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Review Article

Penetration Enhancers Used in Transdermal Drug Delivery System

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ABSTRACT

Transdermal drug delivery systems (TDDS) offer a non-invasive technique to administer therapeutic drugs, although effective drug absorption via the skin is sometimes limited by the barrier function of the stratum corneum. Because natural penetration enhancers are safe and biocompatible, they have become a viable substitute for synthetic chemicals. This review focuses on a number of natural ingredients that improve medication absorption through the skin, such as lecithin, liquorice, bargamot, tulsi, and aloe vera. These enhancers function by altering the lipid structure of the stratum corneum, enhancing solubility and bioavailability of medicines such as NSAIDs, antibiotics, and analgesics. Compared to synthetic enhancers, these natural compounds not only improve drug delivery but also reduce side effects and skin irritation.

INTRODUCTION

When compared to other drug administration routes, transdermal drug delivery is a particularly beneficial option because it circumvents the hepatic first pass metabolism and has a longer duration of action. [1,2] Nevertheless, one of the primary barriers to it is the stratum corneum (SC), the outermost layer of skin. For this reason, pharmaceutical research is becoming increasingly interested in skin penetration enhancers.[3] By reducing the skin's impermeability, penetration enhancers aid in the intended drug's penetration through the skin. The following characteristics are preferred in permeation enhancers: they should be cheap, tasteless, colorless, odorless, non-irritating, nontoxic, nonallergic, and pharmacologically inactive. [4] They should also have good solvent qualities. For a transdermal matrix patch to be effective, it depends on the penetrant's ability to permeate the skin in quantities adequate to sustain 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

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naturally occurring oils (essential oil and vegetable oil), terpenes can be employed as permeation enhancers due to their advantageous properties such as compatibility with drug and Excipients. [5] The review article highlights the usage of NPEs to enhance drug penetration across skin for transdermal delivery systems. It also discusses the parameters for permeation tests. This article discusses how NPEs can enhance drug absorption across skin for the formation of TDDS.

Human Skin as A Barrier:

The human skin is made up of three major layers:

- Epidermis
- Dermis
- Hypodermis

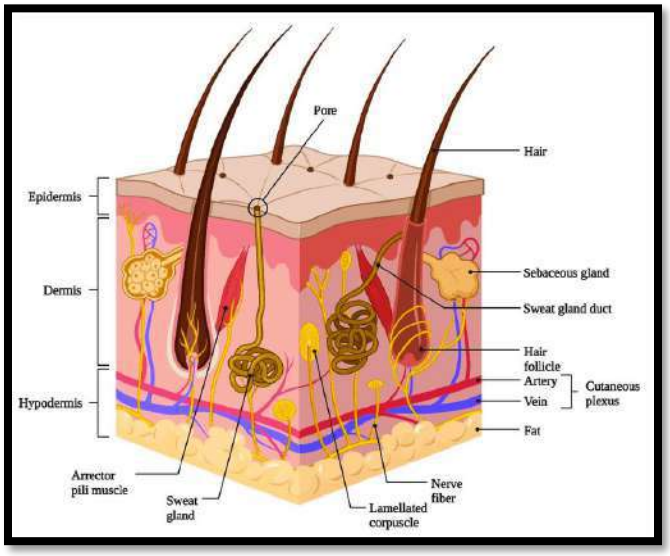

Fig 1: Physiology Of Skin

Skin

Drug delivery can easily reach the surface of the human skin. The average adult's skin has a surface area of around 2 m^2 and it absorbs roughly one-third of the blood that flows through the body. Every square centimeter of skin on an average human has between 40 and 70 hair follicles and between 200 and 250 sweat ducts. The three main tissue layers that make up the skin are as follows: The epidermis, which acts as an infection-resistant barrier and waterproofing layers of the epidermis: From the deepest to the most superficial, the epidermal layers are the

- Stratum basale
- Stratum spinosum
- Stratum lucidum,
- Stratum corneum.

The dermis, the layer of skin that contains the skin's appendages; The hypodermis, or subcutaneous adipose layer, as seen in figure 1.[6] The subcutaneous (SC), the outermost few micrometers of skin, supports the barrier function of the skin. This layer of skin is the most impermeable and forms laminates of compressed keratin-filled corneocytes attached to a lipophilic matrix.

The lipids in this matrix can be characterized in a variety of ways:

- From the skin surface to the base of the SC, they form the only continuous phase
- Among biological membranes, the lack of phospholipids is unusual and the composition
- SC lipids are lacking polar bilayer-forming lipids but exist as multilayered sheets
- The essentially saturated long-chain hydrocarbon tails support a highly ordered structure in an interlocking configuration.

