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Transdermal drug delivery: a simplified pharmacokinetic approach

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Summary

A pharmacokinetic model to describe transdermal drug delivery has been developed. The rate constants in this approach have been assigned on the basis of the physicochemical parameters of the penetrant. The equations produced will allow the estimation of the plasma levels of the drug following the dermal application of a rate-controlling device. This simplified approach will not allow for rate control by the stratum corneum. The model has been used to calculate the theoretical levels of clonidine after it has been applied in a transdermal system.

Introduction

Administration of drugs transdermally has several advantages over conventional techniques. It is possible to minimize first-pass metabolism, patient compliance is good and bioavailability problems inherent in gastrointestinal absorption are avoided. However, the technique has the disadvantage that it can only be used for potent drugs. The stratum corneum limits the amount of drug reaching the blood supply and unless the barrier function is reduced with a penetration enhancer it is unlikely that plasma levels above 100 $ng \cdot ml^{-1}$ will be attained. For controlled steady

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plasma levels the device has to be rate limiting and this has been assumed in our calculations.

In order to assess the potential of transdermal therapy we have developed a pharmacokinetic model which is based on the physicochemical properties of the penetrant. This approach is a continuation of previous work in which a simpler model was used to analyze the urinary excretion of testosterone, benzoic acid and hydrocortisone following topical application (Guy et al., 1982).

The model

A schematic representation of the model is shown in Fig. 1. This is an extension of the scheme described by Guy et al. (1982) which incorporates a zero-order release to the skin but does not include diffusion through the stratum corneum since this has been assumed faster than release from the device. We have continued to consider the rate constants in Fig. 1 in terms of the physicochemical properties of the system.

k_0 describes the zero-order release (amount per unit area per unit time) from the transdermal delivery system. It will be related to the diffusional properties of the penetrant in the polymer matrix of the device or through its rate limiting membrane.

k_2 describes the diffusion of the penetrant through the viable epidermis and in previous work this region of the skin has been assumed to resemble an aqueous protein gel (Scheuplein, 1967). k_2 may be evaluated from the relationship $k_2 = D_v/l_v^2$ where D_v is the diffusion coefficient of the drug through the viable epidermis of thickness l_v.

k_3 is a rate constant which is included to allow for the drug having a strong affinity for the stratum corneum. This may be related either to a partitioning effect or specific binding of the drug to components of the stratum corneum. The ratio k_3/k_2 describes an effective partition coefficient between the stratum corneum and the viable epidermis. We have shown that for a range of compounds the effective partition coefficient is a linear function of the octanol/water partition coefficient (K_{oct}) (Guy et al., 1985) and that $K_{oct}/5$ gives a reasonable value for the effective partition coefficient (i.e. k_3/k_2). Since k_2 can be assessed by a consideration of the diffusional properties of the penetrant through an aqueous protein gel, the value of k_3 can be estimated directly by considering the octanol/water partition coefficient of the drug.

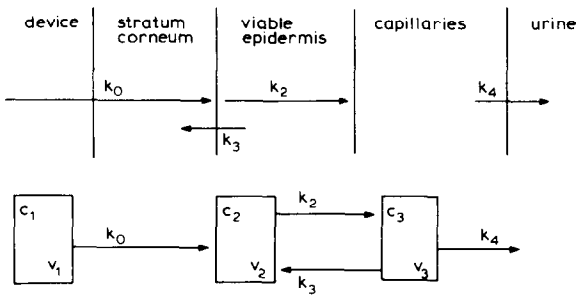

Fig. 1. Schematic representation of the kinetic model.

k_4 is the elimination rate constant of the drug from plasma. It is the normal rate constant that is determined in pharmacokinetic studies when drug loss from the plasma is measured after a drug has been administered intravenously. It is a constant that cannot be estimated from a knowledge of the physicochemical parameters of the drug but has to be assessed or known from separate experimentation.

