Experimental Determination and Mathematical Modelling of Propylene Glycol Transport from Semisolid Vehicles[1)]

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The penetration of the cosolvent and penetration enhancer propylene glycol (PG) into a multilayer membrane system was examined. Consisting of dodecanol (DD) this acceptor system was used to simulate the intercellular lipid pathway across the stratum corneum. Vehicles with 10%, 40% and 60% PG were investigated. Using a pharmacokinetic description based on Fick's first law of diffusion, the transport rate of PG was simulated. A parameter estimation was carried out to obtain a kinetic velocity parameter k_{PG} for the transport. k_{PG} depends on the diffusion coefficient, the area of application, and the pathlength. The data were validated by determining confidence intervals. The extent of the penetration of PG into the lipophilic acceptor system was shown to be quantitative. The data presented are useful for further investigations to assess the solvent drag effect caused by PG penetration. The multilayer membrane model was found to provide reasonable results with respect to accuracy and reproducibility.

Key words dermal absorption; propylene glycol; artificial membrane; mathematical model

Propylene glycol (PG) is widely used as an excipient in topical dosage forms and acts as both cosolvent and penetration enhancer. Many efforts have been made to evaluate its mechanism of action. To predict the cutaneous and percutaneous absorption of drugs which are formulated with PG, three processes have to be taken into account: Improvement of drug solubility in the vehicle,[2,3)] modification of the solubility characteristics of the skin,[4)] and cotransport.[5-7)]

It was found that PG itself is able to penetrate into acceptor systems such as skin or artificial membranes which involve the last two items above.[5,6)]

In the present study, *in vitro* penetration of PG was quantified, and the penetration of PG from different vehicles into a multilayer membrane system[8)] was investigated. The membranes consisted of dodecanol (DD) as an acceptor lipid which was incorporated in a collodium matrix. Using this model system, it was possible to simulate the intercellular lipid pathway across the skin.[7)]

A mathematical model based on Fick's first law of diffusion was developed in order to describe the transport of PG into the membranes and to derive velocity parameters for this process.

The data presented describe *in vitro* penetration of PG into an artificial membrane system. The mathematical model equation developed in this work should improve our understanding of this process.

Experimental

Chemicals PG was supplied by Aldrich Chemie, Steinheim, Germany. 1,2-Butandiol, used for GC/MS, was obtained from Merck-Schuchardt, Hohenbrunn, Germany; methanol was purchased from Carl Roth GmbH & Co., Karlsruhe, Germany.

Penetration Studies. Multilayer Membrane System The model apparatus consists of polyacrylate (Piacryl, Piesteritz, Germany) cells. One cell is outlined in Fig. 1. At least 4 cells were fitted together and placed in a chamber maintained at 32 ± 0.2 °C during the experimental period. Each acceptor system contained three DD membranes and a subsequent dialysis (Nephrophan®, Filmfabrik Wolfen, Germany) membrane to receive penetration profiles.

