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A Review on Terpenes Permeation Enhancement Based on the Lipophilicity of the Drugs

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ABSTRACT

Terpenes are chief constituents of essential oils. These are very widely used as permeation enhancers in transdermal formulations. These are made up of several isoprene units (C_5H_8) and are classified based on the number of isoprene units. Monoterpenes contain two isoprene units $C_{10}H_{16}$, sesquiterpenes contain three isoprene units $C_{15}H_{24}$, Diterpenoids contain four isoprene units $C_{20}H_{32}$, Triterpenoids contain six isoprene units $C_{30}H_{48}$, Tetraterpenoids contain eight isoprene units $C_{40}H_{64}$. They are further divided into acyclic, monocyclic, bicyclic etc., based on the number of carbon atoms present. In the present article a review on different types of terpenes is given based on the lipophilicity of the drug.

Keywords: Terpenes, Isoprene units, Monoterpenes, Carbon atoms, Lipophilicity

INTRODUCTION

Salient "barrier properties" of outermost layer of skin stratum corneum has always been a challenge in delivery of drugs through skin. Transdermal drug delivery system offering significant clinical benefits over other dosage forms has become a proven technology in last two decades. It not only offers controlled and predetermined rate of release of drug into the patient, but also maintains steady state blood concentration. It's a desirable form for drug delivery because of its obvious advantages [1-3] such as

- Avoidance of first pass metabolism.

- Predictable and prolonged duration of action.
- Minimizing side effects that are undesirable.
- Utility of shorter half-life drugs.
- Improving physiological and pharmacological response.
- Avoiding the variation in drug levels, inter-and intra-patient variations.
- And most importantly, providing patients compliance [4,5].

Numerous methods have been employed to mitigate stratum corneum permeability and the most commonly used approach is of sorption promoters, also known as penetration enhancers [2].

Absorption of the drug through the skin is enhanced by the permeation enhancers provisionally by quickly enhancing the skin penetrability. Their function is to transfer the drugs that are ionizable (Example: timolol maleate), unaffected (Example: heparin); and also maintain drug levels in blood, higher dose of less possibly active drugs (Example: Oxymorphone), and to transport high molecular weight hormones and peptides and to reduce the lag time of transdermal delivery system [6,7] (Figure 1).

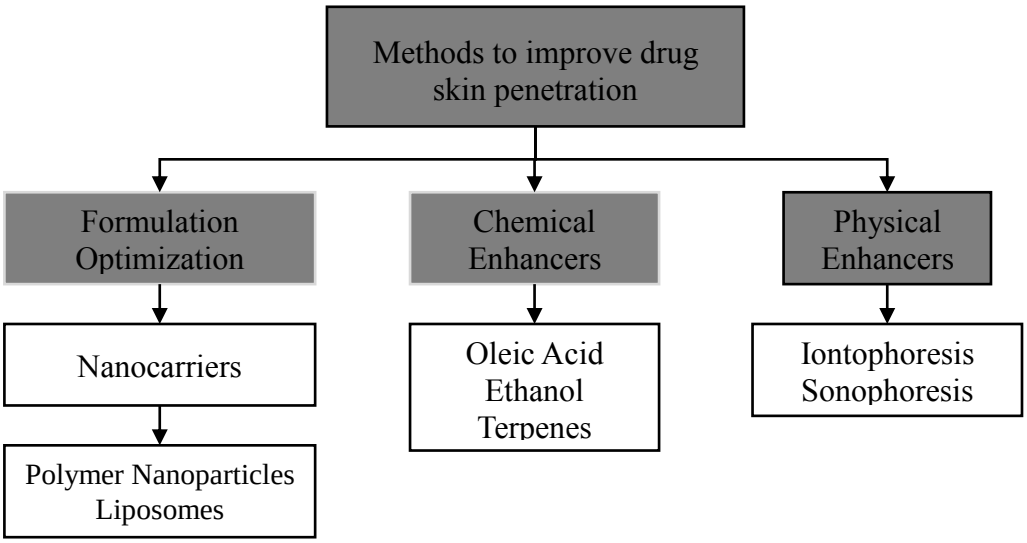


Figure 1: Diverse approaches for improving drug penetration.

