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Influence of propylene glycol as cosolvent on mechanisms of drug transport from hydrogels

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Abstract

The in vitro penetration of topical glucocorticoids (GC) betamethasone 17-valerate (BMV), hydrocortisone 17-butyrate (HCB) and hydrocortisone (HC) into an artificial lipid acceptor and excised human skin was examined using binary hydrogels with varying propylene glycol (PG) content. The relationship between the physicochemical properties of the model drugs in binary PG/water mixtures and the rate and extent of their penetration into artificial lipid membranes was studied. As a function of the drug solubility and partition behavior between lipid acceptor and PG/water mixtures, two directions were found in which PG affects the penetration of the GCs used. The lipophilic BMV, providing a higher solubility in the acceptor lipid than in PG/water mixtures of the formulations, penetrates thermodynamically controlled. In this case, PG acts only as cosolvent. For the more hydrophilic HC with higher solubilities in PG/water mixtures than in the acceptor medium, the amount penetrated increases with increasing PG content of the formulation. This result is surprising because of the expectation that the rate and extent of penetration decrease with decreasing partition coefficients. PG penetrates rapidly into the artificial acceptor and into excised human skin. It acts as both cosolvent and enhancer. In the case of HC transport, the enhancer effect is supposed to be a solvent drag effect of PG. HCB seems to penetrate thermodynamically controlled up to 40% PG. However, if PG contents of 60 and 80% are used in the gels the drag transport mechanism dominates. The results obtained from the studies with the lipophilic acceptor membranes were confirmed using excised human skin.

Keywords: Penetration; Thermodynamic control; Solvent drag; Glucocorticoid; Propylene glycol; Artificial lipid acceptor; Excised human skin

1. Introduction

Alcohols and glycols are routinely used to solubilize lipophilic drugs in aqueous vehicles. Among the polyvalent alcohols PG is one of the most important cosolvents.

By increasing drug solubility with PG both increased and decreased permeation of drugs through artificial membranes and skin was measured. The results were obtained in relation to a standard preparation or with increasing PG con-

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tents of binary mixtures, respectively. These observations question the action of PG as a potential penetration enhancer (Poulsen et al., 1968; Sarpotdar and Zatz, 1986; Barry and Bennett, 1987).

Several authors have reported that the action of such solvents as PG is based on a pure cosolvent effect (Barry, 1983; Ritschel and Sprockel, 1988). In this case, the thermodynamic activity of the drug, which is affected by the vehicle composition, determines the drug penetration.

Only limited data demonstrate an enhancer effect of PG. For HC permeation experiments indicate a greater effect from saturated solutions of the corticoid applied with a PG vehicle than with the standard formulation (Barry and Bennett, 1987). However, the effect could not be confirmed with other lipophilic drugs such as betamethasone 17-benzoate (Bennett et al., 1985).

On the other hand, an increased flux of metronidazole and oestradiol from binary PG/glycerol mixtures through excised human skin was measured (Mollgaard and Hollgaard, 1983a). Simultaneous permeation profiles of the drugs and PG were found (Mollgaard and Hollgaard 1983b). Yamada et al. (1987) developed a theoretical model, trying to explain the PG penetration enhancement of molsidomine caused by PG and oleic acid.

Biophysical investigations have been carried out in order to gain more detailed insight into the mechanism of PG action on the molecular level. On pretreating stratum corneum samples with PG/water mixtures for a short time, neither a deviation of the lipid melting endotherms nor changes of the peak shapes were detected (Goodman and Barry, 1989). The authors suggested that PG acts by solvating the α-keratin structures of the cells, due to broadening of the protein denaturation peak. In this way, PG could be involved in transcellular diffusion enhancement. Bouwstra et al. (1991) combined DSC studies with the small angle X-ray technique. A shift of the lipid melting endotherms to lower transition temperatures was detected when the SC samples were soaked for 24 h in pure PG . Therefore, a disordering of the lamellar lipid structures was taken into account. In contrast, X-ray studies could not demonstrate this assumed perturbation of the intercellular lipid structure. The distance of the lamelles remained unaffected. The authors supposed that PG interacts with the polar head group regions of the lipids by replacing bound water, resulting in a slight shortening of the mean alkyl chain length in the bilayers. However, neither IR studies nor electron microscopy could finally clarify which kind of changes within the stratum corneum are responsible for the permeation promoting effect.

The aim of this work was to determine in which direction PG acts if GCs with different physicochemical properties are selected as model penetrants. Furthermore, an evaluation was carried out in order to ascertain whether a simple model system equipped with an artificial lipid acceptor can be used for studying these effects.