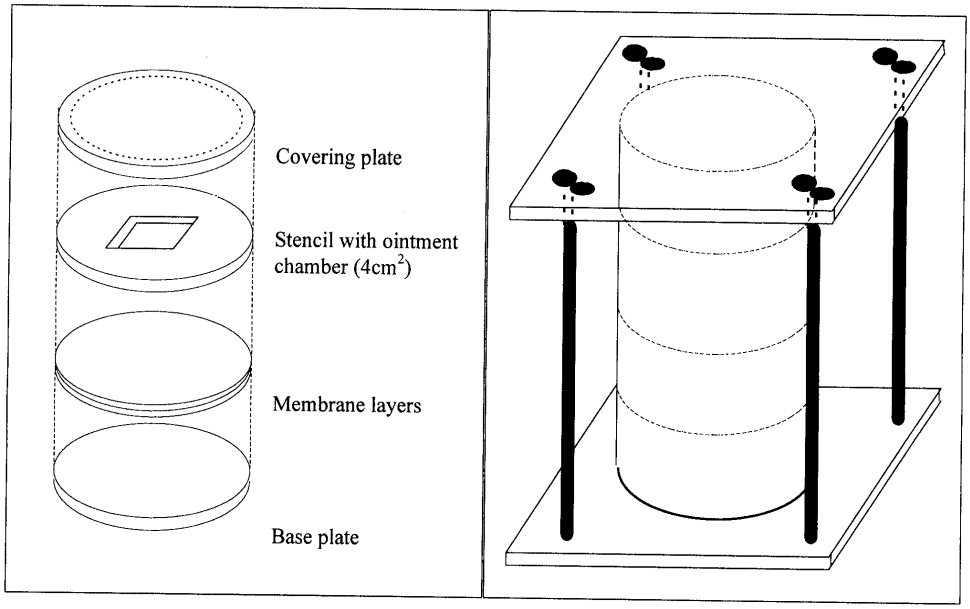

Fig. 1. Multilayer Membrane System

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The topical formulations (10 mg), which contained either 10%, 40% or 60% PG, 0.7% carboxymethylcellulose and water, were applied ($n=4$) to an exposed membrane area (4.0 cm^2), so that the thickness of the application was comparable to therapeutic situations. The experiments were carried out at 32 ± 0.2 °C. At selected time intervals (see below) the model apparatus was removed from the thermostated chamber, the amount of the applied formulation remaining on the exposed surface was removed, and the membranes were separated.

Preparation of the Membranes The technique for preparations of the membranes has been described.[9] Two grams of DD and 100 g collodium 4% were dissolved in a mixture of ethanol and ether (1.5:8.5, v/v) 200 g. This mixture was placed on a membrane preparing apparatus (self production, Fig. 2) providing membranes of uniform thickness (25 μm) and DD content (11.3 μl). The resulting membranes were cut into a circular shape ($r=2$ cm) after solvent evaporation.

Analytical Assays The amount of PG penetrated into each membrane was measured using GC/MS with 1,2-butandiol as internal standard. A Hewlett Packard gas chromatograph 5890, Series II, Waldbronn, Germany, was equipped with a MS detector 5971A. The capillar column (Permabond FFAP-DF-0.1, 25 m, 0.25 i.d.) operated at 250 °C, and samples of 1 μl were injected. Under these conditions PG had a retention time of 5.8 min.

Mathematical Analysis The penetration into the multilayer membrane acceptor was regarded as passive partitioning from the compartment 'vehicle' into the compartment 'DD membranes' (Fig. 3). The properties within the two compartments were assumed to be homogeneous. In this case, Fick's first law of diffusion can be applied to describe the intercompartmental transport taking into consideration the partition behaviour. Fick's first law is generally used under steady-state and pseudo-steady-state conditions so that percutaneous absorption data can be simulated.[10] Under these circumstances the widely used application of Fick's law by Higuchi[11] describes the penetration into sink acceptors from vehicles with constant time-independent drug concentrations, which is not generally the case.

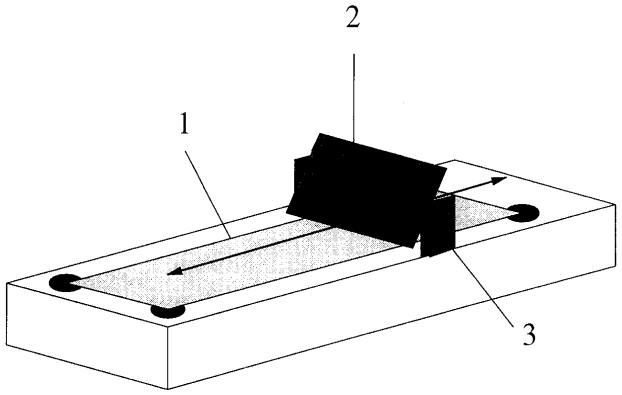

Fig. 2. Membrane Preparation Apparatus

The metal sheet (2) is attached to side pieces (3) that move up and down the glass plate (1), and distributes the lipid membrane solution homogeneously on the plate where the organic solvent can evaporate. The angle between the metal sheet and the glass plate can be varied resulting in different membrane depths.

