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The effect of sorption promoters on percutaneous permeation of a model zwitterion — baclofen

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Abstract

In vitro percutaneous penetration of baclofen, a model zwitterion, in the presence of penetration enhancers was investigated to better characterize a porous polar pathway of diffusion across the stratum corneum. The following sorption promoters were studied: DMSO, urea, propylene glycol (PG), sodium lauryl sulphate (SLS), ethanol 95%, Azone, oleic acid (OA) and OA/PG system. No significant increase of penetration or skin accumulation of baclofen was observed when DMSO, urea, PG, Azone or OA were used. The presence of SLS or OA/PG in the vehicle resulted in high penetration rates and uptake of baclofen but this effect was observable only after 30 h and was accompanied with signs of the barrier damage. Ethanol 95% was the only vehicle which promoted baclofen penetration despite its lower solubility in this solvent which is attributed to new pore formation. Penetration rate and skin accumulation of the zwitterion depend on its solubility in the vehicle.

Keywords: Percutaneous absorption; Penetration enhancement; Pore pathway; Ionic transport; Baclofen; Zwitterions

1. Introduction

Passive transport of ions across stratum corneum is still a subject of controversy. Mechanism of permeation based on partitioning and diffusion in the intercellular lipid domain of stratum corneum is well established, but this model does not explain the phenomenon of transcutaneous, passive or iontophoretically enhanced, transport of ions. Amino acids, ionized in the whole range of pH, are a good model to investigate permeation of skin by ions.

In the previous study, passive transport of lysine, aspartic acid and histidine was observed (Sznitowska et al., 1993). For all three amino acids, apparent permeability coefficients (K_p) from aqueous solutions were in the same range, $1.2–4.7 \times 10^{-8}$ cm/s, and were independent of the charge of the molecules. The calculated apparent diffusion constants are of the same magnitude as those characteristic for nonionic polar com-

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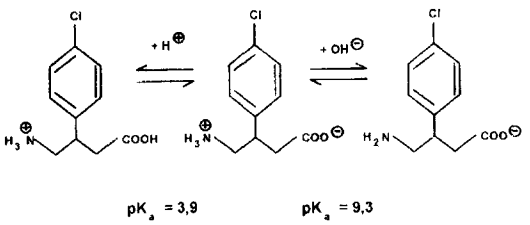

Fig. 1. Zwitterionic character of baclofen.

pounds ($3-6 \times 10^{-11}$ cm^2/s), which suggests the same route of penetration. A long T_{lag} of 20–30 h indicated that intact stratum corneum, not skin appendages, was the site of the ionic transport.

The results support a new physical model of the stratum corneum which is composed of two parallel pathways: the lipoidal pathway and the hydrophilic pore pathway (Barry and Bennett, 1987; Ghanem et al., 1987; Berner and Cooper, 1987). The pores are aqueous regions in the stratum corneum but it is still unclear whether they are located intra- or intercellularly and their exact characteristics are also unknown. From the fact that the penetration rate for polar molecules is small, it may be concluded that the hydrophilic pathway occupies only a small volume fraction in the stratum corneum and is tortuous and discontinuous.

The studies on percutaneous absorption of amino acids are continued with a derivative of γ-aminobutyric acid, baclofen, a muscle relaxant (Fig. 1). The experiments presented herein were performed in order to further characterise the porous pathway of diffusion, investigating penetration of baclofen in the presence of ethanol or other hydrophilic or lipophilic sorption promoters.

Besides ethanol (Kurihara-Bergstrom et al., 1990; Ghanem et al., 1992, Maitani et al., 1995), no any promoter has been studied before in regard to its effect on the porous pathway of penetration and ionic passive diffusion across the skin. Ruland and Kreuter (1992) investigated influence of several penetration enhancers on the permeation of amino acids through hairless mouse skin but their action on the porous pathway of penetration was not discussed.