However, the resistivity of the membrane cannot be fully explained by the unusual lipid matrix, and it has been suggested that the structure of the SC as a whole plays a role in the barrier properties of the membrane. Because keratinocytes resemble a brick-and-mortar structure, this membrane is said to be impermeable to water compared to other biological membranes and evidence from visualization studies to localize multiple penetrants within intercellular channels, kinetic analysis of in vivo skin permeation rates of model compounds, and thermotropic biophysical studies of lipid domains further support a transport role for this pathway.[7]

Penetration Enhancers

Penetration enhancers facilitate skin permeability by promoting the transfer of compounds [8]. They play a crucial role in transdermal drug delivery systems (TDDS) utilized to enhance the flux (J). Flux represents the quantity of material flowing through a unit cross-sectional area at time (t). [9]

Ideal properties of penetration enhancers:

- Pharmacologically inert, non-allergic, non-irritating, and non-toxic.
- Compatibility with excipients and drugs.
- No pharmacological activity in the body.
- Acceptable cosmetically.
- Odorless, tasteless and colorless.
- Allow therapeutic agents into the body while preventing loss of endogenous material unidirectionally.
- Chemical and physical stability.
- Reproducible and predictable duration of action.
- Good solvent properties. [10,11].

Classification Of Penetration Enhancers

Table 1: Classification Of Penetration Enhancers

Types/Techniques of penetration enhancers	Mechanism of action	Examples
1. Chemical enhancers	They act by three mechanisms[8] 1.By distruption of highly ordered structure of stratum corneum lipid. 2.By interaction with intercellular protein. 3.By improved partition of the drug or solvent into stratum corneum.	1.Sulphoxides and similar chemicals-dimethyl sulphoxide(DMSO),dimethyl formamide(DMF),dimethyl acetamide(DMAC) 2.Azones 3.Pyrrolidones 4.Fattyacids–Lauric acid, Myristic acid and capric acid 5.oxizolidinones (4-decycloxazolidine-2-one) 6.Amine and Amides –Urea 7.Surfaceactiveagents–sodium lauryl sulphate, Benzalkonium chloride 8.cyclodextrins
2. Drug Vehicle Based	Interaction of enhancers with stratum corneum and development of SAR for enhances with optimal characteristics and minimal toxicity[8]	Ion pairs and complex Coacervates chemical potential adjustment
3. Natural Penetration enhancers	Mechanism for Terpenes It may increase one or more of following effects[8] 1.Partition coefficient 2.Diffusion coefficient 3.Lipid Extraction 4.Drug Solubility 5.Macroscopic Barrier Perturbation 6.MolecularOrientation of Terpenes Molecule with Lipid Bilayer	1.Terpens-Menthol, Linalool, Limonene, Carvacrol. 2.Essential oil-Basil oil, Neem oil, Eucalyptus, Chenopodium, Ylang- Ylang.
4. Physical Enhancers	These are variable techniques available for increasing the penetration by physical separation and magnetic and ultrasonic.	1. Iontophoresis 2. Sonophoresis 3. Phonophoresis 4. Magnetophoresis 5. Electroporation 6. Thermophoresis 7. Radiofrequency 8. Needleless injection 9. Hydration of stratum corneum 10. Stripping of stratum corneum
5. Biochemical Approach	They act by modifying substances by converting it in to suitable form.	1.Synthesis of bio-convertible pro drugs 2.co-administration of skin metabolite Inhibitors
6. Miscellaneous Enhancers	Having Various Mechanism	1.Lipid synthesis inhibitors 2.Phospholipids 3.Clofibric acid 4.Dodecyl –N,N-Dimethyl

Natural Penetration Enhancers (NPES)

In the pharmaceutical industry, NPEs are a relatively new class of penetration enhancer. More research is required in this area to create a stable transdermal formulation with natural penetration enhancers (NPEs) that can be scaled up for commercial transdermal medication products because of its benefits, which include low cost and a better safety profile.[12]

Mechanism Of Action of Penetration Enhancers: The miscibility and solution enhancers can be responsible for improved transdermal distribution of water soluble drugs. Mechanism to promote penetration of oil soluble medicines are caused by partial leaching of epidermal lipids by improving drug permeability through the skin. To improve penetration of lipophilic compounds there required to change partitioning features at the stratum corneum live tissue interface. This could be achieved by combining a penetration enhancer including a co-solvent. Some enhancers make keratin swell and leach out necessary structural material from the stratum corneum, which reduces diffusional resistance and increasing the permeability. [13,14]

