QUASI-STEADY STATE MODEL FOR PERCUTANEOUS ABSORPTION OF LOCAL ANESTHETICS

K.J. Miller Jr. and D.O. Shah

Center for Surface Science and Engineering
Departments of Chemical Engineering and Anesthesiology
University of Florida, Gainesville, Fl., USA 32611

There have been many models proposed which attempt to predict the diffusion of substances through the skin. The major assumption made in most of these models is that of steady state with respect to concentration profile within the skin. A new model has been developed which avoids the limiting assumptions of previous work and allows the prediction of concentration within the skin as well as flux through the skin at any time.

$$C(x,t) \approx C(0,t) + (C(L,t) - C(0,t))\frac{x}{L} + \frac{2}{\pi}\sum_{1}^{\infty}\frac{C(L,t)(-1)^n - C(0,t)}{n}\sin\left[\frac{n\pi x}{L}\right]e^{-Dn^2\pi^2 t/L^2}$$

$$C(i,t) = C(i,0) + \frac{AD}{V_i L}\left\{\int_0^t\left[(C(j,t) - C(i,t)) + 2\sum_{1}^{\infty}(C(j,t)(-1)^n - C(i,t))\,e^{-Dn^2\pi^2 t'/L^2}\right]dt'\right\}$$

Where $i,j = 0,L\ (i \neq j)$

The model is a numerically integrated pseudo steady state expression of one-dimensional Fickian diffusion with variable boundary conditions. Comparison of theoretical calculations and measured diffusion of an anesthetic mixture reveal the inadequacy of this simple model. Reasonable fit can be achieved for short (or long) times depending on the effective diffusion coefficient used. Unfortunately, this simple model cannot fit data throughout the course of the diffusion process because it predicts higher (or lower) rates of diffusion in the late (or early) regime. This divergent behavior is assumed to be caused by the swelling of the skin over the course of the experimentation. To account for this, the measured time dependent thickness of nude mouse skin is incorporated into the model.

$$L = 6.9029 \times 10^{-2} + 4.9499 \times 10^{-2}\,t - 4.4692 \times 10^{-3}\,t^2 \quad (t < 5 \text{ hours})$$

$$L = 0.18821\,t^{5.0642 \times 10^{-2}} \quad (t > 5 \text{ hours})$$

L [=] cm
t [=] hours

This newer model is able to predict, within experimental error, the concentration or flux in a closed or open system from exposure through equilibrium or steady state.

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1. K. J. Miller Jr., Y. K. Rao, S. R. Goodwin, and D. O. Shah, *In Vitro* Transdermal Diffusional Properties of Tetracaine From Topical Formulation, in Prediction of Percutaneous Penetration Proceedings, April 1991, R. C. Scott, R. H. Guy, and J. Hadgraft (eds), IBC Technical Services, London, (in press), (1992).

2. K. J. Miller Jr., G. B. Westermann-Clark, and D. O. Shah, Quasi-Steady State Model for Percutaneous Penetration of Local Anesthetics, in Prediction of Percutaneous Penetration Proceedings, April 1991, R. C. Scott, R. H. Guy, and J. Hadgraft (eds), IBC Technical Services, London, (in press), (1992).

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K J Miller Jr[1], G B Westermann-Clark[1], and D O Shah[1,2]

Center for Surface Science and Engineering, Departments of [1]Chemical Engineering and [2]Anesthesiology, University of Florida, Gainesville, FL 32611

1. Introduction

Many models predict percutaneous absorption, but most assume the drug concentration-profile of the drug within the skin has reached steady state (i.e. the concentration profile is linear within the skin).[1-4] Although steady state may be a valid assumption for drugs that diffuse quickly, these models cannot predict the early stages of drug diffusion which disobey the linear concentration-profile assumption.

When a substance is applied to the skin, the existing steady state changes suddenly. Where no drug was present, there is now a high concentration at the external surface. Predictions of the concentration profile within the skin can help predict the drug flux through the skin. Such predictions are valuable for substances that have relatively

low therapeutic or toxic levels. These substances can have profound effects long before steady state is reached.[5] In other applications, (e.g. dermatclogical applications), knowledge of drug concentration versus depth within the skin is useful.[6]

Drug diffusing into drug-free skin initially creates an exponential concentration profile.[5] With time, the concentration profile approaches a straight line (i.e. steady state). If the amount of drug crossing the skin is small and if a linear concentration profile is achieved quickly, then assuming steady state is valid. During steady state, determining concentration is relatively easy; prior to steady state, calculations are more difficult.
The quasi-steady state model is for cases where the steady state assumption is questionable. The sole assumption being that the concentrations on either side of the skin change much more slowly than the concentration within the skin. After considering the relative sizes and initial concentrations of the regions involved, this assumption is often seen to be valid.

2. Methods

The model developed here is a numerically integrated, quasi-steady state, one-dimensional Fickian diffusion model with appropriate boundary conditions. The model, which uses

an effective diffusion coefficient for the drug, describes the diffusion of drug from a finite donor phase, through the skin, into a receptor phase. The in vitro and in vivo forms of the model differ only in the conditions at the inner boundary of the skin. For in vitro diffusion in a Franz cell, the receptor phase is a finite sink, while for in vivo diffusion the receptor phase concentration would be determined by skin binding and metabolizing the drug and the circulatory system's removal of drug.

2.1 Theoretical Development

The cross sectional area for diffusion is A, the effective diffusivity is D, the time since application of the drug is t, the drug concentration in the donor phase is $C_1(t)$, and the drug concentration in the receptor phase is $C_2(t)$. The region of interest lies between x=0 (donor phase boundary) and x=L (receptor phase boundary) and the effects of boundary layers are neglected (concentrations at the skin surfaces equal bulk concentrations).

The differential equation for one-dimensional diffusion through a stagnant (solid) medium such as skin is:[7]

$$\frac{\partial C}{\partial x} = - D \frac{\partial^2 C}{\partial x^2} \qquad (1)$$

The initial condition is C(0)=0. If the boundary conditions are independent of time, then this equation can be analytically integrated to obtain:[8]

$$C(x,t) = C_1 + (C_2 - C_1)\frac{x}{L} + \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{C_2(-1)^n - C_1}{n}\sin\left(\frac{n\pi x}{L}\right)e^{-D n^2\pi^2 t/L^2} \qquad (2)$$

If the boundary concentrations change slowly relative to the concentration within the skin (quasi-steady state), then the above analytical solution can still be used, but the boundary conditions then become weak functions of time.[9] These boundary conditions for the concentrations are mass balances. Evaluating these mass balances requires integration of the concentration equation to find the cumulative fluxes through the skin. For the donor and receptor phases the mass balances respectively, are:

$$C_1(t) = C_1(0) - \frac{A}{V_1}\int_0^t N\big|_{x=0}\,dt =$$

$$C_1(0) - \frac{A}{V_1}\int_0^t\left(-D\frac{\partial C(x,t)}{\partial x}\Big|_{x=0}\right)dt =$$

$$C_1(0) + \frac{AD}{V_1}\int_0^t\left(\frac{\partial C(x,t)}{\partial x}\Big|_{x=0}\right)dt \qquad (3)$$

$$C_2(t) = C_2(0) + \frac{A}{V_2}\int_0^t N\big|_{x=L}\,dt =$$

$$C_2(0) + \frac{A}{V_2}\int_0^t\left(-D\frac{\partial C(x,t)}{\partial x}\Big|_{x=L}\right)dt =$$

$$C_2(0) - \frac{AD}{V_2}\int_0^t\left(\frac{\partial C(x,t)}{\partial x}\Big|_{x=L}\right)dt \qquad (4)$$

Where:

