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Review Article

OILS AS PENETRATION ENHANCERS FOR IMPROVED TRANSDERMAL DRUG DELIVERY: A REVIEW

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ABSTRACT

Transdermal drug delivery system is the most suitable system for delivering the drugs with shorter half-life and poor solubility. It improves the drug safety and therapeutic efficacy as the drug delivery through it occurs in a controlled manner. Interpretation of the biochemical composition and barrier function exerted by the stratum corneum has lead for the exploration of different sources for improving the percutaneous absorption. Skin is the suitable site for drug administration for local and systemic actions. Penetration enhancement is an improving technology that leads to the increase in the count of drugs for TDDS. The present review reports the role of Natural oils in enhancing the permeation of drugs through skin because of possessing different features like natural origin, favorable penetration enhancement and partitioning action in the skin by the oils. Various natural oils, their classification and influence as penetration enhancers were discussed in this study.

Keywords: Permeation enhancers, natural oils, essential oils, fixed oils, transdermal.

INTRODUCTION

Transdermal route is the most suitable route for drug administration that has shorter biological half-life. The drug absorption across the skin layers varies for different drugs. Penetration enhancers are used for the drug permeation enhancement across skin mucosa. Penetration enhancer is also called as absorption promoter or absorption enhancers because it promotes the drug or penetrant absorption across the skin[1, 2].

SKIN

Structure of skin

Skin is a complex biological structure constituting many layers and is the only organ in the body that is most accessible. The skin functions are to safeguard the major internal parts of the body from the external effects, regulation of temperature, sensation and water balance. A normal adult human body skin covers around two square meters surface area and gets about one-third of the blood circulating in the body.

Layers of skin[3, 4]:

The three layers of the skin are;
Epidermis,
Dermis and
Hypodermis.

Epidermis

The epidermis is a stratified, squamous, keratinizing epithelium which is the topmost layer of skin. Above 90% are the keratinocytes, which is accountable for the barrier characteristics of the skin. The physical properties, shape, and size of keratinocytes change during migration to skin surface. The uppermost layer epidermis is again splitted up into five anatomical layers microscopically, of which the outer most layer is stratum corneum with approximately 100-150 micrometers thickness that is exposed to the external environment which does not receive any blood flow. Underneath the epidermis, the capillaries system of dermis circulates blood across the whole body. An active ingredient enters into the stream of blood if it has the penetrating ability into the stratum corneum. A normal drug can traverse the layer through the only process called passive diffusion.

Dermis

The dermis is predominantly made of connective tissue and is the substantial layer of the skin that assists epidermis. The junction between epidermis and dermis layer is known as dermal- epidermal junction which acts as a physical barrier for larger molecules. This layer may be classified into papillary and reticular dermis. Papillary is the outlying segment of the dermis and is probably thinner. Papillary region is completely of elastin and collagen fibres aligned vertically and attached to dermal-epidermal junction. Reticular region of dermis is with fibres arranged horizontally.

Hypodermis

This is the layer of adipose tissue that links dermis, aponeurosis and fasciae of the muscles. The subcutaneous adipose tissue is highly integrated with the dermis through the networks of blood vessels and nerves. This layer constitutes loose connective tissue and the thickness differs according to the body surface.

PERMEATION ENHANCERS

Permeation enhancers are the substances that functions by lowering the potential of the barrier characteristics of skin so that it turns more permeable for the drug molecules to traverse the skin rapidly. The drug diffusivity in the stratum corneum (SC) can be increased by these substances by liquefying the skin lipids or by denaturing skin proteins. The mechanism of action of permeation enhancers are –

(1) Disordering of the skin lipids
(2) Enhancers and intracellular proteins interactions
(3) Enhancement in partition of the drug into skin, adding co-enhancers or co solvents[3].

Penetration Enhancers - Ideal Properties[3, 4]

1. These substances must be pharmacologically, inert non toxic, non allergic, non- irritating.
2. It must be compatible with drug as well as other excipients.
3. It should not have any pharmacological action within the body.
4. It must be acceptable cosmetically with a favorable skin feel.
5. It must be inodorous, colorless, tasteless and economical and possess ideal solvent properties.
6. It must have chemical and physical stability.
7. The period of drug action should be both foreseeable and reproducible.
8. It must be trialed or tested in scientific laboratories.

Advantages & disadvantages of penetration enhancers[5]
Advantages

- The penetration rate and therapeutic efficiency of the drug can be increased efficiently by using penetration enhancers.
- Absorption of the unabsorbable drugs can be increased by the use of penetration enhancers.
- The transdermal absorption for topical preparations can be increased.
- The penetration rate of drug in transdermal drug delivery systems depends on penetration enhancers.
- In some cytotoxic drugs terpenes like limonene in propylene glycol solution act as effective penetration enhancers[6].

Disadvantages

- The use of various concentrations of different penetration enhancers is restricted.
- The concentration of the enhancers varies from drug to drug.
- A few penetration enhancers react with the drug, affecting the body which leads to side effects[6].

ENHANCERS OF TRANSDERMAL DRUG DELIVERY SYSTEMS

Enhancers act by rupturing stratum corneum layer and by improving the penetrant solubility, it increases the permeation of active ingredients. Disruption occurs due to denaturation of proteins, randomization and fluidization of intercellular lipids or intercellular expansion and delamination. Types of enhancers of TDDS are[5, 7, 8];

1. Physical enhancers,
2. Particulate systems,
3. Chemical enhancers,
4. Drug vehicle based,
5. Natural penetration enhancers,
6. Biochemical Approach.

