ASM Sc. J., 20(1), 2025
https://doi.org/10.32802/asmscj.2025.1631

Mathematical Model for Estimating Skin Permeation Parameters

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Mathematical modelling of drug transport to the skin is useful to gain fundamental understanding on the drug permeation mechanism for formulation design. For this purpose, the diffusion equation from Fick's law of diffusion is commonly used to model the transport of drug through the skin. In this paper, this diffusion equation was solved using Laplace transform with appropriate initial and boundary conditions representing infinite dosing. The solution was then inverted numerically using the Weeks method and used to fit drug experimental data for the estimation of the apparent partition coefficient, P_1 and apparent diffusion coefficient, P_2. To test this model, particularly on the best curve fitting algorithm to use, the estimated P_1 and P_2 values were compared to those reported in literature. Three curve fitting methods, namely simple loop, particle swarm optimization (PSO) and non-linear least squares (NLS), were evaluated. The result suggests that PSO and NLS can provide P_1 and P_2 estimates that are comparable to those reported in the literature.

Keywords: skin; drug permeation; particle swarm optimisation; non-linear least squares

I. INTRODUCTION

Drug delivery through the skin serves as an attractive alternative to conventional drug administration systems such as oral and parenteral routes. The delivery method offers several advantages over the conventional method such as steady and controlled release of medication over a long period of time, low frequent dosing, avoidance of the first-pass metabolism, and improved drug therapeutic effect (Grammatikopoulou *et al.*, 2021; Park *et al.*, 2022; Karthikeyan & Sivaneswari, 2024). Drug transport from formulations through the skin is an important phenomenon that is usually mathematically modelled based on the diffusion principle using Fick's second law and principle of mass transfer (Pontrelli & Monte, 2014; Khanday *et al*, 2017; Yadav *et al.*, 2022; Čukić & Galovic, 2023). Mathematical model is a valuable way for gaining a better insight into the fundamental physics underlying bio-transport processes and for assessing parameters defining skin permeability, partition and diffusion coefficients, drug dissociation and association rates (Monte *et al.*, 2015; Liu *et al.*, 2020; Jenner *et al.*, 2021). A proper estimation of drug permeation parameters from the model is particularly important for modulating the formulation properties for effective delivery of drugs through the skin.

Several studies have reported the potential of mathematical models to estimate drug permeation parameters (Herkenne *et al.*, 2007; Nozaki *et al.*, 2016; Defraeye *et al.*, 2021). In such studies, permeation parameter estimation is commonly performed by fitting the diffusion model solution to the in vitro permeation data using a nonlinear-curve fitting software package such as Scientist® 3.0 by Micromath®. In this study, the analytic solution of the diffusion model is first derived by Laplace transform technique. Then, the estimation of model permeation parameters is performed by inverting the

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Laplace domain solutions into the time domain and by fitting the model to experimental data points using a curve fitting method. In Python, the model inverted the diffusion equation using the Weeks method (Kano *et al.*, 2021; Kamran *et al.*, 2024) and curve fits the solution to a set of data for the estimation of the apparent partition, P_1, and apparent diffusion, P_2, parameters.

II. MATERIALS AND METHOD

Permeation experiments can be conducted using infinite and finite dose regiments with the former being commonly performed to characterise the pharmacokinetic parameters. A drug permeation experimental system involves the membrane (or skin) placed between the donor and receptor compartments (Figure 1). In the experiment, the amount of drug that permeates through the membrane/skin from the donor to the receptor compartments is measured. In an infinite dose study, the drug concentration on the membrane (skin) remains constant throughout the experiment while the concentration changes in a finite dose study. In the following section, the Laplace solution of the diffusion equation for an infinite dose study is first presented. This is followed by an overview of the curve fitting methods considered in this study.

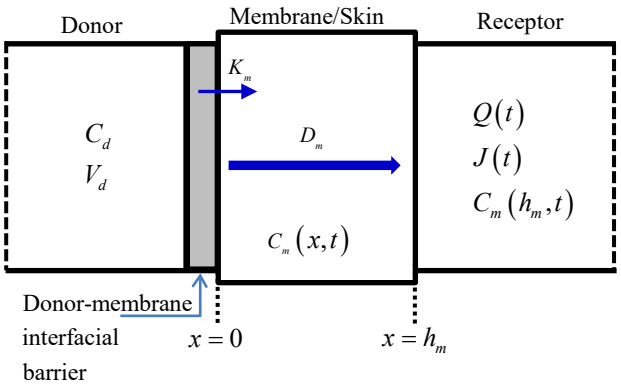

Figure 1. Schematic representation of *in vitro* drug permeation through a membrane or the skin