N is the drug flux in the +x direction

V_1 is the volume of the drug dose

V_2 is the volume of the receptor phase

The mass balances (eqs. 3 and 4) contain derivatives of the concentration profile with respect to position (x). To obtain these derivatives, the analytical solution for the concentration profile (eq. 2) is differentiated with respect to position.

$$\frac{\partial C(x,t)}{\partial x} = (C_2 - C_1)\frac{1}{L} + \frac{2}{\pi}\sum_{n=1}^{\infty}\frac{C_2(-1)^n - C_1}{n}\left[\frac{n\pi}{L}\right]\cos\left[\frac{n\pi x}{L}\right]e^{-Dn^2\pi^2 t/L^2} =$$

$$(C_2 - C_1)\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty}(C_2(-1)^n - C_1)\cos\left[\frac{n\pi x}{L}\right]e^{-Dn^2\pi^2 t/L^2} \qquad (5)$$

The mass balance equations require the above derivative to be evaluated at the boundaries (x=0 and x=L).

$$\frac{\partial C(x,t)}{\partial x}\Big|_{x=0} = (C_2 - C_1)\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty}(C_2(-1)^n - C_1)\cos(0)\,e^{-Dn^2\pi^2 t/L^2} =$$

$$(C_2 - C_1)\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty}(C_2(-1)^n - C_1)e^{-Dn^2\pi^2 t/L^2} \qquad (6)$$

$$\frac{\partial C(x,t)}{\partial x}\Big|_{x=L} = (C_2 - C_1)\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty}(C_2(-1)^n - C_1)\cos(n\pi)\,e^{-Dn^2\pi^2 t/L^2} =$$

$$(C_2 - C_1)\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty}(C_2 - C_1(-1)^n)\,e^{-Dn^2\pi^2 t/L^2} \qquad (7)$$

Equations 6 and 7 can now be put into equations 3 and 4, the time dependent boundary conditions.

$$C_1(t) = C_1(0) + \frac{AD}{V_1}\int_0^t \left[(C_2(t) - C_1(t))\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty} (C_2(t)(-1)^n - C_1(t))\, e^{-Dn^2\pi^2 t/L^2} \right] dt =$$

$$C_1(0) + \frac{AD}{V_1 L}\int_0^t \left[(C_2(t) - C_1(t)) + 2\sum_{n=1}^{\infty} (C_2(t)(-1)^n - C_1(t))\, e^{-Dn^2\pi^2 t/L^2} \right] dt \qquad (8)$$

$$C_2(t) = C_2(0) - \frac{AD}{V_2}\int_0^t \left[(C_2(t) - C_1(t))\frac{1}{L} + \frac{2}{L}\sum_{n=1}^{\infty} (C_2(t) - C_1(t)(-1)^n)\, e^{-Dn^2\pi^2 t/L^2} \right] dt =$$

$$C_2(0) + \frac{AD}{V_2 L}\int_0^t \left[(C_2(t) - C_1(t)) + 2\sum_{n=1}^{\infty} (C_1(t)(-1)^n - C_2(t))\, e^{-Dn^2\pi^2 t/L^2} \right] dt \qquad (9)$$

Equations 8 and 9 are numerically integrated to get the boundary concentrations as functions of time. The integration scheme used is quite simple.

$$C^{t+\Delta t} = C^t + \Delta t \left[\frac{dC}{dt} \right]^t \qquad (10)$$

Substituting equations 8 and 9 into equation 10 gives explicit, time dependent expressions for the donor and receptor phase concentrations.

$$C_1^{t+\Delta t} = C_1^t + \frac{A D \Delta t}{V_1 L}\left[C_2^t - C_1^t + 2\sum_{n=1}^{\infty} (C_2^t(-1)^n - C_1^t)\, e^{-Dn^2\pi^2 t/L^2} \right] \qquad (11)$$

$$C_2^{t+\Delta t} \approx C_2^t + \frac{A D \Delta t}{V_2 L}\left[C_1^t - C_2^t + 2 \sum_{n=1}^{\infty} (C_1^t (-1)^n - C_2^t)\, e^{-D n^2 \pi^2 t / L^2} \right] \qquad (12)$$

Adopting dimensionless groups gives further simplification.

$$\varphi_1 = \frac{A L}{V_1} = \frac{V_s}{V_1} \qquad (V_s = \text{Skin Volume})$$

$$\varphi_2 = \frac{A L}{V_2}$$

$$\tau = \frac{L^2}{D \pi^2} \qquad \text{(Time Constant)}$$

$$g = \frac{\Delta t}{\tau} \qquad \text{(Dimensionless Step Size)}$$

$$j \qquad \text{(Time Index)}$$

$$C_1^{j+1} = C_1^j + \frac{g}{\pi^2} \varphi_1 \left[C_2^j - C_1^j + 2 \sum_{n=1}^{\infty} (C_2^j (-1)^n - C_1^j)\, e^{-j g} \right] \qquad (13)$$

$$C_2^{j+1} = C_2^j + \frac{g}{\pi^2} \varphi_2 \left[C_1^j - C_2^j + 2 \sum_{n=1}^{\infty} (C_1^j (-1)^n - C_2^j)\, e^{-j g} \right] \qquad (14)$$

The only dimensional quantities in the final expressions for the boundary concentrations are the boundary concentrations themselves. The model is developed in this way so that raw diffusion data ($C_2(t)$ vs. t) can be used to find the time constant and, in turn, the effective diffusivity. Figure 1 shows the model results; the insert shows the response of the receptor phase just after applying the drug. To determine the concentration profile inside the skin,

boundary conditions values (from eqs. 13 and 14) are cycled back into the analytical solution for the concentration profile (eq. 2).

Figure 2 shows the concentration within the skin (calculated by equations 2, 13, and 14) as a function of position (x=0 is the external surface) for different dimensionless times (experimental time/time constant). Such calculations assume the drug diffusion coefficient is the same everywhere in the skin, i.e. that the skin can be considered a homogeneous medium for diffusion. If one views the skin as stratified, then the model may easily be modified to include a series of layers in which the drug has different diffusivities. Each layer is then described by the same equations (eqs. 2, 13, and 14) and shares boundary conditions with adjacent layers. Another possible view of skin structure is as mortar and bricks. In this case, diffusion occurs through different media simultaneously and some diffusion resistances are in parallel while others are in series. This case, although not impossible to model, presents significant mathematical difficulties. Drug diffusivities are unavailable for various regions within the skin, therefore the approach is to adopt an effective or apparent diffusivity resulting from diffusion in several layers.

To compare experimental data with the theoretical model, the effective diffusivity (or equivalently, the effective time constant) of the experimental data can be found. A program was written to compare the experimental data to the theoretical model and estimate the effective time constant. If the model is valid, then the time constant calculated from the data should not vary with time.

2.2 Modification of Model to Include Skin Swelling

The time constant is proportional to the square of the skin thickness. This skin swelling can affect the diffusion of drugs through the skin during in vitro diffusion or in vivo diffusion with occlusion.

To assess the degree of swelling in vitro, the thickness of skin was measured versus time immersed in water. A nude mouse skin sample of known cross sectional area was weighed, and with its density assumed to be approximately that of water, the thickness of the skin was estimated. The sample was then immersed in water and its mass monitored with time. During this experiment, the cross sectional area was assumed fixed and water entering through the edge of the skin sample was neglected. Water was assumed to increase the skin's volume proportional to its bulk density (1 g/ml). Therefore, the change in mass was related to a change in volume with a

constant cross sectional area. Since the change in volume was assumed to occur in only one dimension, the time dependent thickness could be determined.

Thicknesses were then correlated as L(t) for use in the diffusion model. Using L(t) in the quasi-steady state model precludes the use of a dimensionless model since the model now contains an additional time dependent function (L(t)) with a different time scale. Therefore, one must return to equations 11 and 12 and add an equation for L(t).