Table 1: Classification and penetration enhancers and techniques[9]

Types/Techniques of penetration enhancers	Mechanism of action	Examples
1. Chemical enhancers	They act by – Disruption of the highly ordered lipids of the stratum corneum. Chemical interaction with the intercellular proteins. By improving the partition of drug into the stratum corneum.	1. Sulphoxides and similar chemicals 2. Azones 3. Pyrrolidones 4. Fattyacids 5. oxizolidinones 6. Amine and Amides 7. Surface active agents 8. Cyclodextrins
2. Drug Vehicle Based	The enhancers interact with stratum corneum and initiate penetration.	Ion pairs and complex Co-acervates with chemical potential adjustment
3. Natural Penetration enhancers	They act with different mechanisms like – Partition coefficient Diffusion coefficient Lipid Extraction Drug Solubility Macroscopic Barrier Perturbation Molecular Orientation of Terpenes Molecule with Lipid Bilayer	1. Terpenes like menthol, linalool, limonene, carvacrol. 2. Essential oils like basil oil, neem oil, eucalyptus, chenopodium, ylang- ylang.
4. Physical Enhancers	The physical enhancers act by variable techniques and increase the penetration. This can be achieved by physical separation, magnetic and ultrasonic techniques.	1. Iontophoresis 2. Sonophoresis 3. Phonophoresis 4. Magnetophoresis 5. Electroporation 6. Thermophoresis 7. Needleless injection 8. Hydration of stratum corneum 9. Stripping of stratum corneum

5. Biochemical Approach	They act by modifying substances and converting them to suitable form.	1. Synthesis of bio-convertible prodrugs. 2. Co-administration of skin metabolite Inhibitors
6. Vesicular[10]	Act as drug carriers and carry the entrapped drug across the cell membrane. Penetration of the individual lipid components into the stratum corneum and subsequently altering the intercellular lipid lamellae within this skin layer. Provide controlled and sustained transdermal drug delivery.	1.Lipid synthesis inhibitors 2. Phospholipids

NATURAL OILS

Oil is any neutral, non-polar chemical substance which is a thick liquid at room temperature. It is lipophilic ("fat loving" or miscible with oils) and also hydrophobic ("water fearing" or water immiscible) in nature. Oils having a high content of hydrogen and carbon are usually slippy and flammable. The usual definition of oil involves the classes of chemical constituents that may be unrelated in properties, structure and uses. Oils could be from vegetable, animal, or petrochemical sources and are volatile or non-volatile. They have wide applications in pharmaceuticals, food, lubrication, fuel and the processing of plastics, paints, and other substances.

Natural oils play a promising role as permeation enhancers in TDDS. They include fixed oils and essential oils. Essential oils are also known as volatile oils which get evaporated in the external environment unlike fixed oils.

Table 2: Difference between fixed oils and essential oil[11]

Volatile oil	Fixed Oil
Also known as an essential oil.	Also known as natural non-volatile oil.
Volatile oil evaporates when placed under room temperature	Fixed oils do not evaporate at room temperature
They can be extracted easily by the distillation process	They require other specific techniques for extraction.
There is no spot (permanent stain) remains after evaporation	Some type of spot (permanent stain) left after evaporation
They are unable to undergo saponification	Fixed oils saponify easily.
Cleoptenes & stearoptenes mixtures are termed as volatile oils	Esters of higher groups of fatty acids & glycerin are known as fixed oils.
These oils have high refractive index	These oils have low refractive index
These are optically active.	These are optically inactive.
They are extracted mainly from leaves, roots, petals and bark.	They are extracted from seeds of the plant.

ESSENTIAL OILS

An essential oil was named as "Quinta essential" earlier which means the useful and efficient constituent of a drug. It is a liquid which is hydrophobic in nature and consists of the substances that have volatile aroma from plants. These are the essences which are highly-concentrated and are extracted from different segments of aromatic plants, including leaves, bark, and flowers. The oils can be used in various ways, such as in aromatherapy, skin-care products, etc. These are also called as ethereal oils, volatile oils, or just with the name of their source of plant, for example, oil of eucalyptus. Oil is "essential" means that it bears an essence, or characteristic aroma of the plant. These oils are considered as the aromatic liquid compounds expressed from natural sources like plants. They could be found in different fragments of plants like, seed (almond), leaves (oregano), peel (bergamot), flower (jasmine), berries (juniper), bark (sassafras), rhizome (ginger), wood (agar wood),resin (frankincense), and petals (rose). These oils are considered as the "chemical weapons" of the plants kingdom as their compounds can avert insects, or guard the plants against fungal or bacterial affects. Essential oils are pure, intricate, multicomponent systems consisting primarily of terpenes and some non-terpene compounds. Besides having therapeutic properties, these are extensively utilized in the pharmaceutical, food, and perfume (especially) industries[12, 13].

Table 3: Classification of essential oils[7]

S.no	Type	Examples
1.	Hydrocarbon volatile oils	Turpentine, black pepper, hops
2.	Alcohol volatile oils	Peppermint, cardamom, rose, sandalwood, coriander, eucalyptus
3.	Aldehyde volatile oils	Cinnamon, lemon peel, orange peel, lemon grass, bitter almond
4.	Ester volatile oils	Gaultheria, lavender, mustard
5.	Ketone volatile oils	Caraway, Spearmint, buchu, camphor
6.	Oxide volatile oils	Chenopodium, eucalyptus
7.	Phenolic ether volatile oils	Anise, fennel, nutmeg
8.	Phenol volatile oils	Clove, thyme, creosote

Chemically essential oils are classified as;

Non-terpenoids: This group comprises nitrogenated substances, aromatic substances, short-chain aliphatic substances, and sulphur substances. They are not so important than terpenoids regarding their applications.
Terpenoids: These are more predominant commercially and concerning their properties.

