How to Optimize Drug Penetration through the Skin

B. C. Lippold

Summary

The main problem of the therapy with drugs applied to the skin is the high diffusional resistance of the intact stratum corneum. To increase the flux of a given drug the selection of the vehicle is of utmost importance. Incorporation of the drug at its maximal thermodynamic activity leads to the maximal possible flux, as in vivo studies show with different drugs. The formation of supersaturated solutions and dissociation equilibria as well as drug-vehicle interactions and drug depletion also result from the vehicle selection and influence the flux. The resistance of the stratum corneum is not a constant parameter. It may be reduced by specific vehicle effects, penetration enhancers and hydration. Examples for the increase of drug fluxes are given.

1. Introduction

Drugs are applied to the skin for different reasons [1, 2]

- to *act locally* within the dermis (e. g. corticosteroids in dermatics)
- to penetrate into deeper tissues and to display a *regional action* (e. g. NSAID)
- to be absorbed and to *act systemically* (e. g. nitrates)

The main problem of the topical application of many drugs is the high diffusional resistance of the intact *stratum corneum*. Thus for optimal therapy with topically applied drugs it is usually necessary to ensure the maximal possible flux.

What are the variables to maximize the flux?

- properties of the drug
  In most cases we have to deal with a given drug. However, molecular variation or the prodrug concept may be helpful.
- type of the vehicle
  Liquids and ointments will be discussed here, the results can be transferred to other systems.
- state of the skin
  Within this article only the intact skin is considered. However, the resistance of the *stratum corneum* is not at all a constant factor.

These three parameters or variables, drug, vehicle and skin are related to each other according to the triangle of action developed by *Tronnier* [3]. We may add the maximum flux to the action to make clear its importance *(Fig. 1)*.

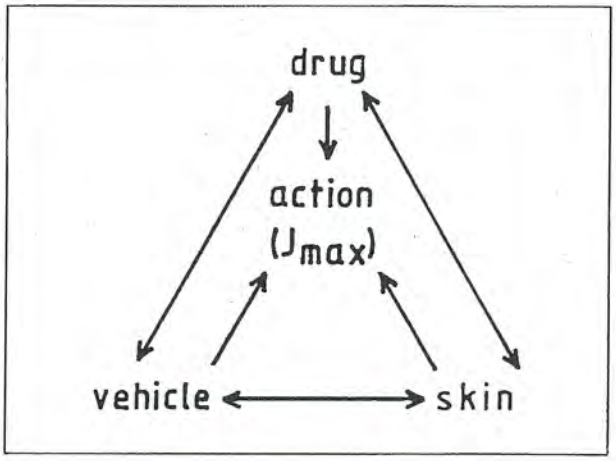

Figure 1

Triangle of action [3]

2. Flux optimization

2.1 Flux optimization by the vehicle

The vehicle may influence the flux of a drug through the *st. corneum* in different ways

- change of the thermodynamic activity of the drug
- extent of drug depletion from the ointment
- formation of supersaturated systems
- formation of a dissociation equilibrium in case of acid or basic drugs

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– drug-vehicle interaction.

All these different points will be illustrated with examples.

Maximal thermodynamic activity

We may look at the *stratum corneum* as a homogeneous partition membrane. Thus, according to the Fickian diffusion laws the penetration rate of a drug dm/dt from a solution-type ointment with concentration c_V increases with the decrease of the solvating capacity of the vehicle for the drug [1, 4, 5], expressed as reciprocal drug solubility $1/c_{sv}$ (Eq. 1–3).

$$dm/dt = (D \cdot PC \cdot A/l)\, c_V \quad \text{Eq. 1}$$

$$PC = c_{sB}/c_{sV} \quad \text{Eq. 2}$$

$$dm/dt = k \cdot c_V/c_{sV} \quad \text{Eq. 3}$$

(D = diffusion coefficient of the drug in the *st. corneum*, PC = partition coefficient of the drug between *st. corneum* and vehicle, A = area of application, l = thickness of the *st. corneum*, c_{sB} = solubility of the drug in the barrier *st. corneum)*

