INTRODUCTION

Transdermal drug delivery offers a very advantageous route for drug delivery compared with the other routes of drug administration having advantages such as bypassing the hepatic first pass metabolism, and longer duration of action [1,2]. However, the barrier function of the skin outermost layer, the stratum corneum (SC) is one of the main limitations to it, and for this reason, skin penetration enhancers are gaining the greatest interest in pharmaceutical research [3].

Penetration enhancers help in the permeation of the desired drug (penetrant) through the skin by lowering the impermeability of the skin. Some properties which are desired in permeation enhancers are the must be pharmacologically inert, nonirritating, nontoxic, nonallergic, compatible with drugs and excipients, odorless, tasteless, colorless, and inexpensive and also have good solvent properties [4].

For a transdermal matrix patch to be successful, it relies on the capability of the penetrant (drug) to penetrate into the skin in quantities which is sufficient to maintain therapeutic levels. During formulating transdermal drug delivery system (TDDS), chemical enhancers are used widely as it helps in reducing the permeation barrier properties of the skin. A number of literature review mentioned that naturally occurring oils (essential oil and vegetable oil) can be employed as permeation enhancers due to their advantageous properties such as compatibility with drug and excipients, nontoxic, less allergic, and easy availability [5].

This review article describes the barrier properties of the skin and various natural permeation enhancers that have been employed to enhance the transdermal permeation of drugs and the different parameters for permeation evaluation.

SKIN AS A BARRIER TO DRUG PERMEATION

The outermost few microns of the skin, the SC, aids to the barrier function of the skin. This layer of the skin is the most impermeable, forming a laminate of compressed keratin-filled corneocytes attached in a lipophilic matrix. The lipids of this matrix are distinguishing in many respects:

- The essentially saturated, long-chain hydrocarbon tail aids a highly ordered, interlock configuration.
- From the skin surface to the base of the SC, they provide the only continuous phase.
- Among the biomembranes, the absence of phospholipid is particular and is a composition (ceramides, free fatty acids, and cholesterol) that is unique.
- The SC lipids exist as multilamellar sheets even though it is having a deficit of polar bilayer forming lipids.
- The SC barrier function is analogous to a brick and mortar assembly is suggested to impart the membrane impermeable to water with respect to other biomembranes. And by the visualization studies localizing several permeants, in the intercellular channels by kinetic analysis of the in vivo skin penetration rates of model compounds and by evidence from thermotropic biophysical studies of lipid domains the transport role of this pathway gets further more support [6].

Transdermal permeation pathways

Transdermal permeation can take place by diffusion through:

A. Through the SC: By means of the transcellular route, drugs can pass through the corneocytes highly hydrated keratins are present in corneocyte, which provides an aqueous environment for which the hydrophilic drugs can pass. Hence, the transcellular pathway is a predominant pathway for hydrophilic drugs.

B. Intercellular permeation: In intercellular pathway, the drug diffusing takes place by means of the continuous lipid matrix.

C. Transappendaged permeation: Only 0.1% of the skin surface area is covered by the hair follicle and sweat glands which limit the area available for the applied drug formulation to come in contact with it. For many drugs, an aqueous pathway is considered desirable but as the sweat is traveling against the diffusion pathway of permeant, permeation may be limited. Lipid-rich sebum fills the sebaceous gland, which may present a barrier for hydrophilic drugs [7].
PHYSICOCHEMICAL ASPECTS OF SKIN PENETRATION

Diffusion of drug through the skin is a passive kinetic process which occurs down the concentration gradient (from a high concentration region to a low concentration region). The steady state equation can be described by Fick's first law of diffusion. The equation describes the rate of transfer (flux, J) of a diffusing substance through the unit area of the membrane and diffusion coefficient, D to the concentration gradient across the membrane (dc/dx).

\[ J = -AD \frac{dc}{dx} \]  

The negative sign in equation (1) is because the diffusion process occurs in the opposite direction to increased concentration. Fick's second law of diffusion, equation (2) can be derived from equation (1) to describe membrane transport under nonsteady state condition:

\[ \frac{dc}{dt} = D \frac{d^2c}{dx^2} \]  

By maintaining the sink conditions in the receptor compartment and maximum fixed concentration in the donor compartment, the equation (2) can be written as:

\[ J = AD \left( \frac{Cm}{h} \right) \]  

Where, Cm is the concentration in the donor-membrane interphase and h is effective diffusional path length. The Cm in equation (3) can be used to replace by vehicle membrane partition coefficient (K) as the ratio between the concentration of permeant in the membrane at the donor-membrane interface and the vehicle in which applied (Cv). Modified Fick's first law of diffusion describes the steady-state flux across the membrane equation.

\[ J_{SS} = ADKCV/h \]  

We can conclude that increased drug flux can be achieved by a change in D, K, and C. The compounds which are skin penetration enhancers should potentially change the solubility or partition behavior of the drug into SC or its diffusion properties or both sometimes change in thermodynamic activity of drugs in the formulation manipulate the flux [8].

