International Journal of Cosmetic Science, 2009, **31**, 1–19

Review Article

Formulation effects of topical emulsions on transdermal and dermal delivery

A. Otto*, J. du Plessis* and J. W. Wiechers†

*Unit for Drug Research and Development, North-West University, Potchefstroom Campus, Private Bag X6001, 2520 Potchefstroom, South Africa and †JW Solutions, Gasthuispolderweg 30, 2807 LL Gouda, The Netherlands

Received 4 March 2008, Accepted 24 June 2008

Keywords: dermal and transdermal delivery, emulsifier, emulsion, skin, vehicle effect

Synopsis

It has been recognized that the vehicle in which a permeant is applied to the skin has a distinctive effect on the dermal and transdermal delivery of active ingredients. The cutaneous and percutaneous absorptions can be enhanced, e.g. by an increase in thermodynamic activity, supersaturation and penetration modifiers. Furthermore, dermal and transdermal delivery can be influenced by the interactions that may occur between the vehicle and the skin on the one hand, and interactions between the active ingredient and the skin on the other hand. Emulsions are widely used as cosmetic and pharmaceutical formulations because of their excellent solubilizing capacities for lipophilic and hydrophilic active ingredients and application acceptability. This review focuses, in particular, on the effect of emulsions on the dermal and transdermal delivery of active ingredients. It is shown that the type of emulsion (w/o vs. o/w emulsion), the droplet size, the emollient, the emulsifier as well as the surfactant organization (micelles, lyotropic liquid crystals) in the emulsion may affect the cutaneous and percutaneous absorption. Examples substantiate the fact that emulsion constituents such as emollients and emulsifiers should be selected carefully for optimal efficiency of the formulation. Moreover, to understand the influence of emulsion on dermal and transdermal delivery, the physicochemical properties of the formulation after application are considered.

Correspondence: Prof. Dr Johann W. Wiechers, JW Solutions, Gasthuispolderweg 30, 2807 LL Gouda, The Netherlands. Tel.: +31 182 586 488; fax: +31 182 586 488; e-mail: johann.wiechers@versatel.nl

Résumé

On sait que le véhicule dans lequel un perméat est appliqué sur la peau a un effet spécifique sur la libération dermique et transdermique des ingrédients actifs. Les absorptions cutanées et percutanées peuvent être augmentées, par exemple par une augmentation de l'activité thermodynamique, une super saturation ou la présence de modificateurs de pénétration. Ainsi, la libération dermique et transdermique peut être influencée par les interactions susceptibles de s'établir d'un côté entre le véhicule et la peau et de l'autre entre l'ingrédient actif et la peau. Les émulsions sont largement utilisées dans les formulations cosmétiques et pharmaceutiques du fait de leurs excellentes capacités de solubilisation des ingrédients actifs lipophiles et hydrophiles, et du fait de leur bonne tolérance. Cette revue traite, en particulier, des effets des émulsions sur la libération dermique et trans-dermique d'ingrédients actifs. On montre que le type d'émulsion (E/H par rapport à H/E), la granulométrie, l'émollient, les émulsifiants, autant que l'organisation des tensioactifs (micelles, cristaux liquides lyotropes) peuvent influencer l'absorption cutanée et percutanée. Des exemples justifient le fait qu'un choix soigné des constituants de l'émulsion comme les émollients et les émulsifiants peut optimiser l'efficacité de la formulation. En complément, pour

comprendre l'influence de l'émulsion sur la libération dermique et transdermique, les propriétés physico-chimiques de la formulation après application sont étudiées.

The effect of the vehicle on dermal and transdermal delivery

Introduction

It has been recognized that the vehicle in which the permeant is applied to the skin has a distinctive effect on the dermal and transdermal delivery of active ingredients. Despite the fact that studies have been performed to investigate the vehicle effect on skin penetration, it is still not fully understood, especially for more complex formulations such as emulsions. In addition, the task of formulating a topical formulation not only includes the optimization for delivery of the active ingredient but also the fulfillment of the requirements for chemical and physical stability, non-toxicity and aesthetic acceptability [1].

The diffusion process of the permeant through the skin is a passive kinetic process along a concentration gradient and Fick's first law (Equation 1) is commonly used to describe the steady-state permeation through the skin.

$$J = \frac{DK(c_V - c_R)}{h} = k_p(c_V - c_R) \quad (1)$$

where J (μg cm^{-2} h^{-1}) is the steady-state flux, D (cm^2 h^{-1}) is the diffusion coefficient, $c_V - c_R$ (μg cm^{-3}) is the concentration gradient of the permeant between the vehicle and the receiver side, K is the partition coefficient of the permeant between the stratum corneum and the vehicle, h (cm) is the diffusional path length and k_p (cm h^{-1}) is the permeation coefficient of the permeant in the stratum corneum. As in most circumstances $c_R << c_V$, Equation 1 can be simplified to Equation 2.

$$J = \frac{DKc_V}{h} = k_p c_V \quad (2)$$

From Equation 2, it is deduced that the flux across the skin may be enhanced by increasing the diffusion coefficient, partition coefficient and/or the concentration of the permeant in the vehicle. All these parameters can be influenced by the vehicle and the interactions that may occur, e.g. interactions between the vehicle and active ingredient, interactions between the vehicle and the skin and interactions between the active ingredient and the skin (Fig. 1) [2]. Moreover, it is likely that these interactions might coincide as the vehicle can interact with the active ingredient as well as with the skin.

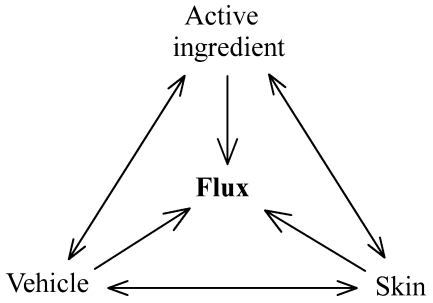

Figure 1 Interaction between active ingredient, vehicle and skin, redrawn from Ref. [3].

In general, by careful selection of the vehicle, the skin penetration of an active ingredient can be optimized. However, the potential interactions imply that it will be an unfeasible task to find a universal formulation that will possess optimized delivery for various kinds of active ingredients. Therefore, the development of an optimized vehicle should rather be considered case by case. Moreover, the formulator has to consider that the composition of the vehicle will change after application to the skin. For example, volatile components (e.g. water, propylene glycol) of the formulation may evaporate, formulation constituents may penetrate into the skin or skin components may be extracted into the vehicle. Hence, the skin penetration of active ingredients is influenced by a continuous change in equilibrium between the active ingredient, vehicle and skin.

Despite the complexity of the vehicle effect on skin penetration, some general guidelines are recognized for enhancing the flux of active ingredients across the skin. It is well known that the flux can be optimized by

- maximum thermodynamic activity of the permeant in the vehicle;
- supersaturation and
- incorporation of penetration enhancers which can increase the solubility of the permeant in the skin or enhance the diffusivity across the skin.

