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REVIEW ARTICLE

Herbal Permeation Enhancers - A New Approach for Transdermal Drug Delivery Systems

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ABSTRACT

Permeation is the penetration of a permeate (such as a liquid, gas or vapors) through a solid surface. Topical administration of therapeutic agents offers many advantages over techniques of drug delivery. This transdermal drug delivery system can transport the drug or macromolecules painlessly through the skin into the blood circulation at a fixed rate. It delivers the therapeutically effective amount of drug across a patient skin. The substance that helps to penetrate the drug into the blood circulation through the skin, is known as permeation enhancer. Human skin surface act as a site of drug application use for both local and systemic effects, among many advantages over other routes, the three crucial ones are avoiding metabolism in the liver, minimal negative effects, and increased bioavailability. Also, Stratum corneum acts as a protective barrier, prevents the loss of essential physiological substances, and acts as permeation resistance. This is the rate limiting step of drug absorption into the skin percutaneously. Permeation enhancement is a new emerging technology that can increase the number of drugs taken trans-dermally. Also, drugs with a short biological half-life could be easily administered. Permeation enhancers work by modifying the skin barrier properties. Like, by use of chemical enhancers acting on the lipids in the stratum corneum or. Enhancement in skin penetration by hydration of the outermost layer of the skin (stratum corneum).

Keywords: Herbal drugs, Human skin, Natural enhancer, Permeation enhancer, Topical preparation, Transdermal.

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INTRODUCTION

Today, ~74% of drugs are taken orally and are not as effective as desired. To improve such characteristics, transdermal drug delivery was brought to existence. This delivery system can transport the drug or macromolecules painlessly through skin into the blood circulation at a fixed rate.[1] Then, one question arises on the utility requirement of pemeation enhancer. These are used in Pharmaceutical Formulations to avoid metabolism in the liver, minimal negative effects and increased bioavailability.[2]

Permeation enhancers are defined as substances that are capable of promoting permeation of drugs into skin. A substance is added to the pharmaceutical formulation to increase a co-administered drug's membrane permeation or absorption rate, used to increase the bioavailability of drugs with normally poor membrane permeation properties. For permeation enhancers to be clinically acceptable, they must increase the bioavailability or increase membrane permeability without damaging the membrane and causing toxicity.[3]

Ideal Characteristics of Permeation Enhancers[4]

1. These materials should be biocompatible, i.e., they should not cause irritation or any allergic response both in the short and long run. Also, it should not induce toxicity.
2. It should be compatible with the drug being given.
3. It should not exhibit any adverse pharmacological activity inside the body.
4. It should not be expensive and possess good solvent properties.
5. It should not have odor, color, and taste.
6. It should be stable chemically as well as physically.
7. The course of action should be reproducible, sustainable, and expeditious.
8. It should be tested *In-vitro* also.
9. It should not cause leakage of body fluids and endogenous materials (unidirectional flow), and as soon as such substances are removed, the skin should immediately restore its natural barrier properties.

MERITS AND DEMERITS OF PERMEATION ENHANCERS

Various Advantages of Permeation Enhancers[5]

- They help to provide permeation rate of drug sufficiently high for therapeutic efficiency
- It facilitates the absorption of non-absorbable drugs through skin.

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- It can amend the transdermal absorption of topical preparation completely.
- It determines the permeation rate of the transdermal drug delivery system.
- The terpenes like limonene in propylene glycol solution are effective permeation enhancer for cytotoxic drugs.

Various Disadvantages of Permeation Enhancers are[6]

- The efficacious concentration varies from drug to drug.
- The use of various permeation enhancers with various concentrations vary
- Physicochemical properties of enhancers are also affecting the side effects in the body.

Transdermal therapeutic systems offers a more reliable mean of administering drug through the skin. (Skin is a natural barrier, so employing enhancement strategies to improve topical bioavailability is necessary). The transdermal drug delivery route is evolving as a potential route due to its advantages of bypassing the hepatic first-pass metabolism, decrement side effects and gastrointestinal effects, amend patience compliance as it is a pain-free self-administration for patients, etc.[3]

PERMEATION PATHWAYS OF SKIN

A molecule can permeate through the skin via either the *Trans-epidermal pathway* (diffusing across the skin layers) or the *Appendageal pathway* (through hair follicles or sweat ducts)