PERMEATION ENHANCERS

Penetration enhancers are the compounds which promote skin permeability [9]. They are an important factor in a TDDS which is used to improve the flux (J). Flux can be defined as the amount of material flowing through the unit cross section area at the time (t) [10].

Ideal properties of penetration enhancers:
- They must be pharmacologically inert, nonallergic, nonirritating, and nontoxic
- It must have compatibility with excipients and drugs
- It must not have any pharmacological activity in the body
- Cosmetically it must be acceptable
- It must be odorless, tasteless, and colorless
- It should allow therapeutic agents into the body but should prevent the loss of endogenous material from the body, i.e., they should work unidirectionally
- It must have chemical and physical stability
- It must have a reproducible and predictable duration of action
- It must have a good solvent property [11,12].

NATURAL PERMEATION ENHANCERS (NPEs)

NPEs are comparatively new class of penetration enhancer in the pharmaceutical industry. Due to its advantages such as low cost, better safety profile, more research need to be focused in this field to develop a stable transdermal formulations containing natural permeation enhancers (NPEs) which can be scale up for commercial transdermal drug product [13].

Papain Papain is isolated from Carica papaya. It is an endocytic plant cysteine protease enzyme [14]. Papain, which is a proteolytic enzyme, was studied in vitro and in vivo permeation of low-molecular-weight heparin (LMWH). The combined administration of LMWH and papain was found to be a new approach in improvement in absorption of orally administered heparin and hence its bioavailability [15].

Piperine Piperine is obtained from mature fruits of Piper nigrum and Piper longum [16]. Piperine was investigated for in vitro permeation of aceclofenac across human cadaver skin, and Fourier transform infrared technology was used to check the possible mechanism from which the results obtained showed that piperine enhances transdermal permeation of aceclofenac by biphasic mechanism involving partial extraction of SC lipid and interaction with SC keratin [17].

Capsaicin Capsaicin is a major alkaloid among capsaicinoids which is produced only in capsicum fruits of the genus capsicum and belonging to the Solanaceae family [18]. The permeation enhancing properties of capsaicin were studied for naproxen taking azone as the standard enhancer and capsaicin were compared to it. Onto the skin, different amount of chosen enhancer was applied before experiment. A formulation containing 5% capsaicin and commercially available naproxen gel formulation was also studied, and the results were compared. It was found that penetration increased when the skin was treated with azone and capsaicin and also some alteration by capsaicin was seen in the SC layer. Hence, it was observed that capsaicin increases the penetration of naproxen through SC, which concludes that capsaicin is quiet capable enhancer of skin like well-known enhancer azone [19].

Myristica fragrans M. fragrans was evaluated as a penetration enhancer in a transdermal gel formulation containing diclofenac sodium as the target drug. Methanolic extracts, chloroform extracts, and n-hexane extracts of M. fragrans were used as a penetration enhancer in comparison to a synthetic enhancer Triton X. It was found that in both in vivo and in vitro studies, methanol and chloroform extract showed better percentage cumulative release (%), and hence, better penetration was shown as compared to the synthetic enhancer [20].

ESSENTIAL OIL

Essential oil is natural products which are extracted from aromatic plants having a concoction of a number of aromatic smelling volatile compounds, primarily consisting compounds such as terpenes, terpenoids, and phenylpropanoids [21]. They can be accepted as a natural alternative to synthetic skin penetration enhancer due to their promising penetration enhancing activity [22].

As penetration enhancer, essential oils help in the delivery of drug compounds into the skin by interacting with the intercellular lipids by different physical processes such as increased disorder, phase separation, and fluidization. As they are penetrated easily by the skin, they are easily excreted also by the body with urine and feces. Hence, due to their better safety profile in comparison with other penetration enhancers, their use is increasing [23].

Essential oil as skin permeation enhancer Permeation enhancer interacts with the tissue components to lessen the barrier properties by partitioning into the SC but do not cause any damage to the underlying skin cell. Both D-limonene and 1, 8-cineole have shown to modify permeant diffusivity by disrupting SC lipid [24].

Eucalyptus oil The oil of eucalyptus can be obtained from a number of species of the Myrtaceae family, such as Eucalyptus citriodora, Eucalyptus dives,
Eucalyptus globulus, Eucalyptus polybractea, and Eucalyptus radiata. By steam distillation of eucalyptus leaves, its oil is extracted. The eucalyptus oil was subjected to permeation studies on full thickness human skin and it was found that the oil enhanced the permeation of chlorhexidine (2% w/v) into the dermis and the lower layer of the epidermis when it was combined with 70% (w/v) isopropyl alcohol and 10% (v/v) eucalyptus oil in comparison to the solution of chlorhexidine/isopropyl alcohol alone [25].

