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Review article

DRUG VEHICLE BASED APPROACHES OF PENETRATION ENHANCEMENT

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ABSTRACT

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. For transdermal delivery of drugs, stratum corneum is the main barrier layer for permeation of drug. So to circumvent the stratum corneum and to increase the flux through skin membrane, different approaches of penetration enhancement are used. Many reviews had described regarding the chemical penetration enhancement but vehicle based enhancement approach is not exploited for reviews. Drug-vehicle based enhancement methods such as drug selection, vesicles and particles, liposomes, prodrugs and ion-pairs, chemical potential of drug, eutectic systems, complexation are used in transdermal research as better alternative method to enhance permeation of drugs through skin. The review presents mainly the routes of penetration through skin and the approaches of drug-vehicle interaction based enhancement to optimise the transdermal delivery system.

Keywords: Transdermal system, Penetration enhancement, Drug-vehicle based, Skin, Flux.

INTRODUCTION

Transdermal delivery of drugs through the skin to the systemic circulation provides a convenient route of administration for a variety of clinical indications. Transdermal delivery systems are currently available containing scopolamine (hyoscine) for motion sickness, clonidine and nitroglycerin for cardiovascular disease, fentanyl for chronic pain, nicotine to aid smoking cessation, oestradiol (alone or in combination with levonorgestrel or norethisterone) for hormone replacement and testosterone for hypogonadism. Despite the small number of drugs currently delivered via this route, it is estimated that worldwide market revenues for transdermal products are US$3B, shared between the USA at 56%, Europe at 32% and Japan at 7%[1]. Around 40% of drug candidate under clinical evaluation are related to transdermal or dermal systems. In USA

the most important clinical market out of 129 drug delivery candidate products under clinical evaluation, 51 % are transdermal or dermal systems. The worldwide transdermal patch market approaches £2 billion, yet is based on only ten drugs- scopolamine (hyoscine), nitroglycerine, tulobuterol, clonidine, estradiol (with and without norethisterone or levonorgestrel), testosterone, fentanyl and nicotine, with a lidocaine patch soon to be marketed[2]. New analysis published in 'U.S. Emerging Transdermal Drug Delivery Technologies Markets', reveals that this market generated revenues worth $1.57 billion in 2002 and is likely to reach a staggering $5.67 billion in 2009[3]. Global TDDS product sales has been given in segments as shown in Fig 1.

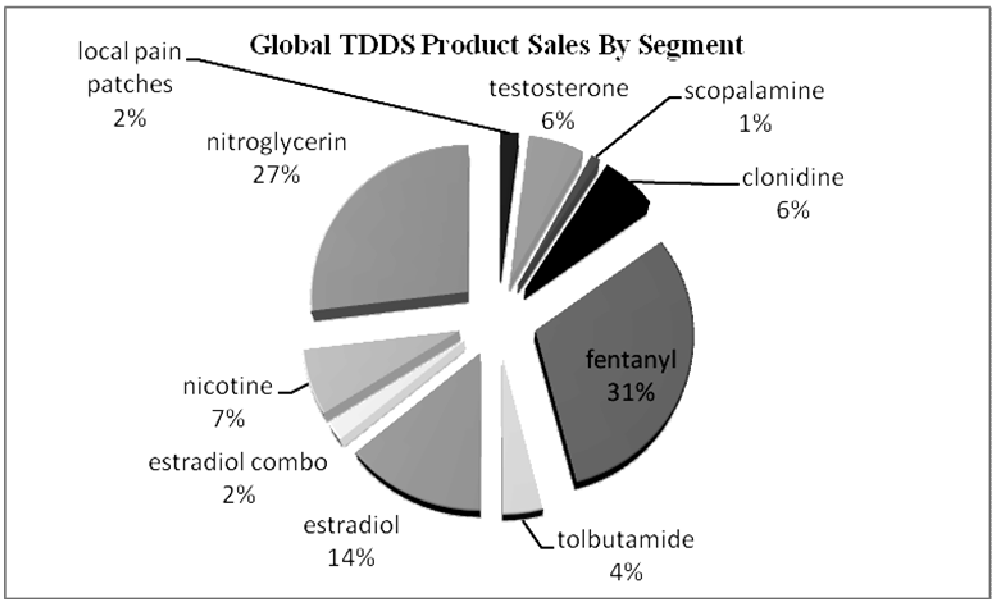

Fig. 1 : Global TDDS product sales

In order for transdermal drug delivery systems to be effective, the drug must obviously be able to penetrate the skin barrier and reach its target in required concentration. Significant effort has been devoted to developing strategies to overcome the impermeability of intact human skin. These strategies include passive and active penetration enhancement and technologies to bypass the stratum corneum. This review describes the routes of penetration, how drug properties influence penetration and the drug-vehicle based techniques that have been used to enhance penetration across human skin.

