Transdermal Drug Delivery: Penetration Enhancement Techniques

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Abstract: There is considerable interest in the skin as a site of drug application both for local and systemic effect. However, the skin, in particular the stratum corneum, poses a formidable barrier to drug penetration thereby limiting topical and transdermal bioavailability. Skin penetration enhancement techniques have been developed to improve bioavailability and increase the range of drugs for which topical and transdermal delivery is a viable option. This review describes enhancement techniques based on drug/vehicle optimisation such as drug selection, prodrugs and ion-pairs, supersaturated drug solutions, eutectic systems, complexation, liposomes, vesicles and particles. Enhancement via modification of the stratum corneum by hydration, chemical enhancers acting on the structure of the stratum corneum lipids and keratin, partitioning and solubility effects are also discussed. The mechanism of action of penetration enhancers and retarders and their potential for clinical application is described.

Keywords: Transdermal delivery, skin penetration, enhancer, retarder.

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%. In a recent market report it was suggested that the growth rate for transdermal delivery systems will increase 12% annually through to 2007 [1]. Transdermal products for cardiovascular disease, Parkinson's disease, Alzheimer's disease, depression, anxiety, attention deficit hyperactivity disorder (ADHD), skin cancer, female sexual disfunction, post-menopausal bone loss, and urinary incontinence are at various stages of formulation and clinical development. The application of transdermal delivery to a wider range of drugs is limited due to the significant barrier to penetration across the skin which is associated primarily with the outermost stratum corneum layer of the epidermis. Consequently the daily dose of drug that can be delivered from a transdermal patch is 5-10 mg, effectively limiting this route of administration to potent drugs. 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 techniques that have been used to enhance penetration across human skin. Physical enhancement technologies such as iontophoresis, electroporation, phonophoresis, microneedles and jet-injectors are reviewed in a separate article in this journal by Cross and Roberts [2] and in other recent review articles [3, 4].

DRUG DELIVERY ROUTES ACROSS HUMAN SKIN

Drug molecules in contact with the skin surface can penetrate by three potential pathways: through the sweat ducts, *via* the hair follicles and sebaceous glands (collectively called the shunt or appendageal route), or directly across the stratum corneum (Fig. **1**). The relative importance of the shunt or appendageal route versus transport across the stratum corneum has been debated by scientists over the years (eg. [5-7]) 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 and colleagues [8, 9] proposed that a follicular shunt route was responsible for the presteady-state permeation of polar molecules and flux of large 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% [10], their contribution to steady state flux of most drugs is minimal. This assumption has resulted in the majority of skin penetration enhancement techniques being focused on increasing transport across the stratum corneum rather than via the appendages. Exceptions are iontophoretic drug delivery which uses an electrical charge to drive molecules into the skin primarily via the shunt routes as they provide less electrical resistance, and vesicular delivery.

