REVIEW ARTICLE

Physical and chemical penetration enhancers in transdermal drug delivery system

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There is considerable interest in the skin as a site of drug application for both local and systemic effect. However, the skin, in particular the stratum corneum, possesses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and to increase the range of drugs for which topical and transdermal delivery is a viable option. The permeation of drug through skin can be enhanced by both chemical penetration enhancement and physical methods. In this review, we have discussed the physical and chemical penetration enhancement technology for transdermal drug delivery as well as the probable mechanisms of action.

Key words: *Chemical penetration enhancers, physical penetration enhancers, skin, transdermal delivery*

INTRODUCTION

The transdermal route now ranks with oral treatment as the most successful innovative research area in drug delivery, with around 40% of the drug delivery candidate products under clinical evaluation related to transdermal or dermal system. The worldwide transdermal patch market approaches two billion pounds, based on some drugs including scopolamine, nitroglycerine, clonidine, estrogen, testosterone, fentanyl, and nicotine, with a lidocaine patch soon to be marketed.[1] The success of a dermatological drug to be used for systemic drug delivery depends on the ability of the drug to penetrate through skin in sufficient quantities to achieve the desired therapeutic effect.[2] Paucity of proper transdermal drug application has many reasons. First, the skin is an excellent permeability barrier[3] refractive to nearly all but small lipophilic molecules,[4,5] as is discussed briefly further in the text. Moreover, achieving high and constant drug flux through the skin is a daunting task, with a low probability of success, unless one compromises the protective skin barrier function. Rather sophisticated techniques must therefore be used to overcome the skin barrier by means other than a hypodermic needle. It was not until recently that several minimally invasive techniques became available.[6-9] Truly noninvasive transdermal drug delivery was achieved more or less contemporaneously with self regulating colloidal carriers[10,11] which are one of the topics of this survey. The focus of this review is on the insights and data generated over the last few years. Older findings are surveyed in reference publications and books, specifically for the epidermis,[12,13] the stratum corneum,[14,15] skin lipids,[16-20] skin permeability/barrier characteristics,[21-25] transport/permeability enhancers,[5,26-28] drug delivery through the skin,[29,30] colloidal drug carries in general,[31] transdermal drug carriers,[32] and phospholipids.[33]

MECHANISM OF SKIN PENETRATION

Drug molecules in contact with the skin surface can penetrate by the following three potential pathways: through the sweat ducts, through the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum [Figure 1]. The relative importance of the shunt or appendageal route *vs* transport across the stratum corneum has been debated by scientists over the years,[34-36] and is further complicated by the lack of a suitable experimental model to permit separation of the three pathways. *In vitro* experiments tend to involve the use of hydrated skin or epidermal membranes, so that appendages are closed by the swelling associated with hydration. Scheuplein *et al.*[37,38] proposed that a follicular shunt route was responsible for the pre-steady state permeation of polar molecules and flux of large