Drug delivery routes across human skin

The skin of an average body covers a surface area of approximately 2 square meters. Its thickness is approximately 2.97 mm; hair follicles are about 10-70 on every square centimeter and sweat

glands 200-250 on every square centimeter. Skin is multilayered tissue consisting of epidermis, dermis and hypodermis. Outermost layer of epidermis is stratum corneum layer. These are compacted, flattened, dehydrated, and keratinized cells. Physiologically, they are inactive and are continuously shed with constant replacement of epidermis layer. They have the water content of only 20 % (other organs have up to 70 %)[4]. Stratum corneum layer is the main barrier layer for permeation of drugs and hence permeation through this layer is the rate-limiting step. The diffusant has two potential entry routes to the blood vasculature, through the epidermis itself or diffusion through shunt pathway mainly hair follicles with their associated sebaceous glands and the sweat ducts. Therefore there are following two major routes of penetration[5] (i) Transcorneal penetration, which includes intra cellular penetration and inter cellular penetration (Trans cellular) and (ii) Transappendegeal penetration**.** In intra cellular penetration drug molecule passes through the cells of the stratum corneum. It is generally seen in case of hydrophilic drugs. As stratum corneum hydrates, water accumulates near the outer surface of the protein filaments. Polar molecules appear to pass through this immobilized water. Non-polar substances permeate through intercellular penetration. These molecules dissolve in and diffuse through the non- aqueous lipid matrix imbibed between the protein filaments[6]. In Transappendegeal penetration (shunt pathway) the drug molecule may transverse through the hair follicles, the sebaceous pathway of the pilosebaceous apparatus or the aqueous pathway of the salty sweat glands. The transappendegeal pathway is considered to be of minor importance because of its relatively smaller area (less then 0.1% of total surface). However this route may be of some importance for large polar compounds[7]. The route through which permeation occurs is largely dependent on physico-chemical characteristics of penetrant most important being the relative ability to partition into each skin phase[8].

The transdermal permeation can be visualized as composite of a series in sequence as:

1. Adsorption of a penetrant molecule onto the surface layers of stratum corneum.
2. Diffusion through stratum corneum and through viable epidermis.
3. Finally through the papillary dermis into the microcirculation.

The viable tissue layer and the capillaries are relatively permeable and the peripheral circulation is sufficiently rapid. Hence diffusion through the stratum corneum is the rate-limiting step. The stratum corneum acts like a passive diffusion medium. So for transdermal drug diffusion, a simple multilayer model can represent the various skin tissue layers (Fig. 2).

