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REVIEW ON: ROLE OF PENETRATION ENHANCER IN TRANSDERMAL PATCH"

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ABSTRACT

The human skin serves as an impediment, a thermo regulator and prevents excessive loss of water from the internal organs. Various ways of transferring the drugs have been developed by modifying the barrier properties of the skin. Today, ~74% of drugs are taken orally and is not found to be as effective as desired. To improve such distinctiveness, transdermal drug delivery was brought to existence. This delivery system is capable of transporting the drug or macromolecules painlessly through skin into the blood circulation at fixed rate. A transversally delivered drug can only show its action when it can cross the transdermal barrier to reach the systemic circulation and for helping on doing that the penetration enhancer are the agents which increase the permeability of the skin which on return maintains the drug level in the blood. Permeation enhancers can be of a chemical type, natural type, and physical type. The present review describes the natural permeation enhancers can be which be engaged for transdermal permeation of drugs.

KEYWORD: macromolecules, permeation enhancers, systemic circulation.

I. INTRODUCTION[1,2]

The worldwide transdermal patch 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 marketed1. Transdermal drug delivery is the administration of a therapeutic agent through intact skin for systemic effect. Transdermal drug delivery offers the following advantages over the oral route for controlled drug delivery.

i. Avoidance of hepatic first pass metabolism.
ii. Ability to discontinue administration by removal of the system.
iii. The ability to control drug delivery for a longer time than the usual gastrointestinal transit of oral dosage form.
iv. The ability to modify the properties of the biological barrier to absorption.

Penetration Enhancers .They reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Techniques used for modifying the barrier properties of the stratum corneum to enhance drug penetration and absorption through skin may be classified into the following categories.

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancement
5. Bioconvertable prodrug

Definition of Penetration Enhancer

Permeation enhancers are the agent which reduced the barrier resistance of stratum cornum without damaging viable cells & modifying the barrier properties of stratum cornum to enhance drug penetration through skin.
Ex. DMSO, Azone, urea, water, fatty-acid.

II. NEED OF PENETRATION ENHANCEMENT[3,4]

Penetration enhancement is the most important consideration for improving flux. Flux (J) can be defined as the amount (M) of material flowing through unit area of cross section (S) of a barrier in unit time (t). Flux can be given by,

J=dM/S.dt

Each phase of the membrane can be characterized in terms of diffusional resistance(R), which usually is the function of thickness (hs) of the phase, the permeant diffusion coefficient (Ds) within the phase, and the partition coefficient (Ks) between the membrane phase and external phase. It can be expressed as,

R=hs/Ds.Ks, P=Ds.Ks/hs

Where P is permeability coefficient. The permeability coefficient is related to membrane flux (J) as given,

J=APs (Cp-Cr),

III. IDEAL PENETRATION ENHANCERS SHOULD POSSESS THE FOLLOWING PROPERTIES [5]

a) Pharmacologically inert
b) Nontoxic, nonirritating, and non-allergenic

c) Rapid onset of action; predictable and suitable duration of action for the drug used
d) Reversible effect of the CPE on the barrier property of SC
e) Chemically and physically compatible with the delivery system
f) Readily incorporated into the delivery system
g) Inexpensive and cosmetically acceptable

Because the skin provides such a formidable barrier to the delivery of most drugs, a broad range of different chemical additives have been tested to enhance transdermal penetration during the last two decades. Much of the cited literature is found in patents (17) as well as pharmaceutical science literature (60). 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 transdermal patches. CPEs can be divided into various groups depending on their functional groups. Enhancers like alcohols, alkyl sulfoxides, and polyols help in increasing the solubility 17 and improving the partition coefficient of the drug (61). Solvents like dimethlysulphate and ethanol increase the permeability of SC by extracting the lipids. Oleic acid, azone, and isopropyl myristate enhance the diffusion of a permeant by disrupting the structure of lipid bi-layers. transcellular diffusion is favored by ionic surfactants, decylmethyl sulfoxides and urea, which interact with the keratin in the corneocytes and disrupts its protein structure.