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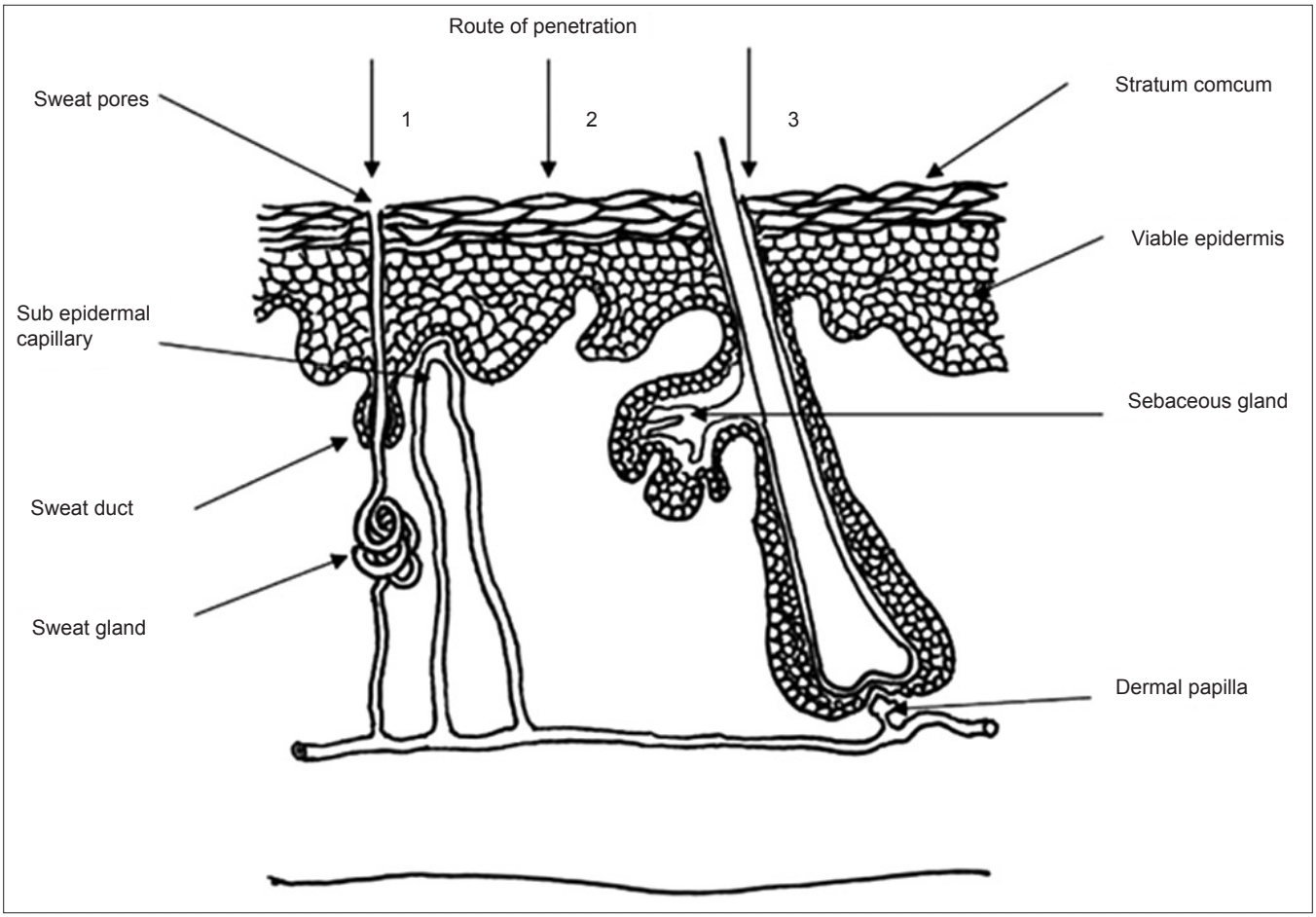

Figure 1: Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles

polar molecules or ions that have difficulty diffusing across the intact stratum corneum. However, it is generally accepted that as the appendages comprise a fractional area for permeation of approximately 0.1%,[39] their contribution to steady state flux of most drugs is minimal. Considerable research effort has been directed towards gaining a better understanding of the structure and barrier properties of the stratum corneum. A recent review by Menon provides a valuable resource.[40] The stratum corneum consists of 10 to 15 layers of corneocytes and varies in thickness from approximately 10 to 15 μm in the dry state to 40 μm when hydrated.[41-43] It comprises a multi-layered 'brick and mortar'-like structure of keratin-rich corneocytes (bricks) in an intercellular matrix (mortar) composed primarily of long chain ceramides, free fatty acids, triglycerides, cholesterol, cholesterol sulphate, and sterol/wax esters.[44] However, it is important to view this model in the context that the corneocytes are not brick shaped, but are polygonal, elongated, and flat (0.2 – 1.5 μm thick, 34 – 46 μm in diameter). The intercellular lipid matrix is generated by keratinocytes in the mid to upper part of the stratum granulosum, discharging their lamellar contents into the intercellular space. In the initial layers of the stratum corneum, this extruded material rearranges to form broad intercellular lipid lamellae,[45] which then associate into lipid bilayers,[46,47] with the hydrocarbon chains aligned and polar head groups dissolved in an aqueous layer [Figure 2]. Because of the lipid content of the stratum corneum, the lipid phase behaviour is different from that of other biological membranes. The hydrocarbon chains are arranged into regions of crystalline, lamellar gel, and lamellar liquid crystal phases, thereby creating various domains within the lipid bilayers.[48] Penetration enhancers may act by one or more of the following three main mechanisms:[1] disruption of the highly ordered structure of stratum corneum lipid; interaction with intercellular protein; improved partition of the drug, co-enhancer, or solvent into the stratum corneum.