2. Materials and methods

2.1. Materials

BMV, HC and PG were purchased from COM-Pharma-Handels GmbH, Hamburg, Germany. HCB and sodium carboxymethylcellulose were supplied by Fluka Feinchemikalien GmbH, Neu-Ulm, Germany.

Collodion 4% (w/w) (Caesar and Loretz GmbH, Hilden, Germany) ethanol (Laborchemie, Apolda, Germany) and dodecanol (DD) (Merck, Darmstadt, Germany) were used to produce the lipid membranes as acceptor system for the penetration studies.

Isopropyl myristate (IPM) (Caesar and Loretz GmbH, Hilden, Germany) was selected for predicting partition coefficients of the drugs.

Methanol and acetonitrile as elution phases for the HPLC assay were obtained from Merck, Darmstadt, Germany.

2.2. Methods

2.2.1. Solubility

The solubility of the GCs was determined using PG/water mixtures prepared from 10 to 80% PG in 10% (w/w) increments, pure PG, water

and DD. BMV, HCB and HC were added in excess. Each sample was then shaken for 24 h at 32 ± 1°C. The samples were centrifuged and the supernatant solutions were assayed for drug content.

2.2.2. Partition coefficients

The partition coefficients of the GCs were determined between PG, water and PG/water mixtures and isopropyl myristate as organic phase. IPM was used as organic phase, since it is most suitable for estimating stratum corneum (SC) partitioning and because of its immiscibility with PG and its water mixtures in contrast to 1-octanol (Hadgraft and Ridout, 1987; Miller et al., 1993).

The drugs were dissolved in water and the two equilibrated phases were filled in suitable vials and shaken for 24 h at 32 ± 1°C. The samples were allowed to separate into both phases. Each phase was then centrifuged and the supernatant samples were analysed by HPLC for the total drug concentration.

The partition coefficient K was calculated using the Nernst equation:

$$K = \frac{a_{org.}}{a_{aqu.}}$$

2.2.3. Preparation of the gels

Required amounts of the GCs were stirred with the corresponding PG/water mixtures to a homogeneous suspension/solution. Sodium carboxymethylcellulose was added to the stirred suspension/solution. The fully swollen gels were filled into vials and were stored cool.

2.2.3.1. Suspension-type gels. Using BMV as 0.25% (w/w), HCB as 0.25% (w/w) and HC as 1.5% (w/w) preparations, it was possible to obtain formulations with the same ratio between applied drug concentration at $t = 0$ (C_0) and drug solubility (C_S) in the corresponding PG/water mixtures.

2.2.3.2. Solution-type gels. BMV was used in a drug concentration (C_0) below the solubility (C_S) in the PG/water mixtures ($C_0 \leq C_S$). The initial concentration of drugs in all formulations was 90% of the solubility.

The solution-type gels were used for studying the dependence of penetration on partitioning into the acceptor membranes.

2.2.4. Penetration studies

2.2.4.1. Multilayer membrane system (MMS). For evaluating the penetration of GCs, the MMS which has been described previously was used (Fürst et al., 1987; Neubert et al., 1991).

A defined amount of the gel (10 mg) was applied to the acceptor system, which was fixed in a penetration cell with an exposed application area of 4 cm^2. To maintain approximate sink conditions, the number of the acceptor membranes was increased up to three layers for testing solution-type gels and three layers for suspension-type gels of HC with a DD content double that for the suspensions of BMV and HCB. The number of acceptor membranes was matched to the solubilities of the GCs in DD.

The penetration cells were fixed in the model construction and thermostated at 32°C ± 1°C. At defined time intervals the model was removed from the thermostating chamber. The penetration cells were separated. Formulation remaining on the first acceptor layer was removed and the membranes were assayed for GC and PG content.

2.2.4.2. Preparation of the lipid membranes. DD, the acceptor lipid, was dissolved in a mixture of ethanol and ether (1.5:8.5). This mixture was filled in a ring of glass with a diameter of 4.0 cm located on a glass plate. The resulting membranes after the solvent mixture was evaporated took up a surface area of 12.5 cm^2.

2.2.5. Excised human skin

2.2.5.1. Application procedure. For the experiments excised human abdominal skin was used.

10 mg of the formulation was applied to a 4 cm^2 area of a selected skin section by means of a specially formed spatula.

The formulation was distributed uniformly. The exact quantity of the gel applied was determined from the difference in weight of the spatula with the formulation and after application.

Immediately after application of the formulation, the skin sample was placed on a synthetic fibre sieve and placed in a glass vessel containing physiological sodium chloride solution. The dermal side of the skin was allowed to be in contact with the solution continuously. Throughout the experiment, the penetration chamber was maintained at a temperature of 32 ± 0.2°C in an incubator.