Almond oil
The extraction of almond oil can be made by steam distillation of twigs and leaves of Malaleuca quinquenervia, of the family Myrtaceae. The major constituents of almond oil was 55-70% 1,8-cineole (oxide) and limonene (monoterpene), 7-15% a-pinene (monoterpene), 2-6% s-pinene (monoterpene), and 2-6% viridiflorol (sesquiterpene). In vitro studies were performed to determine the permeation enhancing effect of almond oil at 10% (w/w) concentration in propylene glycol on estradiol model drug using a hairless mouse skin. It was found that almond oil proved to be more effective in transdermal permeation of estradiol than cajput, myrtle, orange, and cardamom essential oil [26].

Fennel oil
The extraction of fennel oil can be made from the seeds of Foeniculum vulgare, of the family Umbelliferae. On permeation studies, the percutaneous penetration of trazodone hydrochloride was enhanced by fennel oil followed by eucalyptus oil, citronella oil, and mentha oil. The variable physicochemical properties and molecular weights of phytochemicals present in the different essential oils may be the factors for the differences in the permeation enhancment activity between the oils [27].

Black cumin oil
The extraction of black cumin oil is made by steam distillation of the seeds of Cuminum cyminum, of the family Zingiberaceae. Black cumin oil showed a relatively greater permeating effect for the drug carvedilol when it was compared to clove oil, eucalyptus oil, tulsi oil, oelic acid, TWEEN 80 and the enhancement factor was found to be 6.40. Furthermore, Fourier transform infrared spectroscopy studies confirmed the alteration caused by black cumin oil on the permeability of the skin by extracting lipids and by hydrogen bonding which affects other hydrogen bonds between the ceramides [28].

Almond oil
Oil of almond and oelic acid were found as promising carriers/vehicles for enhanced permeability and solubility of aceclofenac. Hence, these oils can be used to develop drug delivery systems for improved bioavailability of aceclofenac [29].

In the study, topically applied ketoprofen gels and patches were formulated and evaluated, and almond oil was checked as a penetration enhancer for ketoprofen gels and patches through artificial membrane/rabbit skin. It was found that almond oil in different concentration as a penetration enhancer enhances the penetration of drugs from transdermal gels and patches across synthetic membrane/rabbit skin but notably when used in 3% concentration [30].

Basil oil
Basil oil was studied for its potential as a permeation enhancer for labetalol hydrochloride with respect to camphor, thymol, genniol, and clove oil. It was suggested that basil oil is having good penetration enhancing property for improved transdermal drug delivery of labetalol [31].

Basil oil was used for the enhancement in bioavailability of flurbiprofen applied transdermally and it was concluded that the bioavailability of the flurbiprofen applied transdermally using basil oil increased by 2.97, 3.80, and 5.56 times in comparison to the flurbiprofen administered orally in albino rats [32].

Alpinia oxyphylla oil
A. oxyphylla oil was extracted from A. oxyphylla and was divided into a higher polarity fraction and a lower polarity fraction. In vitro studies were performed using Franz diffusion cell across the dorsal skin of Wistar rats, the results indicated that the high polarity fraction of A. oxyphylla oil was having more efficient permeation enhancing the effect of indomethacin at concentration 3% and 5% then the lower polarity fraction [33].

Turpentine oil
Turpentine oil on the skin permeation rate of flurbiprofen showed an additive effect when it was added to an optimized cosolvent mixture of propylene glycol and isopropyl alcohol (30-705 [v/v]), and at the concentration of 5% (v/v) of turpentine oil, maximum transdermal penetration rate was obtained [34].

The effectiveness of turpentine oil was investigated for permeation enhancing activity for diclofenac dimethylamino matrix patches across the artificial skin in the Franz diffusion cell. It was found that the oil showed increasing permeation with increasing concentration of turpentine [35].

Rosemary oil
Rosemary oil is extracted from Rosmarinus officinalis. Rosemary oil when investigated for skin permeation enhancing activity for diclofenac sodium topical gel showed enhanced skin absorption at 0.5% and 1% concentration, respectively [36].

Cardamom oil
Cardamom (Elettaria cardamomum) is a common spice of India belonging to the Zingiberaceae family [37]. The oil extracted from cardamom has a number of volatile compounds such as monoterpenes including 1,8-cineole and cis-ocimene and sesquiterpene including guainine and nerodilol [38]. Cardamom oil on in vitro permeation studies through the rabbit abdominal skin showed an increase in penetration of the drugs indomethacin, diclofenac, and piroxicam [39].

