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REVIEW ARTICLE

Permeation Enhancer for TDDS from Natural and Synthetic Sources: A Review

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ABSTRACT

The transdermal drug delivery is now a promising route of drug delivery system. This route has potential advantage of avoiding hepatic first pass metabolism, decrease side effects, gastrointestinal effects, improved patients compliance and increase bioavailability. The major limitation of this route is the difficulty of permeation of drug through skin. The outer most layer of the skin, the stratum corneum provides a protective barrier that prevents the loss of physiologically essential substances and provides greatest resistance to penetration and it is the rate limiting step of percutaneous absorption. Penetration enhancers are the agents which increase the permeability of skin, maintain the drug level in blood and improve the efficacy of drugs. These are nontoxic, inert substances having no therapeutic value but enhance the absorption of drug through skin by different approaches of penetration enhancement, Different studies have been carried out to find safe and suitable permeation enhancer to promote the percutaneous absorption of different drugs. The present review describe synthetic permeation enhancers and natural permeation enhancers with their properties and mechanism of action, it will help in the selection of suitable permeation enhancer for improving the transdermal permeation of poorly absorbed drugs.

KEYWORDS: Transdermal drug delivery system, Permeation enhancer, Natural, Synthetic.

INTRODUCTION

The outer most layer of the skin, the stratum corneum provides a protective barrier that prevents the loss of physiologically essential substances. The stratum corneum provides greatest resistance to penetration and it is the rate limiting step of percutaneous absorption.[1] Penetration enhancers is the agents which increase the permeability of skin. These are nontoxic, inert substances havening no therapeutic value but enhance the sorption of drug through skin by different approaches of penetration enhancement, such as chemical approaches which cause chemical changes by using chemicals such as Pyrrolidones, surface active agents, cyclodextrin, Terpenes, Oxazolidines etc. Physical approaches act by changing the physical properties with the help of techniques such as, Radiofrequency, Pressure waves, Electroporation, Magnetophoreses etc. enhancining the percutaneous penetration of therapeutic agents.[2] The success of a dermatological drug to be used for systemic drug delivery depend upon the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect.[3]

STRUCTURE OF SKIN:

Skin is the multilayered organ composed of four tissue layers, the outermost layer Stratum corneum, the epidermis, the dermis, and the subcutaneous tissue. Stratum corneum (non- viable epidermis), the outermost layer of the skin and is responsible for the barrier function of skin. The stratum corneum consists of lipid (5-15%), protein (75-85%) which is mainly keratin. These may act as buffer and protect the skin from the action of acid and alkalis. Epidermis: This layer resides between the stratum corneum and dermis. And has thickness ranging from 50-100µm. The water content is about 90%. Dermis: This layer is just beneath the epidermis and is made up of a network of robust collagen fibres of fairly uniform thickness with regularly spaced cross-striations. And this layer is responsible for the elastic properties of skin. Subcutaneous tissue: This is the sheet of fat containing areolar tissue, known as the superfacial facia, attaching the dermis to the underlying structure.[4]

PATHWAY OF TRANSDERMAL PERMEATION:

Permeation can occur by diffusion via

1. Transdermal permeation, through the stratum corneum.

2. Intercellular permeation, through the stratum corneum.

3. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands.

Most molecules penetrate through skin via intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architechure.[5]