2.2.5.2. Penetration measurement. All experiments were performed as double determinations with four different operative preparations in each case. The time intervals for the penetration studies were set at 200 min and 24 h after application of the gel. For evaluating the drug content of the skin layers the surface of the skin was first wiped with cotton wool and then fixed to a sublayer of a synthetic fibre.

With a rapidly rotating punch press (diameter 6.0 mm) cylinders were excised from the whole skin. From these horizontal sections cuts in a defined depth of the skin were made with a freezing microtome. At first, the stratum corneum (SC) was removed from the skin by a cut of 10 μm. Then eight sections of 20 μm up to a tissue depth of 160 μm of the viable epidermis were obtained. The remaining tissue, the dermis, was prepared in 40 μm sections. The cuts of each layer were combined to one sample for the analytical assay of the drug or of PG.

2.2.6. Analytical assays

2.2.6.1. Analytical assay for GCs. The drug contents of the artificial lipid membranes and the skin layers were determined by HPLC under the following conditions. Column: Lichrospher, 250 mm (RP 18), 5 μm particle size; mobile phase (HC), methanol/water, 70:30; flowrate, 1.0 ml/min; mobile phase (BMV/ HCB) acetonitrile/water, 55:45; flow rate, 1.8 ml/min; detection, UV at 239 nm; injection volume, 20 μl.

2.2.6.2. Analytical assay for PG. The amount of PG penetrated into the artificial acceptor and

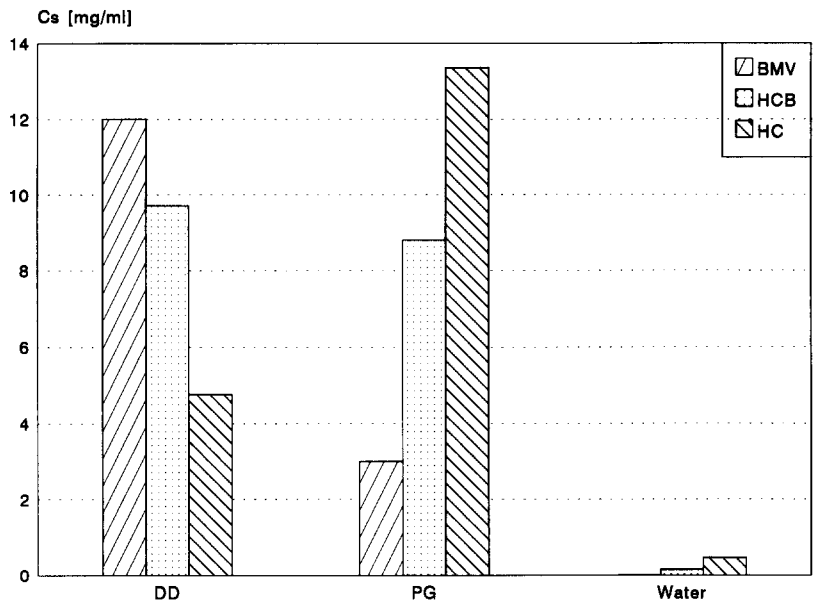

Fig. 1. Solubility of BMV, HCB and HC in DD, PG and water.

excised human skin was measured by gas chromatography combined with mass spectrometry (GC-MS).

The gas chromatograph used was obtained from Hewlett Packard (GC 5890). Conditions were as follows. Column, DP-5 (phenylmethyl silicone oil), 30 m, diameter 0.2 mm; injection volume, 2 μl; detection, MSD/HP 5971; temperature, 40°C (start); 250°C (final value).

3. Results and discussion

The aim of the study was to determine the mechanisms of penetration of lipophilic drugs from simply constructed hydrogels. Furthermore, we attempted to evaluate whether results obtained from a simple penetration model with an artificial lipophilic acceptor system could be confirmed using human skin.

The multilayer membrane system (MMS) according to Fürst/Neubert was used to investigate the mechanisms of penetration of the model drugs as a function of the PG concentration of the vehicle (Fürst et al., 1987). The acceptor system of the MMS consists of several sheets of lipophilic, isotropic partition membranes.

It should be possible to correlate the extent of the penetrated drug with the partitioning and solubility parameters, when the lipophilic drugs penetrate the SC via the 'lipid pathway'. The existence of such a correlation indicates that the transport of drug is not affected by an enhancer effect (Barry, 1989). For this case, the anisotropic SC can be considered as an isotropic lipophilic acceptor and can be replaced by an artificial one with lipophilic properties.