Terpenes

Terpenes are transdermal permeation enhancers used in transdermal preparations for simplifying penetration of drugs [3]. These are extractions of essential oils containing hydrocarbons that occur naturally (based on combinations of isoprene units) [8]. They apparently have less toxicity, high percutaneous enhancement abilities and low cutaneous irritancy at low concentrations (1-5%) [9,10]. Terpenoids differ from terpenes in having an additional functional group along with hydrocarbons. These form the main constituents of essential oils derived from medicinal plants and flowers. These are used as fragrances in perfumery, as flavours (in food additives), as penetration enhancers in medicines and aromatherapy.

They are defined as natural products whose structures that are divided into several isoprene units; hence they are also termed as isoprenoids. Each such unit consists of five-carbons having two unsaturated bonds with a branched chain. Apart from carbon and hydrogen, terpenes also contain oxygen such as in carvone, α-thujone, menthol etc., [11].

General formula of natural terpenoid hydrocarbon is $(C_5H_8)_n$. They are classified based on number of carbon atoms present and on chemical group present (alcohol esters ketones etc.,) [12]. Terpenes are obtained from the plants and are volatile in nature. Plants that have compounds like terpenes often possess smells and flavours pleasing and are known as aromatic herbs. These are used all around the world, not only for perfumery and cooking, but also as medicine [13] (Tables 1 and 2).

Table 1: Classification based on number of carbon atoms.

Name of terpenoids	No. of isoprene units	Molecular formula	Examples
Monoterpenoids	Two isoprene units	$C_{10}H_{16}$	Linalool
Sesquiterpenoids	Three isoprene units	$C_{15}H_{24}$	Farnesol
Diterpenoids	Four isoprene units	$C_{20}H_{32}$	Taxol
Triterpenoids	Six isoprene units	$C_{30}H_{48}$	Squalene
Tetraterpenoids	Eight isoprene units	$C_{40}H_{64}$	Carotenoids

Each class is further sub-divided into sub-classes based on number of rings present in the structure (Tables 1 and 2).

Acyclic terpenoids: They contain open structure.

Monocyclic terpenoids: They have one ring in their structure.

Bicyclic terpenoids: They have two rings in their structure.

Tricyclic terpenoids: They have three rings in their structure.

Tetracyclic terpenoids: They have four rings in their structure [2].

Table 2: Classification based on chemical group.

Alcohols	Linalool
Esters and Alcohols	Linalool, Menthol
Aldehydes	Cinnamic Aldehyde
Ketone	Carvone
Phenols	Thymol
Ethers	Anethol
Peroxides	Ascaridole

Mechanism of action

The mechanism of action of terpenes is interruption of the hydrogen bond network at the ceramides in the lipid bilayer and thereby enhances the permeation of the drug. This has been demonstrated by works based on Differential Scanning Calorimetry (DSC) and FT-IR Fourier Transform Infrared Spectroscopy [14]. DSC provides data about changes in stratum corneum on interaction with the terpenes while FT-IR gives details of molecular and conformational changes [2]. Penetration enhancer mechanisms:

1. Disruption of stratum corneum lipids.
2. Interaction with intercellular proteins.
3. Improvement in partitioning of the drug into the stratum corneum.

Composition of terpene is based on the following factors

Lipophilicity

Lipophilicity of the terpene plays a significant role in defining the penetration enhancement effect. It is projected that, terpenes such as limonene which is hydrocarbon in nature exhibit a better penetration enhancement effect for lipophilic drugs (Indomethacin) [2], and conversely, the polar group containing terpenes such as menthol, 1,8-cineole, provide a well penetration enhancement effect for hydrophilic drug (Alfuzosin hydrochloride) [15-17].

Concentration of terpene

Terpenes were applied in a range of 1% to 5% in TDDS as they have less toxicity, high percutaneous absorption and low irritancy. The optimum concentration may be different for different terpenes. With the increase in the terpene concentration penetration enhancement increases drastically. Though, the penetration of the drug was not significantly improved with the further increase in terpene concentration. The increase can be accredited to the ability of the terpene to modify the skin barrier properties, while the decrease could be accredited to the interaction between terpene and the drug [10].

