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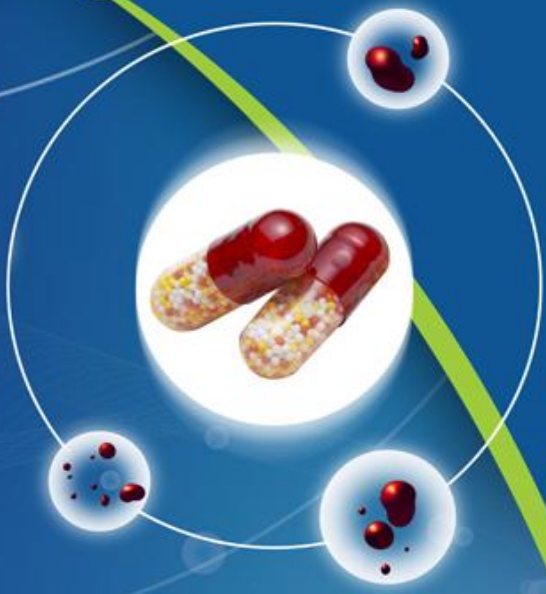

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Research Article

SORPTION PROMOTERS: A NOVEL ENHANCER APPROACH FOR TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT

Topical drug delivery system can be defined as direct effects of formulation or drug containing medication to the skin to get localizing effect of drug or directly cure cutaneous disorders. The skin has evolved to prevent excessive water loss from the internal organs and to limit the ability of xenobiotics and hazardous substances to enter the body. Notwithstanding this barrier function, a number of strategies have been developed by scientists to deliver drugs to and through the skin. Skin as an important site for topical effects so there is considerable interest in the skin for local and systemic effect of drug application. However, in the skin, the stratum corneum is the main barrier for drug penetration there by limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range and number of drugs available for both topical and transdermal delivery. In this review, we have discussed about the various penetration enhancers, their mechanism of action and their potential for clinical application.

Keywords: *Topical Drug Delivery, Skin, Stratum Corneum Modification, Penetration Enhancers, Bioavailability.*

INTRODUCTION

Over the past century, the treatment of illness has been accomplished by administering drug to human body via various routes namely oral, topical, sublingual, rectal, parental etc. The topical drug delivery system is generally used where these systems of drug administration fails or in local skin infection like fungal infection. Topical drug delivery system can be defined as direct effects of formulation or drug containing medication to the skin to get localizing effect of drug or directly cure cutaneous disorders [1]. Topical drug delivery offers the following advantages over the oral route for controlled drug delivery [2].

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- Predictable and extended duration of activity.
- Minimizing under able side effects.
- Utility of short half life drugs.
- Improving physiological and pharmacological response.
- Avoiding the fluctuation in drug levels.
- Provides patient convince.
- Avoidance of hepatic first pass metabolism.
- Ability to discontinue administration by removal of the system.
- The ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form.
- The ability to modify the properties of the biological barrier to absorption.

But one of the major problems in topical drug delivery is the low penetration rate through the outer most layer of skin. Drug delivery via the percutaneous route potentially has many advantages over intravenous and oral administration [3], but human skin is designed

to be a barrier to the passage of molecules either from inside to out or vice versa [4]. The principal barrier to topical drug delivery is the stratum corneum, which poses a formidable barrier to drug penetration, thereby limiting topical and transdermal bioavailability [5]. Many approaches have been employed to mitigate stratum corneum permeability, and the most commonly used approach is that of sorption promoters, also known as penetration enhancers [3, 6].

Skin is the largest organ easily accessible for local and systemic drug administration. For successful dermal or epidermal delivery it is necessary to reversibly overcome the skin barrier. However, skin is an excellent barrier that is naturally adapted to prevent transport of molecules into and out of the body [7].

Thus, even after decades of searching for appropriate ways to deliver drugs through skin, very few topical products are available on the market [8].Different strategies have been proposed to overcome the skin barrier, from more complex enhancement methods such as iontophoresis, electroporation, ultrasound, patches with microneedles and laser treatment, to classical approaches with optimization of the dermal formulation [8 - 11]. The skin has evolved to prevent excessive water loss from the internal organs and to limit the ability of xenobiotics and hazardous substances to enter the body. Notwithstanding this barrier function, a number of strategies have been developed by scientists to deliver drugs to and through the skin.

A BRIEF REVIEW OF SKIN STRUCTURE

The skin can be considered to have four distinct layers of tissue [2].
Non-viable epidermis (stratum corneum)
Viable epidermis
Viable dermis
Subcutaneous connective tissue (hypodermis)

Non-viable epidermis (stratum corneum)

Stratum corneum is the outer most layer of skin, which is the actual physical barrier to most substance that comes in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell is a flat, plate-like structure - 34-44 µm long, 25-36 µm wide, 0.5 to 0.20 µm thick - with a surface area of 750 to 1200 µm2 stocked up to each other in brick like fashion. Stratum corneum consists of lipid (5-15%) including phospholipids, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin.

Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis and has a thickness ranging from 50- 100 µm. The structure of the cells in the viable epidermis is physiochemical similar to other living tissues. Cells are held together by tonofibrils. The density of this region is not much different than water. The water content is about 90%.

Dermis

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis thickness range from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.

Subcutaneous connective tissue:

The subcutaneous tissue or hypodermis is not actually considered a true part of the structured connective tissue is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the circulatory system before reaching the hypodermis, although the fatty tissue could serve as a depot of the drug.

PENETRATION ENHANCERS (SORPTION PROMOTERS OR ACCELERANTS)

Penetration enhancers may be incorporated into formulations in order to improve drug flux

through diverse membranes including gastric epithelia or nasal membranes. Diffusion through skin, controlled by the outer most layers, the stratum corneum, can be regarded as diffusion through a passive membrane [12].

