DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(1), 25-49 (1989)

THE IN VITRO PENETRATION OF HYDROPHILIC AND LIPOPHILIC DRUGS FROM TRANSPARENT OIL-WATER GELS THROUGH EXCISED HUMAN EPIDERMIS: A COMPARATIVE STUDY WITH OTHER DERMATOLOGICAL VEHICLES

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ABSTRACT

Within the scope of evaluating transparent oil-water gels as dermatological vehicles, the percutaneous absorption of both a hydrophilic drug, tetracaine hydrochloride, and a lipophilic drug, benzyl nicotinate, is studied using excised human epidermis. From a comparison of the results with those of release experiments, it appears that in most cases the penetration of both drugs through the epidermis occurs at a much lower rate than their release from the vehicles. This indicates that the penetration process constitutes the rate limiting step.

For both drugs the penetration rate from the transparent oil-water gel through human epidermis is comparable to those from other commonly used vehicles. Due to the higher lipophilicity of benzyl

nicotinate, however, its penetration occurs faster than for tetracaine hydrochloride. As to the influence of drug concentration in the vehicle on penetration rate, the results do not provide a decisive answer.

INTRODUCTION

Transparent oil-water gels (TOW gels) is a term we propose[1] for describing semisolid vehicles that are mainly composed of hydrophilic surfactant(s), oil and water and whose main characteristics are clarity, homogeneity, optical isotropy, thermodynamical stability and the occurrence of resonance. On account of their cosmetic and usage characteristics, and because of some of their physico-chemical and technological features[1], such TOW gels can be considered potential dermatological vehicles. From our literature survey[1], however, it does not only appear that little attention has been given to the fundamental structural and physico-chemical characteristics of these gels, but also that investigations into the biopharmaceutical characteristics of these gels are extremely scarce. Only two such investigations have been reported[2,3].

Therefore the biopharmaceutical characteristics of a model TOW gel whose physico-chemical properties were investigated[4,5,6] are now studied with two model drugs: a hydrophilic drug, tetracaine hydrochloride (THCl) and a lipophilic drug, benzyl nicotinate (BN). The TOW gel is composed of two emulsifying agents, Cetiol(R) HE and Eumulgin(R) B3, of an oily liquid, isopropyl palmitate, and of water. In the first part of this study[5], the in vitro release of both drugs from the TOW gel was studied in comparison with other commonly used vehicles. Through this study an attempt was made to elucidate a first aspect in the complexity

of interdependent processes which occur in the functional unit drug-vehicle-skin and which control the penetration of a topically applied drug.

The second part of this biopharmaceutical investigation is reported here and aims at simulating the in vivo process of percutaneous absorption of both drugs from the various vehicles in an in vitro penetration experiment. Among the many methods described in the literature a diffusion cell method measuring drug diffusion from the vehicle through excised human epidermis into a liquid acceptor phase is chosen. This method allows investigating drug release from the vehicles and drug penetration through the skin under comparable conditions, so that conclusions as to the rate limiting step in the process of percutaneous absorption can also be drawn.

In further experiments the influence of drug concentration as well as drug lipophilicity on the penetration rate is also studied.

MATERIALS AND METHODS

Materials

For the preparation of the dermatological vehicles involved in the experiments the following materials are used as supplied without further purification: polyoxyethylated glycerol stearic acid ester (Cetiol(R) HE, Henkel, D-Düsseldorf), polyoxyethylated cetostearyl alcohol (Eumulgin(R) B3, Henkel, D-Düsseldorf), isopropyl palmitate (U.S.N.F. XVI), white soft paraffin (Ph. Belg. V), white wax (Ph. Belg. V), spermaceti (Ph. Belg. V), oleyl oleate (oleylium oleinicum DAB7, Cetiol(R), Henkel, D-Düsseldorf), sorbitan mono-oleate (Span 80(R), Atlas,

D-Essen), sorbitan sesquioleate (Arlacel® C, Atlas, D-Essen), cetostearyl alcohol (Ph. Belg. V), cetomacrogol 1000 (Texofor® AIP, ABM Chemicals, GB-Cheshire), decyl oleate (cera liquida DAB, Cetiol® V, Henkel, D-Düsseldorf), liquid paraffin (Ph. Belg. V), hard paraffin (Ph. Belg. V), cetrimide (cetyltrimethylammonium bromide Ph. Belg. V), methylcellulose (methylcellulose sol. 2% ca 400 mPas, P. Helv. 6), propylene glycol (Ph. Eur.), polyethylene glycol 4000 and 400 (Ph. Belg. V), cetyl alcohol (Ph. Belg. V), phenylmercuric nitrate (U.S.N.F. XVI) and demineralized water.