The different physicochemical properties of BMV, HCB and HC result in different solubilities in DD, water, pure PG and their mixtures with water (Fig. 1 and Table 1). Solubility in water is regarded as the basic criterion of lipophilicity (Yalkowsky, 1981). The drugs used are practically insoluble in water. Based on this fact, the PG content in the gels can be used to control the amount of drug dissolved that is available for diffusion at the beginning of the penetration process in the binary mixtures (Table 1). The importance of PG as cosolvent increases with the lipophilicity of the drug. On the other hand, the reverse of this relationship was found for the solubility of GCs in DD (Fig. 1).

The partition coefficients between PG/water mixtures and IPM decrease with increasing PG contents in the mixtures (Table 1).

To characterize the dependence of the penetration of GCs on the partitioning behavior, penetration studies were carried out with solution-type gels of BMV (Bendas et al., 1993). For this purpose, gels with PG contents from 10 to 80% PG were investigated, containing the drug as a defined amount below the saturation solubility

Table 1
Solubility of BMV, HCB and HC in PG/water mixtures and partition coefficients between IPM and PG/water mixtures

PG content of the formulation (%)	Solubility (mg/ml) of BMV	$K_{IPM/PG\ water}$BMV	Solubility (mg/ml) of HCB	$K_{IPM/PG\ water}$HCB	Solubility (mg/ml) of HC	$K_{IPM/PG\ water}$HC
0		321		16.5		0.66
10	0.016	102	0.22	10.5	0.68	0.34
20	0.023	72.7	0.39	6.5	1.74	0.23
30	0.064					
40	0.20	5.5	1.39	3.95	2.53	0.19
50	0.59					
60	1.08	2.6	3.62	2.6	4.66	0.15
70	1.60					
80	2.11	0.99	6.93	1.7	10.46	0.12
90						
100	3.1	0.32	8.88	0.35	13.36	0.08

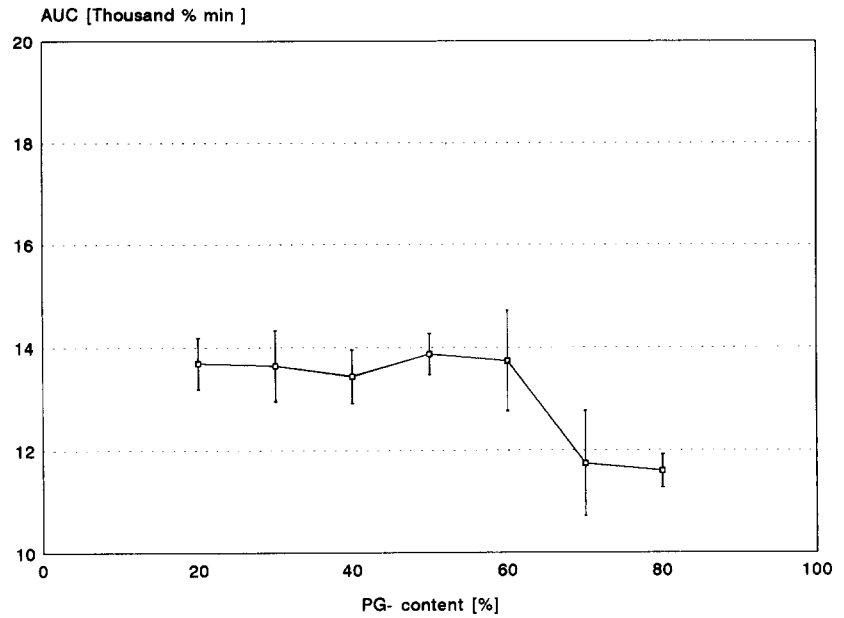

Fig. 2. In vitro penetration of BMV from solution-type gels as a function of PG content.

(Fig. 2). The AUC was used as a quantitative parameter to characterize the rate and extent of penetration in vitro according to Brockmeier (1981, 1986).

From 10 to 40% PG, the penetration of BMV is almost unaffected, whereas it is slightly increased between 40 and 60%. In contrast, PG contents higher than 60% cause a decrease in

