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Report

Topical Drug Delivery from Thin Applications: Theoretical Predictions and Experimental Results

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Stainless-steel templates of various thicknesses (75, 200, 800, and 1600 μm) were used to apply propylene glycol/water gels containing methyl or propyl *p*-aminobenzoates to silicone rubber membranes, and drug delivery was studied with the use of the Bronaugh diffusion cell under conditions in which the drug was initially in thermodynamic equilibrium with respect to the application and membrane. Theoretical diffusion profiles were generated with the use of a model which assumes that diffusional gradients exist within the application. To use the model equation, previously derived for the initial condition in which the drug is in thermodynamic equilibrium with respect to the application and membrane, drug diffusivity in both the application and the membrane and the drug's membrane/vehicle partition coefficient were independently determined. In general, agreement between experimental and theoretical results was within 25%.

KEY WORDS: topical delivery; thin films; diffusion cells; flow-through.

INTRODUCTION

Topical drug delivery is insufficiently researched, and the mechanisms whereby drugs are delivered from thinly applied applications into and through the skin are poorly understood. A methodology for the application of topical formulations to membranes has been described recently (1). Although the results obtained from these studies revealed that the technique was reliable, flaws existed within the experimental approach which limited its usefulness. In particular, the flow-through diffusion cell used in these studies exhibited slow transport of the receiver contents to the collection site, which shifted the diffusional profiles toward longer times, resulting in loss of early detail. Additionally, the membranes used in these early studies showed a tendency to adsorb the model permeants. This paper reports on experiments performed with an improved experimental design in which these problems have been surmounted. The experimental results are presented and compared with theoretical predictions generated from a recently derived equation (2) describing drug release from topical applications of known thickness.

MATERIALS AND METHODS

Materials. Methyl and ethyl *p*-aminobenzoate (Aldrich, Milwaukee, WI) were used as received. Propyl and pentyl *p*-aminobenzoate were synthesized by a previously described method (3). Methyl and propyl *p*-aminobenzoate were used as model permeants; ethyl and pentyl *p*-aminobenzoate were used as internal standards in the HPLC assays. HPLC-grade methanol (Mallinckrodt, Paris, KY) was used for all assays. Fillerless, nonreinforced dimethylpolysiloxane sheets (Silastic medical-grade polymer, Gift, Dow Corning, Midland, MI) were manufactured at a thickness of 250 μm as described in a following section and were used as membranes. Propylene glycol (Fisher, Fair Lawn, NJ) was used in the gels, and carboxypolymethylene (Carbopol 940, B. F. Goodrich, Cleveland, OH) was used as the gelling agent. Diethylene oximide (Morpholine, Sigma) and sodium hydroxide (Fisher) were used as the neutralizing agents for gels prepared with and without propylene glycol, respectively. Pentanol (Sigma) and *p*-nitrobenzoyl chloride (Sigma) were used in the synthesis of pentyl *p*-aminobenzoate. The propyl ester was synthesized from *p*-aminobenzoic acid and propyl alcohol (Sigma, St. Louis, MO). 3A alcohol and chloroform (Sigma) were used as solvents in the synthesis.

Manufacture of Membranes. Fillerless dimethylpolysiloxane membranes were prepared by first adding a catalyst to uncured dimethylpolysiloxane. The beaker containing this mixture was placed under vacuum for 10 min to draw off unwanted air bubbles. The mixture was poured into a 250-μm-deep mold (comprised of a stainless-steel base covered by a polyethylene sheet and a 250-μm-thick template), and a straight edge was drawn across the upper face of the template in order to spread the polymer solution. A polyethylene sheet was then placed atop the polymer film, and an upper plate was lowered into place. The entire membrane-forming apparatus was placed into a Carver press, and 2000 lb/in.^{2} of pressure was applied for 20 min. In order to assure that the curing of the polymer was complete, the apparatus was left overnight in an oven maintained at 50°C. To test for uniformity, the membrane was placed between two glass

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cover slides, and a micrometer was used to measure the thickness. A minimum of five measurements was made on each membrane. Overall, the average membrane thickness was found to be 250 μm (±20 μm).