Thus, if we take one vehicle as standard, the steady state flux from different test vehicles (same concentration as the standard) should change in proportion to the ratios of the drug solubilities in the standard and test vehicles [7, 8]. Accordingly, we may define the ratio of the steady state fluxes of the test and standard as factor f (f >1 in case of increased flux of the test, f <1 with decreased flux, respectively). The factor f should be equal to the relative thermodynamic activity of the drug in the test vehicle related to a standard vehicle $\gamma_{T/ST}$, if other penetration enhancing effects are excluded.

$$f = \gamma_{T/ST} = c_{sV\text{-Standard}}/c_{sV\text{-Test}} \quad \text{Eq. 4}$$

In cases where the solubilities of the drug in the vehicles c_{sV} are very high we may better use other parameters to predict and optimize the flux. It is consistent to determine the partition coefficients of the drug between the vehicles and a second reference phase RP (aqueous in case of lipophilic vehicles) [6]. The resulting $PC_{V/RP}$-values again are related to $\gamma_{T/ST}$.

$$\gamma_{T/ST} = PC_{V\text{-Standard/RP}}/PC_{V\text{-Test/RP}} \quad \text{Eq. 5}$$

The relative thermodynamic activity of the drug in a test vehicle equals also the ratio of the head space concentrations of the drug above the test and standard vehicles (as far as detectable), both vehicles containing the same drug concentration [6].

As an expression of the penetration rate of methyl nicotinate the reciprocal value of the latency times until onset of an erythema may serve. *Figure 2* shows dose/response curves for silicone oil (SI) and caprylic/capric acid triglycerides (CCT) solution-type ointments. The horizontal distance gives again the factor f. In cases of dose/response curves this factor describes how much less or more of the drug has to be incorporated in a test vehicle to give the same response as the standard. We called it bioavailability factor [7], which equals f in Eq. 4. In *Figure 3* these f-values for seven different ointments are plotted vs the relative thermodynamic activities of the drug in the different vehicles $\gamma_{T/ST}$ [6]. There exists a clear correlation, the slope however should be 1, but is less.

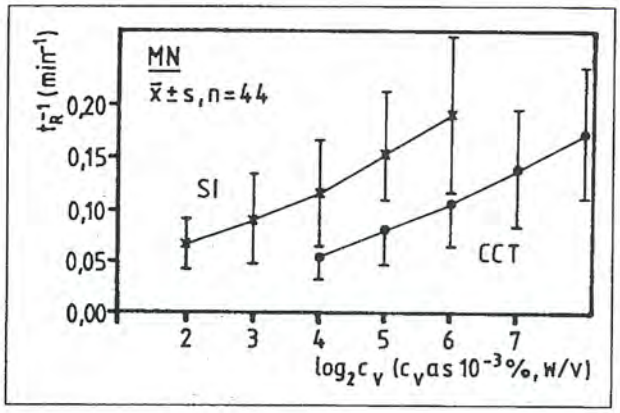

Figure 2

Concentration/response curves of methyl nicotinate dissolved in silicone oil (SI) and caprylic/capric acid triglycerides (CCT) for the reciprocal of the latency time until onset of an erythema t_R

$\bar{x} \pm s$, n = 44; methyl nicotinate concentration in 10^{-3}% (w/v) as log to the base of 2; liquids gelified with 10% polyethylen 10,000 or silicone 1,000,000