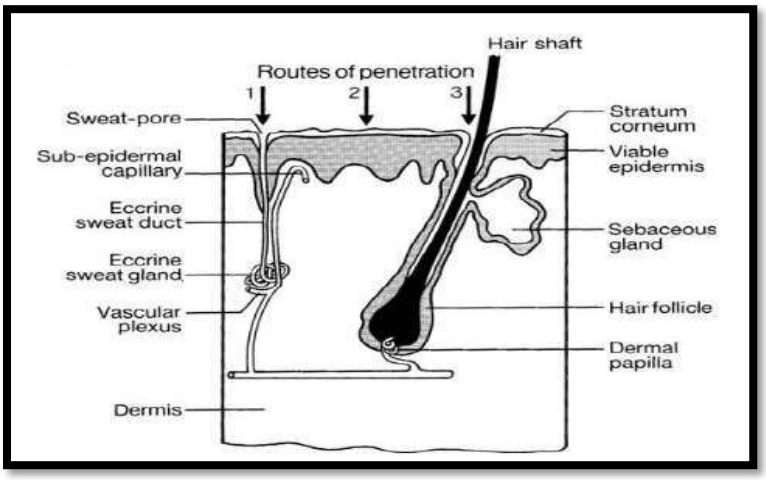

Fig 2: Simplified diagram of skin structure and macroroutes of drug penetration: (1) via the sweat ducts, (2) across the continuous stratum corneum, or (3) through the hair follicles with their associated sebaceous glands.

Routes Of Drug Transport Via Human Skin:

Chemical penetration is effectively and selectively inhibited by human skin. [15] The stratum corneum is typically the most important control element, and accelerant techniques aim to minimize the hindrance this barrier causes in order to maximize drug flux, though occasionally. The follicular pathway might also be significant. A molecule can enter the viable tissue at the skin's surface in three different ways: through eccrine sweat ducts, through hair follicles with their sebaceous glands, or through the continuous horny layer. This pathway typically contributes little to steady-state drug flux due to its low fractional appendageal area (about 0.1%), with the exception of ions and very polar molecules that have difficulty crossing intact stratum corneum. [16]

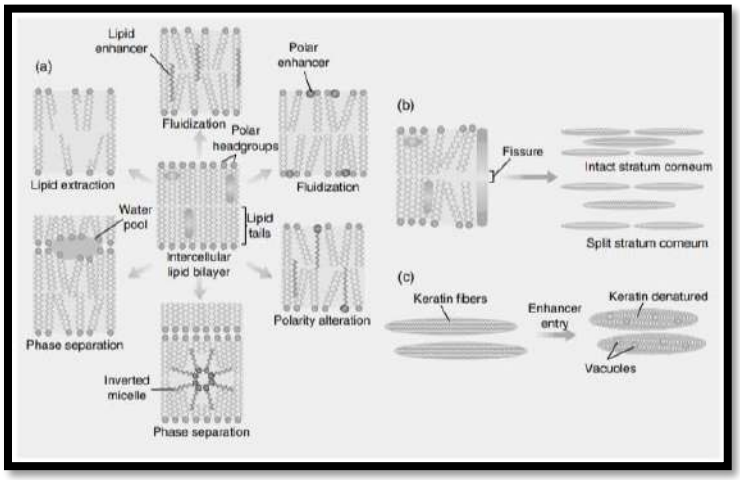

Fig 3: Some actions of penetration enhancers on human stratum corneum:

(a) Action at intercellular lipids. Some of the ways by which chemical penetration enhancers attack and modify the structured intercellular lipid domain of the stratum corneum. (b) Action at desmosomes and protein structures. Such dramatic disruption by accelerants (particularly potent solvents) as they split the stratum corneum into additional squamous and individual cells would be

clinically inappropriate. (c) Action within corneocytes, Swelling, further keratin denaturation, and vacuolation within individual horny layer cells would not be so drastic but would usually be cosmetically challenging. (Reprinted with permission from Barry, B.W., Nature Biotechnology,22, 165, 2004.)

Examples Of Natural Penetration Enhancers.

Piperidine:

Mature fruits of Piper nigrum and Piper dulcis are used to make Piperine longum. The in vitro penetration of piperine was examined. Cutting human cadaver skin with aceclofenac, and fourier transform infrared utilising technology, the potential method from which the findings demonstrated that piperine improves transdermal Aceclofenac penetration by a biphasic mechanism including partial SC lipid extraction and its relationship with sc keratin.[17].

