

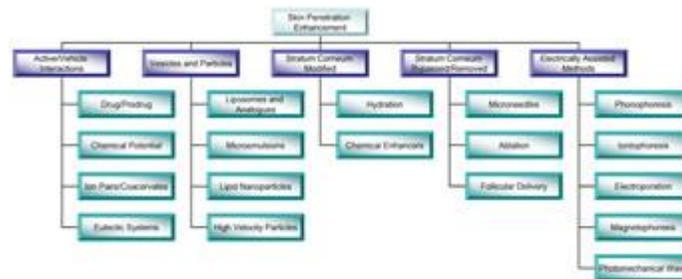
Strategies for Skin Penetration Enhancement

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1 Introduction

Dermatological and cosmetic preparations frequently contain active principles which can only act when they penetrate at least the outermost layer of the skin. However, the efficacy of topically applied actives is often suboptimal because the transport into the skin is slow due to the resistance of the outermost layer of the skin, the stratum corneum. Most small water-soluble non-electrolytes therefore diffuse into the systemic circulation a thousand times more rapidly when the horny layer is absent. Thus, a variety of means have been studied in attempts to overcome this barrier. Such strategies include physical, biochemical, and chemical methods ([Figure 1](#)).

Figure 1: Principal strategies for optimizing skin penetration



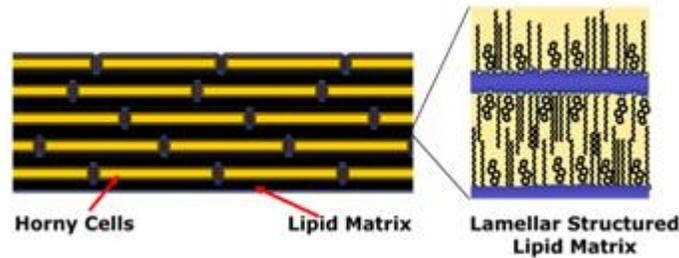
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2 Structure of the skin barrier

The skin is the largest human organ and consists of three functional layers: epidermis, dermis, and subcutis. It has a wide variety of functions. One major task of the skin is to protect the organism from water loss and mechanical, chemical, microbial, and physical influences. The protective properties are provided by the outermost layer of the skin, the epidermis. Although its thickness measures on average only 0.1 mm (from 0.02 mm on the face up to 5 mm on the soles of the feet) it is specially structured to fulfill this challenging task. Out of the five layers of the epidermis, it is mainly the uppermost layer (horny layer; stratum corneum) which forms the permeability barrier.

The stratum corneum consists of horny skin cells (corneocytes) which are connected via desmosomes (protein-rich appendages of the cell membrane). The corneocytes are embedded in a lipid matrix. Thus the structure of the stratum corneum can be roughly described by a “brick and mortar” model [1]. The corneocytes of hydrated keratin comprise the bricks and the epidermal lipids fill the space between the dead cells like mortar ([Figure 2](#)).

Figure 2: Schematic structure of the stratum corneum according to the brick and mortar model. The horny cells are embedded in a lamellar structured lipid matrix



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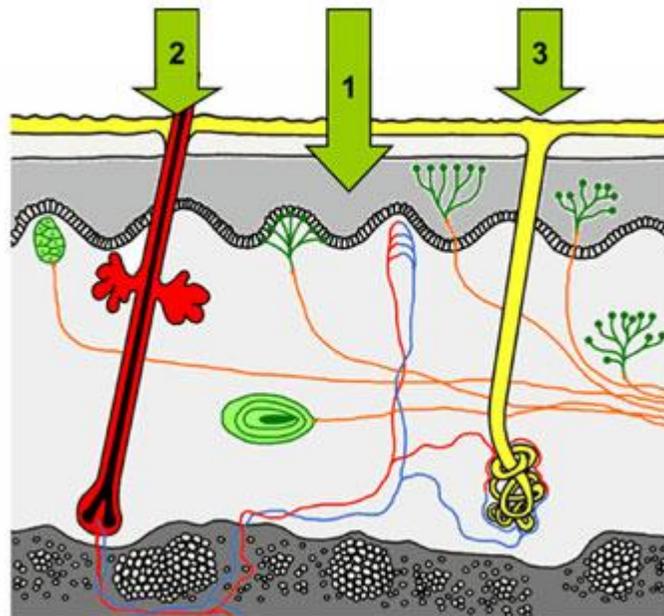
The epidermal lipids comprise 10 to 30 % of the total volume of the stratum corneum. The major components are: ceramides, fatty acids, cholesterol, and cholesterol esters [2]. The lipids are organized as multiple lipid bilayers which form regions of semi-crystalline gel and liquid crystals domains [3].