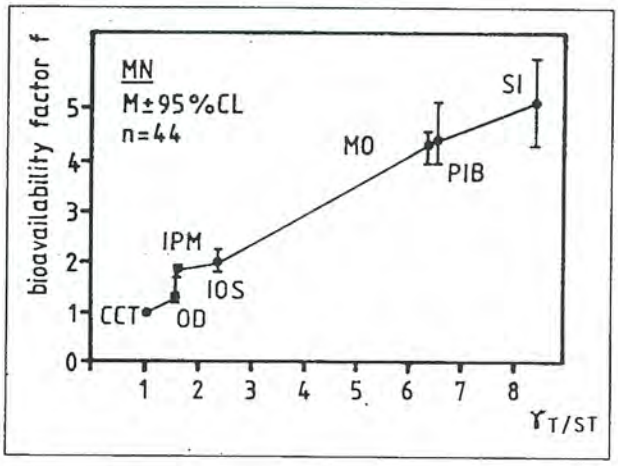

Figure 3

Bioavailability factor f for different methyl nicotinate ointments vs the respective relative thermodynamic activities $\gamma_{T/ST}$

CCT = standard; response is the reciprocal of the latency time until onset of an erythema after log-transformation; medians ± 95% confidence limits from n = 44 individual f-values; OD = octyl dodecanol, IOS = isooctyl stearate, PIB = polyisobutylene

It can be assumed that the depletion of the drug especially from vehicles with the drug in high relative thermodynamic activity like silicone oil, polyisobutylene and mineral oil (SI, PIB, MO) applied as thin films with very low drug concentration and thus fast reduction of the penetration rate is the main reason for the reduced biological activity. The fast concentration decrease in thin films of applied methyl nicotinate ointments is indicative for this hypothesis [6].

A similar example is given in *Figure 4* [8]. Betamethasone-17-benzoate was dissolved in different mixtures of mineral oil (MO) and caprylic/capric acid triglycerides (CCT) with different solution capacities. The blanching effects, characterized as scores and expressed as % of maximal possible score, were plotted vs the logarithmic concentration. Again the resulting factors f are plotted vs the relative thermodynamic activities $\gamma_{T/ST}$ *(Fig. 5)*. As with methyl nicotinate a remarkable correlation is obtained, nevertheless the slope is less than 1, a consequence of drug depletion. Using suspensions of betamethasone-17-benzoate in these vehicles (maximal thermodynamic activity), the maximal blanching effect was obtained in all cases, regardless of the composition of the vehicle and the amount of drug incorporated (*Fig. 6* and *7*). Thus, vehicles with low solubilities seem preferable because of low drug need. In a clinical trial neurodermitic patients were treated in a bilateral left to right comparison with two betamethasone-17-benzoate preparations of the

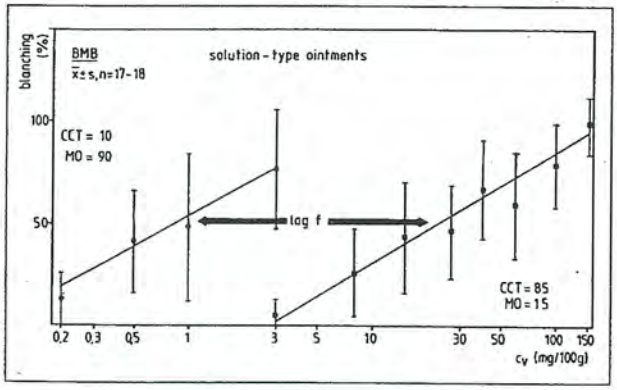

Figure 4

Concentration/response curves of betamethasone-17-benzoate dissolved in mixtures of mineral oil (MO) and caprylic/capric acid triglycerides (CCT) for the relative blanching effect (maximum effect = 100 %) $\bar{x} \pm s$, n = 17–18; 12 h occlusion; liquids gelified with approx. 10 % polyethylene 10,000