Please note that these effects will result in an increased transport into the skin as well as in

some cases across the skin. The guidelines to enhance transdermal delivery will therefore not be the same as enhancing dermal delivery.

Thermodynamic activity

Thermodynamic activity describes the escaping tendency of the permeant from the vehicle into the skin and is the actual driving force for diffusion. The thermodynamic activity of a permeant is at unity when the permeant is at its saturation concentration in the vehicle. It has been shown that if no interaction occurs between the skin and vehicle, the flux of a particular active ingredient was the same from different saturated vehicles though the concentration of the permeant varied significantly [4–6]. Conversely, in subsaturated vehicles, the thermodynamic activity is reduced and depends on the concentration gradient (simplified to concentration in the vehicle) and activity coefficient of the permeant. The correlation between thermodynamic activity and concentration is described by Equation 3.

$$a_V = \gamma_V c_V \tag{3}$$

where a_V is the thermodynamic activity, γ_V is the activity coefficient and c_V is the concentration of the permeant in the vehicle. In indefinitely diluted solutions, where the interaction among the permeant molecules and between permeant and vehicle components are negligible, the thermodynamic activity is equal to the concentration. However, in more concentrated and complex formulations, the interactions among permeant molecules and between permeant and vehicle components are not insignificant, and the thermodynamic activity of the permeant becomes lower than the actual concentration and depends on the activity coefficient γ_V. By substituting c_V in Equation 2 and defining the partition coefficient as the quotient between the activity coefficient of the permeant in the vehicle and in the skin ($K = \gamma_V/\gamma_S$), Equation 4 was derived to describe the flux as a function of the thermodynamic activity of the permeant in the vehicle [7].

$$J = \frac{Da_V}{h\gamma_S} \tag{4}$$

Solubility is a crucial factor determining the thermodynamic activity. Comparing two subsaturated vehicles containing the same concentration of an active ingredient, the thermodynamic activity of the active ingredient will be higher in the vehicle with the lower solubility. If the solubility of the active ingredient in the vehicle is known, the escaping tendency (thermodynamic activity) can be predicted from the ratio of concentration to solubility of the active ingredient in the vehicle and can be correlated to the flux. This correlation is only valid under the prerequisite that no interactions between vehicle and skin occur [8].

The solubility parameter, δ, is one approach to predict the solubility of the permeant in the vehicle as well as in the skin and can be used to optimize skin permeation. δ expresses the cohesive forces between like molecules, and the mutual solubility becomes greater the closer the δ values of the two molecules match (e.g. solute and solvent). The solubility parameter of porcine skin was predicted to be approximately 10 $(\text{cal cm}^{-3})^{1/2}$ [9]. According to the solubility theory, it was hypothesized that vehicles with a solubility parameter similar to the one of the skin enhances the flux of the permeant across the skin [10, 11]. On the other hand, a vehicle with a solubility parameter close to the one of the permeant may reduce the partitioning into the skin and therefore decrease the diffusion across the skin [12, 13]. However, using the solubility parameter to decide on a vehicle for an active ingredient can only be a first approach as exceptions exist [10] and the determination of solubility parameters for more complex vehicles will be complicated.

Supersaturation

In the previous paragraph, it was described that the thermodynamic activity of a permeant in saturated vehicles is at unity and therefore the flux of a permeant is the same from saturated vehicles. However, with supersaturated vehicles, the thermodynamic activity exceeds unity and the flux is increased with increasing degree of saturation [14–16]. As a consequence, supersaturation is an approach to optimize dermal and transdermal delivery without affecting the barrier properties of the skin [14].

Different techniques exist to obtain supersaturated vehicles and they include the method of mixed cosolvent systems [14, 17], the 'molecular form' technique similar to the cosolvent method [18], the evaporation of volatile vehicle

components [19–21] and the uptake of water from the skin into the formulation [22]. A disadvantage of supersaturated vehicles is that they are thermodynamically unstable, because the active ingredient tends to recrystallize and that would result in the loss of the permeation enhancement. Consequently, the storage of such systems for longer periods of time can be critical and it is advisable to form supersaturated systems *in situ* or prior to application to the skin. Moreover, the addition of anti-nucleating agents can be functional to inhibit recrystallization and stabilize the supersaturated vehicle. Polymers such as hydroxypropylmethyl cellulose [23], carboxymethyl cellulose [24] and polyvinyl pyrrolidone [16] are examples of anti-nucleating agents. Other studies have shown that supersaturation and therefore enhanced skin penetration could also be obtained by using the amorphous form of the active [25] or by the formation of inclusion complexes with hydroxypropyl-β-cyclodextrin [26], which increased the solubility of the active ingredient.

Penetration modifiers

Chemical penetration modifiers affect the skin barrier properties by diffusing into the stratum corneum and altering the solubility properties of the skin for the permeant and/or disrupting the lipid packing of the stratum corneum. The former results in the change of the partition coefficient K between the skin and vehicle, and the latter influences the diffusion process of the permeant through the skin and hence alters the diffusion coefficient D. Example of penetration modifiers which act *via* altering the solubility of the permeant in the skin are diethylene glycol monoethyl ether (Transcutol®: Gattefossé, Saint-Priest, France) and propylene glycol. Conversely, oleic acid and laurocapram (Azone®: Nelson Research Inc., Irvine, CA, USA) are known examples of penetration modifiers that migrate into intercellular lipid bilayers and alter the order of the lipid packing [27–29].

However, the modes of action of penetration modifiers are more complex and can include interaction with intracellular keratin, modification of the desmosomal connections between the corneocytes as well as altering the metabolic activity [30]. These various mechanisms (affecting stratum corneum lipids, proteins and/or partitioning behaviour) were outlined in the lipid-protein partitioning theory [31].

Here, the term penetration modifier was used instead of penetration enhancer. The reason is that a study presented by Michniak-Kohn at the AAPS meeting 2007 (San Diego, CA, U.S.A) showed that the effects of penetration enhancers as well as penetration retardants depend on the vehicle. Different vehicles (water, ethanol, propylene glycol and polyethylene glycol) were used to incorporate known penetration enhancers [Azone® and *S,S*-dimethyl-*N*-(4-bromobenzoyl) iminosulphurane] and penetration retardants [Azone® analogue N-0915 and *S,S*-dimethyl-*N*-(2-methoxycarbonylbenzenesulphonyl)iminosulphurane]. The enhancing and retardant effect of these compounds has been described in the literature [32, 33]. Depending on the vehicle, the penetration of a model compound was enhanced or retarded by the penetration enhancers and vice versa. Therefore, the term penetration modifier might be more appropriate as enhancement or retardation can occur because of the vehicle effect.