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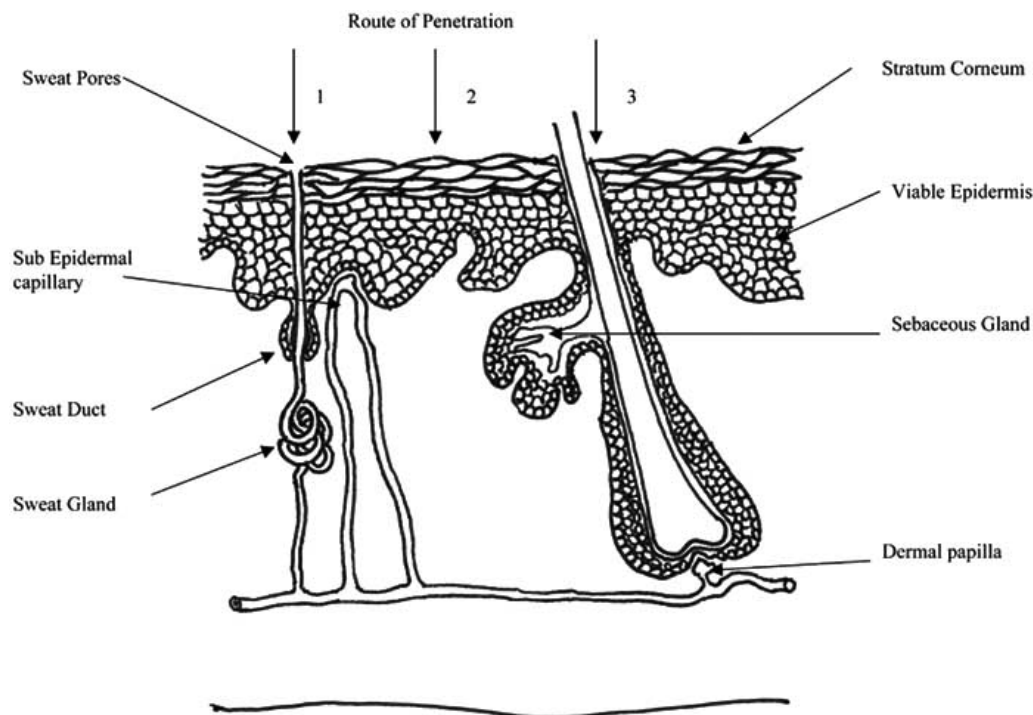
Fig. (1). Simplified representation of skin showing routes of penetration: 1. through the sweat ducts; 2. directly across the stratum corneum; 3. via the hair follicles.

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 [11]. The stratum corneum consists of 10-15 layers of corneocytes and varies in thickness from approximately 10-15 µm in the dry state to 40 µm when hydrated [12-14]. 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 sulfate and sterol/wax esters [15]. 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 [16], which then associate into lipid bilayers [17, 18], with the hydrocarbon chains aligned and polar head groups dissolved in an aqueous layer (Fig. **2**). As a result of the stratum corneum lipid composition, 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 [19]. The presence of intrinsic and extrinsic proteins, such as enzymes, may also affect the lamellar structure of the stratum corneum. Water is an essential component of the stratum corneum, which acts as a plasticizer to prevent cracking of the stratum corneum and is also involved in the generation of natural moisturizing factor (NMF), which helps to maintain suppleness.

In order to understand how the physicochemical properties of the diffusing drug and vehicle influence permeation across the stratum corneum and thereby optimise delivery, it is essential to determine the predominant route of drug permeation within the stratum corneum. Traditionally it was thought that hydrophilic chemicals diffuse within the aqueous regions near the outer surface of intracellular keratin filaments (intracellular or transcellular route) whilst lipophilic chemicals diffuse through the lipid matrix between the filaments (intercellular route) [9] (see Fig. **2**). However, this is an oversimplification of the situation as each route cannot be viewed in isolation. A molecule traversing via the transcellular route must partition into and diffuse through the keratinocyte, but in order to move to the next keratinocyte, the molecule must partition into and diffuse through the estimated 4-20 lipid lamellae between each keratinocyte. This series of partitioning into and diffusing across multiple hydrophilic and hydrophobic domains is unfavourable for most drugs. Consequently, based on more recent data (for example [16, 20-23]) the intercellular route is now considered to be the major pathway for permeation of most drugs across the stratum corneum. As a result, the majority of techniques to optimise permeation of drugs across the skin are directed towards manipulation of solubility in the lipid domain or alteration of the ordered structure of this region (Fig. **3**).

