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Research paper

Utilizing vehicle imbibition by a microporous membrane and vehicle viscosity to control release rate of salbutamol

G. Imanidis*, R. Imboden[1]

School of Pharmacy, University of Basel, Basel, Switzerland

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Abstract

The possibility to control the release rate of salbutamol through the hydrophobic Celgard® 2500 polypropylene membrane by varying the composition and the viscosity of hydrophilic drug vehicles was investigated. The use of the polypropylene membrane as a control membrane for reservoir-type drug delivery systems was envisaged and water, glycerol, isopropyl alcohol and ethanol, pure or as binary mixtures were studied as vehicles. With varying composition of the vehicle, a sharp change of its imbibition by the membrane from practically none to a complete filling of the membrane pores occurred, which coincided with a steep rise of the drug permeability for the membrane. From this was inferred that the vehicle-filled pores were the dominant permeation pathway, while when no vehicle was imbibed, transport took place by way of the polymer domain of the membrane. In case of imbibition, the permeation rate could be modulated in a predictable fashion by adjusting the viscosity of the vehicle. This demonstrated that drug release could be controlled by utilizing the in situ interaction of the vehicles with this membrane, leading to imbibition and establishment of a permeation pathway with pre-determined viscosity in the pores of the membrane.

Keywords: Salbutamol; Celgard® polypropylene membrane; Vehicle imbibition; Membrane-controlled drug release

1. Introduction

In previous work [1], the permeation of salbutamol through the Celgard® 2500 microporous polypropylene membrane was studied using purely aqueous drug vehicles with different pH values. The amphoteric properties of salbutamol were found to play an important role for membrane permeation; permeation rates, however, were invariably low which was attributed to the inherent properties of the membrane, foremost its lack of wetting by water. In an earlier report [2], the permeation of salicylic acid, a model drug, through the Celgard® membrane had been studied using lipids as vehicles. These vehicles were shown to modify the permeation characteristics of the membrane. This was explained based on the in situ interaction of the lipids with the membrane, resulting in imbibition of the vehicle into the membrane pores. The pore pathway appeared to dominate membrane permeation and it was proposed that drug release rate was modulated based on the viscosity of the lipid vehicles, which were imbibed into the pores.

In the present work, the permeation of salbutamol through the Celgard® membrane was studied using hydrophilic, water-containing or water-miscible vehicles. Glycerol, isopropyl alcohol and ethanol were used as solvents; these are commonly used for reducing the hydrophilicity of water. The goal was to evaluate these vehicles with respect to their suitability for improving drug permeation compared to that obtained with pure water [1] and identify potential methods to prospectively control drug delivery rate. These vehicles were evaluated as an alternative to the lipid vehicles employed earlier [2], which may be

* Corresponding author. School of Pharmacy, University of Basel, Totengaesslein 3, 4051 Basel, Switzerland. Tel.: +41-61-261-7940; fax: +41-61-261-7907.

[1] Present address: Drossapharm, 4144 Arlesheim, Switzerland.

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impractical to use, for example because of drug insolubility or incompatibility with components of the delivery system. pH 9.5 was normally used, because it provided the greatest permeation in the previous study [1].

2. Materials and methods

2.1. Drug and drug vehicles

Salbutamol was used in its base form. Drug vehicles were prepared using glycerol anhydrous, pharmacopoeia grade, >98% (E. Merck, Darmstadt, Germany), isopropyl alcohol, ACS, ≥99.5% (Fluka Chemie, Buchs, Switzerland), ethanol absolute, pharmacopoeia grade, ≥99% (Merck) and distilled water. These solvents were used pure or as binary mixtures prepared volumetrically. The pH of vehicles containing water was stabilized with the Teorell and Stenhagen universal buffer system [1,3]. This buffer was prepared in distilled water and its pH was adjusted in the final solvent mixture containing the drug.

The viscosity of the vehicles at 30°C was determined with a concentric cylinder viscometer (Brookfield, LVTDV-II, Stoughton, MA), which was calibrated with the Brookfield viscosity standard fluid 10.