Role of essential oils as permeation enhancers

Skin contributes the predominant site for the administration of essential oil and it is obvious that it is the foremost route for dermatological care. Essential oil permeation through skin is a complex process that includes many feasible steps beginning from its application to the existence of its molecules in systemic circulation. But still, they have been shown evidence of penetration into and across the skin and exert local therapeutic actions[14, 15]. The three ways of crossing the stratum corneum are shown in Figure 2.

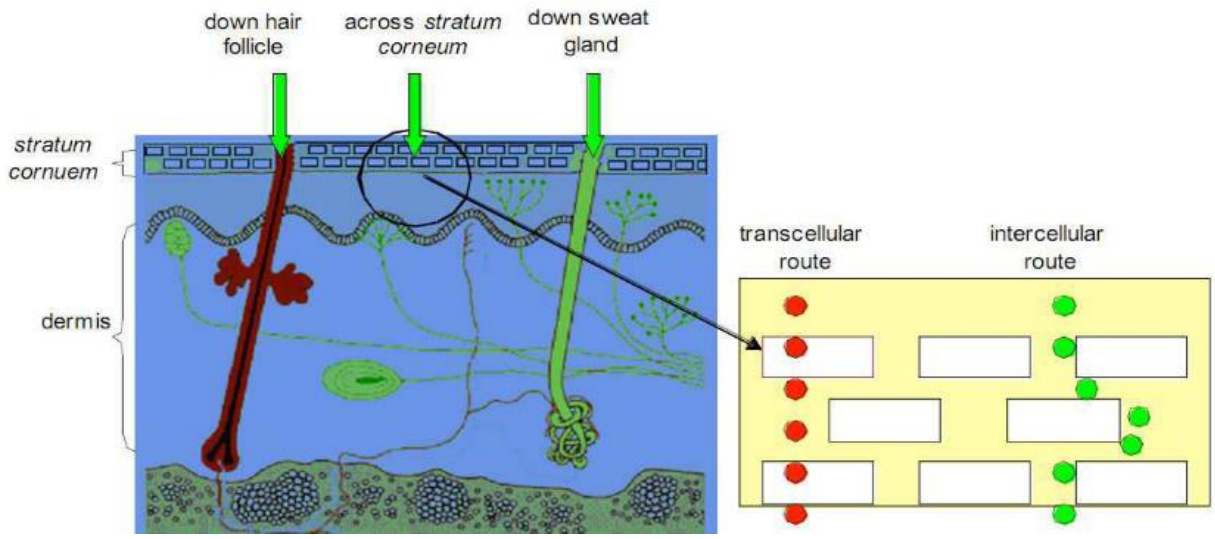

Figure 2: Routes of absorption of essential oil

ESSENTIAL OILS AS SKIN PENETRATION ENHANCERS

Penetration enhancers enter into the stratum corneum by partitioning with the skin and interact with components of skin tissues so that the barrier characteristics of the layer are reduced without damaging the basal skin cells[16]. 1, 8 cineole and D-limonene both have been shown to modify the permeant diffusivity by rupturing the lipid bilayers of stratum corneum[17, 18].

TERPENES

Terpenes are the mostly accepted penetration enhancers for penetration of drugs across human skin and have been gaining considerable attention for its application in the industry of pharmacy.

The grouping of the terpenes has been structured out depending on the count of isoprene or isopentane units existing in the principal molecular skeleton[19, 20, 21].

Table 4: Classification of terpenes[7, 22]

S.No.	Terpenes	Carbon atoms	Isoprene units
1	Monoterpenes	10	2
2	Sesquiterpenes	15	3
3	Diterpenes	20	4
4	Sesterterpenes	25	5
5	Triterpenes	30	6
6	Carotenoids	40	8
7	Rubber	> 500	> 100

Monoterpenes and sesquiterpenes are the major components present in the essential oils and the rest of the terpenes are components of resins, waxes, balsams, and rubber[14, 23, 24]. Examples of monoterpenes include limonene, geraniol, nerol, and linalool, etc. Examples of sesquiterpenes include farnesol, nerolidol, etc.

Eucalyptus oil

Eucalyptus oil is an essential oil extracted from various plant species of the family Myrtaceae, which comprises Eucalyptus dives, Eucalyptus citriodora, Eucalyptus polybractea, Eucalyptus globules and Eucalyptus radiata. Eucalyptus oil is extracted by steam distillation of the leaves of these plants[18]. It is also called as eucalyptol and is identified by various synonyms: cajeputol, cineol, 1,8-cineol, 1,8-epoxy-p-methane, eucalyptol, cineole,1,3,3-trymethyl-2oxabicyclo(2,2,2)octane[25]. Eucalyptus oil is used as penetration enhancer in ketoconazole transferosomal gel. A study was performed on the penetration enhancement of ketaconazole with different essential oils, and it was found that ketaconazole containing eucalyptus oil showed good permeation pattern compared to the rest of formulations with other permeation enhancers[26].

In another study penetration enhancement was evaluated through excised human skin. 5-flurouracil was taken as the model drug and it was formulated with various essential oils like chenopodium, ylang and anise. In this study, it was investigated that eucalyptus and chenopodium oils were the most effective drug permeation enhancers [27].

Turpentine oil

By the distillation process of the resin produced by the species of the plants called conifers (Coniferaespp), turpentine oil is extracted. It is the most frequently used oil as evident from the Ancient Greeks.

