INTRODUCTION
Penetration enhancement means a measure of the degree to which a formulation is successful in increasing the permeability of skin, mucosa or a test membrane, and the penetration enhancers are agents, which increase the permeability of the skin or temporarily reduce the impermeability of the skin. According to Chien et al. Penetration enhancers have no therapeutic value but can transport the sorption of drugs from drug delivery system through skin. There are following necessities for penetration enhancement of drugs.
- To maintain the level in blood.
- To improve the battery (Efficacy) of less potent drugs with higher dose e.g. Oxymorphone.
- High molecular weight drugs like peptides (insulin), proteins and hormones (LHRH) can be delivered through transdermal route.
- To increase the delivery of ionizable drugs at physiological pH, e.g. Timolol maleate.
- To deliver the impermeable drugs e.g. TRH, LRH, heparin, amino glycosides antibiotics.
- To reduce the lag time of transdermal drug delivery system, e.g. lignocain, asido-thymidine (AST).

Chemical Enhancers
The key to altering the polar pathway is to cause protein conformational change or solvent swelling. Chemical penetration enhancers may act by one or more of three main mechanisms, i.e. by disruption of the highly ordered structure of stratum corneum lipid, by interaction with intercellular protein or by improved partition of the drug, co-enhancer or solvent into the stratum corneum. Some enhancers act on both polar and non-polar path way by altering the multilaminate pathway for penetration. A useful way to consider factors affecting drug permeation rate through the stratum corneum is via the simple equation given below for steady state flux.

\[
d m / dt = D Co K / h
\]

Where Co is the constant concentration of drug in donor solution, K is the partition coefficient of the solute between the membrane and the bathing solution, D is the diffusion coefficient and h is thickness of membrane. The various chemicals used as enhancer are;

**Sulphoxides and similar chemicals**
Dimethyl sulphoxides (DMSO) is one of the earliest and most widely studied penetration enhancers, and is often used in many areas of pharmaceutical sciences as a universal solvent. Since DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as a accelerant. DMAC (Dimethylacetamide) and DMF (Dimethylformamide) are similarly powerful aprotic solvents. However, Southwell and Barry, 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. DMF irreversibly damages human skin membranes but has been found in vivo to promote the bioavailability of betamethasone-17-benozaate as measured by vasoconstrictor assay. 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. De-cyemethylsulfoxide (DCMS) is thought to promote permeation enhancement as a result of protein DCMS (De-
cylmethyisulfoxide) interaction creating aqueous channels, in addition to lipid interactions. Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) is a highly lipophilic material with 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 between 0.1-5% but more often between 1-3%. Azone partitions into a bilayer lipid to disrupt their packing arrangement but integration into the lipid is unlikely to be homogeneous. Azone molecules may exist dispersed within the barrier lipid or separate domains within the bilayer. Pyrrolidones

N-methyl-2-pyrrolidone was employed with limited success as a penetration enhancer for captopril when formulated in a matrix-type transdermal patch. 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. Fatty acid

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 of Aungst who employed a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone. Shin et al studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonic surfactant (polyoxyethylene-2-oleyl ether, poloxyethylene-2-stearly ether) on the release of tripropidone. Lauric acid in Propylene glycol enhanced the delivery of highly lipophilic antiestrogen. Oleic acid greatly increased the flux of many drugs such as increasing the flux of salicylic acid 28-fold and 5-flourouracil flux 56-fold through human skin membrane in vitro. Essential oil, terpenes and terpenoids

The essential oils of eucalyptus, chamipodium and ylang-ylang have been found to be effective penetration enhancers for 5-flourouracil transversing human skin in vivo. Cornwell et al investigated the effect of 12 sesquiterpenes on the permeation of 5-flourouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-flourouracil. L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin as well as disruption of miramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin. Oxazolidinones

The Oxazolidinones have 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-decylloxazolidin-2-one has been reported to localize the delivery of many active ingredients such as retinoic acid and diclofenac sodium in skin layers. Amines and amides

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. Dimethylacetamide and dimethylformamide are less potent penetration enhancing chemical alternatives to DMSO (Dimethyl sulphoxides). At low concentrations their activity as enhancers is a result of partitioning into the keratin regions. At higher concentrations they increase lipid fluidity by disruption of lipid packing as a result of solvation shell formation around the polar head groups of the lipids. Surface active agents

