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Review Article

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PENETRATION ENHANCERS: ROLE IN TRANSDERMAL DRUG DELIVERY SYSTEM

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ABSTRACT

The Penetration enhancers are agents, which increase the permeability of the skin or temporally reduce the impermeability of the skin. Penetration enhancers or promoters are agents that have no therapeutic properties of their own but can transport the sorption of drugs from drug delivery system onto the skin. Numerous harmless and non-toxic penetration-enhancing compounds were found from both natural substances and synthetic products. The transdermal route has been identified as one of the highly potential routes of systemic drug delivery and provide the advantages of escaping of the first-pass effect, ease of use and withdrawal (in case of side effects), and better patient compliance. However, the major limitation of this route is the difficulty of permeation of drug through the skin. To improve the transdermal drug delivery, penetration enhancers are used which penetrate into skin to reversibly decrease the barrier resistance. Numerous compounds have been evaluated for penetration enhancing activity, including sulphoxides (dimethylsulphoxide; DMSO), Azones (laurocapram), pyrrolidones (2-pyrrolidone; 2P), alcohols and alkanols (ethanol or decanol), glycols (propylene glycol), surfactants and terpenes. Transdermal delivery of organic liquids such as DMSO (dimethylsulphoxide), DMF (dimethyl formamide) and DMAC (Dimethyl acetamide) has been investigated as potential penetration enhancing compounds.

Keywords: Transdermal delivery; Skin penetration; Penetration enhancers; Techniques.

INTRODUCTION

The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through the skin in sufficient quantities to achieve the desired therapeutic effect. The worldwide transdermal patches in market approaches £2 billion, based on only ten drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed. Introducing medicine to the general circulation through the skin is seen as a desirable alternative to take it by mouth. Patients often forget to take their medicines, and even the most faithfully compliant get tired of swallowing pills, especially if they must take several each day. Additionally, by passing the gastrointestinal (GI) tract would removed the GI irritation that frequently occurs and avoid partial first-pass inactivation by the liver.[1]

Administration of drugs through injections is the most common route which includes the intravenous, intramuscular and subcutaneous routes. Needle phobia is one of the main offsets, which can cause the drug injection traumatic. Administration through intravenous injections needs experienced or properly trained personnel, because it is difficult to insert a needle or catheter into a vein.[2]

In order to avoid the above mentioned problems from conventional routes of drug delivery, alternative routes like eyes, mucosal membranes, vagina and skin to deliver therapeutics into the body are used.[2]

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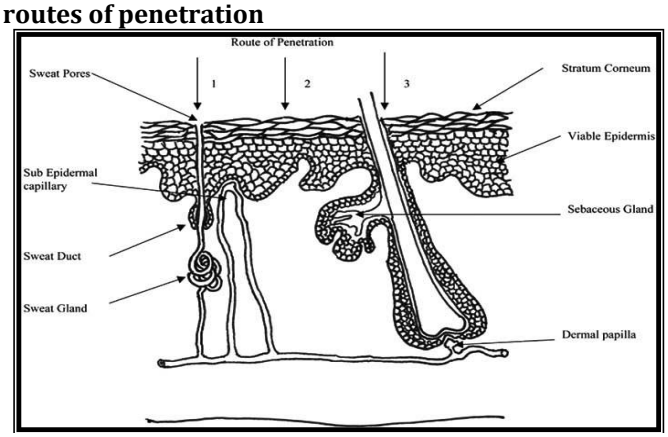
SKIN: A BARRIER FOR TRANSDERMAL PERMEATION

It is considered for the skin to have four distinct layers of tissue:

1. Stratum Corneum (non-viable epidermis)
2. Viable epidermis
3. Viable dermis
4. Hypodermis (subcutaneous connective tissue).

Figure 1. Simplified representation of skin showing routes of penetration



TRANSDERMAL ROUTES OF PENETRATION

- Through the sweat ducts
- Directly across the stratum corneum
- Via the hair follicles

Stratum Corneum (non-viable epidermis)

Stratum corneum is the outer most layer of skin, which is the physical barrier to the most substances that come in contact with the skin. The stratum corneum is 10 to 20 cell layer thick over most of the body. Each cell have flat, plate

like structure 34-44 µm long, 25-36 µm wide, and 0.5 to 0.20 µm thick with a surface area of 750 to 1200 μm^2 stocked up to each other in brick like fashion. Stratum corneum consists of different lipids (5-15%) including phospholipid, glycosphingolipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is mainly keratin. The stratum corneum consist of 10-15 layers of corneocytes which varies in thickness from approximately 10-15 µm in the dry state to 40 µm when hydrated. The intercellular lipid matrix is generated by keratinocytes in the middle to upper part of the stratum granulosum, discharging their lamellar contents into the intercellular space. Water is an essential component of the stratum corneum, which behaves as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps in the maintaining suppleness.