A. Infinite Dose Model

The skin permeation model is usually created based on diffusion principle using Fick's second law and the principle of mass transfer governed by Equation (1) (Crank, 1975; Liu *et al.*, 2020).

$$\frac{\partial C_m(x,t)}{\partial t} = D_m \frac{\partial^2 C_m(x,t)}{\partial x^2}, \quad 0 \le x \le h_m,\ t \ge 0. \tag{1}$$

Here, $C_m(x,t)$ [mass per volume] is the drug concentration in the membrane (skin) at distance x and time t, h_m [length] is the membrane thickness and D_m [length square per time] is the diffusion coefficient of the drug in the membrane. The solution of Equation (1) can be derived by Laplace transform using the initial condition (2) and boundary conditions (3) and (4). Initially, no drug is present in the membrane, as given by

$$C_m(x,0), \quad 0 \le x \le h_m,\ t \ge 0. \tag{2}$$

The boundary condition at the donor surface ($x = 0$, $t > 0$) is defined by

$$C_m(0,t) = K_m C_d(0,t), \tag{3}$$

where K_m is the drug partition coefficient and C_d is drug concentration in the donor phase at any time. For an infinite dose study, C_d remains constant over time.

The receptor fluid is constantly stirred to keep the contents homogeneous and constantly replenished to maintain a sink condition. The boundary condition at the receptor surface ($x = h_m$, $t > 0$) is defined by

$$C_m(h_m,t) = 0. \tag{4}$$

The Laplace transform solution of Equation (1) based on these initial and boundary conditions is given as Equation (5) where $t_d = h_m^2/D_m$ is the characteristic time of drug diffusion through the membrane/skin.

$$\overline{C}(x,s) = \frac{K_m C_d \sinh\left[\sqrt{st_d}\left(\frac{1-x}{h_m}\right)\right]}{s\sinh\left(\sqrt{st_d}\right)} \tag{5}$$

According to Fick's first law of diffusion, the flux J of solute from the skin to the receptor is given by

$$J = -AD_m \left.\frac{\partial \overline{C}(s,t)}{\partial x}\right|_{x=h_m}, \tag{6}$$

while the equation of the infinite dose cumulative amount $\overline{Q(s)}$ permeated is defined by

$$\overline{Q}(s) = J \cdot \frac{A}{s} = \frac{P_1 A C_d}{s\sqrt{\frac{s}{P_2}}\sinh\left(\sqrt{\frac{s}{P_2}}\right)}, \tag{7}$$

with $P_1 = K_m h_m$ and $P_2 = D_m/h_m^2$. Here, it should be noted that a bar over a function denotes Laplace transform, s denotes Laplace variables, t denotes time variables, A is the

area of drug application, C_d is the initial donor drug concentration while P_1 and P_2 are the model parameters to be estimated by curve fitting. To provide more confidence in the numerical method (Weeks method) used in our model, the following Fourier transform solution (8) of Equation (1) based on initial and boundary conditions (2)-(4) was employed.

$$Q(t) = P_1 C_d A\left[P_2 t - \frac{1}{6} - \frac{2}{\pi^2}\sum_{n=1}^{\infty}\frac{(-1)^n}{n^2}e^{-P_2 n^2 \pi^2 t}\right] \quad (8)$$

B. Model Testing Data

Table 1 lists the permeation data obtained from Santos (2008) for model testing. These permeation data represent infinite dose profiles of a hypothetical scenario of a drug (1 μmol/mL) diffusing through a 0.0015 cm membrane with a lag time of 3 hours. As shown in Figure 2, these profiles were generated randomly by Santos (2008) with a 20% variation from the original permeation curve for model testing purposes. These data were adopted in this study to allow comparison of the estimated P_1 and P_2.

Table 1. Data from Santos (2008) for model testing

Time, t (h)	Permeation (μmol × 10⁻³ / cm²) Data				
	1	2	3	4	5
2	0.19	0.20	0.20	0.21	0.21
4	1.25	1.13	1.65	1.30	1.42
6	2.53	3.19	2.99	3.64	3.27
8	4.27	4.28	4.14	4.09	5.61
10	7.02	7.60	5.89	8.25	5.72
12	9.03	8.71	7.29	8.88	7.22
14	11.05	8.77	11.97	9.91	12.40
16	14.85	12.04	13.07	14.45	13.71
18	15.23	13.97	14.63	15.24	14.88
20	18.32	15.85	15.89	18.43	17.18
22	18.71	20.00	19.54	18.99	20.02
24	19.91	21.03	24.90	22.31	23.56