Assay. Methyl *p*-aminobenzoate and propyl *p*-aminobenzoate were assayed by previously described HPLC methods (1). Gel samples were prepared for HPLC analysis by first weighing a gel segment and placing it into a screw-top test tube. Five milliliters of a 10% (w/v) solution of CaOH was added, along with an appropriate volume of an aqueous solution of the internal standard. The test tube was then placed onto a shaker and agitated until the gel appeared to be totally disrupted. This mixture was filtered, and 5 ml of ether was added. After shaking the ether/water mixture for 5 min, the ether phase was removed and placed into a separate test tube. The ether was evaporated, the extracted drug and internal standard were reconstituted via the addition of 1 ml of mobile phase, and samples were assayed by HPLC. Linear standard curves were obtained by performing the extraction procedure on standard solutions of methyl *p*-aminobenzoate containing a uniform amount of blank gel.

Solubility Studies. An excess of ester was mixed with the solvent system under study and placed into a jacketed flask. The resulting suspension was stirred at 33°C for 3 days. Initial studies indicated that equilibrium was achieved within a day. Samples were collected in triplicate on day 2 and day 3, the latter as a check on the equilibrium condition. Samples were obtained via warmed, glass-wool-tipped pipets. The glass-wool wad removed all particulate matter as the samples were drawn. The samples were appropriately diluted with mobile phase and assayed by HPLC.

Determination of Partition Coefficients. For most of the conditions under which transport was studied, an equilibrium method (4) was used to determine the membrane/vehicle partition coefficient. Fillerless dimethylpolysiloxane membrane segments were ground into very small pieces, and portions of this material were weighed into screw-top test tubes. A known volume of a drug solution of known initial concentration was then placed into the test tube, and the mixture was placed into a shaker bath at 33°C. For each vehicle studied, several tubes were prepared, samples were withdrawn from the bath at 2, 4, 6, and 7 hr, and the resulting solution concentrations were determined. For all cases, equilibrium was reached within 4 hr, irrespective of the vehicle, as evidenced by a leveling out (no further decrease) in the solution concentration. Partition coefficients were calculated from the difference in starting and equilibrium solution concentrations with the use of Eq. (1) (see Data Treatment). For the purposes of calculation, the density of the dimethylpolysiloxane was assumed to be unity, which is a reasonable approximation (5).

For the systems containing only propylene glycol as the solvent, an alternative method of estimation was used, which was necessitated by the difficulty in detecting differences in starting and equilibrium concentrations for these systems. A small piece of membrane was weighed and placed into a drug/vehicle suspension which had been equilibrated for 3 days by constant stirring at 33°C. The membrane was allowed to equilibrate with the suspension for 3 days, then withdrawn and carefully but quickly washed with distilled water to remove drug particles adhering to the surface of the membrane. The membrane was placed into 10 ml of methanol and, after 24 hr, it was removed and placed into a fresh methanol bath for another 24 hr. The methanol solutions were then pooled and assayed for drug concentration, and the drug's membrane solubility was calculated from these data. Partition coefficients were estimated by dividing the drug's membrane solubility by the drug's solubility in the solvent system under consideration.

Preparation of Gels. Gels were prepared which consisted of methyl and propyl *p*-aminobenzoate dissolved in various propylene glycol/water solvent systems. The solvent systems used were water, 20% propylene glycol/80% water, 50% propylene glycol/50% water, and propylene glycol. For the water and 20% propylene glycol/80% water systems, 1 g of Carbopol 940 was dispersed via constant stirring in 97 ml of a solution of methyl or ethyl *p*-aminobenzoate. Gelling was effected upon neutralization of the dispersion by the addition of 2 ml of 10% sodium hydroxide. For the 50% propylene glycol/50% water and propylene glycol systems, 2 ml of morpholine was mixed with 97 ml of a drug solution, and 1 g of Carbopol 940 was dispersed via constant stirring. The mixture was heated to 70°C to facilitate gelling. The amount of drug dissolved in each gel was equivalent to 50% of its solubility in the solvent system under study.