Simplified model of the human skin for mechanistic analysis of skin permeation

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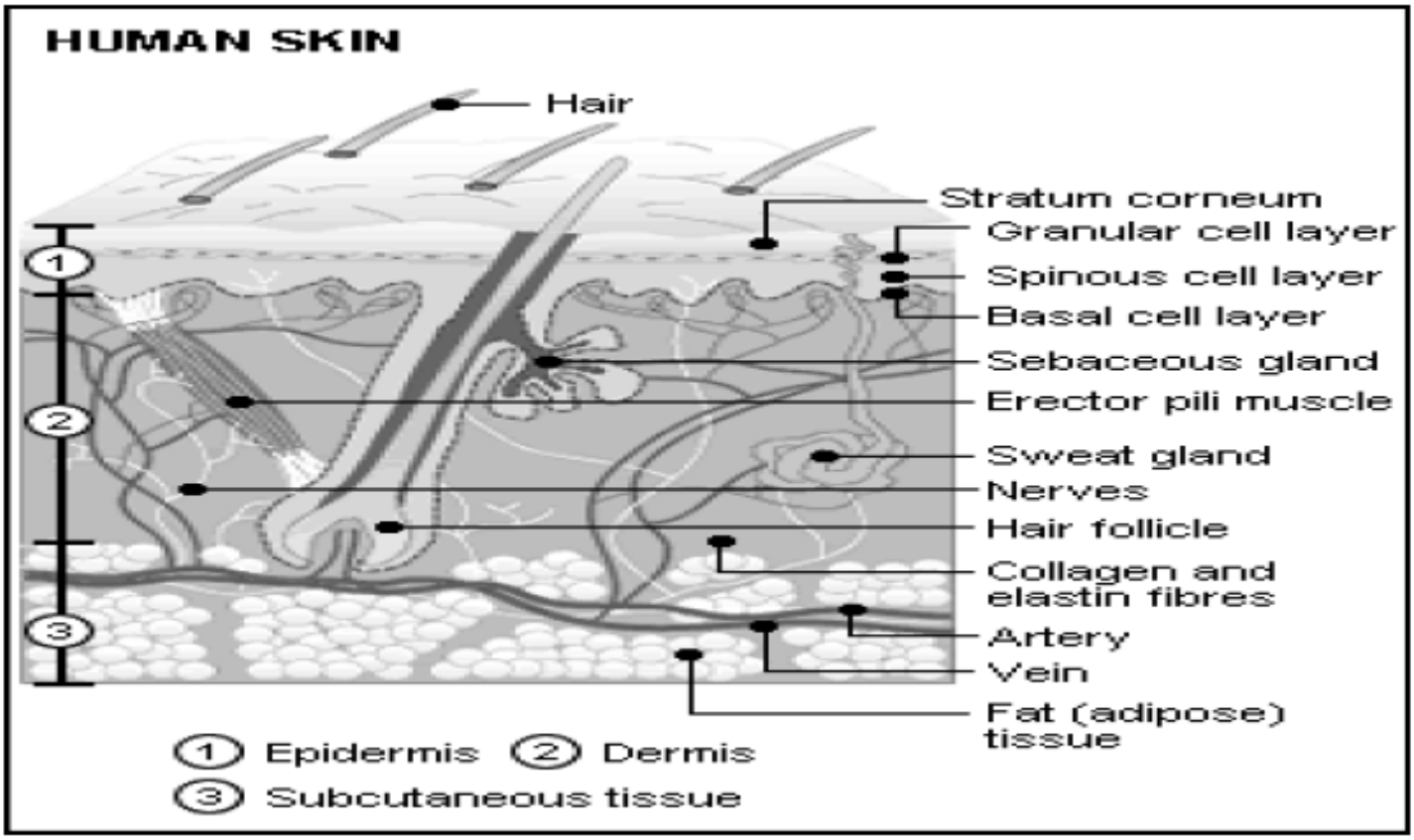