3. Results

3.1 Quasi-Steady State Model

The quasi-steady state model is compared to in vitro diffusion data for tetracaine from propylene glycol-saline solutions. Table 1 shows the calculated time constants for 10, 20, 40, 50, 60, and 70% (v/v) propylene glycol. For all propylene glycol concentrations, the calculated time constant increases with time. This is equivalent to saying that the apparent drug diffusion coefficient through the skin decreases with time.

Note that drug solubility in the solvent must be considered when modelling is attempted. For a super-

saturated solution the actual concentration in the donor phase would be the saturation concentration and not the overall concentration. In addition, the model is designed to allow the donor phase concentration to fall as drug is transported across the skin. If the solution is super-saturated, the concentration of the donor phase will remain constant as drug continues to dissolve and enter the donor phase solution.

The curves in Figure 3 are the best fits achieved with the quasi-steady state model assuming a single time constant for each curve. The plotted points in Figure 3 are the average for three experiments. The error is the maximum deviation from the average. Although the fits in Figure 3 are well within the error bars, the quasi-steady state model cannot follow the diffusion data both early and late in an experiment. This failure to follow experimental data for extended periods leads to a modification that incorporates skin swelling.

3.2 Quasi-Steady State Model with Skin Swelling

As already noted, one reason for the increasing time constants could be the swelling of the skin in vitro. Figure 4 shows the thickness of nude mouse skin versus time as

measured by the method in section 2.2. Note that skin thickness would increase by a factor of about three over the course of a typical diffusion experiment (8-9 hrs.).

To fit this swelling, two equations (parabolic and exponential) are used; one for the early, rapid swelling of the first 4 to 5 hours and one for the later, slower swelling (these equations are shown in Figure 4). The variable skin thickness is incorporated into the quasi-steady state model by allowing L to change during integration.

A computer program calculates the effective diffusivity of each experimental measurement while accounting for skin swelling. Table 2 shows that the effective diffusivities are more stable when the model incorporates skin swelling. Thus, the addition of the variable swelling of the skin improves the model. Minimizing the variance with respect to the effective diffusion coefficient gives the best fits to the experimental data (Figures 5A-F). As noted earlier, the large error bars in Figure 5, which result from three mouse skins being used for each point, do not shed much light on goodness-of-fit. Fits for <u>each</u> <u>skin</u> look similar to those in Figure 5 except that the data have more scatter about the curve fits. Although the fits to the data in both Figures 3 and 5 are well within experimental error, the fits with swelling incorporated (Figure 5) generally follow the data better than the fits where swelling is ignored (Figure 3).

While significantly improving predictions of the diffusion of tetracaine through nude mouse skin, model predictions over extended periods with skin swelling are only fair to good. Since the experiments used untreated skin, there may have been some deterioration. However, the long term model predictions typically overestimate the concentration in the receptor phase and deterioration of skin structures should increase rather than decrease the apparent diffusivity. In any event, the period of interest for local anesthetics is short and, over several hours, model predictions of average receptor phase concentrations are excellent. The accuracy of these predictions of bulk concentrations suggests that average concentrations at skin surfaces and within the skin are accurately predicted.

Many factors that may influence diffusion have not been considered. These include the diffusion of propylene glycol and saline through the skin, as well as the changing propylene glycol-saline concentration within the skin as swelling occurs. Boundary layers are neglected, but the ability of the model to predict the bulk reservoir concentrations is well within experimental error. Thus, further development of the model to include solvent diffusion and boundary layers is viewed as unproductive.

The careful reader will note that the diffusion of tetracaine in propylene glycol-saline solutions does not

follow an easily discernable trend. This topic is the subject of "In Vitro Diffusional Properties of Tetracaine From a Topical Formulation" submitted for publication in Predictions of Percutaneous Penetration Proceedings, April 1991.

4. Conclusions

1. Inclusion of time dependent skin swelling in the model reduces its effect on diffusion resulting in very accurate predictions of the receptor phase concentration of tetracaine diffusing from propylene glycol and saline through nude mouse skin for up 8 hours.

2. The quasi-steady state model accurately predicts average boundary concentrations versus time for percutaneous absorption; the accuracy of predictions could not be duplicated by any steady state model.

3. For tetracaine diffusing through nude mouse skin from propylene glycol-saline solutions, the model can estimate the drug concentration within skin as a function of position and time after application.

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CAPTIONS

FIGURE 1: Theoretical donor and receptor phase concentrations versus time for non-swelling model. (Insert: receptor phase concentration at short time).

FIGURE 2: Theoretical concentration profile across skin for various times by non-swelling model.

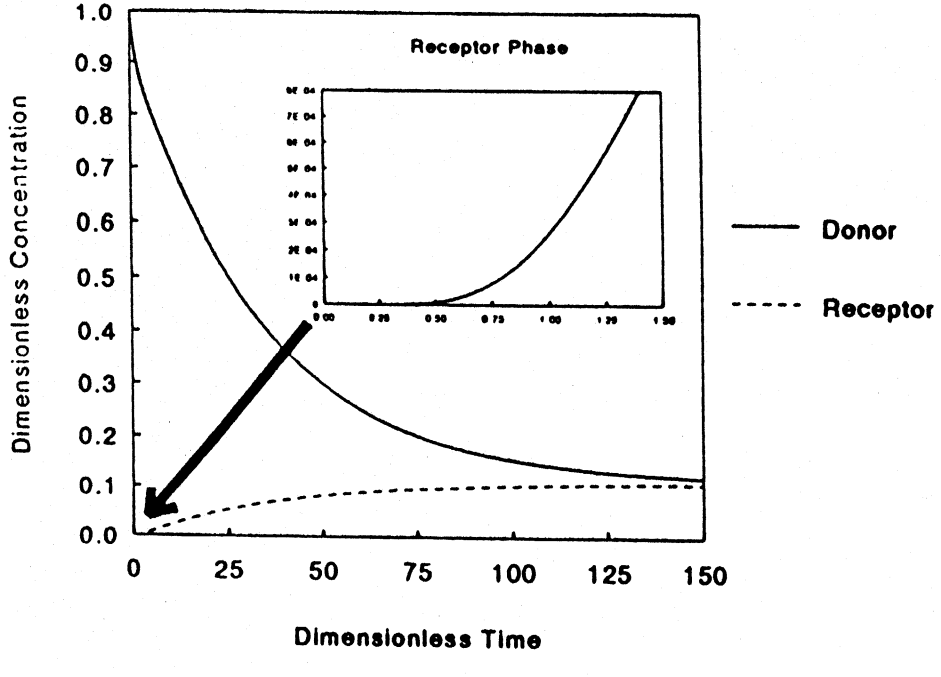
TABLE 1: Apparent time constants calculated by non-swelling model for tetracaine in acidified propylene glycol-saline solutions.

FIGURE 3: Comparison of in vitro experimental diffusion data and non-swelling model for tetracaine in acidified propylene glycol-saline solutions.

FIGURE 4: Experimentally determined skin thickness versus time immersed in water and correlation equations.

TABLE 2: Apparent diffusivities calculated by swelling model for tetracaine in acidified propylene glycol-saline solutions.

FIGURE 5: Comparison of in vitro experimental diffusion data and swelling model for tetracaine in acidified propylene glycol-saline solutions.