Measurement of Methyl p*-Aminobenzoate Gel Diffusion Coefficients.* The device used in the measurement of methyl *p*-aminobenzoate gel diffusion coefficients consisted of two syringes whose ends were cut and ground flat. A gel containing the drug in solution was placed into one syringe and a gel containing no drug was placed into the other syringe. The gel was troweled flush with the flat ends of the syringes, and the syringes were joined at the flat ends, clamped, and placed into a water-tight plastic bag. The entire apparatus was immersed in a 33°C water bath, and after 5 to 7 hr the apparatus was retrieved from the bath and the two halves were very carefully separated at the gel interface. With the use of a plunger the gel was extruded from the syringe incrementally. Small gel segments (0.1–0.2 cm) were sliced off at the edge of the syringe with a glass cover slide and set aside to be weighed. Knowledge of a gel segment's weight, along with the syringe's cross-sectional area and the gel density, allowed for the calculation of the depth of a gel segment. By assaying the gel segments for methyl *p*-aminobenzoate, relative concentration versus distance profiles were constructed.

Application of Vehicle Films. A template with an application area of 0.32 cm^2 was used to obtain films of a specified thickness. Although the procedure for spreading the films was identical to the method previously described (1), the application device differed in that no stainless steel support screen was used. In addition, applications were occluded through the use of a tight-fitting cap, as opposed to the glass cover used in the previous studies.

Permeation Studies. Permeation studies were carried out with the use of a diffusion cell designed by Bronaugh (Crown Glass, Co., Sommerville, NJ). This flow-through cell was advantageous in that the receiver compartment has a volume of only 0.15 ml, allowing for rapid turnover of solvent in the chamber and near-immediate transfer of permeated substance to the collecting tubes in the fraction collector. The latter was also facilitated by using narrow-bore tubing (0.25 mm) and the minimal-length tubing (1.5 in.) to reach the collection point. In all experiments, pH 7.0 phosphate buffer was used as the solvent and was perfused at a rate of 0.7 ml/min. All studies were carried out at 33 ± 1°C. A vehicle film was applied to the membrane, the membrane and vehicle were allowed to equilibrate for approximately 2 hr, and the template and membrane were placed into the diffusion cell. The cell cap was screwed into place, and an inlet tube was connected to the cell. Samples were collected at preset intervals with an automatic fraction collector. The mass of drug collected during a particular interval was normalized by the total recovery of drug during the experiment, and normalized mass was plotted versus time.

DATA TREATMENT

Determination of Partition Coefficients. The following equation (4) was used for estimating the partition coefficient from the drug distribution experiment:

$$K = \frac{(C_0 - C_e) \cdot V}{C_e\,W} \qquad (1)$$

where C_0 is the initial solution concentration, C_e is the solution concentration at equilibrium, V is the volume of the solution, and W is the weight of the membrane.

Calculation of Membrane Diffusion Coefficients. The diffusion coefficient of the drug in the membrane was determined from the following equation:

$$D_m = \frac{P_T h_m D_{aq}}{K(D_{aq} - P_T \Sigma h_{aq})} \qquad (2)$$

where P_T is the steady-state permeability coefficient, h_m is the membrane thickness, K is the membrane/vehicle partition coefficient, D_{aq} is the aqueous diffusion coefficient, and Σh_{aq} is the sum of the aqueous diffusion layer thicknesses.

Determination of Gel Diffusion Coefficients. An explicit solution to the diffusion problem at hand has been presented (6):

$$C = \frac{C_0}{2}\left[1 - erf\frac{x}{2\sqrt{Dt}}\right] \qquad (3)$$

The diffusion coefficient of the model compound in each of the gel systems studied was deduced from experimental data by plotting C/C_0 versus distance and fitting the data to Eq. (3) with the use of BMDP, a computer program which iteratively performs nonlinear regression to obtain a best fit to the data. This method provides an estimate of the diffusivity, the accuracy of which is subject to errors associated with the regression method.