Trans-epidermal Pathway

In the trans-epidermal pathway, the permeant traverses the intracellular and/or extracellular spaces from the epidermis to the dermis and hypodermis. The molecule may do so either *TRANSCELLULARLY* or *INTERCELLULARLY*. The transcellular route requires that the permeant traverse the alternating layers of cells and extracellular matrix.[7] This involves a sequence of partitioning and diffusion into alternating hydrophilic and lipophilic domains. The cells and substances that comprise the hydrophilic or lipophilic domains vary between skin layers, but generally, the interiors of cells are more hydrophilic than the extracellular matrix. The permeant navigates the tortuous path within the extracellular matrix in the intercellular route without traversing the cells. Small hydrophilic molecules generally favor the transcellular route over the intercellular route and vice versa for lipophilic molecules.[8]

Appendageal Pathway

The appendageal (or shunt) pathway encompasses permeation through hair follicles (the trans follicular route) or sweat ducts.[9] The trans-follicular route has gained significant research interest in recent years and is covered in a separate chapter It is widely accepted that the trans-epidermal pathway is usually the predominant pathway of skin permeation and that under sink conditions, diffusion across the stratum corneum constitutes the rate-limiting step that determines the overall flux of the permeant.[10]

The contribution of the appendageal pathway to percutaneous transport is generally considered secondary, since appendageal features typically account for only around 0.1 % of skin surface area (though this is higher at somebody sites such as the forehead), and early studies suggested that the spatial density of appendages did not correlate with the flux of permeants across the skin.[11] Nonetheless, the relative contribution of these pathways will vary depending on the physicochemical properties of the permeant and the formulation. Highly lipophilic drugs may be retained in the lipophilic stratum corneum and resist partitioning into the more hydrophilic viable epidermis.[12] Thus, the stratum corneum's clearance from, rather than diffusion across, may become the rate-limiting step for highly lipophilic drugs. Similarly, the appendageal pathway may be more important for highly hydrophilic molecules such as caffeine and electrolytes and large molecules with low diffusion coefficients that are thus effectively precluded from the trans-epidermal pathway.[13] The relative importance of each pathway may also change with time—various studies have shown that the appendageal pathway rapidly but transiently predominates before being overtaken by the trans-epidermal pathway at steady state.[14]

MECHANISM OF ACTION OF PERMEATION ENHANCERS

Skin Absorption Promoters may act by one or more of three potential mechanisms according to the lipid-protein-partitioning theory. Firstly, penetration enhancers can alter the inter-cellular lipid structure between the corneocytes to increase diffusivity. Secondly, they can modify intracellular protein domains within the horny layer. Thirdly, they may increase the partitioning of the drug into the skin tissue demonstrates the possible mechanism of drug penetration. The three main functions of penetration enhancers include:

Lipid Disruption

Interaction with the polar head group of lipids via hydrogen and ionic bonding.

Changes in hydrogen sphere in lipid and affect the packaging at the head region. Increase volume of the aqueous layer swelling and hydration. They change the structure of stratum corneum lipid organization and

make it permeable for the drug, e.g. Azone, terpenes, fatty acids, Dimethyl sulfoxide (DMSO), and alcohol.[15]

Protein Modification

They interact with keratin and corneocytes, open up the dense protein structure, and make it more Permeable, e.g., Ionic surfactants.[16]

Partitioning Promotion

Many solvents change the solution properties of the horny layer and increase the partition of a drug, co-enhancer and co-solvents.

TYPE OF PERMEATION ENHANCER

Different types of permeation enhancers have been summarized in Figure 1.

Chemical Enhancer

One approach in improving transdermal drug delivery (across the skin) by reversibly decreasing the barrier resistance is chemical permeation enhancers (CPEs). Numbers of compounds have been evaluated for permeation enhancing activity, including alcohols, azone, esters, glycols, fatty acids, pyrrolidone, sulphoxides, terpenes etc.[17] The present review considers the various types of CPEs and their mechanisms of action.