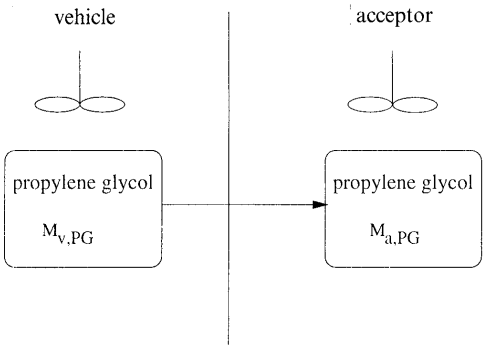

Fig. 3. Compartment Model for PG Penetration from Hydrogels into an Acceptor System (DD Membranes)

Stirred systems are assumed.

To derive the intercompartmental transport kinetics for the penetration model shown in Fig. 3 the following time dependent form of the diffusion law was used taking into account the partition between vehicle and acceptor:

$$\frac{dM_{a,PG}}{dt}=-\frac{DA}{h^*}(c_A-P\cdot c_V)_t \tag{1}$$

where M is the mass penetrated into the acceptor (A), c are the time-dependent concentrations in the vehicle (V) and the acceptor (A), h^* is the diffusion way, D the diffusion coefficient, A the area of application, and P describes the partition behaviour of the penetrant between vehicle and acceptor. In this case, P is not the partition coefficient as PG is miscible with both phases and penetrates quantitatively from the vehicle into the acceptor system. It was derived using the final penetration data (described by Bendas[6]).

Since the acceptor was regarded as one compartment a parameter k_{PG} describing the penetration kinetics into this compartment was introduced:

$$k_{PG}=\frac{DA}{h^*} \tag{2}$$

It was obtained substituting c by M/V:

$$\frac{dM_{a,PG}}{dt}=k_{PG}\cdot\left(P\frac{M_V}{V_V}-\frac{M_A}{V_A}\right) \tag{3}$$

where V are the volumes and M_V is the amount of PG remaining in the vehicle. Denoting the applied mass of the penetrant (PG) by M_o and taking into account the relation

$$M_{v,PG}(t)=M_o-M_{a,PG}(t)\,, \tag{4}$$

the following equation was derived :

$$\frac{dM_{a,PG}}{dt}=k_{PG}\cdot\left(P\frac{M_o-M_{a,PG}}{V_V}-\frac{M_{a,PG}}{V_A}\right) \tag{5}$$

with the initial condition

$$M_{a,PG}(0)=0 \tag{6}$$

The analytic solution of the initial value problem (Eqs. 5, 6) is given by

$$M_{a,PG}=\frac{\dfrac{P\cdot M_o}{V_V}}{\dfrac{P}{V_V}+\dfrac{1}{V_A}}\left[1-e^{-k_{PG}\{(P/V_V)+(1/V_A)\}t}\right] \tag{7}$$

P is

$$P=\frac{c_A}{c_V}=\frac{\dfrac{M_{a,PG\infty}}{V_A}}{\dfrac{M_o-M_{a,PG\infty}}{V_V}} \tag{8}$$

Equation 7 was fitted to the experimental data to get the kinetic parameter k_{PG}. The confidence intervals were then calculated. Due to the nonlinearity of the solution of the initial value problem (Eq. 5), (Eq. 6) with respect to the estimated parameter k_{PG}, approximate confidence intervals were calculated using only first order information.[12]

The software MATLAB (The Mathworks, Inc., Natick, Mass., U.S.A.) was used for all calculations.

Results and Discussion

The statistical analysis of the penetration of PG is given in Table 1. It was found that PG penetrates almost completely into the multilayer membrane system. The GC/MS method was shown to have sufficient accuracy and sensitivity (Table 1). The standard deviations are below than 10 % and correspond to values found in other examinations with the multilayer membrane system.[6,8] Higher deviations for smaller time t-periods probably result from the influence of the temperature since the membrane system is very sensitive to differences in room temperature for $t\leq15$ min. It was found that PG penetrates