3 Routes of Penetration

[Figure 3](#) illustrates the possible pathways for a penetrant to cross the skin barrier. Accordingly, a molecule may use two diffusional routes to penetrate normal intact human skin: the appendageal route and the transepidermal route.

The appendageal route comprises transport via the sweat glands and the hair follicles with their associated sebaceous glands. These routes circumvent penetration through the stratum corneum and are therefore known as shunt routes. Although these routes offer high permeability, they are considered to be of minor importance because of their relatively small area, approximately 0.1% of the total skin area. The appendageal route seems to be most important for ions and large polar molecules which hardly permeate through the stratum corneum [4].

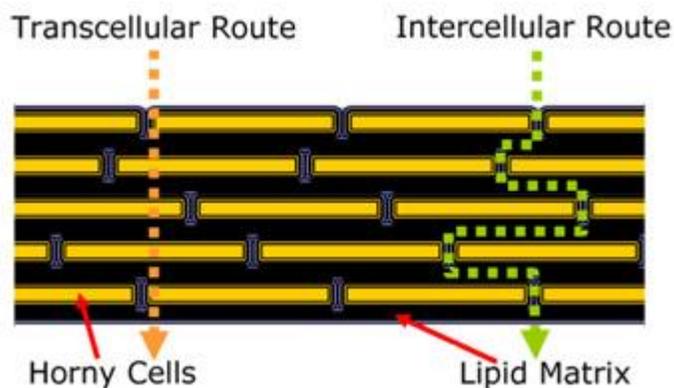
Figure 3: Possible pathways for a penetrant to cross the skin barrier. (1) across the intact horny layer, (2) through the hair follicles with the associated sebaceous glands, or (3) via the sweat glands



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Transepidermal transport means that molecules cross the intact horny layer. Two potential micro-routes of entry exist, the transcellular (or intracellular) and the intercellular pathways ([Figure 4](#)). The principal pathway taken by a penetrant is decided mainly by the partition coefficient ($\log K$). Hydrophilic drugs partition preferentially into the intracellular domains, whereas lipophilic permeants (octanol/water $\log K > 2$) traverse the stratum corneum via the intercellular route. Most molecules pass the stratum corneum by both routes. However, the tortuous intercellular pathway is widely considered to provide the principal route and major barrier to the permeation of most drugs [5].

Figure 4: Schematic diagram of the two microroutes of penetration.



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Considering that the skin is such a heterogeneous membrane, it is surprising that simple diffusion laws can be used to describe the transport through the skin.

For steady-state conditions this can be described with Fick's first law of diffusion:

$$J = \frac{KD}{h}(c_0 - c_i)$$

Where J is the flux per unit area, K is the stratum corneum-formulation partition coefficient of the active, and D is its diffusion coefficient in the stratum corneum of the thickness h; c_0 is the concentration of active substance applied to the skin surface, and c_i is its concentration inside the skin.

4 Penetration Enhancement

The perfect barrier properties of the epidermis restricts the transport through the skin to molecules with certain properties such as low molecular weight (< 500 Dalton), moderate lipophilicity (octanol–water partition coefficient between 10 and 1000), and modest melting point (< 200 °C) correlating with good solubility. Even when an active substance exhibits such properties, it is usually necessary to find additional means to increase its transport across the skin.

4.1 Supersaturation

Supersaturation is a means to increase skin penetration without alteration of stratum corneum structure [6]. The mechanism of enhancement is based simply on the increased thermodynamic activity of the drug. This increases the concentration gradient ($c_0 - c_i$) in the Fick's law and thus forces the active principle out of the formulation and into and across the stratum corneum. Several methods can be used to produce supersaturated systems:

- Heating and subsequent cooling
- Removal of a solvent
- Reaction of two or more solutes to produce a compound which is less soluble
- Addition of a substance to a solution that reduces the solubility of the solute

However, supersaturated systems are thermodynamically unstable and inherently tend to recrystallize. Therefore special efforts are necessary to transiently stabilize the supersaturated system for an appropriate period of time, e.g. addition of polymers as antinucleant in order to delay recrystallization.