PHYSICAL PENETRATION ENHANCERS

Electroporation

The use of electropermeabilization as a method of enhancing diffusion across biological barriers dates back as far as 100 years.[49] Electroporation involves the application of high-voltage pulses to induce skin perturbation. High voltages ($\geq$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.[50] The increase in skin permeability is

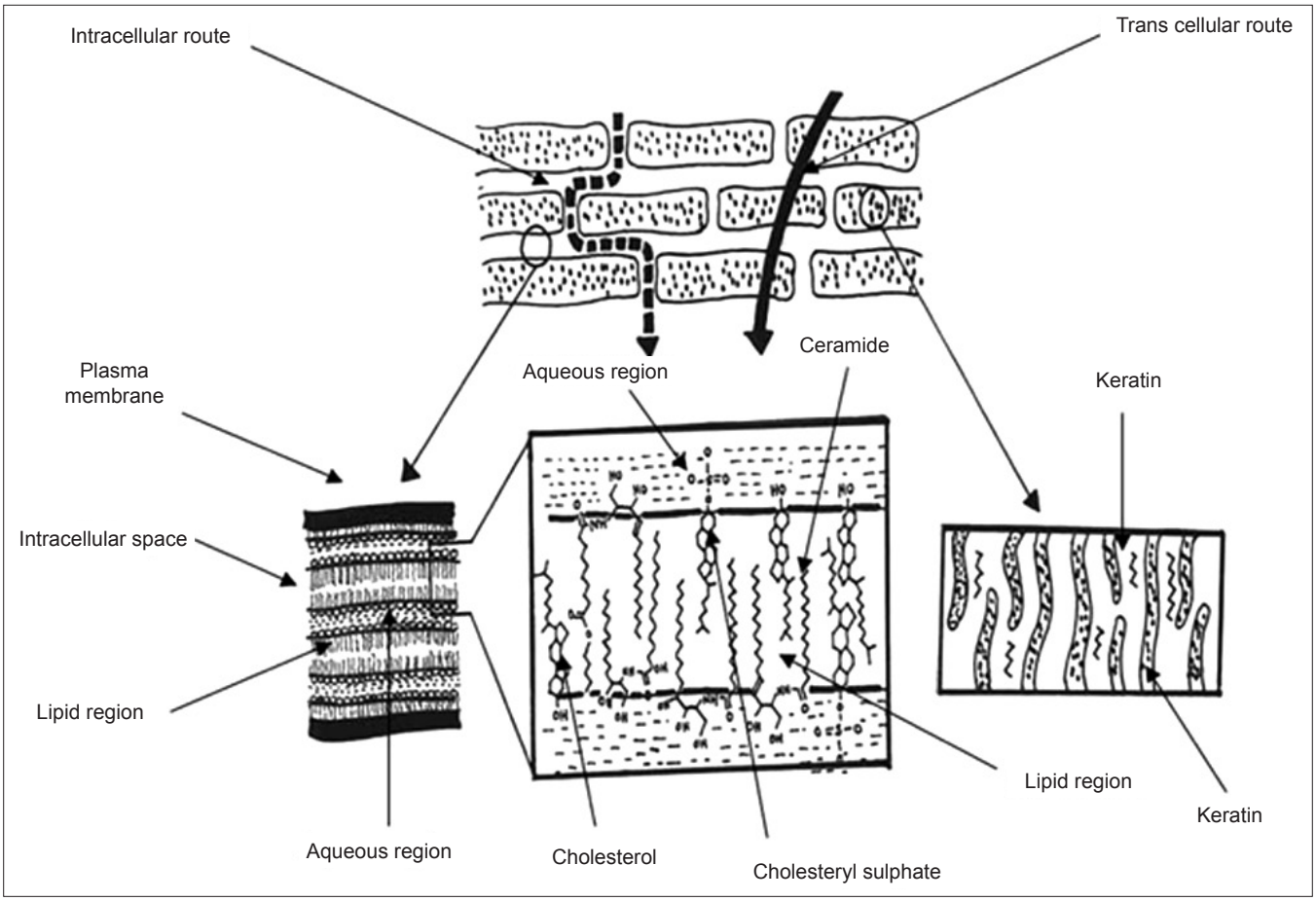

Figure 2: Diagrammatic representation of the stratum corneum and the intercellular and transcellular routes of penetration

suggested to be caused by the generation of transient pores during electroporation.[51] The technology has been successfully used to enhance the skin permeability of molecules with differing lipophilicity and size (i.e., small molecules, proteins, peptides, and oligonucleotides), including biopharmaceuticals with a molecular weight greater that 7 kDa, the current limit for iontophoresis.[52]