IV. MECHANISM OF CHEMICAL PENETRATION ENHANCER[6,7]

Penetration enhancers may act by one or more of three main mechanisms1
1. Disruption of the highly ordered structure of stratum corneum lipid.
2. Interaction with intercellular protein.
3. Improved partition of the drug, coenhancer or solvent into the stratum corneum.
The enhancer act by altering one of three pathways. The key to altering the polar pathway is to cause protein conformational change or solvent swelling. The fatty acid enhancers increased the fluidity of the lipid protein portion of the stratum corneum. Some enhancers act on both polar and nonpolar pathway by altering the multilaminate pathway for penetration. Enhancers can increase the drug diffusivity through skin proteins. The type of enhancer employed has a significant impact on the design and development of the product2. A useful way to consider factors affecting drug permeation rate through the stratum corneum is via the simple equation given below for steady state flux1. If we plot the cumulative mass of diffusant, m, passing per unit area through the membrane , at long time the graph approaches linearity and its slope its yield the steady flux,
dm/dt = D Co K /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 the diffusion coefficient and h is thickness of membrane. From the above equation, we increase the ideal properties of a molecule that would penetrate stratum corneum well. These are.
• 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.

V. APPROACHES OF PENETRATION ENHANCEMENT[8,9]

A. Drug vehicle based
1. Drug selection
2. Vesicles and particles
3. Prodrugs and ion pairs
4. Chemical potential of drug
5. Eutectic systems
6. Complexes

B. Physical method
1. Iontophoresis
2. Ultrasound (phonophoresis and sonophoresis)
3. Mechanoporation (Microneedle based devices)
4. Electroporation
5. Laser radiation and photomechanical waves
6. Magnetophoresis
7. Thermophoresis
8. Needleless injection
9. Radio frequency
10. Skin abrasion
11. Carriers and vehicles
a. Micro emulsions
b. Nan emulsions/
c. Solid lipid nanoparticles
d. Multiple emulsions
e. Micro or nanocapsules

12. Vesicular carriers
a. Liposome
b. Niosomes
c. Transfersomes
d. Ethosomes
e. Aquasomes

C. Chemical penetration enhancers
1. Azone
2. Sulphoxides and similar chemicals
3. Pyrrolidones
4. Fatty acids
5. Essential oil, terpenes, and terpenoids
6. Oxazolidinones
7. Urea
8. Water

9. Alcohols, fatty alcohols, and glycols
10. Surfactants

D. Biochemical Method of enhancement

a. Stratum corneum modification
b. Hydration
c. Lipid Fluidisation

VI. CLASSIFICATION OF PERMIATION ENHANCER[10]

A. Physical Permeation Enhancer

1. Electroporation

The use of electropermeabilization as a method of enhancing diffusion across biological barriers dates back as far as 100 years. Electroporation involves the application of high-voltage pulses to induce skin perturbation. High voltages (≥100 V) and short treatment durations (milliseconds) are most frequently employed. Other electrical parameters that affect delivery include pulse properties such as waveform, rate, and number. The increase in skin permeability is suggested to be caused by the generation of transient pores during electroporation. The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size, including biopharmaceuticals with a molecular weight greater that 7 kDa, the current limit for iontophoresis.