Viable epidermis

This layer of the skin resides between the stratum corneum and the dermis which has a thickness ranging from 50-100 µm. Cells are held together by tonofibrils. The density of the region is not much different than water. The water content is about 90%.

Dermis

Dermis is just below the viable epidermis. It is a structural fibrin and very few cells which are like, it can be found histologically in normal tissues. Dermis thickness ranges from 2000 to 3000 µm and consist of a matrix of loose connective tissue composed of fibrous protein embedded in an amorphous ground substance.

Hypodermis (subcutaneous connective tissue)

The subcutaneous tissue or hypodermis is not considered a true part of structured connective tissue, which is composed of loose textured, white, fibrous connective tissue containing blood and lymph vessels, secretory pores of the sweat gland and cutaneous nerves.[2-5, 12]

PATHWAY OF TRANSDERMAL PERMEATION

Percutaneous Absorption

When topically a drug system is applied, the drug diffuses out of its carrier or vehicle which is depend on where the molecules are placed down, it is divided into either the stratum corneum or the sebum filled ducts of the pilosebaceous glands. Inward movement of diffusion process continues from these locations to the viable epidermal and dermal points of entry. In this way the concentration gradient is established across the skin upto the outer reaches of skin's microcirculation where the drug is swept away by the capillary flow and rapidly distributed in the whole body.

Transepidermal absorption

It is generally believed that the Transepidermal pathway is principally responsible for diffusion across the skin. The main resistance encountered along with this pathway in the stratum corneum. Permeation by the Transepidermal route is firstly involves the partitioning into the stratum corneum. Then diffusion takes place across to this tissue. The current popular belief is that the most substances diffuse through the stratum corneum via the intercellular lipoidal route. In the extreme of polarity, lipophilic molecules concentrate inside and diffuse with relative ease through the horny layer's intercellular region. When a permeating drug exits at the stratum corneum, it enters in the wet cell mass of the epidermis and since the epidermis having no direct blood supply, now the drug is diffuse across it to reach the vasculature immediately. The epidermal cell membranes are tightly joined so that there is no intercellular space for ions and polar non electrolyte molecules to diffusionally squeeze through it. Thus, permeation requires continuous crossing of cell membranes, each crossing become a thermodynamically prohibitive event for the water-soluble species. Consequently, on the basis of more recent data the intercellular route is now considered to be the major pathway for permeation of most drugs through the stratum corneum. So the majority of techniques are used to optimize permeation of drugs across the skin are directed towards manipulation of solubility in the lipid domain or alteration of the ordered structure of different regions of the skin.

Transfolicular absorption (shunt pathway)

The skin's appendages allow secondary revenues for permeation. Sebaceous and eccrine glands are the only appendages which are considered as shunts bypassing the stratum corneum. Drug molecules are in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, via the hair follicles and sebaceous glands (collectively called the shunt or appendageal route) or through directly across the stratum corneum. It is the follicular shunt route which was responsible for the presteady state permeation of polar molecules and also for flux of large polar molecules or ions that have problem in diffusing across the intact stratum corneum. However, it is generally accepted that the appendages having a fractional area for permeation of approximately 0.1% and their contribution to the steady state flux for most drugs is minimal.[6,14]

ABSORPTION OF DRUG

The permeation of drug across the stratum corneum obeys Fick's first law where the steady state flux(J) is related to the diffusion coefficient(D) of the drug in the stratum corneum over the diffusional pathlength or membrane thickness(h), the partition coefficient(P) between the stratum corneum and the vehicle, and the applied drug concentration(C_0) which is assumed as constant:[7]

$$\frac{dm}{dt} = J = \frac{DC_0P}{h}$$

PENETRATION ENHANCERS

Penetration enhancers are the agents that help in the absorption of penetrant through the skin by temporarily lowers the impermeability of the skin. Ideally, these sudstances should be pharmacologically inert, nonirritating, nontoxic, non-allergenic, and compatible with the drugs and excipients, odorless, tasteless, colorless, and inexpensive and also have good solvent properties. The enhancer should not show the loss of body fluids, electrolytes, and other endogenous materials, and on its removal the skin should quickly regain its barrier nature. No single penetration enhancer having all the required properties.[16]