4.2 Water as penetration enhancer

Hydration of the stratum corneum is one of the primary measures to increase the penetration of most active compounds. Water opens up the compact structure of the horny layer. The water content of the horny layer can be increased either by delivering water from the vehicle to the skin or by preventing water loss from the skin when partially occlusive formulations are applied to the skin.

[Table 1](#) summarizes general effects of carrier systems on the stratum corneum water content and on the penetration of active ingredients.

Table 1: Effects of carrier systems on the stratum corneum water content and on the penetration of active ingredients

Vehicle	Example/Constituents	Effect on skin hydration	Effect on skin permeability
Occlusive Dressings	Plastic film, unperforated waterproof patch	Prevent water loss; full hydration	Marked increase
Lipophilic vehicles	Paraffins, oils, fats, waxes, fatty acids, fatty alcohols, esters, silicones	Prevent water loss; may produce full hydration	Marked increase
Absorption bases	Unhydrous lipids plus w/o emulsifiers	Prevent water loss; marked hydration	Marked increase
Absorption bases	Unhydrous lipids plus o/w emulsifiers	Prevent water loss; marked hydration	Marked increase
W/O systems	W/O creams W/O emulsions	Retard water loss; raised hydration	Increase
O/W systems	O/W creams O/W emulsions	Can donate water; slight hydration increase	Slight increase
Humectants	Water-soluble vehicles; glycerol, glycols	Can withdraw water; decreased hydration	Possible decrease or act as chemical enhancer
Powder	Clays, shake lotions	Aid water evaporation; decreased excess hydration	Negligible effect on stratum corneum

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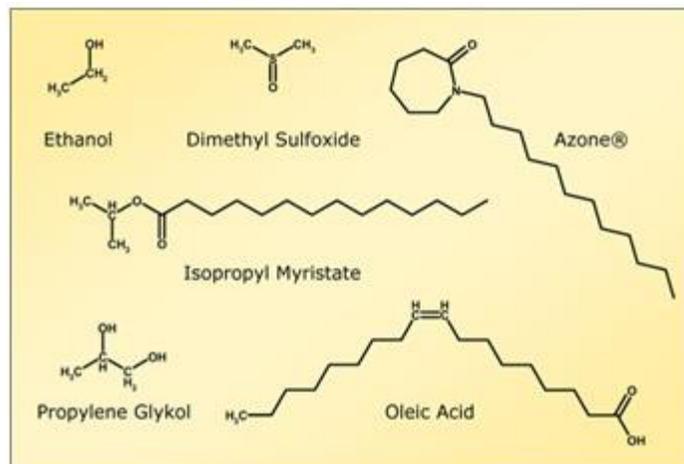
4.3 Chemical Enhancers

Several excipients are able to promote the transport of an active substance across the skin barrier by a variety of mechanisms. The most important are [7]:

- Extraction of lipids from the stratum corneum
- Alteration of the vehicle/skin partitioning coefficient
- Disruption of the lipid bilayer structure
- Displacement of bound water
- Loosening of horny cells
- Delamination of stratum corneum

Chemical enhancers can be categorized into different groups ([Figure 5](#)). Solvents like alcohols, alkylmethyl sulfoxides, and polyols mainly increase solubility and improve partitioning coefficient. Moreover, some solvents, e.g. Dimethylsulphat (DMSO), ethanol, may extract lipids, making the stratum corneum more permeable. Oleic acid, Azone® (epsilon-Laurocapram), and isopropyl myristate are typical examples of chemical enhancers which intercalate into the structured lipids of the horny layer where they disrupt the packing. This effect makes the regular structure more fluid and thus increases the diffusion coefficient of the permeant. Ionic surfactants, decylmethyl sulfoxide, DMSO, urea interact with the keratin structure in the corneocytes. This opens up the tight protein structure and leads to an increased diffusion coefficient D mainly for those substances which use the transcellular route.

Figure 5: Chemical structure of typical chemical penetration enhancers



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An unfortunate feature of many potent chemical enhancers is that they irritate due to their ability to interact effectively with the corneocytes and the intercellular lipid structure.