Chemical structure of the terpene

Percutaneous absorption of hydrophilic drugs is better enhanced by terpenes with polar functional groups. This is due to the interaction of the amide groups of the SC ceramides more competitively than the terpenes with a carbonyl group. Due to this disruption it facilitates the diffusion of drugs through the SC [2,17]. The chain structure of a terpene might increase the penetration enhancement effect better than a ring structure [2]. Less effect of penetration was observed in terpenes with a ring structure (menthol and camphor) when compared to terpenes with a long chain alkyl structure such as nerolidol and oleic acid [18-20].

Boiling point of terpenes

The boiling point of terpene is inversely related to its skin permeation enhancing capacity. e.g., Cineole has boiling point of 173°C is an effective enhancer for the skin permeation of zidovudine when compared to other terpenes with higher boiling point. (Carvone 230°C, Menthone 210°C, Menthol 215°C) [2,21].

Vaporization of terpenes

Terpenes with lower energy of vaporization show greater permeation than those with high energies of vaporization towards hydrophilic drugs (5-fluorouracil) [22,23].

Definite study of different terpenes

Nerolidol

Nerolidol (3,7,11-trimethyl-1,6,10-dodecatrien-3-ol), also known as peruviol. It is a natural sesquiterpene [24-40] alcohol present in the essential oils of various plants with a floral odour [41-46]. Nerolidol was found to exist as one of the bioactive compounds which are responsible for the biological activities demonstrated by essential oils of the plants [24]. Data showed that the worldwide usage of nerolidol per annum ranges from 10 to 100 metric tonnes [47]. For example, [24] nerolidol is often incorporated in cosmetics (e.g., shampoos and perfumes) and non-cosmetic products (e.g., detergents and cleansers) [24,46]. It is also widely used in the food industry as a flavour enhancer [24] since it is approval by U.S. Food and Drug Administration as a safe food flavouring agent [48].

Ayman Kattan et al., studied the percutaneous permeation of hydrocortisone alcoholic hydrogel (HC) on hairless mouse skin [11] using a diffusion cell technique. It contained one of 12 terpenes and their selection [14] was based on their lipophilicity (log P 1.06-5.36). In this study Flux, cumulative receptor concentrations, skin content, and lag time of HC [11] were measured. It was then compared with the control gels (containing no terpene). Additionally, the enhancing effect of the terpene was determined by the HC skin [11] content and the solubility of HC in the alcoholic hydrogel solvent mixture.

Study trials of *in-vitro* penetration have revealed mixed results of terpene [14] enhancement in hairless mouse skin. This was attributed to their ability to enhance the flux of HC. Greatest enhancement for HC flux (35.3-fold over control) was seen with Narolidol with its highest lipophilicity (log P=5.36 ± [11] 0.38). Fenchone with low lipophilicity (log P=2.13 ± 0.30) has the

[11,14] lowest enhancement of HC flux (10.1-fold over control) [23]. Investigation primarily to study the effect of terpenes (menthone, limonenoxide, carvone, nerolidol and farnesol) with different concentrations (0.25, 0.5, 1.5 and 2.5%, v/v) on transdermal absorption of diclofenac sodium by ethanol; glycerine; phosphate buffer solution in ratio of 60:10:30 was carried out using Franz diffusion cells fitted with rat skin and evaluated. Additionally, solubility property of diclofenac sodium using different concentrations of terpenes was also investigated.

The results showed that though there was a profound skin penetration and a negligible effect of terpenes on the drug solubility. The results showed that for diclofenac sodium the effect of enhancement was highest (nerolidol>farnesol> carvone>menthone>limonen oxide). Nerolidol had highest penetration effect of 198-fold increase in permeability coefficient of diclofenac sodium followed by farnesol with a 78-fold increase [5,24,28].