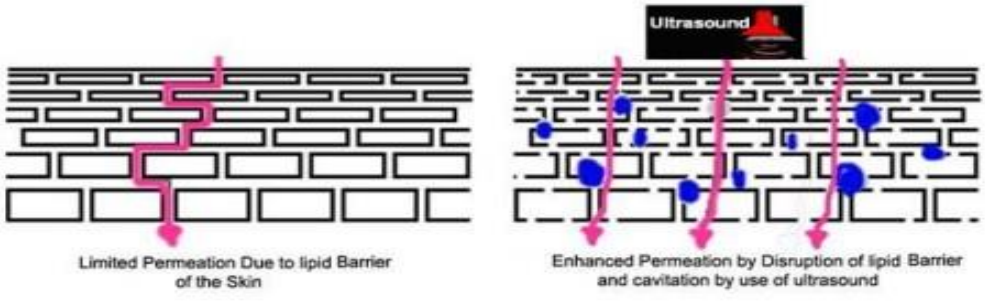
2. Iontophoresis

This method involves enhancing the permeation of a topically applied therapeutic agent by the application of a low-level electric current, either directly to the skin or indirectly via the dosage form. Increase in drug permeation as a result of this methodology can be attributed to either one or a combination of electrorepulsion (for charged solutes), electro-osmosis (for uncharged solutes), and electroperturbation (for both charged and uncharged) mechanisms. Parameters that affect design of an iontophoretic skin delivery system include electrode type, current intensity, pH of the system, competitive ion effect, and permeant type. The launch of commercialized systems of this technology either has occurred or is currently under investigation by various companies. Extensive literature exists on the various types of drugs investigated using iontophoretic delivery. The Phoresor™ device (Iomed Inc., Salt Lake City, UT) was the first iontophoretic system to be approved by the Food and Drug Administration in the late 1970s as a physical medicine therapeutic device. In order to enhance patient compliance, the use of patient-friendly, portable, and efficient iontophoretic systems have been under intense development over the years. Such improved systems include the Vyteris and E-Trans iontophoretic devices. Previous work has also reported that the combined use of iontophoresis and electroporation is much more effective than either technique used alone in the delivery of molecules across the skin. The limitations of iontophoretic systems include the regulatory limits on the amount of current that can be used in humans (currently set at 0.5 mA/cm 2) and the irreversible damage such currents could do to the barrier properties of the skin. In addition, iontophoresis has failed to significantly improve the transdermal delivery of macromolecules of greater than 7,000 Da.

Figuer-1: Intophorsis.

3. Ultrasound

Ultrasound involves the use of ultrasonic energy to enhance the transdermal delivery of solutes either simultaneously or through pretreatment, and is frequently referred to as sonophoresis. The proposed mechanism behind the increase in skin permeability is attributed to the formation of gaseous cavities within the intercellular lipids on exposure to ultrasound, resulting in disruption of the stratum corneum. Ultrasound parameters such as treatment duration, intensity, and frequency are all known to affect percutaneous absorption, with the latter being the most important. Although frequencies between 20 kHz to 16 MHz have been reported to enhance skin permeation, frequencies at the lower end of this range (<100 kHz) are believed to have a more significant effect on transdermal drug delivery, with the delivery of macromolecules of molecular weight up to 48 kDa being reported.



Figuer-2: Ultrasound.

4. Laser radiation and photomechanical waves

Lasers have been used in clinical therapies for decades, and therefore their effects on biological membranes are well documented. Lasers are frequently used for the treatment of dermatological conditions such as acne and to confer facial rejuvenation, where the laser radiation destroys the target cells over a short frame of time (~300 ns). Such direct and controlled exposure of the skin to laser radiation results in ablation of the stratum corneum without significant damage to the underlying epidermis. Removal of the stratum corneum by this method has been shown to enhance the delivery of lipophilic and hydrophilic drugs. The extent of barrier disruption by laser radiation is known to be controlled by parameters such wavelength, pulse length, pulse energy, pulse number, and pulse repetition rate. Pressure waves which can be generated by intense laser radiation, without incurring direct ablative effects on the skin, have also been recently found to increase the permeability of the skin. It is thought that pressure waves form a continuous or hydrophilic pathway across the skin due to expansion of the lacunae domains in the stratum corneum. Important parameters affecting delivery such as peak pressure, rise time, and duration have been demonstrated. The use of pressure waves may also serve as a means of avoiding problems associated with direct laser radiation. Permeants that have been successfully delivered in vivo include insulin, 40 kDa dextran, and 20 nm latex particles. A design concept for a transdermal drug delivery patch based on the use of pressure waves has been proposed by Doukas and Kollias.

5. Magnetophoresis

This method involves the application of a magnetic field which acts as an external driving force to enhance the diffusion of a diamagnetic solute across the skin. Skin exposure to a magnetic field might also induce structural alterations that could contribute to an increase in permeability. In vitro studies showed a magnetically induced enhancement in benzoic acid flux, which was observed to increase with the strength of the applied magnetic field. Other in vitro studies using a magnet attached to transdermal patches containing terbutaline sulphate demonstrated an enhancement in permeant flux which was comparable with that attained when 4% isopropyl myristate was used as a chemical enhancer.

