IJPHT Journal
Papers Having Good Impact
International Journal of Pharmacy and Herbal Technology-ISSN NO: 2583-8962 (Online)

A REVIEW OF NATURAL PERMEATION ENHANCER FOR TRANSDERMAL DRUG DELIVERY SYSTEM AND PERMEATION EVALUATION

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ABSTRACT:

Because of the constant and ideal blood concentration, side effects are reduced to minimum. Its medication effectiveness and bioavailability are higher. The human Drug delivery systems that are transdermal have been around for a while. For dermatological conditions, topically administered creams and ointments were the most often used techniques in the past. Some of these formulations have a systemic side effect, which suggests absorption through the Dermis. Many medications have been used topically to treat the entire body.Transdermal delivery systems, in their broadest definition, refer to any drug compositions applied topically and meant to release the active ingredient into the bloodstream. Systems for transdermal therapy have been developed to Give regulated, ongoing cutaneous distribution of medications to the bloodstream. It is commonly recognized that skin is rather impervious, which is linked to its dual protective properties against microbial invasion and the retention of physiologically necessary substances like water.With TDDS, gastrointestinal side effects are reduced, administration frequency is decreased, and first pass metabolism is avoided. skin is a complex organ with numerous histological layers. The largest organ in the body is the skin.Furthermore, prodrugs, liposomes, thermosetting gels, iontophoretic and sonophoretic systems, and prodrugs are examples of advanced transdermal carriers

Keywords: *Transdermal Drug Delivery System (TDDS), prodrug, thermosetting gels, liposomes*

INTRODUCTION:

Transdermal application is an excellent choice because it avoids first-pass metabolism by the liver and has a longer duration of action than other methods of administration. However, the outer layer of the skin acts as a barrier[1].One of its primary components is the stratum corneum (SC).carriers, which is why skin penetration enhancers are becoming more and more common in pharmaceutical research. Transdermal drug delivery is the process of applying discrete, self-contained dosage forms to intact skin to allow for controlled drug delivery at a predetermined rate through the skin. Transdermal medicine delivery can be used to stop gastrointestinal absorption associated risks of pH-related alterations and enzymatic deactivation. The transdermal route has a faster metabolism than the digestive system, so this method also permits smaller dosages of medications. When compared to other drug delivery techniques, transdermal administration provides a highly beneficial approach However, the stratum corneum (SC), the outermost layer of skin, is one of the main obstacles to it[19],[20] Skin penetration enhancers are therefore being used more frequently in pharmaceutical research.

.By reducing the barrier to entry, penetration enhancers aid in the desired drug's (penetrant) skin penetration.the skin's impermeability. Certain characteristics are required of penetration enhancers:

they should be low-cost, odorless, colorless, tasteless, nontoxic, nonallergic, nonirritating, and pharmacologically inert. They should also have good solvent properties.[2,3]

SKIN AS A PROTECTION AGAINST DRUG PERMEATING.