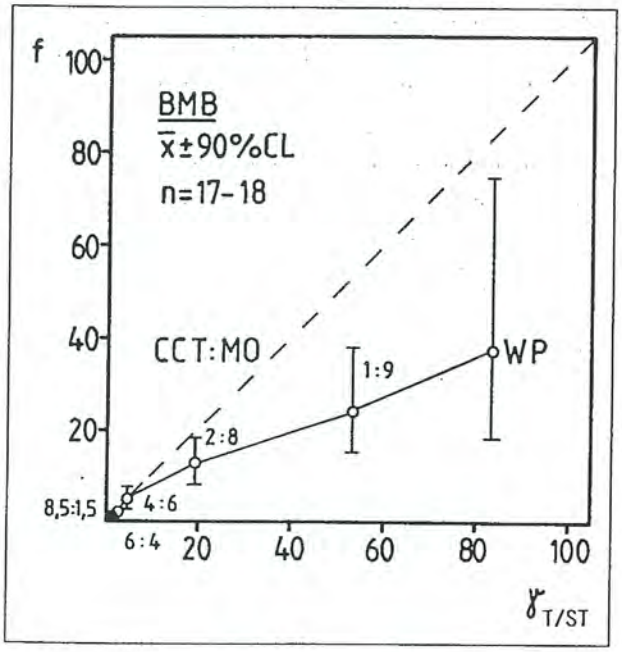

Figure 5

Bioavailability factor f for different betamethasone-17-benzoate ointments vs the respective relative thermodynamic activities $\gamma_{T/ST}$ standard: CCT/MO = 85/15, response is the blanching effect; $\bar{x} \pm 90$ % confidence limits from n = 17–18 individual f-values; WP = vehicle based on white petrolatum

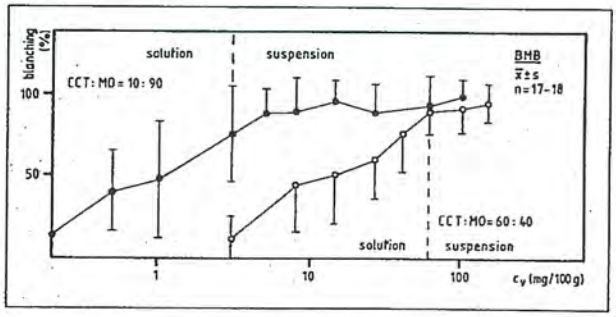

Figure 6

Concentration/response curves of betamethasone-17-benzoate dissolved or suspended in mixtures of mineral oil (MO) and caprylic/capric acid triglycerides (CCT) for the relative blanching effect CCT/MO = 60/40 and 10/90; details see Figure 5

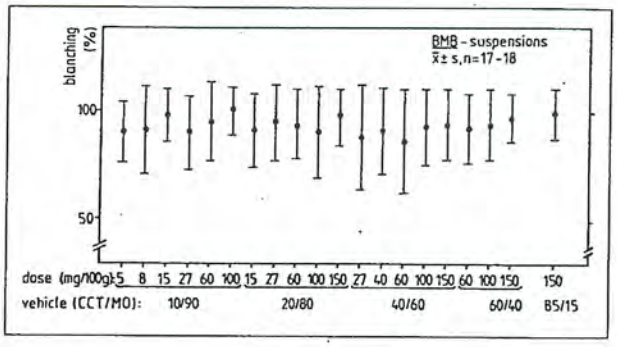

Figure 7

Relative blanching effect of all tested suspension-type ointments of betamethasone-17-benzoate in CCT/MO-mixtures; details see Figure 5

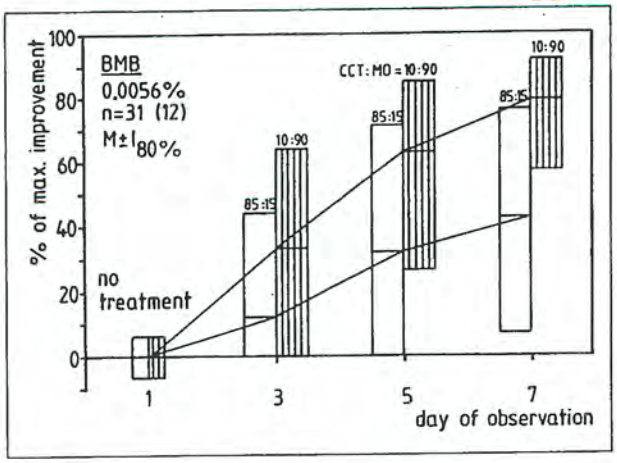

Figure 8

Development of the regression of cutaneous symptoms on bilateral body sides in relation to time, expressed in % of maximal possible healing; neurodermatitis patients, significant differences on day 3, 5 and 7, n = 30 and 12 respectively on the 7th day

same concentration, one a solution-type, the other a suspension-type ointment. The superiority of the suspension-type ointment is clearly demonstrated in *Figure 8* [9].

