once other techniques have demonstrated a chemical's accelerant activity, it consistently yields evidence of the mechanism of action of an enhancer through changes in lipid peak shifts[51]. Figure 3 shows the mechanism of action of terpene.

2.4 Different Types of Terpenes as Penetration Enhancers

2.4.1 Menthol

Menthol is GRAS for usage in medicinal products and is a potent sorption promoter. It was applied topically to increase the penetration of several active medicinal substances such as imipramine, propranolol, triamcinolone, and caffeine following topical administration, either by itself or in combination with other terpenes such as limonene[52,53]. Research in the scientific literature has also documented the synergistic usage of terpenes in conjunction with the iontophoresis technique. Al-Khalili *et al.,*[54] created gel formulations of buspirone hydrochloride (1% and 2%, respectively) based on ethanol/water (50:50 v/v). Using two distinct polymers (hydroxypropyl methylcellulose and carboxymethylcellulose), two different gel formulations were created. They assessed the impact of vehicle pH, API concentration, and density on the transdermal distribution of buspirone hydrochloride aided by iontophoresis. Research findings indicated that elevating the concentration of buspirone hydrochloride did not affect the drug's iontophoretic flux. The drug's iontophoretic flux doubled when formulation density increased from 0.05 to 0.1 MA/cm^2 [54].

2.4.2 Limonene

The permeability of amphiphilic (6-mercaptopurine) and hydrophobic (butyl paraben) medications was demonstrated to be improved by limonene, but it was discovered to be ineffective at boosting the permeability of water-soluble chemicals such as mannitol. It proved that limonene showed deeper skin penetration than substances like bisabolol, ethanol, span 20, oleic acid, and 1,8-cineole[55]. The primary component of citrus fruit peels is limonene, a colourless, transparent liquid hydrocarbon (chiral molecule) that belongs to the cyclic monoterpene class[56]. D-limonene (+)-limonene, the (R)-enantiomer, is found in citrus fruit. The term dipentene refers to racemic limonene[57]. Commercial citrus fruit D-limonene is extracted using either centrifugal separation or steam distillation. Although D-limonene is safe for human consumption[58], it may irritate the skin when administered topically.

When Compared to oxygenated linalool and cineole (when mixed with propylene glycol), then limonene enhanced the permeability of haloperidol which is effective, according to research by Lim *et al.*[59]. It was applied to the skin of the female human abdomen. While linalool and cineole only marginally improved the penetrability of haloperidol and lengthened the lag time of haloperidol transport, limonene increased it 26.5-fold and decreased the lag time[59]. Compared to oleic acid, limonene was found to have a higher penetration value for dihydrotestosterone in the skin of hairless rats[60].

2.4.3 Carvone

Carvone is a terpenoid . The essential oil extracted from caraway, spearmint (Mentha spicate), and dill seeds have a large amount of carvone. It has applications in both the food and flavour industries. Products for air refreshing are also made with it. They are employed in alternative medicine and aromatherapy. Mahfuzelmastas *et al.,* demonstrated how to purify S-carvone, which was extracted from mentha spicate (Family- Lamiaceae), using chromatographic techniques, and to characterize it using FTIR, NMR, and GS-MS methods. The *in vitro* research aimed to assess S-carvone's antioxidant capacity. The results showed that S-carvone has higher antioxidant activity than α-tocopherol when compared to the standard antioxidant[61].

2.4.4 Linalool

This terpene alcohol is produced naturally and has several industrial applications, but its main draw is its pleasant scent. Vaddi *et al.,*[62] evaluated the PE properties of linalool compared to terpineol and carvacrol, two other penetration enhancers. They made a 5% w/v solution of every PE in propylene glycol to make the transdermal administration of haloperidol easier. Haloperidol flux and solubility were both shown to have increased. The outcomes showed that

Table 1. The various types of terpenes with their sources, structures, and dosage forms

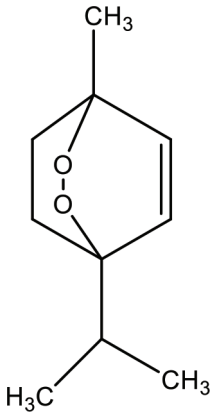
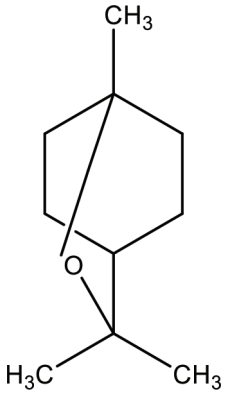
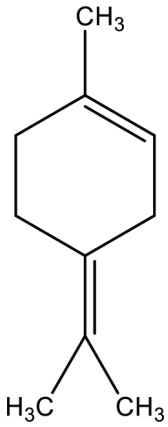
Terpene and its Type	Sources	Structure	Drug	Dosages form	Molecular wt. and chemical formula	Description	References
Ascaridole (Mono terpene peroxide)	Found in *Zanthoxylum schinifolium*		5-Fluorouracil	Gel	($C_{10}H_{16}O_2$) 148.202g/mol	It functions as a plant metabolite, an antinematodal medication, and an antileishmanial agent. It is an organic peroxide, an organic heterobicyclic molecule, and a monoterpenoid p-menthane.	63
1,8 cineol (Mono terpene)	Found in *Curcuma xanthorrhiza*		Valsartan	Gel	($C_{10}H_{18}O$) 154.249g/mol	It is used as a flavouring agent.	64-66
Terpinolene (Mono terpene)	Found in *Camellia sinensis*		Dapiprazole	Transdermal formulation	($C_{10}H_{16}$) 136.23g/mol	Terpinolene appears as a liquid that is either light amber or water-white in colour. It is not as thick as water and is not soluble in it. Used for resin and plastic production. It functions as a plant metabolite, sedative, insect repellent, and volatile oil component.	67

Table 1. Continued...

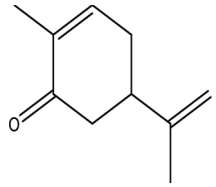
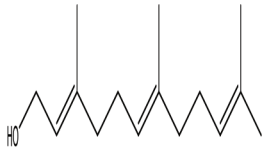
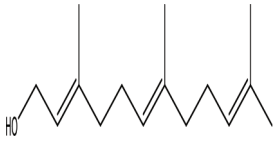
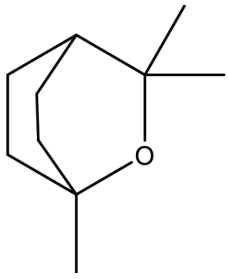
Terpene and its Type	Sources	Structure	Drug	Dosages form	Molecular wt. and chemical formula	Description	References
Carvone (Ketone)	Natural product found in *Artemisia judaica,Citrus reticulata*		Lysozyme	Transdermal formulation	($C_{10}H_{14}O$) 150.22g/mol	It performs an allergenic function. As a natural anti-fungal agent, it belongs to the Carvone family of plants.	68
Geraniol (Mono terpenes alcohol)			Caffeine	Transdermal preparation	($C_{10}H_{18}O$) 154.25g/mol	Geraniol is a common allergy to chemicals. Two physiologic consequences of geraniol include increased histamine release and cell-mediated immunity.	69
Farnesol (Sesquiterpene alcohol)	Obtained from Aristolochia triangularis		Diclofenac sodium	Transdermal preparation	($C_{15}H_{26}O$) 222.37g/mol	The liquid form of farnesol is colourless and has a light flowery scent.	70
Nerolidol (Sesqui terpene alcohol)			-	Trans dermal preparation	($C_{15}H_{26}O$) 222.37g/mol	used in the fragrance formulation of luxury cosmetics	71
Cineole (Ether)	Found in *Curcuma xanthorrhiza*				($C_{10}H_{18}O$) 154.249g/mol -	It is used as a flavouring agent.	72
Linalool (Monoterpenes alcohol)	Natural product found in *Camellia sinensis*		Labetalol	Trans dermal preparation	($C_{10}H_{18}O$) 154.25g/mol	used as an antibacterial agent, a volatile oil component,.	62

Table 1. Continued...

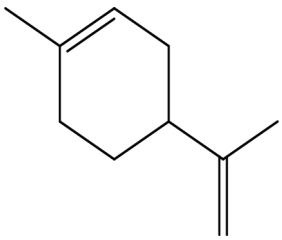
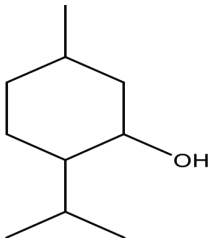
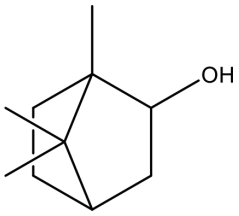
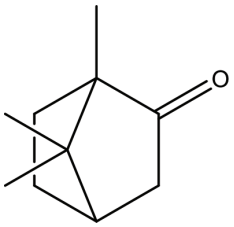
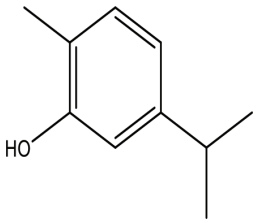
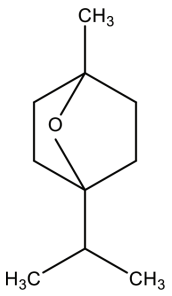
Terpene and its Type	Sources	Structure	Drug	Dosages form	Molecular wt. and chemical formula	Description	References
Limonene (Monoterpenes)	Natural product found in *Camellia sinensis*		Ondansetron hydrochloride	Transdermal preparation	($C_{10}H_{16}$) 136.24g/mol	Used as a dispersion agent for oils, resins, paints, lacquers, varnishes, and furniture polishes, and as a solvent for rubber, rosin, and waxes.	73
Menthol (Monoterpenes alcohol)	Found in *Solanum tuberosum*		Methotrexate	Gel	($C_{10}H_{10}O$) 156.27g/mol	It acts as a counterirritant on mucous membranes and skin, which results in a local anaesthetic or analgesic effect.	74
Borneol (Monoterpenes)	*Salvia officinalis,Cyperus rotundus*		5-Fluorouracil	Transdermal drug delivery	$C_{10}H_{18}O$ 154.249g/mol	Used to make perfumes.	75-77
Camphor (Monoterpenes)	Found in *Otanthus maritimus ,Tetradenia riparia*		5-Fluorouracil	Transdermal drug delivery	$C_{10}H_{16}$ 152.233g/mol	Used to make moth proofings, pharmaceuticals, and flavourings.	76,78
Carvacrol (Monoterpenes)	Natural product found in *Callistemon citrinus*		Haloperidol	Transdermal drug delivery	$C_{10}H_{14}O$ 150.22g/mol	In microbiology, carvacrol is frequently utilized as an antibacterial and antifungal agent.	66
1,4-Cineole (Monoterpenes)	Sources is *Mangnolia officinalis*		Propanolol hydrochloride	Topical drug delivery	$C_{10}H_{18}O$ 154.249g/mol	It functions as a depressant of the central nervous system, a fumigant pesticide, and a plant metabolite.	37,38, 75

Table 1. Continued...