PENETRATION ENHANCEMENT THROUGH OPTIMISATION OF DRUG AND VEHICLE PROPERTIES

Drug permeation across the stratum corneum obeys Fick's first law (equation 1) where steady-state flux (J) is related to the diffusion coefficient (D) of the drug in the stratum corneum over a diffusional path length or membrane thickness (h), the partition coefficient (P) between the
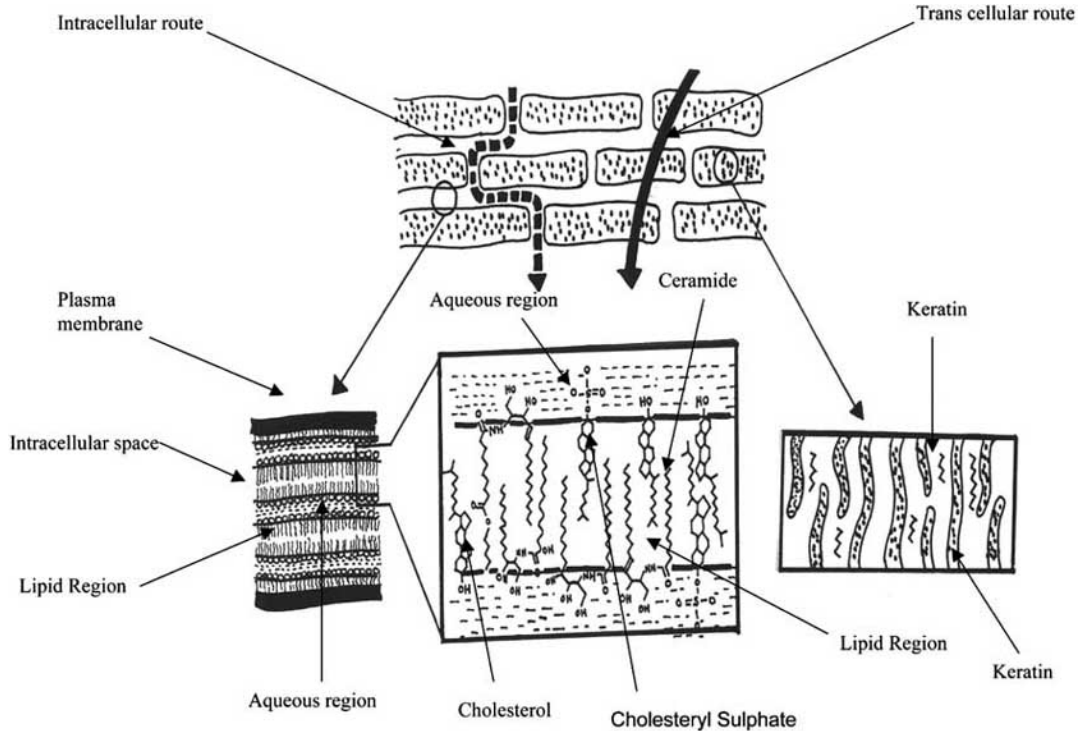
Fig. (2). Diagrammatic representation of the stratum corneum and the intercellular and transcellular routes of penetration (adapted from [3]).
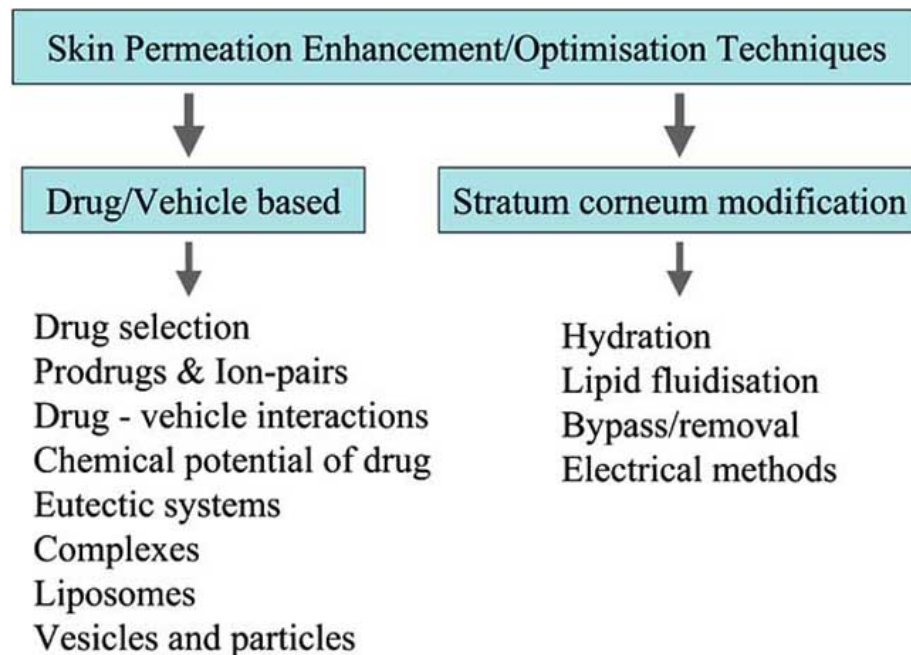