Water

Water and surfactants are common constituents in cosmetic and pharmaceutical formulations and they also play an important role in penetration modification. Water is well known for its skin penetration modification. The increase in water content in the stratum corneum (skin hydration) generally results in an increase in transdermal delivery of both hydrophilic and lipophilic permeants [34]. Pharmaceutical and cosmetic formulations may increase skin hydration by either occlusion (ointments, w/o emulsions) or by providing water from the vehicle to the stratum corneum (o/w emulsions). On the other hand, other vehicle constituents are hygroscopic (pure glycerol) and hence may decrease the water content of the skin [35] with the result of penetration retardation. However, one should be careful with a generalization as it has also been reported that occlusion does not necessarily enhance transdermal delivery of hydrophilic compounds [36] and the mechanisms of how water acts as penetration modifier are not fully understood yet [30].

Surfactants

Surfactants are used in formulations as emulsifiers, wetting agents and solubilizers and have the

potential to irritate the skin. The application of surfactants may lead to inflammation induced by the direct interaction of the surfactants with epidermal keratinocytes, which results in the release of cytokines [37]. Moreover, protein denaturation [38] and swelling of the stratum corneum may also result from the interaction of surfactants with keratin [39]. In addition to their irritant potential, surfactants may also deplete intercellular lipids from the stratum corneum resulting in the dehydration of the stratum corneum [40] and the different effects of surfactants on the skin (inflammation, direct cytotoxic effects, lipid extraction) can impair the skin barrier function [41].

The effect of surfactants on skin permeation depends on the type and the concentration of the surfactants, e.g. the permeation of diazepam across rat skin was more enhanced by ionic surfactants than by non-ionic surfactants and the enhancement ratio increased with an increasing surfactant concentration in the water-propylene glycol vehicle [42]. In contrast, the incorporation of non-ionic surfactants (polyoxyethylene nonylphenyl ether) in an aqueous solution reduced the skin permeation of benzocaine and the flux of benzocaine was inversely related to the surfactant concentration. This result was attributed to the solubilization of benzocaine in surfactant micelles as the flux was proportional to the concentration of free benzocaine (not solubilized in micelles) in the vehicle [43].

It was stated in an earlier study that surfactants exhibit a biphasic concentration effect; the percutaneous absorption is increased at low surfactant concentrations (below critical micelle concentration, CMC) whereas the absorption is decreased at higher concentrations (above CMC) [44]. This was attributed to two opposing effects of the surfactants on skin permeation. They can interact with the skin disrupting the skin barrier (predominantly at lower concentrations); however, surfactants can also interact with the permeant, e.g. solubilizing the permeant in micelles and therefore decreasing the thermodynamic activity in the vehicle [45].

This is in accordance with another study from Sarpotdar and Zatz [46] investigating the effect of vehicle composition on the CMC of two non-ionic surfactants (polysorbate 20 and polysorbate 60) and determining the influence of the concentration of surfactant monomers (or CMC) on the percutaneous absorption of lidocaine. They found that with a high concentration of propylene glycol in the vehicle, the CMC increased as well as the permeation of lidocaine. It is assumed that only the surfactant monomer is capable of penetrating the skin, thus changing the barrier resistance of the skin. Therefore, the higher concentration of surfactant monomers in the vehicle containing a higher concentration of propylene glycol (which increased the CMC) may explain the permeation enhancement of lidocaine. These examples showed that the effect of surfactants on permeation does not only depend on the type and concentration of the surfactant but also on the vehicle.

Cosmetic and pharmaceutical formulations

Introduction

Cosmetic and pharmaceutical formulations for topical application are multifaceted and can range from simple liquids, e.g. aqueous solutions and suspensions, to semisolids, e.g. gels, emulsions and ointments, to solid systems, e.g. powders and transdermal patches [47]. This review will focus on the topical application of emulsions and their effect on cutaneous and percutaneous absorption. Emulsions are widely used as cosmetic and pharmaceutical formulations because of their excellent solubilizing properties for lipophilic and hydrophilic active ingredients and good end-user acceptability because of the pleasant skin sensory characteristics [48].

Emulsions

Introduction

Depending on the consistency, emulsions can range from liquid formulations (lotions) to semisolid formulations (creams). They are heterogeneous systems comprising at least two immiscible liquid phases where one liquid is dispersed as globules (dispersed phase) in the other liquid (continuous phase). If the oil phase is dispersed in the water phase, it is termed an oil-in-water (o/w) emulsion. Conversely, a water-in-oil (w/o) emulsion consists of a water phase dispersed in an oily continuous phase. Which type of emulsion is formed depends mainly on the type of emulsifiers, which is characterized by the hydrophilic-lipophilic balance (HLB). The HLB is a scale from 1 to 20 and the higher the HLB, the more hydrophilic is the surface active agent. According to the Bancroft rule, the phase in which the emulsifier dissolves

better constitutes the continuous phase. However, a change in the Bancroft rule was suggested by Harusawa *et al.* [49] proposing that the phase in which the surfactant forms micelles constitutes the external phase independently of the solubility of the surfactant monomers in oil and aqueous phase.

In addition to simple emulsions, multiple emulsions can be formed. Multiple emulsions consist either of oil globules dispersed in water globules in an oily continuous phase (o/w/o) or of water globules dispersed in oil globules in a continuous water phase (w/o/w). The size of the globules of the dispersed phase in emulsions can range between 0.15 and 100 μm [50]. Moreover, emulsions in contrast to micro-emulsions, are thermodynamically unstable and necessitate the incorporation of emulsifiers for prolonged stabilization.

Emulsifiers

An emulsifying agent is a substance which stabilizes the emulsion. However, it should be kept in mind that no absolute classification exists as some constituents can comprise different functions [51], e.g. triethanolamine is used as emulsifier, thickener and emollient.

There are different types of emulsifying agents including surfactants, polymers, proteins (gelatin) and finely divided solid particles (bentonite). What is common for all of the different emulsifiers is that they prevent the coalescence of droplets of the dispersed phase. However, the method of stabilization varies, e.g. reduction of interfacial tension and therefore reduced tendency for coalescence (surfactant), steric hindrance by formation of a film at the oil-water interface (surfactant, polymer, fine particles), electrostatic repulsion in the presence of a surface charge (ionic surfactant) and/or the viscosity increase of the continuous phase (polymers, gel-forming surfactants) [52].

Instead of using a single emulsifying agent, it is common practice to use blends of emulsifiers in the formation of cosmetic and pharmaceutical emulsions. Most of these mixed emulsifiers consist of ionic or non-ionic surfactants and fatty amphiphiles, which can be added separately during the emulsification process or as a pre-manufactured blend (emulsifying wax) [51]. Some examples of emulsifier combinations are given in Table I.

In addition to promoting the stability of emulsions, mixed emulsifiers and emulsifying waxes have additional functions, e.g. enhancing emulsification during the manufacturing of emulsions by stabilizing the oil droplets and controlling the rheological properties of the formulation [51].