2. Materials and methods

2.1. Materials

Baclofen ($\pm$) was a gift from Research Biochemicals Incorporated (Natick, MA, USA) or from Pharmaceutical Works in Starogard Gd. (Poland) — the physicochemical identity of both substances was confirmed (Sznitowska et al., 1995b). Ethanol 95% v/v was produced by Polmos (Starogard Gdanski, Poland), 1,2-propylene glycol (PG) was purchased from VEB Laborchemie Apolda (Germany), oleic acid (OA) from Merck (Darmstadt, Germany), sodium lauryl sulfate (SLS) and dimethylsulfoxide (DMSO) from Ubichem (Eastleigh, GB), urea from POCh (Gliwice, Poland), and Azone® from Research Triangle Pharm. (Durham, NC, USA). Sodium azide was obtained from Sigma (St. Louis, MO, USA). Acetonitril was chromatography grade (Merck, Darmstadt, Germany), methanol was obtained from POCh (Lublin, Poland) and was redistilled before use.

Human cadaver full-thickness skin was excised from the thigh of 20 individuals (age 20–70) and stored at -30°C before use.

2.2. Permeation experiment

The skin was mounted in two-chamber flow-thru teflon diffusion cells (Crown Glass Company, Somerville, NJ, USA) with the penetration area 0.64 cm^2. The receiver was 4.0 ml of 0.9% sodium chloride solution containing 0.005% sodium azide and it was recirculated beneath dermal side of the skin with a speed 4.7 ml/h. Temperature of the diffusion cells was maintained at 37°C. A period of equilibration of 6–8 h was allowed and then the receiver solution was replaced with a fresh portion and 300 μl of the appropriate donor solution was placed onto the skin. Every 12 h, up till 60 h, the receiver solution was entirely removed and replaced with a fresh saline. The donor solution was also exchanged every 24 h.

Saturated solutions of baclofen at 37°C, separated from undissolved particles by filtration, were used as donor solutions. The solvents were as follows: water, ethanol 95% (v/v), 50% PG,

Table 1
Pharmacokinetic parameters characterizing percutaneous penetration of baclofen in the presence of different penetration enhancers

Sorption promoter	T_{lag} [h]	J_{ss} [μg/cm^2/h] or (J_{30h})	C_s[mg/ml]	K_p[$\times 10^8$ cm/s]	A_{epid}[μg/cm^2]	A_{der} [μg/cm^2]
Water as a vehicle						
—	<6	0.18	4.6	1.1	6.5 ± 2.3	9.1 ± 4.0
DMSO	24	0.10	1.6	1.5	2.7 ± 0.8	1.6 ± 1.0
PG	**	(0.17)	3.8		3.8 ± 1.7	5.2 ± 2.8
Urea	24	0.16	5.0	0.8	6.9 ± 1.5	5.9 ± 1.6
SLS	**	(1.3)	5.5		37.1 ± 5.8	30.1 ± 7.8
Ethanol 95% as a vehicle						
—	<6	0.14	0.4	10	3.4 ± 1.1	2.1 ± 1.2
Azone	**	(0.09)	0.4		3.0 ± 1.7	4.4 ± 2.6
OA	**	(0.09)	0.45		5.0 ± 1.8	3.9 ± 2.2
OA + PG	**	(0.90)	1.75		32.3 ± 13.8	57.8 ± 16.7

**a steady state is not achieved, presented values of the flux were measured after 30 h (J_{30h}).
J_{ss}, steady-state flux.
C_s, concentration of baclofen in donor solution.
K_p, apparent permeability coefficient calculated as J_{ss}/C_s.
A_{epid}, amount of baclofen in epidermis after 60 h of penetration (mean ± S.D.; n = 5–7).
A_{der}, amount of baclofen in dermis after 60h of penetration (mean ± S.D.; n = 5–7).

50% DMSO, 0.2% SLS, 10% urea (all the above in water), 2% OA, 3% Azone (both in ethanol 95%) and 2% OA in ethanol and PG (1:1) (OA/PG). The concentrations of sorption promoters are given as weight ratios.

2.3. Extraction of baclofen from the skin tissue

After 60 h, the permeation experiment was terminated by removing the donor solution and washing the skin surface several times with water. The area of the skin which had been exposed to the donor and receiver solutions was excised and epidermis was separated mechanically from dermis, after a short heat exposure, when necessary. The tissue was weighed and placed into 3.0 ml of water containing 0.003% sodium azide and was shaken for 48 h at 37°C. After that time it was transferred to a fresh extraction medium for another 24 h.