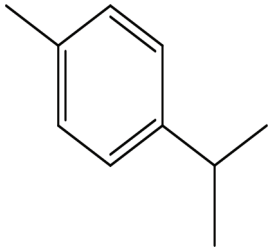
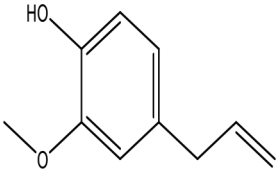
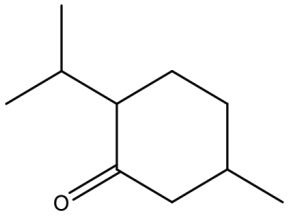
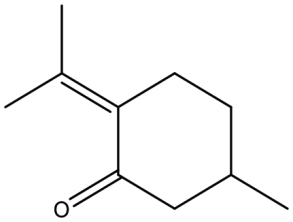
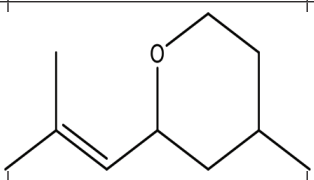
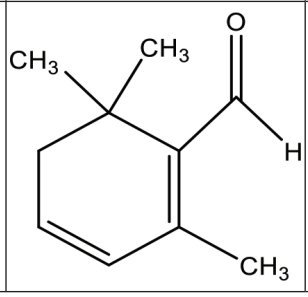
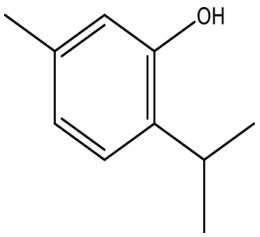
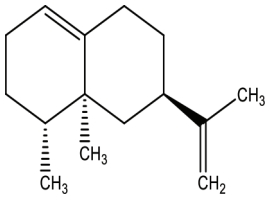
Terpene and its Type	Sources	Structure	Drug	Dosages form	Molecular wt. and chemical formula	Description	References
Cymene (Monoterpenes)	Natural product found in *Camellia sinensis*		Hydrocortisone	Topical drug delivery	$C_{10}H_{14}$ 134.22g/mol	It functions as a urine metabolite in humans, a plant metabolite, and a volatile oil component.	79
Eugenol (Monoterpenes)	Naturally occurring phenolic molecules are found in several plants such as cinnamon, clove, and bay leaves.		Valsartan Glibenclamide Glipizide Tamoxifen	Topical drug delivery	$C_{10}H_{12}O_2$ 164.201g/mol	It is used in dentistry to treat toothache and pulpitis.	80
Menthone (Monoterpenes)	Found in *Minthostachys mollis*		Tamoxifen Valsartan Halobetasol propionate	Topical drug delivery	$C_{10}H_{18}O$ 154.249g/mol	used as a Flavouring agent and Herbal remedy.	36, 81,82
Pulegone (Monoterpenes)	Sources are *Minthostachys mollis*		Zudovudine,Insuline,ferulic acid	-	$C_{10}H_{16}O$ 152.233g/mol	Used in the Dental product and herbal medicine.	36
Rose oxide (Monoterpenes)	Found in *Daphne Odora*		Propanolol hydrochloride	Topical drug delivery	$C_{10}H_{18}O$ 154.249g/mol	Used in the Cosmetic product.	37,38
Safranal (Monoterpenes)	Found in *Camellia sinensis*		Fluconazole	Transungal delivery	$C_{10}H_{14}O$ 150.218g/mol	Used as a Flavouring agent.	37,38

Table 1. Continued...

Terpene and its Type	Sources	Structure	Drug	Dosages form	Molecular wt. and chemical formula	Description	References
Thymol (Monoterpenes)	*Acanthospermum australe*		Nicardipine Hcl		$C_{10}H_{14}O$ 150.22g/mol	Used for Bacterial and fungal infection.	83
Valen-cene (Sesquit erpenes)	*Humulus lupulus*		Itraconazol	Invasome	$C_{15}H_{24}$ 204.351g/mol	Used asa Flavouring agent.	84

using linalool produced the largest increase in drug permeability[62].

3. Essential Oils

Essential oils are aromatic secondary metabolites that are typically harvested or distilled from plants. They find widespread application in various industrial domains, including food preservatives and fragrances, cleaning products, antioxidants and antiaging properties in cosmetics, and phytotherapeutic and aromatherapeutic substances in healthcare. Essential oils are used primarily for their antibacterial and antiviral qualities in the treatment of a wide range of illnesses[85]. Table 2 The MOA of essential oils is similar to the Terpenes.

4. Fatty Acids

Fatty acids have two main components are carboxylic acid group and an aliphatic hydrocarbon chain at the end. The number, location, and arrangement of double bonds vary. They could also have additional substituents and branching.; and they differ in the length of their aliphatic chains, which can be saturated or unsaturated. Numerous fatty acids are safe and effective sorption promoters when employed as permeation enhancers (Table 3). They have a higher potential for improving the absorption of lipophilic medications. Fatty acids are a skin penetration enhancer that is considered therapeutically appropriate based on the following benefits:

- Extremely high skin flux
- No issues with skin irritation or sensitization
- Good drug compatibility

Transdermal formulations containing fatty acids seem to mitigate skin irritation and sensitization, a prevalent issue linked to some medications. Many different long-chain fatty acids may be useful as enhancers of skin penetration. Fatty acids' boosting properties are dependent on several factors, such as:

- The physico-chemiccal properties of the permeants
- The means of delivering the permeants
- The identified fatty acid
- Chemical structures of the fatty acids[121,122]

Numerous research are conducted that alkyl chain length of the Fatty acids.influences the absorption of pharmaceuticals through the skin[123]. Multiple analyses have shown that the improving impacts of saturated fatty acids were highest for C10 and C12 fatty acids[124]. The structure and classification of terpenes is shown in Figure 4.

Table 2. The various types of essential oils with their sources, structures, and dosage forms

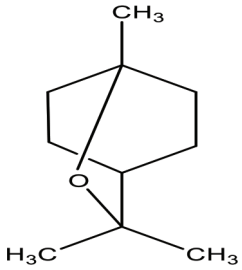
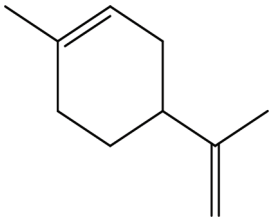
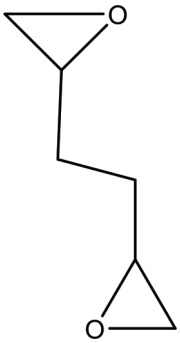
Essential Oil and their active constituents	Sources and family	Structure	Drug	Dosages form	Boiling point	Description	References
Eucalyptus oil (Geranyl oil)	*Eucalyptus citriodora, Eucalyptus dives,Eucalyptus radiata* (Family-*Myrtaceae*) (Active Constituents-Geranyl oil)		Nystatin	Topical gel	176-177˚C	eucalyptus oil has anti-plaque, antibacterial, and anticariogenic properties so it is frequently utilized in oral hygiene products.	63
Niaouli oil (1,8 Cineol)	*Melaleuca quinquenerviz* (Family-*Myrtaceae*) (Active constituents -1,8 Cineol)		Estradiol	Transdermal preparation	163˚C	it helps clear up congestion and irritation in the nose and treats acne.	86
Turpentine oil (limonene)	*Pinus longifolia* (family-*Pinaceae*) (Active constituents – (limonene)		Flurbiprofen	Transdermal preparation	154˚C	Turpentine oil is a paint solvent that's also used to make cosmetics and soap. It is also used on meals, household cleaners, and fragrances.	87
Alpinia oxyphllya oil	*Ocimum basilicum* (Family-*Zingiberaceae*) Active constituent-(6,7-diepoxide)		Indomethacin, Nalbuphine	Hydrogel	200˚C	It improves digestion, acts as a diuretic, and tonic, relieves mental exhaustion and cold symptoms, and treats upper respiratory tract infections and spasms.	88
Tulsi oil	*Ocimum basilicum* (Family-*Lamiaceae*) Active constituents-Linalool		Sulfamethoxazole	Topical gel	215˚C	Used in treating acne.	89

Table 2. Continued...