These agents function primarily by adsorption at interfaces and thus interact with biological membranes contributing to the overall penetration enhancement of compounds. Cationic surfactants (e.g. Benzalkonium chloride) are more destructive to skin tissues causing a greater increase in flux than anionic surfactants. The latter, in turn, produce greater increases in flux than nonionic surfactants. Anionic surfactants may function by alteration of the barrier function of the stratum corneum as a result of removal of water soluble agents that act as plasticizers. Sodium lauryl sulphate has been implicated in reversible lipid modification with resultant disruption of the stratum corneum and enhanced permeation. In addition, nonionic surfactants are purported to be able to emulsify sebum, consequently altering partitioning potential of drugs in favour of enhanced permeation. Cyclodextrins: These compound 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. PHYSICAL ENHANCERS

Medicated Tattoos

Medicated tattoos are a modification of temporary tattoos which contain an active drug medicament for transdermal delivery. The tattoo contains a drug layer, a colored design layer, and an adhesive layer that binds to the skin. There is no predetermined duration of therapy. The manufacturer provides a color chart that can be compared to the color of the patient’s tattoo to determine when the tattoo should be removed. The drugs used in medicated tattoos prototypes include acetaminophen, vitamin C etc. Pressure Wave

Pressure waves generated by intense laser radiation, can permeabilize the stratum corneum as well as the cell membrane. PW are 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. 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 hours. The enhancing effect of such a mechanism on caffeine permeation has been reported. Radiofrequency

Radiofrequency involves exposure of the skin to a high frequency alternating current of 100 KHz that results in the formation of heat-induced microchannels in the cell membrane. The drug delivery rate is controlled by the number and depth of microchannels formed, which depends on the properties of the microelectrodes in contact with the skin during treatment. Skin delivery of testosterone and human growth hormone are in progress by use of this device.
Microporation

Microporation acts as an external driving force to enhance drug delivery across the skin. It induces alteration in the skin’s structure that could contribute to an increase in permeability. Magnetoliposomes consist of magnetic nanoparticles wrapped by a phospholipid bilayer which can be successfully applied for drug delivery systems, magnetic resonance imaging markers for cancer diagnosis, and thermal cancer therapy.29

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.30 Iontophoretic delivery of drugs would be beneficial in the treatment of skin disorders such as skin cancer, psoriasis, dermatitis, hypertrophic scars.31 It has been widely used to treat conditions of the eye, ear, nose, teeth, and mouth. It has been used for extraction of analytes (such as glucose) from the body.32

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. Larger macromolecules have also been delivered by electroporation, including insulin, vaccines, oligonucleotides, and microparticles. Several compounds such as calcine and LHRH drugs have also been studied for increased transdermal absorption by electroporation.33

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Microportion

Microporation involves the use of microneedles that are applied to the skin so that they pierce only the stratum corneum and increase skin permeability. They are usually drug-coated projections of solid silicon or hollow, drug-filled metal needles.34 Micromachined needles are not tall enough to stimulate nerve endings, which lie deeper within the skin. In contrast to conventional hypodermic needles, drug delivery to the epidermis using microneedles is therefore completely pain-free and results in minimal tissue damage. This ease of use means that such delivery systems are highly suited to self-administration or to use in developing countries.35

Needleless injection

Needleless injection involves a pain-free method of administration of drugs to the skin. This technique involves firing the liquid or solid particles at supersonic speeds through the stratum corneum.39 The mechanism involves forcing compressed gas such as helium or nitrogen through the nozzle with the resultant drug particles entrained within the jet flow, reportedly traveling at sufficient velocity for skin penetration. Problems with this technique include the high developmental cost for both the device and dosage form and the inability to program or control drug delivery to compensate for intersubject differences in skin permeability.36

Sonophoresis / Phonophoresis

Sonophoresis is a technique which involves the use of ultrasonic energy to enhance skin penetration of active substances.37 Transdermal enhancement is particularly significant at low frequency regimes (20 KHz < f <100 KHz) than when induced by high frequency ultrasound.38 Ultrasound parameters such as treatment duration, intensity, pulse length, and frequency are all known to affect percutaneous absorption with frequency being the most important.39 Several antibiotics including tetracycline, biomycin, and penicillin have been sonophoretically administered for the therapy of skin diseases.40

FORMULATION ENHANCER

Penetration enhancement with special formulation approaches is mainly based on the usage of colloidal carriers. Submicron-sized particles are intended to transport entrapped active molecules into the skin. Such carriers include liposomes, transferosomes, ethosomes, niosomes, nanoemulsions, and solid-lipid nanoparticles. The various approaches made into formulations to enhance the penetration are:

Prodrugs and ion-pairs

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavorable partition coefficients.41 The intrinsic poor permeability of the very polar 6-mercaptoaparine was increased up to 240 times using S8-acyloxymethyl and 9-dialkylaminomethyl promoieties42 and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives.43 The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs44, naltrexone45, nalbuphine46, buprenorphine47, β-blockers48 and other drugs.