6. Thermophoresis

The skin surface temperature is usually maintained at 32°C in humans by a range of homeostatic controls. The effect of elevated temperature (nonphysiological) on percutaneous absorption was initially reported. Recently, there has been a surge in the interest of using thermoregulation as a means of improving the delivery profile of topical medicaments. Previous in vitro studies have demonstrated a 2- to 3-fold increase in flux for every 7 to 8°C rise in skin surface temperature. The increased permeation following heat treatment has been attributed to an increase in drug diffusivity in the vehicle and in the skin because of increased lipid fluidity. Vasodilation of the subcutaneous blood vessels as a homeostatic response to a rise in skin temperature also plays an important role in enhancing the transdermal delivery of topically applied compounds. The in vivo delivery of nitroglycerin, testosterone, lidocaine, tetracaine, and fentanyl from transdermal patches with attached heating devices was shown to increase as a result of the elevated temperature at the site of delivery. However, the effect of temperature on the delivery of penetrants greater than 500 Da has not been reported.

7. Microneedle-based devices

One of the first patents ever filed for a drug delivery device for the percutaneous administration of drugs was based on this method. The device as described in the patent consists of a drug reservoir and a plurality of projections extending from the reservoir. These microneedles of length 50 to 110 mm will penetrate the stratum corneum and epidermis to deliver the drug from the reservoir. The reservoir may contain drug, solution of drug, gel, or solid particulates, and the various embodiments of the invention include the use of a membrane to separate the drug from the skin and control release of the drug from its reservoir. As a result of the current advancement in microfabrication technology in the past 10 years, cost-effective means of developing devices in this area are now becoming increasingly common.

8. Needleless injection

Needleless injection is reported to involve a pain-free method of administering drugs to the skin. This method therefore avoids the issues of safety, pain, and fear associated with the use of hypodermic needles. Transdermal delivery is achieved by firing the liquid or solid particles at supersonic speeds through the outer layers of the skin by using a suitable energy source. Over the years there have been numerous examples of both liquid (Ped-O-Jet® , Iject® , Biojector2000® , Medi-jector® , and Intraject®) and powder (PMED™ device, formerly known as PowderJect® injector) systems. The latter has been reported to deliver successfully testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin.

9. Radio frequency

Radio frequency involves the exposure of skin to high-frequency alternating current (~100 kHz), resulting in the formation of heat-induced microchannels in the membrane in the same way as when laser radiation is employed. The rate of drug delivery is controlled by the number and depth of the microchannels formed by the device, which is dependent on the properties of the microelectrodes used in the device. The Viaderm device (Transpharma Ltd., Lod, Israel) is a hand-held electronic device consisting of a micro-projection array (100 microelectrodes/cm 2) and a drug patch. The microneedle array is attached to the electronic device and placed in contact with the skin to facilitate the formation of the microchannels. Treatment duration takes less than

a second, with a feedback mechanism incorporated within the electronic control providing a signal when the microchannels have been created, so as to ensure reproducibility of action. The drug patch is then placed on the treated area. Experiments in rats have shown that the device enhances the delivery of granisetron HCl, with blood plasma levels recorded after 12 hours raising 30 times the levels recorded for untreated skin after 24 hours.

10. Suction ablation

Formation of a suction blister involves the application of vacuum or negative pressure to remove the epidermis whilst leaving the basal membrane intact. The cellpatch® (Epiport Pain Relief, Sweden) is a commercially available product based on this mechanism. It comprises of a suction cup, epidermatome (to form a blister), and device (which contains morphine solution) to be attached to the skin. This method which avoids dermal invasivity, thereby avoiding pain and bleeding, is also referred to as skin erosion. Such devices have also been shown to induce hyperaemia in the underlying dermis in in vivo studies, which was detected by laser Doppler flowmetry and confirmed by microscopy, and is thought to further contribute to the enhancement of dextran and morphine seen with this method.

11. Skin abrasion

These techniques, many of which are based on techniques employed by dermatologists in the treatment of acne and skin blemishes, involve the direct removal or disruption of the upper layers of the skin to enhance the permeation of topically applied compounds. The delivery potential of skin abrasion techniques is not restricted by the physicochemical properties of the drug, and previous work has illustrated that such methods enhance and control the delivery of a hydrophilic permeant, vitamin C vaccines and biopharmaceuticals. One current method is performed using a stream of aluminium oxide crystals and motor-driven fraises. Sage and Bock also described a method of pretreating the skin before transdermal drug delivery, which consists of a plurality of microabraders of length 50 to 200 mm. The device is rubbed against the area of interest to abrade the site, in order to enhance delivery or extraction.