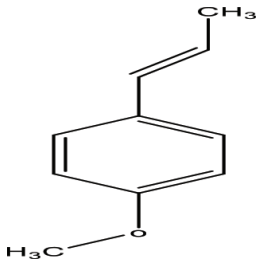
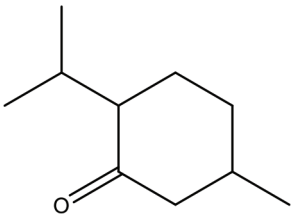
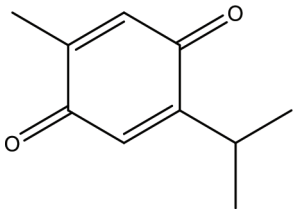
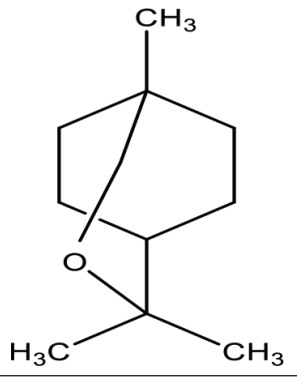
Essential Oil and their active constituents	Sources and family	Structure	Drug	Dosages form	Boiling point	Description	References
Sweet Basil	*Ocimum basilicum* (Family-*Oleaceae*) Active constituents-Linalool		Labetalol hydrochloride, Indomethacine	Topical preparation	177˚C	Used in ear infections.	90
Fennel oil	*Foeniculum vulgare* (Family-*Apiaceace)* Active constituent-Anethol		Trazodone hydrochloride	Topical preparation	227˚C	fennel is used in food, and medicine.	91
Peppermint oil	*Mentha piperita* (Family-*Lamiaceae*) Active constituents-menthone		Salicylic acid	Transdermal patches	215˚C	It has been applied to the management of bloating linked to irritable bowel syndrome and lactose intolerance.	92
Black cumin oil	*Cuminum minimum* (Family-*Apiaceae*) Active constituent-Thymoquinone		Losartan	Topical preparation	350˚C	benefit blood sugar control help reduce eczema help reduce the risk of metabolic syndrome	93
Cardamom oil	*Elettaria cardamomum* (Family-*Zingiberaceae*) Active constituent-1,8-cineole		Prednisolone, Diclofenac, Piroxicam	Topical preparation	188˚C	It has antibacterial and antioxidant properties.	94

Table 2. Continued...

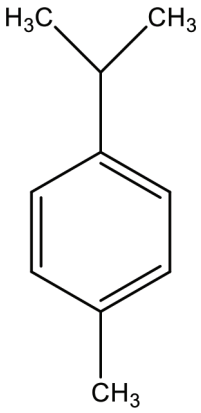
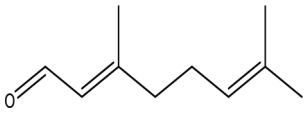
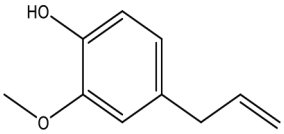
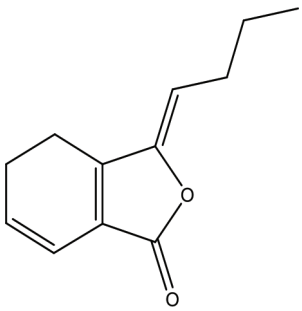
Essential Oil and their active constituents	Sources and family	Structure	Drug	Dosages form	Boiling point	Description	References
Lemon oil	*Citrus sinensis, Citrus reticulata* (Family-*Ritaceae*) Active constituent-P-cymene		Salicylic acid	Transdermal patches	176˚C	Lemon oil is used to treat rheumatism, fungal infections, arthritis, respiratory problems, and kidney stones. It also lowers blood pressure and soothes sore throats. it also helps treat diabetes, Alzheimer's disease, and dandruff.	95-99
Lemon grass oil	*Cymbogon citratus* (Family-*Geamineae*) Active constituent-Citral		Salicylic acid	Transdermal patches	224˚C	To treat gingival and periodontal diseases, a mouthwash containing lemongrass oil was created and its anti-plaque effectiveness was evaluated.	100,101
Clove oil	*Eugenia caryophyllata* (Family-*Myrtaceae*) Active constituent-Eugenol		Ibuprofen	Hydrogel	251˚C	Along with its antioxidant properties, clove oil has antiviral, anticancer, fungicidal, and antibacterial properties.	102,103
Angelica oil	*Angelica Sinensis* (Family-*Apiaceae*) Active constituent-Ligustilide		Ibuprofen	Hydrogel	55-56˚C	it is used to treat anemia, menstruation problems, and gynecological conditions, avoid gastrointestinal harm, and enhance renal and hepatic function.	104,105

Table 2. Continued...

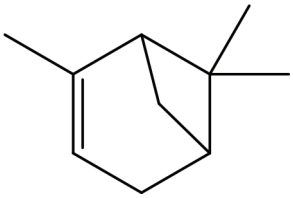
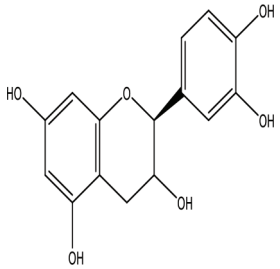
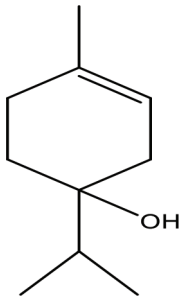
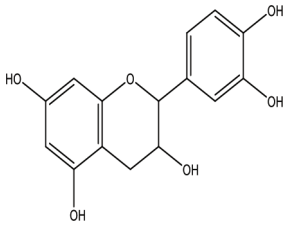
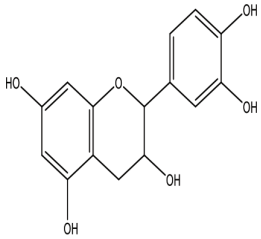
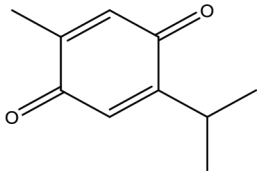
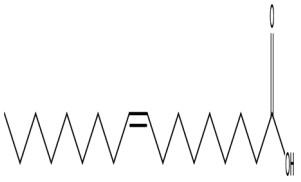
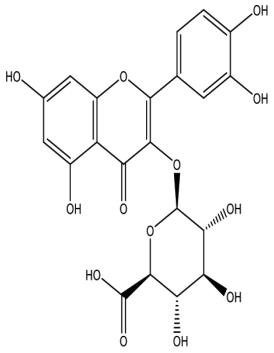
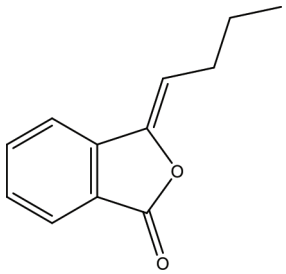
Essential Oil and their active constituents	Sources and family	Structure	Drug	Dosages form	Boiling point	Description	References
Cyperus oil	*Cyperus scariosus* (Family-*Cyperaceae*) Active constituent-alpha-pinene		Ibuprofen	Hydrogel	55-59˚C	Treatments for dysmenorrhea, cervical cancer, menstrual problems, bronchitis, renal and vesical calculi, and dysuria are among the therapeutic uses.	106,107
Cinnamon oil	*Cinnamomum zeylanicum* (Family-*Lauraceae*) Active constituent--catechins		Ibuprofen	Hydrogel	194-234˚C	Using mouse models, the impact of cinnamon oil on cognitive functioning in Alzheimer's disease was also investigated. It was determined that the extract from cinnamon impeded the development of the Ab oligomers that cause Alzheimer's disease.	108,109
Tea tree oil	*Melaleuca alternifolia* (Family-*Myrtaceae*) Active constituent-Terpinen-4-ol		Losartan	-	165˚C	In addition, tea tree oil possesses anticancer, antiviral, and antifungal properties. It is used to treat persistent gingivitis, seborrheic dermatitis, acne vulgaris, and wound healing.	110,111

Table 2. Continued...

Essential Oil and their active constituents	Sources and family	Structure	Drug	Dosages form	Boiling point	Description	References
Rose oil	*Rosa damascene* (Family-*Rosaceae*) Active constituent-		Losartan	-	176˚C	using rose oil inhalation as an aromatherapy to treat pain.	112
Neem oil	*Azadirachta indica* (Family-*Meliaceae*) Active constituent-catechin		Sulfamethoxazole	Topical gel	180-190˚C	Neem oil is useful in treating diabetes, vitiligo, periodontitis, and ulcers.	113
Nigella oil	*Nigella sativa* (Family-*Ranunculaceae*) Active constituent-Thymoquinone		Carvedilol	-	60˚C	benefit blood sugar control help reduce eczema	114
Avocado oil	*Persea americana* (Family-*Lauraceae*) Active constituents-Oleic acid		Flurbiprofen	Emulgel	250˚C	utilized to enhance vision in the medical field.	115,116
Caraway oil	*Carcum carvi* (Family-*Umbelliferae*) Active constituents-Quercetin-3-glucuronides		Salicylic acid	Transdermal patches	193-231˚C	useful for alleviating pain and enhancing symptoms that are typical of PDS and EPS.	117,118
Chuanxiong oil	*Ligusticum chuanxiong* (Family-*Apiaceae*) Active constituents-Butylidene phthalide		-	-	197˚C	In Chinese medicine, it has been frequently utilized to treat cardiovascular disease.	119,120