Saturated and supersaturated solutions

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. This can be demonstrated based on Equation, terms of thermodynamic activities 49

\[
\frac{dm}{dt} = \alpha \frac{d\gamma}{dh} \quad \text{(2)}
\]

Where \(\alpha\) is the thermodynamic activity of the permeant in its vehicle and \(\gamma\) is the effective activity coefficient in the membrane. This dependence on thermodynamic activity rather than concentration was elegantly demonstrated by Twist and Zatz.50 Supersaturated solutions can occur due to evaporation of solvent or by mixing of co-solvents. Clinically, the most common mechanism is evaporation of solvent from the warm skin surface which probably occurs in many topically applied formulations. In addition, if water is imbibed from the skin into the vehicle and acts as an antisolvent, the thermodynamic activity of the permeant would increase.51 Increases in drug flux of five- to ten-fold have been reported from supersaturated solutions of a number of drugs.52 These systems are inherently unstable and require the incorporation of antinucleating agents to improve stability. Magreb et al.53 reported that the flux of oestradiol from an 18-times saturation system was increased 18-fold across human membrane but only 13-fold in silastic membrane.

Eutectic Systems

The melting point of a drug influences solubility and hence skin penetration. The melting point of a drug delivery system is at its highest thermodynamic activity as is the case in a supersaturated solution. This can be demonstrated based on Equation, terms of thermodynamic activities 49

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pain-free venepuncture and other procedures. A number of eutectic systems containing a penetration enhancer as the second component have been reported, for example: ibuprofen with terpenes, menthol and methyl nicotinate; propranolol with fatty acids; and lignocaine with menthol. A number of eutectic systems containing a penetration enhancer as the second component have been reported, for example: ibuprofen with terpenes, menthol and methyl nicotinate; propranolol with fatty acids; and lignocaine with menthol.

Complexes
Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. The ring has a hydrophilic exterior and lipophilic core in which appropriately sized organic molecules can form non-covalent inclusion complexes resulting in increased aqueous solubility and chemical stability. Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-mtoluamide (DEET) and the stability and photostability of sunscreens.

In a recent review of the available data, it has been concluded that the effect on skin penetration may be related to cyclodextrin concentration, with reduced flux generally observed at relatively high cyclodextrin concentrations, whilst low cyclodextrin concentrations resulting in increased flux. Recently it has been concluded that complexation with HP-β-CD had no effect on the flux of cortisone through hairless mouse skin by either of the proposed mechanisms.

Hydration
Hydration of the stratum corneum is one of the primary measures to increase the penetration of both hydrophilic and lipophilic permeants. Increased skin hydration may swell and open up the compact structure of the stratum corneum, leading to an increase in penetration. (Table 1)

Liposomes
Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. Studies have focused on delivery of agents via liposomes like anti-psoriatic agent via ethanolic liposomes, caffeine for hyperproliferative diseases, catechins, enoxacin. Recent studies have tended to be focused on delivery of macromolecules such as interferon, gene delivery and cutaneous vaccination.

Transfersomes
These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant and 3-10% ethanol. The driving force for penetration into the skin is the Transdermal gradient caused by the difference in water content between the restively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to 100%). Studies have been focused on delivery of agents like vaccines, retinyl palmitate, estradiol, copper, zinc, superoxide dismutase, insulin. In some cases the transfersomes drug delivery with some physical enhancement method iontophoresis for estradiol and microneedles for docetaxel.

Ethosomes
These are liposomes with high alcohol content (up to 45%) capable of enhancing penetration to deep tissues and the systemic circulation. Studies have been focused on transdermal ethosomal delivery of agents like minoxidil, testosterone, and comparative study had also been done on ethosomal vs liposomal system of trihexyphenidyl hydrochloride (THP).

Niosomes
Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. In particular, alkyl polyglucosides (APGs) have been studied for several types of applications. APGs have already shown their capability to form vesicular structures and their properties led us to explore the possibility of using APGs containing niosomes as carriers for the topical. Studies have been focused on niosomal transdermal delivery of agents like estradiol (proniosomal formulation), ketorolac (proniosomal formulation), immunological adjuvants, tretinoin for psoriasis, photodamage and skin cancer, carriers of anti-inflammatory drugs, diagnostic imaging agents, diclofenac diethylammonium, levonorgestrol.