Farnesol

Farnesol is a 15-carbon complex. It is an acyclic sesquiterpene alcohol. It is a colourless liquid, hydrophobic in nature and thus insoluble in water, but miscible with oils. Farnesol can be extracted from essential oils such as citronella, neroli, cyclamen, lemon grass, tuberose, rose, musk, balsam and tolu. It is used in perfumery for sweet floral scent [28]. Method for enhancing perfume scent is by a co-solvent that controls the volatility of the odorants. It is especially used in the lavender perfumes. It is also used as a natural pesticide for mites [28,33] and for several other insects. It has been recommended to function as a chemo preventive and anti-tumour agent [25]. It is being used as a deodorant in cosmetic products because of its anti-bacterial activity [28]. The enhancement effect for diclofenac sodium given by Anna Herman et al. was that at the concentration of 0.25% the rank of order of terpenes was farnesol>carvone>nerolidol>menthone>limonene [5,11,26,44].

Limonene

Limonene a clear, colourless liquid hydrocarbon (chiral molecule) is classified as a cyclic monoterpene and is the major constituent of citrus fruit peels [49]. Citrus fruit contains D-limonene (+)-limonene), which is the (R)-enantiomer. Racemic limonene is known as dipentene [50]. Centrifugal separation or Steam distillation is the two methods from which D-Limonene is obtained from citrus fruits commercially. D-Limonene is safe for humans' use [51], but when applied on skin may cause irritation.

In their work Lim, et al., concluded that limonene was more effective than oxygenated linalool and cineole (in combination with propylene glycol) for improving the permeability of haloperidol. It was done across female human abdominal skin. Limonene enhanced the penetrability of haloperidol 26.5-fold and reduced the lag time of haloperidol transport whereas linalool and cineole showed only moderate enhancement and prolonged lag time [27]. Limonene was reported to have a superior penetration value for dihydrotestosterone into hairless rat skin compared to oleic acid [28].

In an investigation by Moghimi et al., where terpenes of 4 diverse chemical classes, namely hydrocarbons (d- limonene), alcohols (geraniol), epoxides (pinene oxide) and cyclic ethers (1, 8-cineole) were used for pre-treatment of third-degree burn Escher from abdominal and lower external burns the permeation flux of silver sulphadiazine (anti-microbial drug), was improved. The enhancement ratio was found to be highest for limonene (about 9 times the normal flux), followed by geraniol (5.5 times) pinene oxide (4.3 times), eucalyptus oil (4.7 times) and α-pinene oxide (4.3 times). Terpenes showed a slight increase in permeation lag-

times while limonene had a 20% decreases in the lag time. The better partition of the drug into the Eschar can be attributed to the increased permeation of silver sulphadiazine. Both increased diffusion coefficient as well as partitioning play a role when terpenes were used on intact skin [29]. Ketoprofen was investigated for percutaneous permeation of two systems (d-limonene and oleic acid). Percutaneous absorption was higher with d-limonene, but it also produced greater skin damage. In case of verapamil hydrochloride, a higher concentration of d-limonene (20%) was effective in increasing its permeation significantly [30]. The model drug Finasteride, which is a lipophilic 5-α reductase inhibitor was selected by Prasanthi et al., aimed to evaluate *in-vivo* iontophoretic transdermal drug delivery of novel lipid-based vesicular carriers (invasomes). Formulation IF1 containing lipophilic terpene limonene (0.5%) enhanced permeation by 21.17-fold when compared with control (aqueous solution) in rat kin [31].

Curcumin has bioavailability problems with poor aqueous solubility. Lakshmi et al., increased the solubility of curcumin was by complexing with cyclodextrin (CD) and Hydroxy propyl β cyclodextrin (HPβCD) [18]. This was later formulated as invasomes and then incorporated into HPMC gel to prepare as a transdermal preparation. Curcumin cyclodextrin complexes were [18] prepared by physical mixture and co-precipitation method. Invasomes containing 0.5% limonene, 1.0% fenchone, 1.5% nerolidol were individually prepared using mechanical dispersion technique.