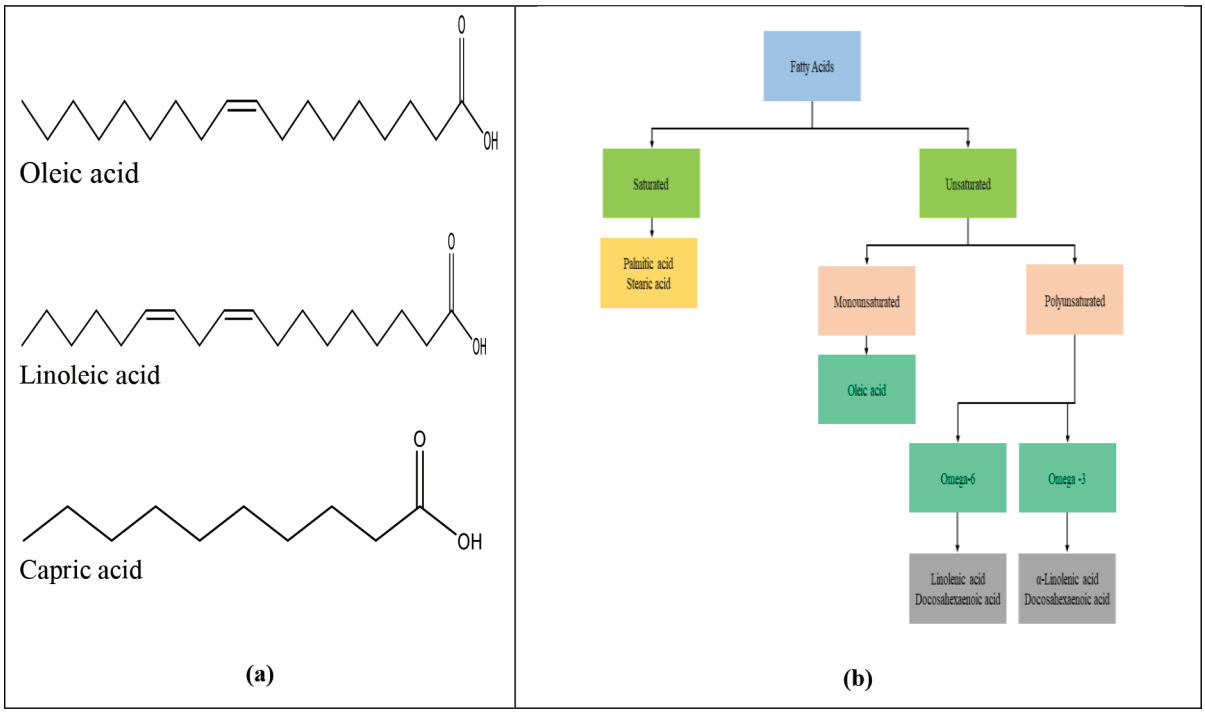


Figure 4. **(a).** The structure of fatty acids; **(b).** classifications.

It has been demonstrated that fatty acids interact with the SC lipids, and certain fatty acids are known to increase skin penetration[125,126]. It has been demonstrated that the degree of saturation, alkyl chain length, and structure of fatty acids influence their effectiveness as permeability enhancers[127]. It was shown that unsaturated fatty acids promote greater magnitudes of permeation improvement over the skin when compared with saturated fatty acids of the same chain length. It was shown that the type of cosolvent utilized substantially affects the augmentation of fatty acid permeability. As a result, fatty acids show synergistic improvements in impact with cosolvents found in transdermal formulations; but it is unknown what effects fatty acids solely have on permeation enhancement[128].

The fatty acids that are often found in food, cosmetics, and pharmaceutical products were the permeation enhancers evaluated in this study. Additionally, it was demonstrated that bond saturation affected the enhancer activity and that unsaturated long-chain fatty acids exhibited a higher enhancement than their corresponding saturated fatty acids. Moreover, it appeared that the fatty acids' branching influenced their increased penetration activity[128]. Polyunsaturated fatty acids, like arachidonic, PUFA-linoleic, and alpha-linolenic acids, have been found to enhance skin penetration more than monounsaturated fatty acids. It was observed that unsaturated fatty acids work better than saturated fatty acids to improve medication absorption via the skin[129]. The influence of fatty acids on penetrating the SC is determined by the relationship between the permeability of fatty acids through the skin's outer layer and their interaction with skin lipids.

Fatty acid concentrations also appear to affect the boosting properties of these compounds. Meloxicam was discovered to penetrate human cadaver skin more deeply as the concentration of oleic acid rose from 0.4 to 1%. It has been demonstrated that a range of fatty acids enhances the percutaneous absorption of both lipophilic and hydrophilic medications.

Extensive research has been performed on the MOA of oleic acid (C18 D9:10), a cis-unsaturated fatty acid booster that is frequently used, on the skin[129]. However, no explanation has been fully accepted so far, and penetration augmentation may be the consequence of multiple mechanisms working together. In this regard, it has been previously shown that, under specific hydration and temperature conditions, Phospholipid

liposome alkyl chains and lipids extracted from the SC may coexist within the same lamellae as an equilibrium between liquid-crystalline and gel states[130]. It is possible to think of the boundaries separating the "solid" and "liquid" domains as "disordered" or permeable interfacial "defects," which may be connected to higher permeability. These "defects" may be emphasized by the heterogeneous insertion of unsaturated fatty acids, such as oleic acid, which would favour the movement of tiny (polar) molecules, like water. Solid/fluid phase separation appears in certain combinations of phospholipids and cis-unsaturated fatty acids. These results might explain the enhanced effect of oleic acid at physiological temperatures (below the lipid transitions detected by DSC). According to studies using DSC and Raman spectroscopy, this impact seems to be specific to cis-unsaturated fatty acids[130].

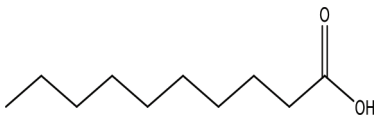
The oral mucosal membranes have been the subject of similar research. Turunen *et al.*[131] investigated the impact of oleic acid on human buccal epithelial cells labeled with various fluorophores[131]. The findings demonstrated that oleic acid significantly disturbs the hydrophobic area and the polar head group of the membrane lipids, leading to significant drops in anisotropy values. Clancy *et al.*[132], proposed that the penetration-enhancing impacts of oleic acid/ethanol are enhanced by epidermal lipid extraction, which makes sense given that ethanol has extracting properties of its own. Nevertheless, using oleic acid/PG methods to extract SC lipids has been recommended. oleic acid penetrates the skin, it dissolves some lipoidal components and aids in the drug's transit after it has been dissolved in PG. oleic acid may dissolve large cholesterol concentrations (around 175mg/ml), which could serve as a membrane stabilizer[133].

Oleic acid, an octadec-9-enoic acid with a Z conformation at the C-9 double bond, is widely used as a permeation enhancer in topical and transdermal formulations due to its beneficial properties. It enhances permeation by increasing skin fluidity and diffusivity . At higher concentrations, oleic acid separates into a distinct phase within lipid bilayers, potentially creating discrete lipid domains[134]. This phase separation can introduce permeability disruptions within the lipid bilayer, aiding the passage of hydrophilic drugs through the membrane, likely due to the conformation of the double bond[135]. ATR-FTIR studies on human volunteers treated with per-deuterated oleic acid confirmed this mechanism. Research has examined various model drugs using oleic acid as a penetration enhancer, showing significant effects on the SC, especially in membranes with a higher content of phytosphingosine-based ceramides. A study using Raman spectroscopy to assess oleic acid permeation in rat skin demonstrated a time-dependent increase in oleic acid flux, correlating with changes in lipid peak intensities.

Table 3. The various types of fatty acids with their structures, dosage forms, and chemical formula

Fatty acid	Structure	Drug	Doses form	Chemical formula and Molecular weights	Description	References
Linoleic acid		Aspal otone	Transdermal delivery	$C_{18}H_{32}O_2$ (280.4g/mol)	Improve permeation across the rat's skin	136
α-Linolenic acid		Insulin	Iontop horetic patch	$C_{18}H_{30}O_2$ (278.4g/mol)	Increased epidermal transport	137
Caprylic acid		Ketorolac	Transdermal patches	$C_8H_{16}O_2$ (144.21g/mol)	Increased percutaneous absorption	138

Table 3. Continued...

Fatty acid	Structure	Drug	Doses form	Chemical formula and Molecular weights	Description	References
Capric acid		Melatonin	Gel	$C_{10}H_{20}O_2$ (172.26g/mol)	Skin permeation is enhanced	139
Lauric acid		Albuterol sulfate	Hydrogel	$C_{12}H_{24}O_2$ (200.32g/mol)	Increased delivery from polymeric gel	140
Palmitic acid		LHRH	Patches	$C_{16}H_{32}O_2$ (256.42g/mol)	Increased percutaneous absorption	141
Oleic acid		Ondansetron	Transdermal delivery	$C_{18}H_{34}O_2$ (282.5g/mol)	Increased permeation	141

5. Conclusion

For the medication delivery community, one of the main concerns is large molecules permeating the skin. As a penetration enhancer, various natural fatty acids, terpenes and essential oils have been utilized. Such a class of NPEs includes terpenes and essential oils, which the FDA has classified as GRAS due to their shown ability to greatly increase the penetrability for both hydrophilic and lipophilic compounds with little to no negative cutaneous effects. Terpenes increase a drug's permeability by breaking down the densely packed lipid structure of the SC, increasing the drug's diffusivity in cell membranes, or rapidly partitioning the drug into epithelial cells. The major way that terpenes work is by their interaction with SC intercellular lipids. Terpenes have been used in Ancient times for medical purposes. They have been employed as Permeation Enhancers for transdermal or transmucosal administration systems recently. Terpene effects on skin permeability are commonly measured using DSC and FTIR. These penetration enhancers can be used to improve and address the shortcomings of drug delivery systems, particularly transdermal drug administration systems. Owing to their non-irritating and non-toxic characteristics, these are regarded as extremely effective classes of permeation enhancers for various medications.