Figure1: Structure of skin

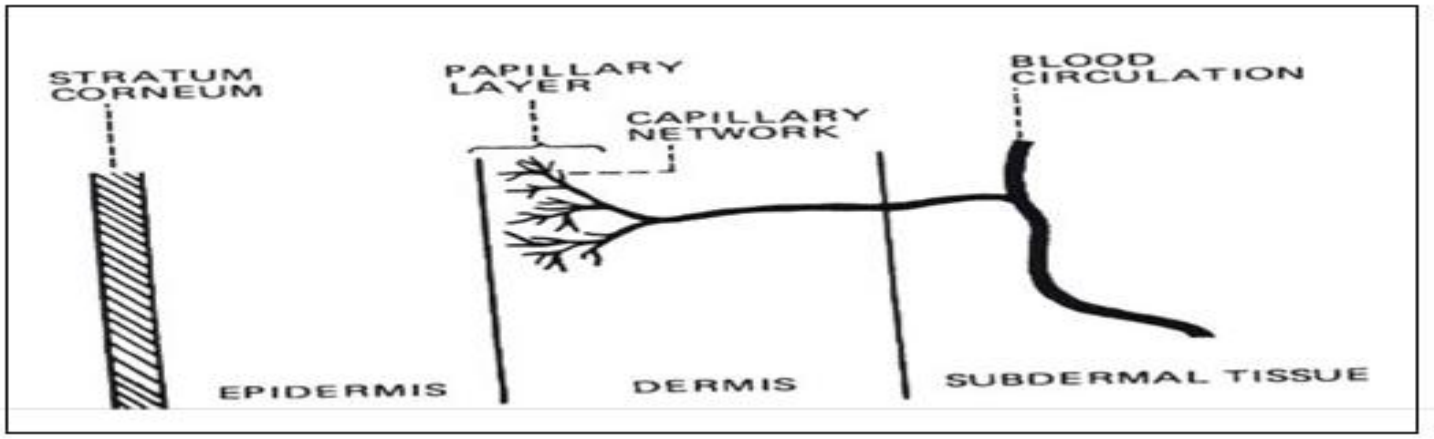


Figure 2: Pathway of transdermal permeation

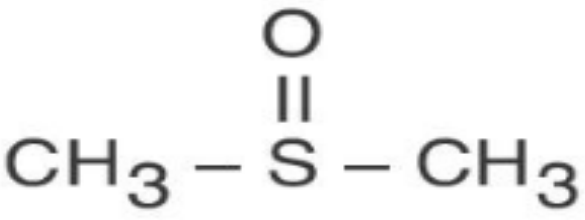
PERMEATION ENHANCERS:

There is great interest among pharmaceutical scientist to develop chemical permeation enhancers, natural permeation enhancers and physical method that can increase percutaneous absorption of therapeutic agents.[6]

SYNTHETIC PERMEATION ENHANCERS:

Chemical substances temporarily diminishing the barrier of the skin and known as accelerants or sorption promoters can enhance drug flux. many classes of chemical permeation enhancers used including sulfoxides, azoneanalogues, fatty acids, oxazolidinones, pyrrolidones, surfactants etc.[7]

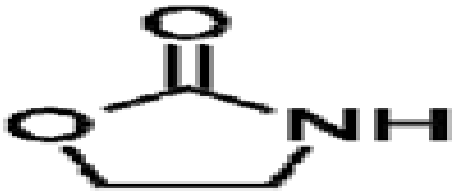
SULPHOXIDES AND SIMILAR COMPOUNDS:



Methylsulfinylmethane

Dimethyl sulfoxide (DMSO) is a molecule with a long history in pharmaceutics and is now well established as a penetration enhancer in topical pharmaceutical formulations. It is currently used for this purpose in diclofenac sodium topical solution and idoxuridine topical solution. This article reviews the mechanism of action of DMSO as a pharmaceutical penetration enhancer, the characteristics of the molecule that facilitate transdermal drug delivery, and studies of efficacy and safety. Dimethyl sulfoxide is a safe and effective mechanism for facilitating the transdermal delivery of both hydrophilic and lipophilic medications to provide localized drug delivery.[8] The permeation enhancers, DMSO at a concentration of 10% (w/w) has shown an improvement in the Transcutaneous Permeation of Alfuzosin HCl.[9] The insulin-loaded microemulsion containing 10% oleic acid, 38% aqueous phase, and 50% surfactant phase with 2% DMSO as permeation enhancer showed maximum permeation flux and can be transdermally administered in the treatment of insulin-dependent diabetes mellitus with improved patient compliance.[10] It was reported that peneteration enhancer DMSO is used for tradsdermal drug delivery for ACV Increased percentage of DMSO 10% as compared to 5% in aqueous solution enhanced transdermal flux 2.36 fold greater.[11] The DMSO is useful for enhancing the skin permeability of acyclovir from transdermal therapeutic system containing carbopol 934 gel as acyclovir.[12]
Decylmethyl sulfoxide (DCMS) in combination with ethanol increase the flux of oxymorphone hydrochloride.[13]

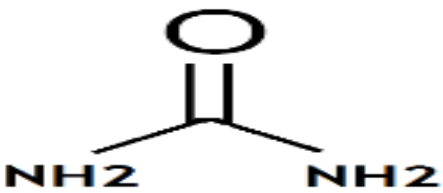
OXAZOLIDINONES:



1,3-oxazolidin-2-one

The influence of a permeation enhancer on the properties of phospholipid black foam films has been studied and the permeation enhancer is said to optimize the delivery of active ingredients into through the stratum corneum.The evaluation of the coefficient of gas permeability with 4-decyl oxazolidin-2-one concentration is also addressed.[14]