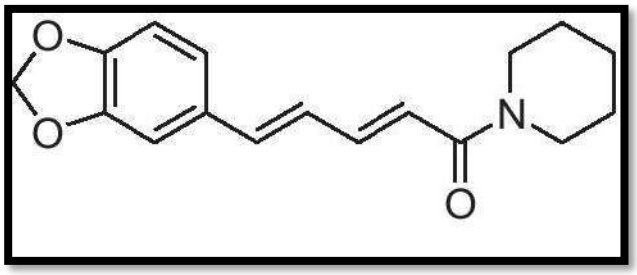

Fig 4: Piperidine

Essential Oil

Natural substances called essential oils are made up of several volatile aromatic compounds that are derived from aromatic plants. The chemicals mainly made up of substances like terpenes, additionally, phenylpropanoids and terpenoids.[18] Accepting them as a organic substitute for synthetic skin penetration enhancer because of their encouraging activity for increasing penetration. [19]

Essential oils aid with drug delivery by improving penetration of substances by their interaction with the lipids between cells in the skin via several physiologic mechanisms including heightened disorder, phase fluidisation as well as division. Due of their ease of skin penetration, they are quickly eliminated by the body through urine and faeces. So, because of its higher level of safety compared to other penetrating enhancers; more people are using them.[20]

Niaouli Oil:

Niaouli oil can be obtained by steam distilling the leaves and twigs of Melaleuca quinquenervia, a member of the Myrtaceae family. 55–70% of the main ingredients in niaouli oil were 1,8-cineole (oxide), contains the monoterpene limonene (7–15%) and the monoterpene a-pinene (2–6%). 2-6% viridiflorol (sesquiterpene) and s-pinene (monoterpene). In vivo research was done to find out how permeation enhanced the impact of 10% (w/w) concentration of niaouli oil in propylene glycol on a hairless mouse skin utilising a pharmacological model for oestradiol. It was found that niaouli oil was more successful in transdermal penetration of compared to essential oils of cardamom, myrtle, orange, and cajput. [21]

Fig 5: Niaouli Oil

Fennel Oil:

The seeds of the Umbelliferae plant, Foeniculum vulgare, can be used to extract fennel oil. According to penetration tests, the percutaneous

fennel oil improved trazodone hydrochloride permeation, mentha oil, citronella oil, and eucalyptus oil come next.

Fig 6: Fennel Oil

The molecular weights and physical-chemical characteristics of phytochemicals contained in the various essential oils could be the cause of the variations in the activity that enhances permeability between the oils.[22]

Black Cumin Oil:

Steam distillation is the method used to obtain black cumin oil from Cuminum cyminum seeds. The black cumin oil revealed carvedilol has a comparatively stronger permeating impact when it was contrasted with tween 80, clove oil, eucalyptus oil, tulsi oil, and oleic acid and it was discovered that the enhancement factor was 6.40. Moreover, fourier studies using transform infrared spectroscopy verified the modification resulting from the extraction of black cumin oil on the skin's permeability of lipids and through the influence of hydrogen bonding on other hydrogen bonds ceramide to ceramide.[23]

Fig 7: Black Cumin Oil

Almond Oil:

Almond oil and oleic acid were identified as potential carriers/vehicles to improve the ability of aceclofenac to pass through and dissolve in a body.

Fig 8: Almond Oil

Therefore, these oils have the potential to be utilized in creating better drug delivery systems which enables aceclofenac's absorption into the body.[24] Topical ketoprofen gels and patches were administered in the research study, formulated, assessed, and almond oil was examined for its ability to penetration enhancer for improving the performance of ketoprofen gels and patches across artificial membrane. Different concentrations of almond oil were discovered in order to increase the penetration of drugs from transdermal gels and patches applied on artificial membrane/rabbit skin. however, especially effective at a 3% dilution.[25]

Basil Oil

Research has investigated the potential of basil oil as a permeation enhancer for labetalol hydrochloride in comparison to camphor, thymol, geraniol, and clove oil. It has been suggested that basil oil exhibits excellent properties for enhancing penetration, thus improving the transdermal delivery of labetalol [26]. Basil oil was utilized to enhance the bioavailability of transdermally applied flurbiprofen. The study concluded that the bioavailability of flurbiprofen when applied transdermally with basil oil increased by 2.97, 3.80, and 5.56 times compared to orally administered flurbiprofen in albino rats.[27]

Fig 9: Basil Oil

Alpinia Oxyphyllia Oil:

Oil extracted from Alpinia oxyphylla, which was divided into a higher polarity fraction and a lower polarity fraction, is known as A. oxyphylla oil. Franz diffusion cell was used to conduct in vitro studies on the dorsal skin of Wistar rats, which showed that the highly polar fraction of A. oxyphylla oil had a more effective permeation-enhancing impact on indomethacin at concentrations of 3% and 5% compared to the less polar fraction. [28]