6. References

1. Das A, Ahmed AB. Natural permeation enhancer for transdermal drug delivery system and permeation evaluation: A review. Asian J Pharm Clin Res. 2017; 10(9):5-9. https://doi.org/10.22159/ajpcr.2017.v10i9.19389
2. Barry BW. Dermatological formulations: percutaneous absorption.. http://pascalfrancis.inist.fr/vibad/index.php?action=getRecordDetail&idt=PASCAL83X0453251
3. Barry BW. Mode of action of penetration enhancers in human skin. J Control release. 1987; 6(1):85-97. https://doi.org/10.1016/0168-3659(87)90066-6
4. Barry BW. Modern methods of promoting drug absorption through the skin. Mol Aspects Med. 1991; 12(3):195-241. https://doi.org/10.1016/0098-2997(91)90002-4 PMid:1770837
5. Guy RH, Hadgraft J. The effect of penetration enhancers on the kinetics of percutaneous absorption. J Control release. 1987; 5(1):43-51. https://doi.org/10.1016/0168-3659(87)90036-8
6. Kolarsick PAJ, Kolarsick MA, Goodwin C. Anatomy and physiology of the skin. J Dermatol Nurses Assoc. 2011; 3(4):203-13. https://doi.org/10.1097/JDN.0b013e3182274a98
7. Wilson BD, Moon S, Armstrong F. Comprehensive review of ultraviolet radiation and the current status on sunscreens. J Clin Aesthet Dermatol. 2012; 5(9):18.

8. Romanovsky AA. Skin temperature: Its role in thermoregulation. Acta Physiol. 2014; 210(3):498-507. https://doi.org/10.1111/apha.12231 PMid:24716231 PMCid:PMC4159593
9. Tansey EA, Johnson CD. Recent advances in thermoregulation. Adv Physiol Educ. 2015; https://doi.org/10.1152/advan.00126.2014 PMid:26330029
10. Zhou SS, Li D, Zhou YM, Cao JM. The skin function: A factor of anti-metabolic syndrome. Diabetol Metab Syndr. 2012;4:1-11. https://doi.org/10.1186/1758-5996-4-15 PMid:22537765 PMCid:PMC3567429
11. Alkilani AZ, McCrudden MTC, Donnelly RF. Transdermal drug delivery: Innovative pharmaceutical developments based on disruption of the barrier properties of the stratum corneum. Pharmaceutics. 2015; 7(4):438-70. https://doi.org/10.3390/pharmaceutics7040438 PMid:26506371 PMCid:PMC4695828
12. Sandby-Møller J, Poulsen T, Wulf HC. Epidermal thickness at different body sites: Relationship to age, gender, pigmentation, blood content, skin type and smoking habits. Acta Derm Venereol. 2003; 83(6):410-3. https://doi.org/10.1080/00015550310015419 PMid:14690333
13. Böhling A, Bielfeldt S, Himmelmann A, Keskin M, Wilhelm K. Comparison of the stratum corneum thickness measured *in vivo* with confocal Raman spectroscopy and confocal reflectance microscopy. Ski Res Technol. 2014; 20(1):50-7. https://doi.org/10.1111/srt.12082 PMid:23909688
14. Russell LM, Wiedersberg S, Delgado-Charro MB. The determination of stratum corneum thickness An alternative approach. Eur J Pharm Biopharm. 2008; 69(3):861-70. https://doi.org/10.1016/j.ejpb.2008.02.002 PMid:18424094 PMCid:PMC2577912
15. Eckhart L, Lippens S, Tschachler E, Declercq W. Cell death by cornification. Biochim Biophys Acta (BBA)-Molecular Cell Res. 2013; 1833(12):3471-80. https://doi.org/10.1016/j.bbamcr.2013.06.010 PMid:23792051
16. Betts JG, DeSaix P, Johnson E, Johnson OKJE, Kruse DH, Poe B, *et al*. Anatomy and physiology, chapter 19. OpenStax Coll Rice Univ Houston, Texas. 2017; 24.
17. Wickett RR, Visscher MO. Structure and function of the epidermal barrier. Am J Infect Control. 2006; 34(10):S98-110. https://doi.org/10.1016/j.ajic.2006.05.295
18. Li X, Jasti BR. Design of controlled release drug delivery systems. (No Title). 2006; http://server0.unhas.ac.id/tahir/BAHAN-KULIAH/BIO-MEDICAL/NEW/HANBOOK/22_Design_Of_Controlled-release_Drug_Delivery_Systems.pdf
19. Matsui T, Amagai M. Dissecting the formation, structure and barrier function of the stratum corneum. Int Immunol. 2015; 27(6):269-80. https://doi.org/10.1093/intimm/dxv013 PMid:25813515
20. Shirshin EA, Gurfinkel YI, Priezzhev AV, Fadeev VV, Lademann J, Darvin ME. Two-photon autofluorescence lifetime imaging of human skin papillary dermis *in vivo*: Assessment of blood capillaries and structural proteins localization. Sci Rep. 2017; 7(1):1171. https://doi.org/10.1038/s41598-017-01238-w PMid:28446767 PMCid:PMC5430894
21. Nguyen AV, Soulika AM. The dynamics of the skin's immune system. Int J Mol Sci. 2019; 20(8):1811. https://doi.org/10.3390/ijms20081811 PMid:31013709 PMCid:PMC6515324
22. Lovászi M, Szegedi A, Zouboulis CC, Törőcsik D. Sebaceous-immunobiology is orchestrated by sebum lipids. Dermatoendocrinol. 2017; 9(1):e1375636. https://doi.org/10.1080/19381980.2017.1375636 PMid:29484100 PMCid:PMC5821166
23. Wong R, Geyer S, Weninger W, Guimberteau J, Wong JK. The dynamic anatomy and patterning of skin. Exp Dermatol. 2016; 25(2):92-8. https://doi.org/10.1111/exd.12832 PMid:26284579
24. Driskell RR, Jahoda CAB, Chuong C, Watt FM, Horsley V. Defining dermal adipose tissue. Exp Dermatol. 2014; 23(9):629-31. https://doi.org/10.1111/exd.12450 PMid:24841073 PMCid:PMC4282701
25. Kanikkannan N, Singh M. Skin permeation enhancement effect and skin irritation of saturated fatty alcohols. Int J Pharm. 2002; 248(1-2):219-28. https://doi.org/10.1016/S0378-5173(02)00454-4 PMid:12429475
26. Kligman AM. Topical pharmacology and toxicology of dimethyl sulfoxide-Part 1. J Am Med Assoc. 1965; 193(10):796-804. https://doi.org/10.1001/jama.1965.03090100042010 PMid:14329978
27. Ben-Shabat S, Baruch N, Sintov AC. Conjugates of unsaturated fatty acids with propylene glycol as potentially less-irritant skin penetration enhancers. Drug Dev Ind Pharm. 2007; 33(11):1169-75. https://doi.org/10.1080/03639040701199258 PMid:18058312
28. Fox LT, Gerber M, Plessis J Du, Hamman JH. Transdermal drug delivery enhancement by compounds of natural origin. Molecules. 2011; 16(12):10507-40. https://doi.org/10.3390/molecules161210507 PMCid:PMC6264261
29. Dwibhashyam VS, Ratna VJ. Chemical penetration enhancers - An update. Indian Drugs. 2010; 47(4):5-18.
30. Prasanthi D, Lakshmi PK. Terpenes: Effect of lipophilicity in enhancing transdermal delivery of alfuzosin hydrochloride. J Adv Pharm Technol Res. 2012; 3(4):216-23. https://doi.org/10.4103/2231-4040.104712 PMid:23378942 PMCid:PMC3560127
31. Williams AC, Barry BW. Penetration enhancers. Adv Drug Deliv Rev. 2012; 64:128-37. https://doi.org/10.1016/j.addr.2012.09.032
32. Zhao K, Singh J. Mechanisms of percutaneous absorption of tamoxifen by terpenes: Eugenol, D-limonene and menthone. J Control Release. 1998; 55(2-3):253-60. https://doi.org/10.1016/S0168-3659(98)00053-4 PMid:9795076
33. Naik A, Guy RH. Infrared spectroscopic and differential scanning calorimetric investigations of the stratum