In a study on the rate of permeation of flurbiprofen, turpentine oil has shown an additive effect when added to an optimized mixture of co-solvent isopropyl alcohol-propylene glycol. The rate of transdermal penetration was maximum with turpentine oil at a concentration of 5% (v/v) and was found to be appreciably more effective than tulsi oil at the similar concentration[28]. The reason for this is increased breakdown of stratum corneum layer that is commonly induced by terpenes. Turpentine oil was used for improving the permeation of diclofenac diethylamine (DDEA) from matrix transdermal

patches. It is also used to increase the flux in ketaconozole transdermal films. The transdermal films of ketaconozole deliver therapeutic concentrations of the drug in a steady and prolonged manner throughout the day. Turpentine oil acts as a good penetration enhancer which results in improvement of drug flux[29].

From this study it is observed that raising concentration of turpentine oil shows a direct effect with increasing permeation of drug. Turpentine oil constitutes terpenes that could have a synergistic effect of permeation of the drug and it causes an increase in permeation of drugs because of increased breakdown of stratum corneum[30].

Peppermint oil

Oil of Peppermint can be extracted by steam distillation of the leaves, flower buds and stems of the plant Mentha piperita of Labiatae or Lamiaceae family. The vital components of the oil are: menthone (12–20%, ketone), menthol (34–44%, phenolic alcohols), 1, 8-cineole (eucalyptol, 2–5%, oxide), menthofurane (4–9%, furanoids), menthyl acetate (4–10%, ester), and pulegone (2–5%, ketone). It is used as analgesic, for controlling appetite, for stimulating digestion/function of gallbladder and as anti-viral, anti-inflammatory, anti-tumoral, anti-parasitic, and as anti-bacterial aid. Peppermint oil was shown to enhance the penetration rate of curcumin through rat skin at 3% concentration[31].

Fennel oil

The steam distillation of the crushed seeds of the plant Foeniculum vulgare, of the family Umbelliferae or Apiaceae, extracts Fennel oil. The major constituents are 12–16% fenchone (ketone), 60–80% *trans*-anethole (phenolic ester), 3–5% α-pinene (monoterpene), linalol (alcohol), and 2–5% methyl chavicol (phenol). It acts as analgesic, anti-septic, digestive aid, anti-parasitic, anti-spasmodic agent, anti-tumoral, and anti-inflammatory agent and also enhances metabolism.

In a study on the influence of various essential oils containing terpenes on the penetration of the drug trazodone hydrochloride, fennel oil at 10% has increased the permeation and transdermal flux of the drug across the epidermal layer of mouse compared to all other essential oils used in the study[32].

Farnesol[33]

Farnesol is a sesquiterpene alcohol which is obtained from other essential oils like citronella, lemon grass, neroli, tuberose, balsam and tolu. It is mainly used as a perfumery to emphasize the odors. In a study, it was reported that farnesol (0.25% v/v) enhances the permeation of diclofenac sodium. It was found that the permeability of diclofenac sodium increased 78-fold times when compared to the preparation without farnesol. The order of permeation enhancement of other terpenes along with farnesol - farnesol > carvone > nerolidol > menthone > limonenoxide[33].

Menthol[33]

Menthol is obtained from Mentha piperata. The main form of menthol is (-)-menthol. . It is mostly used in antipruritic creams and as upper respiratory tract decongestant. Menthol is traditionally the most effective penetration enhancer along with limonene that can be considered as a prototype for the use of terpenes as penetration enhancers. Menthol is widely used as a transdermal enhancer for various types of drugs including imipramine hydrochloride, caffeine, triamcinolone, propranolol hydrochloride, hydrocortisone. Menthol shows a synergistic application along with other terpenes like cineole and terpineol in iontophoresis. This showed increase in the flux of busiprone hydrochloride by more than 200-fold compared to a 15-fold increase using iontophoresis without the terpenes[33].

D-Limonene

The by-product procured from the citrus juice industry is D-Limonene. This is a main constituent of the oil which is expressed from the citrus fruit rinds. The existing two important grades for D-Limonene are technical grade and food grade.

The existence of d-limonene in the felodipine transdermal formulation has produced an increase in the permeability of the drug through skin[34].

Camphor

Camphor is a translucent crystalline solid, white in colour and has strong aromatic odour. Camphor is readily found in the wood of camphor laurel (Cinnamomum camphora). It can be artificially processed from the turpentine oil. It possesses medicinal uses also. Camphor is easily penetrated across stratum corneum and exerts a cooling feel.

In a Study on the effect of permeation enhancers on penetration of carvedilol through the abdominal skin of rat, camphor at concentration of 5% has shown maximum permeation and higher flux compared to all other permeation enhancers used in the study[35].

Table 5: Essentials oils as skin penetration enhancers for transdermal drug delivery[33, 36]

Essential oil	Drug	Animal/Human study	Characterization
Eucalyptus, anise, chenopodium, ylang ylang oils[33]	5-fluorouracil	Human skin	Eucalyptus and chenopodium were most suited for the study as they showed 30-fold increase in drug permeability coefficient whereas ylang ylang and anise oils showed only 8-fold and 3-fold increase in permeation.
Eucalyptus, peppermint, turpentine oils[33]	5-fluorouracil	Human skin	Eucalyptus, peppermint, turpentine showed 60-fold, 46-fold and 28-fold increase in the drug permeability coefficient, respectively
Turpentine oil	Ibuprofen	Animal cellulose membrane and abdominal skin	Hydrogel with 1 % ibuprofen and 3% turpentine oil showed a maximum flux of 10.87 mg/cm2 /h across artificial skin and 17.26 mg/cm2 /h across rabbit abdominal skin
Peppermint oils, Rosemary, ylang	Aminophylline	Human skin	All oils enhanced the permeation of aminophylline but their effects were less than that of ethanol as enhancer
Tulsi, turpentine oils	Flurbiprofen	Animal skin	Bioavailability of flurbiprofen with reference to orally administered flurbiprofen in rats was found to increase by 2.97, 3.80 and 5.56 times with transdermal patch formulation without enhancer, 5% (v/v) tulsi and turpentine oil formulations, respectively