- Chemical enhancers are agent that interacts with skin constituents to promote the drug flux
- Many agents have been studied and evaluated for enhancement properties
- Yet their inclusion in skin formulation is limited due o unknown mechanisms and toxicity

Example: surfactant(SLS, tween 80), bile salts and derivative(Na glycocholate), fatty acid and derivative(oleic acid, caprylic acid), chelating agent(EDTA, citric acid), sulphoxide(DMSO, DMA, DMF), polyols(PG, PEG, glycerol), monohydric alcohols(ethanol, 2-propanol) etc.[18]

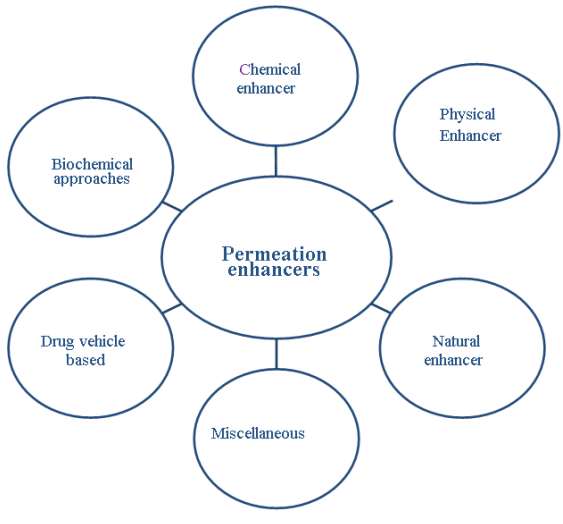

Figure 1: Depicts the various methods to enhance permeation

Physical Enhancer

Many physical methods for drug permeation enhancement and improve bioavailability of the stratum corneum (SC) such as micro-needles, heating, iontophoresis, electroporation, ultrasound, etc.

On the other hand, nanotechnology has shown remarkable potential in target specific delivery of drugs in the body. the role of nanocarrier systems and physical enhancers and their possible combination to improve the passage of molecules through the organ systems.[19]

Biochemical Approach

Synthesis of Bio-convertible Pro-drugs

Pro-drugs help to obtain an optimal partition coefficient for entering the skin barrier. After absorption and diffusion to the viable tissues, enzymes convert the pro-drug into the active form. Many steroids have been designed using this approach.[20] N-acyl derivatives were formed to increase permeability of 5-fluorouracil to 25 times. S6-acyloxymethyl and 9-dialkylaminomethyl pro-moieties acted as permeation enhancers to 6-mercapto-purine and increased its permeation to up to 240 times. Pro-drugs have also been used to increase skin permeability of anti-inflammatory drugs, which are non-steroidal like nalbuphine, buprenorphine, β-blockers, and others.[21]

Co-administration of Skin Metabolism Inhibitors

One of the interventionists approaches proposed for permeation promotion through human skin is to interfere with barrier homeostasis by altering one or all of the processes of bringing together the lamellar membranes, synthesis, assembly, secretion, processing, and activation.[22] Synthesis inhibitor temporarily blocks the synthesis of ceramide, fatty material and cholesterol. This method is nowadays increasingly experimented to enhance drug permeation of drugs that exhibit poor permeability across normal skin. Fluvastatin increases lidocaine hydrochloride's octanol/water partition coefficient by 50 times, the in vivo uptake doubled.[23]

Drug Vehicle Based

Drug-vehicle based enhancement methods such as drug selection, vesicles, and particles, liposomes, pro-drugs and ion-pairs, the chemical potential of the drug, eutectic systems, complexation are used in transdermal research as better alternative methods to enhance permeation of drugs through the skin.[24]

Naturally Occurring Oils as Permeation Enhancers

These natural products have got potential to nhance the permeation of the drug through skin by reversibly

reducing the skin barrier resistance.[25] Natural products are the most reliable means of permeation enhancement of trans-dermally administered drugs and permit broader classes of drugs through the stratum corneum.[9] They are safe, non-toxic, pharmacologically inert, non-irritating, and non-allergenic to use as permeation enhancers. Various natural sources have been investigated for potential skin permeation enhancement activity. Some of the natural sources have been discussed below.[10] Essential oils and their constituents may be preferred over the traditionally used synthetics materials as safe and suitable permeation enhancers to promote the percutaneous absorption of hydrophilic and lipophilic drugs from topical formulation into the lower skin layers.[26]

Eucalyptus oil

Eucalyptus oil can be obtained from numerous Myrtaceae family species, including *Eucalyptus citriodora, Eucalyptus dives, Eucalyptus globules Eucalyptus polybractea,* and *Eucalyptus radiata*. The oil is extracted by steam distillation from the leaves. That formulation containing eucalyptus oil has the highest percentage of drug release.[27] Eucalyptus oil is an effective skin permeation enhancer and it contains 1,8-cineole, a monoterpene cyclic ether that can enhance permeation of both lipophilic and hydrophilic compounds. 5-fluorouracil, was used to investigate the permeation enhancing activities of eucalyptus, chenopodium, ylang-ylang, and anise essential oils through excised human skin.