Generation of Theoretical Release Profiles. In order to generate relative mass versus time profiles, a theoretical model was used. An equation in terms of the Laplace transform in which drug is assumed to be initially in equilibrium with respect to the membrane and vehicle has been described (2) and is

$$\frac{M^*}{M_\infty} = \frac{\sqrt{D_m}K}{(h_v + h_m K)(s^{3/2})}\left\{\left(\sinh\sqrt{\frac{s}{D_v}}h_v \cosh\sqrt{\frac{s}{D_m}}h_m + K\sqrt{\frac{D_m}{D_v}}\sinh\sqrt{\frac{s}{D_m}}\,h_m \cosh\sqrt{\frac{s}{D_v}}h_v\right)\Big/ \left(K\sqrt{\frac{D_m}{D_v}}\cosh\sqrt{\frac{s}{D_v}}h_v \cosh\sqrt{\frac{s}{D_m}}h_m + \sinh\sqrt{\frac{s}{D_v}}h_v \sinh\sqrt{\frac{s}{D_m}}h_m\right)\right\} \qquad (4)$$

The terms in this equation are defined as follows: K is the membrane/vehicle partition coefficient, D_m is the membrane diffusion coefficient, D_v is the diffusivity in the vehicle application, and h_v and h_m are the thicknesses of the vehicle and membrane, respectively. Theoretical profiles were produced by this equation with the use of a computer program which uses the fast Fourier transform (9) to invert numerically a Laplace transform. The program was written in Fortran (7) and run on an IBM AT compatible computer.

RESULTS AND DISCUSSION

In order to use Eq. (4) to generate theoretical relative mass versus time profiles, it was necessary to determine several parameters associated with each given drug–vehicle system studied. These parameters were the drug's membrane/vehicle partition coefficient and the drug's diffusivity in both the gel and the membrane. In addition, it was necessary to determine the solubility of the methyl and propyl ester in each of the solvent systems used in order to carry out the experiments in a way such that in every system the drug was initially at approximately 50% of its maximum solubility or thermodynamic activity.

Table I shows the values of the solubilities and partition coefficients for the methyl and propyl *p*-aminobenzoate in the solvent systems at 33°C. As expected, the partition co-

Table I. Solubility and Partition Coefficients for Methyl and Propyl *p*-Aminobenzoate in the Various Solvent Systems at 33°C

	Methyl ester		Propyl ester	
Vehicle	Solubility (mg/ml)	Partition coefficient	Solubility (mg/ml)	Partition coefficient
Water	2.28	0.23	0.64	3.2
20% propylene glycol/80% water	4.41	0.090	1.47	1.1
50% propylene glycol/50% water	20.5	0.023	16.4	0.15
Propylene glycol	93.1	0.0057	281.0	0.0068

efficients decrease as the percentage of propylene glycol is increased, which reflects the solvent's increased affinity for the drug. For each of the propylene glycol/water systems studied, the ratio of the solubility in a given vehicle to the solubility in water closely parallels the ratio of the partition coefficient from water to the partition coefficient from the mixed vehicle. This seems to rule out the possibility that the presence of propylene glycol significantly alters the drug's solubility in the membrane. This is further reinforced by results of studies in which the solubility of the methyl ester in a silicone rubber membrane was directly determined. The solubility of the methyl ester in the membrane, as determined by the equilibration of the membrane with 50% propylene glycol and neat propylene glycol saturated solutions, was 0.48 and 0.53 mg/ml, respectively, a difference found to be statistically insignificant (Student's t test, $P < 0.05$).