Fig. (3). Techniques to optimise drug permeation across the skin.

stratum corneum and the vehicle, and the applied drug concentration (C_0) which is assumed to be constant:

$$\frac{dm}{dt} = J = \frac{DC_0P}{h} \tag{1}$$

Equation 1 aids in identifying the ideal parameters for drug diffusion across the skin. The influence of solubility

and partition coefficient of a drug on diffusion across the stratum corneum has been extensively studied and an excellent review of the work was published by Katz and Poulsen [24]. Molecules showing intermediate partition coefficients (log $P_{octanol/water}$ of 1-3) have adequate solubility within the lipid domains of the stratum corneum to permit diffusion through this domain whilst still having sufficient hydrophilic nature to allow partitioning into the viable tissues of the epidermis. For example a parabolic

relationship was obtained between skin permeability and partition coefficient for a series of salicylates and non-steroidal anti-inflammatory drugs [25]. The maximum permeability measurement being attained at log P value 2.5, which is typical of these types of experiments. Optimal permeability has been shown to be related to low molecular size [7] (ideally less than 500 Da [26]) as this affects diffusion coefficient, and low melting point which is related to solubility. When a drug possesses these ideal characteristics (as in the case of nicotine and nitroglycerin), transdermal delivery is feasible. However, where a drug does not possess ideal physicochemical properties, manipulation of the drug or vehicle to enhance diffusion, becomes necessary. The approaches that have been investigated are summarised in (Fig. **3**) and discussed below.

1. Prodrugs and Ion-Pairs

The prodrug approach has been investigated to enhance dermal and transdermal delivery of drugs with unfavourable partition coefficients [27, 28]. 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 optimising 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 [29] and that of 5-fluorouracil, a polar drug with reasonable skin permeability was increased up to 25 times by forming N-acyl derivatives [30-34]. The prodrug approach has also been investigated for increasing skin permeability of non-steroidal anti-inflammatory drugs [35-39], naltrexone [40], nalbuphine [41, 42], buprenorphine [43, 44], -blockers [45] and other drugs [27]. 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 ion-pairs 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 [46-48]. In general permeability increases of only two to three-fold have been obtained although Sarveiya *et al.* [49] recently reported a 16-fold increase in the steady-state flux of ibuprofen ion-pairs across a lipophilic membrane.

2. Chemical Potential of Drug in Vehicle – Saturated and Supersaturated Solutions

The maximum skin penetration rate is obtained when a drug is at its highest thermodynamic activity as is the case in a supersaturated solution. This can be demonstrated based on Equation 1 rewritten in terms of thermodynamic activities [50]:

$$\frac{dm}{dt} = \frac{aD}{h} \tag{2}$$

Where   is the thermodynamic activity of the permeant in its vehicle and   is the effective activity coefficient in the membrane. This dependence on thermodynamic activity rather than concentration was elegantly demonstrated by Twist and Zatz [51]. The diffusion through a silicone membrane of saturated solutions of parabens in eleven different solvents 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 [52]. Increases in drug flux of five- to ten-fold have been reported from supersaturated solutions of a number of drugs [52-58]. These systems are inherently unstable and require the incorporation of antinucleating agents to improve stability. Magreb et al [59] 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 may provide an antinucleating effect thereby stabilizing the supersaturated system.