Ideal Properties of Penetration Enhancers

- Although many chemicals have been evaluated as penetration enhancers in human or animal skins, to-date none has proven to be ideal. Some of the more desirable properties for penetration enhancers acting within skin have been given as [13, 14].
- They should be non-toxic, non-irritating and non-allergenic.
- They would ideally work rapidly, and the activity and duration of effect should be both predictable and reproducible.
- They should have no pharmacological activity within the body—i.e. should not bind to receptor sites.
- The penetration enhancers should work unidirectional, i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
- When removed from the skin, barrier properties should return both rapidly and fully.
- The penetration enhancers should be appropriate for formulation into diverse topical preparations, thus should be compatible with both excipients and drugs.
- They should be cosmetically acceptable with an appropriate skin 'feel'.

Mechanism of Penetration Enhancers

Skin penetration enhancers (SPEs) are used in many topical and transdermal medicines to promote the transport of drugs into and across human skin [15]. The proposed mechanisms of action of chemical enhancers may be categorized into two groups.

The first mechanism is based on an increase in the solubility of the permeant in the stratum corneum (SC) by transiently changing the solubility parameter of the skin. Consequently, there may be an improvement in the flux of the drug through the skin [15 - 17]. Simple solvents, such as propylene glycol, ethanol, and Transcutol are believed to act in this way [15].

The second mechanism involves a change in the order of the structured lipids of the SC. This effectively fluidizes the lipid domain thereby increasing the diffusion coefficient of the permeant. It is considered that IPM acts in this way that is, it enters the lipid layers of the SC and reduces the close packing of fatty acids within the skin [15]. This ultimately results in increased mobility of SC lipids and reduced diffusion resistance to permeation.

Pathways of Penetration Enhancers

Permeation can occur by diffusion, shown in fig. 1. [14, 18]

Transdermal permeation, through the stratum corneum. Intercellular permeation, through the stratum corneum. Transappendaged permeation, via the hair follicle, sebaceous and sweat glands.

Most molecules penetrate through skin via intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass its elegant molecular architecture. The method employed for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories [19].

- Chemical enhancement
- Physical enhancement
- Biochemical enhancement
- Super saturation enhancement
- Bio convertable prodrug

Functions of Penetration Enhancers

On the basis of lipid portioning concept, there are three main functions of penetration enhancers [9].

- **Lipid Disruption:**

  The enhancers change the structure of stratum corneum lipid organization and make it permeable to drugs. eg. Azones, Terpenes, Alcohols, fatty acids, and DMSO.

- **Proteion Modification:**

  Ionic surfactant, DMSO with keratin in corneocytes and open up the dense protein structure and make it more permeable.

- **Partitioning Promotion:**

  Many solvents change the solution properties of horny layer and thus increasing the partitioning of drug, co-enhancers, and co-solvents.

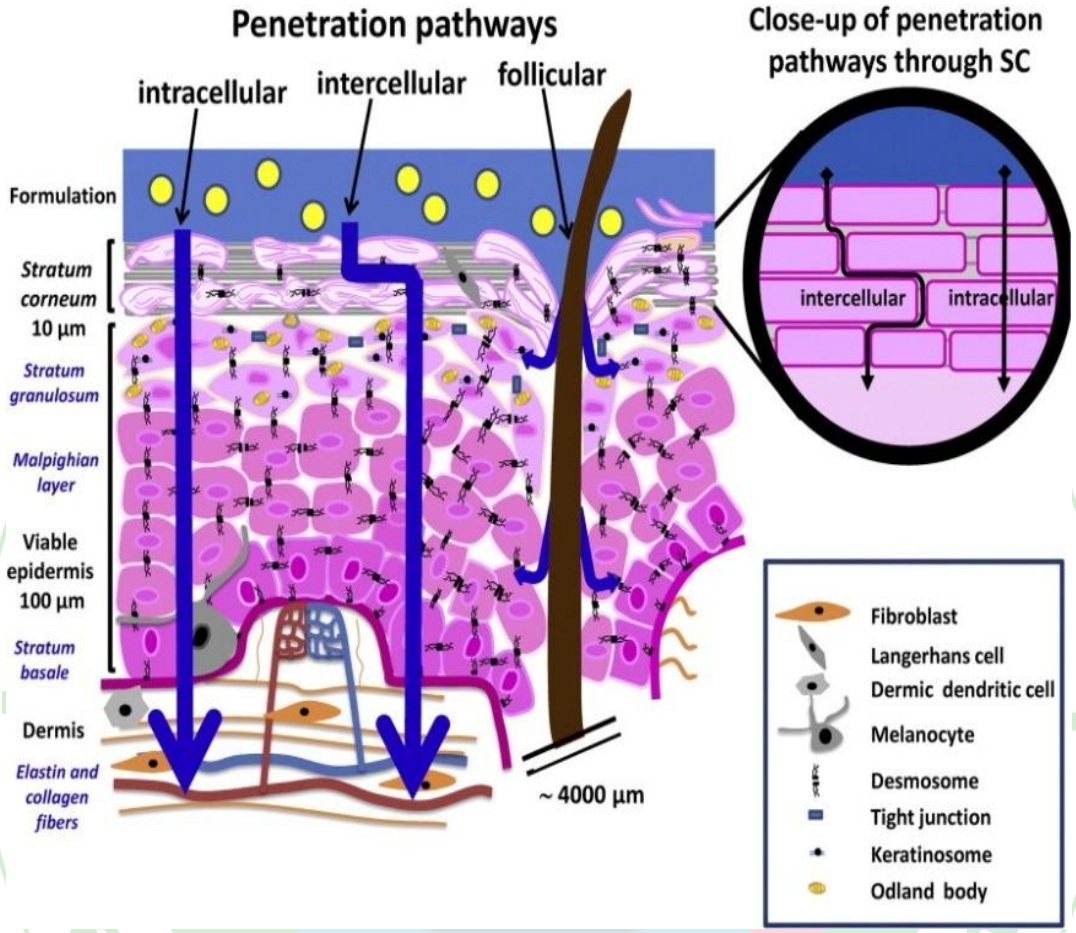

Figure 1: Pathways of penetration enhancers

APPROACHES OF PENETRATION ENHANCERS

The approaches for providing topical drug delivery of various therapeutic substances are:

Chemical Based Approach or Drug and vehicle interactions

- Selection of correct drug or prodrug
- Ion pairs and complex coacervates
- Eutectic systems
- Hydration
- Chemical penetration enhancers

Physical Based Approach

- Ultrasound (Phonophoresis, Sonophoresis)
- Iontophoresis
- Electroporation
- Magnetophoresis
- Pressure wave

Vesicles and Particles Based Approach

- Liposomes and other vesicles
- Niosomes
- Transfersomes
- Phospholipids

Others Approach

- Microneedle array
- Stratum corneum ablated
- Follicular delivery

- Solvents at high concentrations
- Metabolic interventions

Drug and vehicle interactions or chemical based approach

Selection of correct drug or prodrug

Drug should be selected in such a way that it fits in the criteria of topical drug delivery as given in Table 1. The prodrug design strategy generally involves addition of a promoiety to increase partition coefficient [20], and hence solubility and transport of the parent drug in the stratum corneum. Upon reaching the viable epidermis, esterases release the parent drug by hydrolysis thereby optimizing solubility in the aqueous epidermis. The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S-6- acyloxymethyl and 9-dialkylaminomethyl promoieties [21].

TABLE I: Parameters for Drug Selection

Parameters	Ideal limits
Aqueous solubility	>1mg/ml
Lipophilicity	10<Ko/w<1000
Molecular weight	<500 Daltons
Melting point	<2000 ^{0}C
pH of aqueous saturated solution	5-9
Dose deliverable	<10mg/day

Ion pairs and complex coacervates

Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ion pairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralized so that the complex can partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug, which can diffuse within the epidermal and dermal tissues [22].

Eutectic systems

The melting points of a drug influences solubility and hence skin penetration. According to regular solution theory, lower the melting point, greater the solubility of a material in a given solvent including skin lipids. The melting point of a drug delivery system can be lowered by formation of a eutectic mixture: a mixture of two components which, at a certain ratio, inhibit the crystalline process of each other, such that the melting point of the two components in the mixture is less than that of each component alone. A number of eutectic systems containing a penetration enhancer as the second components have been reported, for example: Ibuprofen with terpenes [23], and methyl nicotinate [24], propranolol with fatty acids [25], and lignocaine with menthol [26].

Hydration

Water is the most widely used and safest method to increase skin penetration of both hydrophilic [27], and lipophilic permeants [28]. The water content of the stratum corneum is around 15 to 20% of the dry weight but can vary according to humidity of the external environment. Additional water within the stratum corneum could alter permeant solubility and thereby modify partitioning from the vehicle into the membrane. In addition, increased skin hydration may swell and open the structure of

the stratum corneum leading to an increase in penetration, although this has yet to be demonstrated experimentally.

Soaking the skin in water, exposing the membrane to high humidities or, as is more usual under clinical conditions, occluding the tissue so preventing epidermal water loss can allow the stratum corneum to reach water contents in equilibrium with that of the underlying epidermal skin cells. Thus, on occlusion, the water content of this outer membrane can approach 400% of the tissue dry weight. Many clinically effective preparations and products such as ointments and patches are occlusive, which provides one mechanism of enhanced drug delivery; numerous patch formulations deliver drugs at higher than would be expected rates due to modification of the stratum corneum water content.

For example, Scientists showed that the diffusion coefficients of alcohols in hydrated skin were ten times that observed in dry skin [29]. Hydration can be increased by occlusion with plastic films; paraffins, oils, wax as components of ointments and water-in-oil emulsions that prevent epidermal water loss and oil-in-water emulsions that donate water. Of these, occlusive films of plastic or oily vehicle have the most profound effect on hydration and penetration rate [30].

Chemical penetration enhancers (CPEs)

The use of CPEs over the other techniques has certain advantages, including design flexibility of the patch and ease of patch application over a large area (>10 cm2) [31]. A broad range of different chemical additives have been tested to enhance topical penetration during the last two decades. Much of the cited literature is found in patents [32] as well as pharmaceutical science literature [33]. Even though many chemical entities have been identified, only a few were introduced in the market due to several limitations, which include their economic feasibility and the toxic effects on skin, which make them undesirable for developing topical drug delivery.

Chemicals used as penetration enhancers those have the following properties:

Low molecular mass, preferably less than 600Da, when D tends to be high. Adequate solubility in oil and water so that membrane concentration gradient may be high. High but balanced (optimal) K (if too large, may inhibit clearance by viable tissue). Low melting point, correlating with good solubility as predicted by ideal solubility theory.

Sulphoxides and similar chemicals

Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aportic solvent shown in fig. 2 which hydrogen bonds with itself rather than with water. It is colourless, odourless and is hydroscopic and is often used in many areas of pharmaceutical sciences as a "universal solvent". DMSO alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer - spillage of the material onto the skin can be tasted in the mouth within a second. Although DMSO is an excellent accelerant, it does create problems. The effect of the enhancer is concentration-dependent and generally co solvents containing > 60% DMSO are needed for optimum enhancement efficacy. However, at these relative high concentrations, DMSO can cause erythema and wheal of the stratum corneum. Denaturing of some skin, protein results in erythema, scaling, contact uticaria, stinging and burning sensation [34]. Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as an accelerant. Dimethylacetamide (DMAC) and dimethylformamide (DMF) are similarly powerful aportic solvents. However, Researcher showing a 12-fold increase in the flux of caffeine permeating across a DMF-treated human skin concluded that the enhancer caused irreversible membrane damage [35].