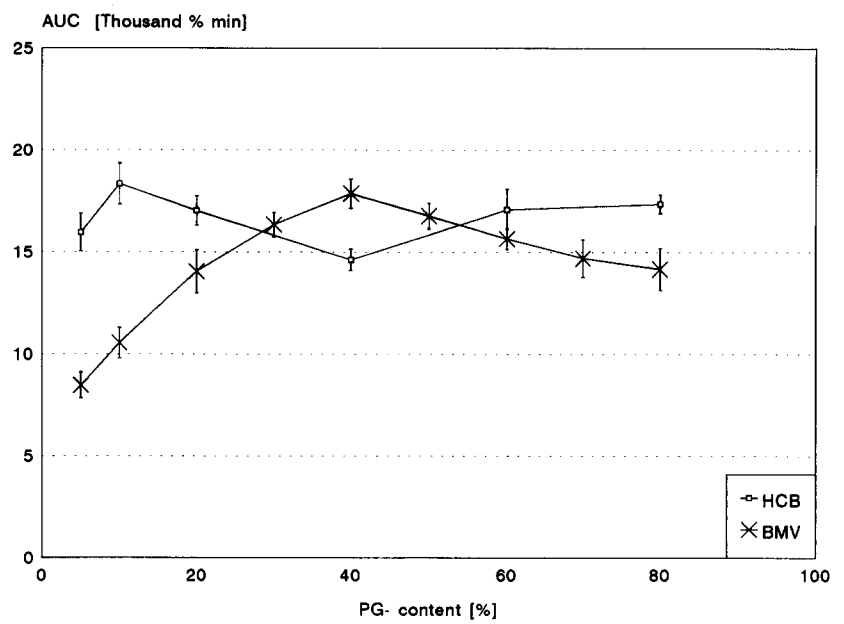

Fig. 3. In vitro penetration of BMV and HCB from suspension-type gels as a function of PG content.

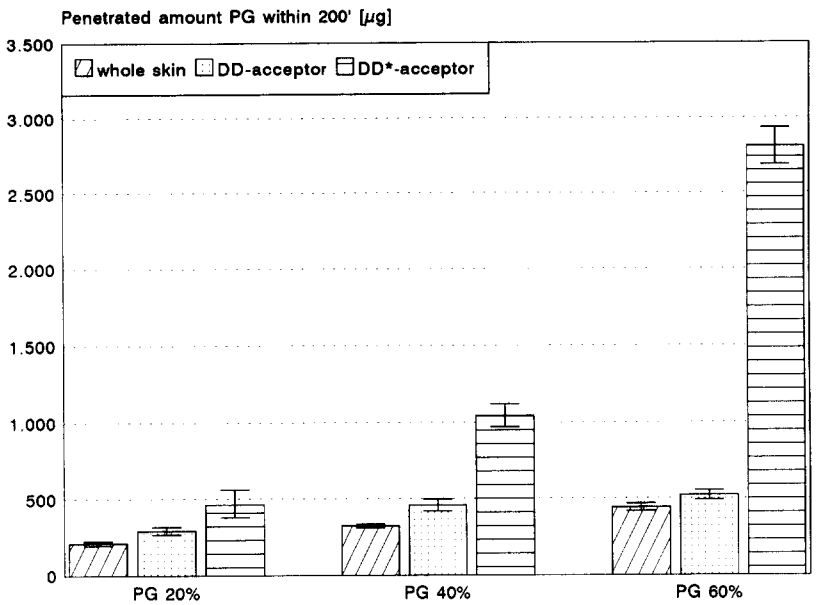

Fig. 4. Penetration of PG into the lipophilic membranes of the MMS (DD 3-layer acceptor, DD* 3-layer acceptor/double DD content) and excised human skin.

penetration of BMV due to an increase of the affinity of BMV to the vehicle. High affinities result for PG contents which cause small solubilities of BMV. The penetration behavior remains unaffected. An increase in the partition coefficients with decreasing PG contents in the vehicle does not influence the penetration of BMV when less than 40% PG in the gel is used. In this range of PG content the partition coefficients do not improve the penetration of BMV.

For the penetration of BMV from suspension-type gels with increasing PG contents, a maximum curve was obtained (Fig. 3). Considering the results for the solution-type gels the decrease in