2.4. Analytical procedure

HPLC analysis was performed in order to measure concentration of baclofen in the sampled receiver fluid and in the extraction media. The analysis was done using Merck-Hitachi (Darmstadt, Germany) HPLC apparatus and LiChrospher RP-18 column (Merck). The mobile phase consisted of acetonitrile: methanol: 0.02 M potassium dihydrogen orthophosphate (5:15:80 w/w), pH 3.5 was adjusted with phosphoric acid. The mobile phase flow rate was 0.9 ml/min. Baclofen was detected at 220 nm.

2.5. Solubility studies

The solubility of baclofen was determined in each of the systems used as vehicles in the permeation experiment by shaking excess quantity of the substance in the relevant solvent for 24 h at 37°C. After this period, samples were taken and, after filtration, diluted with water and analysed by HPLC for the solute content.

3. Results

Saturated solutions of baclofen were applied on the skin. Solubilities of baclofen in the vehicles under investigation at 37°C were determined in order to find out concentrations of the permeant in the donor solutions. The values obtained are presented in Table 1. Baclofen is slightly soluble

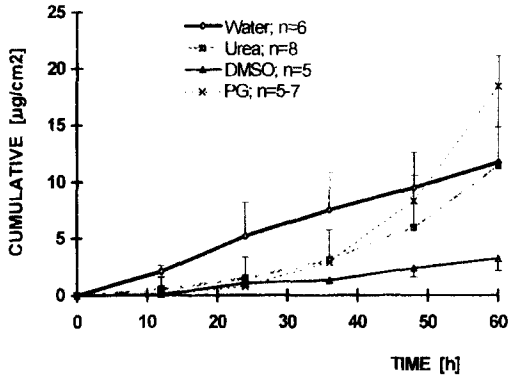

Fig. 2. Effect of polar penetration enhancers on the permeation of baclofen from saturated aqueous solutions. All data represent the mean ± S.D.

in water and its solubility in 95% ethanol is 10 times smaller. PG and DMSO are also less capable of dissolving baclofen in comparison to water. Neither Azone nor OA and urea increased baclofen solubility. Only a slight raise of the solubility, less than 20%, can be noticed in the presence of a surfactant, SLS, at its concentration higher than CMC (CMC = 0.02%).

Using HPLC method baclofen can be determined in the receiver fluid or skin extract in concentrations as little as 60 ng/ml (for this concentration, sd = 10%). The retention time is about 11 min and direct injection of the sample, following filtration, is possible since none of the substances eluted from the skin interferes.

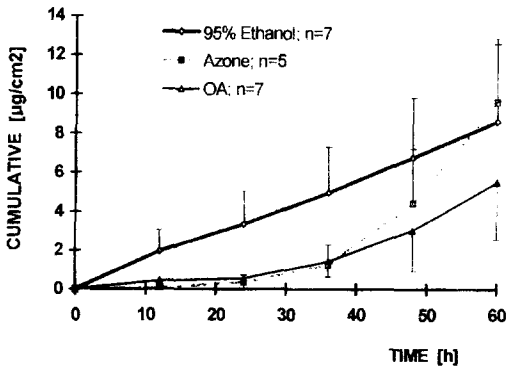

Fig. 3. Effect of lipophilic penetration enhancers on the permeation of baclofen from saturated ethanolic solutions. All data represent the mean ± S.D.

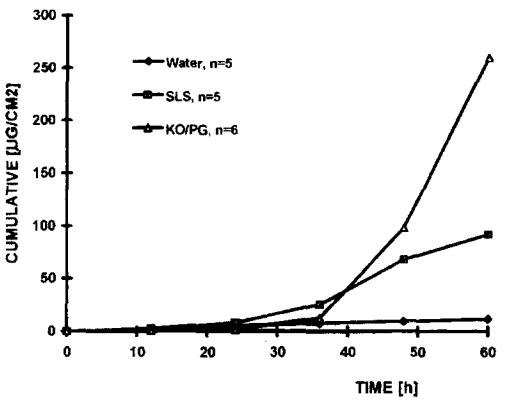

Fig. 4. Effect of SLS and PG/OA system on the permeation of baclofen from saturated solutions. All data represent the mean ± S.D.