Niaouli Oil

Niaouli oil is extracted through steam distillation from the leaves and twigs of *Melaleuca quinquenervia*, which is part of the Myrtaceae family. This oil is used for treating respiratory/sinus and urinary tract infections, allergies, and hypertension. Its key constituents is 55–70% 1,8-cineole (oxide) and limonene (monoterpene), 7–15% α-pinene (monoterpene), 2–6% β-pinene (monoterpene) and 2–6% viridiflorol (sesquiterpene).[28] *In-vitro* studies were performed using hairless mouse skin to determine the permeation enhancement effect of different essential oils at a 10% (w/w) concentration in propylene glycol on estradiol as a model drug. Niaouli essential oil proved to be more effective than cajuput-, cardamom-, melissa-, myrtle- and orange essential oils for enhancing the transdermal permeation of estradiol.[29]

Alpinia oxyphylla Oil

Alpinia oxyphylla is a member of the ginger (Zingiberaceae) family used in oriental herbal medicine. Essential oils from *A. oxyphylla* were extracted and subsequently divided into a lower-polarity fraction and a higher-polarity fraction. The lower-polarity fraction contained eight sesquiterpenes. The high-polarity fraction consisted of seven sesquiterpenes.[16] During an *in-vitro* study with Franz diffusion cells using dorsal skin of Wistar rats, the high-polarity fraction of *A. oxyphylla* essential oil was more efficient in enhancing the skin permeation of indomethacin at concentrations of 3 and 5% than the lower-polarity fraction. The *A. oxyphylla* essential oils showed no irritancy and/or toxicity with the high-polarity fraction showing lower irritation than the low-polarity fraction.[30]

Turpentine Oil

Turpentine oil is obtained after distillation of the resin that is secreted by conifers (*Coniferae* spp). It is one of the most common essential oils. Turpentine oil showed an additive effect on the skin permeation rate of flurbiprofen when added to an optimized co-solvent mixture of propylene glycol-isopropyl alcohol (30:70% (v/v)). A maximum transdermal permeation rate was obtained with turpentine oil at a 5% (v/v) concentration and was found to be significantly more effective than tulsi oil at the same concentration. This is probably due to an increased disruption of the stratum corneum, which is normally caused by terpenes, although it caused minor skin irritation.[31] When compared to the binary solvent vehicle alone, 5% (v/v) turpentine oil had a significantly lower lag time for flurbiprofen flux across the skin.

Sweet Basil and Tulsi Oil

Sweet basil oil is obtained with the steam distillation of the leaves, stems, and flowers of *Ocimum basilicum* from the Lamiaceae or Labiatae (mint) family. This essential oil has numerous medicinal properties such as anti-inflammatory, muscle relaxant, anti-spasmodic, anti-viral and anti-bacterial. The key constituents include: methylchavicol (estragol) (40–80%, phenol), linalol (5–10%, alcohol), 1,8-cineole (1–7%, oxide) and eugenol (1–10%, phenol).[32] The influence of *O. basilicum* or basil essential oil extract on the permeation of drugs through the skin was investigated *in-vitro* by employing Franz diffusion cells using the dorsal skin of Wistar rats.

Cardamom Oil

Cardamom oil is distilled from *Elettaria cardamomum* (cardamom), part of the ginger (Zingiberaceae) family. It is used as an anti-spasmodic, expectorant and anti-parasitic agent.[33] The key constituents of this oil includes: α-terpinyl acetate (45–55%, ester), 1,8-cineole/eucalyptol (16–24%, oxide), linalol (4–7%, alcohol), linalyl acetate (3–7%, ester) and limonene (1–3%, monoterpene) it was found with an *in-vitro* permeation study through rabbit abdominal skin that the oil enhanced the permeation of indomethacin, diclofenac and piroxicam.[34] It was determined that

the enhancing effect of cardamom depended on its concentration, with a 1% (v/v) concentration being more effective than 0.5% (v/v).