Fennel, eucalyptus, citronella, mentha oils	Trazodone hydrochloride	Animal epidermis	Percutaneous penetration flux for trazodone hydrochloride was increased with skin pretreatment by 10% essential oils in the following order: fennel oil > eucalyptus oil > citronella oil > mentha oil
Turpentine, eucalyptus, peppermint oils	Ketoconazole	Animal skin	Formulation containing eucalyptus oil showed better permeation of ketoconazole than formulations containing other essential oils as permeation enhancers
Eucalyptus oil[36]	Chlorhexidine digluconate	Highly thick human skin	2% (w/v) chlorhexidine digluconate in combination with 10 % (v/v) eucalyptus oil and 70% (v/v) isopropyl alcohol, significantly increased the amount of drug into the skin within 2 min after application compared with a solution of chlorhexidine digluconate / isopropyl alcohol alone
Peppermint, tea tree, eucalyptus oils	Benzoic acid	Human breast or abdominal skin	Peppermint oil in 0.1% and 1.0% (v/v) concentrations showed the most significant effect on skin penetration of benzoic acid
Black cumin, tulsi, clove, eucalyptus, oils	Carvedilol	Excised animal abdominal skin	5 % (v/v) black cumin essential oil was better penetration enhancer with an enhancement factor of 6.40 for carvedilol than clove oil, eucalyptus oil, tulsi oil, oleic acid and Tween 80

FIXED OILS

Fatty acids constitute an aliphatic hydrocarbon chain, which may be saturated or unsaturated, with one terminal carboxyl group. These are studied to be efficacious permeation enhancers of skin and are considered as safe and non-toxic. Many esters of fatty acids along with fatty acids are used as permeation enhancers. It has been observed that the fatty acids which are unsaturated are more successful than the saturated equivalents in increasing percutaneous permeation of drugs. Fixed oils are mainly procured from the different plant seeds. They are differentiated based on its origin (vegetable and animal).

Table 6: Classification of vegetable oils and fats

Oils and Fats (Vegetable)			
Fats	**Non-drying oils**	**Semi-drying oils**	**Drying oils**
Cocoa butter	Olive oil	Castor oil	Linseed oil
Kokum butter	Peanut oil	Mustard oil	Poppy seed oil
Nutmeg butter	Almond oil	Sesame oil	Hemp oil
Coconut oil	Croton oil	Rape seed oil	Walnut oil
Palm oil	Rice bran oil	Cotton seed oil	
Mango kernel oil		Safflower oil	

Table 7: Classification of animal oils and fats

Oils and Fats (Animal)			
Marine animals		**Terrestrial animals**	
Fats	**Oils**	**Fats**	**Oils**
Bone tallow	Cod liver oil	Mutton thallow	Lard oil
	Shark liver oil	Lard	Neat foot oil
	Whale liver oil	Butter suet	

Almond oil

Almond oil is plant oil which was known to increase the permeation of different types of drugs. In a study, it stabilizes and dissolves aspirin leading to an enhancing effect on percutaneous absorption. Hence vaseline- almond oil (7: 3) base allowed better permeation of the drug compared with vaseline ointment alone[37]. In another study, Clotrimazole gel was developed using Tween 80 and almond oil (in various concentrations) as penetration enhancers and evaluated the influence of different enhancers on the absorption or permeation of drug across rabbit skin. Almond oil along with tween 80 has shown synergistic effect[38]. In another subsequent study, almond oil as permeation enhancer was incorporated in various concentrations appreciably enhanced the dermal permeation of the drug from gels and patches containing ketoprofen through rabbit skin or synthetic membrane and was found to be most significant at 3% concentration[39].

Olive oil

This is a fixed oil extracted from the fruits of olea europaea tree. The main constituents are tripalmitin, triolein, tristearate, trilinolein, triarachidi, squalene, monostearate, tocopherol and b-sitosterol. Olive oil can be used as a solvent and in cosmetics as skin and hair conditioner. It is a very potent fatty acid permeation enhancer.

Olive oil as permeation enhancer was used for transdermal permeation of flurbiprofen from transdermal formulation of gel. It was included in the specific formulations in various concentrations to check its enhancing ability on the skin. Olive oil has enhanced the permeation of drug and the topical gels of flurbiprofen were formulated successfully and could be an advantageous topical product[40]. In a study on preparation and evaluation of olanzepine transdermal patches, the formulation containing 10% olive oil has enhanced permeation through rat skin[41].

Sesame oil

It is the oil expressed from the seeds of the plant Sesamum indicum, which is from the Pedaliaceae family. This oil is described as light yellow, transparent oil with nutty odor and taste.

The influence of sesame oil on the Arbutin rrelease has showed that sesame oil acts as an effective permeation enhancer in increased concentrations[42].