Invasomal preparation with 0.5% limonene, 4% ethanol was found to improve the permeation by 8.11 times the control. *In vivo* diffusion studies, [18] *ex vivo* skin permeation studies conducted on CHL1 using rat abdominal skin showed cumulative drug permeation (Q24) of 70.32 mcg/cm, steady state transdermal flux of 3.344 mcg/cm^2 /hr, permeability coefficient of 5.35 cm/hr and lag time of 1 hr when compared with control formulation. [32].

The aim of the research done by Mounika K et al., was to study the permeation of lipophilic drug lamotrigine (LTG) by means of terpenes as permeation enhancers. Transdermal patches were prepared using permeation enhancers namely nerolidol, limonene, linalool, carvone, fenchone, menthol, geraniol, farnesol. LTG patches were prepared by solvent casting method. Research showed the order of cumulative percentage drug release to be limonene>fenchone>linalool>menthol>geraniol>carvone>nerolidol>farnesol. Formulations LLH3Lm (2.5%), [26] LLH3Lm (5%) with Eudragit RL100, HPMC E15LV at 2.5% and 5% limonene concentration showed optimum drug release, improved permeability, decreased lag time (P=0.001) and steady state transdermal flux compared to control formulation. [26,33].

Linalool

Linalool (3,7-dimethyl-1,6-octadien-3-ol) found in large quantities in several plant species is one of the most significant compounds for perfume and flavour industries. Since linalool is a significant intermediate in the production of vitamin E, large-scale processes have been developed for its production. It is used frequently in perfumery and many flowery fragrance compositions for fruity fresh odours like neroli, lavender, lily of the valley [52,53].

The penetration enhancement capacity of haloperidol (HP) was compared by Vaddi et al., in the alcoholic terpenes carvacrol, linalool, and α-terpineol at 5% w/v in propylene glycol (PG) to increase the *in vitro* permeation through human skin. The molecular orientation within the lipid layer is attributed to the increased penetration with linalool. The HP-stratum corneum (SC)

binding studies elucidated the enhancement mechanism along with Fourier transform infrared spectroscopy, and differential scanning calorimetry [34].

Geraniol

Geraniol is a commercially significant terpene alcohol in the essential oils of several aromatic plants. It is one of the most vital molecules in the flavour and fragrance industries and also in the products produced by the industries. In addition to its pleasing odour, it also exhibits insecticidal and repellent properties and used as a natural pest control agent showing low toxicity. It has been suggested to characterize a new class of chemoprevention agents for cancer. Other biological activities such as antimicrobial, anti-inflammatory and some anti-oxidant effects have also been explored [54,55]. It is a monoterpenoid alcohol.

The enhancing effect of permeation enhancer which included geraniol, cis-nerolidol, (-)-Menthol, thymol, 1,8-cineole, menthone, (-)-fenchone and (+)-limonene were investigated [56-58]. *In-vitro* percutaneous absorption of diclofenac sodium across abdominal male Wistar rat skin from carbomer gels containing propylene glycol was examined. The results indicated that the alcohol terpenes were efficient penetration enhancers for better penetration of diclofenac sodium. The results also indicated Geraniol having best penetration property for diclofenac sodium's permeability coefficient with nearly 20-fold increase. It was followed by nerolidol (14-fold increase) and menthol (11-fold increase). Thymol was proved to be inefficient as it was an aliphatic alcohol. It showed a slight increase with limonene (hydrocarbon terpene); whereas fenchone and menthone (ketone terpenes) were less effective and the oxide terpene (1,8-cineole) proved to be a poor penetration enhancer. The acyclic terpenes, geraniol and nerolidol, showed the best enhancing effects of the alcohols tested. The presence of hydrocarbon tail groups besides a polar head group makes the structures of these terpenes suitable for disordering the lipid packing of the stratum corneum [35].

Godwin, et al., investigated eleven monoterpenes including (+)-limonene, (-)-menthone, (+)-terpinen-4-ol, α-terpineol, 1,8-cineole, (+)-carvone, (-)-verbenone, (-)-fenchone, p-cymene, (-)-neomenthol and geraniol for increased permeation of caffeine through hairless mouse skin. Geraniol was proved to be the most effective penetration enhancer when compared to the other monoterpenes.