Thus, optimization means to use the drug at least in a saturated solution. The use of suspensions is recommended to avoid extensive concentration decrease of the dissolved drug and thus decrease of penetration rate during the application interval. However, it is important to notice the potential influence of drug dissolution rate and thus *particle size* on the penetration rate, especially with low dose preparations. One example with fluocinolone acetonide is given in the literature [10]. Another way to maintain a constant

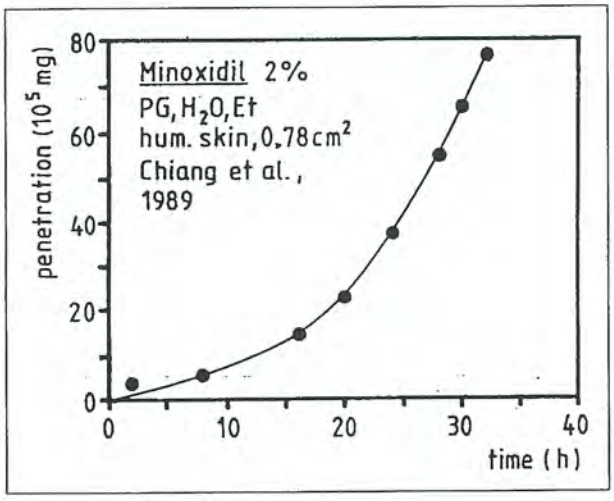

Figure 9

Permeation of minoxidil from 2% solution in propylene glycol, water, ethanol under evaporation, excised human skin, 0.78 cm² [11]

and high flux not using suspensions but nearly saturated solutions is the application of vehicles with high solution capacities. The respective ointments with high concentration of dissolved drug will not show marked *depletion effects* and do not have the problems of suspensions and saturated solutions: possibility of *precipitation, crystal growth* and *dissolution rate control.*

A special case optimizing the thermodynamic activity of the drug in its vehicle is the use of *supersaturated solutions* [11–13]. Supersaturation may be a consequence of the evaporation of volatile components of the vehicle after application like ethanol or the uptake of water by the vehicle as in case of microemulsions. An example of an evaporating system with the drug minoxidil shows *Figure 9* [11].

Simultaneous penetration of unionized and ionized species of a drug

It is well known that ionized drugs generally penetrate slower into the *st. corneum* than the unionized form. However it is advantageous to use suspensions of acid or basic drugs at pH-values where the undissociated species and the dissociated species are pre-

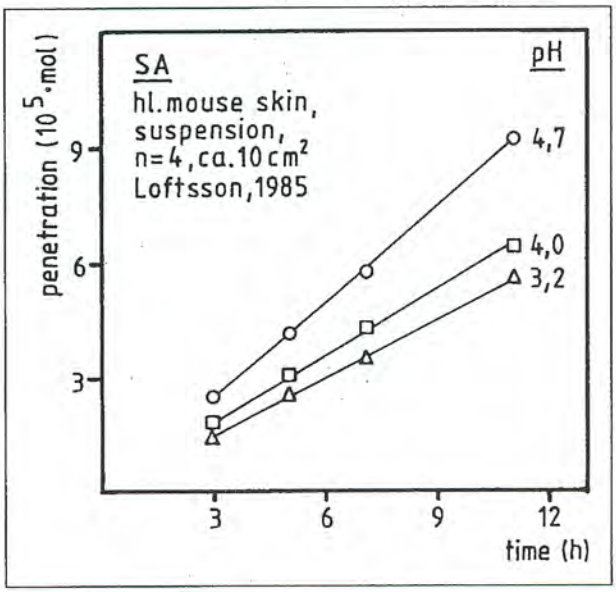

Figure 10

Permeation profiles of salicylic acid through hairless mouse skin from aqueous suspensions. Franz cell, about 10 cm² [9]