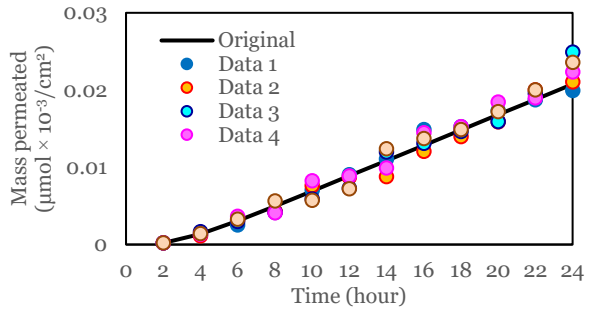

Figure 2. Original permeation profile and the data listed in Table 1 that were generated randomly

A. Curve Fitting Optimisation

In this study, the parameters P_1 and P_2 were estimated by fitting Equation (7) to the data in Table 1. Three curve fitting methods, namely simple loop, particle swarm optimisation and non-linear least squares, were tested to ensure that the estimated P_1 and P_2 for these data are comparable to the estimates by Scientist® that were reported in Santos (2008) and to determine the best curve fitting method to use.

1. Simple loop

The simple loop (SL) method increased the values of P_1 and P_2 within a user-defined range by a certain amount (increment). The Root Mean Square Deviation (RMSE) was calculated for each pair of P_1 and P_2 and the iterated pair(s) of P_1 and P_2 values with the lowest RMSE was returned as the best interval fit values. For the data listed in Table 1, the interval defined for the search using this method is [0.010, 0.060] with an increment of 0.001 to cover the range of P_1 and P_2 estimated by Santos (2008). This means that P_1 and P_2 values are respectively varied from 0.010 to 0.060 with an increment of 0.001, resulting in 51×51 pairs of P_1 and P_2 values.

2. Particle Swarm Optimization

The Particle Swarm Optimization (PSO) method estimates parameters by finding the optimal set of parameter values in the model that minimises the disparity between the model predictions and the experimental data in the search space (bound) using the user choice objective function (Ahmed, 2022). The objective function used in this work is the sum of squared errors, S (P_1, P_2), defined as:

$$S(P_1, P_2) = \sum_{i=1}^{N}\left(Y_i - Q(t_i, P_1, P_2)\right)^2. \quad (9)$$

Here, Y_i is observed data from experiment, Q (t_i, P_1, P_2) is the predicted values from the model equation and N is the number of data points.

This study implemented the PSO algorithm in Python 3.9 for the estimation of P_1 and P_2 through curve fitting. To estimate the value of the parameters, the upper and lower bounds, which served as search bound, for each parameter must be defined. Other input parameters include number of particles, iteration numbers and inertia weight. The algorithm iteratively updates position and velocity of each

particle within the search bound based on the current best position. The best position (or fit) was decided by minimising the disparity between the model predictions and the experimental data, as defined by the objective function.

3. Non-linear least squares

The non-linear least squares (NLS) method estimates parameters by finding the parameter values of the model parameters that minimise the difference between the predicted values from the model and the experimental data (Griva *et al.*, 2009). The error between the predicted and experimental values is typically measured using the sum of squared errors or the mean squared error. In this study, this method was implemented using the curve fit function in Python 3.9. The range of P_1 and P_2 can be specified but is not required for this method. It should be noted that even if the bounds imposed for SL and PSO were used, the P_1 and P_2 estimated using this NLS approach, in this study, would remain the same.

III. RESULT AND DISCUSSION

To ensure that the model performance is comparable to Scientist®, the permeation parameters, P_1 and P_2, obtained through curve fitting by the simple loop (SL) method, Particle Swarm Optimization (PSO) and non-linear least squares (NLS) were compared to those reported by Santos (2008). The curve fitting was performed on each of the five data sets listed in Table 1 for various time intervals, namely 2-24 (t=2 to t=24), 2-22 (t=2 to t=22), 2-20 (t=2 to t=20), 2-18 (t=2 to t=18) and 2-16 (t=2 to t=16), to allow comparison of the results using SL, PSO and NLS with the those by Scientist®. Figure 3 shows that, using the NLS method, the model fits the data well with $R^2 > 0.95$ (Chicco *et al.*, 2021) for all time intervals. Fitting with the SL and PSO methods based on the defined bounds and increments, resulted in an equally good fit with $R^2 > 0.94$ across all time intervals. Since the fittings using SL, NLS and PSO are visually the same, the illustration of the fittings using SL and PSO are omitted.