Table I Examples of emulsifier combinations

Emulsifier combination	Reference
Cetearyl glucoside/Cetearyl alcohol	[53, 54]
Sucrose cocoate/Sorbitan stearate	[54, 55]
Cetrimide/Cetostearyl alcohol	[56, 57]
Cetomacrogol/Cetostearyl alcohol	[58, 59]
Steareth-2/Steareth-21	[60]
Synperonic PE/F127 (block copolymer of ethylene oxide and propylene oxide)/Hypermer A60 (modified polyester)	[61, 62]
Isostearic acid/Triethanolamine	[63]
Cetylstearyl alcohol/Cetylstearyl alcohol sulphate (Emulsifying wax DAB 8)	[64]
Lecithin (mixture of phospholipids, e.g. phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol)	[65]
Cetostearyl alcohol/Sodium lauryl sulphate (Emulsifying Wax BP)	[66]
Cetostearyl alcohol/Polyoxyethylene alkyl ether	[67]
Polysorbate 60/Sorbitan monostearate	[68]

Amphiphilic association structures

Introduction

Because of the amphiphilic molecular structure of surfactants, they have the tendency to aggregate and to form amphiphilic association structures, e.g. micelles and lyotropic liquid crystals in the aqueous or oily phase [69]. These association structures can also be formed in emulsions in an excess of surfactant molecules when more surfactant is present as needed to build-up the monolayer at the water-oil interphase. Two different groups of amphiphilic association structures can be distinguished. Micelles and vesicles are formed in solutions, which appear isotropic and translucent; whereas lyotropic liquid crystals form a separate phase [50] and most of them exhibit optical anisotropy.

When considering the lamellar phase in emulsions, the liquid crystalline phase and the gel phase need to be distinguished. In the gel phase, also called the ordered state, the hydrocarbon chains are closely packed and exist in a crystalline form, whereas above the transition temperature the hydrocarbon chains melt and a disordered

liquid-like state is obtained. This disordered phase above the transition temperature is called the liquid crystalline phase [70].

Liquid crystals

Liquid crystals are intermediate substances between the liquid and the solid state, as they exhibit properties of both the states. For example, liquid crystals have the ability to flow (liquid state property), and their molecules show some positional and orientational order similar to the crystalline state and therefore exhibit optic anisotropy (solid state property). Liquid crystalline phases are also called mesophases and accordingly, molecules that are able to form liquid crystalline phases are termed mesogens. Depending on whether the phase transition into the liquid crystalline state is caused by temperature or by adding a solvent, thermotropic and lyotropic liquid crystals can be distinguished [71]. As solvents are present in emulsions, the formation of the latter is of importance in cosmetic and pharmaceutical emulsions. Therefore, only lyotropic liquid crystals are discussed further.

Lyotropic liquid crystals

Surfactants and polar lipids are amphiphilic compounds which form lyotropic liquid crystals in the presence of water [72]. The three typical lyotropic liquid crystals are lamellar (lamella unit), hexagonal (cylindrical unit) and cubic (spherical unit) and they are illustrated in Fig. 2.

According to thermodynamics, micelles are always favoured. However, the self-assembly of amphiphilic compounds to thermodynamically disfavoured structures such as the hexagonal and lamellar phase was explained by geometric limitations, which restrict the shape of micelles beyond a critical aggregation number [73]. The amphiphilic association structure was related to the geometry of the amphiphilic molecule and the critical packing parameter P was expressed according to Equation 5.

$$P = \frac{v}{l_c a} \tag{5}$$

where v is the volume of the hydrocarbon chain, a is the cross-sectional area of the head group and l_c is the critical length of the hydrocarbon chain. P-values below $^1/_3$ are associated with the formation of spheres such as micelles and the cubic phase. With P-values between $^1/_3$ and ½, packing into cylinders (hexagonal phase) and with P-values between ½ and 1, packing into bilayers (lamellar phase) are obtained. Therefore, with increasing concentration of amphiphilic molecules, transition occurs from cubic phase to hexagonal phase to lamellar phase (Fig. 2). Depending on the lipophilicity of the solvent and the HLB of the amphiphilic compound, hexagonal (more hydrophilic) or inverse hexagonal phase (more lipophilic) can occur [71]. The same applies to the spheres, e.g. micelles and inverse micelles.

Amphiphilic association structures in emulsions

The occurrence of a liquid crystal as third phase in the emulsion increases the viscosity and stability of the emulsion [72]. There are different modes of action. The liquid crystalline phase (e.g. several surfactant bilayers) can surround the dispersed droplets and act as a barrier against coalescence and/or can extent as a three-dimensional network into the continuous phase and reduce the mobility of the emulsion droplets [74]. Moreover, it was found that the adsorption of liquid crystals at the oil-water interface considerably reduced the van der Waals attraction forces that cause coalescence, therefore protecting emulsions against coalescence [75].

The liquid crystalline phases in emulsions are not only consisting of the surfactant molecules but

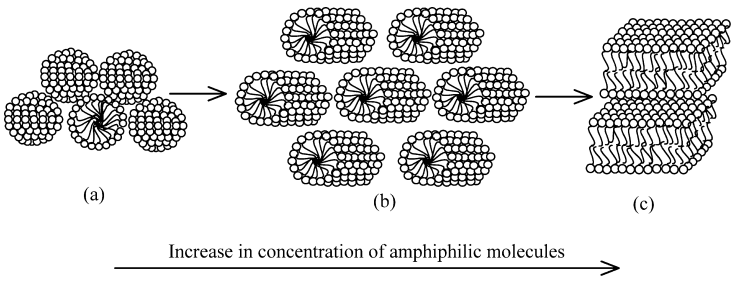

Figure 2 Schematic illustration of typical lyotropic liquid crystals: (a) cubic phase, (b) hexagonal phase and (c) lamellar phase.

can also incorporate water, oil as well as active ingredient [50]. The entrapment of water leads to the differentiation between interlamellarly fixed (bound) and bulk (free) water. The appearance of interlamellarly fixed water in liquid crystal containing emulsions may provide prolonged skin hydration with a possible enhancement of skin penetration [53, 76]. Santos *et al.* [77] stated that the transepidermal water loss was reduced by the application of o/w emulsions with liquid crystals compared with emulsions without liquid crystals.

On the other hand, the active ingredient can also interact with liquid crystals and can be incorporated in the polar or non-polar layers depending on the lipophilicity of the active ingredient. Another possibility than the incorporation of the active ingredient in the layers is the lateral inclusion between the surfactant molecules. The incorporation of an active ingredient into liquid crystals can increase its solubility [78] as well as affect the packing parameter of the surfactant molecules with the consequence of a phase transition [71]. Moreover, phase transition may result in a change of important properties of the vehicle, i.e. rheological behaviour, stability, solubility and release [79, 80].

