Permeability Investigation and Transdermal Drug Delivery Using Natural Permeation Booster Systems : A Literature Review

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Abstract –

Because of its benefits of skipping first-pass metabolism in the liver, fewer digestive issues and negative repercussions, improved patient adherence because It is a painless method of self-administration for patients., and so on, topical medication administration is becoming a viable option. The difficulty of drugs passing through the stratum corneum (skin's top layer) protects the underlying tissues from the external environment., which is a big downside of this route. A skin-administered medicine can only work if it can get past the skin membrane and into the blood circulation, and penetration enhancers aid with that by increasing the skin's permeability, which in turn keeps the drug level in the blood stable. Chemical, natural, and physical permeation enhancers are all available. The current review discusses natural permeation enhancers that can be used to improve medication transdermal penetration.

Keywords - Penetration enhancers, Transdermal barriers, Transdermal medication delivery system.

Introduction :

Transdermal medication delivery is a particularly beneficial method for drug administration as contrasted to other routes, since it prevents hepatic first-pass Biotransformation and has a prolonged duration of action. However, one of the key restricts the skin's outermost layer function as a barrier, the corneum stratum (SC), which is why skin permeation boosters are attracting the most attention in pharmaceutical research. By decreasing the skin's barrier properties, penetration boosters aid within the permeation of intended substance (penetrant) through the skin. Permeation enhancers should have features such as being Chemically harmless, non-irritating and non-allergic, non-toxic and compatible with medications and excipients, odourless, flavourless, colourless, and inexpensive, as well as having decent solvent properties. [(4)]The

capacity of the penetrant (medicine) to permeate into the skin in adequate concentrations to sustain medicinal concentrations is critical for the effectiveness of a transdermal matrix patch. Chemical boosters are commonly utilized when developing transdermal drug delivery systems (TDDS) because they aid to reduce the skin's permeation obstacle characteristics. According to a variety of literature reviews, naturally existing Oils can be used. used as permeation boosters because of their beneficial qualities such as drug and excipient compatibility, nontoxicity, low allergy potential, and ease of procurement. The barrier qualities of the skin, as well as several natural permeation boosters that have been used to improve medication transdermal penetration and the many metrics for permeation assessment, are discussed in this review article.

1. SKIN AS A DRUG PENETRATION OBSTACLE

The Stratum corneum, or the skin's topmost few microns, helps the skin's protective barrier. This is the most impenetrable covering of the skin, consisting of a lamination of compacted corneocytes linked in a lipophilic matrix and packed with keratin. The lipids in this system stand out for a number of reasons:

- They constitute the only uninterrupted from the top of the skin phase to the horny layer's base.
- The dearth of phospholipid is notable among biological barriers, as is the content (ceramides, cholesterol and free fatty acids).
- Even though there is a lack of polar multilayer building lipids, horny layer lipids appear as multilamellar sheets.

However, the membrane's resistance cannot be addressed by the unique lipid matrix, and the design of the horny layer as a whole has been suggested to influence the membrane's obstacle characteristic. The corneocyte, which looks like a mortar and bricks construction, is thought to make the membrane impervious to water when compared to other cell membranes. The transport significance of this system is further supported by visualization experiments that localize numerous kinetic permeants in intercellular channels investigation of *skin in vivo* permeation rates of model chemicals, and thermotropic biophysical studies of lipid domains provide evidence.

1.2.Mechanisms of transdermal penetration

Diffusion allows for transdermal penetration through:

a) Through the horny layer: Medicines can enter through the corneocytes via the transcellular pathway because corneocytes contain extensively hydrated keratins, which offer a hydrophilic environment in which hydrophilic drugs can penetrate. As a result, the transcellular pathway is the most common route for hydrophilic medicines.

b) Intercellular penetrability: The medicine diffuses across a continuous lipid matrix in the intercellular route.

c) Trans-appendaged permeation: The hair follicle and glands sweat cover just 0.1 percent of the surface skin area, restricting the region that can be reached by the pharmaceutical formulations used in the application. A hydrophilic channel is preferred for many medications, however, because perspiration travels in opposition to the permeant's diffusion route, penetration may be reduced. The sebaceous gland is filled with lipid-rich sebum, which might also act as a barrier to hydrophilic medicines.