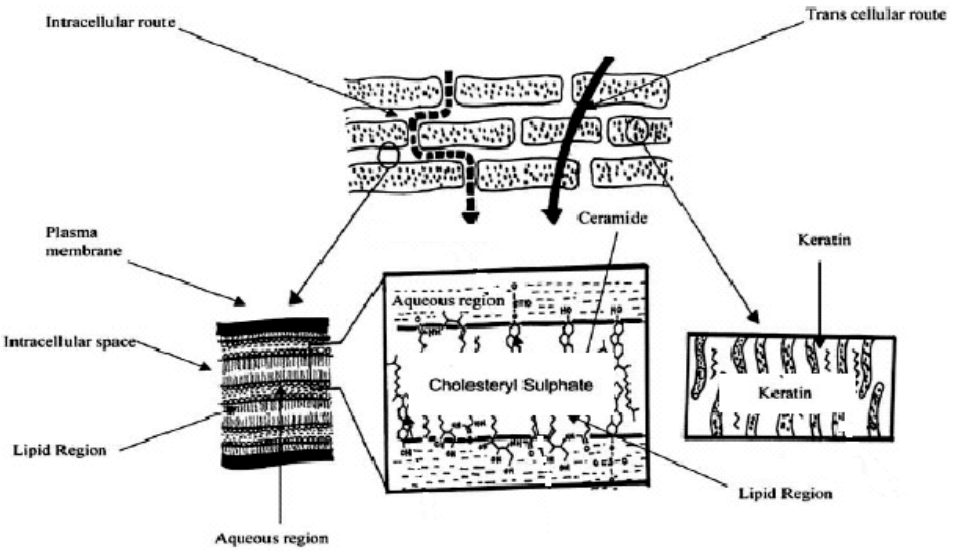

Fig. 2 : Structure of skin and mechanism of penetration into skin

Need of penetration enhancement

Penetration enhancement is the most critical factor in transdermal systems, so as to improve flux. Flux (J) can be defined as the amount (M) of material flowing through unit cross section (S) of a barrier in unit time (t). Flux can be given by: J=dM/S.dt[9]. 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), where Cp-Cr is the difference in permeant concentration across the membrane and A is the area of application[10].

Approaches of penetration enhancement

Some ways for circumventing the stratum corneum barrier are

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. Chemical penetration enhancers

1. Sulphoxides
2. Alcohols
3. Polyols
4. Alkanes
5. Fatty acids
6. Esters
7. Amines and amides
8. Terpenes
9. Surface active agents

C. Physical method

1. Iontophoresis
2. Ultrasound (phonophoresis and sonophoresis)
3. Magnetophoresis
4. Electroporation
5. Laser radiation and photomechanical waves
6. Radio frequency
7. Thermophoresis
8. Microneedle based devices
9. Skin puncture and perforation
10. Needleless injection
11. Suction ablation
12. Application of pressure
13. Skin stretching
14. Skin abration

The current review deals with the drug vehicle based approaches of penetration enhancement.

A. Drug vehicle based

1. Drug selection

Drug should be selected in such a way that it fits in the criteria of transdermal delivery as given in table 1

Table 1: Parameters for Drug selection[11,12,13,14,15,16]

Parameters	Ideal limits
Aqueous solubility	>1mg/ml
Lipophilicity	$10<K_{o/w}<1000$
Molecular weight	<500 Daltons
Melting point	$<200^{o}C$
pH of aqueous saturated solution	5-9
Dose deliverable	<10mg/day

2. Vesicles and particles

2.1. Liposomes

Liposomes are colloidal particles formed as concentric bimolecular layers that are capable of encapsulating drugs. They are lipid vesicles that fully enclose an aqueous volume. These lipid molecules are usually phospholipids with or without some additives.[10] Cholesterol may be included to improve bilayer characteristics of liposomes; increasing microviscosity of the bilayer, reducing permeability of the membrane to water soluble molecules, stabilizing the membrane and increasing rigidity of the vesicles. Liposomes acts by penetrating the epidermis, carrying the drug into

skin and those large multilamellar vesicles could lose their external bilayer during penetration and these liposome lipids penetrate into the stratum corneum by adhering onto the surface of the skin and, subsequently destabilizing, and fusing or mixing with the lipid matrix. Thereafter, they may act as penetration enhancers, loosening the lipid structure of the stratum corneum and promoting impaired barrier function of these layers to the drug, with less well-packed intercellular lipid structure forms, and with subsequent increased skin partitioning of the drug[17]. Studies have focused on delivery of agents via liposomes like anti-psoriatic agent via ethanolic liposomes[18], caffeine for hyperproliferative diseases[19], catechins[20], enoxacin[21]. Liposomal system also increases the stability of some drugs like amphotericin B. When amphotericin B is entrapped in liposomes appeared to be more stable than the free amphotericin B in solution and powder forms, when stored at low temperature (<30^{o}C) and protected from light[22]. Lipid compositions of liposomes also affect permeation through skin as when Triamcinolone permeation was compared among various lipid compositions, different vesicle sizes (0.2, 0.4 and 1 μm), charges (positive, negative and neutral), as well as between multilamellar vesicles (MLV:0.5-10μm) and small unilamellar vesicles (SUV: 0.02-0.05 μm), all the liposomal formulations resulted in significantly higher flux and permeability of triamcinolone acetonide than a commercial triamcinolone acetonide ointment[23]. Recent studies have tended to be focused on delivery of macromolecules such as interferon[24], gene delivery[25] and cutaneous vaccination[26], in some cases combining the liposomal delivery system with other physical enhancement techniques such as electroporation[27], iontophoretic delivery of enkephalin formulated in liposomes. Liposomal delivery of drugs also prevents the drug from degradation as in case of enkephalin. When enkephalin was delivered iontophoretically at its isoelectric point, from liposomes carrying positive or negative charge on their surface, resulted in permeation of radioactivity which was same or less than that of the controls when analyzed by liquid scintillation counting. When analyzed by radiochromatograpy detector on HPLC, degradation of enkephalin during transport was observed, with several degradation peaks in the chromatogram. The degradation was less in liposome formulations, as compared to controls[28], liposomes encapsulating ketoprofen–