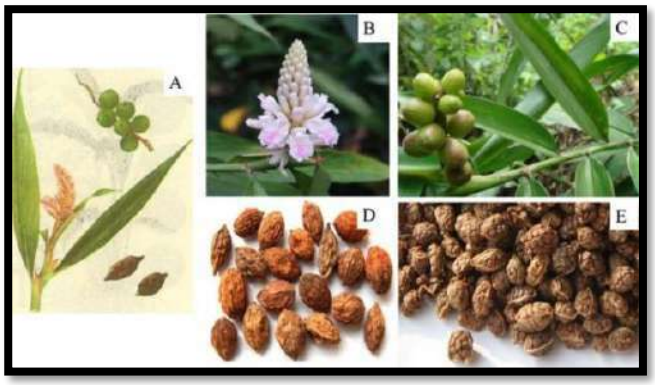

Fig 10: Alpinia Oxyphyllia Oil

Terpentine Oil:

An optimized cosolvent mixture with turpentine oil added had an additive effect on the skin permeation rate of flurbiprofen. The highest transdermal penetration rate was achieved at a concentration of 5% (v/v) of turpentine oil and a mixture of propylene glycol and isopropyl alcohol (30-705 [v/v]). In the Franz diffusion cell, the efficacy of turpentine oil was examined for its ability to improve the permeation of diclofenac dimethylamine matrix patches across the artificial skin. It was discovered that as the turpentine concentration increased, the oil showed increasing permeation.[29]

Fig 11: Turpentine Oil

Rosemary Oil:

Rosmarinus officinalis is used to extract rosemary oil. When diclofenac sodium topical gel's skin penetration was examined, rosemary oil demonstrated improved skin absorption at 0.5% and 1% concentrations, respectively.[30]

Fig 12: Rosemary Oil

Cardamom Seed Oil:

A common spice in India, cardamom (Elettaria cardamomum) is a member of the Zingiberaceae family.[31] The extracted oil from Numerous volatile substances, including monoterpenes like 1,8-cineole and cis-ocimene and sesquiterpenes like guanine and nerodilol, are found in cardamom.[32] In vitro penetration studies using rabbit abdominal skin and cardamom oil revealed higher drug penetration for piroxicam, diclofenac, and indomethacin.[33]

Fig 13: Cardamom Seed Oil

Yarrow:

Yarrow (Achillea millefolium) contains many chemical compounds, including: Essential oils: Borneol, 1-octen-3-ol, camphor, p-cymene, caryophyllene oxide, 1,8-cineole, myrtenol, thymol, and spathulenol. From which it was discovered that borneol successfully encouraged the transdermal penetration of the model medications, including salicylic acid and ibuprofen.[34]

Fig 14: Yarrow

Terpenes:

Terpenes are a prominent choice in transdermal drug delivery studies. There is a wide variety in this class. The physicochemical characteristics of a particular terpene, particularly its lipophilicity, influence how it affects the skin. Smaller terpenes with nonpolar groups, on the other hand, are thought to be superior skin penetration enhancers.[35] By altering the lipid bilayers of the skin, terpenes have also been shown to improve drug diffusibility and partitioning into the skin.[36] As skin penetration enhancers for hydrophilic and lipophilic drugs, they are comparatively safe.[37]

Terpenes' Part In Transdermal Delivery

Typically, terpenes and terpenoids are the components of oil that is volatile. To categorize terpenes, the basic chemical structure is made up of several repeating isoprene (C5H5) units such as Sesquiterpenes have three isoprene units (C15), diterpenes have four (C20), monoterpens have two (C10). Terpenes can be divided into three categories:

- Bicyclic,
- Monocyclic
- Acyclic/linear.

For a very long time, terpenes have been used as flavoring and fragrance ingredients as well as medications. It has been discovered that the essential oils of ylang, chenopodium, and eucalyptus are efficient penetration enhancers.[38] This agent works by altering the stratum corneum's solvent properties, which enhances medication distribution throughout tissues.

Mechanism Of Action of Terpenes:

By removing lipids from the stratum cornea, terpenes improve drug diffusion by causing lipid domain reconfiguration and barrier rupture. The competitive hydrogen bonding of oxygen-containing monoterpenes with ceramide head groups may be the mechanism causing barrier disruption. This would destroy the interlamellar hydrogen bonding network of the stratum corneum's lipid bilayer and create new polar routes or channels. [39]

Lemon Grass:

Lemon grass contain farnesol as its chemical constituents also numerous essential oils, including citronella, neroli, cyclamen, tuberose, balsam, and tolu, contain farnesol. It's a monoterpene.