more slowly from the vehicle with 10% of PG than for the other vehicles. This is expressed by the introduced velocity parameter k_{PG} (Table 2). k_{PG} is lower for the penetration from the hydrogel with 10% PG than for those with a higher weight fraction of PG. The higher amount of PG available in the vehicles with 40% and 60% PG, respectively, should be responsible for this phenomenon. This phenomenon is discussed in the literature for the transport into and across the skin as well[13] and is traced back to the decrease in membrane resistance. However, while this is easily explained for the skin due to the water extraction properties of PG,[13] this explanation is not valid for the DD membranes since they do not contain any water. The extraction of DD by PG can also be excluded according to Bendas.[6] One could hypothesize that the supply of PG from the vehicle is involved in the penetration kinetics of PG and, therefore, reduces the value of the kinetic parameter k for the hydrogel with 10% PG. Furthermore, decreasing PG weight fractions lead to reduced thermodynamic activities of PG and to declining penetration velocities expressed by the parameter k_{PG}.

Table 1. Penetration of PG from Vehicles with 10, 40 and 60% PG (Amount of PG Applied = 1000, 4000 and 6000 μg, Respectively) into DD Membranes ($n=4$), Mass Penetrated into the Acceptor $M_{a,PG} \pm$ Standard Deviation (S.D.) in [μg] for the Times t in [min]

t	$M_{a,PG}$ 10% PG ± S.D.	$M_{a,PG}$ 40% PG ± S.D.	$M_{a,PG}$ 60% PG ± S.D.
5	116.9 ± 1.2	769.7 ± 112.5	828.3 ± 105.6
10	—	1207.7 ± 37.5	2245.8 ± 120.1
15	213.4 ± 19.8	1754.4 ± 48.6	2427.0 ± 142.5
20	218.4 ± 9.2	1787.7 ± 162.0	3241.5 ± 323.4
30	356.6 ± 14.0	1946.7 ± 170.0	3595.0 ± 323.5
35	—	2835.2 ± 13.8 ($n=2$)	—
50	—	3160.3 ± 51.2	—
60	550.4 ± 7.4	—	4702.5 ± 108.7
80	695.7 ± 27.1	—	—
100	753.2 ± 1.2	3654.3 ± 190.7	5390.0 ± 137.1
120	849.4 ± 2.6	—	—
180	954.4 ± 29.8	4050.3 ± 72.5 ($n=2$)	5856.5 ± 9.2 ($n=2$)

The parameter estimation led to a reasonable fit of the experimental data (Fig. 4). This was verified by determining the confidence intervals (Table 2). Therefore, the model equation (Eq. 5) derived for the initial value problem (Eqs. 3, 4) appears suitable to describe the experimental data for the penetration process of PG. This should be useful for further studies concerning mathematical modelling of drug penetration as it is possible to determine the extent of the cotransport of a drug dissolved in PG.

The study presented here is the basis for further investigations dealing with the solvent drag effect caused by PG penetration (see also Ref. 3). This co-transport of drugs dissolved in PG could be assessed mathematically depending on drug properties such as solubility and partition behaviour.

Considering the mathematical model described above, homogeneous compartments were assumed to be relevant. As shown in Fig. 5 for the gel with 10% PG, however, PG is not distributed homogeneously in the DD membranes until 180 min. Up to this point diffusion within the DD membranes generates penetration profiles. Fick's second law of diffusion should be used to utilize these profiles in order to derive the parameters describing the diffusion process within the DD membranes, *e.g.* the diffusion coefficient. Calculating diffusion coefficients, the comparison between *in vitro* membrane data and skin data will be possible in order to evaluate the multilayer membrane model. This is important not only for the

Table 2. Estimated Kinetic Parameter k_{PG} with 90% Confidence Intervals for the PG Transport from Vehicles with 10%, 40%, and 60% PG into DD Membranes (Partition Value $P=9.7$)

Vehicle in % PG	k_{PG} in $cm^3 \cdot s^{-1}$	Confidence interval level 90%
10	$2.38 \cdot 10^{-4}$	$[2.38, 2.39] \cdot 10^{-4}$
40	$4.98 \cdot 10^{-4}$	$[4.96, 5.01] \cdot 10^{-4}$
60	$5.49 \cdot 10^{-4}$	$[5.46, 5.52] \cdot 10^{-4}$