Figs. 2–4 present cumulative amounts of baclofen penetrating across the skin vs time of penetration. Transport parameters, flux J_{ss}, permeability coefficient K_p and T_{lag}, are given in Table 1. The steady state fluxes of baclofen from aqueous or ethanolic solutions were equal, 0.18 ± 0.05 and 0.14 ± 0.07 $\mu g/cm^2/h$, respectively. However, calculated K_p is 10 times larger for the ethanolic solution. T_{lag} values were short, less than 6 h. The presence of sorption promoters, urea or DMSO, resulted in longer T_{lag}, i.e. about 24 h. When PG, SLS, OA or Azone were present in the donor solution, penetration rate of baclofen increased constantly and a steady state was not achieved. For these vehicles, the penetration rate determined after 30h is given ($J_{30\ h}$) in order to demonstrate a magnitude of an enhancement effect (Table 1). In these cases, K_p could not have been calculated.

The amounts of baclofen extracted from the skin tissue with water during the periods of extraction 0–24 h, 24–48h and 48–72h were: 90.7 ± 1,7; 6.1 ± 0.4 and 3.2 ± 1.9% of the total amount extracted after 72 h (n = 6). Thus 72 h was considered to be sufficient time for extraction of baclofen in order to determine its absorption into the skin. Amounts of baclofen found in epidermis and dermis at 60 h of the permeation experiment, calculated for 1 cm^2, are presented in Table 1. The mean values were in the range 2.7–6.9 $\mu g/cm^2$ in epidermis and 1.6–9.1 $\mu g/cm^2$

in dermis. When SLS in water or OA/PG system in ethanol were used as vehicles the values were several times higher. Fig. 5 presents relationship between amounts of baclofen found in epidermis and solubility of baclofen in the vehicle. Linear relationship can be noted for the aqueous vehicles. A linear regression analysis yields an equation $y = 1.235 \times +0.343$ and a correlation coefficient $r = 0.915$.

4. Discussion

Passive percutaneous transport of a model zwitterion, baclofen, has been observed in vitro from aqueous or ethanolic vehicles. On the basis of pK_a values (Fig. 1), it may be estimated that, at the experimental conditions, a form of zwitterion dominates in the aqueous solutions although pH of the vehicles was not strictly controlled. Also in ethanol 95%, a zwitterion is the most likely form of baclofen molecule. From the previous studies, however, it was concluded that an ionic form does not significantly influence the penetration rate of amino acids through the skin (Sznitowska et al., 1993; Sznitowska and Berner, 1995). Saturated solutions of baclofen have been chosen as donor phases to achieve maximum flux from each vehicle.

Sorption promoters, lipophilic or hydrophilic in nature, were chosen to study their influence on the rate of percutaneous absorption of baclofen. Although mechanism of their action on the skin is extensively investigated, there is still much doubt in regard to the sites of their accumulation and action in the stratum corneum. Urea improves stratum corneum water holding capacity (Williams and Barry, 1992), SLS probably acts by solubilizing the intercellular lipids and changing conformation of the intracellular keratin, PG increases solubility of the permeant in the stratum corneum, DMSO interacts with keratin and lipid polar head groups loosening these structures (Barry, 1987). All the above are reported to enhance skin penetration of polar drugs. Also Azone, although lipophilic in character, acts as a good sorption promoter for hydrophilic drugs, while it anchors among the alkyl chains of the intercellular lipids and fluidizes this region (Ogiso et al., 1992; Sugibayashi et al., 1992). OA acts in the similar way but the difference must exist because, opposite to Azone, its enhancing effect was mostly observed for nonpolar drugs (Barry, 1987; Barry and Bennett, 1987; Loftsson et al., 1989). However, when OA is used together with PG, their effect is synergistic and enormous enhancement in penetration of polar molecules is observable (Barry and Bennett, 1987; Ruland and Kreuter, 1992). Ethanol is a very well known sorption promoter for lipophilic drugs like nitroglycerine, estradiol or fentanyl, it is capable of increasing their solubility and diffusivity in stratum corneum. When used in high concentrations it is able to extract lipids and reorganize their structure, also altering protein conformation; altered or additional pores may be formed and diffusion of polar molecules is increased (Kurihara-Bergstrom et al., 1990; Ghanem et al., 1992).