Tetracaine hydrochloride (USP XX) and benzyl nicotinate (Siegfried AG, CH-Zofingen) are chosen as hydrophilic and as lipophilic drug model respectively.

In addition to these materials sodium chloride (krist. reinst, Ph.Eur., Merck, D-Darmstadt) and sodium azide (reinst, Merck, D-Darmstadt) are used.

Composition of the Dermatological Vehicles

The composition of the vehicles investigated in the experiments is described in Table 1. All vehicles contain 1.0% w/w of THCl or BN, except the TOW gel where concentrations of 0.5 up to 2.5% w/w are used.

Preparation of the Dermatological Vehicles

TOW gel is prepared as described elsewhere[4]. VAS is used as supplied. WO, OWN, OWK, PEG, MC and MCP are prepared in a standardized way according to their usual manufacturing procedures.

For the incorporation of the drugs the following methods are applied. THCl is dissolved in and processed with the aqueous phase of the vehicles

TABLE 1

Composition of the Dermatological Vehicles under Investigation

Vehicle	Abbreviation	Type of vehicle	Composition	%w/w
1. Transparent oil-water gel	TOW gel	Transparent oil-water gel	Polyoxyethylated glycerol stearic acid ester Polyoxyethylated cetostearylalcohol Isopropyl palmitate Water + 0.002% phenylmercuric nitrate	18.0 15.0 8.0 59.0
2. White soft paraffin	VAS	Carbogel	White soft paraffin	100.0
3. Cremor sorbatis '67'	WO	W/O emulsion gel	White wax Spermaceti Oleyl oleate Sorbitan mono-oleate Sorbitan sesquioleate Water + 0.002% phenylmercuric nitrate	18.8 9.4 28.1 2.7 8.0 33.0
4. Cremor cetomacrogolis	OWN	O/W emulsoid gel with a nonionic emulsifier	Cetostearyl alcohol Cetomacrogol 1000 Decyl oleate Water + 0.002% phenylmercuric nitrate	12.0 3.0 20.0 65.0
5. Cetrimide cream	OWK	O/W emulsoid gel with a cationic emulsifier	Cetostearyl alcohol Liquid paraffin Hard paraffin Cetrimide Water + 0.002% phenylmercuric nitrate	13.5 10.0 25.0 1.5 50.0
6. Methylcellulose gel I	MC	Hydrogel	Methylcellulose 400 Water + 0.002% phenylmercuric nitrate	4.5 95.5
7. Methylcellulose gel II	MCP	Hydrogel	Methylcellulose 400 Propyleneglycol Water + 0.002% phenylmercuric nitrate	4.5 10.0 85.5
8. Polyethylene glycol gel	PEG	Hydrophilic gel	Polyethylene glycol 4000 Polyethylene glycol 400 Cetyl alcohol Water + 0.002% phenylmercuric nitrate	42.75 42.75 4.50 10.00

during their preparation. In order to obtain solution type vehicles in all cases, THCl is also incorporated in VAS as an aqueous solution. To this end the drug is dissolved in 5% v/w of water containing 0.002% phenylmercuric nitrate . The resulting preparation is a W/O emulsion. In most cases **BN** is added to and processed with the oily phase of the vehicles. Only for VAS, MC and MCP it is triturated with the vehicle using mortar and pestle. With MC and MCP an O/W emulsion is formed.

The preparations are maintained at room temperature for at least 48 hours prior to their examination.