Theory

The different rate constants described above are related to one another by a series of straightforward differential equations. In terms of Fig. 1 the rate equations may be written as follows:

$$\frac{dc_1}{dt} = -\frac{k_0}{l_d} \tag{1}$$

$$\frac{dc_2}{dt} = \frac{V_1}{V_2} \cdot \frac{k_0}{l_d} - k_2 c_2 + \frac{V_3}{V_2} \cdot k_3 c_3 \tag{2}$$

$$\frac{dc_3}{dt} = \frac{V_2}{V_3} \cdot k_2 c_2 - (k_3 + k_4) c_3 \tag{3}$$

$$\frac{dc_4}{dt} = \frac{V_3}{V_4} \cdot k_4 c_3 \tag{4}$$

where l_d is the thickness of the applied transdermal device.

The solution to the kinetic equations is simplified by normalizing the concentrations with respect to the concentration in compartment 1 at $t = 0$, i.e.

$$u_i = c_i/c_0 \qquad (i = 1, 2, 3, 4) \tag{5}$$

Using this procedure, the equations are then solved by the use of Laplace transforms:

$$s\bar{u}_1 - 1 = \frac{-k_0}{l_d c_0 s} \tag{6}$$

$$s\bar{u}_2 = \frac{V_1}{V_2} \cdot \frac{k_0}{l_d c_0 s} - k_2 \bar{u}_2 + \frac{V_3}{V_2} \cdot k_3 \bar{u}_3 \tag{7}$$

$$s\bar{u}_3 = \frac{V_2}{V_3} \cdot k_2 \bar{u}_2 - (k_3 + k_4) \bar{u}_3 \tag{8}$$

$$s\bar{u}_4 = \frac{V_3}{V_4} \cdot k_4 \bar{u}_3 \tag{9}$$

Consideration of these equations gives a value for $\bar{u}_3$, the normalized concentra-

tion of the drug in the plasma,

$$\bar{u}_3 = \frac{V_1 k_2 k_0}{l_d V_3 c_0 s} \cdot \frac{1}{(s+\alpha)(s+\beta)} \tag{10}$$

where α and β are the roots of the quadratic

$$s^2 + s(k_2 + k_3 + k_4) + k_2 k_4 = 0 \tag{11}$$

In order to establish what this concentration is in real time it is necessary to invert from the Laplace variables, which gives

$$c_3 = \frac{Ak_0}{V_3}\left\{\frac{1}{k_4} + \frac{\beta \exp(-\alpha t) - \alpha \exp(-\beta t)}{k_4(\alpha - \beta)}\right\} \tag{12}$$

where A is the area of the device in contact with the skin. The expression assumes that k_0 is invariant during the period of application.

Results and Discussion

Eqn. 12 may be used to estimate the plasma time profiles for drugs that are applied transdermally in a device which is rate limiting. It may also be used to calculate the zero-order delivery rate required to generate specific plasma levels. This will be illustrated by considering theoretical curves which cover a range of physicochemical properties. For the purposes of illustration the volume of distribution, V_3, has been taken to be 5 litres and a clearance rate of 0.23 h^{-1} ($t_{0.5}$ = 3 h) has been assumed.

k_2 is characteristic of the diffusion of the penetrant in the viable epidermis and may be estimated on the basis of the molecular weight of the drug and a knowledge of the known diffusional properties of benzoic acid. Benzoic acid has been considered in detail elsewhere and k_2 has been assigned a value of 2.9 h^{-1} (Guy et al., 1982).