In our experiments, fluxes of baclofen from both aqueous and ethanolic solutions are almost the same (Table 1). However, when baclofen concentration in both vehicles is taken into consideration, the resulted K_p is 10 times higher for the ethanolic than aqueous system — the maximal effect observed in this study. Such enhancement is small, however, in comparison to 100-fold increase of mannitol penetration rate reported by Ghanem et al. (1992). This discrepancy may reflect difference between human and hairless mouse skin but further studies are required to confirm such assumption.

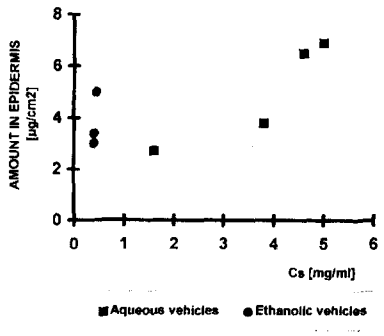

Fig. 5. Amount of baclofen in epidermis after 60 h of penetration from aqueous and ethanolic vehicles, with or without sorption promoters, versus baclofen solubility in the vehicle.

Enhanced penetration of ions may be expected in the presence of these promoters which influence the penetration rate of polar drugs. Surprisingly, however, in our studies the presence of sorption promoters resulted even in lower fluxes of baclofen. Also, Ruland and Kreuter (1992) did not observe increased fluxes of amino acids in the presence of several sorption promoters. The reasons for such phenomenon may be very complex. Generally solubility of baclofen in the vehicle and osmotic events may be relevant for the effects observed.

Although solubility of the permeant in the vehicle is not important for diffusion rates in the membranes if the process is governed by partitioning mechanism and thermodynamic activity of the permeant in the vehicle is constant, but solubility is the most important factor when the membrane is porous (Berner and Cooper, 1987). The pores are filled with the vehicle and the amount of the permeant in the membrane, as well as its penetration rate, depend on the solubility in this domain. Decreased solubility of baclofen in the vehicle containing 50% PG or 50% DMSO resulted in lower penetration rates in comparison to the pure aqueous system. This can not be an explanation for decreased flux from aqueous vehicle containing 10% urea since baclofen solubility in this vehicle is even slightly higher than in water. It must be noticed, however, that 10% urea is a hypertonic solution (1670 mOsm/l) and osmotic processes may cause the back-flux of water from the receiver fluid, consequently reducing the flux of baclofen. Such an effect was already reported when percutaneous penetration of amino acids from hypertonic solutions containing NaCl or sorbitol was studied (Sznitowska et al., 1995a).

The same flux of baclofen from water and 95% ethanol is not consistent with the theory that rate of penetration is proportional to the permeant solubility in the vehicle, because baclofen solubility in water is 10 times higher than in 95% ethanol. A conclusion may be drawn that ethanol promotes changes in the porous pathway and consequently increases permeability of baclofen, as can be clearly shown by comparison of K_p values (Table 1). There is already evidence in literature that high-ethanol levels result in new effective pore formation, probably due to some reorganization of lipid regions or lipid extraction (Ghanem et al., 1992).

Neither OA nor Azone substantially increases the penetration of baclofen across skin. This may be evidence that reorganization of intercellular lipids in the alkyl chain region does not cause new pores formation. It is difficult to explain the opposite effect, these sorption promoters caused lower fluxes of baclofen in comparison to the pure ethanolic vehicle. The effect of these lipophilic sorption promoters on ethanol ability to extract lipids has not been studied yet, so the hypothesis that they protect lipids and prevent new pore formation needs to be verified by further studies.