12. Carriers and vehicles

a) Micro or nanocapsules

These are composed of multiple concentric bilayers of surfactant separated by a polar liquid medium, generally water in which the hydrophilic additives can be incorporated. Their lipid core allows encapsulation of lipid additives, and their multilamellar (lipid/water) structure creates good skin affinity leading to cutaneous penetration and good hydration.

b) Nanoemulsions/submicron emulsions/miniemulsions

These are oil-in-water emulsions with an average droplet size ranging from 100 to 500 nm. They have very good stability and they do not undergo phase separation during storage. They have a liquid lipophilic core and are appropriate for lipophilic compound transportation. Many studies showed reduced transepidermal water loss, which means support to the barrier function of the skin. Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays.

c) Solid lipid nanoparticles

Solid lipid nanoparticles (SLNs) have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide, and glucocorticoids. It is thought that their enhanced skin penetrating ability is primarily due to an increase in skin hydration caused by the occlusive film formed on the skin surface by the SLN. A 31% increase in skin hydration has been reported following 4 weeks application of SLN-enriched cream.

d) Multiple emulsions

These w/o/w emulsions consist in the dispersion of a w/o emulsion in an aqueous phase under several conditions. One can incorporate different water-soluble ingredients (even if they are incompatible) and also oil soluble additives. Like SLNs, these substances will be protected and release sustained by controlling droplet breakdown. These systems can have high oily phase contents (65%, Trixera, Bain emollient, Avθne) and thus present good hydration. Their efficacy has been demonstrated in dermatology to treat stretch marks (Triffadiane, CS Dermatologie)

e) Microemulsion

These formulations have been shown to be superior for cutaneous delivery compared with other conventional vehicles. These systems are identified as transparent mixtures of water, oil, and surfactants. They are thermodynamically stable and optically isotropic. Microemulsions are spontaneously produced in a narrow range of oil-water-surfactant composition, represented on pseudo ternary diagram phases. They are dynamic systems with continuously fluctuating interfaces. Their good dermal and transdermal delivery properties could be attributed to their excellent solubilising properties. Their high solubilising properties improve biodispensibility, and thus reduce the efficient dose thereby increasing tolerability. Furthermore, their restructuring effect on skin and hair (because of their high lipid content) make microemulsion formulations adapt to altered skin and hair conditions.

B. Chemical Permeation Enhancer

The use of CPEs over the physical techniques has certain advantages, including design flexibility of the patch and ease of patch application over a large area (>10 cm2) (3). An ideal penetration enhancer should reversibly reduce the barrier resistance of the SC without damaging the skin cells. According to Finnin et al. (59).

1. Sulphoxides and similar chemicals

Dimethyl sulphoxide (DMSO) is one of the earliest and most widely studied penetration enhancers. It is a powerful aportic solvent which binds with hydrogen rather than with water. It is colorless, odorless, 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 greater than 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 proteins results in erythema, scaling, contact urticaria, stinging, and burning sensation. Because DMSO is problematic for use as a penetration enhancer, researchers have investigated a similar chemically-related material as an accelerant. Dimethylacetamide and dimethylformamide (DMF) are similarly powerful aportic 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-benzoate 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 ß sheet.

2. Azone

Azone (1-dodecylazacycloheptan-2-one or laurocapran) was the first molecule specifically designed as a skin penetration enhancer. Azone is a colorless, odorless liquid with a melting point of -7°C and it possesses a smooth, oily but yet nongreasy 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 to 5%, but more often between 1 to 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 lipoid or separate domains within the bilayer.

3. Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules includinghydrophilic (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, when formulated in a matrix-type transdermal patch.

4. 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. Shin and Lee studied various penetration enhancers like glycols (diethylene glycol and tetraethylene glycol), fatty acids (lauric acid, myristic acid, and capric acid), and anionic surfactant (polyoxyethylene-2-oleyl ether, polyoxy ethylene-2-stearly ether) on the release of triprolidone.

5. 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 have long been used as medicines as well as flavouring 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. The effect of 12 sesquiterpenes on the permeation of 5-flurouracil in human skin was investigated. Pretreatment of epidermal membranes with sesquiterpene oil or using solid sesquiterpenes saturated in dimethyl isosorbide increased the absorption of 5-flurouracil. 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.