Further in vivostudies showed that a 30 min pre-treatment of rabbit abdominal skin with 5% cardamom oil in an alcohol-water vehicle (1:1) increased the peak area of the plasma concentration time curve of piroxicam (AUC 0–24 h) 67.09-fold when compared to nontreatment. In addition, an absolute bioavailability of 83.23% was obtained. Results after a 60 min pre-treatment were not significantly different from that after a 30 min pre-treatment.[35]

Peppermint Oil

Peppermint oil is extracted by steam distillation from the stems, leaves, and flower buds of the plant *Mentha piperita* from the Lamiaceae or Labiatae family. The key constituents of the oil include: menthol (34–44%, phenolic alcohols), menthone (12– 20%, ketone), menthofurane (4–9%, furanoids), 1,8-cineole (eucalyptol, 2–5%, oxide), pulegone (2–5%, ketone) and menthyl acetate (4–10%, ester). The oil is used to relieve pain, control appetite, stimulate digestion/gallbladder function, and as an anti-inflammatory, anti-tumoral, anti-viral, anti-bacterial, and anti-parasitic agent, Peppermint oil showed the most significant effect on skin integrity. Therefore, it was studied further to determine its effect on the percutaneous permeation of benzoic acid at different concentrations.[36] Results showed that the peppermint oil was generally protective against the permeation of the hydrophilic drug at the lower concentrations of 0.1% and 1.0% (v/v).

Fennel Oil

Fennel oil is obtained from steam distillation of the crushed seeds of *Foeniculum vulgare*, which is part of the Apiaceae or Umbelliferae family. Its main components is 60–80% *trans*-anethole (phenolic ester), 12–16% fenchone (ketone), linalol (alcohol), 3–5% α-pinene (monoterpene) and 2–5% methyl chavicol (phenol). It can be used as a digestive aid, anti-septic, anti-spasmodic, analgesic and anti-parasitic agent. It also has anti-inflammatory, anti-tumoral characteristics and can increase metabolism[14] fennel oil was found to be the most effective enhancer for the percutaneous permeation of trazodone hydrochloride, nevertheless, pre-treatment with 10% fennel oil in propylene glycol showed an enhancement ratio of 9.25 compared to the control.[37]

Black Cumin Oil

Black cumin essential oil is obtained with steam distillation from the seeds of *Cuminum cyminum* of the Apiaceae or Umbelliferae family.It can be used as an immune stimulant, digestive aid, liver protectant, antioxidant, anti-inflammatory, anti-tumoral and anti-viral. Its major components include: Cuminaldehyde (16–22%, aldehyde), γ-terpinene (16–22%, monoterpene), β-pinene (12–18%, monoterpene), *p*-mentadienal (25–35%, aldehydes) and *p*cymene (3–8%, monoterpenes).[15] Black cumin oil was a better permeation enhancer with an enhancement factor of 6.40 for the model lipophilic drug, carvedilol, compared to clove oil, eucalyptus oil tulsi oil, oleic acid and Tween 80.[38] Thermal analysis (Differential Scanning Calorimetry or DSC) of 5% (v/v) black cumin oil in isopropyl alcohol indicated that the oil could extract lipids (fluidizing the skin) and cause α-keratin denaturation that alters the skin protein composition. This creates a passage for the drug to cross the dermis.

Aloe Vera

A. vera gel increased the *in-vitro* skin permeation of compounds depending on their molecular weights, with an apparent inverse correlation between enhancement ratio and molecular weight of the compound. Some constituents of the Aloevera gel itself also penetrated the skin, which was interestingly dependent on the molecular weight of the co-applied compounds. Thus the permeation enhancement effect of the aloe gel was explained by a probable pull effect of complexes formed between the compound and the enhancing agent within the aloe gel.[39]

Vegetable Oils

The compositions are formulated with one or more vegetable oils as skin permeation enhancers; a preferred composition contains coconut oil and soybean oil. Drug delivery systems for administering drugs trans-dermally in combination with the vegetable oil-based enhancer compositions are also provided.