DMF irreversibly damages human skin membranes but has been found *in vivo* to promote the bioavailability of betamethasone-17-benzoate as measured by vasoconstrictor assay [36, 37]. DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels. The mechanism of the sulphoxide penetration enhancers is widely

used to denature protein and, on application to human skin, has been shown to change the intercellular keratin conformation, from α helical to β sheet.

It has been postulated that DMSO denatures the intercellular structural proteins of the stratum corneum, or promotes lipid fluidity by disruption of the ordered structure of the lipid chains. In addition, DMSO may alter the physical structure of the skin by elution of lipid, lipoprotein and nucleoprotein structures of the stratum corneum. Decylmethylsulfoxide (DCMS) is thought to promote permeation enhancement as a result of protein-DCMS interaction creating aqueous channels, in addition to lipid interactions.

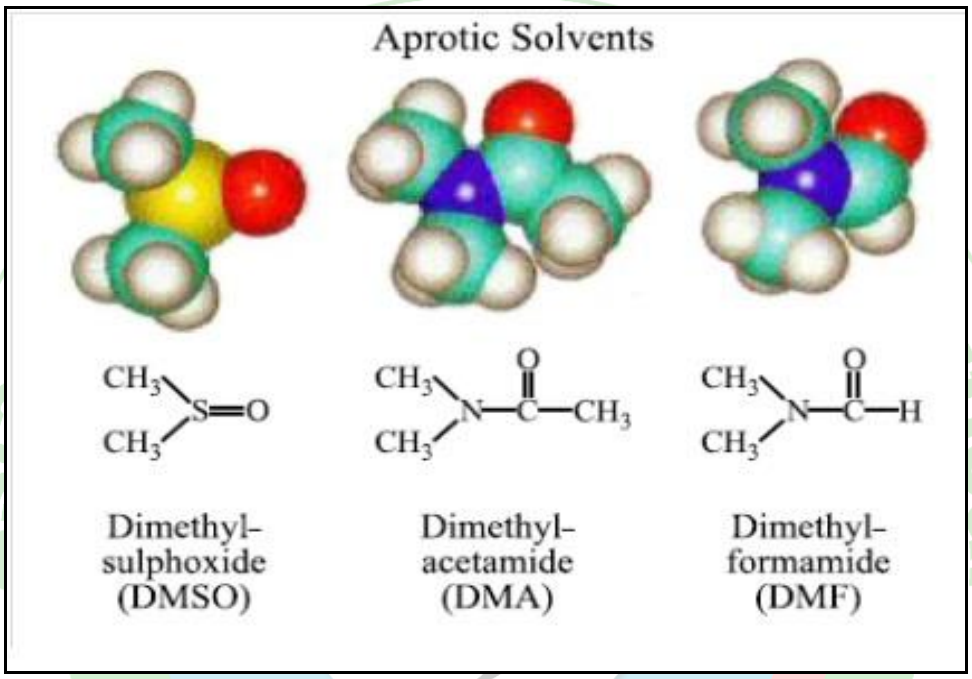

Figure 2: Aprotic solvents which act as potent penetration enhancers.

Alkanes

Long chain alkanes (C7-C16) have been shown to enhance skin permeability by non-destructive alteration of the stratum corneum barrier [38]. These findings were confirmed in studies in which nonane was investigated as an enhancer [39], although there must be some destructive solubilisation and biochemical extraction caused by these lipophilic solvents.

Azones

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule shown in fig. 3 specifically designed as a skin penetration enhancer. Azone is a colourless, odourless liquid with a melting point of - 7 ºC and it possesses a smooth, oily but yet non-greasy feel. Azone is a highly lipophilic material with a log p octanol / water of around 6.2 and it is soluble in and compatible with most organic solvents including alcohol and propylene glycol.

Azone enhances the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is most effective at low concentrations, being employed typically between 0.1- 5% but more often between 1-3% [4]. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone increases the fluidity of the lipid layer, while PG increases the water content of the proteinaceous region and helps azone partition into the aqueous region. A combination of these two helps the penetration of hydrophilic drugs greatly [40, 41].

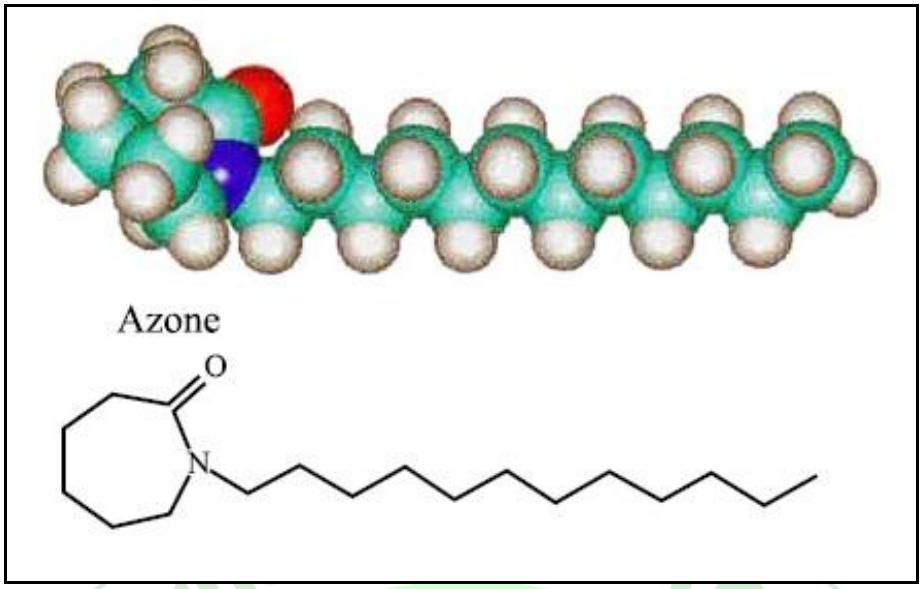

Figure 3: Azone, the first molecule to be synthesised so as to act as a skin penetration enhancer.

Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g. mannitol and 5-flurouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-pyrolidone was employed with limited success as a penetration enhancer for captopril gel formulations [42].

The pyrrolidones partition well into human stratum corneum within the tissue and they may act by altering the solvent nature of the membrane. Pyrrolidones have been used to generate reservoirs within the skin membrane. Such a reservoir effect offers a potential for sustained release of a permeant from the stratum corneum over extended time periods [43].

Urea

Urea promotes topical permeation by facilitating hydration of the stratum corneum and by formation of hydrophilic diffusion channels within the barrier. As urea itself possesses only marginal penetration enhancing activity, attempts have been made to synthesis analogues containing more potent enhancing moieties.

Thus Wong and co-workers synthesized cyclic urea analogues and found them to be as potent as Azone for promoting indomethacin across shed snake skin and hairless mouse skin

Cyclic urea permeation enhancers are biodegradable and non-toxic molecules consisting of a polar parent moiety and a long chain alkyl ester group. As a result, enhancement mechanism may be a consequence of both hydrophilic activity and lipid disruption mechanism [44].

Fatty acids and Esters

Percutaneous drug absorption has been increased by a wide variety of fatty acids shown in fig. 4 and their esters, the most popular of which is oleic acid. A general trend has been seen that unsaturated fatty acids are more effective in enhancing percutaneous absorption of drugs than their saturated counterparts. It is of interest to note that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains and some structure - activity relationships have been drawn from the extensive studies employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone [45, 46]. Study of various penetration enhancers like glycols (diethylene glycol and tetra ethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and non ionic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone [47]. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestroge [48]. Oleic acid greatly

increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-flurouracil flux 56-fold through human skin membrane *in vitro* [49]. The enhancer interacts with and modifies the lipid domains of the stratum corneum as would be expected for a long chain fatty acid with cis-configuration.

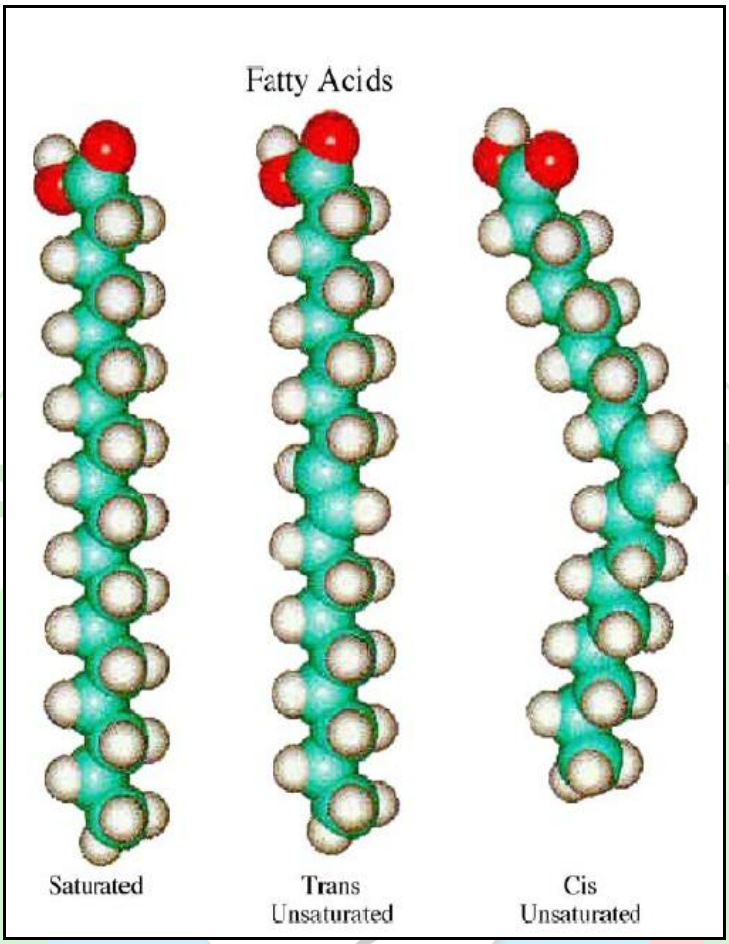

Figure 4: Fatty acids, illustrating the different space-filling properties of saturated and trans/cis unsaturated hydrocarbon tails.

Alcohols, fatty alcohols and glycols

Alcohols may influence topical penetration by a number of mechanisms. The alkyl chain length of the alkanols (fatty alcohols) is an important parameter in the promotion of permeation enhancement. In addition, lower molecular weight alkanols are thought to act as solvents, enhancing the solubility of drugs in the matrix of the stratum corneum [50]. Disruption of the stratum corneum integrity through extraction of biochemicals by more hydrophobic alcohols almost certainly also contributes to enhanced mass transfer through this tissue [51].

Ethanol is the most commonly used alcohol as a topical penetration enhancer. Ethanol acts as a penetration enhancer by extracting large amounts of stratum corneum lipids. It also increases the number of free sulphydryl groups of keratin in the stratum corneum proteins. Usually, pretreatment of skin with ethanol increases the permeation of hydrophilic compounds, while it decreases that of hydrophobic ones [52]. The molecular complexity of different glycol molecules is a determinant of their efficacy as permeation enhancers.