cyclodextrin complexes with hydroxy propyl-β-Cyclodextrin resulted in a significant improvement of drug dissolution properties. In particular, coevaporated systems with hydroxy propyl-β-Cyclodextrin gave rise to an 11-fold increase in dissolved drug amount. Entrapment in multilamellar vesicles (MLV) of ketoprofen-complexation complexes was successfully obtained, in spite of the destabilizing effect of complexation due to its complexing capacity toward the vesicle membrane components, such as cholesterol. The enhanced water solubility of the drug- complexation complex allowed its entrapment in the internal aqueous phase of the vesicle, instead of in the external bilayers, thus assuring a more stable drug encapsulation in the carrier and a better control of drug release[29]. When enoxacin was encapsulated liposomally prepared by cholesterol and palmitic acid and their effects were compared when delivered iontophoretically, the permeation of enoxacin from dimyristoyl-L-a phosphatidylcholine/ cholesterol was lower than that of stratum corneum liposomes. This result may be because the cholesterol incorporated phospholipids are more cohesive and compressible in the electric field, which prevents the release of drug from liposomes. Moreover, the palmitic acid in stratum corneum liposomes may act as a penetration enhancer and modify the lipid components of skin. There was no significant difference between the amount of enoxacin in the skin reservoir of stratum corneum liposomes and free drug after palmitic acid pretreatment, suggesting that palmitic acid has a significant effect on the partition of enoxacin in the skin reservoir for both free enoxacin and enoxacin from stratum corneum liposomes[22].

2.2. Transfersomes

These are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant and 3-10% ethanol. Liposomes are too large to pass through pores of less than 50nm in size; transfersomes up to 500nm can squeeze to penetrate the stratum corneum barrier spontaneously. The driving force for penetration into the skin is the "Transdermal gradient" caused by the difference in water content between the restively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to 100%). Evidence of presence of vesicles between the corneocytes in the outer layers of the stratum corneum has been demonstrated by electron and fluorescence microscopy[30]. For vesicles

to remain swollen, they must follow local hydration gradient and penetrate into hydrated and deeper skin layers of viable epidermis and dermis. Traditionally liposomes are expected to confine to surface or upper layers of stratum corneum, where they dehydrate and fuse with skin lipids. Secondly transferosomes work best under *in vivo* conditions. Vesicles must adapt their size and/or shape, dependent on bilayer stability and elasto-mechanics, to overcome an otherwise confining pore. Ultradeformable lipid vesicles (transferosomes) can penetrate the skin and does not causes any changes in semi-permeable barriers that remain unfragmented after delivery. Evidence from double label confocal laser scanning microscopy (CLSM) experiments and direct size measurements confirms it[31]. Data indicate that as much as 50% of a topical dose of a protein or peptide penetrates skin *in vivo* in 30 minutes. Five potential mechanisms of action of these liposomes were assessed

1. A free drug process-drug releases from vesicles and independently penetrates skin.
2. Enhancement due to release of lipids from vesicles and interaction with skin lipids.
3. Improved drug uptake by skin.
4. That different entrapment efficiencies of the liposomes controlled drug input.
5. Penetration of stratum corneum by intact liposomes.

Studies have been focused on delivery of agents like vaccines[32], retinyl palmitate[33], estradiol[34], copper, zinc, superoxide dimutase[35], insulin[36]. In some cases the transferosomes drug delivery with some physical enhancement method iontophoresis for estradiol[37] and microneedles for docetaxel[38].