sent (preferably the pH_{max} for maximal solubility of both species) [14]. Doing so, the penetration rate will increase because both species will penetrate at the same time. An example with salicylic acid is shown in *Figure 10:* The penetration increases with increasing pH because salicylate is formed additionally in the suspension [15].

Prevention of drug/vehicle interaction

Depending on the use of special additives and excipients formulating an ointment strong binding of drug may occur reducing the drug amount available for penetration. As an example the blanching effect of betamethasone-17-benzoate in white petrolatum without and with 3% colloidal silicone dioxide is shown in *Figure 11* (blanching effect expressed as % of maximal response). With colloidal silicone dioxide about 50 times more betamethasone-17-benzoate has to be taken to get the same effect [8].

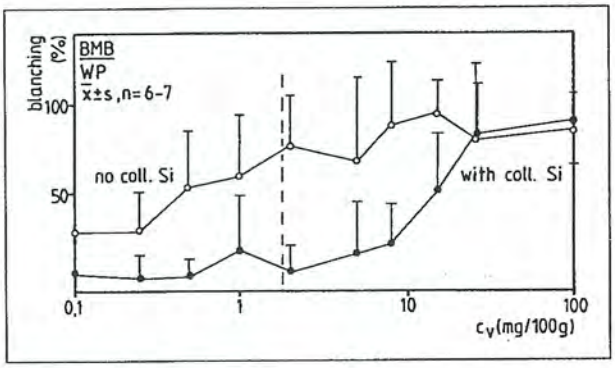

Figure 11

Concentration/response curves of betamethasone-17-benzoate dissolved in a vehicle based on white petrolatum without and with 3% colloidal silicone dioxide for the relative blanching effect; details see Figure 5

2.2 Flux optimization by reduction of the stratum corneum resistance

The *st. corneum* is not a diffusional barrier with constant properties. Its diffusional resistance may be reduced by

- specific vehicle effects
- penetration enhancers and
- hydration, occlusion

Specific vehicle effects were detected for example with isopropyl myristate (IPM) in case of methyl nicotinate [6] as model drug. Using IPM as vehicle, the concentration of methyl nicotinate at the same thermodynamic activity as the standard CCT can be lowered to about 80% to get the same latency time until onset of an erythema (non steady state conditions). This means an enhancement factor EF of nearly 1.2, EF describing the ratio of the factors f and $\gamma_{T/ST}$ *(Fig. 12)* [6, 14]. Studying the penetration rates at steady state with methyl nicotinate preparations from glass chambers applied to the upper arms IPM again was superior to CCT [16]: The penetration rate of methyl nicotinate from IPM was higher by the enhancement factor of approx. 2.0 applying the drug at the same thermodynamic activity. With dibutyl adipate (DBA) as vehicle the penetration rate increases by the enhancement factor EF of about 2.3 in comparison to CCT, again at the same thermodynamic activity *(Fig. 12)*. These effects may be called "specific vehicle effects".