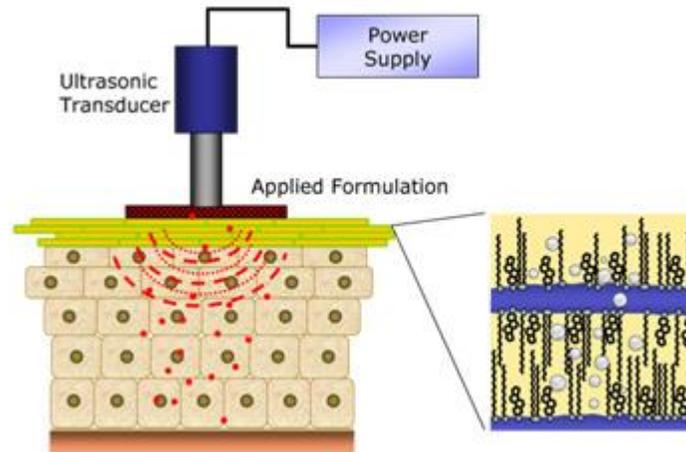
4.4 Physical Enhancement Techniques

Hydration of the horny layer and addition of chemical enhancers that temporarily alter the barrier properties can enhance the flux of active substances. However, all these principles have clear limitations concerning the delivery of sufficiently high amounts of ionic molecules, large molecular weight actives and substances with low potency. These limitations of chemical enhancement can be overcome to some extent by physical enhancement technologies [8].

4.4.1 Phonophoresis

Phonophoresis (or sonophoresis) uses ultrasound energy in order to enhance the skin penetration of active substances [8]. When skin is exposed to ultrasound, the waves propagate to a certain level and cause several effects that assist skin penetration. [Figure 6](#) depicts the processes that can contribute to phonophoresis. One of these effects is the formation and subsequent collapse of gas bubbles in a liquid called cavitation. The force of cavitation causes the formation of holes in the corneocytes, enlarging of intercellular spaces, and perturbation of stratum corneum lipids. Another effect is heating which is mainly due to the energy loss of the propagating ultrasound wave due to scattering and absorption effects. The resulting temperature elevation of the skin is typically in the range of several degrees centigrade. This temperature rise will increase the fluidity of the stratum corneum lipids as well directly increase the diffusivity of molecules through the skin barrier. These main effects can be assisted by acoustic microstreaming caused by the acoustic shear stress which is due to unequal distribution of pressure forces. In addition, ultrasound can push particles through by pressure increase in the skin, although only slightly.

Figure 6: Basic principle of phonophoresis. Ultrasound pulses are passed through the probe into the skin fluidizing the lipid bilayer by the formation of bubbles caused by cavitation.

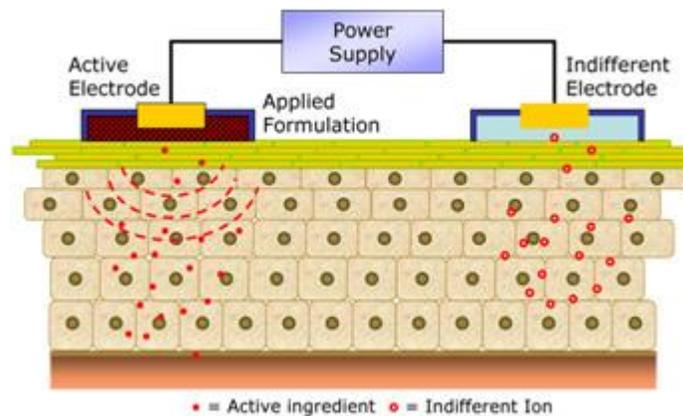


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4.4.2 Iontophoresis

The basic principle of iontophoresis is that a small electric current is applied to the skin. This provides the driving force to primarily enable penetration of charged molecules into the skin. A drug reservoir is placed on the skin under the active electrode with the same charge as the penetrant. An indifferent counter electrode is positioned elsewhere on the body. The active electrode effectively repels the active substance and forces it into the skin (Figure 7). This simple electrorepulsion is known as the main mechanism responsible for penetration enhancement by iontophoresis. The number of charged molecules which are moved across the barrier correlates directly to the applied current and thus can be controlled by the current density. Other factors include the possibility to increase the permeability of the skin barrier in the presence of a flow of electric current and electroosmosis. Contrary to electrorepulsion, electroosmosis can be used to transport uncharged and larger molecules. Electroosmosis results when an electric field is applied to a charged membrane such as the skin and causes a solvent flow across this membrane. This stream of solvent carries along with it dissolved molecules. It enhances the penetration of neutral and especially polar substances.