Dermal and transdermal delivery from emulsions

Introduction

Many studies have been performed to investigate the effect of various formulations including emulsions on dermal and transdermal delivery. Emulsions have been compared with e.g. ointments, micro-emulsions, aqueous suspensions, liposome formulations and gels. From these studies, it is very difficult to draw general conclusions because the various emulsions differed in their composition as well as physicochemical properties. In addition, different active ingredients were included, different control formulations were used and the experimental setup varied (type of skin, amount of donor phase, different receptor phases, occluded vs. unoccluded conditions, etc.). All these factors will influence the skin penetration and permeation as well as the interpretation of the experimental data. Therefore, a more systematic approach is preferred to develop an understanding of how dermal and transdermal delivery is affected by emulsions. Other research groups have performed studies to investigate the effect of some emulsion properties (e.g. type of emulsion, emollient, emulsifier and lamellar liquid crystal structure, droplet size) on cutaneous and percutaneous absorption and this will be illustrated in more detail.

Type of emulsion

It was for a long time presumed that the penetration of an active ingredient is higher when it is dissolved in the continuous phase of the emulsion [81]. For example, the dermal delivery of the lipophilic sunscreen agent, ethylhexyl methoxycinnamate, was higher from the w/o emulsion than from the o/w emulsion most probably because of the occlusion effect of the oily vehicle [82]. But other studies have shown a discrepancy. It was observed by Dal Pozzo & Pastori [83] that the skin permeation of lipophilic parabens was enhanced from o/w emulsions compared with the w/o emulsion. This was explained by a higher affinity of the parabens for the vehicle than for the stratum corneum in case of the w/o emulsion. Another study performed by Wiechers [81] investigated the effect of formulations on the dermal and transdermal delivery of various active ingredients with different lipophilicities. Unexpectedly, the transdermal delivery of the various compounds was similar from the o/w and w/o emulsions, whereas the dermal delivery was higher from the emulsion where the active ingredient was incorporated in the dispersed phase. Hence, the problem is more complex and a systematic approach is advantageous.

Several studies using different active ingredients have been performed to compare different types of emulsions (o/w, w/o and w/o/w) with identical composition. This allowed the investigation of only the effect of the type of emulsion without the influence of different formulation ingredients. For glucose and lactic acid, which are examples of water-soluble compounds, it was found that the skin uptake of both compounds as well as the flux of glucose across skin was in the following order: o/w > w/o/w > w/o [62, 84]. The dosing condition did not change the effect of the type of emulsion on the transdermal delivery of glucose as the rank order of the emulsions was the same for unoccluded finite dose and occluded infinite dose [85]. The higher skin uptake as well as flux from the o/w emulsion compared with the w/o/w emulsion was explained by a higher concentration of

glucose and lactic acid in the external phase of the o/w emulsion. Moreover, an increase in the hydration level of the stratum corneum caused by the exposure to the external aqueous phase could have been another reason for enhanced skin penetration of the hydrophilic compounds. On the contrary, the lower skin penetration from the w/o emulsion compared with the o/w emulsion was explained by a change in the partition coefficient between the vehicle and stratum corneum.

In the case of metronidazole, a model compound with intermediate polarity, the rank order of the emulsions differed between finite and infinite dosing. After infinite dose application, the steady state flux from the o/w and w/o/w emulsion was similar but both were higher than from the w/o emulsion [86]. In contrast, after finite dose application, the percutaneous absorption was similar for the three emulsions and was related to the rate of water loss during application [61]. The differences in behaviour for metronidazole and glucose might be the rate and extent of partitioning of the compounds between the aqueous and oily phase of the emulsions.

A study from Lalor *et al.* [87] exhibited that the emulsifier (surfactant) and its distribution between oil and water phase played an important role in the thermodynamic activity of the permeants in the vehicle. For example, Tween 60, the surfactant used in the o/w emulsion, is mainly distributed into the aqueous phase of the emulsion, where it aggregated into micelles and solubilized the three test permeants, methyl, ethyl and butyl *p*-aminobenzoate, thereby reducing the thermodynamic activity. However, the solubility of the three compounds in the oil phase of the same o/w emulsion was similar to the solubility in the oil without surfactant indicating no solubilizing effect of the emulsifier in the oil phase of the o/w emulsion. Similar results were obtained with the w/o emulsion where the emulsifier Arlacel 83 was nearly entirely distributed into the oil phase of the emulsion and the aqueous phase was, in effect, free of the emulsifier. This yielded no solubility increase in the aqueous phase compared to water, but the solubility of each compound was increased in the oil phase because of the formation of inverse micelles. Furthermore, the study revealed that the thermodynamic activity of the compounds in the external phase of the emulsions was the driving force for permeation through the polydimethylsiloxane membrane as the permeability coefficients were similar for the intact emulsion and the corresponding isolated external phase.

Emollients

In cosmetics, an emollient is defined as any substance that can soften the skin and protect it from dryness, although it needs to be clarified here that dermatologists often call a formulation that softens the skin an emollient instead of a single ingredient with that capability. It is usually oil which prevents water loss from the skin. Wiechers *et al.* [88] introduced a method called 'Formulating for Efficacy', for selecting the appropriate emollients to optimize skin delivery from emulsions. The formulation should be designed in such a way that the active ingredient is incorporated at a concentration close to maximum solubility (maximum thermodynamic activity) but the solubility in the formulation should be much lower than the solubility in the stratum corneum to maximize the partition coefficient K between the stratum corneum and formulation.

Therefore, the polarity of the formulation has to be considered and the relative polarity index (RPI) was established, which was originally based on the octanol-water partition coefficient ($K_{o/w}$). The RPI compares the polarity of the active ingredient relative to the polarity of the stratum corneum and the polarity of the emollient. In case of an emulsion, the concept of the RPI is employed for the emollients in the phase in which the active ingredient is dissolved. The larger the polarity differences between formulation and active ingredient, the greater the driving force for partitioning into the skin; however, at the same time, the solubility of the active ingredient in the formulation decreases.

To find the appropriate emollients for the formulation, it is recommended as a first step to identify the primary emollient (in case of a lipophilic active) or water-miscible solvent (in case of a hydrophilic active) for which the RPI of the emollient-active ingredient combination is very small. This will ensure a good solubility of the active ingredient in the primary emollient. The second step consists of selecting the secondary emollient or solvent with a high RPI value so as to reduce and adjust the solubility of the formulation just above the preferred concentration of the active ingredient in the formulation. The reduction of the solubility will increase the driving force for

penetration into the skin. This approach was used to prepare a delivery-optimized emulsion for octadecenedioic acid, which was compared to a non-optimized emulsion. It was shown that dermal and transdermal delivery could be enhanced using the delivery-optimized formulation (Fig. 3).

Penetration modifiers in emulsions

This section of penetration modifiers in emulsions is discussed as a separate paragraph, although some known penetration modifiers, e.g. propylene glycol and isopropyl myristate, are commonly used as emollients and solvents in cosmetic emulsions. Therefore, this section is an addition to the previously discussed paragraph of the effect of emollients on dermal and transdermal delivery.