2.2. Membrane and Vehicle Imbibition by the Membrane

The Celgard® 2500 membrane (Hoechst Celanese Corp. Charlotte, NC) was used which was characterized previously in detail [2,4]. The porosity of the membrane and its volume fraction occupied by drug vehicle, which may enter the pores of the membrane by imbibition, were determined by weight and buoyancy measurements following equilibration with the vehicles, as described in detail elsewhere [2]. Based on these measurements, the membrane volume, V, was subdivided into the following fractions:

$$V = f_{pol}V + \varepsilon V + \delta V \quad (1)$$

where, f_{pol} is the volume fraction corresponding to the polymeric material, ϵ is the volume fraction of the air-filled pores and δ is the volume fraction occupied by vehicle imbibed into the pores; hence, $\epsilon + \delta$ corresponds to the total porosity of the membrane.

2.3. Permeation

Permeation through the Celgard® membrane was determined in glass diffusion cells as described in detail earlier [1].

Different vehicle compositions containing drug were used in the donor chamber. The composition of the receiver solution was always identical to that of the donor vehicle in order to prevent diffusional transport of vehicle components and osmotic transport particularly of water through the membrane. Drug concentration in the donor was between 25 and 30 mg/ml for ethanol and isopropyl alcohol-aqueous buffer vehicles, except for pure isopropyl alcohol where it was about 12 mg/ml, while for isopropyl alcohol-glycerol vehicles it was around 20 mg/ml. These concentrations were equal to or just under the drug solubility in the vehicles at pH 9.5, wherever pH was applicable.

The duration of the permeation experiments varied between 250 and 5000 min depending on whether the permeation rate was high (short duration) or low (long duration) and was set according to the criterion discussed earlier [1]. Sink conditions as defined in [2] were maintained in the receiver solution throughout the experiment, by adjusting the sampling volume of the receiver solution.

Sampling was carried out as before [1] except that sample volume varied between 1 and 5 ml. The samples were diluted with water, when necessary, and Salbutamol was assayed by HPLC as previously described [1], except that the mobile phase was acetonitrile/0.02 M phosphate buffer pH 3, in a ratio 6/94. Permeability coefficients were determined as before [1].

3. Results and discussion

When in contact with the membrane, vehicles with different chemical compositions differed strongly in terms of their imbibition into the pores of the membrane (Table 1). Pure aqueous buffer was not imbibed, leaving the pores of the membrane to be entirely occupied by air. When increasing amounts of isopropyl alcohol were added to the aqueous buffer, no substantial change of imbibition was observed for isopropyl alcohol contents ≤21%, yet a sudden increase of imbibition was observed between 21 and 25% (Fig. 1, upper). For an isopropyl alcohol content ≥25%, the volume fraction of the membrane occupied by vehicle remained essentially constant. In the latter composition range, practically all air was displaced from the pores of the membrane which were entirely filled with vehicle. The fraction of polymeric material was roughly

Table 1
Vehicle imbibition by the membrane

Vehicle	f_{pol}^{c}	ϵ^{c}	δ^{c}
Aqueous buffer 100%[a]	0.485	0.515	0.001
2% v/v IPA[b] in aqueous buffer[a]	0.495	0.494	0.011
10% v/v IPA[b] in aqueous buffer[a]	0.511	0.461	0.028
21% v/v IPA[b] in aqueous buffer[a]	0.475	0.481	0.045
25% v/v IPA[b] in aqueous buffer[a]	0.457	0.021	0.522
50% v/v IPA[b] in aqueous buffer[a]	0.483	0	0.517
IPA[b] 100%	0.488	0.002	0.509
Glycerol 100%	0.479	0.506	0.015
25% v/v IPA[b] in glycerol	0.481	0.013	0.507
50% v/v IPA[b] in glycerol	0.454	0.058	0.487

[a]Vehicles at pH 9.5.
[b]IPA: isopropyl alcohol.
[c]Parameters were defined in Eq. (1).