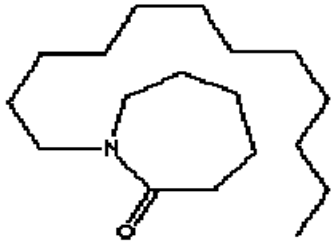
UREA:



Diaminomethanol

It promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and non toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism.[15]

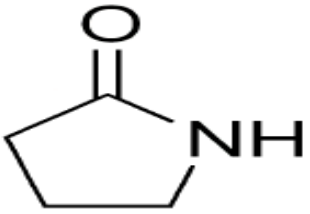
AZONE:



1-dodecylazacycloheptan-2-one

Azone is an effective penetration enhancer for the percutaneous delivery of certain topically applied drugs. Fundamental physicochemical experiments have been performed to elucidate the mechanism of action of Azone, the penetration enhancing effect of Azone is believed to be due to its increasing the fluidity of the intercellular lipid bilayers of the stratum corneum. Phospholipid vesicles were chosen as a simple model to represent these bilayers. The effect of Azone on phase transition temperature and lipid fluidity was studied using turbidity and fluorescent probe (pyrene excimer) technique. [17]
The influence of 1-dodecylazacycloheptan-2-one (Azone) on the *in vitro* permeation of hairless mouse skin and human epidermis by hydrocortisone was studied.[18]

PYRROLIDONES:



2-Pyrrolidone

Pyrrolidones used as penetration enhancers for numerous molecules including hydrophilic (mannitol and 5-flurouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-pyrolidone was employed with limited success as a permeation enhancer for captopril when formulated in a matrix type transdermal patch.[19] The enhancing effect of pyrrolidone derivatives on the percutaneous penetration of sulfaguanidine,

aminopyrine and sudan III was investigated using in vitro technique and excised rat skin. 1-Methyl (MP), 1-hexyl (HP) and 1-lauryl-2-pyrrolidone (LP) were used as penetration enhancers. Aminopyrine showed high penetration through skin although sulfaguanidine and sudan III showed little penetration. Pyrrolidone derivatives enhanced their penetrations. Especially HP and LP enhanced the penetration of sulfaguanidine to a high extent. Sudan III was not detected in the receptor phase regardless of the presence of enhancer. Pyrrolidone derivatives significantly increased the skin accumulation of sulfaguanidine, aminopyrine and sudan III. Penetration of pyrrolidone derivatives was also determined. These results suggested the usefulness of pyrrolidone derivatives as percutaneous penetration enhancers.[20]

ALCOHOL, GLYCOL, AND GLYCERIDES:

Ethanol is the most commonly used alcohol as a transdermal penetration enhancer. It increases the permeation of ketoprofen from a gel-spray formulation and triethanolamine

salicylate from a hydrophilic emulsion base.[21] It also acts as a vehicle formenthol in increasing the penetration of methyl paraben.[22] Ethanol in combination with TCP and with water were used as two cosolvent systems for water were used as two cosolvent systems for zalcitabine, didanosine, zidovudine, tegafur, alclofenac and ibuprofen. The permeation rate of zalcitabine, didanosine and zidovudine increased as the volume fraction of ethanol in the two cosolvent systems was increased, and it reached a maximum at 50–60% v/v of ethanol.[23] Flux of tegafur, alclofenac, and ibuprofen was higher from the ethanol-water cosolvent system than from the ethanol-TCP system.[24] A saturated solution of terpenes in a PG-water cosolvent system enhanced the flux of 5-FU, terpene activity being dependent on PG content and with the maximum flux obtained from formulations containing 80% PG. Also, PG increases drug partitioning and drug permeation. PG, in combination with azone, enhancers on the permeation of BPL across rat skin was studied using side-by-side diffusion cells. Pyrrolidones and menthol at low concentrations (5% w/v or less) and PG at 30% w/v concentration were effective as penetration enhancers for BPL.[28] Urea analogues were effective in enhancing the permeation of 5-FU only when PG was used as a vehicle. Short-chain glycerides are also effective as permeation enhancers (e.g., TCP). For instance, glycerine tricaprylate (caprylic acid triglyceride) in combination with ethanol is used as a solvent system.[29] TCP is an excellent hydrophobic vehicle and promoted the permeability of tegafur combined with ethanol. Glyceryl monocaprylate enhanced the partitioning of papaverine across hairless rat skins.[30] Sefsol 318, a medium-chain glyceride, increased the permeation of papaverine hydrochloride by almost 820 times by increasing the fluidity of the lipoid membrane of the stratum corneum.[31]