Coconut Oil

Coconut oil is extracted from the kernel or meat of matured coconuts harvested from the coconut palm (Cocos nucifera). It has various applications in food, medicine, and industry. The colour of the oil varies from a light yellow to a brownish yellow colour. The oil is also referred to as copra oil and contains average amounts of caproic- (0.2 - 0.8%), caprylic- (5 - 9%), palmitic- (7 - 11%), stearic (1 - 3%) and oleic- (5 - 8%) acids. More than 90% of the fatty acids in this oil are of low molecular weight and are saturated, which makes coconut oil the richest source of medium chain, fatty acids (C6-, C8- and C10). Due to significant concentrations of lauric acid, this oil will pass abruptly from a brittle solid to a liquid, within a narrow temperature range. It, furthermore, melts rapidly and completely below body temperature, due to the low molecular weight of the lauric acid[43].

A study was conducted to check the enhancing property of coconut oil. A transdermal drug delivery system of gabapentin was prepared with a cosolvent and microemulsion. Coconut oil was taken as the oil phase of the microemulsion. The in vitro drug release of the drug showed that there was significant increase in the skin permeation of the drug[44].

Cardamom oil

Cardamom oil commonly called poppy seed oil is a crude drug extract obtained from the seeds of Elettaria cardamomum was found to be used as effective permeation enhancer. The vital components of cardamom seed are acetyl terpineol and terpineol.

It was found in a study of crude drugs dermal permeation enhancement that, the permeation of prednisolone in vitro was found to be increased by the vital components in the cardamom seed[45]. In another study, indomethacin permeation was appreciably increased following the treatment of cardamom oil in vitro as well as in vivo studies[46]. In a subsequent study, for enhancing the permeation of drug, different extracts of crude drugs were assessed for permeation by employing in vitro and in vivo methods using a model skin membrane of rabbit skin. The best and foremost result were shown by the acetonic extract of two species of cardamom i.e., Amomum cardamomum and Elettaria cardamomumin improving the permeation of indomethacin[47].

FISH OILS

Fish oils can be produced from the fish liver or the body of the fish. The natural source for the fatty acids docosahexaenoic acid (DHA),eicosapentaenoic acid (EPA), and docosapentaenoic acid (DPA) is contributed by their lipids. The distinctive order of fatty acid contents and high extent of unsaturation separates fish oils from other oils. The refined oil contains about 90% of triglycerides and the rest include mono and diglycerides, some lipids (e.g., phospholipids) and unsaponifiable stuff (e.g., fatty alcohols, sterols, hydrocarbons, glyceryl ethers, vitamin A, D and E). Various unsaturated fatty acids which include (EPA) and (DHA) form the acid part of the glycerides[48].

Cod liver oil

Cod-liver oil procures from the fresh liver of cod. A fatty acid extract is obtained in the course of refining the medicinal cod-liver oil. Of that, saturated acid stake up 17% of total extract, predominantly of palmitic acid (10.4%), and the remaining extract constitutes unsaturated fatty acids like oleic acid (15–16%), DHA (11.9%), EPA (9.3%), palmitoleic acid (6.4%), gondoic acid (9.4%), *cis*-vaccenic acid (4.4%), and gadoleic acid (7.8%)

It was known from the literature that the oil of Cod liver extract at 5% concentration has enhanced the penetration of ergotamine tartrate used for the treatment of migraine[49]. Another successive study showed that there was 50 to 70 times improvement in the flux of the drug when the cod-liver oil extract was added to propylene glycol saturated with the acyclovir drug depending on the concentration (5%, 10%, and 30% (w/w)) of the cod liver oil extract. Unusually, the highest enhancement of the skin permeation of acyclovir was seen with the lowest concentration of the extract[50].

CONCLUSION

It is known that the transdermal drug administration serves effectively over oral delivery of drugs in the present decade and this has evolved the research to overcome the skin barrier function. The membrane of the skin functions as a barrier to the external medium, through which drug absorption occurs. The penetration enhancer functions by modifying the barrier characteristics of skin reversibly by enhanced fluidity of the membranes or by promoting the drug solubility inside the skin. Thus, penetration enhancement is an improving technology that leads to the increase in number of drugs for transdermal drug delivery, assuring that skin becomes the eminent system of drug delivery in the future. The aim of the present review was to summarize that natural oils can be the proficient permeation enhancers for TDDS in view of their natural source of origin, appreciable skin penetrating ability, cost effective, and no toxicity. It was found that the natural oils as permeation enhancers has reported promising enhancement of drug permeation across skin safely. It is to be noted that the efficacy of the penetration enhancers depends on their concentration as well as drug's physico-chemical characteristics. Terpenes, which are the natural volatile oils, are deemed as clinically acceptable permeation enhancers because of their favorable percutaneous enhancement, transformable actions on the SC lipids, and show no toxicity. It can be concluded that research or exploration is beneficial for scaling up of the system of natural permeation enhancers and execute the manufacture of the dosage forms with natural oils as penetration enhancers on economic scale as a result natural permeation enhancers will play a prominent role in progress of useful and efficient transdermal products in future.