Receptor Phase
Dimensionless Concentration
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
25
50
75
100
125
150
Dimensionless Time
Donor
Receptor

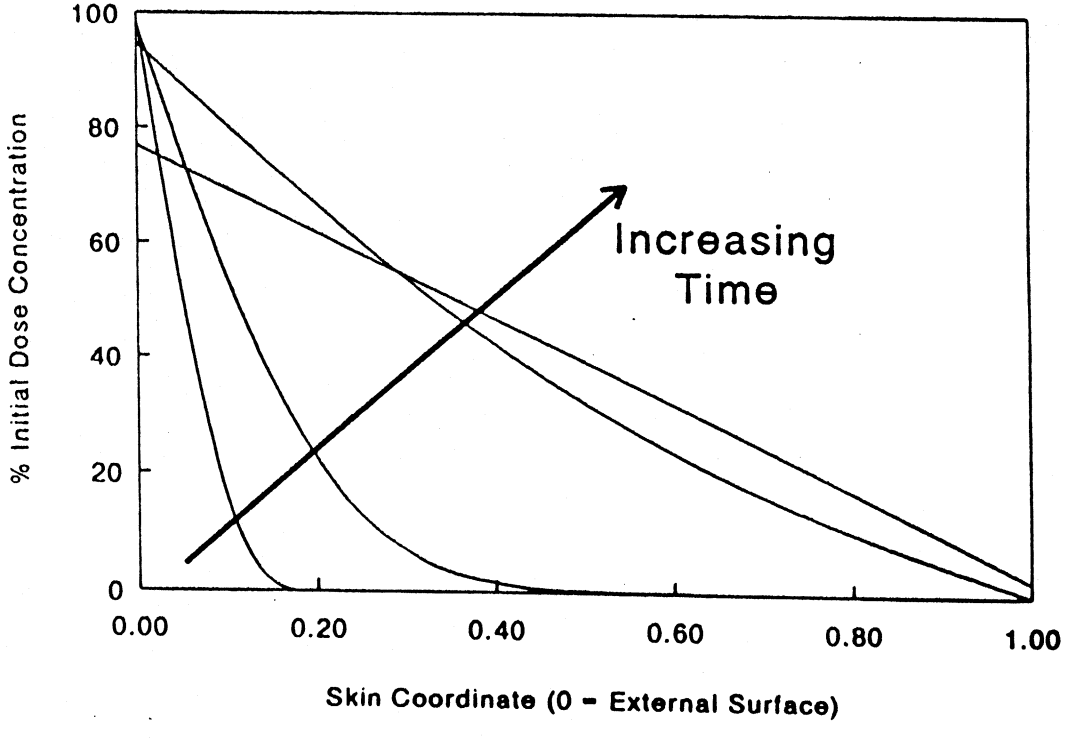
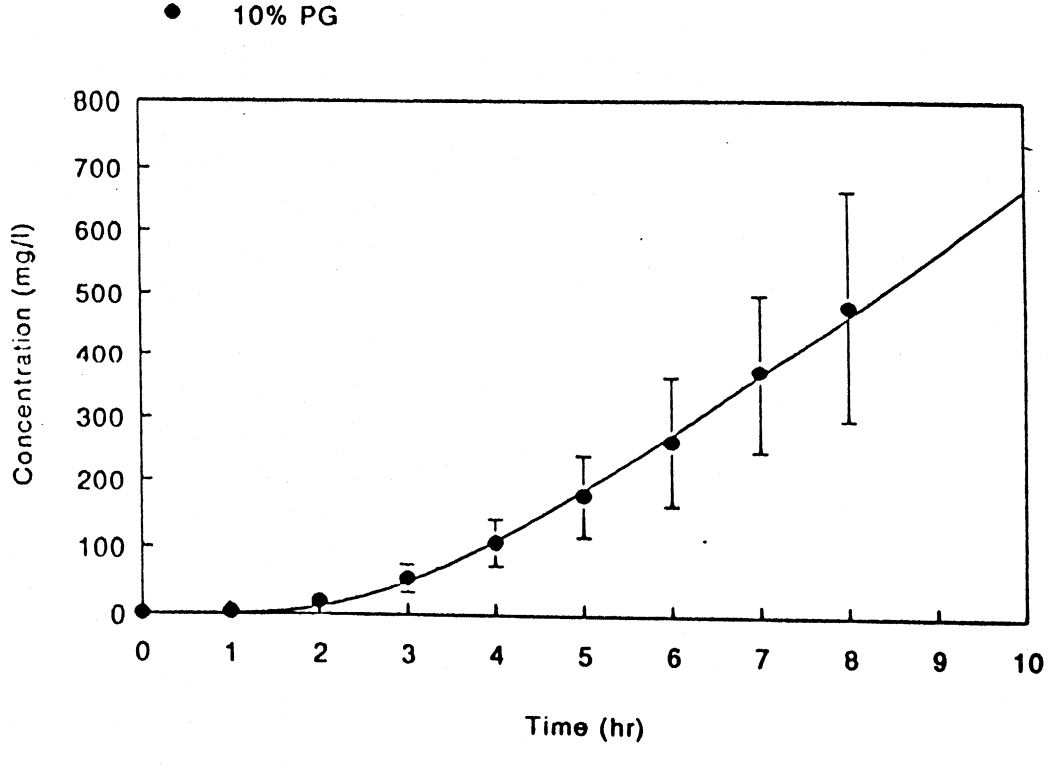
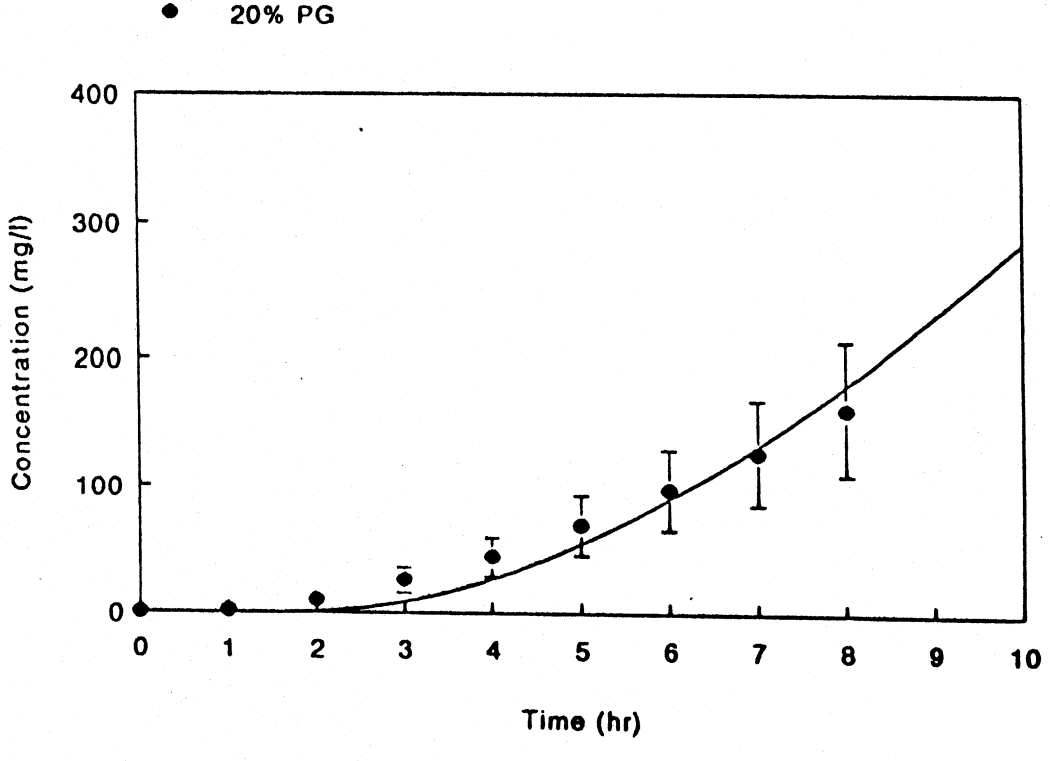

100
80
60
40
20
0
0.00
0.20
0.40
0.60
0.80
1.00
% Initial Dose Concentration
Increasing
Time
Skin Coordinate (0 = External Surface)