CYCLODEXTRINS:

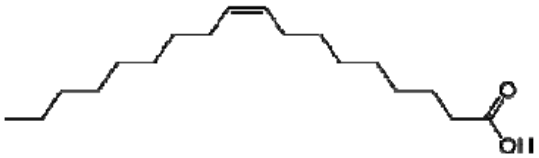
Cyclodextrins (CDs) constitute a class of penetration enhancers that have advantages over other conventional penetration enhancers. Some CD derivatives form complexes with drug molecules to quickly establish equilibrium with free molecules of drug in the formulation, resulting in increased availability. [32]

It was concluded that cyclodextrins act as permeation enhancers carrying the drug through the aqueous barrier, from the bulk solution towards the lipophilic surface of biological membranes where the drug molecules partition from the complex into the lipophilic membrane.[33]

ALKYL-n, n-Disubstituted Amino Acetates:

New alcohol derivatives of N,N-disubstituted amino acids with a low toxicity have been synthesized and evaluated for their transdermal penetration enhancing effects on the transport of indomethacin from petrolatum ointments across shed skin of black rat snake (Elaphe obsoleta). The derivatives show excellent penetration enhancement of indomethacin, as high as 3.8 times that of Azone. Experiments involving the pretreatment of the snake skins with dodecyl N,N-dimethylamino acetate indicated that pretreatment of the skin increased the skin permeability significantly.[34]

FATTY ACIDS AND ESTERS:



(9Z)-Octadec-9-enoic acid

A large number of fatty acids and their esters have been used as permeation enhancers. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. It was reported that an increase of 6.5-fold to 17.5-fold in the permeation rate of flurbiprofen through rat skin by unsaturated fatty acids, while no significant increase was observed with saturated fatty acids.[35] Moreover, they have a greater enhancing effect on lipophilic drugs. Addition of oleic acid to an Ethanol: water (50:50) cosolvent system markedly improved the skin

permeation of zalcitabine, didanosine and zidovudine whereas addition of the same to ethanol:TCP (50:50) produced no enhancement across hairless rat skin. It was suggested that viscous TCP reduced the thermodynamic activity of oleic acid.[36] It was reported that the except saturated FA-PG and alpha-linolenic acid C18:3(n-3)-PG mono-conjugates, unsaturated fatty acids (e.g.oleic and linoleic acids) after conjugation to PG may be safe and effective enhancers for delivering topical drugs.[37] The combined effect of oleic acid and propylene glycol on the percutaneous penetration of Tenoxicam and its retension in the skin.[38] The effects of pretreatment period with 80% dimethyl sulfoxide (DMSO) and 10% oleic acid in propylene glycol (PG) on the percutaneous absorption of piroxicam from its gel form through rabbit abdominal skin were investigated.[39] It was reported that the penetration enhancers for the transdermal permeation of melatonin was enhanced by all saturated and unsaturated fatty acids across both rat and porcine skin. There was a parabolic relationship between the carbon chain length of saturated fatty acids and the enhancement of melatonin permeation across rat and porcine skin. For rat skin, the maximum flux was observed with undecanoic acid (45.33 μg cm^{-2} h^{-1})which enhanced the flux of melatonin 8.6 times compared with the control, whereas lauric acid produced the maximum flux of melatonin (24.98 μg cm^{-2} h^{-1}; 4-7 times); times across porcine skin.[40] It was reported that the effects of fatty acids commonly present in cosmetic and topical formulations on permeation enhancement across human epidermal membrane (HEM) lipoidal pathway when the fatty acids saturated the SC lipid domain without cosolvents (*Emax*).[41] The skin permeation enhancement of was evaluated using the excised hairless rat skin. Enhancement was marked in the case papaverine hydrochloride by free fatty acids (C3-C12), monoglycerides (side chains C5-C12) and caprylic acid(C8)ester of glyceryl monocaprylate. [42]

SURFACTANTS:

Surfactants polysorbate 20 and 80 used as penetration enhancers for transdermal delivery of drugs. Furthermore, the higher the concentration of the penetration enhancer, the higher the permeability of ascorbic acid (AA). Increase in AA permeation was achieved with enhancer concentrations as low as 1 %. This is important because these surfactants, being non-ionic, are much less damaging to the skin than other classes of surfactants and enhancers.[43] It was reported that the transdermal drug delivery system of risperidone containing nonionic surfactant as permeation enhancer was able to deliver drug up to 3 days at a flux equivalent the high dose currently marketed oral product from the patch containing surface area 10 cm2 with no skin irritation.[44]