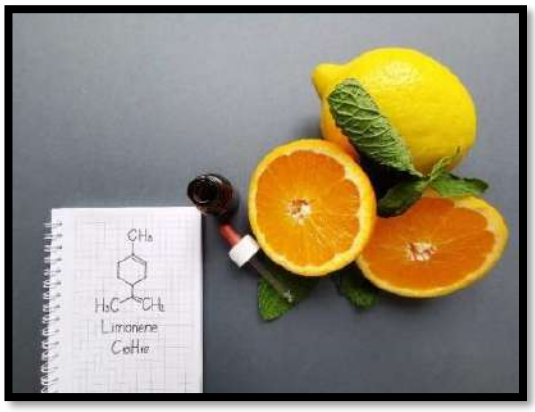

Fig 15: Lemon Grass

In comparison to other terpenes, farnesol (0.25%) was found to enhance diclofenac sodium permeation in the following order: Farnesol >carvone > nerolidol > menthone >limonenoxide.[40]

Menthol And Limonene:

The flowering tops of Mentha piperita are used to extract menthol, one of the powerful penetration enhancers. Limonene and menthol collectively serve as a model for terpenes that have the potential to improve penetration. [41]

Fig 16: Menthol

Eucalyptol:

Eucalyptol is a monoterpenoid and cyclic ether that goes by several synonyms, including 1, 8-cineole, cajeputol, cineole, and eucalyptol. Eucalyptol's spicy aroma and taste make it useful

in the flavoring, fragrance, and cosmetics industries. Additionally, 1, 8-cineole has been utilized to facilitate the percutaneous absorption of various lipophilic medications via the skin of hairless mice. [44]

Fig 17: Eucalyptol

Eugenol:

Eugenol's ability to improve drug permeation for the oxicam class nonsteroidal anti-inflammatory drug Lornoxicam was assessed. Rat skin was used to create lornoxicam transdermal patches, which were subsequently used in vitro experiments in a Franz diffusion cell. Eugenol has been shown in vitro experiments to enhance lornoxicam's penetration through rat skin.[45]

Fig 18: Eugenol

Borneol:

Five model drugs were used to examine the transdermal permeation-enhancing activity of borneol: 5-fluorouracil, antipyrine, aspirin, It was discovered that borneol successfully encouraged the transdermal penetration of the model medications, including salicylic acid and ibuprofen.[46]

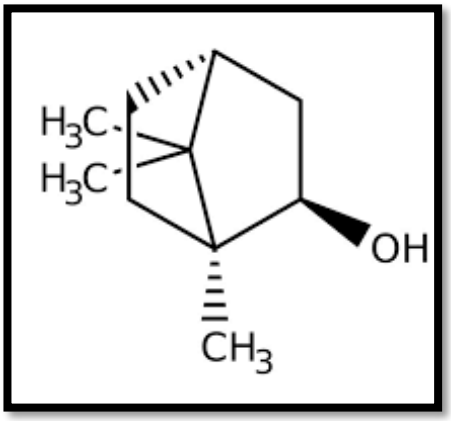

Fig 19: Borneol

Turmeric:

Ayurvedic and Chinese medical systems have long employed turmeric to treat a variety of skin conditions, including warts, acne, and skin rashes. [47] Turmeric contains an active ingredient called curcumin, which has anti-inflammatory, qualities that are antibacterial, antiviral, antifungal, and antioxidant. In the treatment of skin disorders, there is a definite need for a skin-delivered curcumin product that could target afflicted tissues directly. Nonetheless, curcumin has limited passive skin penetration from basic lipid-based carriers and a reasonably high lipophilicity (log P 3.6). Several methods have been demonstrated to enhance curcumin's skin penetration, including liposomes filled with soybean phospholipids,[48] Tween 20 micelles enclosed in a chitin shell,[49] and chitin nanogels (CCNGs) loaded with curcumin.[50] all of which sought to increase curcumin solubility and dispersion in water-based media.

Fig 20: Turmeric

Aloe Vera:

Aloe Vera (Aloe barbadensis Miller) is part of the Lilaceal family. Two new US patent applications assert that Aloe Vera increases the skin permeation of medications that are co-formulated. There are two potential ways to permit the skin. This penetration enhancer (1) enhances the medication's solubility inside the SC by changing how the medication is divided into the SC or (2) they have an impact the medication's dispersion throughout the SC via causing the lipids in the skin to become disorganised. Lignins are the structural component of cellulose, permits penetrating qualities. Aloe Vera has the ability to permeate every layer of the skin, and this could be beneficial in improving the way that specific medication molecules pass through the skin, as lignins can permeate the skin's hardened region.[51] According to a 2004 US patent, the amount of fentanyl that permeated the skin increased by up to 50% when Aloe Vera oil (Aloe Vera extract macerated in soybean oil) was added to formulations containing fresh macerated Aloe barbadensis leaves that were formulated with fentanyl (Tisa-Bostedt et al., 2004).[52] A therapeutic hurdle is presented by the extrahepatic toxicity and limited absorption of statins. Because of the side effects that lower the patient's quality of life and compliance, increasing the dosage to address the low bioavailability is not practical. The current objective is to reduce extrahepatic toxicity while optimizing drug delivery to target tissue or cells. Because of the negative effects, it is necessary to find novel ways to distribute statins, including transdermal delivery.