6. Oxazolidinones

Oxazolidinones are a new class of chemical agents which have the potential for use in many cosmetic and personal care product formulations. This is due to their ability to localize coadministered 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.

7. Urea

Urea promotes transdermal permeation by facilitating hydration of the stratum corneum and by the formation of hydrophilic diffusion channels within the barrier. Cyclic urea permeation enhancers are biodegradable and nontoxic 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.

8. Water

In general, increased tissue hydration appears to increase transdermal delivery of both hydrophilic and lipophilic permeants. However, Bucks and Maibach cautioned against such a generalisation, stating that occlusion does not necessarily increase percutaneous absorption, and that transdermal delivery of hydrophilic compounds may not be enhanced by occlusion. Furthermore, they warned that occlusion could cause some local skin irritation with clear implications for the design and manufacture of transdermal and topical preparations. Considering the heterogeneous nature of human stratum corneum, it is not surprising that water within this membrane is found in several 'states.' Typically, from thermal analysis and spectroscopic methodologies, some 25 to 35% of the water present in stratum corneum can be assessed as 'bound' that is associated with some structural elements within the tissue. The remaining water within the tissue is 'free' and is available to act as a solvent within the membrane for polar permeants.

9. Alcohols, fatty alcohols, and glycols

Ethanol is commonly used in many transdermal formulations and is often the solvent of choice for use in patches. It is also commonly employed as a cosolvent with water for ensuring sink conditions during in vitro permeation experiments. As with water, ethanol permeates rapidly through human skin with a steady state flux of approximately 1 mg cm 2 /h Ethanol has been used to enhance the flux of levonorgestrel, estradiol, hydro-cortisone, and 5-fluorouracil through rat skin and of estradiol through human skin in vivo. However, when using an ethanol water cosolvent vehicle, the enhancement effect of ethanol appears to be concentration dependent.

10. Surfactants

As with some of the materials described previously (for example ethanol and propylene glycol), surfactants are found in many existing therapeutic, cosmetic, and agrochemical preparations. Usually, surfactants are added to formulations in order to solubilise lipophilic active ingredients, and so they have potential to solubilise lipids within the stratum corneum. Typically composed of a lipophilic alkyl or aryl fatty chain, together with a hydrophilic head group, surfactants are often described in terms of the nature of the hydrophilic moiety. Anionic surfactants include sodium lauryl sulphate (SLS), cationic surfactants include cetyltrimethyl ammonium bromide, the nonoxynol surfactants are non-ionic surfactants, and zwitter ionic surfactants include dodecyl betaine. Anionic and cationic surfactants have potential to damage human skin; SLS is a powerful irritant and increase the transepidermal water loss in human volunteers in vivo, and both anionic and cationic surfactants swell the stratum corneum and interact with intercellular keratin. Nonionic surfactants tend to be widely regarded as safe. Surfactants generally have low chronic toxicity and most have been shown to enhance the flux of materials permeating through biological membranes.

Successful transdermal drug delivery requires numerous considerations owing to the nature and function of the site of application. It should always be kept in mind that the basic functions of the skin are protection and containment. As per these rulings, it would seem exceptionally difficult to cross the skin for systemic absorption. However, with continuous exploration of the structure, function, and physicochemical properties of the skin, more and more new drug products are being developed for transdermal delivery. The safe and effective drug delivery is the ultimate target for each and every new technology ever explored. 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. In recent years, the use of a number of biophysical techniques has aided in our understanding of the nature of the stratum corneum barrier and the way in which chemicals interact with and influence this structure. A better understanding of the interaction of enhancers with the stratum corneum and the development of structure activity relationships for enhancers will aid in the design of enhancers with optimal characteristics and minimal toxicity.

C. Biochemical Method Of Enhancement

Stratum Corneum Modification.

a) Hydration

Water is the most widely used and safest method to increase skin penetration of both hydrophilic and lipophilic permeants. The water content of the stratum corneum is around 15 to 20% of the dry weight but varies as per 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 it is yet to be demonstrated experimentally. For example, Scheuplein and Blank showed that the diffusion coefficients of alcohols in hydrated skin were ten times that observed in dry skin. Hydration can be increased by occlusion with plastic films, paraffins, oils, waxes as components of ointments and water-in-oil emulsions that prevent transepidermal 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. A commercial example of this is the use of an occlusive dressing to enhance skin penetration of lignocaine and

prilocane from EMLA cream in order to provide sufficient local anaesthesia within about 1 hour.