PENETRATION ENHANCEMENT TECHNIQUES

The application of transdermal delivery of drugs is limited due to the significant barrier to penetration across the skin which is associated with the outermost stratum corneum layer of the epidermis. The daily dose of drug may be delivered from a transdermal patch is 5-10mg.[7]

Penetration enhancement through optimisation of drug and vehicle properties

Prodrugs and Ion-Pairs

Prodrugs: The prodrugs are used to enhance dermal and transdermal delivery of drugs with unfavorable partition

coefficient. The prodrug involves addition of a promoiety to increase partition coefficient and 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.

Ion pairs: Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ion pairs has been used to increase stratum corneum penetration of charged molecules. Adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralized so the complex may partition into and permeate through the stratum corneum. Then the ion-pair dissociates in the aqueous viable epidermis releasing the parent charged drug which may diffuse within the epidermal and dermal tissues.[17]

Chemical Potential of Drug in Vehicle: Saturated and Supersaturated Solutions

Skin penetration rate is maximum when a drug is at its highest thermodynamic activity as in a supersaturated solution. Supersaturated solutions can occur due to evaporation of solvent or by mixing of cosolvents. Water is imbibed from the skin into the vehicle and acts as an antisolvent, the thermodynamic activity of the permeant increases. These systems are unstable and require the incorporation of antinucleating agents to improve stability.

Eutectic Systems

The melting point of drug induces solubility and hence skin penetration. According to regular solution theory lower the melting point, the 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. It is 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. The 1:1 eutectic mixture (m.p. 18°C) is oil which is formulated as an oil-in-water emulsion, maximizing the thermodynamic activity of the local anaesthetics. A number of eutectic systems containing a penetration enhancer as the second component are available such as ibuprofen with terpenes, menthol and methyl nicotinate; propranolol with fatty acids; and lignocaine with menthol. The melting point of the drug is depressed to around or below skin temperature for enhancing drug solubility.[7, 13]

Complexes

Cyclodextrins are large molecules, with molecular weights greater than 1000 Da, they will not readily permeate the skin. Complexation of drugs with cyclodextrins is used to enhance aqueous solubility and drug stability. Cyclodextrins contain 6, 7 or 8 dextrose molecules (α-, β-, γ-cyclodextrin) bound in a 1,4- configuration to form rings of various diameters. 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. Derivatives of β-cyclodextrin with increased water solubility are used in pharmaceutical formulation.

Liposomes and Vesicles

There are many cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, enzymes etc. A variety of encapsulating systems including Liposomes, deformable liposomes or transfersomes, ethosomes and niosomes had been evaluated. Liposomes are colloidal particles formed as concentric biomolecular layers having the capability of encapsulating drugs. The liposomes either penetrate the stratum corneum then interact with the skin lipids to release drug or their components enter the stratum corneum. Transfersomes are vesicles composed of phospholipids and their main ingredients are 10-25% surfactant (such as sodium cholate) and 3-10% ethanol.[6, 7] Ethosomes are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation. Alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thay allows the soft, malleable ethosomes to penetrate. Niosomes are vesicles composed of nonionic surfactants that had been evaluated as carriers for a number of drug and cosmetic applications.

Solid lipid Nanoparticles

Solid lipid nanoparticles are used as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids. Their enhanced skin penetration is due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN.[6, 13]

Penetration enhancement by stratum corneum modification

There are many chemicals and methods to reduce the barrier capability of the stratum corneum to promote skin penetration. The enhancer activity of water, surfactants, essential oils and terpenes, alcohols, dimethyl sulfoxide (DMSO), Azone analogues has been tested. The activity of penetration enhancers can be expressed in terms of an enhancement ratio (ER):[12]

$$ER = \frac{Drug\ permiability\ coefficient\ after\ enhancer\ treatment}{Drug\ prmeability\ coefficient\ before\ enhancer\ treatment}$$

Hydration

Water is widely used and safest method to increase skin penetration of both hydrophilic and lipophilic permeants. The water content of the stratum corneum is about 15 to 20% of the dry weight but it can vary according to humidity of the external environment. Additional water within the stratum corneum can change permeant solubility and modify partitioning from the vehicle into the membrane. Increased skin hydration can swell and open the structure of the stratum corneum leading to an increase in penetration. Hydration can be increased by occlusion with plastic films; paraffins, oils, waxes and water-in-oil emulsions that prevent transepidermal water loss and oil-in-water emulsions that donate water. Occlusive films of plastic or oily vehicle have the most profound effect on hydration and penetration rate.