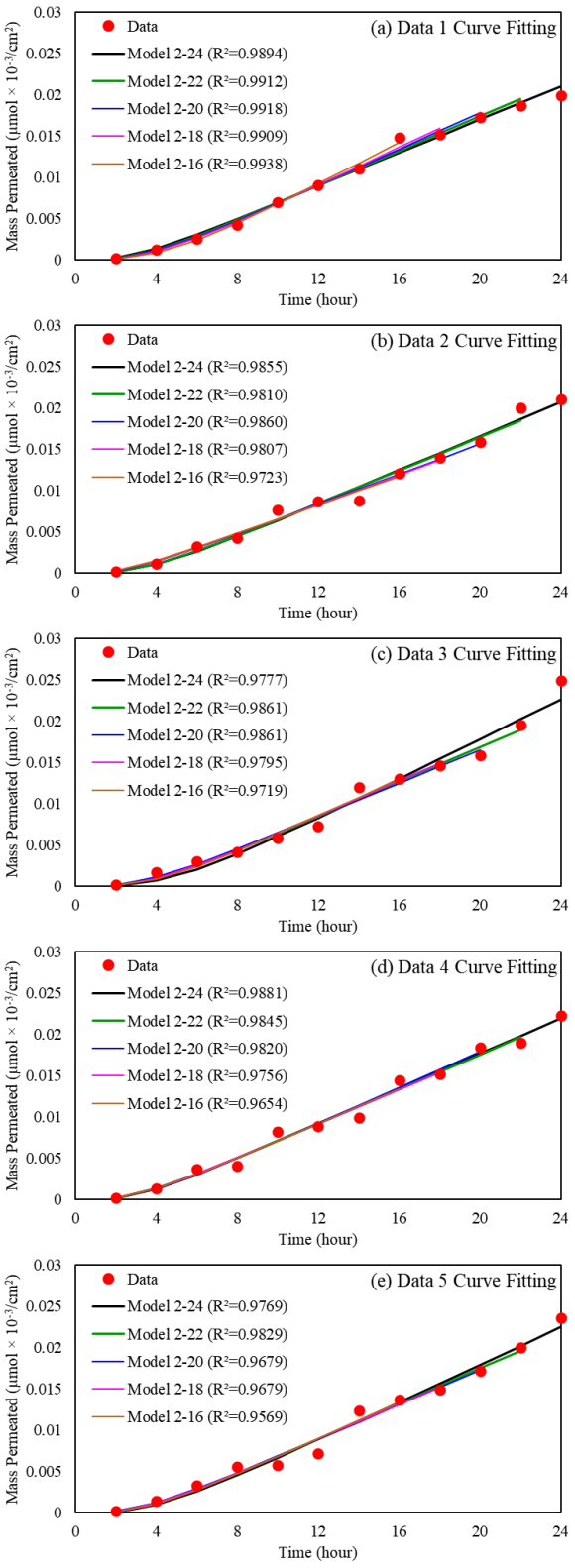

Figure 3. Fitted permeation profile of (a) Data 1, (b) Data 2, (c) Data 3, (d) Data 4 and (e) Data 5 using the NLS method. The data in Table 1 are indicated as red dots. For each data, curve fitting was made for time intervals 2-24, 2-22, 2-20, 2-18 and 2-16.

The mean and standard deviation of the P_1 and P_2 estimated for the five data sets in each time interval are calculated and listed in Table 2 along with the Relative Standard Deviation (RSD), which measures the relative level of data variability. A smaller RSD value indicates greater precision and consistency in data while a greater RSD value indicates higher variability. The results using SL, PSO and NLS are largely comparable to the Scientist® results, except for the time interval 2-16. It should be noted that Scientist® performed non-linear regression analysis (least squares fit) so NLS estimated value is expected to be similar to that of Scientist®. It can be seen from Table 2 that the calculated mean and standard deviation of P_1 and P_2 estimated using NLS are similar to the mean and standard deviation reported in Santos (2008), which were obtained using Scientist®, except for the interval 2-16. At the time of this study, access to Scientist® cannot be acquired. Hence, further checking of this result by running the analysis independently using the software cannot be performed.