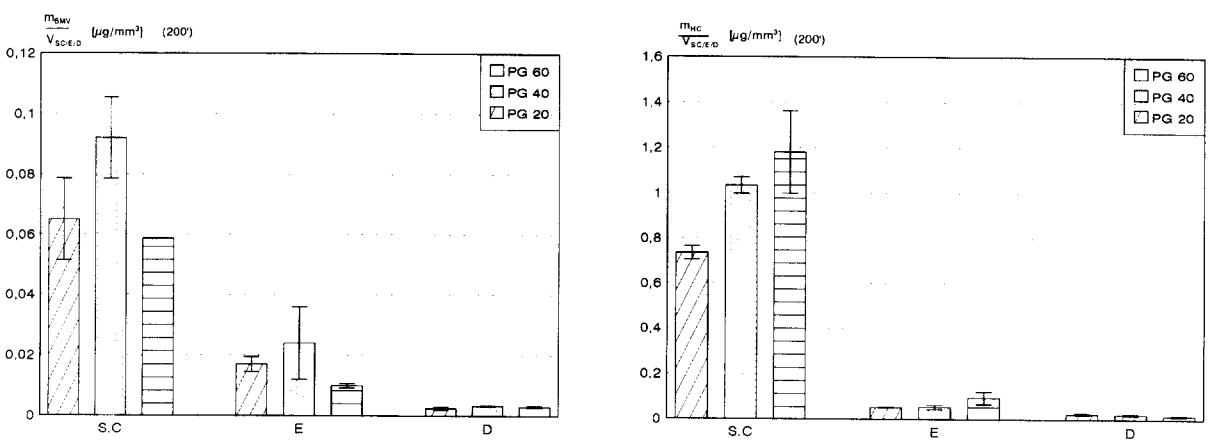

Fig. 5. In vitro penetration of BMV and HC into the various skin layers of excised human skin as a function of PG content. (a, left) BMV; (b, right) HC.

penetration of BMV from 40 to 80% PG from the suspension-type gels is obviously caused by decreased partition coefficients due to increasing drug affinity to the vehicle. The increase of the solubility of BMV with increasing PG concentrations from 10 to 40% leads to an improvement of the penetration of BMV. This enhancement of penetration ceases if a threshold value of affinity augmentation is achieved.

For BMV, it could be shown that PG acts only as a cosolvent. Therefore, the penetration behavior, which is thermodynamically controlled, can be predicted by physico-chemical parameters such as solubility and partition coefficients.

Although PG penetrates considerably into the lipophilic membranes of the artificial acceptor system, the penetration of BMV remains unaffected by this process (Fig. 4).

The formulations with 20, 40 and 60% PG were investigated as to their influence on BMV penetration into excised human skin. Using the more complex skin as acceptor system, the same dependence on the penetration of the PG content was found for BMV (Fig. 5a). With 40% PG in the vehicle the greatest amount of drug was measured in the whole skin. Whereas a more detailed consideration of the skin as a function of the skin depth shows the same relationship of concentration profiles between the stratum corneum (SC), the viable part of the epidermis (E) and the PG content of the formulation as for the intact skin, the permeation of BMV into the dermis (D) was independent of the PG content of the formulation.

The solubility of the more lipophilic HCB in PG/water mixtures exceeds the solubility measured for BMV (Table 1). Consequently, the partition coefficients of HCB between IPM and the PG/water mixtures decrease more than for BMV (Table 1). Therefore, the maximum amounts penetrated should be shifted to lower PG contents of the formulation if the penetration of HCB is thermodynamically controlled. The experimental results demonstrate a maximum of HCB penetration at 20% PG (Fig. 3). Therefore, if solubility is used as parameter for the beginning of the partitioning controlled penetration process, the penetration of the GCs BMV and HCB is improved up to a solubility of approx. 200 μg/ml in binary, aqueous PG/water mixtures. At PG contents

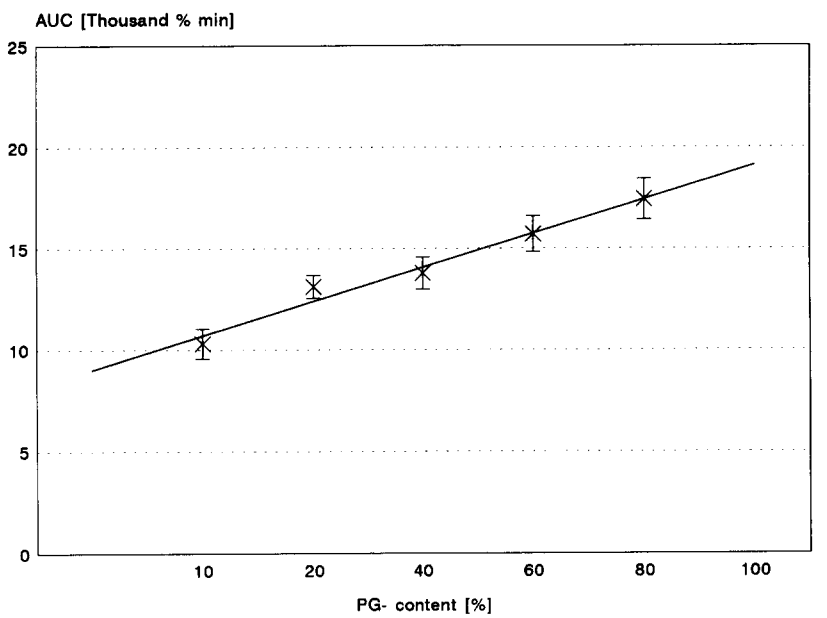

Fig. 6. In vitro penetration of HC from suspension-type gels as a function of PG content.

