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RESEARCH ARTICLE

CHEMICAL PERMEATION ENHANCEMENT THROUGH SKIN

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Abstract

Skin is a major organ for application of drug both for local and systemic effects. However in skin, the stratum corneum is the main barrier for drug penetration. Penetration enhancement technology is a challenging development that would increase the number of drugs available for transdermal administration. The permeation of drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, skin penetration enhancement approaches have been discussed in order to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. Chemical penetration enhancers that aid absorption of co-administered moieties are currently believed to improve solubility within the stratum corneum or increase lipid fluidity of the intracellular bilayers.

INTRODUCTION

The aim of drug administration via the skin can be local therapy or systemic as in transdermal drug delivery. Skins have number of barrier for penetration through it. To enhance the transport of drug through skin various techniques are applied called as permeation enhancement techniques and agents utilized in it are PENETRATION ENHANCERS. Benefits of intravenous infusion can be closely duplicated without its hassles by using skin as port of entry of drugs. Adverse effects or therapeutic failures frequently associated with intermittent dosing can also be avoided. It can improve patient compliance and also self administrable and drug input can be terminated at any point of time. The outermost layer of skin stratum corneum is about 10 micrometer thick but functions as major barrier towards inwards and outward flux of compounds[1]. It has therefore received considerable interest from research groups wishing to understand and manipulate its barrier function .In research activities in biology and medicine chemistry pharmacy and membrane technology stratum corneum is often modeled as brick-and-mortar[2]. Where the bricks are flattened keratin filled cells[3], the corneocytes, and the role of mortar is played by polar lipids arranged as stacked bilayers parallel to the skin surface. In 1994, Forslid proposed a domain mosaic model for the skin barrier where focus was on the lateral organization of the polar lipids in the bilayer[4,5] in the Domain Mosaic Model (DMM) the polar lipids are arranged laterally in a fashion similar to brick and mortar, but in this case the 'bricks' consists of polar lipids in a crystalline(gel) state as mosaic pieces surrounded by 'mortar' consisting of polar lipids in the fluid states.

Structure of skin: The skin has four layers[6, 7]

1. Epidermis
a) Non-viable epidermis (stratum corneum)
b) Viable epidermis
2. Viable dermis

3. Subcutaneous connective tissue (hypodermis)

Routes for penetration (figure 1 showing route of penetration)
1. Through the sweat ducts
2. Directly across the stratum corneum
3. Penetration via the hair follicle.

Main barriers for drug penetration through skin[8]
1. Stratum corneum
2. High density of skin
3. Low hydration of skin
4. Low area of solute transport (As most solute enters through 0.1 micron intercellular space)

Factors effecting skin absorption[9]
1. Diffusion through stratum corneum
2. Solubility in stratum corneum
3. Partitioning
4. Conditions of skin
5. Effect of moisture
6. Effect of vehicles
7. Effect of concentration of medication
8. Effect of surfactants

Mechanism of permeation enhancement
The Percutaneous penetration passage through the skin, involves:
- Dissolution of a drug in its vehicle,
- Diffusion of solubilized drug from the vehicle to the surface of the skin,
- Penetration of the drug through the layers of the skin.

If we plot the cumulative mass of diffusant m, passing per unit area through the membrane, at long time graph approaches linearity and slope its yield the steady flux ,dm/dt ;
$dm/dt = DCoK / h$ ……..*(1)*
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 diffusion coefficient,
h is thickness of membrane.
The ideal properties of a molecule that would penetrating stratum corneum very well. These are[21, 22]
1. Low mol. wt., preferably less than 600Da
2. Adequate solubility in both oil and water so that, membrane concentration gradient may be high. That is it should be >1 mg/ml
3. High but balanced partition coefficient of the solute between the membrane and the bathing solution. (Lipophilicity 10 <K o/w <100)
4. Low melting point, correlating with good solubility as predicted by ideal solubility theory. (< 200 ^{0} C)

CHEMICAL ENHANCERS:

Chemical enhancers or penetration enhancers or absorption promoters are agents that interact with skin constituents to promote drug flux .Many agents have been studied and evaluated for enhancement properties. Yet their inclusion in skin formulation is limited due to unknown mechanism and toxicity.