Fig 21: Aloe Vera

Bargamot

Citrus fruits high in essential oils, including bergamot, have been found to have the potential to improve natural medication delivery system's ability to penetrate the skin. The reason for its effectiveness is that terpenes work well with the skin's barrier to improve drug absorption. The lipid structure of the stratum corneum is disrupted by the terpenes in bergamot, which facilitates medication permeation. Essential oils, such as bergamot, increase the skin penetration of hydrophobic medications by making them more soluble Security and performance. Generally Recognized As Safe (GRAS) status gives bergamot and its constituents the advantage over artificial enhancers. Compared to conventional synthetic penetration enhancers, natural terpenes—such as those from bergamot—show less toxicity. Although bergamot appears to be a promising natural penetration enhancer.[53]

Fig 22: Bargamot

Tulsi

Transdermal Drug delivery systems can benefit from the use of tulsi oil, a naturally occurring penetration enhancer derived from Ocimum sanctum. By altering the stratum corneum's barrier characteristics, it can increase the rate at which medications penetrate the skin. An investigation was conducted on the ability of tulsi oil and turpentine oil to improve penetration when flurbiprofen, a non-steroidal anti-inflammatory drug, was delivered transdermally.[54] When using natural components like Tulsi instead of synthetic ones, there is a decreased chance of skin irritation.

Fig 23: Tulsi

Liquorice:

Licorice is utilized in transdermal drug delivery systems as a natural penetration enhancer: The active component of licorice root, glycyrrhizic acid (GA), is a multipurpose drug carrier that has the capacity to improve the permeability of cell membranes. Additionally, GA can improve the therapeutic efficacy and bioavailability of medications with low permeability and solubility. Glycyrrhizin can improve membrane permeability and make drugs more soluble in water. In order to lower the energy barrier preventing it from penetrating through the lipid bilayer, it can also create hydrogen bonds with the calcium channel blocker nifedipine. [55] They interact with the stratum corneum's (SC) intercellular lipids to improve drug penetration, and they are both safe and efficacious. [56]

Fig 24: Liquorice

Moringa Oil:

Moringa oil, extracted from the seeds of the Moringa oleifera tree, has surfaced as a potential natural penetration enhancer in transdermal drug delivery systems. Its unique composition, rich in fatty acids and bioactive compounds, components of nitrile glycosides and their derivatives facilitates the permeation of drugs through the skin barrier. Although they don't have any

Fig 25: Moringa Oil

inherent drug activity, they have been shown to increase and support a medication's biological activity, bioavailability, or absorption when used in combination therapy i.e acting as a natural penetration enhancer. Niaziridin, for example, is a nitrile glycoside that has been shown to improve the absorption of vitamins, minerals, and popular antibiotics like ampicillin, tetracycline, and rifampicin.[57] By improving drug absorption in a culture model, the niaziridin-rich fraction of Moringa oleifera significantly increased the activity of rifampicin, ampicillin, and nalidixic acid against both Gram positive and negative microorganisms by 1.2–19 folds in a bioactivity test. [58]

Lecithin:

Lecithin, a natural product, act as a penetration enhancer effectively enhances transdermal drug delivery by reducing skin barrier resistance, facilitating the permeation of both hydrophilic and lipophilic compounds.[59] It acts with the ability to significantly increase medication absorption across the skin barrier. Lecithin functions by altering the lipid structure of the stratum corneum, which lowers skin barrier resistance and promotes medication penetration. It combines chitosan to produce nanoparticles that increase drug entrapment and retention, hence increasing the effectiveness of transdermal delivery.

Fig 26: Lecithin

Pomegranate:

Pomegranate has been investigated for its possible use in transdermal drug delivery systems as a natural penetration enhancer. [60] Pomegranate seed oil (PSO) is mainly composed of unsaturated fatty acids, like ellagic acid, punicic acid, and flavonoids as bioactive substances and these substances may help explain why the fruit has penetration-enhancing qualities.[61]

Fig 27: Pomegranate

Jajoba Oil:

It is used in transdermal drug delivery systems to improve penetration. Microemulsions made with

jojoba oil have the potential to enhance topical medication administration. Microemulsions are simple to make, highly solubilizing formulations with thermodynamic stability. Jojoba oil microemulsions kept at 25 or 40 °C in a dark environment will remain stable for up to six months. [62]