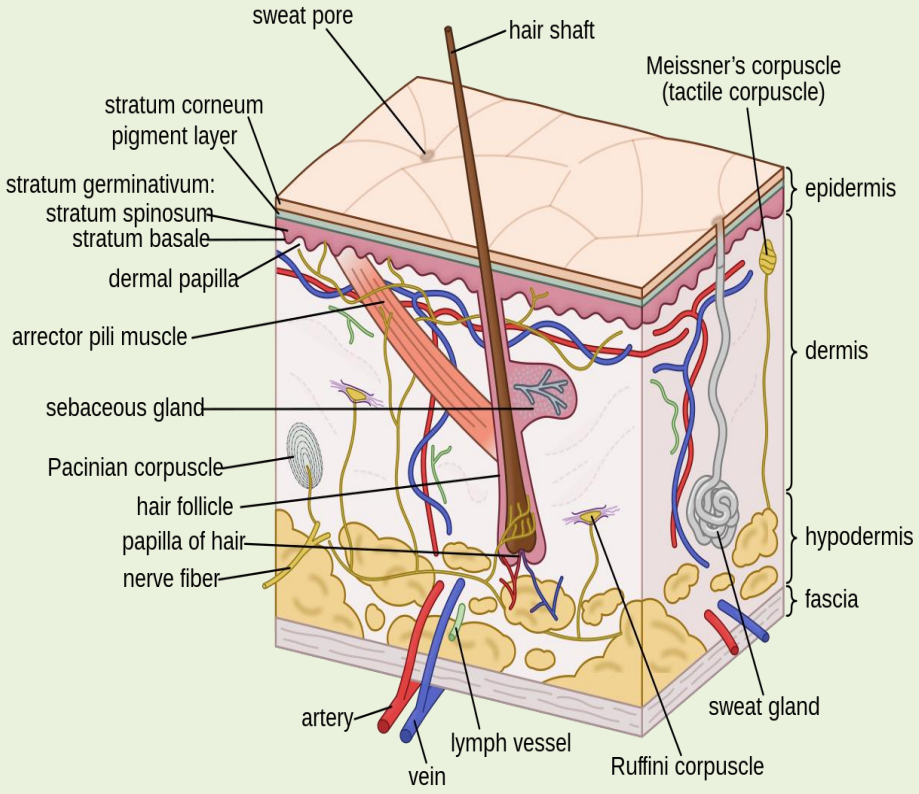

Fig 1 Skin three dimensional

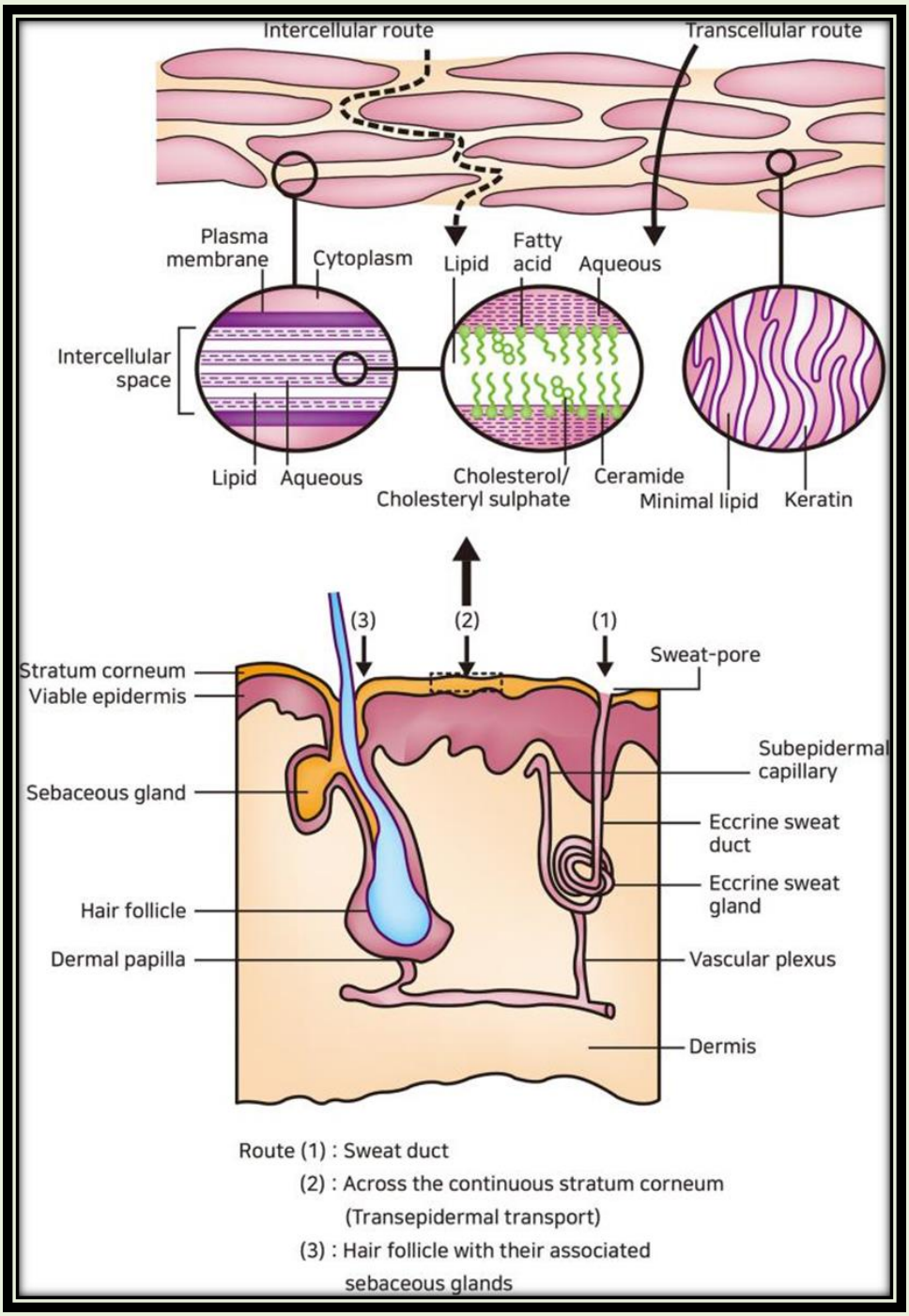

Fig 2: Route of permeation

ENHANCER ACROSS SKIN:

Nevertheless, the peculiar lipid matrix cannot fully account for the resistivity of the membrane, and the It has been proposed that the barrier quality of the membrane is influenced by the SC's overall architecture. It is hypothesized that, in contrast to other biomembranes, the corneocyte, which resembles a brick and mortar assembly, gives the membrane its water impermeability[5]

Transdermal permeation pathways:

Diffusion can result in transdermal penetration through the following channels:

A. Via the SC: Medication can pass through corneocytes via the transcellular route. Because hydrophilic medications are able to pass through an aqueous environment created by corneocytes, this route is frequently used for them.

B. Via the Intercellular pathway: The continuous lipid matrix promotes drug diffusion.

C. Via the Transappendaged pathway: Only 0.1% of the skin surface consists of hair follicles and sweat glands, which limits the area where the drug is used. Collect images to interact with them[6,7]

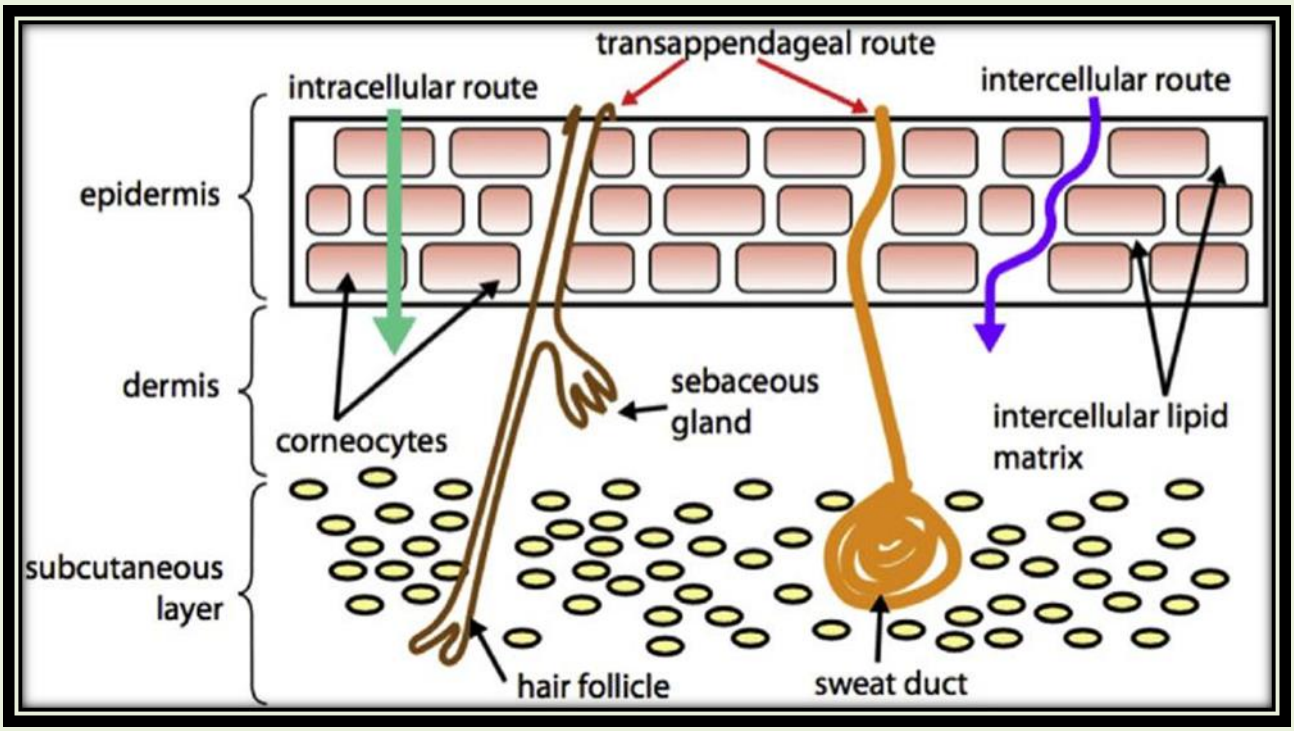

Fig 3: Transdermal permeation Pathways

Advantages of transdermal drug delivery system

Because the transdermal route is safe and convenient, it is an intriguing option for delivery. The advantages of administering medication through the skin to produce a systemic effect are