Table 1. Apparent Time Constants by Non-Swelling Model

Time (hr)	Time Constant (hr) 10% PG	20% PG	40% PG	50% PG	60% PG	70% PG
1	1.575	1.770	-----	------	1.734	1.71
2	2.031	2.339	1.262	1.232	2.465	2.437
3	2.214	2.740	1.700	1.545	2.925	2.933
4	2.292	3.113	1.946	1.720	3.260	3.332
5	2.320	3.322	2.151	1.881	3.572	3.658
6	2.312	3.519	2.321	2.096	3.861	3.993
7	2.254	3.694	2.478	2.063	4.094	4.247
8	2.225	3.800	2.602	2.140	4.333	4.491


10% PG
Concentration (mg/l)
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


20% PG
Concentration (mg/l)
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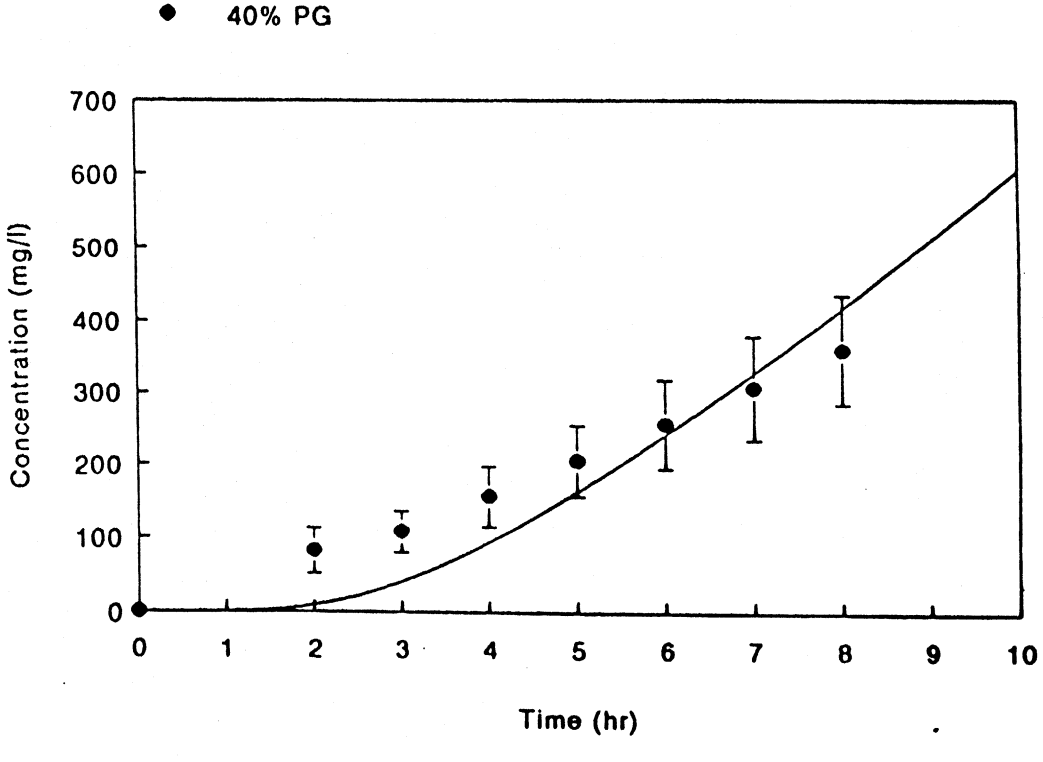
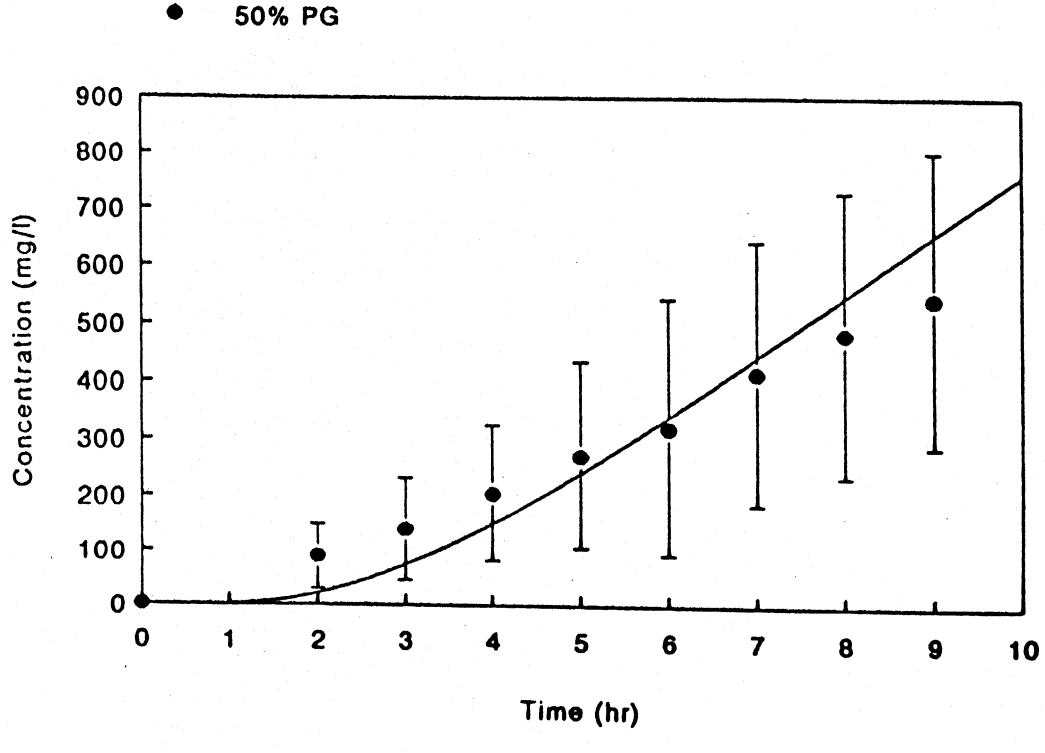
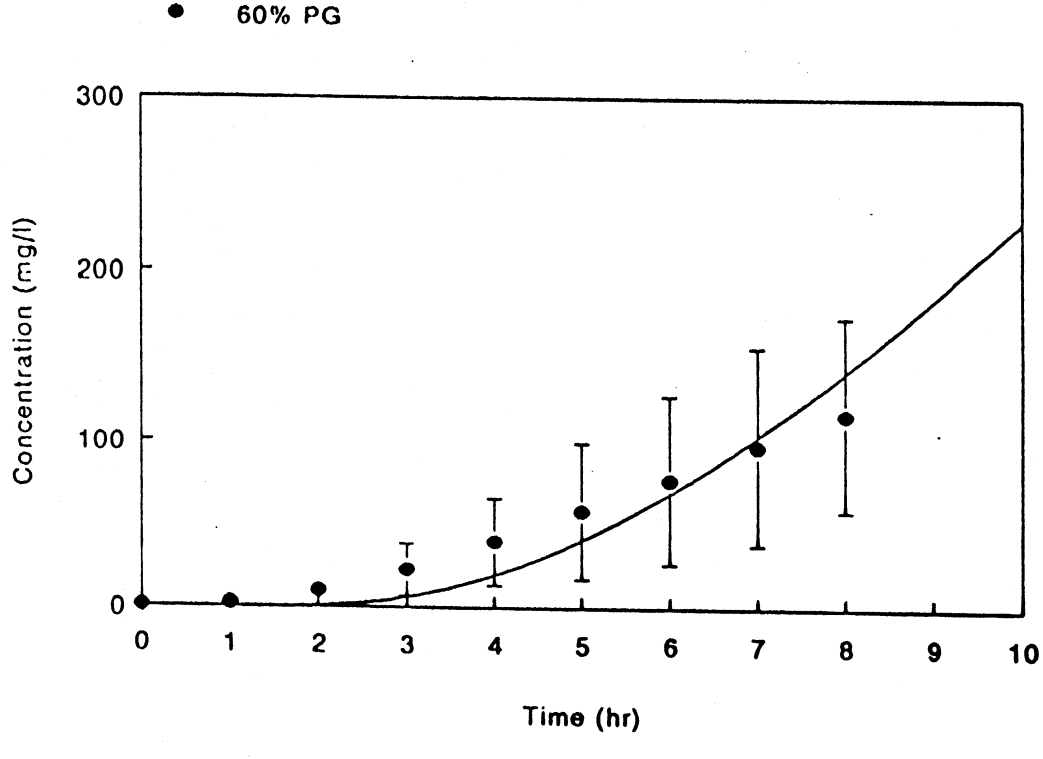
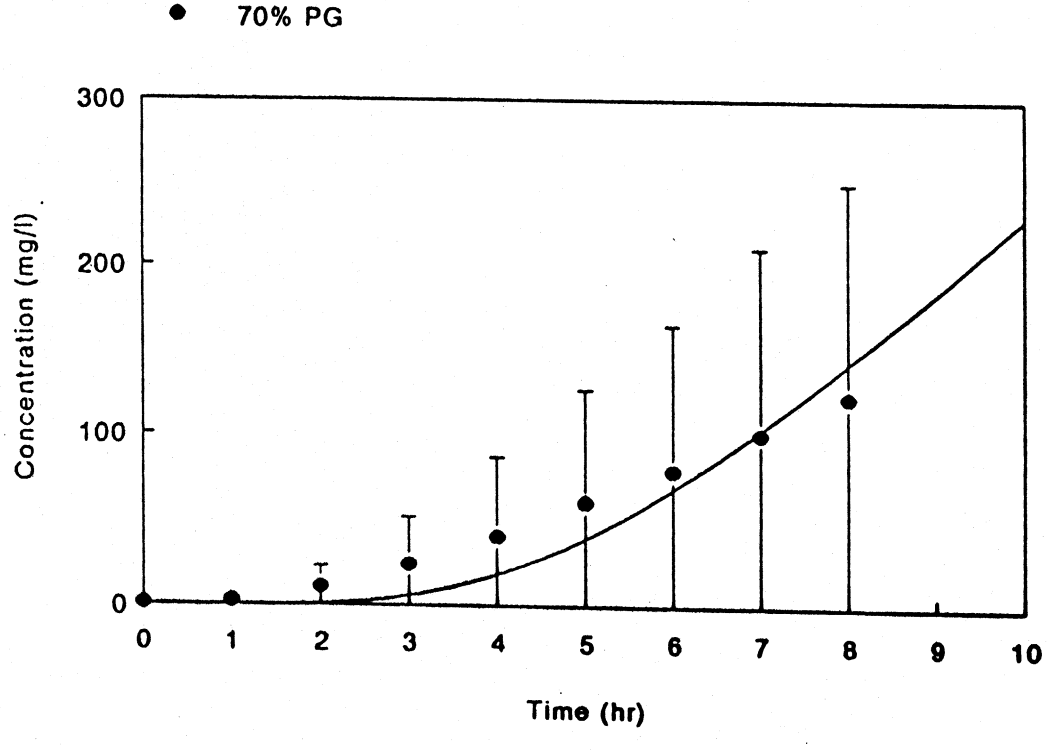
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