The incorporation of various polyalcohols (propylene glycol, glycerol and 1,2-butylene glycol) into emulsions revealed that they could enhance skin permeation of rutin and quercetin with the exception of 1,2-butylene glycol in the case of quercetin. Furthermore, the permeation enhancement was influenced by the concentration of propylene glycol in the emulsion [89].

Sah *et al.* [62] investigated the effect of the inclusion of 5% propylene glycol into an o/w emulsion on the skin penetration of lactic acid. They found that the enhancement ratio (dermal and transdermal delivery) caused by propylene glycol was much higher after the infinite dose application compared with the finite dose application where only the delivery of lactic acid into the epidermis was significantly enhanced. The higher efficiency of propylene glycol in the infinite dose situation was attributed to the higher amount of loading of the penetration modifier onto the skin.

Another study conducted by Ayub *et al.* [90] evaluated the skin penetration and permeation of fluconazole from emulsions containing different penetration modifiers (isopropyl myristate, propylene glycol and diethylene glycol monoethyl ether). Transdermal delivery across mouse skin was increased from emulsions containing isopropyl myristate as oil phase in comparison with paraffin oil. Moreover, propylene glycol could enhance permeation more than diethylene glycol monoethyl ether, independently of the oil phase (isopropyl myristate or paraffin oil). The skin penetration data, conversely, were different from the permeation data and the emulsion containing paraffin oil and propylene glycol exhibited the highest skin accumulation. However, no differences in skin penetration and permeation were found after application of the various emulsions onto pig skin emphasizing the influence of skin from different species on dermal and transdermal delivery.

These examples substantiate the fact that emulsion constituents such as emollients and solvents must be selected carefully for optimal efficiency of the formulation and that the incorporation of a penetration modifier not necessarily enhances skin penetration.

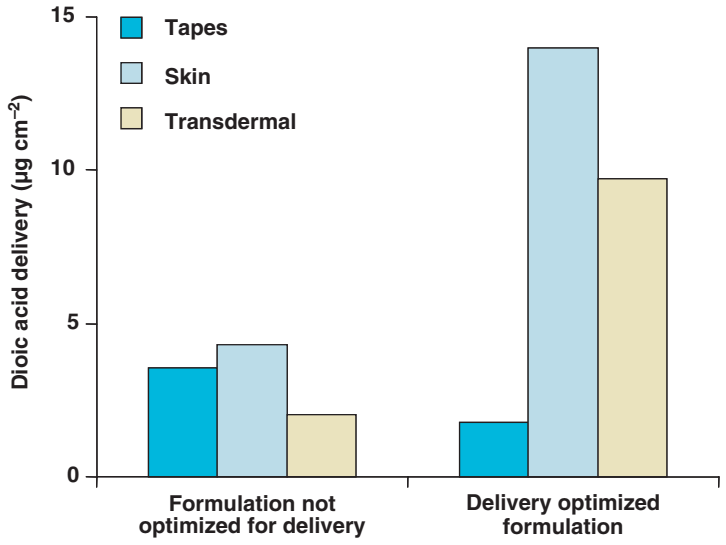

Figure 3 Skin delivery of octadecenedioic acid in a formulation not optimized for skin delivery and a delivery optimized formulation according to the Relative Polarity Index concept. Note that the latter delivers significantly more octadecenedioic acid to the skin. Modified from Ref. [88].

Emulsifier

It was already mentioned before that the emulsifier and its distribution between the oil and water phase in the emulsion is a key factor for the release of the active ingredients. Moreover, it has been shown that the effect of the surfactant on skin penetration depends on the formulation in which it is incorporated.

Few studies have focused on the effect of emulsifiers on skin penetration using the same oil and aqueous phase for the emulsion. Oborska *et al.* [89] incorporated three different polyoxyethylene cetostearyl ethers of various oxyethylene chain lengths (12, 20 and 30) into o/w emulsions and investigated the effect on the permeation of quercetin and rutin through a liposome model membrane. It was found that with increasing length of oxyethylene chain, the permeability coefficients of both permeants decreased, which was more pronounced for rutin.

Montenegro *et al.* [91] in another study focused on the effect of various silicone emulsifiers. The incorporation of these silicone emulsifiers in the same type of emulsion resulted in different skin permeation of ethylhexyl methoxycinnamate, whereas the percutaneous absorption of butylmethoxydibenzoylmethane was not significantly affected. Though the inclusion of different silicone emulsifiers altered the viscosity of the vehicles as well as the release of the active ingredients, these factors could not be related to the modification in permeation. It was assumed that other factors, e.g. change of the thermodynamic activity in the vehicle and modification of the interaction between permeant and emulsion components, could account for the different effects of the emulsifier on skin permeation.

Wiechers *et al.* [88] suggested that the emulsifier system might influence the distribution of the active ingredient within the skin. Emulsions with octadecenedioic acid were prepared according to the 'Formulating for Efficacy' method, which contained the same emollients but different emulsifiers (steareth-2/steareth-21 vs. sorbitan stearate/sucrose cocoate). Permeation studies resulted in similar total skin absorption (dermal + transdermal delivery) because the emollients were not changed; however, the distribution between dermal and transdermal delivery was changed. The emulsion with the emulsifier system sorbitan stearate/sucrose cocoate exhibited a higher transdermal but lower dermal delivery of octadecenedioic acid when compared with the emulsion with steareth-2/steareth-21.

Lamellar liquid crystal structure in emulsions

When investigating the effect of emulsifiers, it is also of relevance to consider the emulsion structure as amphiphilic molecules may form liquid crystalline phases in the emulsions.

A study to evaluate the influence of surfactant organization in emulsions on percutaneous absorption was carried out by Brinon *et al.* [60]. They prepared different o/w emulsions, which only varied in the emulsifier system and hence in structure. Permeation experiments revealed that the emulsions with lamellar liquid crystals in the aqueous phase (triethanolamine stearate, sorbitan stearate/sucrose cocoate and steareth-2/-21) obtained higher flux values of benzophenone-4 compared with the emulsions without lamellar liquid crystals (polysorbate 60, poloxamer 407, acrylates/C_{10-30} alkyl acrylate crosspolymer). Moreover, the highest flux was found for the emulsion with the anionic surfactant, triethanolamine stearate. It was hypothesized that modified interactions between surfactants and permeant might have influenced the interactions between surfactants and stratum corneum. Furthermore, the partitioning into the skin could have been affected. In cases of emulsions without liquid crystals, partitioning could occur between the aqueous phase and the stratum corneum whereas, in cases of emulsions possessing liquid crystals, a modified partitioning could take place between the liquid crystal phase and the stratum corneum.