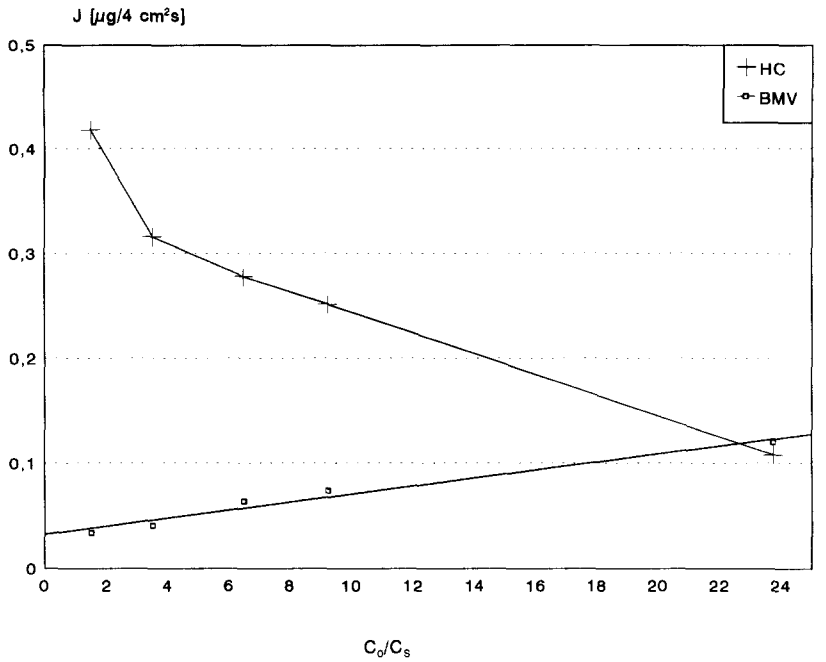

Fig. 7. Relationship between drug flux into the acceptor and thermodynamic activity.

above 40%, the amount of HCB penetrated increases with the PG content in the vehicle.

In comparison to BMV and HCB, the solubility of HC in PG/water mixtures is further increased (Table 1). On the other hand, the partition coefficients of HC are decreased (Table 1). However, the rate and extent of penetration of HC increase with increasing PG contents from 5 to 80% PG in the formulations (Fig. 6).

According to the theory, the drug flux should increase with increased thermodynamic activity, expressed by $1/C_S$. To calculate the penetration rate, the drug flux of BMV and HC through the first membrane of the acceptor system was measured. A linear relationship between thermodynamic activity and penetration rate was obtained for BMV, which penetrates thermodynamically controlled (Fig. 7).

In contrast, the rate of HC penetration decreases with increasing thermodynamic activity (Fig. 7). This implies that particularly for higher PG contents, the penetration rates of HC are increased more than proportionally. Therefore, the enhancement effect of PG does mask the thermodynamically controlled penetration behavior of HC. As observed in the MMS, a rise in the amounts of HC penetrated occurs if excised human skin is used as acceptor. Increased penetration with increasing PG contents in the vehicle was detected in the stratum corneum and the viable part of the epidermis (Fig. 5b). In contrast, the amount of HC permeating into the dermis is also independent of the PG content of the formulation.

Table 2
Solubility of BMV, HCB and HC into the artificial acceptor of the MMS after finished PG penetration

DD/PG mixture PG content (%)	C_s (mg/ml) BMV	C_s (mg/ml) HCB	C_s (mg/ml) HC
0	12.00	9.72	4.70
10	12.24	10.10	4.91
20	12.36	10.15	5.00
40	12.59	10.95	5.21
60	13.03	11.90	5.82
80	13.91	12.60	6.51

Table 3
Relationship between solubility of HC in the acceptor under the influence of PG, solubilized mass HC into a 3- or 4-layer model and penetrated amounts

DD/PG mixture PG content (vehicle) (%)	Cs (HC) (mg/ml)	3-layer model Ms (μg)	4-layer model Ms (μg)	Penetrated amount HC (200′) 3-layer model	Penetrated amount HC (200′) 4-layer model	Penetrated amount HC (200′) 6-layer model
0	4.7	103.6	138.2			
10	4.9	108.0	144.1	65.4%/98.1 μg	65.2%/97.8 μg	
20	5.0	110.25	150.0	70.1%/105.2 μg	74.6%/111.9 μg	
40	5.2	114.6	152.9	73.4%/110 μg	84.0%/126.0 μg	81.7%/122.5 μg
60	5.8	127.9	170.5		91.7%/137.5 μg	
80	6.5	143.3	191.1		97.1%/145.6 μg	