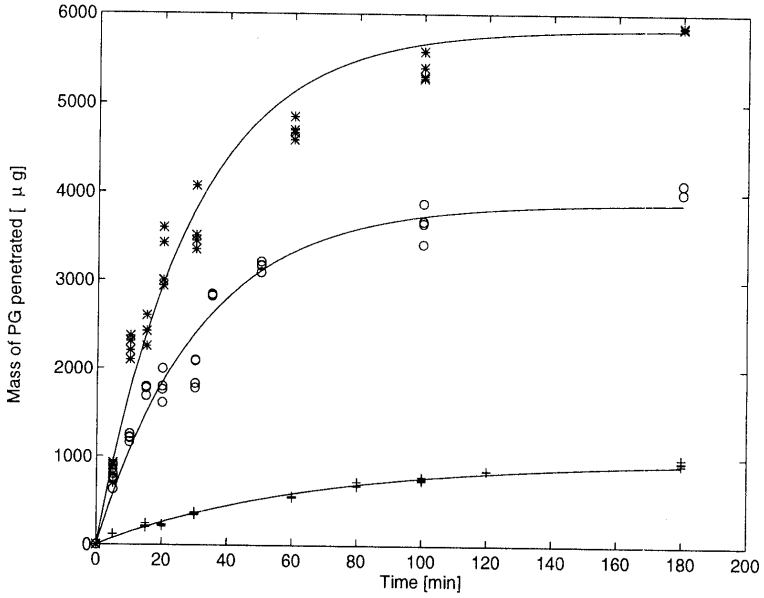

Fig. 4. Parameter Estimation for the Penetration of PG into the Artificial Membrane System

Experimental data for the cumulative amount of PG penetrated into the DD membranes: ***, vehicle with 60% PG; ∘∘∘, 40% PG; + + +, 10% PG.

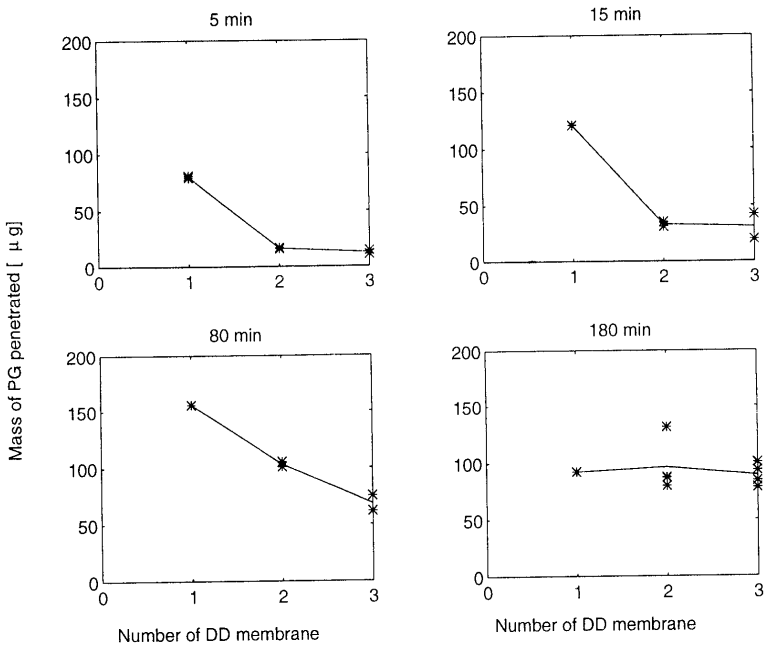

Fig. 5. Penetration Profiles for the PG Penetration into the DD Membrane System after Several Time Periods (5, 15, 80, 180 min)
Hydrogels with 10% PG.

penetration of cosolvents such as propylene glycol, but also for the penetration of potential drugs. In order to assess the role of co-transport processes induced by solvent flow, however, compartmental models such as the mathematical model presented should be useful since they express the quantitative solvent penetration behaviour. To characterize the influence of solvent drag on drug penetration consideration of both the solubility of the co-penetrating drug in the vehicle and the partition behaviour is required, whereas solvent penetration profiles in the membrane are less relevant.

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