Hydrocortisone and triamcinolone acetonide were selected as the model drugs to give a range of drugs with diverse lipophilicities. 1 hr prior to the application of the drug suspension terpenes were applied at 0.4 M in propylene glycol. Significant enhancement of caffeine was reported with Propylene glycol pre-treatment; therefore, geraniol showed an enhancement ratio of 1.76 followed by (+)-neomenthol with a 1.52-fold increase after subtracting the effect of propylene glycol on the penetration of caffeine [36].

Carvone

Carvone is a terpenoids [55]. Carvone is found abundantly in the essential oil from seeds of caraway, spearming (Mentha spicate) and dill [56]. It is used both in the food and flavour industry. It is also used for air freshening products. They are used in aromatherapy and substitute medicine. Mahfuzelmastas et al., showed that S-carvone which was isolated from metha spicate (Fam. Lamiacear) was purified using chromatographic methods, and characterized with GS-MS, FTIR, and NMR techniques. The *in-vitro* studies were performed to evaluate the antioxidant activity of S-carvone. Results were compared with a standard antioxidant, α-tocopherol and they indicate that S-carvone possess high antioxidant activity compared to α-tocopherol [37].

Krishnaiah et al., showed that carvone when employed as penetration enhancer at concentration of 8% (w/w) in a membrane-moderated transdermal therapeutic system of nicardipine hydrochloride which increased by 3-fold with reference to an immediate release capsule dosage form in healthy male volunteers [38].

In another study carvone-based transdermal therapeutic systems (TTS) of nicorandil was prepared. *In-vivo* controlled release profile on dermal application on human volunteers was studied. The *in-vitro* permeation of nicorandil from a carvone based HPMC gel drug reservoir was studied against a control (rat abdominal skin alone) along with the effect of EVA 2825, adhesive-coated EVA 2825 and adhesive coated EVA 2825 (rat skin composite).

The carvone-based drug reservoir system was sandwiched between adhesive-coated EVA 2825-release liner composite and a backing membrane. It was then heat-sealed to produce a circle-shaped TTS (20 cm^2) and was subjected to *in vivo* evaluation on dermal application to human volunteers against oral administration of immediate-release tablets of nicorandil. Steady-state plasma concentration of 20.5ng/ml for ~24 hr in human volunteers was obtained by carvone-based TTS. Desired *in-vivo* controlled release profile of the drug for the predetermined period [39] was obtained by carvone based TTS of nicorandil.

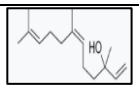
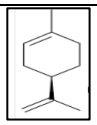
Menthol

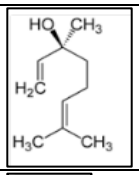
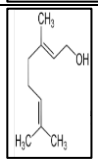
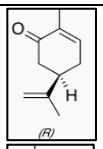
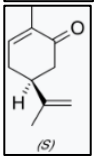
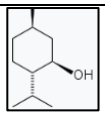
Menthols are naturally occurring compound from plans of the mentha species with typical minty smell and flavour. It is often referred as peppermint oil (from *Mentha pipevita*) or corn mint oil (from *Mentha arvensis*), which is readily extracted from the plant by steam distillation. Menthol is a cyclic terpene alcohol and occurs widely in nature. Very few of such alcohols have chemical properties that make them important for their fragrance of flavour. It is a waxy, crystal-like, clear or white in colour material, which is solid at room temperature and liquefies slightly above. It is widely used for its local anaesthetic and counter irritant abilities for minor throat irritation. Menthol also acts as a weak kappa opioid receptor agonist. Menthol is the most effective penetration enhancer along with limonene. It was used for the drugs such an imipramine hydrochloride [40], propranolol hydrochloride [41], zidovudine [42] etc.

Menthol showed increased skin absorption of testosterone by forming a eutectic mixture with the drug, and thereby [4] lowering its melting point drastically from 153.7°C to 39.9°C, as reflected by Differential Scanning Calorimetry (DSC) [4] studies and increase in solubility and thereby its absorption. Further studies showed the absorption of ceramides and cholesteryl oleate was increased by menthol. Dual mechanism affects skin permeation of menthol: by forming a [4] eutectic mixture with the penetrating compound, thereby increasing its solubility, and by altering the barrier properties of the stratum corneum [43].