Wiechers *et al.* [92] obtained similar results. In their study, a hydrophilic (propagermanium) and a lipophilic (octadecenedioic acid) model compound were included and it was found that the effect of the emulsion structure was different for these two active ingredients. The emulsion with liquid crystalline structure enhanced the transdermal delivery of octadecenedioic acid (Fig. 4), whereas in case of propagermanium, the dermal delivery was increased (Fig. 5). It was postulated that because of slower water evaporation from liquid crystals, the emulsion containing a liquid crystalline phase could maintain the hydrophilic active ingredient solubilized for a longer time in the vehicle, which could favour skin penetration.

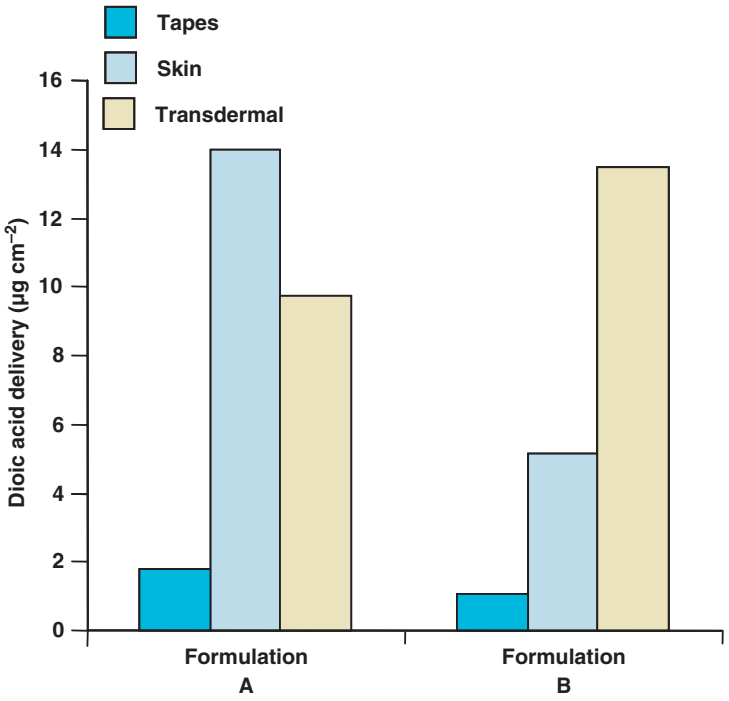

Figure 4 Skin delivery of the lipophilic active ingredient octadecenedioic acid from formulations A and B. Whereas the total quantity of octadecenedioic acid delivered is roughly the same from the two formulations, the site to which the active ingredient is delivered is significantly different. After 24 h, the liquid crystalline formulation B shows significantly more transdermal delivery than the non-liquid crystalline formulation A. Modified from Ref. [92].

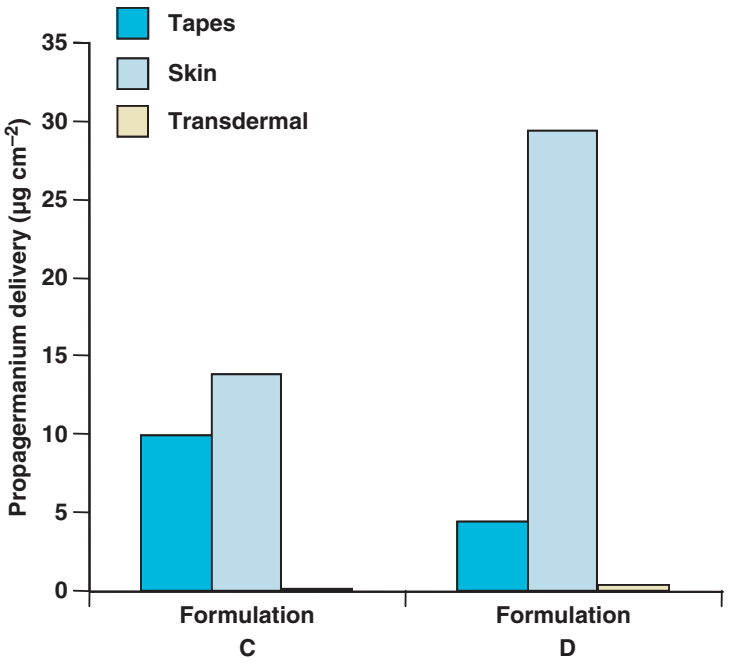

Figure 5 Skin delivery of the hydrophilic active ingredient propagermanium from formulations C and D. Not only has the total quantity of propagermanium delivered increased by more than 40% with the liquid crystalline formulation D, but after 24 h of penetration the propagermanium can also be found at deeper levels in the skin with only a marginal increase in transdermal delivery. Modified from Ref. [92].

In addition, the interaction between the liquid crystalline phase of the emulsion and the intercellular skin lipids yielding a more fluid-permeable lipid packing of the stratum corneum could be another explanation for the enhanced percutaneous absorption of octadecenedioic acid. The interaction between the liquid crystalline formulation and the intercellular skin lipids could have also increased the water content of the stratum corneum resulting in an increased solubility of propagermanium in the skin and therefore enhanced skin penetration.

As emulsions are multiphase systems, Swarbrick and Siverly [93, 94] used a more systematic approach to investigate the effect of liquid crystalline phases on percutaneous absorption. They constructed a phase diagram of polyoxyethylene(20)cetyl ether, dodecanol and water and decided on a two-phase region of an aqueous isotropic micellar solution and a liquid crystalline phase to prepare vehicles of these two phases in different ratios [93]. Subsequent permeation studies revealed that the percutaneous absorption of proxicromil was a function of the percentage of liquid crystalline phase in the vehicle. The proxicromil flux increased with increasing concentration of liquid crystalline phase in the vehicle up to 5–10%, and with a further increase in the percentage of liquid crystalline phase in the vehicle, the flux declined significantly [94].

Monophasic systems of lyotropic liquid crystals

Another approach to obtain more knowledge about the effect of surfactant organization on skin penetration is the investigation of monophasic systems of lyotropic liquid crystals because with the application of only a monophasic system, the situation is somewhat simplified.

Brinon *et al.* [95] studied three different liquid crystalline phases (lamellar, hexagonal and cubic) of polyoxyethylene(4) lauryl ether and polyoxyethylene(23) lauryl ether in water and their effect on transdermal delivery of a lipophilic (ethylhexyl methoxycinnamate) as well as a hydrophilic sunscreen agent (benzophenone-4). The flux of ethylhexyl methoxycinnamate across the skin was similar for all liquid crystalline phases. However, the percutaneous absorption of benzophenone-4 from various liquid crystalline phases differed and was higher from the lamellar phase compared with the hexagonal and cubic phases. Furthermore, the diffusion coefficients of both permeants in the skin as well as in the vehicles were determined and compared. It was concluded that the diffusion in the skin was the rate-limiting step for permeation across the skin. The permeation data could not be correlated to the transport kinetics within the vehicles, which were dependent on the structure of the liquid crystals and the physicochemical properties of the sunscreens.