Solubility of the drug in the delivery vehicle is markedly influenced by the number of ethylene oxide functional groups on the enhancer molecule; this solubility modification may either enhance or retard topical flux depending on the specific drug and delivery environment. The activity of propylene glycol (PG) is thought to result from

solvation of α keratin within the stratum corneum, the occupation of proteinaceous hydrogen bonding sites reducing drug-tissue binding and thus promoting permeation [53].PG is widely used as a vehicle for penetration enhancers and shows synergistic action when used with, for example, oleic acid.

Surfactants

Many surfactants are capable of interacting with the stratum corneum to increase the absorption of drugs and other active compounds from products applied to the skin. Skin penetration measurements are valuable in quantifying these effects and observing the influence of surfactant chemistry and concentration. A surfactant interacts with skin by depositing onto the stratum corneum, thereby disorganizing its structure. Then surfactant can solubilise or remove lipids or water-soluble constituents in or on the surface of the stratum corneum. Finally it can be transported into and through the stratum corneum. This last effect is related to the surfactant and stratum corneum protein interaction and epidermal keratin denaturation [54]. Any application of surfactants in formulations must take account of the ability of these molecules to form micelles, solubilise the active and effectively lower its thermodynamic activity and ultimately its skin permeation.

Anionic surfactants are more effective than cationic and nonionic surfactants in enhancing skin penetration of target molecules. Some anionic surfactants interact strongly with both keratin and lipids. Cationic surfactants interact with the keratin fibrils of the cornified cells and result in a disrupted cell-lipid matrix. Nonionic surfactants enhance absorption by inducing fluidization of the stratum corneum lipids.

Scientists reported that the capacity of the stratum corneum to retain significant quantities of membrane-bound water is reduced in the presence of sodium dodecanoate and sodium dodecyl sulfate. This effect is readily reversible upon removal of the agents. These investigations proposed that anionic surfactants alter the permeability of the skin by acting on the helical filaments of the stratum corneum, and then they cause an expansion of the membrane, which increases permeability [55].

However, more recent findings suggest that impairment of the skin's barrier properties is unlikely to result from changes in protein conformation alone. Based on differential scanning calorimetry results, sodium lauryl sulfate (SLS) disrupted both the lipid and the protein components. The amount of surfactant that penetrates the skin after the disruption of the skin barrier depends on the monomer activity and the critical micelle concentration (CMC). Above the CMC, the added surfactant exists as micelles in the solution and micelles are too large to penetrate the skin. The extent of barrier disruption and penetration enhancement of a surfactant is also strongly dependent on surfactant structure, especially alkyl chain length. In general, studies have shown that surfactants having 12 carbons in their alkyl chain cause more disruption to the skin barrier and allow drugs to penetrate more readily than those that have more or less than 12 carbons. The explanation for this optimum of 12 carbons is not known yet.

Essential oil, terpenes and terpenoids

Terpenes are found in essential oils, and are compounds comprising of only carbon, hydrogen and oxygen atoms, but which are not aromatic. Numerous terpenes show in fig. 5 has long been used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodium and ylang-ylang have been found to be effective penetration enhancers for 5-flouorouracil transversing human skin *in vivo* [3].

Researcher investigated the effect of 12 sesquiterpenes on the permeation of 5-flurouracil in human skin [56]. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5- fluorouracil. L-menthol has been used to facilitate *in vitro* permeation of morphine hydrochloride through hairless rat skin as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin [57].

One mechanism by which this agent operates is to modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Terpenes may also modify drug diffusivity through the membrane. During steady state permeation experiments using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity through the membrane.

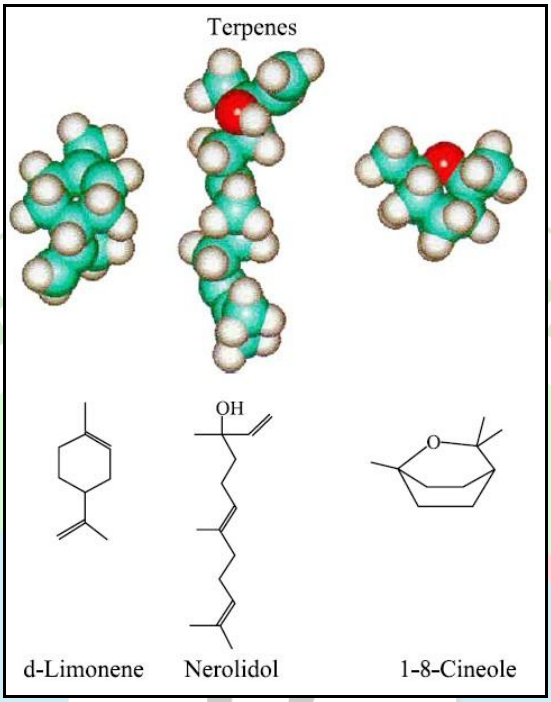

Figure 5: Example of terpenes that promote skin penetration of a variety of drugs.

Cyclodextrins

Cyclodextrins are biocompatible substances that can form inclusion complexes with lipophilic drugs with a resultant increase in their solubility, particularly in aqueous solutions. However, cyclodextrins alone were determined be to less effective as penetration enhancers than when combined with fatty acids and propylene glycol [58].

Oxazolidinones

Oxazolidinones are a new class of chemical agents which have the potential use in many cosmetics and personal care product formulations. This is due to their ability to localize co-administered drug in skin layers, resulting in low systemic permeation. The structural features of these permeation enhancers are closely related to sphingosine and ceramide lipids which are naturally found in the upper skin layers. Oxazolidinones such as 4-decyloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers.