The Diffusion Cell

A polycarbonate diffusion cell was constructed according to the model of Polano and Ponec[7] (see Fig. 1). The cell consists of three parts assembled by means of wings and nuts. The lower part of the cell contains a 0.78 cm^3 acceptor compartment (part A) provided with a sampling port. The second part, holding the donor compartment B, is closed by means of the top cover C. The effective diffusion area amounts to 0.78 cm^2.

Preparation of the Skin Membrane

Selected abdominal human cadaver skin obtained at autopsy is wrapped in aluminium foil and stored at -20°C until use. Immediately before use the subcutaneous fat is removed by careful cutting until the distinctive network pattern of the dermis can be seen. After heating the skin at 60°C for 15 min on wet cotton wool in a closed glass bowl, the epidermis is easily separated from the dermis[8].

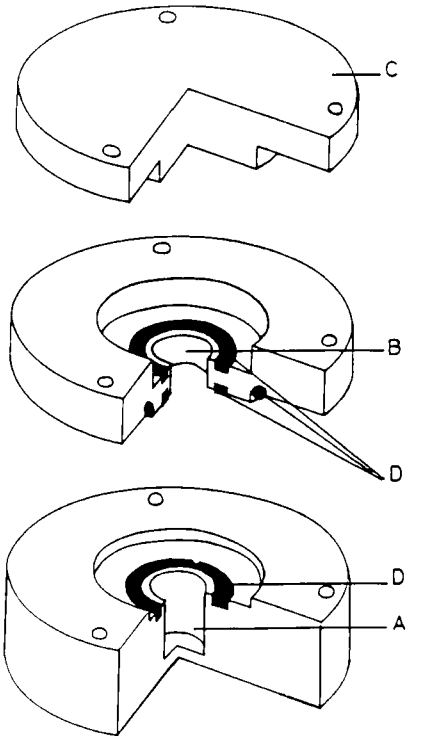

FIGURE 1

Diffusion cell used in the penetration experiment:
A. Acceptor compartment
B. Donor compartment
C. Top cover
D. Rubber sealing ring

Penetration Procedure

Samples of these epidermis sheets are mounted in the diffusion cells and the acceptor compartment is filled with 0.75 ml of physiological saline kept sterile by the addition of sodium azide. After checking the skin samples for leakage the vehicles are applied to the stratum corneum side of the epidermis using the infinite dose technique and the cells are

closed. Throughout the experiment the cells are kept at a temperature of 32°C and agitated. To account for the interindividual variation in skin permeability a reference vehicle - in most cases the TOW gel containing 1% of drug - is investigated simultaneously on each skin specimen. Blanks are also run under the same conditions.

At selected time intervals the acceptor fluid is completely removed through the sampling port and replaced with 0.75 ml of fresh acceptor fluid thus ensuring "sink" conditions. Penetration is measured by analysing the successive acceptor phase samples spectrophotometrically for their drug content at the wavelength of maximum absorption (311 nm for THCl and 263 nm for BN).

The penetration studies are conducted for a period of 7 days.

Treatment of Data

For the evaluation of the penetration of THCl and BN from the various vehicles through the epidermis, the cumulative amount of drug appearing in the acceptor compartment is plotted against time. After a certain lag time a linear relationship, indicating steady-state diffusion can be observed. During the whole steady-state period the penetration process follows zero-order kinetics. Consequently the data can be treated in accordance with Fick's first law by using equation 1, which is generally applied for defining penetration[9,7-13].

$$\frac{dQ}{dt} = K_p.S.C_v \qquad \text{(eq.1)}$$

where $\frac{dQ}{dt}$ = the amount of drug crossing the epidermis per unit of time ($mg.min^{-1}$)

K_p = the permeability constant ($cm.min^{-1}$)

S = effective diffusion area (cm^2)

C_v = initial drug concentration in the vehicle ($mg.cm^{-3}$)

Within the scope of the validity of this model, it is important to mention that during the whole penetration experiment

- sink conditions prevail,
- not more than 10% of the total amount of applied drug penetrates through the skin,
- the composition of the vehicle remains virtually constant.

In some cases, however, drug-vehicle interactions or vehicle-skin interactions can be considered responsible for deviations from the model.