The diffusion coefficients for methyl and propyl p-aminobenzoate were calculated by insertion of previously published 25°C steady-state permeability data (8) as well as partition coefficients (Table I) into Eq. (2). The permeability values were taken directly from the previously published paper in which the Franz diffusion cell was used to study the diffusion of the first five homologous p-aminobenzoates through 254-μm silicone rubber membranes. To use Eq. (2), it was also necessary to obtain D_{aq} and Σh_{aq} (the sum of the aqueous diffusion layer thicknesses surrounding the silastic membrane when it was configured in the diffusion cell). D_{aq} was taken from the literature (3) and Σh_{aq} was calculated by use of the equation $P_T = D_{aq}/\Sigma h_{aq}$, which is operative for the condition in which diffusion is controlled by the aqueous diffusion layers, a condition which prevails for the diffusion of pentyl p-aminobenzoate through silicone rubber. Therefore, Σh_{aq} was obtained by insertion of the permeability coefficient for pentyl p-aminobenzoate and D_{aq} into this equation. The literature value for the activation energy of p-aminoacetophenone is 7.55 kcal/mol, and this value was used to extrapolate the 25°C data to 33°C. Use of this value was reasonable in light of the similarities in size and chemical nature of the p-aminobenzoates and p-aminoacetophenone. At 33°C these values are 2.99×10^{-6} cm^2/sec for the methyl ester and 1.47×10^{-6} cm^2/sec for the propyl ester at 33°C. The twofold difference in these values is somewhat surprising when one considers the small difference in molecular volume between the two compounds. In a study by Flynn and Yalkowsky (3) the diffusivities of methyl and ethyl p-aminobenzoate in dimethylpolysiloxane membranes were virtually unchanged when determined by the lag time method. However, in a paper by Flynn *et al.* (5) investigating the permeability of alkanols through silicone rubber membranes, the diffusivity of n-propanol was found to be less than half of that observed for methanol when these values were calculated from steady-state permeability and partition coefficient data. It is possible that the large differences in diffusivities obtained by the lag time method and from steady-state data may be due to experimental error associated with the later method, as the calculation is based on two independent experimental measurements. Thus it appears that the calculation of a diffusion coefficient is somewhat dependent upon the methodology employed, and so the diffusivity values deduced in the present study are certainly within reasonable expectations.

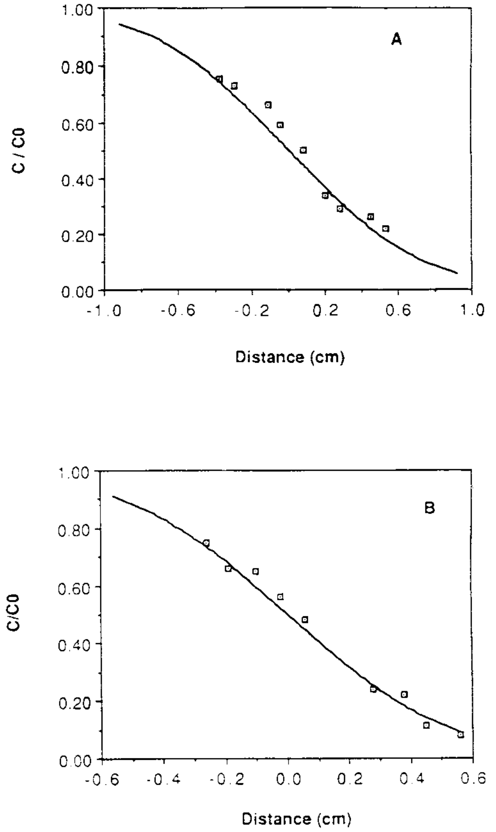

Fig. 1. Relative concentration versus distance (cm) for methyl p-aminobenzoate diffusion through a water gel (A) and a 50% propylene glycol/50% water gel (B).

Relative concentration versus distance profiles for methyl p-aminobenzoate diffusion in gels whose internal phases consist of water and 50% propylene glycol/50% water are shown in Fig. 1. As is expected, C/C_0 approximates 0.5 at the gel–gel interface ($X = 0$). The diffusivity of a drug in a solvent is proportional to the drug's molecular volume raised to the ⅓ power. Based upon the molecular volume ratios of the compounds under study, the diffusivity of the propyl ester in a particular gel system was obtained by multiplication of the diffusivity of the methyl ester by 0.95. These diffusivity values are found in Table II.

In Fig. 2, methyl ester delivery from a 75-μm application of a 50% propylene glycol/50% water gel is compared to theoretical predictions based upon Eq. (4), using all independently determined values for the mass transfer parameters.