This compound has a higher molecular weight and lipophilicity than other solvent-type enhancers, physical characteristics that may be beneficial in terms of a reduction in local toxicity because of the lack of effective absorption of these enhancers into the lower skin layers where irritation is likely to be occur [59].

Physical Based Approach

Ultrasound (Phonophoresis, Sonophoresis)

Sonophoresis is a technique which involves the use of ultrasonic energy to enhance skin penetration of active substances. Topical enhancement is particularly significant at low frequency regimes (20 KHz < f <100 KHz)

than when induced by high frequency ultrasound [60]. Ultrasound parameters such as treatment duration, intensity, pulse length, and frequency are all known to affect percutaneous absorption with frequency being the most important [61].

The mechanism of permeation involves the disruption of the stratum corneum lipids by the formation of gaseous cavities, thus allowing the drug to pass through the skin. Sonophoresis of hypotensive agents and papain has been used in the treatment of eye diseases. Several antibiotics including tetracycline, biomycin, and penicillin have been sonophoretically administered for the therapy of skin diseases [62].

Iontophoresis

Iontophoresis is the process of enhancing the permeation of topically applied therapeutic agents through the skin by the application of electric current. The drug is applied under an electrode of the same charge as the drug, and an indifferent counter electrode is positioned elsewhere on the body. The active electrode effectively repels the active substance and forces it into the skin. Increase in drug penetration by iontophoresis can be due to following mechanisms: [63].

The first mechanism proposes that the drug is forced across the skin by simple electronic repulsion of similar charges. Anionic drugs can cross the skin by using a negatively charged working electrode. Similarly, cationic drugs can cross the skin when a positively charged electrode is used.

The second explanation suggests that the electric current enhances the permeation by inhibiting the skins ability to perform its protective barrier function.The third states that iontophoresis causes water, a very effective penetration enhancer, to enter the stratum corneum (SC) by electrosmosis. Iontophoresis would be particularly useful in the delivery of hydrophilic drugs produced by biotechnology (peptides and oligonucleotides).

Iontophoretic delivery of drugs would be beneficial in the treatment of skin disorders such as skin cancer, psoriasis, dermatitis, hypertrophic scars. It has been widely used to treat conditions of the eye, ear, nose, teeth, and mouth. It has been also used for extraction of analyses (such as glucose) from the body [64, 65].

Electroporation

Electroporation is another electrical enhancement method which involves the application of short (microsecond or millisecond), high voltage (50-1000 volts) pulses to the skin. The mechanism of penetration is the formation of transient pores due to electric pulses that subsequently allow the passage of macromolecules from the outside of the cell to the intracellular space via a combination of processes such as diffusion and electrophoresis [66]. Larger macromolecules have also been delivered by electroporation, including insulin [67], vaccines [68], oligonucleotides [69], and microparticles [70]. A few model compounds such as calcein [71], and LHRH drugs have also been studied for increased skin absorption by electroporation.

Magnetophoresis

The term magnetophoresis was used to indicate application of a magnetic field and acts as an external driving force to enhance drug delivery across the skin. It induces alteration in the skins structure that could contribute to an increase in permeability [72]. Magneto liposomes consist of magnetic nanoparticles wrapped by a phospholipids bilayer which can be successfully applied for drug delivery systems, magnetic resonance imaging markers for cancer diagnosis, and thermal cancer therapy.

Pressure wave

Pressure waves generated by intense laser radiation, can permeabilize the stratum corneum as well as the cell membrane. Pressure wave is only applied for a very short time (100ns-1μs). It is thought that the pressure waves form a continuous or hydrophilic pathway across the skin due to expansion of lacunae domains in the stratum corneum. A single pressure wave is sufficient to permeabilize the stratum corneum and allow

the transport of macromolecules into the epidermis and dermis.

In addition, the drug delivered into the epidermis can enter the vasculature and produce a systemic effect. For example insulin delivered by pressure waves resulted in reducing the blood glucose level over many hrs. The application of pressure waves does not cause any pain or discomfort and the barrier function of the stratum corneum always recovers. The enhancing effect of such a mechanism on caffeine permeation has been reported [73].

Vesicles and particles [74]

Liposomes and other vesicles

Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. Liposomes acts by penetrating the epidermis, carrying the drug into skin and those large multilamellar vesicles could lose their external bilayer during penetration and these liposome lipids penetrate into the stratum corneum by adhering onto the surface of the skin and, subsequently destabilizing, and fusing or mixing with the lipid matrix. Thereafter, they may act as penetration enhancers, loosening the lipid structure of the stratum corneum and promoting impaired barrier function of these layers to the drug, with less well-packed intercellular lipid structure forms, and with subsequent increased skin partitioning of the drug.

Studies have focused on delivery of agents via liposomes like anti-psoriatic agent via ethanolic liposomes, caffeine for hyper proliferative diseases, catechins, enoxacin. Ethosomes are liposomes with high alcohol content (up to 45%) capable of enhancing penetration to deep tissues and the systemic circulation. It is proposed that the alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate**.**

Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. In fact, if compared with conventional liposomes (phospholipids) niosomes (non ionic surfactant vesicles) offer higher chemical stability, lower costs, and great availability of surfactant classes. Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders.

In fact, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties; both by reducing epidermal water loss and by increasing smoothness via replenishing lost skin lipids.

Transfersomes

These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant and 3-10% ethanol. Liposomes are too large to pass through pores of less than 50nm in size; transfersomes up to 500nm can squeeze to penetrate the stratum corneum barrier spontaneously. Studies have been focused on delivery of agents like vaccines, retinal palmitate, estradiol, copper, zinc, superoxide dismutase, insulin. In some cases the transferosomes drug delivery with some physical enhancement method iontophoresis for estradiol and microneedles for docetaxel.