1.3. Penetration boosters

Compounds that facilitate skin penetration are known as permeation boosters. They are a crucial component of a method for transdermal medication administration, which is utilized to increase flow. The quantity of material moving via the unit cross-sectional area at any certain time (t) is known as flux (J).

Penetration boosters should have the following properties:

- They must be pharmacologically inactive, allergen-free, irritant-free, and non-toxic.
- It must be compatible with excipients and pharmaceutical medicines.
- It must be pharmacologically inactive in the body.
- It must be acceptable in terms of appearance.
- It should let therapeutic chemicals enter and prevent the loss of endogenous material while maintaining the body,i.e., it should act in a one-way fashion.
- It must be both chemical and physical stability.
- Its duration of action must be specified. repeatable and expected.

2. Natural permeation booster

In the pharmaceutical business, NPEs are a relatively new kind of permeation booster. More study is needed this sector to produce stable transdermal preparations among them are scalable natural permeation enhancers (NPEs) for commercial transdermalpharmaceutical products due to benefits like cheaper cost and higher safety profile..

a) **Papain**

Carica papaya is used to make papain. Endocytic cysteine protease from plants. (12)A proteolytic enzyme called papain, was used to investigate low-molecular-weight heparin penetration *in-vitro* and *in-vivo* (LMWH). The use of LMWH and papain in combination was discovered to be a novel method for increasing the oral absorption given heparin and hence its bioavailability.

b) **Piperine**

Ripe fruits of the Piper nigrum and Piper longum trees contain piperine.It was tested for aceclofenac transdermal penetration across the skin of a cadaver *in-vitro*, as well as FTIR technology was utilized to confirm the potential mechanisms. The outcomes demonstrate that piperine maximizes aceclofenac transdermal penetrability by means of aHorny layer lipid is partially extracted during a biphasic phase, and this interaction results in Horny layer keratin.

c) **Capsaicin**

Capsaicin is a significant alkaloid found only in capsicum fruits related to the Solanaceae family and generated solely in the genus capsicum. Capsaicin's permeation-enhancing effects were naproxen was investigated using as the standard enhancer, and comparing it to capsaicin. Before the trial, a different quantity of the selected booster was rubbed on the skin. The effects of a preparation containing threeper cent,in addition, capsaicin as well asa commercially available naproxen gel formulation were tested.When azone and capsaicin were applied to the skin, it was discovered that penetration enhanced, and that capsaicin altered the horny layer.

d) **Essential oil as penetrating booster**

Penetration enhancers interact with tissue constituents to reduce barrier qualities by partitioning into the horny layer, but they do not harm the underlying skin cell. By altering horny layer lipid, Permeant diffusivity has been shown to be altered by D-limonene and 1, 8-cineole.

e) Oil of eucalyptus

Eucalyptus citriodora, Eucalyptus dives, and Eucalyptus globulus are three species of Eucalyptus. are only a few Genus include species, for example essential oils. Their oil is obtained by hydro-distillation of eucalyptus leaves. If eucalyptus oil has been coupled using Isopropyl alcohol at 70% (w/v)as well as 10% (v/v) eucalyptus oil and tested on When compared to merely the chlorhexidine/isopropyl alcohol solution, it was shown that the oil increased the permeability of chlorhexidine (2 percent [w/v]) through to the dermis and bottom layer of an epidermal cell.

f) Niaouli oil

The stems as well as leaves from *Melaleuca quinquenervia*, a member of the *Myrtaceae* family, could be heat distilled to yield niaouli oil. Niaouli oil contained 55-70 percent1,8-cineole (oxide) and limonene (monoterpene), as well as monoterpenes in amounts of 7–15 percent a-pinene, 2–6 percent s-pinene, and 2–6 percent viridiflorol (sesquiterpene). On a surface of a shaved rat, it was examined in vitro as to how niaouli oil at a concentration of 10% (w/w) in propylene glycol affected the permeability of an estradiol test drug. Niaouli oil outperformed cajput, myrtle, orange, and cardamom essential oils for transdermal estradiol penetration.