3. Eutectic Systems

As previously described, the melting point 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 [60]. The 1:1 eutectic mixture (m.p. 18°C) is an 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 component have been reported, for example: ibuprofen with terpenes [61], menthol [62] and methyl nicotinate [63]; propranolol with fatty acids [64]; and lignocaine with menthol [65]. In all cases, the melting point of the drug was depressed to around or below skin temperature thereby enhancing drug solubility. However, it is also likely that the interaction of the penetration enhancer with stratum corneum lipids also contributed to the increased drug flux.

4. 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 (-, -, -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 [66]. Derivatives of -cyclodextrin with increased water solubility (e.g. hydroxypropyl- -cyclodextrin HP- -CD) 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 (DEET) [67] and the stability and photostability of sunscreens [68, 69]. Cyclodextrins are large molecules, with molecular weights greater than 1000 Da, therefore it would be expected that they would not readily permeate the skin. Complexation with cyclodextrins has been variously reported to both increase [70, 71] and decrease skin penetration [66, 72-74]. 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 [75]. As flux is proportional to the free drug concentration, where the cyclodextrin concentration is sufficient to complex only the drug which 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 [76]. 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 [77], the penetration enhancement of cyclodextrin complexation may be an overestimate. Shaker and colleagues recently concluded that complexation with HP- -CD had no effect on the flux of cortisone through hairless mouse skin by either of the proposed mechanisms [78]. This remains a controversial area.

5. Liposomes and Vesicles

There are many examples of cosmetic products in which the active ingredients are encapsulated in vesicles. These include humectants such as glycerol and urea, sunscreening and tanning agents, enzymes, etc. Although there are few commercial topical products containing encapsulated drugs, there is a considerable body of research in the topic. A variety of encapsulating systems have been evaluated including liposomes, deformable liposomes or transfersomes, ethosomes and niosomes.

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 [79]. Phosphatidylcholine from soybean or egg yolk is the most common composition although many other potential ingredients have been evaluated [80]. 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 [81], gene delivery [82] and cutaneous vaccination [83], in some cases combining the liposomal delivery system with other physical enhancement techniques such as electroporation [84]. Their delivery mechanism is reported to be associated with accumulation of the liposomes and associated drug in the stratum corneum and upper skin layers, with minimal drug penetrating to the deeper tissues and systemic circulation (eg. [79, 85-88]. The mechanism of enhanced drug uptake into the stratum corneum is unclear. It is possible that the liposomes either penetrate the stratum corneum to some extent then interact with the skin lipids to release their drug or that only their components enter the stratum corneum. It is interesting that the most effective liposomes are reported to be those composed of lipids similar to stratum corneum lipids [81], which are likely to most readily enter stratum corneum lipid lamellae and fuse with endogenous lipids.

Transfersomes are vesicles composed of phospholipids as their main ingredient with 10-25% surfactant (such as sodium cholate) and 3-10% 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 [89]. 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 [90-93]. They suggest that the driving force for penetration into the skin is the "transdermal gradient" caused by the difference in water content between the relatively dehydrated skin surface (approximately 20% water) and the aqueous viable epidermis (close to 100%). A lipid suspension placed on a non-occluded skin surface is subject to evaporation, and to avoid dehydration transfersomes must penetrate to deeper tissues. Conventional liposomes remain near the skin surface, dehydrate and fuse, whilst deformable transfersomes penetrate via the pores in the stratum corneum and follow the hydration gradient. Extraordinary claims are made for the penetration enhancement ability of transfersomes, such as skin transport of 50-80% of the applied dose of transferosome-associated insulin [94]. More recently Guo *et al.* also demonstrated that flexible lecithin liposomes containing insulin applied to mouse skin caused hypoglycaemia, whilst conventional liposomes and insulin solution had no hypoglycaemic effect [95]. Other researchers who have evaluated transfersomes have also shown that ultradeformable liposomes are superior to rigid liposomes. For example, in a series of studies the skin penetration of estradiol was enhanced more by ultradeformable liposomal formulation (17-fold) than by traditional liposomes (9-fold) [96-98, 99]. Pretreatment of the skin membranes with empty vesicles had minimal effect on drug flux and the size of the

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