From the slopes of the Q versus t curves, calculated by means of linear regression, the permeability constant, K_p , is computed. This K_p value provides a means of characterizing the penetration process of a given drug from a given vehicle through the skin.

RESULTS AND DISCUSSION

Influence of Drug Concentration on Tetracaine Hydrochloride Penetration through Isolated Epidermis

The penetration of THCl from the TOW gel through isolated epidermis is studied at drug concentrations of 0.5%, 1.0% and 2.0%. The results expressed as mean K_p values (eq.1) are listed in Table 2.

TABLE 2

Influence of Tetracaine Hydrochloride Concentration in the TOW Gel on its Penetration

Skin Sample	K_p (10^4 cm.min^{-1})		
	Tetracaine Hydrochloride Concentration (% w/w) in TOW Gel		
	0.5	1.0	2.0
A1	0.65	0.53	
B1	1.35	1.0	1.0
C1	2.2	1.1	0.4
D1	2.2	1.1	
E1		3.9	1.9
F1	2.5	2.4	0.72

The values are the means of at least three estimates per skin sample of the permeability constant Kp.

For the sake of clarity the individual estimates of Kp are omitted in this report. From these individual results, however, a rather important intraspecimen and interspecimen variability in skin permeability becomes apparent. In accordance with the findings of Ponec and Polano[14] and those of Barry[9], variations between skins of different individuals are far more important in our experiments than variations between samples of the same skin.

In spite of this variability in skin permeability, the data suggest that at drug concentrations of 0.5% and 1.0% the permeability constant is nearly identical. At a drug concentration of 2.0%, however,

a lower value for the permeability constant can be inferred for most skin samples. For TOW gels with a THCl concentration exceeding 1% w/w, the process of percutaneous absorption seems thus to be influenced by a concentration dependent phenomenon. On account of the complexity of the percutaneous absorption of a drug and the interacting effects drug, vehicle and skin exert on this process, the nature of this phenomenon is quite difficult to elucidate.

In every respect the thermodynamic activity of THCl in the TOW gel cannot be considered responsible for this concentration dependency in support of which two arguments can be adduced. When taking into account this potential factor in the calculation of K_p by replacing in eq. 1 C_o (the total initial THCl concentration in the gel) with C^o_f (the concentration of free drug in the aqueous phase of the gel)[5], K_p values for the various concentrations still differ markedly. Furthermore, as will be discussed later in this report, not the release of THCl from the TOW gel but its penetration through the skin constitutes the rate limiting step in these experiments.

Influence of the Vehicle on the Penetration of Tetracaine Hydrochloride through Isolated Epidermis

The penetration of THCl from the TOW gel through isolated human epidermis is compared with that from other vehicles commonly used.

For the TOW gel, the cetrimide cream (OWK), the cetomacrogol cream (OWN), the W/O emulsion gel (WO) and the polyethylene glycol gel (PEG) the mean permeability constants, K_p, are summarized in Table 3.

Because of a slight deviation from the model described by eq. 1, the penetration results obtained

TABLE 3

Influence of Vehicle on the Penetration of THCl through Human Epidermis

Skin Sample	K_p (10^6 cm.min^{-1}) for				
	TOW gel	OWK	OWN	WO	PEG
A2	5.2		3.3	7.4	
B2	0.62	1.37	0.88		
C2	0.96			2.44	
D2	2.91				0.56
E2	1.94	3.86			0.25

The values are the means of at least three estimates per skin sample of K_p.

for white soft paraffin (VAS), the methylcellulose gel without (MC) and with propylene glycol (MCP), and water are expressed as the total amount of drug penetrated over a 5000 min period (Table 4).

Taking the TOW gel as a reference, the penetration rates of THCl from the various vehicles can be subdivided in three categories. A first group is formed by the aqueous solution, OWK, and WO, from which the penetration of THCl through the epidermis proceeds at a higher rate than from the TOW gel. For the second group, i.e. OWN, MC, and MCP penetration rates similar to the one observed for the TOW gel are found. PEG and VAS, forming the third group, exhibit a markedly lower penetration rate.