Ideal properties of permeation enhancer[10, 11]
1. Non toxic, nonirritating, non allergic.
2. Ideally work rapidly
3. Pharmacologically inert
4. Predictable and reproducible duration of action
5. Should work unidirectional
6. Skin barrier properties should return both rapidly and fully
7. Cosmetically acceptable

8. Compatible with both excipient and drug

Mode of action[12]

a. By increasing diffusion coefficient of drug
b. By increasing effective concentration of drug in vehicle
c. By improving partitioning between formulation and stratum corneum
d. By decreasing skin thickness

CLASSIFICATION OF PENETRATION ENHANCER[13]

1. Surfactant
- Ionic: Sodium lauryl sulphate (SLS), Sodium laurate, etc
- Non ionic:Tween 80,Polysorbates,etc

2. Bile salt and derivatives
- Sodium glycocholate, Sodium deoxycholate

3. Fatty acids and derivatives
- Oleic acid, Caprylic acid etc

4. Chelating agent
- EDTA, Citric acid etc

5. Sulphoxide
- Dimethyl Sulfoxide, DMA, DMF etc

6. Polyols
- Propylene Glycol, Polyethylene Glycol, Glycerol, etc

7. Alcohols
- Ethanol, 2-propanol, etc

8. Miscellaneous
- Urea, terpenes, terpinoids, phospholipid, water.

Water

The content of human stratum corneum is typically around 15-20% of tissue dry weight. Soaking skin in water, exposing membrane to high humidity or occluding allow stratum corneum to reach water contents in equilibrium with underlying epidermal skin cells. Water content increases to 400%. In general, increased tissue hydration appears to increase transdermal drug delivery of both hydrophilic and lipophilic permeants. Water present in stratum corneum is in two form, bound and free form act as solvent for polar permeants to diffuse. In majority of cases ,hydration of stratum corneum will result in decrease in barrier function .These have been well demonstrated for many penetrant including esters of salicylic acid[33],corticosteroids[34],caffeine[35] ,ibuprofen[36] and several medium chain length alcohol[37]. On other hand, there are sometime drugs whose penetration rates are unaffected or indeed decreased during occlusion. Permeability of hairless mouse skin to water, methanol, and ethanol is unaltered by hydration[37], whereas in similar situation permeation rate of propranolol across human skin is reduced twofold[38].Despite the voluminous literature concerning hydration on percutaneous absorption there are no firm theories on the mechanism underlying the enhancement effect .The collective data, however, indicates that the action is mediated by aqueous solvation of polar regions of glycospingolipids and ceramides. This is supported by the observation that hydration effect are much less marked in the nail plate[39], a tissue containing less than 1% lipid compare to 10% lipid contain stratum corneum. Free water act as solvent and alter solubility of permeants and so its partitioning .The corneocytes take up water and swell ,such swelling of cells would impact upon lipid structure between corneocytes causing some disruption to bilayer packing.

Urea

Urea has been used as hydrating agent scaling condition such as psoriasis and other skin condition. It produces significant stratum corneum hydration, produces hydrophilic diffusion channels and has keratolytic properties usually when used in combination with salicylic acid for keratolysis. Urea itself possesses only marginal penetration enhancing activity. Cyclic urea analogues are found to be potent as a zone for promoting indomethacin. It promotes transdermal permeation hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier[25]. 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.

Essential Oils, Terpenes and Terpenoids

They have been used as medicines, flavoring and fragrance agents. Hydrocarbon terpenes are less potent while alcohol and ketones containing terpenes are moderate while oxide and terpenoid shows greatest enhancement. Smaller terpenes are more active than larger. Non polar (limonene) agents active for lipophilic drugs and polar (methanol) for hydrophilic drugs. By modifying the solvent nature of stratum corneum it improves drug partitioning .Alters thermodynamic activity of permeant terpenes may also modify drug diffusivity through membrane. Terpenes (1, 3, 3 - Trimethyl-2-oxabicyclo [2.2.2.]-octane) are found in essential oils and compounds comprising of only carbon, hydrogen and oxygen atoms, but should not have aromatic ring. Numerous terpenes are used as medicines as well as flavoring and fragrance agents. The essential oils of eucalyptus, chenopodiumylang have been found to be effective enhancers for 5-flouorouracil and ylang found penetration human skin in-vivo[26]. Cornwell et al investigated the effect of 12 sesquiterpenes on the permeation of 5-flurouracil in human skin. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5flurouracil. L-menthol has been used to facilitate in vitro permeation of morphine hydrochloride through hairless rat skin[27] as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin[28-30].The agent modify the solvent nature of the stratum corneum, thus improving drug partitioning into the tissue. Many terpenes permeate human skin well and large amounts of terpene have been found in the epidermis after application from a matrix-type patch. Terpenes may also modify drug diffusivity though the membrane. During steady state using terpenes as penetration enhancers, the lag time for permeation was usually reduced, indicating some increase in drug diffusivity through the membrane following terpine treatment.