corneum barrier function. Drugs Pharm Sci. 1997; 83:87-162.
34. Zhao K, Singh J. *In vitro* percutaneous absorption enhancement of propranolol hydrochloride through porcine epidermis by terpenes/ethanol. J Control release. 1999; 62(3):359-66. https://doi.org/10.1016/S0168-3659(99)00171-6 PMid:10528073
35. Walker RB, Smith EW. The role of percutaneous penetration enhancers. Adv Drug Deliv Rev. 1996; 18(3):295-301. https://doi.org/10.1016/0169-409X(95)00078-L
36. Lan Y, Wang J, Li H, Zhang Y, Chen Y, Zhao B, *et al*. Effect of menthone and related compounds on skin permeation of drugs with different lipophilicity and molecular organization of stratum corneum lipids. Pharm Dev Technol. 2016; 21(4):389-98.
37. Ahad A, Aqil M, Kohli K, Sultana Y, Mujeeb M, Ali A. Role of novel terpenes in transcutaneous permeation of valsartan: Effectiveness and mechanism of action. Drug Dev Ind Pharm. 2011; 37(5):583-96. https://doi.org/10.3109/03639045.2010.532219 PMid:21469947
38. Ahad A, Aqil M, Kohli K, Sultana Y, Mujeeb M, Ali A. Interactions between novel terpenes and main components of rat and human skin: Mechanistic view for transdermal delivery of propranolol hydrochloride. Curr Drug Deliv. 2011; 8(2):213-24. https://doi.org/10.2174/156720111794479907 PMid:21235472
39. Okabe H, Suzuki E, Saitoh T, Takayama K, Nagai T. Development of novel transdermal system containing d-limonene and ethanol as absorption enhancers. J Control release. 1994; 32(3):243-7. https://doi.org/10.1016/0168-3659(94)90234-8
40. Okabe H, Takayama K, Ogura A, Nagai T. Effect of limonene and related compounds on the percutaneous absorption of indomethacin. Drug Des Deliv. 1989; 4(4):313-21.
41. Kikuchi K, Takayama K, Nagai T. Effect of d-limonene on the amounts of ethanol and indomethacin penetrated from aqueous gel ointments to rat skin. Chem Pharm Bull. 1992; 40(11):3108-9. https://doi.org/10.1248/cpb.40.3108 PMid:1477929
42. Ohara N, Takayama K, Machida Y, Nagai T. Combined effect of d-limonene and temperature on the skin permeation of ketoprofen. Int J Pharm. 1995; 1(119):125. https://doi.org/10.1016/0378-5173(95)90675-W
43. Krishnaiah YSR, Satyanarayana V, Karthikeyan RS. Penetration enhancing effect of menthol on the percutaneous flux of nicardipine hydrochloride through excised rat epidermis from hydroxypropyl cellulose gels. Pharm Dev Technol. 2002; 7(3):305-15. https://doi.org/10.1081/PDT-120005727 PMid:12229262
44. Narishetty STK, Panchagnula R. Effect of L-menthol and 1, 8-cineole on phase behavior and molecular organization of SC lipids and skin permeation of zidovudine. J Control Release. 2005; 102(1):59-70. https://doi.org/10.1016/j.jconrel.2004.09.016 PMid:15653134
45. Chang JS, Tsai YH, Wu PC, Huang YB. The effect of mixed-solvent and terpenes on percutaneous absorption of meloxicam gel. Drug development and industrial pharmacy. 2007 Jan 1;33(9):984-9.
46. Dos Anjos JLV, de Sousa Neto D, Alonso A. Effects of 1, 8-cineole on the dynamics of lipids and proteins of stratum corneum. Int J Pharm. 2007; 345(1-2):81-7. https://doi.org/10.1016/j.ijpharm.2007.05.041 PMid:17600646
47. Prasad R, Koul V, Anand S, Khar RK. Effect of DC/mDC iontophoresis and terpenes on transdermal permeation of methotrexate: *In vitro* study. Int J Pharm. 2007; 333(1-2):70-8. https://doi.org/10.1016/j.ijpharm.2006.09.058 PMid:17116378
48. Negishi J. Promoting effect of O-acylmenthol derivatives on the percutaneous absorption of ketoprofen in rats. STP Pharma Sci. 1995; 5:156-61.
49. Nakamura Y, Takayama K, Higashiyama K, Suzuki T, Nagai T. Promoting effect of O-ethylmenthol on the percutaneous absorption of ketoprofen. Int J Pharm. 1996; 145(1-2):29-36. https://doi.org/10.1016/S0378-5173(96)04749-7
50. Obata Y, Maruyama Y, Takayama K. The mode of promoting activity of O-ethylmenthol as a transdermal absorption enhancer. Pharm Res. 2006; 23:392-400. https://doi.org/10.1007/s11095-005-9257-6 PMid:16467993
51. Scott RC. Prediction of percutaneous penetration: Methods, measurements, modelling. Vol. 2. IBC Technical Services; 1991.
52. Narishetty STK, Panchagnula R. Transdermal delivery of zidovudine: Effect of terpenes and their mechanism of action. J Control Release. 2004; 95(3):367-79. https://doi.org/10.1016/j.jconrel.2003.11.022 PMid:15023449
53. Jain AK, Thomas NS, Panchagnula R. Transdermal drug delivery of imipramine hydrochloride: I. Effect of terpenes. J Control Release. 2002; 79(1-3):93-101. https://doi.org/10.1016/S0168-3659(01)00524-7 PMid:11853921
54. Al-Khalili M, Meidan VM, Michniak BB. Iontophoretic transdermal delivery of buspirone hydrochloride in hairless mouse skin. AAPS PharmSci. 2003; 5:61-71. https://doi.org/10.1208/ps050214 PMid:12866941 PMCid:PMC2751522
55. Femenia-Font A, Balaguer-Fernandez C, Merino V, Rodilla V, Lopez-Castellano A. Effect of chemical enhancers on the *in vitro* percutaneous absorption of sumatriptan succinate. Eur J Pharm Biopharm. 2005; 61(1-2):50-5. https://doi.org/10.1016/j.ejpb.2005.02.014 PMid:15925502
56. Ibrahim ME, El-Sawi SA. Quality and quantity of volatile oil resulting from the recycling of different forms of orange peel using drying methods. J Mater Environ Sci. 2019; 10(7):598-603.
57. Difran AJM, Abhinaya H V, Verma S, Sampath S, Umaima U, Swetha BN, *et al*. Extraction of Tyrosine Ammonia Lyase (tal) from *Murraya koenigii* plant for the treatment of hyperpigmentation-involves *in-vivo* analysis on zebrafish

embryos and molecular docking. World J Pharmacol Pharm Sci. 2016; 5:1769-80.
58. Kim YW, Kim MJ, Chung BY, Bang DY, Lim SK, Choi SM, *et al*. Safety evaluation and risk assessment of d-limonene. J Toxicol Environ Heal Part B. 2013; 16(1):17-38. https://doi.org/10.1080/10937404.2013.769418 PMid:23573938
59. Lim PFC, Liu XY, Kang L, Ho PCL, Chan YW, Chan SY. Limonene GP1/PG organogel as a vehicle in transdermal delivery of haloperidol. Int J Pharm. 2006; 311(1-2):157-64. https://doi.org/10.1016/j.ijpharm.2005.12.042 PMid:16451823
60. Clarys P, Alewaeters K, Jadoul A, Barel A, Manadas RO, Préat V. *In vitro* percutaneous penetration through hairless rat skin: Influence of temperature, vehicle and penetration enhancers. Eur J Pharm Biopharm. 1998; 46(3):279-83. https://doi.org/10.1016/S0939-6411(98)00044-7 PMid:9885299
61. Elmastaş M, Dermirtas I, Isildak O, Aboul-Enein HY. Antioxidant activity of S-carvone isolated from spearmint (Mentha Spicata L. Fam Lamiaceae). Journal of liquid chromatography & related technologies. 2006 Jul 1;29(10):1465-75.
62. Vaddi HK, Ho PC, Chan SY. Terpenes in propylene glycol as skin-penetration enhancers: Permeation and partition of haloperidol, fourier transform infrared spectroscopy, and differential scanning calorimetry. J Pharm Sci. 2002; 91(7):1639-51. https://doi.org/10.1002/jps.10160 PMid:12115825
63. Williams AC, Barry BW. Essential oils as novel human skin penetration enhancers. Int J Pharm. 1989; 57(2):R7-9. https://doi.org/10.1016/0378-5173(89)90310-4
64. Yang Z, Teng Y, Wang H, Hou H. Enhancement of skin permeation of bufalin by limonene via reservoir type transdermal patch: formulation design and biopharmaceutical evaluation. Int J Pharm. 2013; 447(1-2):231-40. https://doi.org/10.1016/j.ijpharm.2013.02.048 PMid:23467076
65. Ahad A, Aqil M, Ali A. Investigation of antihypertensive activity of carbopol valsartan transdermal gel containing 1, 8-cineole. Int J Biol Macromol. 2014; 64:144-9. https://doi.org/10.1016/j.ijbiomac.2013.11.018 PMid:24296403
66. Chantasart D, Pongjanyakul T, Higuchi WI, Li SK. Effects of oxygen-containing terpenes as skin permeation enhancers on the lipoidal pathways of human epidermal membrane. J Pharm Sci. 2009; 98(10):3617-32. https://doi.org/10.1002/jps.21666 PMid:19156845
67. Monti D, Saettone MF, Giannaccini B, Galli-Angeli D. Enhancement of transdermal penetration of dapiprazole through hairless mouse skin. J Control release. 1995; 33(1):71-7. https://doi.org/10.1016/0168-3659(94)00079-A
68. Krishnaiah YSR, Satyanarayana V, Bhaskar P. Formulation and *in vivo* evaluation of membrane-moderated transdermal therapeutic systems of nicardipine hydrochloride using carvone as a penetration enhancer. Drug Deliv. 2003; 10(2):101-9. https://doi.org/10.1080/713840367 PMid:12746056
69. Godwin DA, Michniak BB. Influence of drug lipophilicity on terpenes as transdermal penetration enhancers. Drug Dev Ind Pharm. 1999; 25(8):905-15. https://doi.org/10.1081/DDC-100102251 PMid:10434134
70. Nokhodchi A, Sharabiani K, Rashidi MR, Ghafourian T. The effect of terpene concentrations on the skin penetration of diclofenac sodium. Int J Pharm. 2007; 335(1-2):97-105. https://doi.org/10.1016/j.ijpharm.2006.10.041 PMid:17174049
71. Cornwell PA, Barry BW. Sesquiterpene components of volatile oils as skin penetration enhancers for the hydrophilic permeant 5-fluorouracil. J Pharm Pharmacol. 1994; 46(4):261-9. https://doi.org/10.1111/j.2042-7158.1994.tb03791.x PMid:8051608
72. Amnuaikit C, Ikeuchi I, Ogawara K-i, Higaki K, Kimura T. Skin permeation of propranolol from polymeric film containing terpene enhancers for transdermal use. Int J Pharm. 2005; 289(1-2):167-78. https://doi.org/10.1016/j.ijpharm.2004.11.007 PMid:15652209
73. Koyama Y, Bando H, Yamashita F, Takakura Y, Sezaki H, Hashida M. Comparative analysis of percutaneous absorption enhancement by d-limonene and oleic acid based on a skin diffusion model. Pharm Res. 1994; 11:377-83. https://doi.org/10.1023/A:1018904802566 PMid:8008702
74. Bruneton J. Pharmacognosy, phytochemistry, medicinal plants. Intercept Limited; 1999.
75. Zhou W, He S, Yang Y, Jian D, Chen X, Ding J. Formulation, characterization and clinical evaluation of propranolol hydrochloride gel for transdermal treatment of superficial infantile hemangioma. Drug Dev Ind Pharm. 2015; 41(7):1109-19. https://doi.org/10.3109/03639045.2014.931968 PMid:25151873
76. Cui Y, Li L, Zhang L, Li J, Gu J, Gong H, *et al*. Enhancement and mechanism of transdermal absorption of terpene-induced propranolol hydrochloride. Arch Pharm Res. 2011; 34(9):1477-85. https://doi.org/10.1007/s12272-011-0909-2 PMid:21975809
77. Yi QF, Yan J, Tang SY, Huang H, Kang LY. Effect of borneol on the transdermal permeation of drugs with differing lipophilicity and molecular organization of stratum corneum lipids. Drug Dev Ind Pharm. 2016; 42(7):1086-93. https://doi.org/10.3109/03639045.2015.1107095 PMid:26635061
78. Xie F, Chai J-k, Hu Q, Yu Y-h, Ma L, Liu L-y, *et al*. Transdermal permeation of drugs with differing lipophilicity: Effect of penetration enhancer camphor. Int J Pharm. 2016; 507(1-2):90-101. https://doi.org/10.1016/j.ijpharm.2016.05.004 PMid:27154251