Table 2. Estimated P_1 and P_2 parameters using SL, PSO and NLS compared with the estimates from Santos (2008) using Scientist® for various time intervals

Interval (h)	P_1							
	Scientist®		SL		PSO		NLS	
	M±SD (cm)	RSD (%)	M±SD (cm)	RSD (%)	M±SD (cm)	RSD (%)	M±SD (cm)	RSD (%)
2-24	0.026±0.008	30.0	0.028±0.008	28.6	0.026±0.008	30.0	0.026±0.008	30.0
2-22	0.023±0.002	8.6	0.024±0.003	11.0	0.023±0.002	9.1	0.023±0.002	8.7
2-20	0.022±0.004	17.7	0.023±0.004	18.2	0.021±0.004	17.9	0.022±0.004	17.6
2-18	0.023±0.006	25.9	0.025±0.006	25.0	0.023±0.006	24.4	0.023±0.006	25.8
2-16	0.019±0.004	21.1	0.027±0.009	34.8	0.027±0.009	33.3	0.026±0.010	37.1
Interval (h)	P_2							
	Scientist®		SL		PSO		NLS	
	M±SD (cm)	RSD (%)	M±SD (cm)	RSD (%)	M±SD (cm)	RSD (%)	M±SD (cm)	RSD (%)
2-24	0.044±0.009	20.2	0.042±0.006	20.9	0.044±0.009	20.0	0.044±0.009	20.3
2-22	0.046±0.004	8.0	0.045±0.004	9.7	0.046±0.004	8.3	0.046±0.004	8.0
2-20	0.049±0.006	12.9	0.047±0.006	13.3	0.049±0.007	13.0	0.049±0.006	12.8
2-18	0.048±0.009	19.3	0.046±0.009	18.6	0.047±0.008	17.7	0.048±0.009	19.3
2-16	0.053±0.006	11.9	0.044±0.011	24.1	0.045±0.011	23.8	0.046±0.013	28.6

Based on the results presented in Table 2, it appears that the SL, PSO and NLS methods provided more consistent estimation of P_1 and P_2 compared to Scientist®. The mean of P_1 estimated by SL, PSO and NLS ranges from 0.021 to 0.028 for all time intervals while the mean P_1 from Scientist® ranges from 0.019 to 0.026. Similarly, the mean P_2 estimated by Scientist® has a larger range from 0.044 to 0.053 compared to SL, PSO and NLS (0.042-0.049). As illustration, Figure 3 shows that the model result using NLS fits the data well with $R^2 > 0.95$ for all time intervals.

The P_1 and P_2 values estimated via NLS curve fitting using Equation (8) agreed well with the values estimated using the Laplace transform method. Hence, it is highly unlikely that difference between the estimated P_1 and P_2 in this study and those reported in Santos (2008) for the time interval 2-16 was induced by the numerical Laplace inversion method used. The Weeks method has also been previously tested by comparing the numerical result to analytical solution for some initial value problems.

Among SL, PSO and NLS methods, NLS method is recommended for use. Although all three curve fitting methods provided comparable estimations of P_1 and P_2, SL and PSO are limited in the sense that a search bound must be imposed. The range of P_1 and P_2 values for well-studied drugs is widely reported so the search bound can be ascertained for these drugs. But the search bound may not be confidently defined for the less studied or new drugs. SL is deemed the least suitable because the number of P_1 and P_2 values is limited by the user through the specification of the search bound (upper and lower limits of P_1 and P_2) and the increment. Hence, the accuracy of the P_1 and P_2 estimates by SL depends significantly on the search bound and increment imposed by the user. Similar to SL, PSO requires a search bound although the increment is not needed. Nevertheless, if a sufficiently large search bound is imposed for PSO, its

result will be comparable to NLS, which doesn't require a search bound.

IV. CONCLUSION

A mathematical model based on infinite dose study was developed and tested in this study. In the model, the Weeks method is used to numerically invert the solution of the diffusion equation, which is then used to estimate the permeation parameters by curve fitting. The estimated optimal P_1 and P_2 values using three curve fitting algorithms, namely simple loop (SL), Particle Swarm Optimization (PSO) and nonlinear least squares (NLS), were compared to the estimates from Scientist®. The results using SL, PSO and NLS are comparable with the reported results using Scientist® except for the fitting of data within the 2-16 interval. Since Scientist® is performing similar non-linear regression as NLS, their results are expected to be the most comparable, compared to SL and PSO. Estimates obtained using NLS are similar to Scientist® for the intervals 2-24, 2-22, 2-20 and 2-18. Although the estimates using the three curve fitting methods explored in this study are comparable, NLS is preferred mainly because the range of P_1 and P_2 need not be known/specified for curve fitting. The model results using NLS fit the data well for all intervals with $R^2 > 0.95$.

V. ACKNOWLEDGEMENT

The work was supported by the Ministry of Higher Education, Malaysia through the Fundamental Research Grant Scheme (FRGS) (Project Code: FRGS/1/2024/STG06/USM/02/5). The scholarship provided TETFund Nigeria to D.N. Tanko is also gratefully acknowledged.

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