In order to correct the value of k_2 for the molecular weight, the following assumptions are made. The effective radius of the penetrant is proportional to the cube root of the molecular weight. For most drug molecules it is reasonable to approximate diffusion coefficients from the cube-root of the molar volume (Flynn et al., 1974). Considering hydrogels with a high water content, the diffusion coefficient of the substrate in the gel is proportional to the aqueous diffusion coefficient (Flynn et al., 1974). Using the Stokes-Einstein equation (Atkins, 1982), k_2 for the unknown penetrant of molecular weight M_u is given by:

$$k_2 = 2.9 \times \left(\frac{122}{M_u}\right)^{0.3} \tag{13}$$

This relationship shows that the value of k_2 varies little with the molecular weight which is consistent with the notion that this region of the skin resembles an aqueous

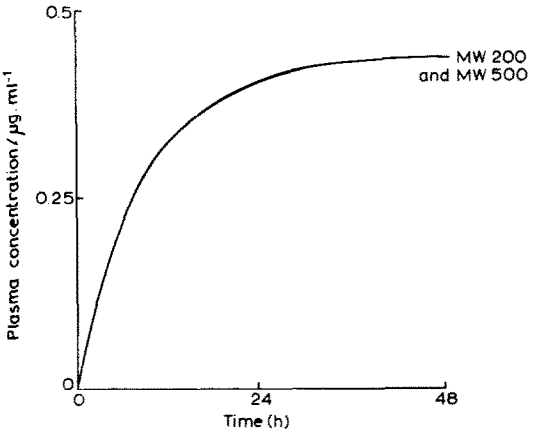

Fig. 2. Plasma concentration–time course generated by Eqn. 12 using the following conditions. Area of application 10 cm^2, volume of distribution 5000 ml. $k_0 = 0.05$ mg·cm^{-2}·h^{-1}; $k_2 = 2.5$ h^{-1} (corresponding to MW 200) and $k_2 = 1.9$ h^{-1} (corresponding to MW 500). In both cases $k_3 = k_2$; i.e. an effective partition coefficient of 1. $k_4 = 0.23$ h^{-1}.

protein gel. The values of k_2 correspond to a diffusion coefficient of $\sim 10^{-7}$ $cm^2 \cdot s^{-1}$ which is also consistent with hindered transport through a gel matrix. The limited way in which the molecular weight of the penetrant alters the concentration of the drug in the plasma is shown in Fig. 2. Under kinetic control from the transdermal device, $k_0 = 0.05$ mg·cm^{-2}·h^{-1}, Fig. 2 shows that changing the molecular weight of the penetrant from 200 to 500 has no effect on the plasma levels.

The partition coefficient of the drug is an important physicochemical variable and one which has a profound effect on the plasma–time profiles. The partitioning

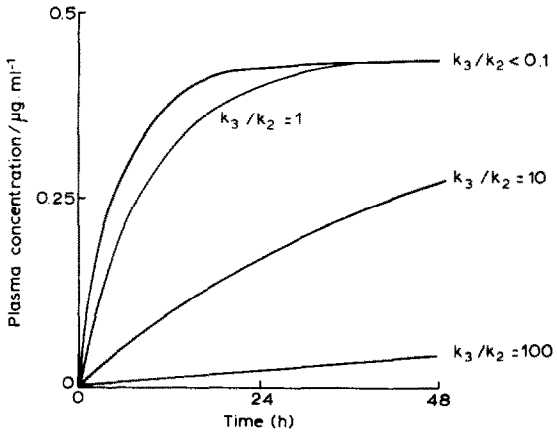

Fig. 3. Plasma concentration–time course showing the effect of partitioning. Area of application 10 cm^2, volume of distribution, 5000 ml. $k_0 = 0.05$ mg·cm^{-2}·h^{-1}; $k_2 = 2.5$ h^{-1}; k_3 variable showing the effect of partitioning; $k_4 = 0.23$ h^{-1}.