2.3. Ethosomes

These are liposomes with a high alcohol content (up to 45%) capable of enhancing penetration to deep tissues and the systemic circulation[39-42]. It is proposed that the alcohol fluidises the ethosomal lipids and stratum corneum bilayer lipids thus allowing the soft, malleable ethosomes to penetrate**.** Studies have been focused on transdermal ethosomal delivery of agents like minoxidil, testosterone[40], and comparative study had also been done on ethosomal vs liposomal system of trihexyphenidyl hydrochloride (THP). THP encapsulated in classical liposomes remained primarily at the surface of the skin, while the ethosomal system was shown to be a highly efficient carrier for enhanced THP delivery through the

skin. The ethosomal system of THP not only enhance the permeation but also showed long-term stability as compared to classical liposomes, makes it a promising alternative for transdermal delivery of THP[41].

2.4. Niosomes

Niosomes are vesicles composed of nonionic surfactants that have been evaluated as carriers for a number of drug and cosmetic applications. In fact, if compared with conventional liposomes (phospholipids) niosomes (non ionic surfactant vesicles) offer higher chemical stability, lower costs, and great availability of surfactant classes[10]. Niosomes seems an interesting drug delivery system in the treatment of dermatological disorders. In fact, topically applied niosomes can increase the residence time of drugs in the stratum corneum and epidermis, while reducing the systemic absorption of the drug. They are thought to improve the horny layer properties; both by reducing transepidermal water loss and by increasing smoothness via replenishing lost skin lipids. In recent years, attention has been focused on sugar-based surfactants for several types of applications like less toxic, highly biodegradable, which are also produced from renewable raw materials. It has also been suggested that sugar moieties may replace ethylene oxide as the polar head of amphiphiles and that sugar-based amphiphiles may substitute ethylene oxide-based surfactants in several applications. In particular, alkyl polyglucosides (APGs) have been studied for several types of applications. Commercial available APGs are mixture of glucosides, which are obtained from degraded starch fractions. APGs are stable at high pH values, but sensitive to low pH where they hydrolise to glucose and fatty alcohol. The main APGs attractiveness lies in their favourable environmental profile: the rate of biodegradation is usually high while the aqueous toxicity is low. In addition, APGs show favourable dermatological properties, being very mild to the skin and eye. This mildness makes this surfactant class attractive for cosmetic products although APGs have also found a wide range of technical applications. APGs have already shown their capability to form vesicular structures and their properties led us to explore the possibility of using APGs containing niosomes as carriers for the topical.[43-47] This area continues to develop with further evaluation of current formulations and reports of other vesicle forming materials. Studies have been focused on niosomal transdermal delivery of agents like estradiol

(proniosomal formulation)[48], ketorolac (proniosomal formulation)[49], immunological adjuvants[50], tretinoin for psoriasis, photodamage and skin cancer[51], carriers of anti-inflammatory drugs, diagnostic imaging agents[52], diclofenac diethylammonium[53], levonorgestrol[54].

2.5. Solid lipid nanoparticles (SLN)

Nanoparticles are colloidal drug delivery systems having a diameter of approximately 200-500nm. SLN have recently been investigated as carriers for enhanced skin delivery of sunscreens, vitamins A and E, triptolide and glucocorticoids[55-59]. It is thought their enhanced skin penetration 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. Studies have been focused on transcutaneous vaccine delivery[60], transdermal DNA delivery[61], mixnoxidil with block copolymer nanoparticles[62] and in combination with physical methods as iontophoretic delivery of triamcinolone acetonide acetate[63], iontophoretic administration of triptorelin loaded nanospheres[64]and microneedle mediated delivery of nanoparticles[65].

2.6. Aspasomes

Ascorbyl palmitate formed vesicles (Aspasomes) in presence of cholesterol and charge inducer dicetyl phosphate, encapsulating azidothymidine solution. The antioxidant potency of aspasome was much better than that of ascorbic acid. Thus, it can find applications as drug delivery system in disorders implicated with reactive oxygen species. Aspasomes enhanced the transdermal permeation of azidothymidine.