40% PG
700
600
500
400
300
200
100
0
Concentration (mg/l)
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


50% PG
Concentration (mg/l)
900
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


60% PG
300
200
100
0
Concentration (mg/l)
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


70% PG
300
200
100
0
Concentration (mg/l)
0
1
2
3
4
5
6
7
8
9
10
Time (hr)

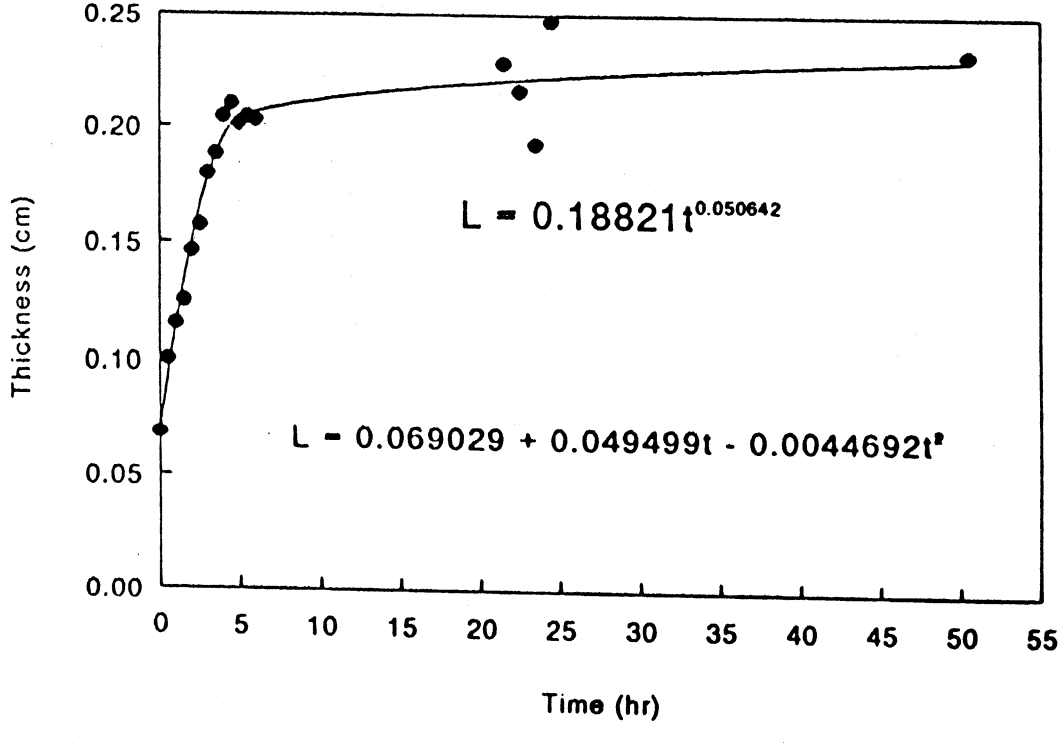
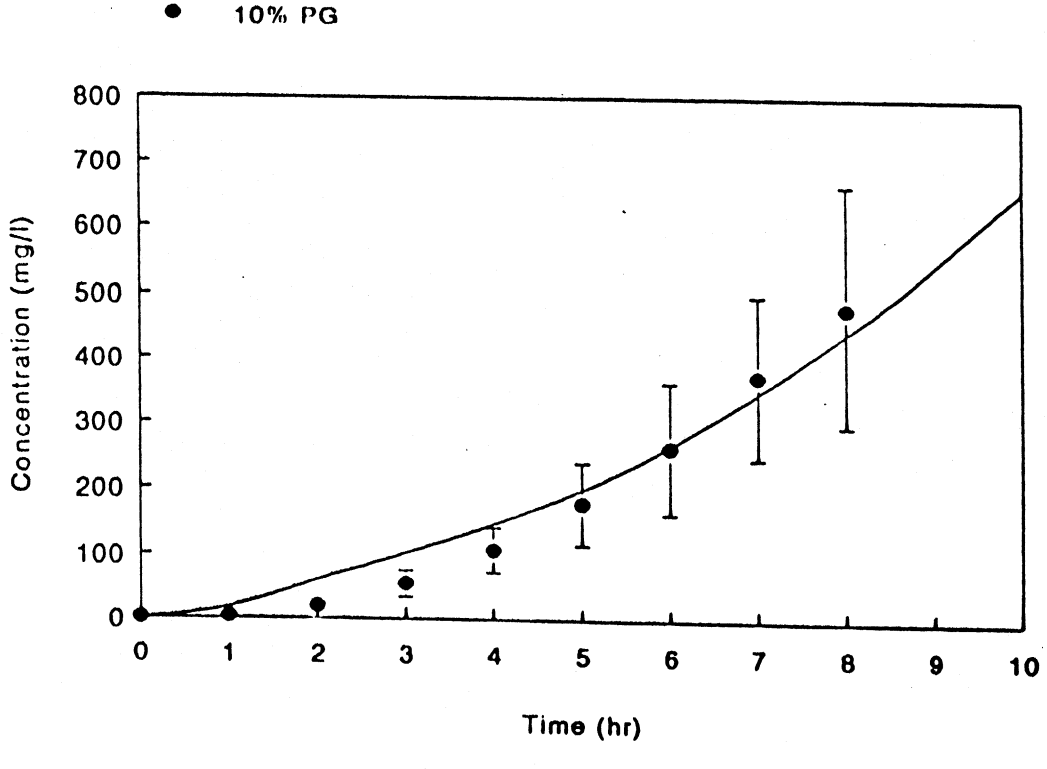
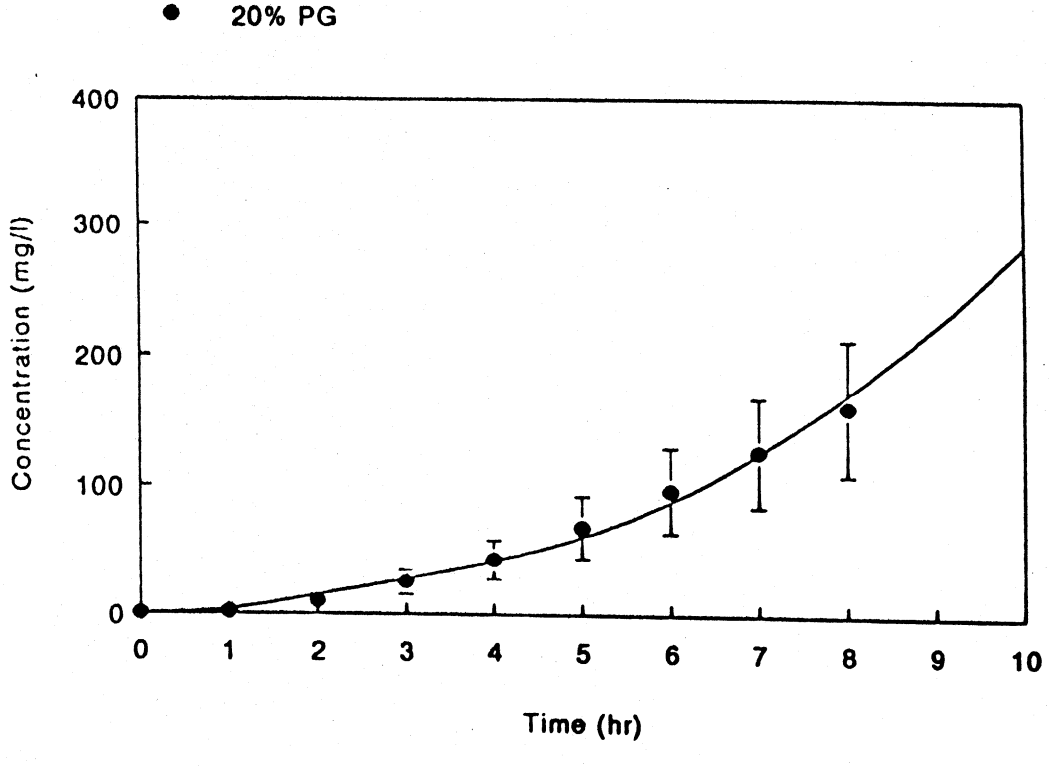
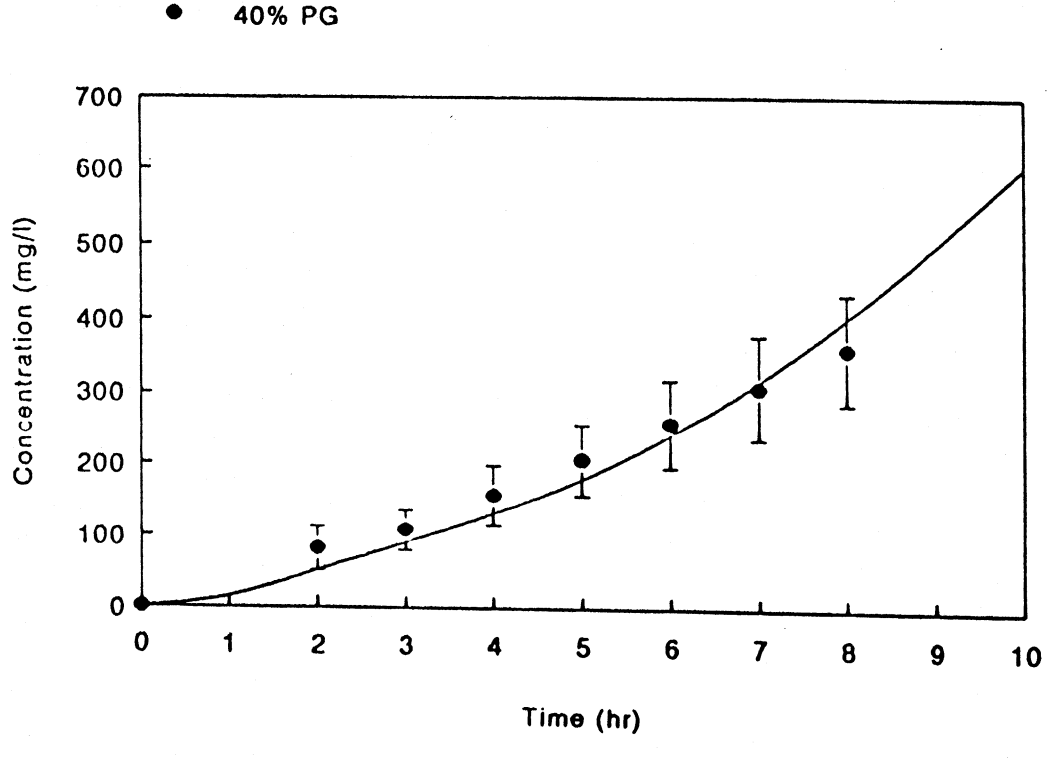

0.25
0.20
0.15
0.10
0.05
0.00
Thickness (cm)
L = 0.18821t^0.050642
L = 0.069029 + 0.049499t - 0.0044692t²
0
5
10
15
20
25
30
35
40
45
50
55
Time (hr)