TABLE 4

Influence of Vehicle on the Penetration of THC1 through Human Epidermis

Skin Sample	Amount (mg) of THC1 Penetrated over a 5000 min Period from					
	TOW gel	MC	MCP	VAS	Water	OWK
F2	0.078		0.088	0.026		
G2	0.078		0.273			
H2			0.082	0.018		0.089
I2		0.179	0.162			
J2		0.133	0.091			
K2		0.108	0.088			
L2	0.130				0.242	
M2	0.070				0.562	
N2	0.021				0.051	
O2	0.034				0.070	

The values are the means of at least three estimates per skin sample of the total amount of drug penetrated over a 5000 min period.

When comparing these results with those of the release experiments[b] as shown in table 5, no general direct correlation between the rank order of the vehicles found in the penetration experiments on the one side and the release experiments on the other hand can be observed. This means that in most cases the rate limiting step in the process of percutaneous absorption is not the release of THC1 from its vehicle, but its penetration through the skin.

TABLE 5

Comparison of the Influence of Vehicle on the Release and on the Skin Penetration of THC1

Release Experiments	Skin Penetration Experiments	
Ranking of the Vehicles in Decreasing Order of Release Rate	Classification of the Vehicles According to Drug Penetration Rate	
MC	Group I	OWK
MCP		WO
TOW gel		
OWN	Group II	TOW gel
PEG		OWN
OWK		MC
WO		MCP
VAS		
	Group III	PEG
		VAS

VAS, however, forms an exception. Compared with the other vehicles VAS exhibits both the slowest release and the slowest penetration of THC1; besides the penetration profile is found to be identical to the release pattern[b]. The Q versus $t^{1/2}$ linearity observed for the second phase of the penetration points to a matrix diffusion-controlled process instead of a membrane controlled diffusion[15,16,17]. This is further substantiated by a comparison of the averaged diffusion coefficient value calculated from the penetration data - i.e. $D = 3.6 \times 10^{-9}$ $cm^2.min^{-1}$ - with the value of the diffusion coefficient derived

from the release data[5] - i.e. D = 4.6 x 10^{-7} $cm^2.min^{-1}$ presuming full contact between the vehicle and the membrane. For VAS the release of THCl from its vehicle must thus be considered the rate limiting step in percutaneous absorption.

When incorporated in a **PEG** gel the penetration of THCl also proceeds at a rather low rate. Drug release from the vehicle is, however, not rate limiting. For other drugs PEG was also found to be an inferior vehicle where percutaneous absorption is concerned[18,19]. PEG gels being strongly hydrophilic and hygroscopic vehicles, an osmotic effect[19] might be responsible for a decreased influx of drug in the skin[20].

For **MC** and **MCP** the nonlinear pattern of drug penetration must be attributed to vehicle-skin interactions. On account of the absence of changes in the penetration flux observed for most other vehicles during the whole steady state period, epidermal deterioration can be excluded[21].

The observed differences in the THCl penetration rates from the various vehicles (see Tables 3 and 4) are the result of multiple interactions occurring in the functional drug-vehicle-skin unit. An elucidation of the reported data therefore is very complex and beyond the scope of this work.

Influence of Benzyl Nicotinate Concentration in the TOW Gel on its Penetration through Isolated Epidermis

The penetration of BN from the TOW gel through human epidermis is studied for different BN concentrations. From the results (see Table 6) it appears that the BN flux through the epidermis is proportional to drug concentration within the concentration limits under investigation.

TABLE 6

Influence of Benzyl Nicotinate Concentration in the TOW Gel on its Penetration through Human Epidermis

Skin Sample	K_p (10^6 cm.min^{-1})			
	Benzyl Nicotinate Concentration (% w/w) in TOW Gel			
	0.5	1.0	2.0	2.5
A3	2.1	2.2	2.4	1.7
B3		5.5	4.9	
C3	5.7	5.0		
D3		6.0		5.8
E3		8.4	6.9	7.0

The values are the means of at least three estimates per skin sample of the permeability constant K_p.