CERAMIDE ANALOGUES:

A series of ceramide analogues including eight different polar head groups and six different chain lengths was synthesised. The compounds were evaluated as permeation enhancer's in vitro using porcine skin. The described relationships could bring more rational approaches in designing new potent enhancers for transdermal formulations.[45]

DENDRIMER:

Tt was investigates that the influence of surface charge, generation and concentration of poly(amidoamine) (PAMAM) dendrimers on skin permeation of a model hydrophilic drug, 5-fluorouracil (5FU).It was reported that lower generation cationic dendrimer is more effective in enhancing the skin permeation of hydrophilic drugs.[46]

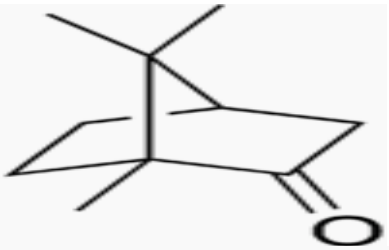
NATURAL PERMEATION ENHANCERS:

Natural permeability enhancers (NPE) represent an advantageous class of Transdermal Drug Delivery Systems (TDDS) in the context of pharmaceuticals. NPE represent a new type of are relatively new to pharmaceutical industry. Further research is desirable in order to scale up NPE systems and implement manufacturing of final dosage forms on commercial scale.[47]

TERPENES:

Terpenes are well recognized penetration enhancers for drug pen iteration across the human skin and have been receiving considerable interest in the pharmaceutical industry for this application.[48]

CAMPHOR:

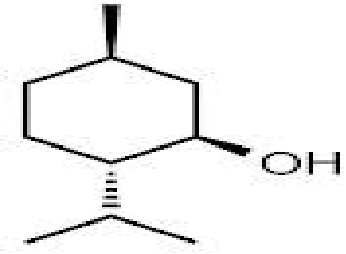


1,7,7-Trimethylbicyclo[2.2.1]heptan-2-one

The effect of vehicles on the *in vitro* permeation of carvedilol from saturated solutions across porcine skin and selected appropriate penetrationat was studied, 5% w/v concentrations were used as penetration enhancers. Skin permeation studies were conducted in Franz diffusion cells using excised porcine ear skin. Solutions containing 5% w/v camphor showed maximum permeation (232.54 μg) in 24 h

with a flux of 3.19 µg/cm^2/h, which was significantly different than the flux obtained using other permeation enhancers.[49]

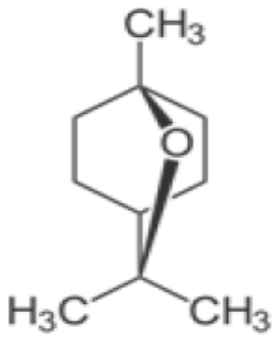
MENTHOL:



(1R,2S,5R)-2-isopropyl-5-methylcyclohexanol

Menthol is an organic compound made synthetically obtained from peppermint or other mint oils. Menthol having the ability to chemically trigger the cold-sensitive TRPM8 receptors in the skin which is responsible for the well-known cooling sensation provokes when inhaled, eaten, or applied to the skin. As a topical analgesic to relieve minor aches and pains such as muscle cramps, sprains. Headaches and similar conditions, alone or combined with chemicals like camphor or capsaicin. In Europe it tends to appear as a gel or a cream, while in the US patches and body sleeves are very frequently used. The mechanism of skin permeation enhancement is, it increase in skin flux, to eight times the base line, could be attributed to the effect of menthol on the skin barrier properties .[50]

Cineole:

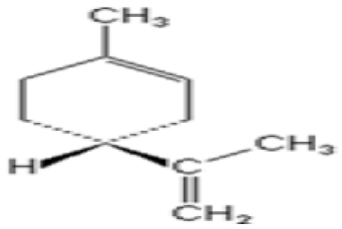


1,3,3-trimethyl-2-oxabicyclo[2,2,2]octane

Eucalyptol is a natural organic compound which is a colourless liquid. It is cyclic ether and a monoterpenoid. Eucalyptol is also known by a variety of synonyms: 1,8-cineol, cajeputol, 1,8-epoxy-p-methane, eucalyptol, cineol, cineole,1,3,3-trymethyl-2oxabicyclo(2,2,2)octane.