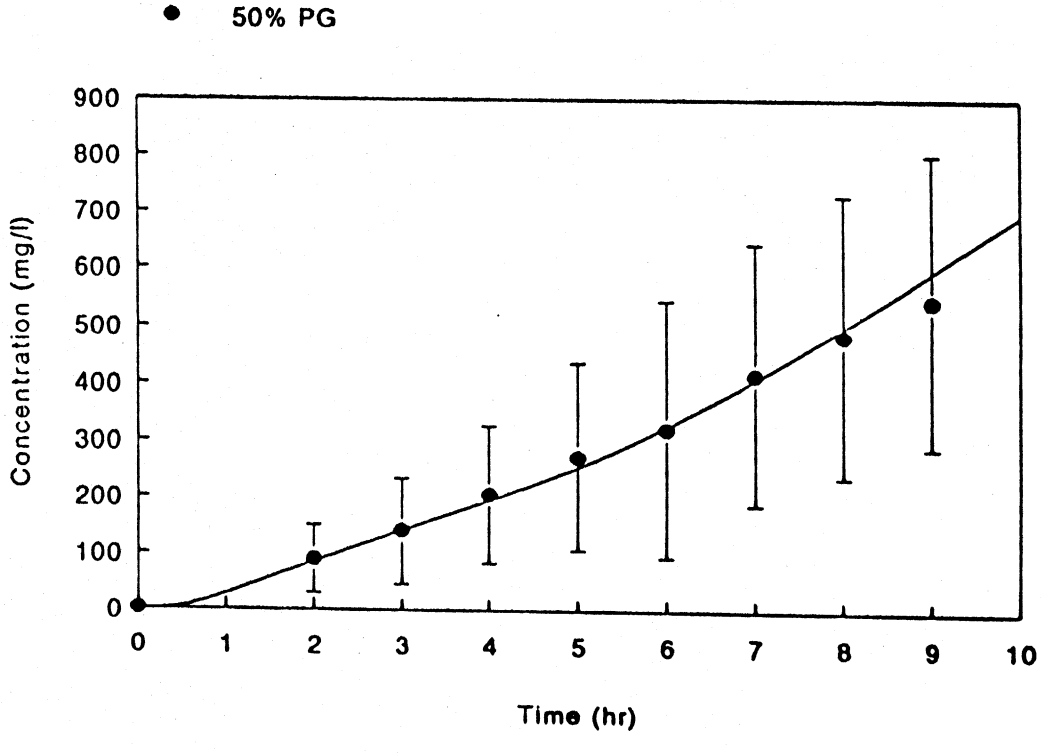
Table 2. Apparent Diffusivities by Swelling Model

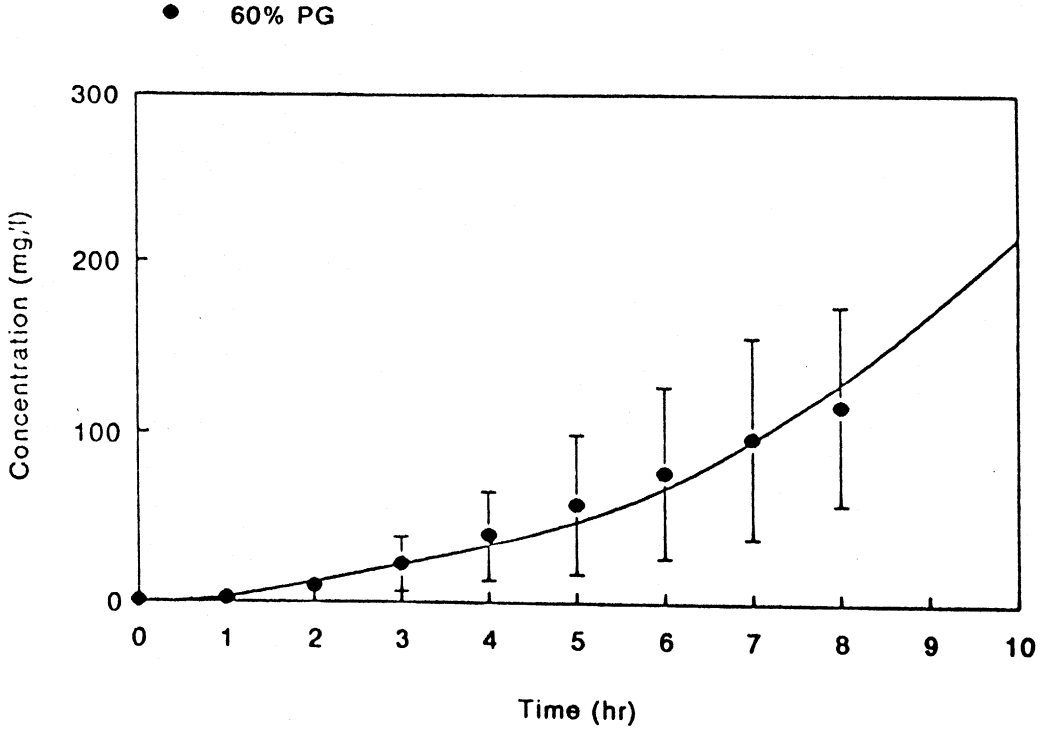
Time (hr)	Diffusivity X 10^7 (cm^2/s) 10% PG	20% PG	40% PG	50% PG	60% PG	70% PG
1	1.84	1.66	----	----	1.71	1.72
2	2.01	1.79	2.88	3.01	1.76	1.78
3	2.23	1.90	2.68	2.97	1.86	1.87
4	2.40	1.95	2.68	3.03	1.94	1.92
5	2.54	2.00	2.66	3.05	1.95	1.94
6	2.61	1.99	2.61	2.96	1.93	1.90
7	2.69	1.95	2.53	3.01	1.88	1.86
8	2.71	1.91	2.45	2.96	1.81	1.80

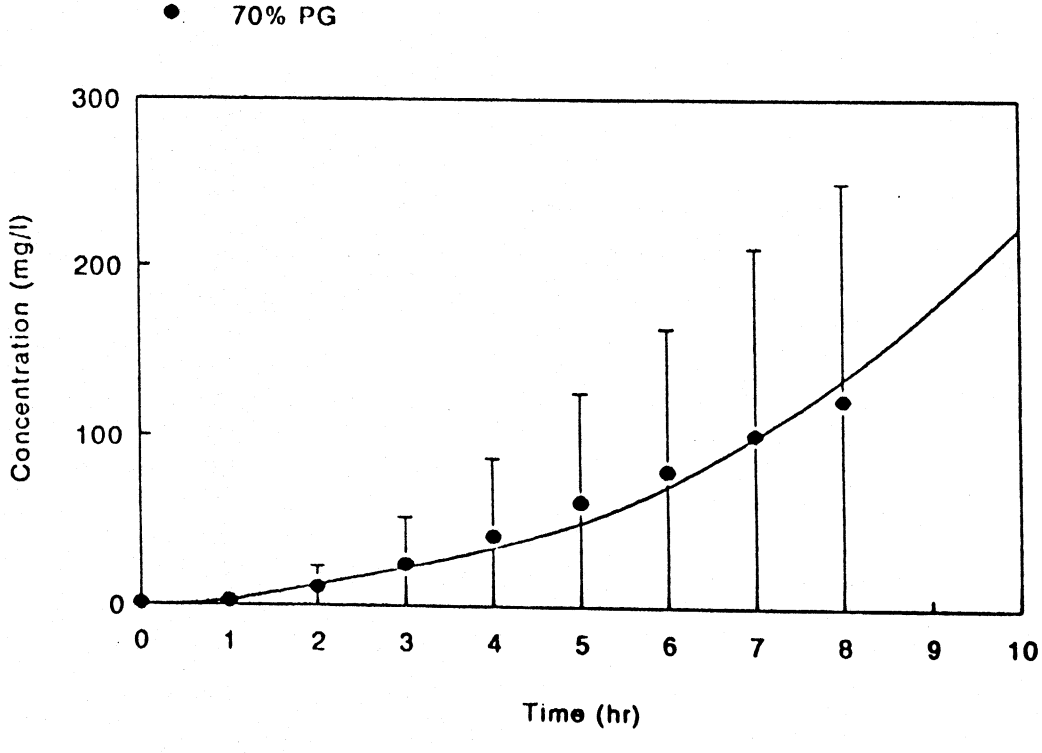

10% PG
Concentration (mg/l)
800
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


20% PG
Concentration (mg/l)
400
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


40% PG
Concentration (mg/l)
700
600
500
400
300
200
100
0
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


50% PG
900
800
700
600
500
400
300
200
100
0
Concentration (mg/l)
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


60% PG
300
200
100
0
Concentration (mg/l)
0
1
2
3
4
5
6
7
8
9
10
Time (hr)


70% PG
300
200
100
0
Concentration (mg/l)
0
1
2
3
4
5
6
7
8
9
10
Time (hr)