Lipid Disruption/Fluidization by Chemical Penetration Enhancers

Many enhancers like Azone, DMSO, alcohols, fatty acids and terpenes, had been shown to increase permeability by disordering or fluidising the lipid structure of the stratum corneum. The diffusion coefficient of a drug is increased as the enhancer molecules form microcavities within the lipid bilayers results increasing the free volume fraction. The enhancers penetrate into and mix homogeneously with the lipids. Oleic acid and terpenes, particularly at high concentration, pool within the lipid domains to create permeable 'pores' that provide less resistance for polar molecules. These effects have been demonstrated using differential scanning calorimetry to measure the phase transition temperature, electron spin resonance study,

fourier transform infrared, Raman spectroscopy and x-ray diffractometry. The enhancement effect of Azone is related to its ability to exist in a 'bent spoon' conformation with the ring at a right angle to the hydrocarbon chain. Permeability enhancement will result from its ability to intercalate between stratum corneum ceramides to create spatial disruption. Intercalation into a lipid bilayer structure of packed ceramides provide additional resistance to the existence of this high energy 'bent spoon' conformation.[1, 15]

Chemical penetration enhancers

Solvents: These materials enhance penetration by swelling the polar pathway and/or by fluidizing lipids. Examples; water, alcohols, methanol and ethanol.

Miscellaneous chemicals: In this category they include urea; a hydrating and keratolyting agent, N, N-dimethyl-m-toluamide; calcium thioglycolate; anticholinergic agents. Recently some potential permeation enhancers have been described on their available data which having effectiveness are sparse. These basically include eucalyptol, cyclodextrins, soyabean casein.

Alkanes: Long chain alkanes (C_7-C_{16}) are showing enhancement in the skin permeability by non-destructive alteration of stratum corneum barrier. Nonane was also investigated as an enhancer, although there are some destructive solubilisation and biochemical extraction caused by these lipophilic solvents.

Alcohol, Glycerides, and Glycol: As a transdermal penetration enhancer ethanol is the most preferable alcohol. It enhances permeation of the ketoprofen from a gel-spray formulation. It is also used to increase the penetration of methyl paraben as a vehicle for menthol. In combination; ethanol with trichloro phenol (TCP) and with water were used as two cosolvent systems for zalcitabine, didanosine, zidovudine, tegafur, alclofenac, and ibuprofen. The rate of permeation of zalcitabine, didanosine, and zidovudine enhanced; is as related as; the volume fraction of ethanol in the two cosolvent systems was increased, and it reaches to the maximum range between 50–60% v/v of ethanol. Short-chain glycerides are also efficient as permeation enhancers (e.g., TCP). A saturated solution of terpenes in the propylene glycol (PG)-water cosolvent system increases the flux of 5-fluoro uracil (5-FU), the maximum flux obtained from a formulation containing 80% PG by terpenes because terpene activity is dependent on PG content and also it increases drug partitioning and drug permeation. PG; in combination with azone, enhances the flux of methotrexate, piroxicam, cyclosporine A, and 5-FU. The flux of estradiols was 10 times higher when PG was used in conjunction with 5% oleic acid.

Azone: Azone (1-dodecylazacycloheptan-2-one or laurocapram) was the first molecule or agent which was specifically designed as a skin penetration enhancer. Azone possesses a smooth, oily but yet non greasy feel. It is a colorless, odorless liquid with a melting point of -7 °C. Azone is a highly lipophilic material and it is soluble in and also compatible with the most organic solvents including alcohol and propylene glycol. It increased the skin transport of a wide variety of drugs including steroids, antibiotics and antiviral agents. Azone is basically most effective at low concentration. Usually it is employed typically between 0.1- 5% but more often between 1- 3%. Azone partitions into the bilayer lipid for disrupting their packing arrangement but also integrated into the lipid; this process is opposite to be homogeneous. It may exist as dispersed within the barrier lipoid or separate domains within the bilayer.