PG penetration modifies the acceptor system (Fig. 4). As a consequence, increased solubility in the acceptor layers and improved partitioning, respectively, are possible reasons for the penetration enhancement. Therefore, the solubility of BMV, HCB and HC was determined in the artificial acceptor after PG penetration (Table 2). The increase in solubility in the acceptor caused by PG is highest for HCB and lowest for HC. Whereas the increased solubility properties of the acceptor for BMV do not affect the sink conditions, real sink conditions are only achieved for HC. The solubility of HC in the acceptor lipid indicates that there is theoretically no sink, if a four-layer model is used (Table 3). On the other hand, 20% PG in the vehicle is already sufficient to bring all of the applied drug solubilized by its penetration into the acceptor. Furthermore, the rate and extent of HC penetration are not influenced if the number of membranes in the acceptor system is increased from four to six. Therefore, the changes in acceptor solubility do not

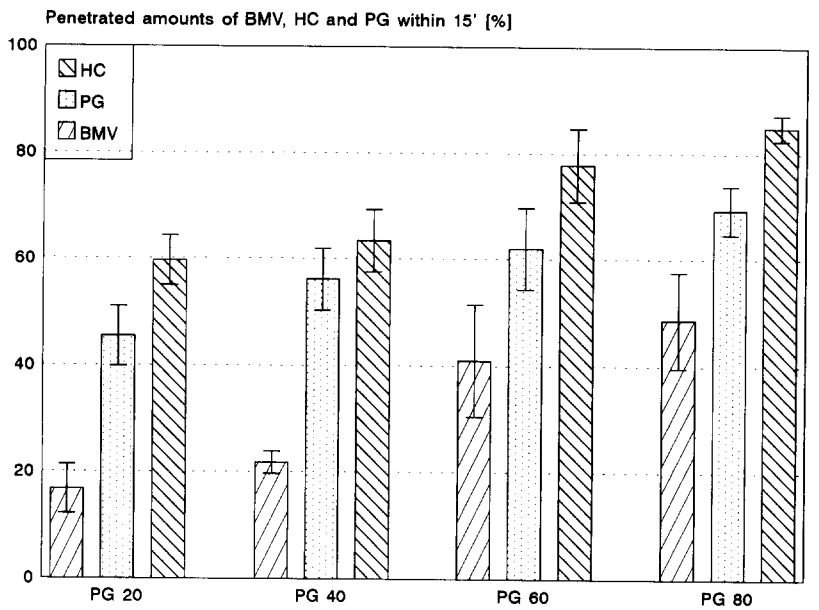

Fig. 8. Penetration of BMV, HC and PG within 15 min into the MMS.

suffice to explain the improved penetration of HC from hydrogels with higher PG contents.

PG increases the capacity of the SC for drug uptake. On this basis, a penetration enhancing effect should be detected for both HC and BMV with increasing PG contents of the formulation. Howevere, this effect occurs only for HC. Therefore, it must be assumed that the transport of HC is realized by a solvent drag effect or 'convective' transport. This is demonstrated by considering the amounts of PG, BMV, and HC penetrated after 15 min (Fig. 8). Within the first 15 min, most of the PG and drug penetrates and the levels of penetrated drug amounts are both related to their solubilities in PG.

4. Conclusions

The results presented in this article illustrate that there are two ways in which PG acts on the drug diffusion from a vehicle into an adjacent acceptor. On the one hand, for BMV a cosolvent action of PG was evident. Under these conditions, penetration is thermodynamically controlled. On the other, the increased affinity of HC to the vehicle does not inhibit penetration. In contrast, the rate and extent of HC penetration increase with increasing PG contents of the formulation. On studying the acceptor changes due to PG penetration, increased solubilities of the GCs in the lipophilic acceptor could be detected. This results in improved partitioning conditions. The fact that with increased solubility of the drugs in PG the amounts of HC increase, which penetrate within the first 15 min, indicates that an additional effect of PG must be taken into account. Therefore, the enhancing effect of PG on HC penetration is probably based mainly on a mediation of the drug molecule-vehicle/acceptor transfer. This effect can be described as a moving of drug molecules with the solvent flow into the acceptor medium (solvent drag effect or convective transport). The solubility of the drugs in PG determines to what extent this effect influences the penetration of drugs in the investigated penetration time interval.

The change in the penetration mechanism of lipophilic drugs due to PG could be characterized using a simple in vitro model system with an isotropic lipophilic acceptor. A qualitative coincidence was found between the results obtained with the MMS and excised human skin.

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