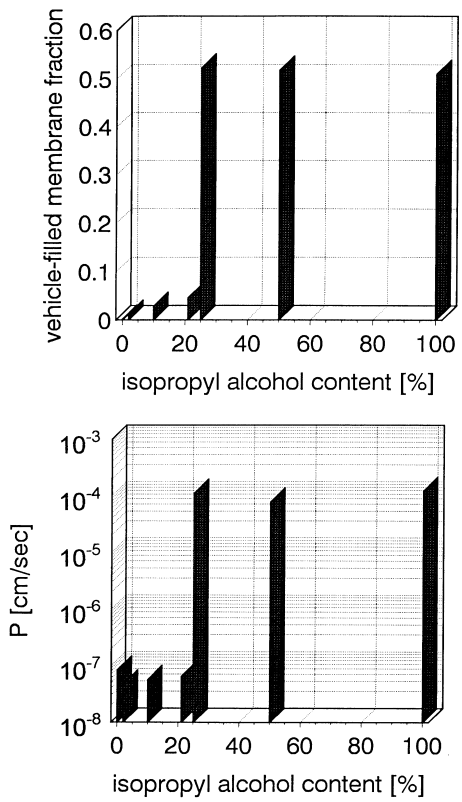

Fig. 1. Upper: fraction of membrane volume occupied by imbibed vehicle (parameter δ) as a function of the isopropyl alcohol content in volume-% of aqueous buffer-isopropyl alcohol vehicles (data taken from Table 1). Lower: permeability coefficients of salbutamol for Celgard® membrane and aqueous buffer-isopropyl alcohol vehicles as a function of the isopropyl alcohol content in volume-% of the vehicles; pH 9.5, where applicable; mean values of three measurements with standard deviations between 1 and 5% relative to the mean, except for pure aqueous buffer where 14 measurements and a standard deviation of 15% apply.

independent of the composition of the vehicle, implying that no swelling of the membrane took place during soaking in the vehicles. This was confirmed by thickness measurements.

This imbibition pattern can be rationalized based on the hydrophobic nature of the Celgard® polypropylene membrane. Water evidently does not wet the membrane and therefore does not enter into its pores. As an increasing amount of the less hydrophilic isopropyl alcohol is added to the aqueous buffer, wetting is improved leading to imbibition. The sudden onset of imbibition within a narrow composition range suggests a rather narrow pore size distribution of the membrane. This was confirmed previously by scanning electron micrographs [2].

Glycerol exhibited no notable imbibition by the membrane, apparently because of its high hydrophilicity. Addition of the less hydrophilic isopropyl alcohol to glycerol elicited an imbibition increase which was analogous to that of water (Table 1).

Permeation always followed zero order kinetics. The permeability coefficients for the aqueous buffer-isopropyl alcohol vehicles are given in Fig. 1, lower. Lag-time varied between 100 and 500 min (average around 300 min) for permeability coefficients of the order of 10^{-8} cm/s while it was practically equal to zero for permeability coefficients of the order of 10^{-4} cm/s.

An abrupt increase of permeability coefficient values by more than three orders of magnitude occurred in the range of isopropyl alcohol content of the vehicle between 21 and 25%. This coincides with the sudden onset of vehicle imbibition by the membrane taking place in the same range of vehicle composition (Fig. 1). The permeability did not change much above and below this composition threshold. These results demonstrate that the presence of vehicle in the pores dramatically raises drug permeation rate.

When no imbibition occurs, permeation can take place only via the amorphous polypropylene domains of the membrane which, at the temperature of the experiment, are in the rubbery state. This permeation pathway gives rise to quite low permeability coefficients, arguably as a result of the high viscosity of the amorphous polymer domains and of the low partitioning of the drug, which has several hydrophilic groups, into the markedly hydrophobic polypropylene [1]. Variation of the vehicle composition in the area below 21% isopropyl alcohol did not seem to significantly affect diffusion or partitioning in the membrane. When the membrane pores are filled with vehicle, permeation can take place through the pores, as well as through the amorphous membrane domains. The resulting strongly elevated permeability coefficients provide evidence that extensive permeation takes place via the pore pathway which, therefore,

Table 2
pH dependence of permeability coefficients

Vehicle composition[c]	P [cm/s] (SEM)[a] [cm/s]		
	pH 3	pH 9.5	pH 12
Aqueous buffer 100%	4.86×10^{-9} (2.2×10^{-10})	8.24×10^{-8} (3.35×10^{-9})	1.7×10^{-8} (9.17×10^{-10})
50% v/v IPA[b] in aqueous buffer	7.68×10^{-5} (1.04×10^{-6})	7.61×10^{-5} (2.57×10^{-7})	7.51×10^{-5} (1.47×10^{-6})