79. El-Kattan AF, Asbill CS, Michniak BB. The effect of terpene enhancer lipophilicity on the percutaneous permeation of hydrocortisone formulated in HPMC gel systems. Int J Pharm. 2000; 198(2):179-89. https://doi.org/10.1016/S0378-5173(00)00330-6 PMid:10767567
80. Ahad A, Aqil M, Ali A. The application of anethole, menthone, and eugenol in transdermal penetration of valsartan: Enhancement and mechanistic investigation. Pharm Biol. 2016; 54(6):1042-51. https://doi.org/10.3109/13880209.2015.1100639 PMid:26510896 PMCid:PMC11132634
81. Furuishi T, Kato Y, Fukami T, Suzuki T, Endo T, Nagase H, *et al*. Effect of terpenes on the skin permeation of lomerizine dihydrochloride. J Pharm Pharm Sci. 2013; 16(4):551-63. https://doi.org/10.18433/J36890 PMid:24210063
82. Wang J, Dong C, Song Z, Zhang W, He X, Zhang R, *et al*. Monocyclic monoterpenes as penetration enhancers of ligustrazine hydrochloride for dermal delivery. Pharm Dev Technol. 2017; 22(4):571-7. https://doi.org/10.1080/10837450.2016.1189936 PMid:27269134
83. Chadha G, Sathigari S, Parsons DL, Jayachandra Babu R. *In vitro* percutaneous absorption of genistein from topical gels through human skin. Drug Dev Ind Pharm. 2011; 37(5):498-505. https://doi.org/10.3109/03639045.2010.525238 PMid:21126208
84. Can AS, Erdal MS, Güngör S, Özsoy Y. Optimization and characterization of chitosan films for transdermal delivery of ondansetron. Molecules. 2013; 18(5):5455-71. https://doi.org/10.3390/molecules18055455 PMid:23666010 PMCid:PMC6270495
85. Reichling J, Schnitzler P, Suschke U, Saller R. Essential oils of aromatic plants with antibacterial, antifungal, antiviral, and cytotoxic properties-an overview. Forschende Komplementärmedizin/Research Complement Med. 2009; 16(2):79-90. https://doi.org/10.1159/000207196 PMid:19420953
86. Monti D, Tampucci S, Chetoni P, Burgalassi S, Bertoli A, Pistelli L. Niaouli oils from different sources: analysis and influence on cutaneous permeation of estradiol *in vitro*. Drug Deliv. 2009; 16(5):237-42. https://doi.org/10.1080/10717540902896297 PMid:19538003
87. Charoo NA, Shamsher AAA, Kohli K, Pillai K, Rahman Z. Improvement in bioavailability of transdermally applied flurbiprofen using tulsi (*Ocimum sanctum*) and turpentine oil. Colloids surfaces B Biointerfaces. 2008; 65(2):300-7. https://doi.org/10.1016/j.colsurfb.2008.05.001 PMid:18579348
88. Fang JY, Leu YL, Hwang TL, Cheng HC, Hung CF. Development of sesquiterpenes from Alpinia oxyphylla as novel skin permeation enhancers. Eur J Pharm Sci. 2003; 19(4):253-62. https://doi.org/10.1016/S0928-0987(03)00118-0 PMid:12885390
89. Sangra M, Jaiswal S, Gupta GD. Topical delivery of sulfamethoxazole: design, evaluation and effect of penetration enhancers. Indo Am J Pharm Res. 2014; 4:2943-3750.
90. Fang JY, Leu YL, Hwang TL, Cheng HC. Essential oils from sweet basil (*Ocimum basilicum*) as novel enhancers to accelerate transdermal drug delivery. Biol Pharm Bull. 2004; 27(11):1819-25. https://doi.org/10.1248/bpb.27.1819 PMid:15516730
91. Das MK, Bhattacharya A, Ghosal SK. Effect of different terpene-containing essential oils on percutaneous absorption of trazodone hydrochloride through mouse epidermis. Drug Deliv. 2006; 13(6):425-31. https://doi.org/10.1080/10717540500395064 PMid:17002970
92. Kaza R, Pitchaimani R. Formulation of transdermal drug delivery system: matrix type, and selection of polymer-their evaluation. Curr Drug Discov Technol. 2006; 3(4):279-85. https://doi.org/10.2174/157016306780368135 PMid:17430104
93. Vashisth I, Ahad A, Aqil M, Agarwal SP. Investigating the potential of essential oils as penetration enhancer for transdermal losartan delivery: Effectiveness and mechanism of action. Asian J Pharm Sci. 2014; 9(5):260-7. https://doi.org/10.1016/j.ajps.2014.06.007
94. Yamahara J, Kashiwa H, Kishi K, Fujimura H. Dermal penetration enhancement by crude drugs: *in vitro* skin permeation of prednisolone enhanced by active constituents in cardamon seed. Chem Pharm Bull. 1989; 37(3):855-6. https://doi.org/10.1248/cpb.37.855 PMid:2752499
95. Bhuiyan MNI, Begum J, Sardar PK, Rahman MS. Constituents of peel and leaf essential oils of *Citrus medica* L. J Sci Res. 2009; 1(2):387-92. https://doi.org/10.3329/jsr.v1i2.1760
96. Faleiro ML, Miguel MG, Ladeiro F, Venancio F, Tavares R, Brito JC, *et al*. Antimicrobial activity of essential oils isolated from Portuguese endemic species of Thymus. Lett Appl Microbiol. 2003; 36(1):35-40. https://doi.org/10.1046/j.1472-765X.2003.01259.x PMid:12485339
97. Silalahi J. Anticancer and health protective properties of citrus fruit components. Asia Pac J Clin Nutr. 2002; 11(1):79-84. https://doi.org/10.1046/j.1440-6047.2002.00271.x PMid:11890643
98. Dosoky NS, Setzer WN. Biological activities and safety of Citrus spp. essential oils. Int J Mol Sci. 2018; 19(7):1966. https://doi.org/10.3390/ijms19071966 PMid:29976894 PMCid:PMC6073409
99. Rozza AL, de Mello Moraes T, Kushima H, Tanimoto A, Marques MOM, Bauab TM, *et al*. Gastroprotective mechanisms of Citrus lemon (Rutaceae) essential oil and its majority compounds limonene and β-pinene: Involvement of heat-shock protein-70, vasoactive intestinal peptide, glutathione, sulfhydryl compounds, nitric oxide and prostaglandin E. Chem Biol Interact. 2011; 189(1-2):82-9. https://doi.org/10.1016/j.cbi.2010.09.031 PMid:20934418
100. Saleem M, Afza N, Anwar MA, Hai SMA, Ali MS. A comparative study of essential oils of Cymbopogon citratus

and some members of the genus Citrus. Nat Prod Res. 2003; 17(5):369-73. https://doi.org/10.1080/14786410310001605823 PMid:14526919