DSC measurements with human *stratum corneum* pretreated with these vehicles showed the following concerning the enthalpies and temperatures of the phase transitions at about 70 and 85°C (n = 7–10, 10 h soaked with lipids) [16]:

Table 1

DSC-measurements with human st. corneum after pretreatment with different vehicles (data of ΔH and T for both transition peaks)

Vehicles	*ΔH*	*T*
CCT	*unchanged*	*unchanged*
IPM	*decrease*	*decrease (8–10 K)*
DBA	*decrease*	*unchanged*
CCT+PL	*decrease*	*unchanged*

Thus, CCT did not influence the lipid bilayers of the *st. corneum*, IPM may fluidise and dissolve the gel-like structure and DBA dissolves the bilayers without

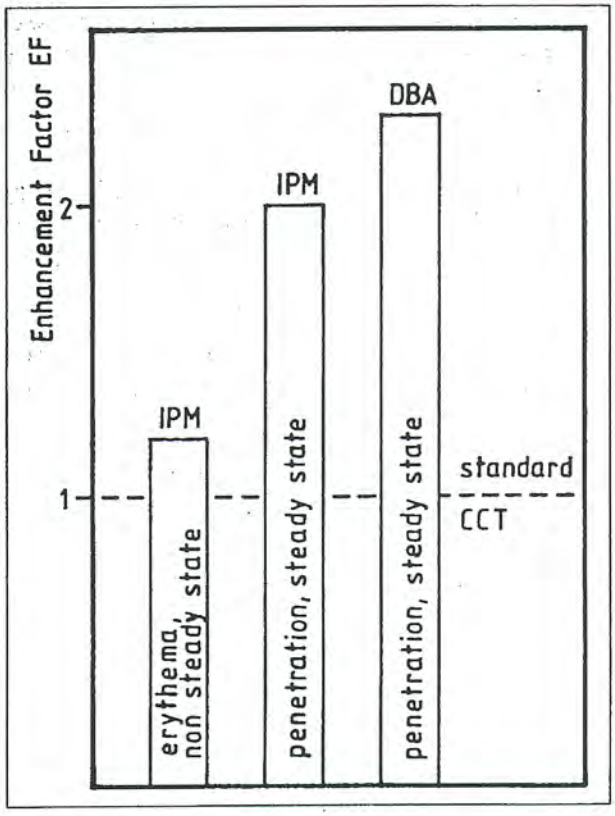

Figure 12

Enhancement factors EF of methylnicotinate in isopropyl myristate (IPM) and in dibutyl adipate (DBA) from latency time and penetration rates

fluidisation. In both cases a reduction of the diffusional resistance may be expected. Thus, specific vehicle effects are comparable to the action of *penetration enhancers*.

Indead, using phospholipids PL (80% phosphatidylcholin) dissolved in CCT at a concentration of 5% an increase of the penetration rate by the factor of approx. 2.5 was observed. The DSC-measurements showed dissolution of the lipid bilayers *(Table 1)* [16].

It is well known that *hydration* of the *stratum corneum* increases the penetration rates of drugs [17, 18]. Hydration may be achieved by applying water vapor impermeable films with all the problems of such an occlusion. However, what *occlusive properties* have vehicles, applied at a practice orientated thickness of 5.7 μm? Measuring the transepidermal water loss (TEWL) it is obvious that only vehicles with very low water vapor transmission WVT and very low solubility for water (<0.2 %) respectively will show occlusivity *(Fig. 13)*. Among the tested vehicles only mineral oil (MO) and white petrolatum (WP) are significant occlusive [19]. However, the effect on penetration is not yet investigated.

Another idea to increase the hydration of the *st. corneum* and thus the penetration rate of drugs is to use *moisturizers*. Moisturizers are frequently used in cosmetics and they improve the water uptake of the skin as can be shown by impedance measurements *in vivo* or directly by weight increase *in vitro*.

However *Figure 14* demonstrates the decrease of the bioavailability factor f below 1 for the latency time of benzyl nicotinate after treatment of the skin with these substances (10%, 20 min; benzyl nicotinate in white petrolatum) [20]. In this case the factor f equals the enhancement factor EF because the drug is applied at the same thermodynamic activity. For example, benzyl nicotinate has to be applied nearly in a 7 fold higher concentration after treatment of the skin with sodium lactate in comparison to the treatment with water to get the same latency time. Only with propylene glycol the penetration is faster (about 2.5 times). These effects can be seen also with other vehicles and with the drug betamethasone-17-benzoate. The reason for these unexpected effects are still not well understood. Possibly the moisturizers bind the water in the *st. corneum* very tightly, thus increasing the diffusional resistance [20].