Fig 28: Jajoba Oil

Coconut Oil:

Coconut oil is becoming increasingly well recognized as a natural penetration enhancer in transdermal medication delivery systems due to its unique properties and safety record. Along with other fatty acids like oleic and linoleic acids, medium-chain fatty acids like lauric acid make up coconut oil. Research indicates that it has the potential to improve medication absorption through the skin barrier, making it a crucial component of transdermal formulations.[63]

Fig 29: Coconut Oil

Papain:

Papain is distinct from papaya Carica. The enzyme in question is an endocytic plant cysteine protease. One proteolytic enzyme called papain was investigated low-molecular-weight permeability in vitro and in vivo of Heparin (LMWH). The administration of papain and LMWH together was discovered to be a novel strategy for increasing oral given heparin, and consequently the bioavailability of it.[64]

Fig 30: Papain

Ginseng:

Panax ginseng in particular has the potential to be used in transdermal medication delivery systems as a natural penetration enhancer. The active ingredient in ginseng is Ginsenosides that may be useful for transdermal drug delivery. It is found that nanoparticles developed from ginsenosides are used to enhance the penetration of insulin.[65] Ginsenosides is an active substances that alter the lipids in the skin barrier to increase the permeability of drugs.

Fig 31: Ginseng

Green Tea:

Green tea extract (GTE) contains a class of chemicals called catechins, which are employed as penetration enhancers in transdermal drug delivery systems. Green tea extract has several pharmacological and antioxidant qualities. One such catechin is epigallocatechin-3-O-gallate (EGCG). Green tea's catechins have the ability to change the stratum corneum's (the skin's outermost layer) lipid structure, increasing the skin's permeability to medications. Green tea has some chemicals that may aid in the solubilization of medications, increasing their bioavailability when given topically. Green tea contains anti-inflammatory properties that may lessen skin irritation and facilitate the delivery of medications through the skin. Green tea's antioxidants can shield the skin from the harmful effects of drugs during their delivery, enhancing skin compliance and general health. Green tea extracts can be added to gels, creams, or patches, among other transdermal formulations, to improve the release and absorption of active pharmaceutical ingredients (APIs)

Fig 32: Green Tea

Table 2. Natural Penetration Enhancers Used in Drugs And Their Category

Penetration Enhancers	Name Of Drugs	Category Of Drug
1. Ginseng	Insuline Lidocaine Hydrocortisone Fentanyl	Anti diabetic agent Anaesthetic Agent Anti inflammatory Opioid analgesic
2. Aloe vera	Theophylline Diaclofenac Diazepam Oxybutynin	Bronchodilators NSAIDS Anxiolytic Anticholinergic
3. olive oil	Metformine Atenolol Acetaminophen	Anti diabeticagent Beta blocker Analgesic
4. Linoleic acid	Acyclovir 5 fluorouracil	Antiviral drug Anti-cancer agent
5. Sage	Clonidine	Antihypertensive
6.Green tea	Ketoprofen Vanlafaxine Metformine	NSAIDs Antidepressants Anti diabetic
7. Rosemary	Gentamicin	Antimicrobial agent

8. Turmeric	Paracetamol	Antipyretic
9. Lemon grass	Fluoxetine Diclofenac	Antidepressants NSAIDs
10. Palmitic acid	Nifedepine	Antidepressants
11. Tulsi	Flurbiprofen	NSAIDs
12. Yarrow	5-fluorouracil, Antipyrine, Aspirin,	Anti-cancer Analgesic NSAIDs
13. Cardamom oil	Piroxicam Indomethacin	NSAIDs NSAIDs
14. Moringa oil	Tetracycline Rifampicin	Antibiotics Antibiotics
15. Eugenol	Oxicam Lornoxiacam	NSAIDs NSAIDs
16. Lecithin	Nesoldipin	Calcium channel blocker
16. Grape seed	Sodium naproxen oxcarbazepine	NSAIDs Anticonvulsants
17. Liquorice	Nefidipin	Calcium channel blocker

CONCLUSION

Transdermal drug delivery is becoming increasingly popular due to its benefits, prompting research into incorporating more pharmaceuticals through this route. Owing to the TDDS's numerous advantages, numerous fresh studies are being carried out to incorporate more recent drugs into the body. Permeation enhancers are used to increase the permeability of poorly absorbed medicines and preserve their bioavailability. It is found that the chemical enhancers seems to have more disadvantages. Their presence is limited to the uppermost few layers of the SC, with minimal penetration. It is so challenging to maintain the appropriate balance between chemical enhancers protection and efficacy in drug penetration. As a result, NPEs and their components play an important role in mitigating pharmaceutical absorption via the skin with less or no side effects.

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