Influence of the Vehicle on the Penetration of Benzyl Nicotinate through Isolated Epidermis

Various vehicles containing 1% of BN are studied for their influence on drug penetration through isolated epidermis. For the TOW gel, OWK, OWN, WO, PEG, and VAS the mean permeability constants, K_p, are listed in Table 7.

For MC and MCP showing a slight deviation from the model described by eq. 1, the penetration results are represented in Table 8 as the averaged total amount of drug penetrated over a 5000 min period. As discussed above for THCl, the good adherence to eq. 1 observed for all other vehicles indicates the absence of epidermal deterioration.

TABLE 7

Influence of Vehicle on the Penetration of BN through Human Epidermis

Skin Sample	K_p (10^{-6} cm.min^{-1}) for					
	TOW gel	OWK	OWN	WO	PEG	VAS
A4	2.4		2.3	2.8	0.8	
B4	7.3					5.3
C4	7.0	6.8	3.0			
D4	2.6			2.5	0.8	3.0
E4	5.1	5.5	5.3			
F4	5.7			5.1		
G4	4.4				1.7	
H4	4.9	5.6				

The values are the means of at least three estimates per skin sample of K_p.

The individual results again clearly show the interindividual and intraindividual differences in skin permeability. For the results concerning the TOW gel the intraspecimen variability calculated as percent standard deviation ranges from 2 to 26%, the interspecimen variability amounts to 33%.

Notwithstanding this intraindividual variation an influence of the vehicle on the penetration of BN through the epidermis can be inferred. This finding indicates that in our study the stratum corneum is no absolute barrier which limits the total amount of drug penetrating per unit of time, as was nevertheless assumed by certain authors [22].

TABLE 8

Influence of Vehicle on the Penetration of BN through Human Epidermis

Skin Sample	Amount (mg) of BN Penetrated over a 5000 min Period from		
	TOW gel	MC	MCP
B4	0.34	1.08	
I4	0.16	0.96	
J4	0.12	1.01	0.92
K4	0.24	1.22	0.81
L4		1.03	0.88

The values are the means of at least three estimates per skin sample of the total amount of drug penetrated over a 5000 min period.

With regard to the penetration rate of BN through the epidermis the vehicles can be subdivided in three categories. Compared to the TOW gel, the hydrogels MC and MCP show higher penetration rates. For the W/O emulsion gel, WO, the O/W emulsoid gels, OWN and OWK, and the carbogel, VAS, permeability constants nearly similar to those calculated for the TOW gel are found. For PEG the permeability constant is markedly lower.

A comparison of these penetration data with the results of the release experiments[b] is shown in table 9 and gives almost the same conclusion as for THC1: whereas in the case of THC1 VAS was an exception, the release of BN from all vehicles proceeds at such a high rate that the subsequent penetration of the drug through the stratum corneum is not hindered.

TABLE 9

Comparison of the Influence of Vehicle on the Release and on the Skin Penetration of BN

Release Experiments	Skin Penetration Experiments	
Ranking of the Vehicles in Decreasing Order of Release Rate	Classification of the Vehicles According to Drug Penetration Rate	
MCP	Group I	MC
MC		MCP
TOW gel		
WO	Group II	TOW gel
VAS		WO
PEG		OWK
OWK		OWN
OWN		VAS
	Group III	PEG

To a certain extent the results of these penetration experiments are comparable with the results of an in vivo study on the influence of the vehicle on the activity of dissolved BN[23]. In this study the vasodilatation produced by BN, incorporated in various vehicles, was evaluated and compared by means of different parameters. Hydrogels seemed to be very active, whereas emulsion gels showed a medium biological activity. With the polyethylene glycol gels the TOW gel belonged to the vehicles exhibiting a poor activity. If the vasodilatation test, however, was carried out under occlusion[24], as a result of increased hydration of the stratum corneum, a marked

TABLE 10

Comparison of the Penetration of THCl and BN from the TOW Gel through Isolated Human Epidermis

Skin Sample	K_p (10^4 cm.min^{-1}) for	
	THCl	BN
A5	2.8	6.2
B5	0.65	3.0
C5	2.8	8.4
D5	2.2	4.4

The values are the means of at least three estimates per skin sample of K_p.

increase in the effectivity of the TOW gel could be observed. This indicates that under our experimental conditions an important hydration of the stratum corneum - originating from the continuous contact of the dermal side of the epidermis sample with the acceptor fluid - prevails.