Figure 7: Basic principle of iontophoresis. A current passed between the active electrode and the indifferent electrode repelling drug away from the active electrode and into the skin.

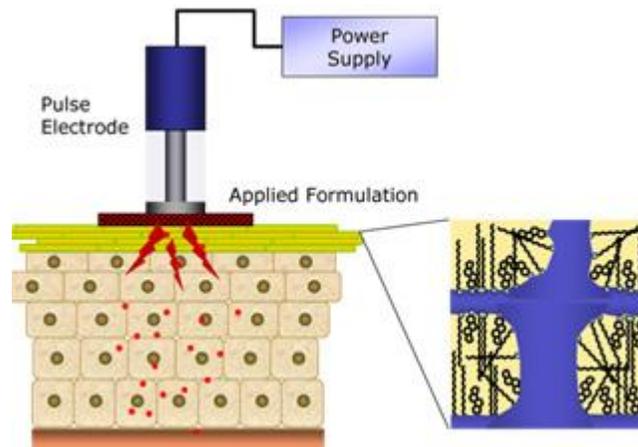


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4.4.3 Electroporation

Electroporation is also based on the application of a voltage to the skin [9]. In contrast to iontophoresis where a low voltage is applied, electroporation requires a large voltage treatment for a short period of 10 μ s to 100 ms. Electroporation produces transient hydrophilic pores (aqueous pathways) across the skin barrier ([Figure 8](#)). These pores allow the passage of macromolecules via a combination of diffusion, electrophoresis and electroosmosis.

Figure 8: Basic principle of electroporation. Short pulses of high voltage current are applied to the skin producing hydrophilic pores in the intercellular bilayers via momentary realignment of lipids.

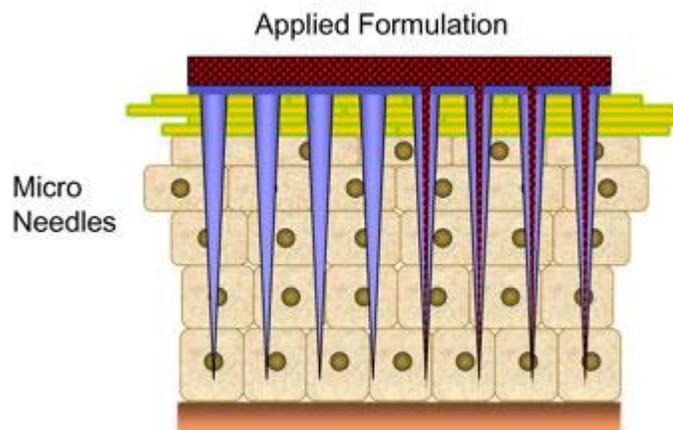


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4.4.4 Microneedles

In the last years, several attempts have been made to enhance the transport of substances across the skin barrier using minimally invasive techniques [10]. The proper function of an appropriate system requires that the thickness of the stratum corneum (10 to 20 μ m) has to be breached. More recent developments focus on the concept of microneedles. Microneedles are needles that are 10 to 200 μ m in height and 10 to 50 μ m in width ([Figure 9](#)). They are solid or hollow and are connected to a reservoir which contains the active principle.

Figure 9: Basic design of microneedle delivery devices. Needles of approximately with or without centre hollow channels are placed onto the skin surface so that they penetrate the stratum corneum and epidermis without reaching the nerve endings present in the upper dermis.



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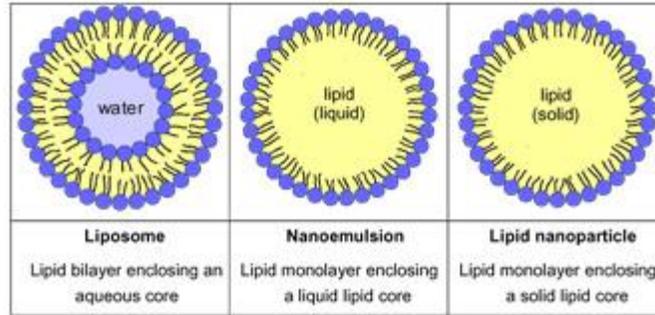
Microneedle arrays are applied to the skin surface so that they pierce the upper epidermis far enough to increase skin permeability and allow drug delivery, but too short to cause any pain to the receptors in the dermis. Therefore there is no limitation concerning polarity and molecular weight of the delivered molecules. The fabrication of such tiny structures became possible with the advent of micromachining technology which is an essential technology for the microelectronic industry.