Fatty acids and Esters: Percutaneous drug absorption has been enhanced by a huge variety of fatty acids and their esters, in which the most popular is oleic acid. A common trend has been considered that unsaturated fatty acids are more effectively enhanced percutaneous absorption than their saturated counterparts. It is observed that many penetration enhancers such as azone contain saturated or unsaturated hydrocarbon chains and on the basis of their structure activity relationships have been selected a range of fatty acids, acids, alcohols, sulphoxides, surfactants and amides as enhancers for naloxone**.** There are some 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) showing their effect on the release of triprolidone. Lauric acid in Propylene glycol increases the delivery of highly lipophilic antiestrogen. Oleic acid hugely enhances the flux of many drugs like increasing the flux of salicylic acid 28-fold and 5-flurouracil flux 56-fold by human skin membrane in vitro. The enhancers influenced with the lipid domains of the stratum corneum and modified as would be expected for the long chain fatty acid with cis- configuration.

Pyrrolidones: Pyrrolidones had been preferred as permeation enhancers for many molecules including hydrophilic (e.g. mannitol and 5-flurouracil) and lipophilic (e.g. progesterone and hydrocortisone) permeants. In a matrix-type transdermal patch formulation; N-methyl-2-pyrolidone was employed with limited success as a penetration enhancer for captopril. The pyrrolidones divided well into human stratum corneum within the tissue and they act by altering the solvent nature of the membrane. Pyrrolidones had been used to produce reservoirs within the skin membrane. So reservoir effect provides a potential for sustained release of a permeant or substance from the stratum corneum over extended time.

Sulphoxides and similar chemicals: Earliest and most widely preferred penetration enhancer is Dimethyl sulphoxides (DMSO). It is colorless, odorless and having hydroscopic nature. It is usually used as a "universal solvent" in many areas of pharmaceutical science. DMSO alone had been applied topically in the treatment of systemic inflammation. DMSO worked frequently as a penetration enhancer and as an excellent accelerant but it does create problems. The spillage of substance onto the skin can be tasted in the mouth within a second. Basically the effect of enhancer is concentration dependent and if cosolvents containing > 60% DMSO then there is a need of optimum enhancement in efficacy. However, at relative high concentrations, it can cause erythema and wheal of the stratum corneum. Then similar chemically related substances as a accelerant have been investigated due to DMSO showing problems in using as a penetration enhancer. Dimethyl acetamide (DMAC) and dimethyl formamide (DMF) are equally powerful aprotic solvents.

Surfactants: There are many surfactants which are capable of interacting with the stratum corneum to enhance the absorption of drugs and other active compounds from products when they are applied to the skin. The surfactant reacts with skin by depositing onto the stratum corneum, through which disorganizing its structure. Then it can

solubilise or remove lipids or water-soluble constituents from in or on the surface of the stratum corneum and thus it can be transported into and through the stratum corneum. Generally, anionic surfactants are more efficient than cationic and nonionic surfactants in increasing skin penetration of target molecules. There are some anionic surfactants which can react strongly with keratin and lipid, whereas the cationic surfactants which can react with the keratin fibrils of the cornified cells and resulting in the disrupted cell-lipid matrix. By inducing fluidization of the stratum corneum lipids, nonionic surfactants increased absorption. Skin penetration measurements are valuable in defining these effects and observing the influence of surfactant chemistry and concentration. Thus, the capacity of the stratum corneum to retain significant quantities of membrane bound water is decreased in the presence of sodium dodecanoate and sodium dodecyl sulfate. This effect may readily reversible on removal of the agents. These investigations gave an idea about that anionic surfactants alter the permeability of the skin through acting on the helical filaments of the stratum corneum so that they resulting in the uncoiling and extension of keratin filaments to form keratin and this will cause an expansion of the membrane, which enhances the permeability. The recent findings suggested that the impairment of skin's barrier nature is unlikely to result from the change in protein conformation alone. Through differential scanning calorimetry results were found that sodium lauryl sulfate (SLS) disrupted both the lipid and the protein components. The disruption of the skin barrier depends on the monomer activity and the critical micelle concentration (CMC) occured by the amount of surfactant that penetrates into the skin and the above CMC, the added surfactant exists as micelles in the solution and micelles are too huge to penetrate the skin. The extent of barrier disruption and penetration enhancement of the surfactant is also strongly depends on surfactant structure, especially on alkyl chain length.