[a]Numbers in parentheses denote standard error of the mean. Number of observations for the aqueous buffer was between eight and 14, for the IPA-aqueous buffer vehicle was equal to three.
[b]Isopropyl alcohol.
[c]Data for purely aqueous vehicles were taken from Ref. [1].

dominates drug permeation through the membrane. This can be explained by the low viscosity of the vehicle compared to the polymeric material and the absence of an unfavourable partitioning step. It is considered unlikely that imbibition of vehicle into the pores alters the properties of the polymeric material to an extent that it would account for the observed increase in permeability. Diffusion of drug in vehicle that is contained in the pores, expectedly did not depend on the chemical composition of the vehicle per se. (For a discussion on the effect of vehicle viscosity on diffusion, see below). Another solvent that is also imbibed by the membrane, i.e. ethanol, gave a membrane volume fraction occupied by vehicle of 0.59 and a permeability coefficient of 1.8×10^{-4} cm/s, these results being quantitatively very similar to and, therefore, confirming those of isopropyl alcohol. The dominance of the vehicle-filled pore pathway in membrane permeation was also demonstrated in an earlier study with the same membrane using lipid vehicles and salicylic acid as a model drug [2].

The dependence of permeation on pH was examined in conjunction with the occurrence, or lack, of vehicle imbibition. In an earlier study, it was shown that salbutamol permeation through polypropylene from purely aqueous vehicles, that were not imbibed by the Celgard® membrane, was highly dependent on pH (Table 2) [1]. This was interpreted in terms of the differences in membrane/water partition coefficients of the different ionized species of salbutamol. When the vehicle was imbibed by the membrane as was the case for the aqueous buffer-isopropyl alcohol vehicle of the data in Table 2, the permeation rate did not depend on pH. This is consistent with the view that permeation takes place predominantly via the vehicle-filled pores, where no partitioning step is involved.

The present results demonstrate that the drug permeability characteristics of the Celgard® membrane can be modified using different drug vehicles. The modification of the permeability relies on the in situ interaction of the vehicle with the membrane, which ultimately leads to the ensuing, or not, of vehicle imbibition by the membrane. Thus, imbibition emerges as the principal event governing permeation, that is effected by variations in the chemical composition of the vehicle.

A practical implication of this may consist in the prospective controlling of the drug release rate using the same membrane, by changing the drug vehicle. However, the change of membrane permeability from non-imbibed to imbibed vehicles was too large and took place within a too narrow composition range to allow a gradual and, therefore, meaningful variation of the release rate of the drug. Yet, since permeation takes place predominantly via the vehicle-filled pores, modulating the diffusion rate in the pores by varying the viscosity of the vehicle should, in theory, provide the possibility to finely adjust the rate of permeation. In an earlier study [2], the effect of various lipid vehicles, which were imbibed by the membrane, on permeability was also explained based on the varying viscosity of those vehicles.

The hypothesis of a viscosity-based control of drug release with vehicles imbibed by the Celgard® membrane is tested in the present work using, in addition to isopropyl alcohol-aqueous buffer, isopropyl alcohol-glycerol vehicles. Pure glycerol was not imbibed by the membrane (Table 1) and gave accordingly a very low permeability coefficient, of the order of 10^{-10} cm/s. When 25%, or more, isopropyl alcohol was added to glycerol, practically complete imbibition of the vehicle into the pores of the membrane was observed. Zero-order permeation kinetics with essentially no lag time was obtained with these vehicles.

Since glycerol is a rather viscous fluid, isopropyl alcohol-glycerol vehicles had a considerably higher viscosity than isopropyl alcohol-aqueous buffer ones. In Fig. 2, permeability coefficients obtained with imbibed vehicles are plotted against the viscosity of the vehicles. The data points lie on a straight line with the slope of −1.06 on the double-logarithmic scale. From this, it can be concluded that the measured permeability coefficients are inversely proportional to the viscosity of the vehicle being imbibed in the pores of the membrane. This reflects what would be predicted by theory for a diffusion process.