Table II. Diffusion Coefficients (cm^2/sec) for Methyl and Propyl p-Aminobenzoate in the Various Solvent Systems at 33°C

	D_{Exp} ($\times 10^6$)	
Vehicle	Methyl ester	Propyl ester
Water	7.00	6.65
20% propylene glycol/80% water	4.70	4.47
50% propylene glycol/50% water	3.30	3.14
Propylene glycol	0.54	0.51

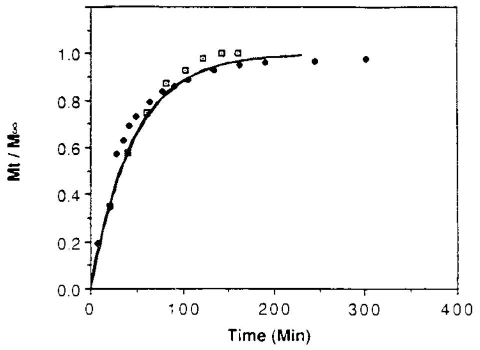

Fig. 2. Relative mass versus time for methyl p-aminobenzoate delivery from a 75-μm application of a 50% propylene glycol gel. Data points represent average results from two separate series of runs (n = 2, n = 3). The solid line represents the theoretical prediction based on Eq. (4).

Agreement with the prediction generated by Eq. (4) is excellent. Figure 3 shows methyl p-aminobenzoate diffusion from water gels when applied in various thicknesses. In general, good agreement between experiment and theory is observed.

The effect of application thickness on the relative release profile of the methyl ester formulated in a 20% propylene glycol gel is shown in Fig. 4, where data are compared with theoretical curves obtained from Eq. (4). In the case of the 75-μm application, the data begin to deviate from the theoretical profile after approximately 10 min. It is possible that this deviation is due partly to evaporation of water from the gel, which could not be totally inhibited, lowering the drug's membrane/vehicle partition coefficient. Included in Fig. 4 is a theoretical curve for the case where the application thickness is zero (h_v = 0). This curve represents the membrane control limit for the relative release profile from a 20% propylene glycol gel. It should be pointed out that the release profile for the 75-μm application falls well outside this limit.

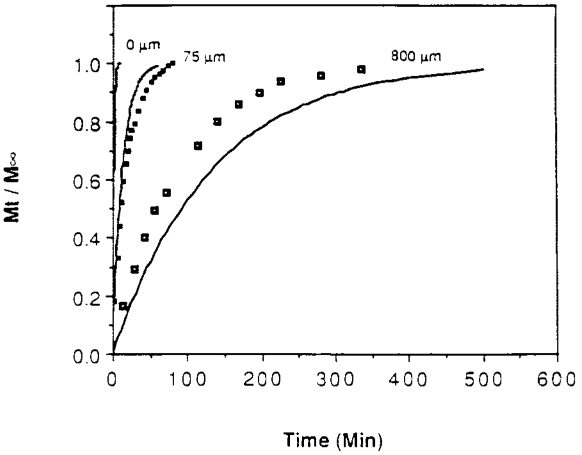

Fig. 4. Relative mass versus time for methyl p-aminobenzoate delivery from a 20% propylene glycol gel. Numbers indicate the thickness (μm) of application. Solid lines represent theoretical predictions based upon Eq. (4).

As the percentage of propylene glycol within a gel is increased, there is a decrease in both the drug's membrane/vehicle partition coefficient and its gel diffusion coefficient. Each of these changes leads to a decrease in the rate at which the drug is delivered into the membrane. These combined effects are illustrated in Fig. 5, where data and theoretical predictions are shown for the methyl ester's diffusion from 75-μm applications in various propylene glycol/water gels. As the propylene glycol concentration is increased in the gels, there is an increase in the time required for each gel to release its total drug content. With the exception of the pure propylene glycol gel, good agreement is observed between experimental and theoretical data. The failure of the propylene glycol gel to follow theory more closely is puzzling. It is suspected that propylene glycol plasticizes the membrane, thus yielding a higher drug diffusivity than that used in the theoretical calculation. Figure 6 shows methyl ester diffusion from 800-μm applications. Once again, the relative amount released at any set time decreases with an increase in the propylene glycol content of the gel. Similar results are shown in Figs. 7 and 8, in which propyl p-amino-