Terpenes, Essential Oils, Terpenoids: Terpenes have been used for many of therapeutic purposes, like in antispasmodics, carminatives, perfumery, and others, but also considered their potential as percutaneous absorption enhancers. By forming a eutectic mixture with the drug, L-Menthol (found in a high proportion in peppermint oil) has been shown to increase the skin absorption of testosterone through which lowering its melting point drastically from 153.7°C to 39.9°C, as observed by differential scanning calorimetry (DSC) studies, and this has leads to increase its solubility and absorption. Eucalyptus oil was found that the most active enhancer, causing a 60-fold increase, while peppermint and turpentine oil showing 48- and 28-fold enhancement, respectively. Mode of action of these enhancers may be seen due to the combined process of partition and diffusion.

Urea: Urea promotes the transdermal permeation by helping in the hydration of stratum corneum and also by forming the hydrophilic diffusion channels within the barrier. Although, urea itself possesses marginal penetration enhancing activity, so the work should have been made to produce analogues containing more potent enhancing moieties. Thus, cyclic urea analogues are found as potent as Azone for promoting penetration of indomethacin across shed snake skin and hairless mouse skin. The category of permeation enhancers including cyclic urea are biodegradable and non-toxic molecules that consist of a polar parent moiety and a long chain alkyl ester group. As a result, the enhancement mechanism can be a consequence of both hydrophilic activity and lipid disruption mechanism.

Miscellaneous Enhancers

Amino Acid Derivatives

N-Dodecyl-l-amino acid methyl ester and n-pentyl-N-acetyl prolinate were the two observed enhancers. On the application of these two enhancers on the excised hairless mouse skin for 1 hr prior to drug treatment produced greater penetration of hydrocortisone suspension. n-Pentyl-Nacetyl prolinate can also enhances the flux of benzoic acid across human cadaver skin. It is toxic at higher doses and produced dose-dependent central nervous system toxicity but nontoxic at low doses. The potency of the biodegradable penetration enhancer dodecyl N, N-dimethylamino isopropionate (DDAIP; dodecyl-N, N-dimethyl-l-alanine) was compared to dodecyl-N, N-dimethylamino acetate (DDAA) and azone, and by other known permeation enhancers. DDAIP showed a dose-dependent enhancement in the flux of 5-fluoro uracil (5-FU) and also better than DDAA and azone.

Cyclodextrin Complexes

Cyclodextrin complexes are the number of drugs that have been formed such a combination usually increases the permeation of drugs. An associated complex of piroxicam with β-cyclodextrin enhanced the drug flux three times across the hairless mouse skin. It basically forms a complex with enhancers like quaternary ammonium salts and alters their critical micellar concentration to higher values, so this has been lead to decrease the toxic effect of such enhancers. Transdermal absorption of alprostadil (AP) from the β-cyclodextrin complex and also from the O-carboxymethyl- O-ethyl- β-cyclodextrin (CME-β-CD) complex was contrast by their properties across hairless mouse skin. HPE-101 (1-[2-(decylthio) ethyl] azacyclopentan-2 one) was comprehended as a permeation enhancer in both cases. A combination of CME-β-CD and HPE-101 increases the topical bioavailability of the drug because the flux from the latter complex was 10 times higher than from the former one.

Enzymes

The topical application of the phosphatidyl choline dependent enzyme phospholipase C developed an enhancement in the transdermal flux of benzoic acid, mannitol, and testosterone due to the importance of the phosphatidyl choline metabolism during maturation of the barrier lipids. There are other three epidermal enzymes (triacylglycerol hydrolase [TGH], acid phosphatase, phospholipase A_2) were also observed for their effect. TGH enhanced the permeation of mannitol, while phospholipase A_2 enhanced the flux of both benzoic acid and mannitol but acid phosphatase was ineffective. Pretreatment of skin with papian fabricated reversible amendment in the protein structure of the stratum corneum. These all structural changes resulted in enhanced permeation of proteins of various molecular weights, with the effect showing decreased and with increased molecular weight.