g) Fennel oil

The seeds of the plant Foeniculum vulgare, a member of the *Umbelliferae* family, will be used to produce oil of fennel Fennel oil comes first, followed by Citronella oil with eucalyptus oil. With mentha oil, trazodone hydrochloride's percutaneous penetration was boostedin permeability testing. Its varied physio-chemical qualities including the molecular mass of substances contained in various basic oils could explain the discrepancies in permeability enhancing activities.

h) Black cumin oil

Black cumin oil is made by steam distilling Cuminum cyminum seeds. Black cumin oil, with an

enhancement factor of 6.40, showed a substantially larger penetrating influence for the drug carvedilol than clove oil, eucalyptus oil, tulsi oil, oleic acid, and Tween 80. Furthermore, black cumin oil influences skin penetration by eliminating lipid, followed by covalent bonds, which impacts other hydrogen connections between ceramides, according to studies using Fourier transform infrared spectroscopy.

i) Almond oil

Almond oil plus oleic acid had been discovered to be effective airlines at improving aceclofenac penetration and bioavailability. As a result, such oils could be employed to design pharmaceutical delivery methods that enhance aceclofenac solubility.[21] The researchers created and tested successfully encapsulated ketoprofen gels and patches, and almond oil has been tested as a ketoprofen gels and patches penetration enhancer via a synthetic surface skin. These were discovered that using almond oil as a penetration enhancer at various concentrations improves drug Transdermal gels and patches penetrate artificial surface skin, especially when used at a 3 percent concentration.

j) Basil oil

Camphor, thymol, geraniol, and clove oil are examples of essential oils. basil oil has been investigated because of its ability as a permeation enhancer of labetalol hydrochloride. Basil oil has been indicated as providing decent penetration boosting properties for better labetalol transdermal medication administration. With albino rats, basil oil has been used to boost the solubility of when compared to flurbiprofen administered directly, it has been discovered that the solubility of flurbiprofen applied transdermally enhanced by around 2.97, 3.80, and 5.56 times.

k) *Alpinia oxyphylla*oil

A. *oxyphylla* extracts were prepared and separated into two fractions: one with greater potential and the other with a lesser potential. These findings of *invitro* investigations utilizing the high polarity fraction of A. Oxyphylla oil had better penetration, increasing the effect of indomethacin between concentrations of 3 and 5 percent, according to Franz diffusion cell over the dorsal skin of Wistar rats.

l) Turpentine oil

Whenever turpentine oil has been introduced to an optimal dispersant combination of 30-705 [v/v] propylene glycol and isopropyl alcoholit had an additional effect upon that skin permeation rate of flurbiprofen, and the greatest transdermal penetration rate has been attained at a level for 5percent (v/v) of turpentine oil. Inside the Franz diffusion cell, the efficiency of turpentine oil as a permeation enhancer The use of diclofenac dimethylamine matrix patches across artificial skin has been investigated. It was discovered that the penetration increased as the concentration of turpentine in oil increased.

m) Rosemary oil

Rosmarinusofficinalis is used to make rosemary oil. Whenever rosemary oil was tested for its ability to improve skin permeation topical diclofenac sodium

gel it demonstrated the increased results of skin at concentrations of 0.5 percent and 1 percent, accordingly.

n) Cardamom oil

Cardamom (*Elettariacardamomum*) is a *Zingiberaceae* spice that is widely used in India. Cardamom oil contains a variety of volatile chemicals, including monoterpenes like cis-ocimene and 1,8-cineole as well as sesquiterpenes like guanine and nerodilol. Cardamom oil increased the penetration of medications indomethacin, diclofenac, and piroxicam in *invitro* permeation experiments along through rabbit abdomen skin.

o) Terpenes

Terpenes were always a popular option in transdermal investigations. Groups come in a huge range of sizes and forms.The chemical and physical features of a terpene, particularly its lipophilicity, have a role in determining its impact on the body. Shorter terpenes containing nonpolar moieties, on the other hand, are claimed to improve skin permeability. Terpenes have also been shown to promote drug fractionation and diffusibility within skin via disrupting a body's lipid cell membranes. For skin penetration enhancers with both aqueous and lipid soluble medicines, they were generally harmless.