Diclofenac is a hydrophobic drug (permeated through lipid pathway in stratum corneum) while it was used as hydrophilic drug (permeated through pore pathways) to study the mechanism of 1-methanol as an enhancer. Results indicated that it enhanced the permeation of both base and salt form of the drug by both the lipid and pore pathways [4,44] (Table 3).

Table 3: Various research on terpenes.

Terpenes	Type	Structure	Boiling Point	Log P	Drug studied	Inference	model	Reference
Nerolidol / Periviol	Sesquiterpene hydrophobic nature		122°C	5.36	Hydrocortisone (HC) Diclofenac sodium	Nerolidol which has the highest lipophilicity (log P=5.36 ± 0.38) provided the greatest enhancement for HC [flux increased 35.3- [5] fold over control] Nerolidol, provided an almost 198-fold increase in permeability coefficient of diclofenac sodium, followed by farnesol with a 78- fold increase	Rat skin Rat skin	23,24
Farnesol	Acyclic sesquiterpene alcohol, hydrophobic		283°C to 284°C	5.31	Diclofenac sodium	For 0.25% concentration of [20] terpenes the rank order was farnesol carvone nerolidol menthone limonene	Rat skin	26
Limonene	Cyclic monoterpene, liquid hydrocarbon, hydrophobic		176°C	4.58	Haloperidol Dihydrotestosterone Ketoprofen Finasteride Curcumin lamotrigine	Permeability of haloperidol increased by 26.5fold Higher penetration when related to oleic acid The enhancement ratio was highest for limonene (about 9 times the normal flux) limonene (0.5%) enhanced permeation by 21.17- [18] fold when compared with control 4% ethanol with 0.5% limonene was found to enhance permeation by 8.11 times the control Formulations LLH3Lm (2.5%), LLH3Lm (5%) with Eudragit RL100, HPMC E15LV at 2.5% and 5% limonene concentration were found to show optimum drug release, improved permeability, steady state transdermal flux and reduced lag time (P<0.001) when related to control	female human abdominal skin hairless Rat skin Rat skin Rat skin Rat abdominal skin Rat abdominal skin	27,28,29,30, 31,32,33

Linalool	Monoterpenoid and alcoholic terpene		198 to 199°C	3.28	Haloperidol	The higher permeation of linalool was attributed to its molecular orientation within the lipid bilayer	Human skin	34
Geraniol	Monoterpenoid and an alcoholic		230°C	3.18	Diclofenac sodium Caffeine Hydrocortisone and triamcinolone acetonide	Geraniol has the best penetration with nearly 20-fold increase in diclofenac sodium's permeability coefficient Most effective penetration enhancer was proved to be geraniol Geraniol exhibited an enhancement ratio of 1.76	Rat skin	35,36
Carvone	Ketone Hydrophobic	 	231°C	1.52	S-Carvone (anti-oxident property) Nicorandil Nicardipine Hydrochloride	Increased anti-oxident property Carvone based TTS provided a steady-state plasma concentration of 20.5ng / ml for ~24 hr in human volunteers At a concentration of 8% nicardipine hydrochloride increased by 3-fold	Human volunteers Human volunteers and rat skin	37,38,39
Menthol	Monoterpene Alcohol		212°C	3.2	Testosterone imipramine hydrochloride propranolol hydrochloride zidovudine	Increase the skin absorption and thereby lowering its melting point by forming eutectic mixture	Rat skin	40,41,42,43, 44

CONCLUSION

From the ancient times terpenes are being used for their therapeutic purpose. In the recent times they are being used as Permeation Enhancers for the delivery of transdermal or transmucosal delivery system. They are safe, non-toxic and non-irritant to the skin. They are the most effective permeation enhancers. Both hydrophilic and lipophilic drugs can be permeated by terpenes like menthol and limonene. Nerolidol was found to increase the penetration effect of hydrophilic drug whereas lipophilic drugs were mostly permeated by limonene. Further research is in progress to harness the enhancement potential of new terpenes.

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