REFERENCES

1. Sushila Saini, Shikha Baghel, Chauhan, Agrawal S S. Recent development in Penetration Enhancers and Techniques in Transdermal Drug Delivery System. Journal of advanced pharmaceutical education and research, 2014; 4(1): 31-40.
2. Sharma A, Saini S. Transdermal drug delivery system. International Journal of Research in Pharmaceutical and Biomedical Science, 2013; 4: 286- 291.
3. Jaydatt K J, Sreenivas S A. Review on chemical permeation enhancer used in Transdermal drug delivery system. International Journal of Science Innovation and Discoveries, 2012; 2: 204-217.
4. Ajay Sharma, Seema Saini, Rana A C. Transdermal Drug Delivery System: A Review. International Journal of Research in Pharmaceutical and Biomedical Sciences, 2013; 4(1): 286-292.
5. Dev Prakash, Amrit Pal Singh, Nishant Singh Katiyar, Kamla Pathak, Devender Pathak and Arti. Penetration

enhancers – The adjuents in transdermal drug delivery. World journal of Pharmacy and Pharmaceutical sciences, 2016; 5(5): 353-357.
6. Kedar Bavaskar, Ashish Jain, Mukesh Patil, Rajan Kalamkar. The Impact of Penetration Enhancers on Transdermal Drug Delivery System: Physical and Chemical Approach, International Journal of Pharma Research & Review, 2015; 4(7): 14-24.
7. Aggarwal S, Agarwal S, Jalhan S. Essential oils as novel human skin penetration enhancer for transdermal drug delivery: a review. International Journal of Pharma and Bio Sciences, 2013; 4(1): 857-868.
8. Vikas S, Seema S, Singh G, Rana A C, Baibhav J. Penetration enhancers: A novel strategy for enhancing transdermal drug delivery. International Research Journal of Pharmacy, 2011; 2(12): 32-36.
9. https://www.slideshare.net/ankitarai710/penetration-enhancer-with-their-examples-55729514.
10. Prasanthi D, Lakshmi P K. Vesicles – Mechanism of transdermal permeation – A review. Asian Journal of Pharmaceutical and Clinical Research, 2012; 5(1): 18-25.
11. Inayat Bashir Pathan, Mallikarjuna Setty C. Chemical Penetration Enhancers for Transdermal Drug Delivery Systems. Tropical Journal of Pharmaceutical Research, 2009; 8 (2): 173-179.
12. Edris A E. Pharmaceutical and therapeutic potentials of essential oils and their individual volatile constituents: A review. Phytother Res, 2007; 21: 308-323.
13. Hamid A A, Aiyelaagbe O O, Usman L A. Essential oils: its medicinal and pharmacological uses. International Journal of Current Pharmaceuticals Res, 2011; 86-98.
14. Singla Vikas, Saini Seema, Singh Gurpreet, Rana A C, Joshi Baibhav. Penetration enhancers: A Novel strategy for enhancing transdermal drug delivery. International Research Journal of Pharmacy, 2011; 2(12):32-36.
15. Williams A C, Barry B W. Essential oils as novel human skin penetration enhancer. International Journal of Pharmacy, 1989; 57: 7-9.
16. Morrow D I J, McCarron P A, Woolfson A D, Donnelly R F. Innovative Strategies for Enhancing Topical and Transdermal Drug Delivery. Open Drug Delivery, 2007; 36-59.
17. Shembale Al, Borole D K and Lohiya R T. Useful permeation enhancers for Transdermal drug delivery, International Journal of Pharmacy Res. and Dev, 2010; 2: 1-6.
18. Pathan I B and Setty C M, Chemical Peniteration enhancers for transdermal drug delivery system. Tropical Journal of Pharmacy Res, 2009; 8(2): 173- 179.
19. Lahora D, Chaudhary V, Shah S K, Swami G, Chaudhary G, Saraf S A. Terpenes: Natural skin penetration enhancers in transdermal drug delivery system. International Journal of Pharmaceutical Res Dev, 2011:39-45.
20. Cornwell P A, Barry B W, Bouwstra J A, Gooris G S. Modes of action of terpene penetration enhancers in human skin; Differential scanning calorimetry, small-angle X-ray diffraction and enhancer uptake studies. Int. J. Pharm, 1996; 127: 9-26.
21. Walker R B, Smith E W. The role of percutaneous penetration enhancers. Adv. Drug Deliver. Rev, 1996;18: 295-301.
22. Lizelle T Fox, Minja Gerber, Jeanetta Du Plessis and Josias H Hamman. Transdermal Drug Delivery Enhancement by Compounds of Natural Origin. Molecules, 2011; 16: 10507-10540.
23. Williams A C, Barry B W. Terpenes and the lipid-protein-partitioning theory of skin penetration enhancement. Pharmaceutical Research, 1991; 8: 17-24.
24. Mathur V, Satrawala Y, and Rajput M S. Physical and Chemical penetration enhancers in Transdermal drug delivery system. Asia Pharmaceutics, 2010; 4:173-183.
25. Dhruba Sankar Goswami, Nidhi Uppal, Sandeep Goyal, Naveen Mehta, Anil Kumar Gupta. Permeation Enhancer for TDDS from Natural and Synthetic Sources: A Review. Journal of Biomedical and Pharmaceutical Research, 2013; 2 (1): 19-29.
26. Reshmy Rajan, Deepa T Vasudevan. Effect of permeation enhancers on the penetration mechanism of transfersomal gel of ketoconazole. Journal of advanced pharmaceutical technology and research, 2012; 3(2): 112–116.
27. Satish Kumar Gupta, Kumar S. Transdermal Drug Delivery Enhancement by Essential Oils of Eucalyptus globules. Advances in Biological Research, 2014; 8 (6): 249-250.
28. Charoo N A, Shamsher AAA, Kohli K, Pillai K, Rahman K. Improvement in bioavailability of transdermally applied flurbiprofen using tulsi (ocinum sanctum) and turpentine oil. Colloid Surface. B, 2008; 65: 300-307.
29. Fu-Liang Wang, Hong-Mei Ji, Jian-You Zhu, Gui-Jun Xu, Yu-Zhong Guan and Ye-Jun Chen. Penetration Enhancement Effect of Turpentine Oil on Transdermal Film of Ketorolac. Tropical Journal of Pharmaceutical Research, 2015; 14 (8): 1341-1348.
30. Nauman Rahim Khan, Gul Majid Khan, Abdur Rahim Khan, Abdul Wahab, Muhammad Junaid Asghar, Muhammad Akhlaq and Abid Hussain. Formulation, physical, *in vitro* and *ex vivo* evaluation of diclofenac diethylamine matrix patches containing turpentine oil as penetration enhancer. African Journal of Pharmacy and Pharmacology, 2012; 6(6): 434-439.
31. Gao ZS, Wang L, Zhang M. Effects of penetration enhancers on curcumin transdermal drug delivery. Zhong Yao Cai, 2012; 35(1): 141-144.
32. Malay K Das, Bhattacharya A, Saroj K Ghosal. Effect of different terpene-containing essential oils on percutaneous absorption of trazodone hydrochloride through mouse epidermis. Drug Delivery, 2006; 13(6): 425-431.
33. Singla Vikas, Saini Seema, Gurpreet Singh, Rana A C, Jodhi Baibhav. Penetration Enhancers: A novel stratergy for enhancing transdermal drug delivery. International Research Journal of Pharmacy, 2011; 2(12): 32-26
34. Diez I, Peraire C, Obach R, Domenech J. Influence of d-limonene on the transdermal penetration of felodipine. European Journal of Drug Metabolism and Pharmacokinetics, 1998; 23(1): 7-12.
35. Ramesh G, Vamshi Vishnu Y, Kishan V, Madhusudan Rao Y. Studies on the influence of penetration enhancers on in vitro permeation of carvedilol across rat abdominal skin. Current Trends in Biotechnology and Pharmacy, 2007; 1 (1): 62-69.
36. Anna Herman and Andrzej P. Herman. Essential oils and their constituents as skin penetration enhancer for transdermal drug delivery: a review. Journal of Pharmacy and Pharmacology, 2014; 47(4): 473-485
37. Ammara HO, Ghorabb M, El-Nahhasa SA, Kamel R. Evaluation of chemical penetration enhancers for transdermal delivery of aspirin. Asian Journal of Pharmaceutical Sciences, 2007; 2 (3): 96-105.
38. Nawaz A, Jan SU, Khan NR, Hussain A, Khan GM. Formulation and in vitro evaluation of clotrimazole gel containing almond oil and tween 80 as penetration enhancer for topical application. Pak Journal of Pharma Sciences, 2013; 26(3): 617-622.
39. Hussain A, Khan GM, Shah SU, Shah KU, Rahim N, Wahab A, Rehman AU. Development of a novel ketoprofen transdermal patch: effect of almond oil as penetration enhancers on in-vitro and ex-vivo penetration of ketoprofen