p) Farnesol

Several essential oils, including Farnesol can be found in Tuberose, balsam, tolu, lemongrass, neroli, cyclamen, and citronella. alcohol from sesquiterpenes, to be precise. which means this is derived from sesquiterpenes. In contrast to certain other terpenes, farnesol (0.25 percent) was shown to enhance diclofenac sodium permeability in the correct sequence: Carvone > nerolidol > menthone >limonene oxide> farnesol.

q) Menthol

Menthol is extracted from the flowering tops of *Menthapiperita*, and was among the most powerful penetration enhancers. Combined, menthol and limonene create a terpene prototype that could be utilised to improve permeability

r) Eucalyptol

Eucalyptol, also called as well as 1, 8-cineole, cajeputol, eucalyptol, and cineole a cyclic ether and monoterpenoid with a variety of aliases. Eucalyptol is used in the cosmetic, fragrance, and flavouring industries due to its fiery aroma and flavour. Many lipid-soluble medicines have been absorbed percutaneously via the shaved rats treated using 1, 8-cineole.

s) Eugenol

Eugenol has been tested for its ability to improve penetration of a nonsteroidal anti-inflammatory medication lornoxicam, which belongs to the oxicam class. Lornoxicam transdermal patches were developed. and they were tested *in-vitro* using rat skin in a Franz diffusion cell. *In-vitro* experiments revealed how eugenol increases lornoxicam penetration through rat skin.

t) Borneol

The transdermal permeability boosting ability of borneol has been tested upon five reference drugs: 5-fluorouracil, antipyrine, aspirin, salicylic acid, and ibuprofen are some of the medications used.

4. Permeation Studies

An assessment of a particle's skin penetration is a critical stage in the evaluation of a Formulating molecule. Furthermore, assessment became a critical stage for both cosmetics and pharmaceutical studies to promote the TDDS skin permeation rates development. The numerous methods for studying a pharmaceutical molecule's transdermal permeation include.

***a) In-vitro* release studies**

With a circular patch placed within the cuvette, phosphate-buffered saline (pH - 7.4) in the cuvette, and the entire system kept at 32°C by hot water circulation through the water jacket and agitated at 40–50 rpm, the Franz diffusion cell can be utilised for in-vitro release research. Throughout the process, the patch was kept in close proximity to the receptor liquid. For the following eight hours, 0.5 ml of the sample was periodically removed and replaced with the same volume of media.Filtering, dilution, and spectrometric analysis were performed on the samples.

***b) In-vivo* release studies**

Animal models-

The first most widely utilized species for transdermal drug testing are the shaved rats, hairless rhesus monkey, guinea pig, and hares. The rhesus monkey is among the most dependable models for *in vivo* evaluation of transdermal administration in humans. Because of availability and price, small-scale animals were favoured for *in-vivo* experiments.

Human volunteers :

A medical phase is the most crucial step in the evolution of a transdermal device, so it involves testing the formulations in healthy volunteers in order to acquire pharmacodynamic and pharmacokinetic data that are needed to assess the formation of harmful effects when formulation administration. C14 radioisotope is being used for medication labelling, determining skin permeation in humans, and detecting radioactivity in excreta, however, care is required to learn how much is staying inside the body and how much is expelled by certain routes.

c) *In-vivo* dermal absorption study

Prior to beginning an *in-vivo* epidermal test method, the dorsal region (about 4 cm 3 cm region) of the hare skin is trimmed clean for the administration of a test drug. This is done before the test is started for 24 hours. A little quantity of a test chemical has been administered to the region, while 1 ml of blood has been collected from the central ear artery at predefined intervals over the course of 24 hours (at 2, 6, 12, and 24 hours). Prior to testing, plasma was collected by centrifuging the blood and kept at 20°C. Headspace gas chromatography-mass spectrometry was used for the study.

Conclusion :

The area of topically applied medication delivery has been fast increasing provides several benefits, that has prompted many studies to combine greater and greater pharmaceuticals via the transdermal route. Because the epidermis acts as a drug permeation barrier, penetration to increase the permeability of poorly absorbed substances, enhancers are utilised.substances. medicines and thus retain their potency. This research paper discusses the various NPEs that can be utilized to accelerate drug penetration across the skin in order to develop transdermal delivery systems, as well as the variables that could be used to conduct permeation tests. Several NPEs have been addressed in this section that can be employed to increase drug absorption through epidermis for such creation of Transdermal drug delivery.

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