In contrast, Gabboun *et al.* [96] came to a different conclusion after determining the skin permeation of salicylic acid, diclofenac acid, diclofenac diethylamine and diclofenac sodium from different liquid crystalline phases (lamellar and hexagonal) as well as isotropic solution of the surfactant polyoxyethylene (20) isohexadecyl ether. They assumed that the diffusion within the donor vehicle was the rate-determining step in skin permeation. The study revealed that with increasing concentration of the surfactant, the vehicle structure changed from isotropic to lamellar to hexagonal phases. During the first phase transition (isotropic to lamellar), the flux of all the permeants decreased except for the flux of diclofenac sodium, which was almost the same. The decrease in flux was explained by the additional constraints on the movement of the active molecules in the vehicle. After the phase transition from the lamellar phase to the hexagonal phase, the modification in percutaneous absorption was different for the various active ingredients and was attributed to the differences in physicochemical properties of the permeants and their interaction with the vehicle.

Incorporation of a penetration modifier, isopropyl myristate, into lamellar liquid crystals of lecithin and water resulted in phase transition and consequently in a change of the permeation behaviour of a model compound, fenoprofen acid [97]. The reversed hexagonal liquid crystal vehicles containing different amounts of isopropyl myristate exhibited minor differences in skin permeability; however, by changing the colloidal structure in the vehicle into a micellar solution, the permeation was significantly enhanced. It was postulated that the phase transition from a hexagonal phase into a micellar solution increased considerably the number of thermodynamically active modifier molecules as they are less bound in the micellar phase. Therefore, the effect of a penetration modifier is also dependent on its incorporation into the microstructure of the vehicle [97].

Another approach is to use a penetration modifier as the structure-forming constituent (mesogen). For example, liquid crystalline phases of the lipid monoolein have been demonstrated to be suitable topical delivery systems. The cubic and hexagonal phases of monoolein have been shown to enhance skin penetration of cyclosporine A, δ-aminolevulinic acid and vitamin K [98–100].

The study from Lopes *et al.* [99] was especially of interest; because it was shown that depending

on the concentration of cyclosporin A, different mesophases (reverse cubic and reverse hexagonal phases) were obtained, which resulted in different dermal and transdermal delivery. The cubic phase enhanced significantly the retention of the active ingredient in the upper layer of the skin (stratum corneum), whereas the hexagonal phase favoured the penetration into deeper layers of the skin (epidermis + dermis) as well as the percutaneous absorption.

A novel method was used by Namdeo and Jain [101] to formulate a liquid crystalline pharmacogel for enhanced transdermal delivery of propranolol hydrochloride (propranolol HCl). The key was that the lamellar liquid crystal was formed by the prodrugs, propranolol palmitate HCl and propranolol stearate HCl, which were comprised of the active ingredient conjugated with fatty acids. These prodrugs exposed amphiphilic properties and could self-assemble into liquid crystals after the addition of water and ethanol. The liquid crystalline pharmacogel enhanced percutaneous absorption considerably compared with the control vehicle, which was propranolol incorporated into carbopol gel. The partitioning was increased and the lag time reduced after application of the pharmacogel. Furthermore, the incorporation of the free fatty acids, palmitic acid or stearic acid (which could enhance permeation), into the control vehicle could not obtain an enhancement ratio close to the one obtained with the pharmacogel.

Droplet size

Some studies indicated that skin penetration is dependent on the droplet size in the emulsion as skin penetration was higher from emulsions with smaller droplets [102, 103]. However, a problem with most of these comparison studies is that the formulations also differ in their composition and therefore, it is difficult to subtract the pure effect of the droplet size. For example, percutaneous absorption from a micro-emulsion might not only be enhanced because of smaller droplet sizes but also because of a higher amount of surfactants and a larger concentration gradient provided by the higher solubilization capacity of the micro-emulsion [104].

A more systematic study has been performed by Izquierdo *et al.* [105] to investigate the effect of droplet size on dermal and transdermal delivery of tetracaine. Two sets of emulsions were incorporated into this study: one set of emulsions with identical composition but different droplet sizes and another set of emulsions with constant surfactant concentration in the aqueous phase but different overall surfactant concentration and droplet size. Interestingly, no correlation could be found between the droplet size and dermal as well as transdermal delivery.

The fate of emulsions after application onto the skin

For understanding the influence of emulsion on dermal and transdermal delivery, it is essential to consider the behaviour of the formulation after application. During the application of an emulsion onto the skin, volatile components evaporate and therefore, phase transitions, inversion, flocculation and coalescence might occur [106]. The change in composition is defined by the relative vapour pressure of the oil and water phase and can be studied with the aid of phase diagrams [50].

Phase changes and inversion during evaporation, in turn, affect the evaporation rate. For example, during evaporation of water from the o/w emulsion with hexadecane as oil phase, the evaporation rate changed abruptly at the inversion to a w/o emulsion. In contrast, the evaporation rate decreased gradually from the w/o emulsion [106]. Evaporation rate was also reduced when the bound water in the lamellar phase was removed [70] or a lamellar phase in the o/w emulsion appeared [63]. The results indicated a relation between the mesomorphic structure and the corresponding evaporation rate [63].

Moreover, it is of interest to determine the vehicle structure of the remaining formulation after completion of evaporation as the remaining film is important in the influence on skin penetration. Evaporation studies on emulsions of vegetable oil and a mixture of steareth-2/ceteareth-20 showed a change in the organization of the liquid crystalline phase during the evaporation of water. Moreover, lamellar phases were still observed after all the water was removed [107].

An interesting study by Friberg and Brin [65] demonstrated that during evaporation of water from an oil-in-water emulsion composed of 3% vitamin E acetate, 17% lecithin and 80% water, vitamin E acetate was gradually absorbed into the lamellar liquid crystalline phase of the emulsion.

The residual film left on the skin would be the lamellar liquid crystal containing the vitamin E acetate homogenously distributed with a thermodynamic activity similar to or higher than that of pure vitamin E acetate. Depending on the relative vapour pressure of the oil and water, the composition during and after evaporation varies. For example, oil containing inverse micelles of surfactant, aqueous micellar solution or lamellar liquid crystals could not be found during or after evaporation. These different compositions will interact differently with the stratum corneum with liquid crystals being less interactive with the lipid order of the stratum corneum than a micellar oil or water solution [50].

Concluding remarks

Emulsions have been shown to be appropriate delivery vehicles for active ingredients. However, the results varied for different emulsion systems and active ingredients. The extraordinary complexity of these vehicles involving different interactions between various emulsion constituents complicates the understanding of the effect of emulsions on dermal and transdermal delivery. Some studies with a more systematic approach provided little insight, for e.g., the effect of the type of emulsion, the effect of droplet size and the influence of the emollient on skin penetration. In addition, some studies showed that the type of emulsifier could also affect dermal and transdermal delivery which could be related to the modification of the vehicle structure.

Acknowledgements

The financial support of Uniqema is greatly appreciated.

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