1. first pass metabolism's avoided.
2. GI incompatibility is avoided.
3. A consistent and long-lasting activity.
4. Reducing unwanted side effects.
5. provides the use of a drug with a short therapeutic window and a short biological half-life.
6. Steering clear of drug level fluctuations.
7. Keep the powerful drug's plasma concentration constant.
8. It's simple to stop therapy at any moment.
9. Increased patient compliance as a result of the removal of several dosage profiles.
10. The capacity to more precisely deliver the medication to a particular location.
11. Ensure that self-administration is appropriate.
12. Improve the effectiveness of therapy.

Disadvantages of TDDS:

1) One or more system components can cause contact dermatitis at the application site in certain patients, which requires stopping the treatment.
2) Greater expense.
3) Ionic drugs should not be used.
4) Could result in allergic responses.
5) It's imperative that the molecular weight be under 500 Dalton
6) Adequate lipid and aqueous solubility; permeate must have a log P (octanol/water) between 1 and 3 in order to cross the SC and penetrate underlying aqueous layers.
7) Only some powerful drugs are suitable for transdermal therapy.
8) Ionic medications are not suitable for transdermal therapy.
9) It is not capable of pulsatile drug delivery.
10) Due to the skin's natural barriers to drug entry, only relatively potent medications are appropriate candidates for transdermal delivery.

Aspects of skin penetration that are physicochemical :

Diffusion refers to the drug's passive kinetic passage through the skin along the drug's concentration gradient-based passive kinetic passage through the skin (from a high concentration area to a low concentration area).

The steady state equation Is defined by Fick's first law of diffusion. This formula gives the concentration gradient across the membrane (dc/dx), the diffusion coefficient D, and the transport rate (flow) of material diffusing across a membrane unit.[8]

$J=-AD\ (dc/dx)$ ……(1)

Since the diffusion process moves in opposite directions with increasing pressure, equation (1) has a negative value. Equation (1) can be used to derive equation (2), Fick's second law of diffusion, which describes transport across membranes under unstable conditions.

$J=-AD\ (dc/dx)$ …… (2)

Over time, the dc/dt concentration varies.

Change in position equals dx.

An expression for equation (2) is as follows:

$J=AD\ (Cm/ħ)$ ……..(3)

If the maximum constant concentration in both the sink in the receiving room and the supply room is maintained. (3), where Cm is the donor membrane interface concentration and is the effective diffusion path length. In equation (3), Cm can be replaced by the ratio of the permeate concentration in the membrane at the donor-membrane interface to the carrier using the membrane (Cv) or the carrier also the membrane partition coefficient (K). The equation of state transmembrane flux is described by a modified Fick's first law of diffusion.

J=ADKCV/h SS ……. (4)

Therefore, changing D, K, and C will result in an increase in drug flux. The drugs' solubility, partition behavior, or diffusion characteristics can be changed by the substances that increase skin penetration[9,10]

PERMEATION IMPROVEMENTS:

The substances referred to as penetration enhancers make the skin more permeable. They are essential to a transdermal drug delivery system.which is employed to improve the flow (J). The amount of material that moves through a given is called flux[11]

Perfect characteristics for penetration enhancers:

1. It must be acceptable in terms of appearance.
2. It needs to be compatible with medications and excipients.
3. Its duration of action needs to be predictable and repeatable.
4. It should function unidirectionally, allowing therapeutic agents to enter the body while preventing the body from losing endogenous material.
5. It needs to possess good solvent properties.
6. They have to be nontoxic, nonallergic, nonirritating, and pharmacologically inert.
7. It needs to be tasteless, colorless, and odorless.
8. It should work in a unidirectional manner, allowing therapeutic agents to enter the body while blocking the extrusion of endogenous material
9. It must possess good solvent properties, a repeatable and consistent duration of action, and chemical and physical stability.
10. It needs to be stable both physically and chemically.
11. It needs to possess good solvent properties.
12. Its duration of action must be dependable and repeatable[13]

Natural Permeation enhancers:

NPEs are a new class of entry into the pharmaceutical industry. More research is needed in this area to develop sustainable conversion models incorporating natural encapsulation processes (NPEs) that can achieve these benefits at low cost and increase safety. Transdermal products are available without a prescription.