TERPENES
In transdermal drug delivery studies, terpenes are one of the major choices. This class includes a heterogeneous range of members. The physicochemical properties of a specific terpene play a role in showing the effect on the skin, in particular, its lipophilicity. However, smaller terpenes with nonpolar groups are said to be better skin permeation enhancers [40]. Terpenes are also reported to increase drug partitioning and diffusibility into the skin by disturbing the lipid bilayers of the skin [41]. They are relatively safe as skin penetration enhancers for both hydrophilic and lipophilic drugs [42].

Farnesol
Farnesol is present in many essential oils, such as citronella, neroli, cyclamen, lemongrass, tuberos, balsam, and tolu. It is a sesquiterpene alcohol. Farnesol (0.25%) was reported to increase the permeation of diclofenac sodium with respect to other terpenes in the following order: Farnesol > carvone > nerolidol > menthone > limonenoxide [43].

Menthol
Menthol, which is one of the potent penetration enhancers, is obtained from the flowering tops of Mentha piperita. Menthol and limonenene together can be used as a prototype of terpenes that can be used as permeation enhancer [44].

Eucalyptol
Eucalyptol is a cyclic ether and a monoterpenoid known by a number of synonyms such as 1, 8-cineole, cajeput, eucalyptol, and cineole. Eucalyptol is used in cosmetic, fragrances and flavoring industries because of its spicy aroma and taste. 1, 8-cineole has also been used for the percutaneous absorption of several lipophilic drugs through the hairless mouse skin [45].

Eugenol
Eugenol was evaluated for permeation enhancing effect for the drug lornoxicam which is a nonsteroidal anti-inflammatory drug of oxicam class. Lornoxicam transdermal patches were formulated which were
then subjected to *in vitro* studies in a Franz diffusion cell using rat skin. *In vitro* studies showed that eugenol does increase the permeation of lornoxicam across rat skin [46].

**Borneol**

The transdermal permeation enhancing activity of borneol was investigated on 5 model drugs, namely, 5-fluorouracil, antipyrine, aspirin, salicylic acid, and ibuprofen and it was found that borneol effectively promoted the transdermal permeation of the model drugs [47].

**PERMEATION STUDIES**

The estimation of percutaneous absorption of a molecule is a very important step in the evaluation of a molecule of TDDS [48]. Moreover, in both pharmaceutical and cosmetic research, to support the development of TDDS skin permeation rates, evaluation has become a very important step [49]. The various ways by which the transdermal permeations of a drug molecule can be studied are.

**In vitro release studies**

Franz diffusion cell is used for carrying out *in vitro* release studies wherein the donor compartment the circular patch is mounted, the receptor compartment of which is filled with phosphate buffer saline (pH - 7.4), and the whole assembly is maintained at 32°C by the warm water circulation through the water jacket and is stirred at 40-50 rpm. The patch was kept in contact with the receptor liquid. About 0.5 ml of sample was withdrawn at regular intervals for 8 hrs and was replaced with the same amount of the medium. The samples were subjected to filtration, diluted, and analyzed spectrophotometrically [50].

**In vivo release studies**

Animal models

Hairless rat, hairless rhesus monkey, guinea pig, and rabbit are the most commonly used species used for evaluating transdermal drug. One of the most reliable models for *in vivo* evaluation of transdermal delivery in man is the rhesus monkey [51]. Animals in small scale are preferred for *in vivo* studies because of economic factors and availability [52].

**Human volunteers**

Clinical phase is one of the important stages in the development of a transdermal device, and in this stage, the formulation is tested in human volunteers for the collection of pharmacokinetic and pharmacodynamics data which are required to evaluate the generation and toxic effect during application of formulation. C14 radioisotope is used for labeling of drug to determine percutaneous absorption in human and measuring the radioactivity in excreta, but for knowing amount residing in a body and amount excreted by other route attention is required [52].

**In vivo dermal absorption study**

For *in vivo* dermal absorption test, the dorsal surface (approximately 4 cm × 3 cm area) of the rabbit skin is first dipped free for the application of the test substance and this is done before 24 hrs of starting the test. The requisite amount of the test substance was applied to the area, and 1 ml of blood sample was withdrawn from the central ear artery at predetermined times over 24 hrs at 2, 6, 12, 24 hrs. Plasma was obtained by centrifuging the blood and was stored at −20°C before analysis. The analysis was done using headspace gas chromatography-mass spectrometry [53].

**CONCLUSION**

The field of transdermal drug delivery due to its advantages has been rapidly developing and which has stimulated various researches to incorporate more and more drugs through transdermal route. Skin serves a limitation for permeation of drugs, and hence, permeation enhancers are used to increase the permeability of the poorly absorbed drugs and hence maintain its bioavailability. The review article summarizes the various NPEs which can be used to accelerate the permeation of drug across skin for the development of transdermal delivery system and the parameters by which the permeation studies can be done. In this article, various NPEs has been discussed which can be used to accelerate the permeation of drug across skin for development of TDDS.

**REFERENCES**


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