b) Lipid Fluidisation

Many enhancers, such as Azone, DMSO, alcohols, fatty acids and terpenes, have been shown to increase permeability by disordering or .fluidising. the lipid structure of the stratum corneum. The diffusion coefficient of a drug increases as the enhancer molecules form microcavities within the lipid bilayers hence increasing the free volume fraction. In some cases the enhancers penetrate into and mix homogeneously with the lipids. However, others such as oleic acid and terpenes, particularly at high concentration, pool within the lipid domains to create permeable .pores. that provide less resistance for polar molecules. Such effects are demonstrated using differential scanning calorimetry (DSC) to measure the phase transition temperature, electron spin resonance (ESR) studies, fourier transform infrared (FTIR), Raman spectroscopy and x-ray diffractometry. These enhancer compounds consist of a polar head group with a long alkyl chain and are more effective for hydrophilic permeates, although increased delivery of lipophilic permeants has also been reported. Permeability enhancement results from its ability to intercalate between stratum corneum ceramides to create spatial disruption.

VII. VESICULAR CARRIERS[11,12,13]

1. Liposome's

Liposomes are colloidal particles formed as concentric biomolecular layers that are capable of encapsulating drugs. Their potential for delivering drugs to the skin was first reported by Mezei and Gulasekharam in 1980 that showed that the skin delivery of triamcinolone acetonide was four to five times greater from a liposomal lotion than an ointment containing the same drug concentration. Phosphatidylcholine from soybean or egg yolk is the most common composition, although many other potential ingredients have been evaluated. Cholesterol added to the composition tends to stabilize the structure thereby generating more rigid liposomes. Recent studies have tended to be focused on delivery of macromolecules such as interferon, gene delivery, and cutaneous vaccination, in some cases combining the liposomal delivery system with other physical enhancement techniques such as electroporation.

2. Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. This area continues to develop with further evaluation of current formulations and reports of other vesicle-forming materials.

3. Transfersomes

Transfersomes are vesicles composed of phospholipids as their main ingredient with 10 to 25% surfactant (such as sodium cholate) and 3 to 10% ethanol. The surfactant molecules act as 'edge activators,' conferring ultradeformability on the transfersomes, which reportedly allows them to squeeze through channels in the stratum corneum that are less than one-tenth the diameter of the transfersome. According to their inventors, where liposomes are too large to pass through pores of less than 50 nm in size, transfersomes up to 500 nm can squeeze through to penetrate the stratum corneum barrier spontaneously.

4. Ethosomes

These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation. It is proposed that alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.

5. Aquasomes

A new class of solid drug carriers, aquasomes, has emerged during the last decade. Aquasomes are three-layered structures (i.e., core, coating, and drug) that are self-assembled through noncovalent bonds, ionic bonds, and Van der Waals forces. They consist of a ceramic core whose surface is noncovalently modified with carbohydrates to obtain a sugar ball, which is then exposed to adsorption of a therapeutic agent. The core provides structural stability to a largely immutable solid. Aquasomes offer an attractive mode of delivery for therapeutic agents belonging to the class of proteins and peptides, because they are able to overcome some inherent problems associated with these molecules. These problems include suitable route of delivery, physical as well as chemical instability, poor bioavailability, and potent side effects. The surface modification with carbohydrates creates a glassy molecular stabilization film that adsorbs therapeutic proteins with minimal structural denaturation. Thus, these particles provide complete protection of an aqueous nature to the adsorbed drugs against the denaturing effects of external pH and temperature, because there are no swelling and porosity changes with change in pH or temperature.

VIII. CONCLUSION[14]

Many existing drugs have to be given via injections which are painful and undesirable as it may be risky also in some cases. Therefore these days skin is a preferred route of drug delivery and it is termed as the transdermal drug delivery system. Drugs entering the systemic circulation have to pass the skin barrier, Stratum Corneum. For this permeation enhancers are required as it is difficult to penetrate though the SC. It is an emerging field with a lot of scope for development. Extensive research going on in this field has manifested the utility of absorption enhancers for increased and easy absorption of drug through the skin. The only drawback is that permeation enhancer is that they tend to produce skin irritation and undesirable patches.

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