The antioxidant property and skin permeation enhancing property indicate a promising future for aspasome as a carrier for transdermal drug delivery system[66].

2.7. High velocity particles

The powderject system fires solid particles (20–100 mm) through stratum corneum into lower skin layers, using a supersonic shock wave of helium gas. The claimed advantages of the system include[67].

- Pain free delivery particles are too small to trigger pain receptors in skin
- Improved efficacy and bioavailability
- Targeting to a specific tissue, such as a vaccine delivered to epidermal cells
- Sustained release, or fast release
- Accurate dosing
- Overcome needle phobia

- Safety - the device avoid skin damage or infection from needles or splashback of body fluids particularly important for HIV and hepatitis B virus.

However, there have been problems with bruising and particles bouncing off skin surfaces. Regulatory authorities will need convincing that high velocity particles smashing through the stratum corneum really do no damage to this elegant structure, which is not readily repaired, nor do they carry surface contaminants such as bacteria into viable skin layers. The leading products in development include lignocaine and levobupivacaine for local anesthesia, proteins (follicle stimulating hormone and β-interferon) and hepatitis B DNA and other vaccines[68-72]. The intraject is a development of the vaccine gun designed to deliver liquids through skin without using needles. It is surprising that, after the widespread use of similar devices for vaccination such as by the US military in Vietnam it was not developed for drug delivery earlier.

3. Prodrugs and ion pairs

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients[73]. The prodrug design strategy generally involves addition of a promoiety to increase partition coefficient and hence 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. The intrinsic poor permeability of the very polar 6-mercaptopurine was increased up to 240 times using S-6- acyloxymethyl and 9-dialkylaminomethyl promoieties[74] and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives[75-79]. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs[80,81], nalbuphine[82,83]. Well established commercial preparations using this approach include steroid esters (e.g. betamethasone-17-valerate), which provide greater topical anti-inflammatory activity than the parent steroids. Charged drug molecules do not readily partition into or permeate through human skin. Formation of lipophilic ionpairs has been investigated to increase stratum corneum penetration of charged species. This strategy involves adding an oppositely charged species to the charged drug, forming an ion-pair in which the charges are neutralised so that the complex can

partition into and permeate through the stratum corneum. The ion-pair then dissociates in the aqueous viable epidermis releasing the parent charged drug, which can diffuse within the epidermal and dermal tissues[84].

4. Chemical potential of drug

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution[85]. The diffusion of paraben from saturated solutions in eleven different solvents through a silicone membrane was determined. Due to the different solubility of the parabens in the various solvents, the concentration varied over two orders of magnitude. However, paraben flux was the same from all solvents, as the thermodynamic activity remained constant because saturated conditions were maintained throughout the experiment. Supersaturated solutions can occur due to evaporation of solvent or by mixing of cosolvents. Clinically, the most common mechanism is evaporation of solvent from the warm skin surface, which probably occurs, in many topically applied formulations. In addition, if water is imbibed from the skin into the vehicle and acts as an antisolvent, the thermodynamic activity of the permeant would increase[85]. Increases in flux of drug upto five to ten folds have been reported from supersaturated solutions of a number of drugs. The potential benefit of supersaturated solutions was first recognized at least three decades ago. Since then little work has been carried out in this area, probably partly due to the thermodynamic instability of these solutions. However, with an understanding of antinucleant polymers, supersaturated solutions can be exploited to enhance percutaneous penetration. Supersaturated solutions were produced by using a cosolvent system and this involves preparing a saturated solubility curve for the drug in a binary cosolvent system. Supersaturated systems have been successful at enhancing skin permeation. The technique involves increasing the thermodynamic activity beyond saturated solubility concentrations and as flux is proportional to thermodynamic activity, an increase in the latter can lead to an increase in flux. The major advantage of this technique is its non-interference with the barrier properties of the stratum corneum. However, supersaturated systems are thermodynamically unstable. Some polymers like polyvinylpyrrolidone (PVP), polyethyleneglycol (PEG), Eudragits, polymethacrylates, polypropyleneglycol (PPG), Dextrin