Comparison of the Penetration of Tetracaine Hydrochloride and Benzyl Nicotinate from the TOW Gel through Isolated Human Epidermis

In order to assess to what extent the differences in characteristics of THCl and BN are reflected in their penetration behaviour, their penetration rate from the TOW gel through human epidermis is compared.

From the results listed in Table 10 it appears that the penetration rate of the lipophilic drug BN is 2 to 5 times higher than the rate observed for THCl.

Considering that the release of both these drugs from the TOW gel occurs at approximately the same rate[b] whereas their penetration rates differ clearly, these data further substantiate our finding that, as far as the TOW gel is concerned, the release of these drugs from their vehicle is not the rate limiting step in the process of percutaneous absorption.

In a study comparing the permeation behaviour of scopolamine and scopolamine hydrobromide from an aqueous solution through epidermis, the permeation of the more lipophilic base form was also found to occur at a higher rate than permeation of the hydrophilic salt form[25].

Although dissolved, unionized substances with a balanced liposolubility preferably diffuse through the skin, thus indicating that lipid barriers play an essential role, for strongly hydrophilic substances hydrophilic diffusional pathways must also exist within the stratum corneum[26]. Polar and apolar molecules appear to diffuse through the stratum corneum by different pathways or mechanisms, for which various possibilities have been suggested[27-31]. Until now, however, the real diffusional pathways have not been elucidated. Yet, the intracellular keratin matrix of the stratum corneum presumably represents the main resistance against drug diffusion[30,32,33].

CONCLUSION

The penetration experiments reported here suggest the existence of a concentration dependent phenomenon in the percutaneous absorption of THCl from the TOW gel. For the permeability constant describing the skin penetration of BN from the TOW gel, however, no concentration dependency can be observed.

The experimental data, both for THCl and BN, allow to infer a distinct influence of the type of vehicle on epidermal drug penetration rate. Since the rank order of the various vehicles for their release rate of THCl and BN and their rank order according to epidermal drug penetration rate do not correspond, drug release from the vehicles is not rate limiting in our penetration experiments. This points to specific vehicle-skin interactions influencing the process of percutaneous absorption. When incorporated in TOW gel THCl as well as BN show a penetration rate comparable to that from other commonly used vehicles. For THCl the percutaneous absorption proceeds at a higher rate if a cetrimide cream or a W/O emulsion gel is used; methylcellulose gels seem to be more appropriate for BN.

The rank order of the vehicles according to the in vitro epidermal penetration rate of BN is in fairly good agreement with the in vivo biological activity of this drug if vasodilatation is tested under occlusion.

A last series of experiments reveals that, although lipophilic drugs, like BN, incorporated in a TOW gel penetrate the skin at a higher rate, hydrophilic drugs also show an important percutaneous absorption from this gel.

Taking into account the complexity of the vehicles under investigation and the complexity of the process of percutaneous absorption resulting from a multitude of vehicle-drug-skin interactions, it is quite difficult to give an unequivocal explanation for the phenomena reported here. This was not the aim of this work, either. The results, however, allow concluding that with regard to the penetration rate of a hydrophilic and a lipophilic model drug, the TOW gel is comparable with other dermatological vehicles commonly used.

ACKNOWLEDGEMENTS

The authors would like to thank Prof. Dr. J. Lauwerijns of the Laboratory of Histo-pathology, Catholic University of Leuven, and the members of his staff for supplying the samples of excised skin.

FOOTNOTES

a. data submitted for publication
b. data submitted for publication

ABBREVIATIONS

TOW gel	:	transparent oil-water gel
THCl	:	tetracaine hydrochloride
BN	:	benzyl nicotinate
VAS	:	white soft paraffin
WO	:	cremor sorbatis '67'
OWN	:	cremor cetomacrogolis
OWK	:	cetrimide cream
MC	:	methylcellulose gel I
MCP	:	methylcellulose gel II
PEG	:	polyethylene glycol gel

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