Phospholipids

Many studies have employed phospholipids as vesicles (liposomes) to carry drugs into and through human skin. However, a few studies have used phospholipids in a non-vesicular form as penetration enhancers.

For example, theophylline was enhanced through hairless mouse skin by 1% phosphatidylcholine in PG, a concentration at which liposomes would not form [75]. Similarly, indomethacin flux was enhanced through rat skin by the same phospholipids and hydrogenated soy bean phospholipids have been reported to enhance diclofenac permeation through rat skin in vivo. There is no compelling evidence to suggest that phospholipids interact directly with stratum corneum packing, though this may be expected

when considering their physico-chemical properties and structures. However, phospholipids can occlude the skin surface and thus can increase tissue hydration which can increase drug permeation. When applied to the stratum corneum as vesicles, phospholipids can fuse with stratum corneum lipids. This collapse of structure liberates permeant into the vehicle in which the drug may be poorly soluble and hence thermodynamic activity could be raised so facilitating drug delivery.

Others Approach

Microneedle array

Microneedles are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. Microneedles are needles that are 10 to 200 µm in height and 10 to 50 µm in width. Microneedles do not stimulate the nerves, so the patient does not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles [76].

Stratum corneum ablated

Stratum corneum ablation can be achieved by micro-dermbrasion which use a stream of aluminum oxide crystals and laser-ablation which use high powered thermal pulse to vaporize a stratum corneum [77].

Follicular delivery

Penetration of topically applied compounds may occur via the stratum corneum as well as via skin appendages, i.e., sweat glands and hair follicles. Initially, skin appendages were not considered to be significant topical penetration routes, as evidence suggested that they accounted for only approximately 0.1% of the skin surface area. These calculations, however, did not take into the account that the hair follicles represent invaginations, which extend deep into the dermis with a significant increase in the actual surface area available for penetration. With a rich perifollicular vascularisation and changes in the differentiation pattern along the follicular duct, the follicle possesses distinct characteristics which favour penetration, and multiple studies suggest that the follicular penetration route may be especially relevant for hydrophilic and high molecular weight molecules, as well as by particle-based drug delivery systems Earliest reports on the participation of hair follicles in percutaneous absorption were based primarily on qualitative, histological studies of dye and stain localization.

Later studies led to increasingly quantitative data, characterizing follicular transport as a highly complex phenomenon. Scientists reported that substances are mainly located in the uppermost cell layers of the stratum corneum, where they are continually depleted due to the physiological process of desquamation. These findings suggest that the stratum corneum only provides a short-term reservoir function. The hair follicles in contrast represent efficient long-term reservoirs (up to 10 days) for topically applied substances, as their depletion occurs only through the slow processes of sebum production and hair growth [78].

Solvents at high concentrations

In addition to the activities of penetration enhancers within the intercellular domain, high levels of potent solvents may have more drastic effects. They may damage desmosomes and protein-like bridges, leading to fissuring of the intercellular lipid and splitting of the stratum corneum squames. Solvent may enter the corneocyte, drastically disrupting the keratin and even forming vacuoles [79]. Such dramatic effects would be even less acceptable to regulatory agencies (and patients) than lesser insults to the intercellular lipid.

Metabolic interventions

A more interventionist approach to penetration enhancement is proposed [80]. Strategies that interfere with any or all of the processes of synthesis, assembly, secretion, activation, processing, or assembling/disassembling of the extracellular lamellar membranes, could promote permeation as barrier homeostasis is altered. As the authors admit, such an approach would pose significant regulatory problems, not least of which would be issues related to increased xenobiotic or microbial

access. The concept of interfering with barrier homeostasis on a relatively long time scale poses a myriad of clinical considerations.

PENETRATION ENHANCERS IN COMMERCIAL FORMULATIONS

Table.2 provides examples of penetration enhancers used in topical preparations currently available in the market of UK and USA. Clearly, the nature and purpose of the formulation will influence the selection of the enhancer. Topical formulations are intended for local action and target the drug to the outer layers of the skin.

Table II: Examples Of Penetration Enhancers Used In Commercial Topical Products.

Active	Trade name	Enhancer
Adapalene	Differin Gel	Propylene glycol
Capsaicin	Qutenza Patch	Diethylene glycol monoethyl ether
Dapsone	Aczone Gel	Diethylene glycol monoethyl ether
Diclofenac Isopropyl alcohol	Mobigel	Ethanol
Diclofenac	Propylene glycol	Dimethyl sulphoxide, Ethanol, Propylene glycol
Diclofenac	Voltarol Emulgel	Isopropyl alcohol, Propylene Glycol
Diclofenac	Voltarol Gel Patch	1,3-Butylene glycol, Propylene glycol
Idoxuridine	Herpid	Dimethyl sulphoxide
Ketoprofen	Feldene	Ethanol
Propylene glycol	Lidoderm	Propylene glycol

CONCLUSION

The entire field of topical drug delivery systems, and especially penetration enhancement, is still in its infancy. It is evident that for the topical route to be effective for systemic drug delivery, particularly if the permeant of interest is poorly absorbed via the skin portal, a penetration enhancer of some form is necessary. The role of the penetration enhancer is to reversibly alter the barrier properties of the skin by improved fluidity of the membrane structures or by facilitation of drug solubility within the skin.

Skin permeation enhancement technology is a rapidly developing field which would significantly increase the number of drugs suitable for topical drug delivery, with the result that skin will become one of major routes of drug administration in the next decade. Research in this area has proved the usefulness of the penetration enhancers in the enhancement of drug permeation through skin. Various approaches discussed in this review are promising. Focus should be on skin irritation with a view to selecting penetration enhancers which possess optimum enhancement effects with minimal skin irritation.

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