Surfactants

Surfactants are characterized by the presence of both polar and non polar group. Increase in membrane transport at low surfactant concentration is normally attributed to ability of molecule to penetrate an eventually disrupt cell membrane structure. Reduction of transport of permeant in surfactant systems is attributed to ability of surfactant to form micelles, and is normally only observed if interaction between micelle permeant occurs. The overall effect of surfactant is result of two opposing effects-interaction with membrane and that of permeant with micelle. They made up of alkyl or aryl side chain with polar head group. Surfactants have potential to damage human skin. Both anionic and cationic surfactant can be used but non ionic surfactants are safe. Non ionic have minor effect while anionic have pronounced effect on penetration enhancement .[15, 18]

Anionic surfactant can penetrate and interact strongly with skin. The amount penetrating is strongly influenced by surfactant structure, primarily by alkyl chain length. Once the surfactant has penetrated the skin they can induce large alterations in barrier function. The most widely studied surfactants in this group are alkyl sulfates, which can penetrate and destroy the integrity of stratum corneum within hours following application. The effect is reversible on upon removal of surfactants suggesting the removal of stratum corneum lipid is not significant to their mechanism of action. Action of this surfactant on skin is undoubtedly related to their ability to interact with and bind to epidermal proteins. Most anionic surfactant can induce swelling of stratum corneum and viable epidermis.[19, 20]

Although significant increases in skin penetration can be achieved using anionic surfactant. Example: sodium dodecyl sulfate can significantly enhance permeation of several diverse chemicals including water, sodium chromate, chlromphenicol, naproxen etc.

Cationic surfactants are reputedly more irritating then anionic and they have not, therefore, been widely studied as skin penetration enhancers. They have been shown to enhance the permeation of several chemicals including potassium and sodium ions, sodium chromate etc. cetyltrimethyl ammonium bromide (CTAB) for example has been shown to bind more readily to epidermal protein than sodium dodecyl sulfate but does not appear to cause swelling. Solubilize lipophilic active ingredient and also potential to solubilize lipids within stratum corneum

Fatty acids

Percutaneous drug absorption has been increased by a wide variety of long-chain fatty acids, the most popular of which is oleic 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[34, 35] . Shin studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid and capric acid) and nonionic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone. It was found that lauric acid should greater enhancement among all. 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-flurouracil flux 56-fold through human skin membrane in vitro[36]. 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[37].
Mostly used are oleic acids and other long chain fatty acid. They are effective at low concentration (<10%) and used for both hydrophilic and lipophilic drugs .Saturated alkyl chain lengths of around C_{10}- C_{12} attached to polar head group yields a potent enhancer. In unsaturated compounds, bent cis configuration is expected to disturb intercellular lipid packing more than Trans. Also used for estradiol, acyclovir, 5FU, Salicylic acid. Interacts with and modifies lipid domains of stratum corneum, discrete lipid domains are induced within stratum corneum bilayer lipid on exposure to oleic acid.

Sulphoxides and its analogues
Dimethyl sulphoxide (DMSO), aprotic solvent which from hydrogen bond with itself rather than with water .Used in many areas of pharmaceutical sciences as a "universal solvent". Sulphoxides promotes both hydrophilic and hydrophobic permeants .Effect is concentration dependent (>60% needed for optimum action).At high concentration – erythema and wheal, may denature proteins. Metabolite dimethyl sulfide produces foul odor on breath .To avoid above side effects researchers have investigated chemically related materials-DMAC and DMF. Dimethyl sulphoxides (DMSO) is earliest and most widely studied penetration enhancers. It is a powerful aprotic solvent. DMSO changes the water structure within the cell. It is use in many areas of pharmaceutical as a "universal solvent" [40]. Dimethyl sulphoxides alone has been applied topically to treat systemic inflammation. DMSO works rapidly as a penetration enhancer. Although DMSO is an excellent accelerant, it does create problems. However, at relative high concentrations, DMSO can cause erythema. Denature protein, changes keratin confirmation from alpha-helical to beta-sheet. Interact with head groups of some bilayer lipids to distort to packing geometry .Also may facilitate drug partitioning from formulation to this universal solvent.

Alcohols, Fatty alcohols and glycols
Ethanol is used most commonly in patches. Used for levonorgestrol, estradiol, 5FU etc. Its effect is concentration dependent at high concentration causes dehydration of biological membrane and decreases permeation. Applied in concentration range from 1-10%.Branched alkanols show lower activity.1-butanol most effective.1-octanol and 1-propranolol to be effective enhancers for salicylic acid and nicotinamide. Alcohol act as solvent. It alters solubility property of tissue leads to improvement in drug partitioning. Volatile nature of ethanol helps in modifying thermodynamic activity of drug. Due to evaporation of ethanol drug concentration increases providing supersaturated state with greater driving force. Solvent drag may carry permeant into tissue. As volatile solvent may extract lipid fraction from skin.[21]