A) **Aloe Vera:**

Fig 4: Aloe vera

The most common type is Aloe Barbadians Miller, also known as Aloe Vera Linn for its medicinal properties. This plant has many uses in food, medicine and cosmetics. Aloe vera gel is a clear, colorless, viscous mucilage gel made from parenchyma cells found in the young leaves of the plant. Penetration enhancers may work by changing the SC of a drug, making it more soluble. Disruption of skin lipids results from drug delivery to the SC and/or penetration affecting drug diffusion across the SC. Histopathological examination of SCs treated with aloe vera oil revealed a novel infiltration mechanism.

B**) Essential Oils:**

Certain plants have volatile, pungent substances called essential oils that are present in their flowers, fruit, leaves, and roots. Many separate essential oils' ability to improve skin penetration has been well studied. Terpenes, terpenoids, and phenyl propanoids are substances found in oils, as well as trace amounts of various volatile organic substances.

Fig 5: Essential oil

Examples of essential oils:

By partitioning into the tissue components, the penetration enhancer interacts with them to decrease the barrier properties. SC, but they don't harm the skin cells underneath. It has been demonstrated that 1, 8-cineole and D-limonene both alter permeability diffusivity by interfering with SC lipid

1)Piperine

Fig 6: piperine

Piperine is made from the ripe fruit of black pepper and long pepper. According to in vitro studies of the penetration of aceclofenac into human cadaveric skin, piperine enhances drug penetration through a two phase process involving partial SC lipid extraction and interaction with SC keratin.An investigation into the potential mechanism was conducted using Fourier transform infrared technology 15,162)

2) **Eucalyptus oil:-**

Fig 7: Eucalyptus oil

Among the species in Myrtaceae family that yeild eucalyptus oil are eucalyptus globuls citriodora, eucalyptus dives, eucalyptus polybractea & eucalyptus radiatata. Oil from eucalyptus leaves is obtained by steam distillation.Eucalyptus oil mixed with 70% (w/v) isopropyl alcohol and 10% (v/v) eucalyptus oil improved chlorhexidine on the permeable dermis and subepidermis (2% [w/v], compared to chlorhexidine/isopropyl alcohol alone).

3) Papain

Fig 8:papain

Piperine is made from fully ripe black and long pepper fruit. According to in vitro studies of the penetration of aceclofenac into human cadaveric skin, piperine enhances drug penetration through a two-phase process involving partial SC lipid extraction and interaction with SC keratin. The researchers used Fourier transform infrared technology to study the underlying process.[13]

4)Capsaicin :-

Fig 9: Capsaicin

Only fruits belonging to the Solanaceae family, specifically those in the capsicum genus, contain capsaicin, the primary alkaloid among capsaicinoids. The penetration-enhancing properties of capsaicin were assessed by contrasting it with the industry standard enhancer azone. Before the experiment, the chosen enhancer was applied to the skin in different concentrations. Additionally, the study and comparison of a naproxen gel formulation available in the market with a 3% capsaicin formulation were conducted.It was discovered that applying azone topically along with capsaicin altered the SC layer and increased penetration. After all, it was found that capsaicin makes naproxen easier for the skin to absorb, suggesting that it is a mild but effective skin enhancer similar to the well-known enhancer azone.[17]

5) Fennel oil: -

Fig 10:fennel oil

The seeds of the family Foeniculum vulgare can be used to extract fennel oil. Umbelliferae. Trachodone hydrochloride's percutaneous penetration was found to be enhanced by fennel oil in permeation studies, with eucalyptus, citronella, and mentha oils following suit. Differences in the penetration-enhancing activity of each essential oil can be attributed to their different molecular weights and different physicochemical properties of the phytochemicals they contain.

CONCLUSION: -

Due to its advantages, the field of transdermal drug delivery is rapidly expanding, leading to many studies involving various transdermal drug delivery systems. Due to the limited ability of drugs to pass through the skin, poorly absorbed drugs increase permeability, thus controlling their bioavailability. Because of its benefits, the field of transdermal drug delivery has been expanding quickly, which has encouraged numerous studies to include an increasing number of drugs via this route.

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