It is not difficult to imagine that microneedle systems can be easily combined with microelectronic elements which can fully control the delivery rate. Furthermore, this type of system could be linked to a micro sensor system which measures the actual concentration of an active molecule which then triggers the release. It can be envisioned that such a “pharmacy on a chip” may be the future of drug delivery.

4.5 Formulation approaches

Penetration enhancement with special formulation approaches is mainly based on the usage of colloidal carriers. Submicron sized particles are intended to transport entrapped active molecules into the skin. Such carriers include liposomes, nanoemulsions, and solid-lipid nanoparticles ([Figure 10](#)) [11]. Most reports cite a localizing effect whereby the carriers accumulate in stratum corneum or other upper skin layers. Generally, these colloidal carriers are not expected to penetrate into viable skin. However, the effectiveness of these carriers is still under debate.

Figure 10: Structure of nanodispersed vehicle systems



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More recently a new type of liposomes called transferosomes has been introduced [12, 13]. Transferosomes consist of phospholipids, cholesterol and additional surfactant molecules such as sodium cholate. The inventors claim that transferosomes are ultradeformable and squeeze through pores less than one-tenth of their diameter. Thus 200 to 300 nm sized transferosomes are claimed to penetrate intact skin. Penetration of these colloidal particles works best under in vivo conditions and requires a hydration gradient from the skin surface towards the viable tissues.

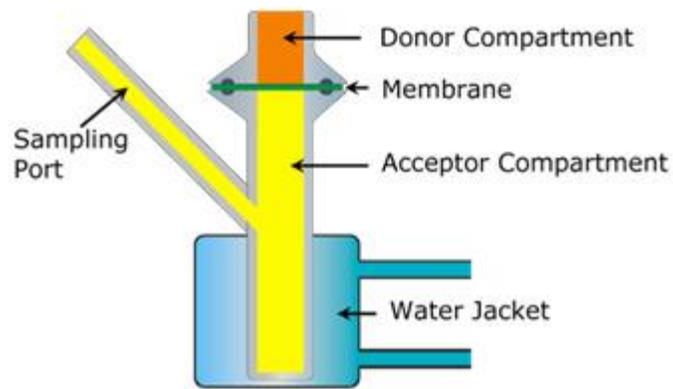
Another formulation approach aiming to enhance skin penetration is the preparation of microemulsions. Such systems consist of water, oil, and amphiphilic compounds (surfactant and co-surfactant) which yield a transparent, single optically isotropic, and thermodynamically stable liquid. Microemulsions can be either oil continuous, water continuous, or bi-continuous. The main difference between macroemulsions and microemulsions lies in the size of the particles of the dispersed phase: these are at least an order of magnitude smaller in the case of microemulsions (10 – 200 nm) than those of conventional emulsions (1 – 20 µm). Typical properties of microemulsions include optical transparency, thermodynamic stability, and solubility of both hydrophobic and hydrophilic components. Penetration enhancement from microemulsions is mainly due to an increase in drug concentration which provides a large concentration gradient from the vehicle to the skin. Furthermore it has been suggested that the surfactants and the oil from the microemulsion interact with the rigid lipid bilayer structure and acts as a chemical enhancer [14].

5 Measurement of skin penetration

The penetration behavior of an active ingredient can be evaluated in vitro, ex vivo, and in vivo.

Most of the data on percutaneous penetration have been gained with in vitro or ex vivo studies by experiments using a Franz-Diffusion chamber ([Figure 11](#)). The donor (formulation) is separated from the acceptor (aqueous buffer solution) by an appropriate barrier. For in vitro studies this barrier can consist of an artificial skin construct (ASC). ASC is cultivated from different cell types and comprises a dermis and an epidermis equivalent [15]. The advantage of ASC is that the properties are more consistent than in natural skin. However, the barrier properties of artificial skin are more closely to that of baby skin. This means it is less restrictive than the skin of adults.