Higher penetration rate from the aqueous solution was observed when SLS was present in the vehicle. This vehicle was the only one among those under investigation which offered significant increase in baclofen solubility, although the increase was only about 20%. The steady state was not achieved since the increasing flux of baclofen was noted during the time of penetration, which is not surprising because SLS is known as a promoter increasing its own penetration, resulting in constant enhancement of the penetration rate of the permeant. Time of penetration, 60 h, is certainly too long for studying penetration in the presence of SLS which causes serious membrane maceration. Penetration rates were much higher than for water and three-fold increase of baclofen flux was noted between 30 h and 54 h, which may be evidence of irreversible changes in the structure of stratum corneum. Even more pronounced degradation of the barrier occurred under exposure to the mixture PG/OA. Up till 30 h, the penetration rate of baclofen was smaller than $1 \mu g/cm^2$ but, during the next 30h, it increased as much as 15 times. It may be concluded that neither SLS nor the mixture of PG with OA promoted baclofen penetration in substantial ranges unless the membrane was irreversibly changed. Ruland and Kreuter (1992) observed also a very pronounced enhancement of transdermal penetration of amino acids in the presence of PG/OA and Azone/PG while other penetration enhancers failed to exert any effect.

When in vitro percutaneous penetration of amino acids was studied, T_{lag} values were 20–30 h, which were attributed to the porous transport across the skin; tortuosity and discontinuity of the pathway was considered to be responsible for such a long T_{lag} (Sznitowska et al., 1993). In the present study, however, T_{lag} values shorter than 6 h are noted for penetration of baclofen from aqueous or ethanolic solutions. On the other hand, a T_{lag} as long as 24h was observed when DMSO or urea were present on the skin. It should be mentioned that in some of the experiments these values of T_{lag} were found also when water or ethanol served as vehicles. The explanation of this phenomenon is not clear.

Time of the permeation experiment, 60 h, has been chosen on the basis of the previous results obtained for other amino acids. Shorter experimental times do not allow to observe prolongation of T_{lag} and small penetration rates for ionic drugs require longer sampling periods, from 10 to 12h, in order to detect the permeant in the receiver fluid with a satisfying accuracy.

The amounts of baclofen recovered from epidermis after 60 h penetration were similar to those recovered from dermis, but a reasonable concentration gradient exists because of the difference in the weight of these two tissues. The mass of isolated epidermis layers was approximately 20 times larger than mass of dermis; there is the same difference in mean concentrations of baclofen in both layers, with higher concentration in epidermis.

The amounts of baclofen found in epidermis at 60 h of the penetration do not correspond with the penetration rate at this time. However, for the aqueous solutions, a linear relationship exists between amount of baclofen absorbed in epidermis and its solubility in the vehicle, as shown in Fig. 5. This is not true for ethanolic solutions; although with the same solubility, baclofen absorption from these vehicles to epidermis is different. Two-fold decrease of baclofen concentration in epidermis when 95% ethanol was the vehicle did not also correspond with ten-fold lower solubility of baclofen in ethanol when compared to water. This may be evidence for increased volume of the pores or other mechanism of diffusion. None of the sorption promoters affected absorption of baclofen to the skin. Neither SLS nor OA/PG system was taken into consideration for the above conclusion because the amounts of baclofen found in epidermis and dermis in the presence of these sorption promoters in the vehicles were extremely high, and probably result from the fact that the barrier was damaged, as has been discussed earlier.

5. Conclusions

The exact nature of the porous pathway in the stratum corneum is still unknown, although it is likely to involve either or both the keratinized protein cell remnants and the polar head regions of the lipid domain. Our results show that constant pore volume is created in the fully hydrated stratum corneum or in the presence of 95% ethanol. Ethanol 95% promotes maximal pore formation and its potential to extract lipids could rather indicate at intercellular location of these pores. The other hydrophilic enhancers cause only minor changes of the volume and tortuosity of the pores during the time of diffusion, but the process is too slow to consider them as penetration enhancers for ionic drugs. Changes in organization of the intercellular lipids caused by lipophilic promoters do not result in enhanced ionic transport and even decreased penetration was observed. Solubility of the zwitterion in the vehicle is a dominant factor influencing the rate of its transdermal penetration and osmotic events, generally dynamics of the stratum corneum hydration, play an important role in this process.

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