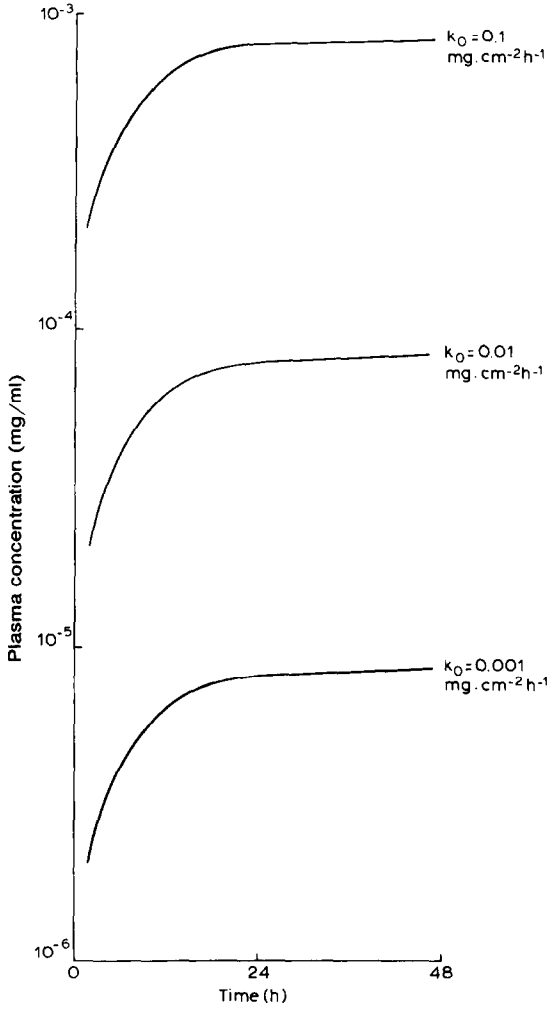

Fig. 4. Plasma concentration–time course showing the effect of the zero-order input rate. Area of application 10 cm^2, volume of distribution 5000 ml. $k_2 = k_3 = 2.5\ h^{-1}$; $k_4 = 0.23\ h^{-1}$.

behaviour between the viable epidermis and the stratum corneum is controlled by the value of k_3. A high value indicates that the drug is held back in the stratum corneum either as a result of a genuine partitioning effect or because of some direct interaction such as binding. If the drug is very lipophilic it will concentrate in the stratum corneum rather than the viable epidermis and perhaps form a substantial reservoir there, this will be modelled by high values of k_3. In general we have found empirically that k_3 may be estimated from the following equation

$$\frac{k_3}{k_2} = \frac{K_{oct}}{5} \tag{14}$$

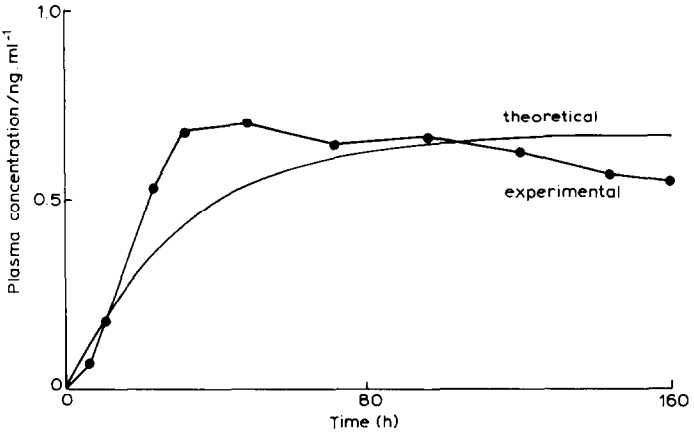

Fig. 5. Theoretical and experimental profile for transdermal application of clonidine using the constants described in the text. The experimental results are from Arndts and Arndts (1984).

where K_{oct} is the octanol water partition coefficient (Guy et al., 1985). The effect of the partition coefficient is shown in Fig. 3. When $k_3/k_2 < 1$, the penetrant is not held back in the stratum corneum and the absolute magnitude of the partition coefficient has little effect. As soon as the value of k_3 exceeds that of k_2 and drug is held up in the outer regions of the skin by a partition effect the plasma levels of the drug are considerably reduced. When very lipophilic drugs are to be delivered using a transdermal device, care has to be taken since levels may be reduced, and the curves in Fig. 3 show that it may take considerable time to establish steady plasma levels. It may be possible to circumvent this latter problem by incorporating a loading dose into the delivery system. The modelling approach outlined here does not take loading or priming doses into account.