Lipid Synthesis Inhibitors

The barrier layer (i.e., stratum corneum) comprises of a mixture of cholesterol, free fatty acids, and ceramides. For normal barrier function these three classes of lipids are needed. On the addition of inhibitors of lipid synthesis enhances the delivery of several drugs like lidocaine and

caffeine. Fatty acid synthesis has been inhibited by 5-(tetradecyloxy)-2-furancarboxylic acid (TOFA) and the cholesterol synthesis is inhibited by the agent fluvastatin (FLU) or cholesterol sulfate (CS) which delayed the recovery of barrier damage produced by antecedent application of penetration enhancers like (DMSO), acetone, and others. It was assumed that the application of conventional chemical penetration enhancers can cause a further boost in the transdermal permeation which was followed by the modulation of lipid biosynthesis.

Phospholipids

Unsaturated fatty acids which contain phospholipids in the hydrophobic group are strong permeation enhancers for percutaneous delivery of numerous topically applied drugs. Accumulation of bifonazole into the skin and the percutaneous penetration of tenoxicam is increased by phosphatidyl glycerol derivative. Phosphatidyl choline derivatives facilitated the percutaneous penetration of erythromycin.[1, 16, 17, 21-27]

Interaction with Keratin

In addition to their effect on stratum corneum lipids, chemicals such as dimethyl sulphoxide (DMSO), decylmethylsulphoxide, urea and surfactants interact with keratin in the corneocytes. Penetration of a surfactant into the intracellular matrix of the stratum corneum, followed by interaction and binding with the keratin filaments, can result in a disruption of order within the corneocyte. This causes an increase in diffusion coefficient, and permeability. In many studies of surfactants, a close relationship between permeation enhancement and lipid bilayer fluidisation had been observed that the lipid lamellae of the stratum corneum is the main site of action rather than the keratin of the corneocytes. These molecules can modify peptide/protein material in the lipid bilayer domain to enhance permeability.

Increased Partitioning and Solubility in Stratum Corneum

Ethanol, propylene glycol, and N-methyl pyrrolidone increase permeant partitioning into and solubility within the stratum corneum. Ethanol is the first penetration enhancer-cosolvent incorporated into transdermal systems. The solubility of skin lipid is about 10 $(cal/cm3)^{1/2}$ therefore if a permeant has a solubility parameter significantly different to 10, then a solvent distributes within the stratum corneum and alter the solubility parameter closer to that of the permeant increases flux.

Combined Mechanisms

Fick's law shows that a combination of enhancement effect on diffusivity and partitioning results in a multiplicative effect. Synergistic effects had been demonstrated for many combinations, such as Azone and propylene glycol, Azone and Transcutol, oleic acid and propylene glycol, terpenes and propylene glycol, various combinations and alcohols eg., N-methylpyrrolidone and propylene glycol, urea analogues and propylene glycol, supersaturation and oleic acid.[8,18]

Stratum Corneum Bypassed or Removed

Microneedle array

Microneedles are applied to the skin so they pierce only the stratum corneum and increase skin permeability. Microneedles are needles, 10 to 200 μm in height and 10 to 50 μm in width. Microneedles do not stimulate the nerves, so the patients do not experience pain or discomfort. They are usually drug coated projections of solid silicon or hollow, drug filled metal needles.[6]

Stratum corneum ablated

Stratum corneum ablation occured 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.

Follicular delivery

Topically applied compounds are penetrated via the stratum corneum as well as via skin appendages, i.e., sweat glands and hair follicles. With a rich perifollicular vascularisation and changes in the differentiation pattern along the follicular duct, the follicle possesses distinct characteristics which favour penetration and then follicular penetration route may be relevant for hydrophilic and high molecular weight molecules, as well as by particle-based drug delivery system. The hair follicles are in contrast with sweat gland that 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.[9,11]

Absorption Enhancement by Energy Input

The possibility of active transfer of drugs through the skin by the action of electrical or other forms of energy such as iontophoresis; phonophoresis and electroporation.