Phospholipids
Mostly used member: 2-pyrrolidone (2P) and N-methyl -2- pyrrolidone (NMP).NMP and 2P are miscible with most organic solvents. Used for numerous molecules including hydrophilic (e.g. mannitol, 5-FU) and lipophilic (hydrocortisone & progesterone) permeants. Phospholipids have greater effect on hydrophilic drugs. They may act by altering the solvent nature of membrane and pyrrolidones have been used to generate reservoirs within skin membrane .Such a reservoir effect offers potential for sustained release of permeant[22]

Eutectic Mixtures
The melting point of drug delivery system can be lowered by formation of eutectic mixture, a mixture of two components which, at certain ratio, inhibit crystalline process of each other. The melting point of drug influences solubility and hence skin penetration. A good example is cream formulation of lignocaine and prilocaine applied under an occlusive film. A number of eutectic systems containing a penetration enhancer as second component have been reported e.g. Ibuprofen with terpenes, menthol and methyl nicotinate; propranolol with fatty acids.[25, 26]

Complexes
Cyclodextrin complexes enhance aqueous solubility and drug stability. The cyclodextrins are relatively large molecules and consequently both they and their complexes are not able to permeate through intact skin easily. Lipophilic CDs are absorbed to greater extent. Enhance the drug thermodynamic activity. The enhancement of drug release from vehicles by improving the drug availability at lipophilic absorptive barrier surface (skin) [27]
Recently used cyclodextrins are β - Cyclodextrin and CME –β – Cyclodextrin for piroxicam and clonazepam respectively.

CONCLUSION

The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. Skin permeation enhancement technology is a rapidly developing field_which would significantly increase the number of drugs suitable for transdermal 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 chemical penetration enhancers in the enhancement of drug permeation through skin. The chemical penetration enhancement methods discussed in this review are promising. A better understanding of the interaction of enhancers with the stratum corneum will help s to enhance the permeation by best choice of enhancer suitable for particular drug.

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TABLE: Examples of drugs with category of chemical enhancers used[17, 18]

Category	Examples	Drugs
Alcohol, gycol	Ethanol, propylene glycol	Ketoprofen, zidovudine, 5-Florouracil
Surfactants	Tweens, spans	Zidovudine, piroxicam, NSAIDS
Terpenes, Terpenoids and Essential oils	Menthol, eucalyptus oil, peppermint oil, limonene, nerolidol	5-FU, Diclofenac, ketoprofen, Verapamil.
Amides	Pyrrolidones, azone	Zidovudine, ketoprofen
Cyclodextrins	β - Cyclodextrin, CME- β-CD	Piroxicam, clonazepam

FIGURE: Figure showing different route of penetration.

ROUTE OF PENETRATION

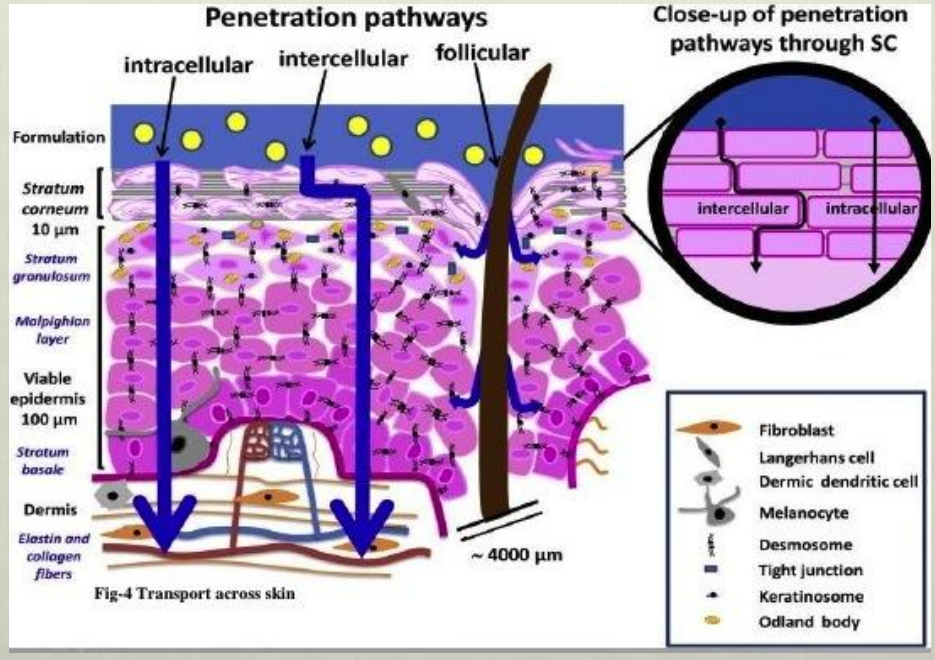

Fig-4 Transport across skin

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