Fig. 4 shows the effect of changing the zero-order delivery rate to the surface of the skin. In order to assess the effect, the effective partition coefficient has been taken to be 1. As expected, the steady-state plasma levels are a direct function of the delivery rate and this rate can be adjusted depending on the physicochemical properties of the penetrant to maintain the appropriate plasma levels.

One drug that has been investigated as a transdermal candidate is clonidine, and for this substance plasma concentrations have been determined (Arndts and Arndts, 1984).

We have used the theoretical model outlined above to predict the steady plasma levels of clonidine achieved after transdermal application. The zero-order rate constant for the clonidine delivery system is 1.6 $\mu g \cdot cm^{-2} \cdot h^{-1}$ and the area of application 5 cm^2 (Arndts and Arndts, 1984). The elimination rate constant, k_4, is 0.08 h^{-1} and the volume of distribution 147 l (Gilman et al., 1980). The other rate constants k_2 and k_3 have been estimated using Eqns. 13 and 14 and a value of K_{oct} of 6.8 (Hansch and Leo, 1979). k_2 and k_3 are thus 2.4 h^{-1} and 3.2 h^{-1}, respectively. The plasma concentration–time profile generated using these constants is given in

Fig. 5. Also included in the figure is the experimental profile from Arndts and Arndts (1984). The agreement considering the simplicity of our theoretical approach is very good. The theoretical model predicts the steady plasma levels achieved. There are two regions which can be identified where the fit may be improved. The present model does not take into account a loading dose of the drug and thus the approach to the constant plasma levels takes longer than found in practice. Also no account is taken of the decrease in the zero-order rate constant as the drug reservoir becomes depleted. Thus, at long times, the model predicts steady levels whereas in reality they begin to fall as seen in Fig. 5.

Nevertheless this simplistic approach provides straightforward kinetic equations which allow calculation of the plasma levels achieved after a drug is applied transdermally. It should be re-iterated that in an ideal transdermal system the device itself is rate limiting. If the device is not rate limiting, the equations generated in this paper will not predict the correct plasma concentration–time course.

Acknowledgements

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References

Arndts, D. and Arndts, K., Pharmacokinetics and pharmacodynamics of transdermally administered clonidine. Eur. J. Clin. Pharmacol., 26 (1984) 79–85.

Atkins, P., Physical Chemistry, Oxford University Press, Oxford, 1982, p. 835.

Flynn, G.L., Yalkowsky, S.H. and Roseman, T.J., Mass transport phenomena and models: theoretical concepts. J. Pharm. Sci., 63 (1974) 479–510.

Gilman, A.G., Goodman, L.S. and Gilman, A., The Pharmacological Basis of Therapeutics, Macmillan, New York, 1980, p. 1700.

Guy, R.H., Hadgraft, J. and Maibach, H.I., A pharmacokinetic model for percutaneous absorption. Int. J. Pharm., 11 (1982) 119–129.

Guy, R.H., Hadgraft, J. and Maibach, H.I., Transdermal absorption kinetics: a physicochemical approach. In Honeycutt, Zweig and Ragsdale (Eds.), Dermal Exposure Related to Pesticide Use, American Chemical Society, Washington, DC, 1985, pp. 19–31.

Hansch, C. and Leo, A., Substituent Constants for Correlation Analysis in Chemistry and Biology, John Wiley, New York, 1979, p. 241.

Scheuplein, R.J., Mechanism of percutaneous absorption. II. Transient diffusion and the relative importance of various routes of skin penetration. J. Invest. Dermatol., 45 (1967) 334–346.