through rabbit skin. Pak Journal of Pharma Sciences, 2012;25(1): 227-232.
40. Hussain A, Khan GM, Jan SU, Shah S, Shah K, Akhlaq M, Rahim N, Nawaz A, Wahab A. Effect of olive oil on transdermal penetration of flurbiprofen from topical gel as enhancer. Pak Journal of Pharma Sciences, 2012;25(2):365-369.
41. Suchika Sharma, Geeta Aggarwal, SanjuDhawan. Design and evaluation of Olanzapine transdermal patches containing vegetable oils as permeation enhancers. Scholars Research Library. Der Pharmacia Lettre, 2010; 2(6): 84-98.
42. Tristiana Erawati , Widji Soeratri, Noorma Rosita, Wida Rukmanajati, Hanifa Rahma. The Influence of Sesame Oil Addition on the Arbutin Release and Penetration in Carbomer Gel Base. International Journal of Pharma Research and Health Sciences, 2014; 2 (3), 241-245.
43. Ame Cowly, Vilijeon JM, J du Plessis, Gerber M. The effect of selected natural oils on the permeation of flurbiprofen through human skin, 2012, Chapeter 2: 35.
44. Chika J. Mbah, Charles O. Nnadi. Transdermal delivery of Gabapentin: Effect of cosolvent and microemulsion on permeation through rat skin. Pharmacology & pharmacy, 2014; 5: 471-478.
45. 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. Chemical Pharmacy Bulletin (Tokyo), 1989; 37(3): 855-856.
46. Huang YB, Fang JY, Hung CH, Wu PC, Tsai YH. Cyclic monoterpene extract from cardamom oil as a skin permeation enhancer for indomethacin: in vitro and in vivo studies. Biological Pharmacy Bulletin, 1999; 22(6): 642-646.
47. Huang YB, Hsu LR, Wu PC, Ko HM, Tsai YH. Crude drug (zingiberaceae) enhancement of percutaneous absorption of indomethacin: in vitro and in vivo permeation. Gaoxiong Yi XueKeXueZaZhi, 1993; 9(7): 392-400.
48. Hjaltason B. Bibl. Nutr. Dieta, Somogyi, JC, Muller, H.R, Eds; Karger Publishing: Basel, New frontiers in the processing and utilization of fish oil. In Nutritional Impact of Food Processing Switzerland, 1989; 96-106.
49. Tsutsumi K, Obata Y, Takayama K, Loftsson T, Nagai T. Effect of cod-liver oil extract on the buccal permeation of ergotamine tartrate. Drug Development Ind Pharmacy., 1998; 24(8): 757-762.
50. Loftsson T, Thormar H, Ólafsson JH, Gunnarsdóttir TM, Hjaltsason B, Gudmundsson G. Fatty acid extract from cod-liver oil: Activity against herpes simplex virus and enhancement of transdermal delivery of acyclovir in vitro. Pharmacy and Pharmacological Communication, 1998; 4: 287-291.

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