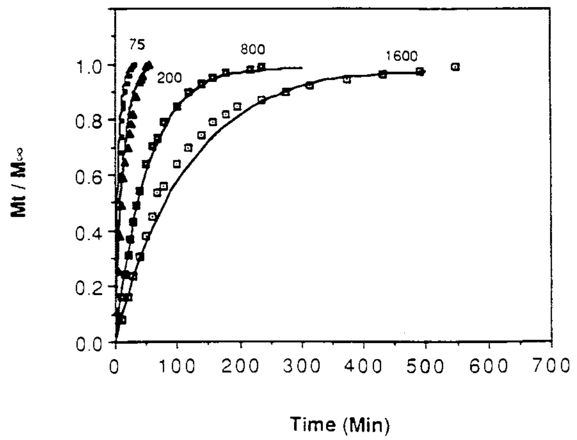

Fig. 3. Relative mass versus time for methyl p-aminobenzoate delivery from a water gel. Numbers indicate the thickness (μm) of application. Solid lines represent theoretical predictions based upon Eq. (4).

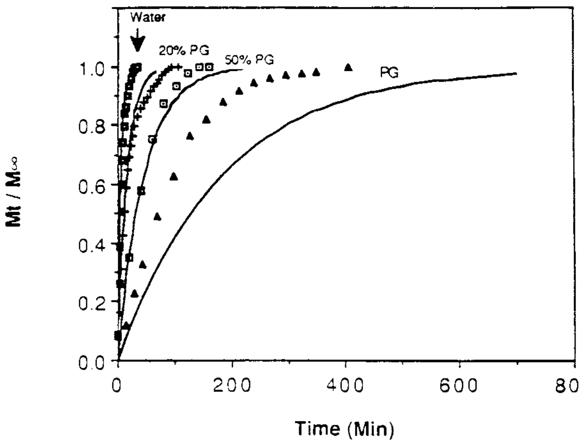

Fig. 5. Relative mass versus time for methyl p-aminobenzoate delivery from 75-μm applications of various propylene glycol (PG)/water gel systems. Gel composition is indicated on each plot. Solid lines represent theoretical predictions based upon Eq. (4).

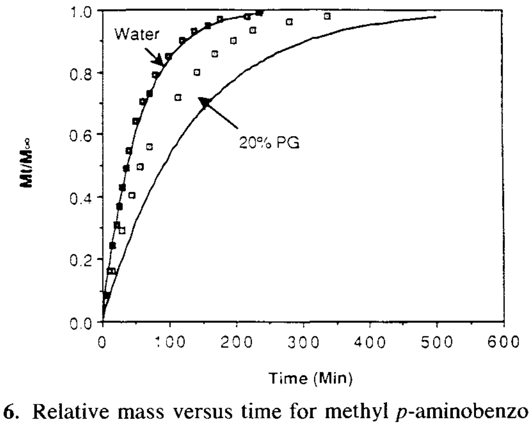

Fig. 6. Relative mass versus time for methyl *p*-aminobenzoate delivery from 800-μm applications of various propylene glycol (PG)/water gel systems. Gel composition is indicated on each plot. Solid lines represent theoretical predictions based upon Eq. (4).

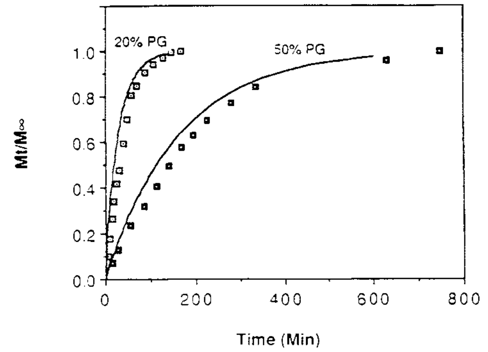

Fig. 8. Relative mass versus time for propyl *p*-aminobenzoate delivery from 800-μm applications of various propylene glycol (PG)/water gel systems. Gel composition is indicated on each plot. Solid lines represent theoretical predictions based upon Eq. (4).

benzoate diffusion from propylene glycol/water gels is shown. In general, data and theoretical predictions are in close agreement. Equation (4) tends to predict a relative release profile which is more compressed in time than that of the data under most of the experimental conditions. This possibly suggests the membrane diffusion coefficient is slightly underestimated.