derivatives, Cellulose esters like cellulose acetate butyrates(CAB) and cellulose acetate propionates(CAP) act as anti-nucleating agents and can control the crystallization process and hence enhance permeation of a number of drugs. The inhibition of crystallization by these polymers has been rarely discussed in the past but more recently a mechanism was proposed based on the adsorption of polymers onto the crystal surface through hydrogen bonding. Hydroxypropyl-β-cyclodextrin (HP-β-CD) acts as an antinucleating agent by stabilizing the supersaturated system of Ibuprofen by forming inclusion complexes and this was demonstrated by infrared spectroscopy and differential scanning calorimetric studies.[86-91] Magreb *et al*. [92] reported that the flux of oestradiol from an 18-times saturation system was increased 18-fold across human membrane but only 13-fold in silastic membrane. They suggested that the complex mixture of fatty acids, cholesterol, ceramides, etc. in the stratum corneum might provide an antinucleating effect thereby stabilizing the supersaturated system. Supersaturated solutions (i.e. nonequilibrated systems) may arise; either by design or via a cosolvent evaporating on the skin.[93] The theoretical maximum flux may then increase manyfold. So, these polymers may be incorporated to inhibit crystallization in unstable supersaturated preparations. The metastability period is usually short, but may be prolonged in transdermal patches because of their mode of preparation, drug dissolution in hot solvents, and evaporation to supersaturation and crystal inhibition by the polymers of the high viscosity matrix or adhesive.

5. Eutectic systems

The melting points of a drug influences solubility and hence skin penetration. According to regular solution theory, the 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: 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. EMLA cream, a formulation consisting of a eutectic mixture of lignocaine and prilocaine applied under an occlusive film, provides effective local anaesthesia for pain-free venepuncture and other procedures. The 1:1 eutectic mixture (melting point 18°C) is oil, which is formulated as an oil-in-water emulsion

thereby maximizing the thermodynamic activity of the local anaesthetics. A number of eutectic systems containing a penetration enhancer as the second components have been reported, for example: Ibuprofen with terpenes[94], and methyl nicotinate[95], propranolol with fatty acids[96], and lignocaine with menthol[97]. In all cases, the melting point of the drug was depressed to around or below skin temperature thereby enhancing drug solubility.

6. Complexes

Complexation of drugs with cyclodextrins has been used to enhance aqueous solubility and drug stability. Cyclodextrins of pharmaceutical relevance 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[98]. Derivatives of β-cyclodextrin with increased water solubility (e.g. hydroxypropyl-β-cyclodextrin) are most commonly used in pharmaceutical formulation. Cyclodextrin complexes have been shown to increase the stability, wettability and dissolution of the lipophilic insect repellent N, N-diethyl-m-toluamide and the stability and photostability of sunscreens[99]. Cyclodextrins are large molecules, with molecular weights greater than 1000 Daltons, therefore it would be expected that they would not readily permeate the skin. Complexation with cyclodextrins has been variously reported to both increase[100] and decrease skin penetration[101]. In a recent review of the available data, Loftsson and Masson concluded that the effect on skin penetration may be related to cyclodextrin concentration, with reduced flux generally observed at relatively high cyclodextrin concentrations, whilst low cyclodextrin concentrations resulting in increased flux[98]. As flux is proportional to the free drug concentration, where the cyclodextrin concentration is sufficient to complex only the drug that is in excess of its solubility, an increase in flux might be expected. However, at higher cyclodextrin concentrations, the excess cyclodextrin would be expected to complex free drug and hence reduce flux. Skin penetration enhancement has also been attributed to extraction of stratum corneum lipids by cyclodextrins[102]. Given that most experiments that have reported cyclodextrin mediated flux enhancement

have used rodent model membranes in which lipid extraction is considerably easier than human skin, the penetration enhancement of cyclodextrin complexation may be an overestimate. Shaker *et al.* recently concluded that complexation with HP-β-CD had no effect on the flux of cortisone through hairless mouse skin by either of the proposed mechanisms.[103] However, this remains a controversial area.

CONCLUSION

The search for the ideal skin penetration enhancer has been the focus of considerable research effort over a number of decades. Although many potent enhancers have been discovered, in most cases their enhancement effects are associated with toxicity, therefore limiting their clinical application. However drug-vehicle based approaches of penetration enhancement technique does not compromise skin barier function as do chemical and physical penetration enhancement technique and hence it can serve as the better alternative. 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.

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