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.[53-57] 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.[50] The launch of commercialised 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.[50,55,58-60] 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.[61-63] 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.[64]

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.[65]

Ultrasound parameters such as treatment duration, intensity, and frequency are all known to affect percutaneous absorption, with the latter being the most important.[66] 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.[65,67,68]

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.[69-71] 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.[69] 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.[72-74] 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.[75,76] 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,[77] 40 kDa dextran, and 20 nm latex particles.[72] A design concept for a transdermal drug delivery patch based on the use of pressure waves has been proposed by Doukas and Kollias.[74]

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.[78] 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.[79]

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.[80] 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[81,82] 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.[83] 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.[84,85] The *in vivo* delivery of nitroglycerin,[84] testosterone, lidocaine, tetracaine,[86] and fentanyl[87] 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.

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.[88] 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.[89-91]

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.[92] The latter has been reported to deliver successfully testosterone, lidocaine hydrochloride, and macromolecules such as calcitonin and insulin.[93-95]

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 rising 30 times the levels recorded for untreated skin after 24 hours.[96]

Suction ablation

Formation of a suction blister involves the application of vacuum[97] 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.[98] 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,[99] 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.

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[71] and biopharmaceuticals.[100-102] One current method is performed using a stream of aluminium oxide crystals and motor-driven fraises.[71,103] Sage and Bock[104,105] 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.

Carriers and vehicles

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.

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.[106] Nanoemulsion viscosity is very low, which is interesting because they can be produced as sprays.

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.[107-114] 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.[115]

Multiple emulsions

These w/o/w emulsions consist in the dispersion of a w/o emulsion in an aqueous phase under several conditions.[116] 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, Avène) and thus present good hydration. Their efficacy has been demonstrated in dermatology to treat stretch marks (Triffadiane, CS Dermatologie).

Microemulsions

These formulations have been shown to be superior for cutaneous delivery compared with other conventional vehicles.[117] 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 pseudoternary 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.

Vesicular carriers

Liposomes

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 who 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.[118] Phosphatidylcholine from soybean or egg yolk is the most common composition, although many other potential ingredients have been evaluated.[119] 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,[120] gene delivery,[121] and cutaneous vaccination,[122] in some cases combining the liposomal delivery system with other physical enhancement techniques such as electroporation.[123]

Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications.[124-129] This area continues to develop with further evaluation of current formulations and reports of other vesicle-forming materials.

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.[130] 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.[131-134]

Ethosomes

These are liposomes with high alcohol content capable of enhancing penetration to deep tissues and the systemic circulation.[135-138] It is proposed that alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate.

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.[139] 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.[140] 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.[141]

CHEMICAL PENETRATION ENHANCERS

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.[142] 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.[143] 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.[144,145] DMSO may also extract lipids, making the horny layer more permeable by forming aqueous channels.[146] 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.[147,148]

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%.[149] 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.[150]

Pyrrolidones

Pyrrolidones have been used as permeation enhancers for numerous molecules including hydrophilic (e.g., mannitol and 5-flurouracil) and lipophilic (progesterone and hydrocortisone) permeants. N-methyl-2-pyrolidone was employed with limited success as a penetration enhancer for captopril, when formulated in a matrix-type transdermal patch.[151]

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.[152,153] Shin and Lee[154] 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.

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*.[155] The effect of 12 sesquiterpenes on the permeation of 5-flurouracil in human skin was investigated.[156] 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[157] as well as diffusion of imipramine hydrochloride across rat skin and hydrocortisone through hairless mouse skin.[158,159]

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.[160,161] 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.[162]

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.[163]

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.[164] 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.[165] The remaining water within the tissue is 'free' and is available to act as a solvent within the membrane for polar permeants.

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.[166] Ethanol has been used to enhance the flux of levonorgestrel, estradiol, hydro-cortisone, and 5-fluorouracil through rat skin[167] and of estradiol through human skin *in vivo*.[168] However, when using an ethanol water cosolvent vehicle, the enhancement effect of ethanol appears to be concentration dependent.

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.[169]

FUTURE TRENDS

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.

CONCLUSION

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 the major routes of drug administration in the next decade. Research in this area has proved the usefulness of physical and chemical penetration enhancers in the enhancement of drug permeation through skin. The physical and chemical penetration enhancement methods discussed in this review are promising. Focus should be on skin irritation, with a view to selecting penetration enhancers which possess optimum enhancement effects with minimal skin irritation.

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