Aspasomes
Ascoryl palmimate formed vesicles (Aspasomes) in presence of cholesterol and charge inducer dicetyl phosphate, encapsulating azidothymidine solution. Aspasomes enhanced the transdermal permeation of azidothymidine. The antioxidant property and skin permeation enhancing property indicates a promising future for aspasome as a carrier for transdermal drug delivery system.

High velocity particles
The powderject system fires solid particles (20–100 mm) through stratum corneum into lower skin layers, using a supersonic shock wave of helium gas. The leading products in development include lignocaine and levobupivacaine for local anaesthesia, proteins (follicle stimulating hormone and β-interferon) and hepatitis B DNA and other vaccines. The intrajeject is a development of the vaccine gun designed to deliver liquids through skin without using needles.

Solid lipid nano particles (SLN)
Nanoparticles are colloidal drug delivery systems having a diameter of approximately 200-500nm. SLN have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. Studies have been focused on transcutaneous vaccine delivery, transdermal DNA delivery, mixnoxidil with block copolymer nanoparticles and in combination with physical methods as iontophoresic delivery of triamcinolone acetonideacetate.

CONCLUSION
The skin and other membrane (stratum corneal, epidermis) in the body serve as a barrier to the external environment, rendering the absorption of drugs including corticosteroids and other medicinal agents. Penetration enhancers are applied to improve the efficacy of the drugs through the intact skin. They itself doesn’t possess any therapeutic effect, but they enhance the penetration of drugs across the membrane. Different approaches are applied like, chemical which offers the penetration by chemical changes or by use of chemicals such as Azone, sulphoxides. fatty acids, terpenoids. Physical approaches by changing the physical properties and by the aid of techniques such as magnetophoresis, ionatophoresis, and electroporation. Formulation enhancer technique in which the carrier and complexing agents such as β cyclodextrin. These techniques are very useful in pharmaceutical industry as most of drugs have less permeable behavior.

REFERENCES
Table 1: Effects of carrier systems on the stratum corneum water content and on the penetration of active ingredients.

<table>
<thead>
<tr>
<th>Vehicle</th>
<th>Example/Constituents</th>
<th>Effect on skin hydration</th>
<th>Effect on skin permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occlusive Dressings</td>
<td>Plastic film, unperfused water proof patch</td>
<td>Prevent water loss, full hydration</td>
<td>Marked increase</td>
</tr>
<tr>
<td>Lipophilic vehicles</td>
<td>Paraffins, oils, fats, waxes, fatty acids, fatty alcohols, esters, silicones</td>
<td>Prevent water loss, may produce full hydration</td>
<td>Marked increase</td>
</tr>
<tr>
<td>Absorption bases</td>
<td>Unhydrous lipids plus w/o emulsifiers</td>
<td>Prevent water loss, marked hydration</td>
<td>Marked increase</td>
</tr>
<tr>
<td>W/O systems</td>
<td>W/O emulsions</td>
<td>Retard water loss, raised hydration</td>
<td>Increase</td>
</tr>
<tr>
<td>O/W systems</td>
<td>O/W creams, O/W emulsions</td>
<td>Can donate water, slight hydration increase</td>
<td>Slight increase</td>
</tr>
<tr>
<td>Humectants</td>
<td>Water-soluble vehicles; pyrrolidinyl glycolts</td>
<td>Can withdraw water; decreased hydration</td>
<td>Possible decrease or aid as chemical enhancer</td>
</tr>
<tr>
<td>Powder</td>
<td>Clays, shake lotions</td>
<td>Aid water evaporation; decreased excess hydration</td>
<td>Negligible effect on stratum corneum</td>
</tr>
</tbody>
</table>

Figure 1: stratum corneum, intercellular and transcellular routes of penetration

Figure 2: Process of magnetophoresis

Figure 3: Basic principle of iontophoresis. A current passed between the active electrode and in different electrode repelling drug away from the active electrode and into the skin.
Figure 4: Basic principle of electroporation: high voltage short pulses current are applied to skin producing hydrophilic pores in the intercellular bilayers via momentary realignment of lipids.

Figure 5: Microneedle delivery devices.

Figure 6: Schematic view of human skin and microneedle array.

Figure 7: Section view of the present needle injection device.

Figure 8: Needleless syringe.

Figure 9: Structure of nanodispersed vehicle systems.