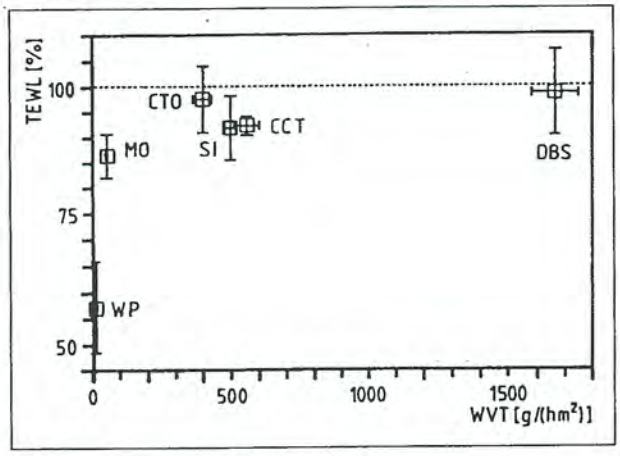

Figure 13

Reduction in transepidermal water loss (TEWL) of different vehicles (after application of 5.7 μm) vs water vapor transmission (WVT) of these lipids (10 μm); CTO = cetearylisoctanoate

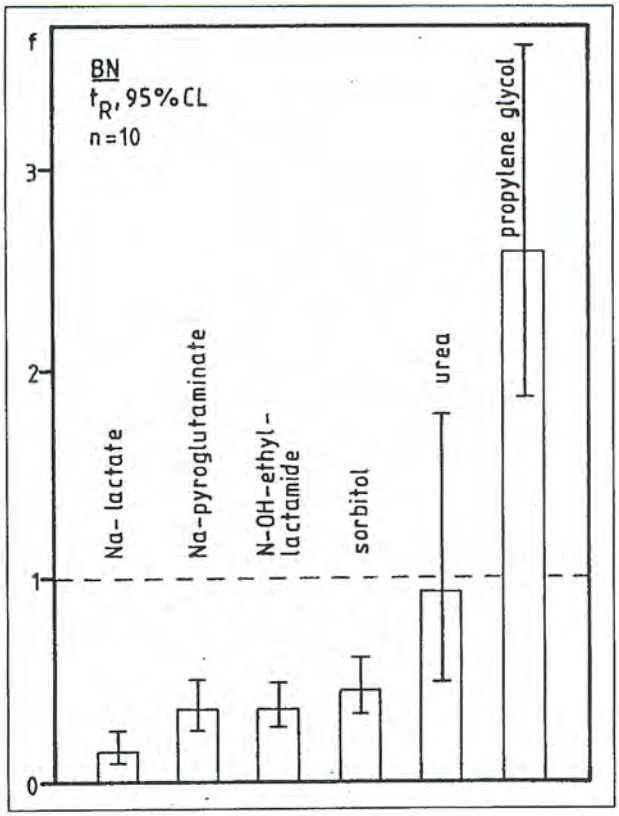

Figure 14

Influence of skin pretreatment with moisturizers and propylene glycol on the bioavailability factor f of benzyl nicotinate from white petrolatum, response is the reciprocal of the latency time until onset of an erythema, pretreatment with water (standard) = 1; $x \pm 95\%$ confidence limits, n = 10

3. Conclusion

Before all others there is one possibility to increase the flux of a drug through the skin: incorporation of the drug at its maximal thermodynamic activity, deduced from solubility or partition data. Concerning the vehicle supersaturated systems and the parallel diffusion of undissociated and dissociated species of a drug may further increase the penetra-

tion rate. Strong drug-vehicle interactions and fast drug depletion from the applied system have to be prevented. Selecting a vehicle attention should be given to possible reduction of the *stratum corneum* resistance by specific vehicle effects or penetration enhancers and to increased uptake of free water by the *st. corneum*.

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