The permeability coefficient, P_{pores}, corresponding to the pore pathway may be described by Eq. (2).

$$P_{\text{pores}} = \delta \frac{F D_{\text{veh}}}{\tau h} \tag{2}$$

with

$$D_{\text{veh}} = \frac{kT}{6\pi r \eta} \tag{3}$$

where, δ is the volume fraction of the membrane occupied by vehicle, F is a dimensionless molecular restriction factor depending on the ratio of diameters between the drug mole-

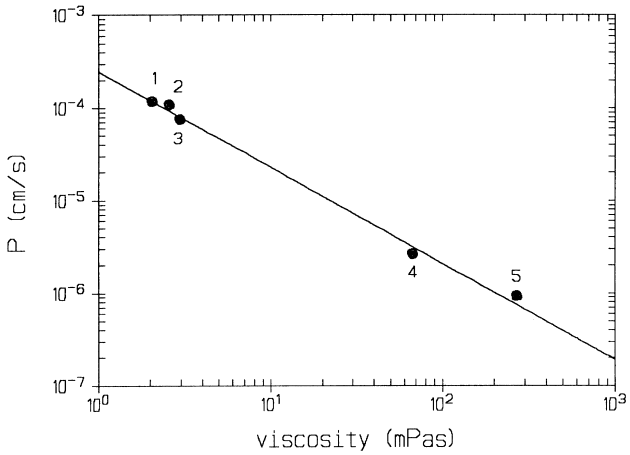

Fig. 2. Experimental permeability coefficients for vehicles imbibed by the membrane as a function of vehicle viscosity; mean values of three measurements with standard deviations between 1 and 5.5% relative to the mean. Numbers correspond to the following vehicles: 1, isopropyl alcohol 100%; 2, 25% v/v isopropyl alcohol in aqueous buffer pH 9.5; 3, 50% v/v isopropyl alcohol in aqueous buffer pH 9.5; 4, 50% v/v isopropyl alcohol in glycerol; 5, 25% v/v isopropyl alcohol in glycerol.

cule and the pores, h is the thickness of the membrane, τ is tortuosity factor, D_{veh} is diffusion coefficient of the drug in the vehicle, k is the Boltzmann constant, T is absolute temperature, η is vehicle viscosity and r is the molecular radius of the drug.

Combining Eq. (2) with Eq. (3), provides a theoretical expression for the proportionality constant of the relationship P_{pores} versus $1/\eta$ (Eq. (4)).

$$P_{pores} = \frac{\delta F k T}{6\pi r \tau} \frac{1}{\eta} \quad (4)$$

An experimental value for this constant is obtained from the fitted line of Fig. 2, and is equal to 2.611×10^{-9} N/m. By equating this number with the expression from Eq. (4), an estimate for the parameter τ can be obtained. For the calculation, the following numerical values were used: for δ, 0.508, which is an average value of all vehicles involved; for h, 25 μm; for F, 1, since the pore diameter is far greater than the molecular diameter; for r, 3.98×10^{-10} m, which was estimated from the Stokes–Einstein equation (Eq. (3)) using a diffusion coefficient of the drug in distilled water (viscosity = 0.89 mPas) at 25°C of 6.16×10^{-6} cm^2/s. The resulting tortuosity factor, τ, is equal to 4.34. This value is in rather good agreement with the one reported earlier for this membrane with lipid vehicles (i.e. 3.33) [2] and is considered to be reasonable in view of the pore structure of the Celgard® membrane. The departure of the value of tortuosity from unity might be due to the high density of fibrils occupying the pores of the membrane, which result from the amorphous domains of the membrane upon stretching.

These results clearly demonstrate that the rate of membrane permeation of the drug is controlled in a predictable fashion by the viscosity of the vehicles which are imbibed in the pores of the membrane. Thus, vehicles which interact in situ with the membrane and enter into its pores can be utilized for modulating the drug release rate characteristic of the membrane, by appropriately selecting their viscosity. Comparison of the present work with earlier studies shows that this mechanism for release control applies irrespective of the chemical nature of the vehicle, provided that imbibition takes place which leads to the establishment of the pore pathway for permeation.

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