Figure 11: The Franz Diffusion Chamber

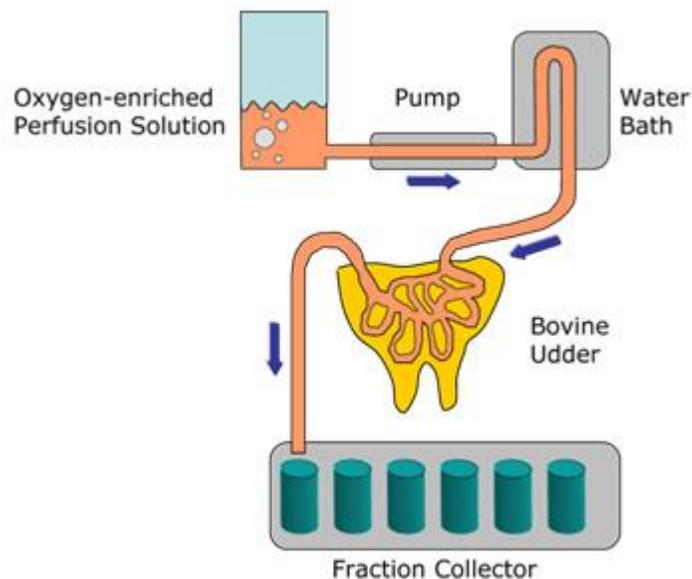


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Ex vivo studies use animal or human cadaver skin as the barrier. Due to market differences in the barrier properties animal skin is not always an accurate predictor for the situation in human. The cadaver skin can be used in a whole but more frequently excised skin is taken for the experiments. In this case the stratum corneum is separated from the rest of the skin by a special preparation technique.

Also very useful for ex vivo studies is the bovine udder skin (BUS) model which was developed 10 years ago [16]. The udder is from slaughter house material and can be maintained in culture at high vitality for 8 – 10 hours. A warmed, oxygen enriched Tyrode solution is pumped through the venous system of the udder. Test substances are applied topically and the perfusate can be analyzed for the penetrant (Figure 12). In addition, the BUS model allows to assess the distribution of a substance in the udder skin from either tape stripping or punched biopsies. Moreover, the BUS model can be used to measure irritation caused by a certain formulation.

Figure 12: Scheme of the experimental set up of the isolated perfused bovine udder skin model

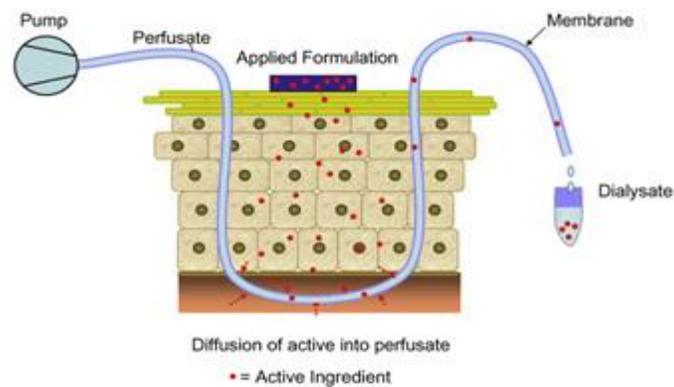


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For human in vivo penetration studies the active content in different layers of the stratum corneum can be determined after tape stripping or with the aid of some advanced spectroscopic methods, e.g. ATR (attenuated total reflection) spectroscopy.

A more advanced in vivo technique is microdialysis ([Figure 13](#)). For cutaneous microdialysis a small probe equipped with a semipermeable hollow fiber is inserted superficially in the dermis. The principle of microdialysis is that a physiological solution pumped through the probe is in equilibrium with the diffusible molecules in the surrounding tissue. Therefore the concentration of a solute in the dialysate is proportional to the concentration in the tissue and allows direct monitoring of the in vivo penetration behavior of a active ingredient. With such studies the influence of formulation variables as well as skin condition can be evaluated.

Figure 13: Schematic drawing of the principle of microdialysis



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6 Conclusions

The skin has an extremely good barrier function and to improve the penetration of active ingredients it is frequently necessary to employ enhancement strategies. The understanding of the barrier architecture and the mechanisms of penetration has improved and many of the different determinants are understood. This knowledge enables to develop both passive (chemical) and active (physical) approaches to facilitate the entry of active molecules into the skin. However, skin penetration enhancement could destroy the skin barrier formed by the lipid and protein and thus induce side effects. Such unwanted effects are in most cases directly correlated to an increase in transepidermal water loss (TEWL). Briefly, high TEWL means high skin penetration, and high skin penetration means greater skin barrier impairment. Future strategies should therefore aim to optimize the balance between the TEWL increase and effectiveness of the penetration enhancement.

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