Eucalyptol suppository is used for the treatment of some respiratory ailments. Because of its pleasant spicy aroma and taste, eucalyptol is used in flavourings, fragrances, and cosmetics. It is also an ingredient in many brands of mouthwash and cough suppressant. 1, 8- Cineole has been used to promote the percutaneous absorption of several lipophilic drugs through hairless mouse skin .[51]

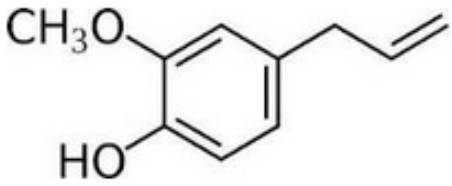
LIMONENE:



1-methyl-4(1-methylethenyl)-cyclohexane

It was found that the influence of limonine on bioavailability of nicardipine hydrochloride from membrane moderated transdermal therapeutic system in human volunteers.[52]

EUGENOL:



4-Allyl-2-methoxyphenol

Eugenol is an allyl chain-substituted guaiacol. Eugenol is a member of the allylbenzene class of chemical compounds. It is a clear to pale yellow oily liquid extracted from certain essential oils especially from clove oil, nutmeg, cinnamon, and bay leaf. It is slightly soluble in water and soluble in organic solvents. It has a pleasant, spicy, clove-like odour. Cloves are the aromatic dried flower buds of a tree in the family Myrtaceae. It is native to Indonesia and used as a spice in cuisines all over the world. Eugenol, a component of clove, may reduce the ability to feel and react to painful stimulation. Therefore, use of clove products on the skin with other numbing or pain-reducing products such as lidocaine / prilocaine cream, theoretically it may increase effects.[53] FT-IR and partitioning studies reveal that the enhancement in the permeability coefficient of drug by Eugenol is due to lipid extraction and improvement in the partitioning of the drug to the SC.[54]

BASIL OIL:

The present investigation aims to develop transdermal gel of naproxen containing tulsi oil as a natural penetration enhancer for improved penetration of naproxen. The mechanism of action of tulsi oil is not well established yet but it might be possible that it modifies the barrier properties of stratum corneum temporarily to enhance percutaneous absorption. The present work investigates effectiveness of basil oil, a volatile oil containing alcoholic terpenes, as a potential penetration enhancer for improved skin permeation of labetolol

hydrochloride (LHCl) with reference to camphor, geraniol, thymol, and clove oil. Basil oil is proposed as a promising penetration enhancer for improved transdermal drug delivery of labetolol.[55]

PAPAIN:

This study was to evaluate an effect of the proteolytic enzyme papain on permeation of low molecular weight heparin (LMWH) *in vitro* and *in vivo*. The co-administration of papain with heparin represents a new approach in improvement of absorption and bioavailability of orally administered heparin.[56]

PIPERINE:

Piperine, an amide alkaloid of black pepper, was investigated for transdermal enhancer activity using human cadaver skin in vitro with aceclofenac as the model drug. Furthermore, FT-IR studies were conducted to understand to possible enhancement mechanism. These results indicate that piperine enhances transdermal permeation of aceclofenac by biphasic mechanism involving partial extraction of stratum corneum (SC) lipid and interaction with SC keratin.[57]

SESQUITERPENE COMPONENTS OF VOLATILE OILS AS SKIN PENETRATION ENHANCERS:

Twelve sesquiterpene compounds, derived from natural volatile oils, were investigated as putative skin penetration enhancers for human skin. Pre-treatment of epidermal membranes with sesquiterpene oils, or solid sesquiterpenes saturated in dimethyl isosorbide, increased the rate of absorption of the model hydrophilic permeant, 5-fluorouracil (5-FU). This study has shown that sesquiterpene compounds, which are of low toxicity and cutaneous irritancy, can promote 5-FU absorption across human skin. Sesquiterpene compounds, therefore, show promise as clinically-acceptable skin penetration enhancers.[58]

ALMOND OIL:

The aim of the study was to formulate and evaluate topically applied ketoprofen gels and patches and to see the effect of naturally occurring almond oil as penetration enhancer on the penetration of ketoprofen through artificial membrane/rabbit skin. Almond oil as penetration enhancer in various concentrations significantly enhances the penetration of drug from transdermal gels and patch across synthetic membrane/rabbit skin but was most significant when used in 3% concentration.[59]

VITAMIN E:

Vitamin E is used as human skin penetration enhancer.[60]

CHITOSAN:

Chitosan is a bioadhesive, viscous nature polymer and also will act as penetration enhancer that increases transcorneal permeation of the drug. Study on the mechanisms of chitosan and its derivatives used as transdermal penetration enhancers.[61] It was reported that the mechanisms of transdermal enhancement of Chitosan, , N-trimethyl chitosan (TMC) and mono-N-carboxylmethyl chitosan (MCC) are closely related to their effects on the secondary structure of keratin and water content in SC, cell membrane potential and fluidity.[62]

FULVIC ACID:

It was reported that mucoadhesive nasal in situ gel drug delivery was very beneficial in case of BCS class III drugs like Sumatriptan succinate in presence of fulvic acid due to its permeation enhancing effect, which was extracted from shilajit.[63]

Penetration enhancing potential of corn (maize) oil, groundnut oil and jojoba oil on in vitro permeation of olanzapine across rat skin was studied.[64]

The present study was conducted to formulate and evaluate flurbiprofen transdermal gel. Olive oil was used as penetration enhancer and was added in different concentrations to some selected formulations to see its enhancement effect on in vitro drug release profiles.[65]

Transdermal patches of olanzapine were aimed to be prepared to overcome the side effects by oral application. The strategy was formulation of eudragit-based polymeric films to prepare transdermal patches by using nonionic (span-20), anionic (sodium lauryl sulfate), cationic surfactant (benzalkonium chloride), and vegetable oil (olive oil) as permeation enhancers. The patches were subjected to physicochemical, in vitro release and ex vivo permeation studies.[66]

Table 1: List of permeation enhancers:

Sr. No.	Synthetic permeation enhancers	Natural permeation enhancers
1	Dimethyl Sulphoxide[9,10,11,12]	Camphor[49]
2	Decylmethyl sulfoxide[13,67,73]	Menthol[50,70]
3	Oxazolidinones[14]	Cineole[51,70]

4	Urea[15,68,70,72,74,77]	Limonene[52,70]
5	Azone[16,17,18,67,73,76]	Euginol[53,54]
6	Pyrrolidones[19,20]	Basil oil (Tulsi oil) [55]
7	Ethanol[21]	Papain[56]
8	Isopropylalcohol[68]	Piperine[57]
9	Polyethylene glycol[69,74,75]	Sesquiterpine component of volatile oil as skin permeation enhancers[58]
10	Propylene glycol[70,73, 74,77]	Almond oil[59]
11	Glycerine[77]	Vitamin E[60]
12	Glyceryl monocaprylate[30]	Chitosan[61,62,78]
13	Sefsol[31]	Fulvic acid[63]
14	Cyclodextrins[32,33]	Corn (maize oil) [64]
15	Alkyl-n,n-disubstituted aminoacetates[34]	Groundnut oil [64]
16	Sodium oleate[38]	Jojoba oil[64]
17	Palmitoleic acid[39]	Olive oil[65,66]
18	Surfactants[43,44]	Ascorbic acid[74]
19	Span-20[71]	Glycyrrizin[79]
20	Sodium Lauryl sulphate[71]	Aloe[80]
21	Benzalkonium chloride[71]	
22	Ceramide analogues[45]	
23	Dendrimer[46]	

CONCLUSION:

The skin membrane in the body serves as a barrier to the external environment, through which absorption of drugs occurs. Penetration enhancers are applied to improve the permeation of the poor permeable drug through the skin. They do not have any therapeutic effect but they enhance the penetration of drugs across the membrane. Different approaches are applied like synthetic and natural penetration enhancers such as Azone, Sulphoxide, Fatty acids, oxazolidiones, eugenol, papain, almond oil, Chitosan, piperidine, Aloe etc., which explained with their properties and mechanism of action. These approaches are very useful in transdermal drug delivery system of drugs having poor permeable behaviour and this technology is a rapidly developing field which significantly increase the number of drugs suitable for transdermal drug delivery. Naturally occouring volatile oils i.e., terpenes appear to be clinically acceptable permeation enhancer as indicated by high percutaneous enhancement ability.

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