Iontophoresis

Iontophoresis is an electrochemical process that enhances the transport of some solute molecules by creating a potential gradient with an applied electrical current or voltage through the skin tissue. It induces an increased migration of ionic drugs into the skin through electrostatic repulsion at the active electrode: negative ions are delivered by the cathode and positive ions by the anode. Iontophoresis device consists of a battery, microprocessor controller, drug reservoir and electrodes. Iontophoresis involves the use of small amounts of physiologically acceptable electric current for moving the charged or ionized drugs through the skin. Placing an ionized solution of the drug in an electrode of the same charge and applying a current, the drug is repelled from the electrode into the skin. A new iontophoresis system is called Numby Stuff (IOMED) that is used in achieving local anesthesia of the skin and is a painless, needle less system.[10,19]

Phonophoresis

Phonophoresis (ultrasound, sonophoresis, ultra-sonophoresis and ultra-phonophoresis) is the transport of drugs through the skin using ultrasounds. It is a combination of ultrasound therapy to achieve therapeutic drug concentration at selected sites in the skin. It is used by physiotherapist. The drug is mixed with a coupling agent in this technique. Usually a gel but sometimes creams or ointments are used, which transfer ultrasonic energy through the coupling agent from the phonophoresis devices to the skin. The ultrasonic unit has a sound transducer head emitting energy at 1 MHZ at 0.5 to 1 W/cm^2. It involves disruption of lipid of the stratum corneum, allowing the drug to pass through the skin.

The drug-containing coupling agents were applied to the skin immediately followed by the ultrasound unit. Today, the product is applied to the skin and after a period of time, absorption of the drug begins into the skin and then, ultrasound is applied. Ultrasounds emitted from the unit are actually sound waves that are outside the normal hearing range. Ultrasound waves can be reflected and absorbed by the medium, just like regular sound waves.

There are some effects that results from ultrasound include cavitations involve the formation and collapse of very small air bubbles in a liquid contact with ultrasound waves. The efficient mixing is the result of Microstreaming which is closely associated with cavitations, by inducing eddies in small volume elements of a liquid. This can enhance dissolution of suspended drug particles resulting in a higher concentration of drug near the skin, for absorption. Heat produces from the conversion of ultrasound energy to heat energy and can occur at the surface of the skin as well as in deeper layers of the skin.

The vehicle containing drugs must be formulated to provide good conduction of the ultrasonic energy to the skin. The product must be smooth, non-gritty and having low viscosity for ease of the application and ease of movement of the transducer head during the ultrasonic process. Gels work very well as a medium. Emulsions could be used but the oil: water interfaces in emulsions can disperse the ultrasonic waves, resulting in a reduction of the intensity of the energy reaching the skin.[10]

Electroporation

Electroporation is also electrical enhancement method which involves the application of short, high voltage (50-1000 volts) pulses to the skin. The mechanism of penetration is the formation of transient pores due to electric pulses that allow the passage of macromolecules from extracellular space to the intracellular space via a combination of processes such as diffusion and electrophoresis. Larger macromolecules including insulin, microparticles, vaccines, and oligonucleotides are also delivered by electroporation.[9]

Magnetophoresis

The term magnetophoresis is used to indicate the application of a magnetic field and acts as an external driving force to enhance the drug delivery across the skin. It increases alteration in the skins structure that can contribute to an increase in permeability. Magneto-liposomes consist of magnetic nanoparticles, that is 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.[9]

Pressure wave

By intense laser radiation the pressure waves have been generated. This could permeabilize the stratum corneum as well as the cell membrane. Pressure wave (PW) is the only one which is applied for a very short time (100ns-1μs) period. Due to the expansion of lacunae domains in the stratum corneum, the pressure waves form a continuous or hydrophilic pathway get through the skin. A single pressure wave is adequate to permeabilize the stratum corneum and also allow the movement of macromolecules to go into the dermis and epidermis. This results the drug delivery into the epidermis and then the drug can enter into the vasculature and produce a systemic effect. Example; insulin delivered by pressure waves result in reducing the blood glucose level over several hours. Pain or discomfort does not appear on the application of pressure waves and the barrier tasks of the stratum corneum constantly recovered.[11,20]

CONCLUSION

The Skin penetration or permeation enhancement technique is a very much rapid developing field which would sufficiently increase the several number of drugs suited for transdermal drug delivery system that resulting the skin as a major route for administration. Penetration enhancers tend to work well with co solvents such as propylene glycol (PG) or ethanol. Synergistic effects are found between enhancers such as Azone, oleic acid and terpenes with PG. Most penetration enhancers have a complex concentration dependent effect, Azone which is effective in promoting the transdermal flux for many drugs when it is used at 1% in PG but which is far less effective when applied at higher concentration or neat. Potential mechanism of action of enhancers is varied, and can range from direct effects on the skin by modification of the formulation. These agents are not only specific for the stratum corneum but also for the deeper layers of the skin to viable epidermal cells.

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