As in the case of the methyl ester, there is a large discrepancy between the data and the theoretical prediction for the 75-μm application of a propylene glycol gel containing the propyl ester. Figure 9 compares the diffusional profiles for the methyl and propyl esters in 75-μm applications of propylene glycol gels. The model predicts a sizable difference in the diffusional profiles for the two esters, for although the partition coefficients are virtually identical, there is a sizable difference in the membrane diffusion coefficients. However, the experimental profiles are virtually superimposable, and both show a much faster relative release profile than predicted, indicating that the diffusivities are closer than estimated from independent experiment and theory. This strengthens the argument that propylene glycol in these systems is changing the diffusional characteristics of the membrane, resulting in similar membrane diffusion coefficients for the methyl and propyl esters. However, as pointed out earlier, there is no evidence to suggest that the presence of propylene glycol is affecting the partition coefficient. Providing diffusivities are comparable, the diffusional profiles for the two compounds are expected to be similar, as their estimated partition coefficients are virtually the same.

In summary, a methodology for the study of drug release from topical applications has been refined such that realistic, reproducible finite dose diffusional profiles are readily obtained. A systematic investigation into the role of vehicles in drug delivery from topical applications reveals that the application thickness, partition coefficient, and vehicle diffusion coefficient work together in determining a characteristic drug diffusion profile for a particular system. A previously derived model equation has been tested for the case where the application and membrane are assumed to be in thermodynamic equilibrium prior to the initiation of an experiment. Theoretical profiles have been generated by insertion of experimentally determined parameters into the equation, and for most cases, agreement between theoretical predictions and experimental results is within 25%. The utilization of this new *in vitro* testing methodology, together with the theoretical model which has been presented, may aid in the development of topical gels and ointments as well

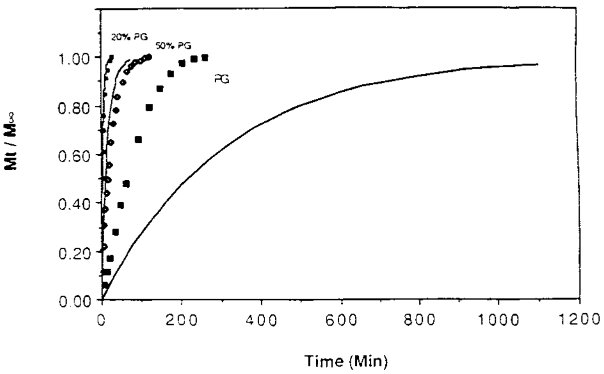

Fig. 7. Relative mass versus time for propyl *p*-aminobenzoate delivery from 75-μm applications of various propylene glycol (PG)/water gel systems. Gel composition is indicated on each plot. Solid lines represent theoretical predictions based upon Eq. (4).

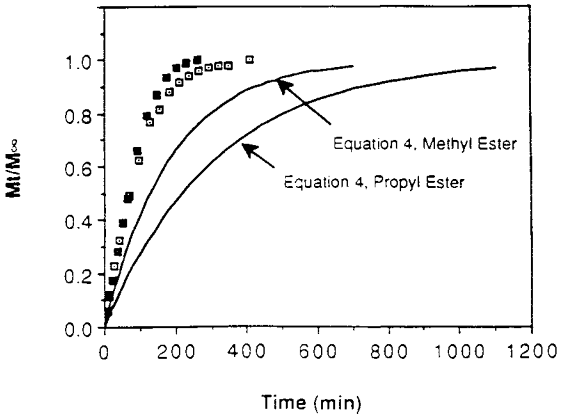

Fig. 9. Comparison of methyl (■) and propyl (□) ester delivery from 75-μm propyleneglycol gels. Solid lines represent theoretical predictions based upon Eq. (4).

as transdermal patches in which drug is contained within the adhesive.

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