101. Kukkamalla MA, Bhat SG, Pentapati KC, Goyal R. Antiplaque efficacy of lemongrass oil mouthwash-an *in-vitro* study. Glob J Med Res. 2012; 12(7):19-24.
102. Lee KG, Shibamoto T. Antioxidant property of aroma extract isolated from clove buds [*Syzygium aromaticum* (L.) Merr. et Perry]. Food Chem. 2001; 74(4):443-8. https://doi.org/10.1016/S0308-8146(01)00161-3
103. Prashar A, Locke IC, Evans CS. Cytotoxicity of clove (*Syzygium aromaticum*) oil and its major components to human skin cells. Cell Prolif. 2006; 39(4):241-8. https://doi.org/10.1111/j.1365-2184.2006.00384.x PMid:16872360 PMCid:PMC6496679
104. Zhao KJ, Dong TTX, Tu PF, Song ZH, Lo CK, Tsim KWK. Molecular genetic and chemical assessment of radix *Angelica* (Danggui) in China. J Agric Food Chem. 2003; 51(9):2576-83. https://doi.org/10.1021/jf026178h PMid:12696940
105. Li A, Han L, Han CC. Antioxidant and neuroprotective activities of essential oil, isolated from Chinese herb pairs of *Angelica sinensis* and *Sophora flavescens*. J Appl Pharm Sci. 2012:1-4.
106. Słoczyńska K, Powroźnik B, Pękala E, Waszkielewicz AM. Antimutagenic compounds and their possible mechanisms of action. J Appl Genet. 2014; 55:273-85. https://doi.org/10.1007/s13353-014-0198-9 PMid:24615570 PMCid:PMC3990861
107. Lin CH, Peng SF, Chueh FS, Cheng ZY, Kuo CL, Chung JG. The ethanol crude extraction of Cyperus rotundus regulates apoptosis-associated gene expression in HeLa human cervical carcinoma cells *in vitro*. Anticancer Res. 2019; 39(7):3697-709. https://doi.org/10.21873/anticanres.13518 PMid:31262896
108. Shan B, Cai YZ, Brooks JD, Corke H. Antibacterial properties and major bioactive components of cinnamon stick (Cinnamomum burmannii): activity against foodborne pathogenic bacteria. J Agric Food Chem. 2007; 55(14):5484-90. https://doi.org/10.1021/jf070424d PMid:17567030
109. Molania T, Moghadamnia AA, Pouramir M, Aghel S, Moslemi D, Ghassemi L, *et al*. The effect of Cinnamaldehyde on mucositis and salivary antioxidant capacity in gamma-irradiated rats (a preliminary study). DARU J Pharm Sci. 2012; 20:1-5. https://doi.org/10.1186/2008-2231-20-89 PMid:23351595 PMCid:PMC3556024
110. Ren W, Qiao Z, Wang H, Zhu L, Zhang L. Flavonoids: Promising anticancer agents. Med Res Rev. 2003; 23(4):519-34. https://doi.org/10.1002/med.10033 PMid:12710022
111. Pazyar N, Yaghoobi R, Bagherani N, Kazerouni A. A review of applications of tea tree oil in dermatology. Int J Dermatol. 2013; 52(7):784-90. https://doi.org/10.1111/j.1365-4632.2012.05654.x PMid:22998411
112. Gholamhoseinian A, Fallah H. Inhibitory effect of methanol extract of *Rosa damascena* Mill. flowers on α-glucosidase activity and postprandial hyperglycemia in normal and diabetic rats. Phytomedicine. 2009; 16(10):935-41. https://doi.org/10.1016/j.phymed.2009.02.020 PMid:19380218
113. Biswas K, Chattopadhyay I, Banerjee RK, Bandyopadhyay U. Biological activities and medicinal properties of neem (*Azadirachta indica*). Curr Sci. 2002; 1336-45.
114. Pankaj S, Lokeshwar T, Mukesh B, Vishnu B. Review on neem (Azadirachta indica): thousand problems one solution. Int Res J Pharm. 2011; 2(12):97-102.
115. Flores M, Saravia C, Vergara CE, Avila F, Valdés H, Ortiz-Viedma J. Avocado oil: Characteristics, properties, and applications. Molecules. 2019; 24(11):2172. https://doi.org/10.3390/molecules24112172 PMid:31185591 PMCid:PMC6600360
116. de Oliveira AP, Franco E de S, Barreto RR, Cordeiro DP, de Melo RG, de Aquino CMF, *et al*. Effect of semisolid formulation of *Persea americana* Mill. (avocado) oil on wound healing in rats. Evidence-Based Complement Altern Med. 2013; 2013. https://doi.org/10.1155/2013/472382 PMid:23573130 PMCid:PMC3614059
117. Krishnaiah D, Devi T, Bono A, Sarbatly R. Studies on phytochemical constituents of six Malaysian medicinal plants. J Med plants Res. 2009; 3(2):67-72.
118. Samojlik I, Lakic N, Mimica-Dukic N, Đaković-Švajcer K, Bozin B. Antioxidant and hepatoprotective potential of essential oils of coriander (Coriandrum sativum L.) and caraway (*Carum carvi* L.)(Apiaceae). J Agric Food Chem. 2010; 58(15):8848-53. https://doi.org/10.1021/jf101645n PMid:20608729
119. Zhang C, Liu R, He J, Ma Z, Zhang X. Chemical compositions of *Ligusticum chuanxiong* oil and lemongrass oil and their joint action against *Aphis citricola* Van Der Goot (Hemiptera: Aphididae). Molecules. 2016; 21(10):1359. https://doi.org/10.3390/molecules21101359 PMid:27754334 PMCid:PMC6272882
120. Liang MJ, He LC, Yang GD. Screening, analysis and *in vitro* vasodilatation of effective components from *Ligusticum Chuanxiong*. Life Sci. 2005; 78(2):128-33. https://doi.org/10.1016/j.lfs.2005.04.038 PMid:16154159
121. Aungst BJ. Fatty acids are skin permeation enhancers. Percutaneous penetration Enhanc. 1995; 277-87. https://doi.org/10.1016/0169-409X(95)00078-L **https://link.springer.com/article/10.1023/A:1015921702258**
122. Aungst BJ, Rogers NJ, Shefter E. Enhancement of naloxone penetration through human skin *in vitro* using fatty acids, fatty alcohols, surfactants, sulfoxides and amides. Int J Pharm. 1986; 33(1-3):225-34. https://doi.org/10.1016/0378-5173(86)90057-8
123. Morimoto K, Tojima H, Haruta T, Suzuki M, Kakemi M. Enhancing effects of unsaturated fatty acids with various

structures on the permeation of indomethacin through rat skin. J Pharm Pharmacol. 1996; 48(11):1133-7. https://doi.org/10.1111/j.2042-7158.1996.tb03908.x PMid:8961160

124. Komata Y, Inaoka M, Kaneko A, Fujie T. *In vitro* percutaneous absorption of thiamine disulfide from a mixture of propylene glycol and fatty acid. J Pharm Sci. 1992; 81(8):744-6. https://doi.org/10.1002/jps.2600810804 PMid:1403716
125. Cooper ER. Increased skin permeability for lipophilic molecules. J Pharm Sci. 1984; 73(8):1153-6. https://doi.org/10.1002/jps.2600730831 PMid:6491922
126. Barry BW, Bennett SL. Effect of penetration enhancers on the permeation of mannitol, hydrocortisone and progesterone through human skin. J Pharm Pharmacol. 1987; 39(7):535-46. https://doi.org/10.1111/j.2042-7158.1987.tb03173.x PMid:2886623
127. Kandimalla K, Kanikkannan N, Andega S, Singh M. Effect of fatty acids on the permeation of melatonin across rat and pig skin *in-vitro* and on the transepidermal water loss in rats *in-vivo*. J Pharm Pharmacol. 1999; 51(7):783-90. https://doi.org/10.1211/0022357991773140 PMid:10467952
128. Nanayakkara GR, Bartlett A, Forbes B, Marriott C, Whitfield PJ, Brown MB. The effect of unsaturated fatty acids in benzyl alcohol on the percutaneous permeation of three model penetrants. Int J Pharm. 2005; 301(1-2):129-39. https://doi.org/10.1016/j.ijpharm.2005.05.024 PMid:16019171
129. Chi SC, Park ES, Kim H. Effect of penetration enhancers on flurbiprofen permeation through rat skin. Int J Pharm. 1995; 126(1-2):267-74. https://doi.org/10.1016/0378-5173(95)04137-0
130. Papahadjopoulos D, Jacobson K, Nir S, Isac I. Phase transitions in phospholipid vesicles Fluorescence polarization and permeability measurements concerning the effect of temperature and cholesterol. Biochim Biophys Acta (BBA)-Biomembranes. 1973; 311(3):330-48. https://doi.org/10.1016/0005-2736(73)90314-3.
131. Turunen TM, Urtti A, Paronen P, Audus KL, Rytting JH. Effect of some penetration enhancers on epithelial membrane lipid domains: evidence from fluorescence spectroscopy studies. Pharmaceutical research. 1994 Feb;11:288-94.
132. Clancy MJ, Corish J, Corrigan OI. A comparison of the effects of electrical current and penetration enhancers on the properties of human skin using spectroscopie (FTIR) and calorimetric (DSC) methods. International journal of pharmaceutics. 1994 Apr 25;105(1):47-56.
133. Kitagawa S, Sawada M, Hirata H. Fluorescence analysis with diphenylhexatriene and its ionic derivatives of the fluidity of liposomes constituted from stratum corneum lipids: Contribution of each lipid component and effects of long-chain unsaturated fatty acids. Int J Pharm. 1993; 98(1-3):203-8. https://doi.org/10.1016/0378-5173(93)90057-M
134. Ongpipattanakul B, Burnette RR, Potts RO, Francoeur ML. Evidence that oleic acid exists in a separate phase within stratum corneum lipids. Pharm Res. 1991; 8:350-4. https://doi.org/10.1023/A:1015845632280 PMid:2052523
135. Naik A, Pechtold LARM, Potts RO, Guy RH. Mechanism of oleic acid-induced skin penetration enhancement *in vivo* in humans. J Control release. 1995; 37(3):299-306. https://doi.org/10.1016/0168-3659(95)00088-7
136. Gwak HS, Chun IK. Effect of vehicles and enhancers on the *in vitro* skin penetration of aspalatone and its enzymatic degradation across rat skins. Arch Pharm Res. 2001; 24:572-7. https://doi.org/10.1007/BF02975168 PMid:11794538
137. Bhatia KS, Singh J. Synergistic effect of lontophoresis and a series of fatty acids on LHRH permeability through porcine skin. J Pharm Sci. 1998; 87(4):462-9. https://doi.org/10.1021/js970301f PMid:9548900
138. Cho YA, Gwak HS. Transdermal delivery of ketorolac tromethamine: effects of vehicles and penetration enhancers. Drug Dev Ind Pharm. 2004; 30(6):557-64. https://doi.org/10.1081/DDC-120037486 PMid:15285328
139. Gwak HS, Kim SU, Chun IK. Effect of vehicles and enhancers on the *in vitro* permeation of melatonin through hairless mouse skin. Arch Pharm Res. 2002; 25:392-6. https://doi.org/10.1007/BF02976645 PMid:12135116
140. Chisty MNA, Bellantone RA, Taft DR, Plakogiannis FM. *In vitro* evaluation of the release of albuterol sulfate from polymer gels: effect of fatty acids on drug transport across biological membranes. Drug Dev Ind Pharm. 2002; 28(10):1221-9. https://doi.org/10.1081/DDC-120015355 PMid:12476868
141. Dimas DA, Dallas PP, Rekkas DM. Use of an 8132 asymmetrical factorial design for the *in vitro* evaluation of ondansetron permeation through human epidermis. Pharm Dev Technol. 2004; 9(1):39-48. https://doi.org/10.1081/PDT-120027416 PMid:15000465