Supporting Pharmacological Studies

In-vitro Permeation Study, the permeation studies were performed using an automated flow-through apparatus (Perme-Gear I-Line Cells, ILC14). The rat epidermal membrane was mounted onto the dynamic diffusion cell with the stratum corneum side facing the donor compartment and the dermal side facing the receptor compartment. The diffusion cell was equilibrated overnight at 32°C with a continuous 0.05 M phosphate buffer (pH 7.4) flow through the receptor compartment. The effective diffusion area was 0.5 cm^2. Rat epidermis (Sprague-Dawley rats, 5–10 g) was used as a skin model for this study. The care and use of the animals were following institutional guidelines. The neonate (2–3 days old) rats were euthanized using carbon dioxide asphyxiation before the experiments, and full-thickness skin was

surgically removed from each rat. Rat epidermis was prepared by a heat separation technique.[39] The entire skin of neonate rats was soaked in water at 60°C for 1 minute, followed by careful removal of the epidermis. Rat epidermis, so prepared, was washed with water and examined for physical damage by using a magnifying lens. Rat epidermis free from physical damage was used in the *in-vitro* permeation study. One gram of each of the commercial or experimental cosmetic formulations was filled in the donor cell. After predetermined times (1, 2, 3, 4 h), samples were collected from the receptor compartment and analyzed by HPLC method. Triplicate experiments were run for each product under investigation.[40]

In-vivo Permeation Study

In this study, each preparation was applied repeatedly (every 30 min) over 4 hours on neonatal rats' dorsal side (7–8 cm 2). The area of skin used in the permeation study was removed and rat epidermis was prepared (as described under '*In-vitro* Permeation Study'), crushed and extracted with methanol, and subjected to HPLC analysis for estimating the amount of T/TA retained in rat epidermis. Triplicate experiments were run for each product under investigation. In order to further follow up the permeation, we repeated the same in vivo experiment.[41]

We separated the full-thickness neonatal rat skin, cut it into small pieces, extracted it with methanol, and centrifuged, and the filtered supernatant was assayed for T and TA content by the abovementioned HPLC method. The purpose of this procedure was to assess if any vitamin permeated through the stratum corneum might have been retained in the deeper skin layers. Control experiments were run on naïf animals to determine naturally present vitamins. The work described in this article was carried out following The Code of Ethics of the World Medical Association. (Declaration of Helsinki) for experiments involving animals.

Permeation Enhancer by Hydration Therapy

In skin permeation by hydration of the stratum corneum, or by using chemical enhancers acting on the lipids and keratinized structures in the stratum corneum, partitioning and solubility effects is a promising tool in potential clinical applications. Permeation enhancement is a new emerging technology that can increase the number of drugs taken trans-dermally. Also, the drugs with a short biological half-life could be easily administered enhancement.[42]

Water is the most common and safe penetration enhancer used to transport both drug and cosmetic materials into the skin. Hydrating the skin or using moisturizers can be the easiest way to deliver hydrophilic molecules effectively. The water content of the SC is usually 5 to 10%, which can be increased up to 50% under occlusive conditions. In 1987, Barry reported that water molecule acts in both inter and intra-cellular pathways to enhance the permeation of both hydrophilic and lipophilic drugs. In case of the intracellular region, in dry conditions, the SC provides a significant barrier to drug molecules because of the presence of several hydrogen bonding group. Since the SC becomes hydrated, the proteinaceous region takes up water. The arrangement of protein of that region becomes disordered and water starts competing for the hydrogen binding sites on the protein, reducing the interaction between them. In this way, permeation of molecules through the intracellular pathway increases.[37,38] Barry also stated that water molecules bind with the polar head group and form a small hydration shell via hydrogen bonding in the lipid bilayer region. This leads to the loosening of lipid packing and extending the hydrophilic domain.[43] However, later studies found that water does not cause a massive lipid disorder, it may cause slight disordering of a small population of the SC lipid. Water also found not to swell lipid bilayer but can be present in very small quantities in the polar head group of the lipid bilayer region. The excess amount of water the SC absorbs may be present in the corneocytes (intracellular region) or as a separate phase in the intercellular region.[44]

CONCLUSION

Many existing drugs have to be given via injections which are painful and undesirable as they may be risky also in some cases. Therefore, these days skin is a preferred route of drug delivery, and it is termed the transdermal drug delivery system. Drugs entering the systemic circulation have to pass the skin barrier, Stratum Corneum. For this permeation enhancers are required as it is difficult to penetrate through the SC. The permeation enhancer functions by altering the barrier characteristics of skin membranes or by increasing the drug solubility inside the skin. The current review aims to summarize the natural sources reported as promising herbal & natural permeation enhancers. Permeation enhancer can be used as a tool to achieve an effective dosage of the drug to enter therapeutically within the skin.

It can be concluded that research or exploration is beneficial for scaling up the system of natural permeation enhancers, and executing the dosage forms with natural permeation enhancers will play a prominent role in the progress of useful and efficient transdermal products in the future.

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