A Mathematical Model To Determine Feasibility of Drug Delivery through Transdermal Route

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A mathematical model has been developed, taking into consideration the physicochemical and pharmacokinetic properties of drug molecules to theoretically determine their feasibility of being delivered transdermally. This model has been used to assess the potential of delivering ketorolac tromethamine through transdermal route. The application of the model indicated that the drug under consideration (ketorolac tromethamine) is a suitable drug candidate that can be developed into a transdermal dosage form.

The transdermal route of administration cannot be employed indiscriminately for all the drugs. The objective of this paper is to rationally deduce the feasibility of the selected drug candidate at an early stage of development by examining its physicochemical and pharmacokinetic properties.

The major parameters of drug molecules which are inter-related and are to be considered wholistically for transdermal delivery include, physicochemical properties, biological properties, type of delivery system required and requirement of penetration enhancers[1].

Transdermal drug delivery is suitable only for drugs for which the daily dose is less, i.e., a few mg, as only small quantities of the active substance can be delivered through the skin after overcoming its barrier properties. Another factor of great importance in the selection of drugs is its biologic half-life. The lower the half life, the faster the rate at which steady state levels in blood are attained. In order to appreciate the importance of physicochemical properties of a drug in transdermal delivery, a basic knowledge of the transfer processes from the device into and through the skin is required[1]. The predominant processes involved in transdermal delivery are partition and diffusion. In general, the diffusion of drugs in polymers is more sensitive to molecular size. Empirical relationships have been generated to relate diffusion coefficient (D) with molecular weight (M), e.g., $\text{Log } D = -S_M \log M + K_M$, where S_M and K are constants[2].

The physicochemical and biological properties of the compound also determine the loading dose of a particular drug to be incorporated into a transdermal device. The presence of a loading dose can alter the time required for a drug to reach steady state levels. It is possible to optimise the amount to minimise the time required to reach steady state. Also the optimum value for logarithm of octanol-water partition coefficient must be around 2 for maximum transdermal penetration of the drug[2]. A mathematical model that identifies drugs suitable for transdermal delivery is deduced by using a kinetic description of percutaneous absorption represented schematically in Fig. 1[2].

Mathematically, the series of equations resulting from the said scheme can be solved to produce a complex exponential solution for the concentration of drug in the plasma[2]. The drug input kinetics from a membrane controlled transdermal drug delivery system[1] illustrated in Fig. 1, is described by K_{IN} for the patch. K_{IN} consists of a first-order component (K_r) accounting for drug release from the contact adhesive and a zero-order contribution (K_0) representing the membrane determined flux of drug from the reservoir. K_r takes into account the competition for the drug between the patch and the stratus corneum. If the system is well designed, K_r will be small. K_1 and K_2

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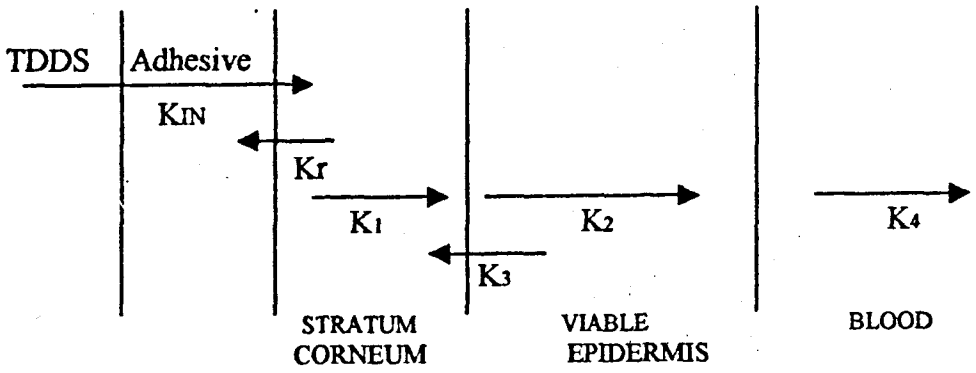

Fig. 1 : Schematic representation of transdermal drug delivery

Key : K_{IN}: Input kinetics from the patch, Kr : Accounts for competition of the drug between patch and stratum corneum, K_1 : First order rate constant for drug transport across the stratum corneum, K_2 : First order rate constant for drug transport across the viable tissue, K_3 : Rate constant describing the partitioning process at stratum corneum - viable epidermis interface, K_4 : Elimination rate constant for drug from the plasma.

are first-order rate constants describing drug transport across the stratum corneum and viable tissue, respectively[2]. K_1 and K_2 being proportional to the corresponding diffusion coefficients through these layers of skin, K_1 and K_2 may be related to the cube root of the penetrant molecular weight, as in Eqn.1-2.

$$K_1 = C.M.^{-1/3} \quad — 1$$
$$K_2 = C.M^{-1/3} \quad — 2$$

where, M is the molecular weight of the penetrant and C is a constant.

Equation 1 is assumed to be valid for diffusion in the skin. The values of K_1 and K_2 have been established for benzoic acid (BA) and hence can be used in Eqn. 3 and 4 to calculate the corresponding values for other drug molecules feasible of being delivered transdermally[4].

$$K_1 = K_1^{BA} (M^{BA}/M)^{1/3} \quad — 3$$
$$K_2 = K_2^{BA} (M^{BA}/M)^{1/3} — 4$$

The rate of the partitioning process at the stratum corneum - viable epidermis interface is taken into account by the rate constant K_3. The ratio K_3/K_2 can be approximated empirically by the octanol-water partition coefficient (K) divided by 5. Lipophilic drugs having a high value of K_3 are held back in the stratum corneum. An example of lipophilic drug delivered transdermally is estradiol and has a high value of K_3, indicating that K_3 presumably plays an important role in determining the drug residence time within the skin[2]. Moreover, if the compound is susceptible to enzymatic degradation, then a very slow transport step at the stratum corneum-viable epidermis interface may adversely affect the subsequent bioavailability[2].

$$\text{Hence, } K_3/K_2 = K/5 \text{ —— } 5$$

Therefore if K is known, on the basis of the physicochemical properties itself, K_1, K_2, K_3 can be calculated for any penetrant. Now K_4, is the elimination rate constant of the drug from the plasma[6] that cannot be determined from the physico chemical properties of the drug. For the purposes of modelling, it can be assumed that the clearance is first order and K_4 can be determined from the terminal half life for elimination as per Eqn. 6.

$$K = \frac{0.693}{t_{1/2}} — 6$$

The equations resulting from the scheme given in Fig. 1 are solved to produce a complex exponential solution for the concentration of drug in the plasma.

The zero-order and the first-order components can be separated as follows:[2]

$$c = \{AK^{o}K_1K_2/Vd\}\ \{1/xyz - e^{-\alpha t}/x(x-y)(x-z)\ e^{-\beta t}/y(y-x)(y-z) - e^{-\gamma t}/(z-x)(z-y)\} + [\{Mad\ K^{1}.\ K_1K_2/Vd\}]\ [\{e^{-\alpha t}/(y-x)(x-w)(x-\mu)\} - \{e^{-\beta t}/(x-y)\ .\ (y-w)(y-\mu) - \{e^{-\omega t}/(x-w)(w-y)\ (w-\mu)\} - \{e^{-\mu t}/(x-\mu)\ (\mu-y)(\mu-w)\}] \ldots 7$$

In the equation 7, the zero order contribution, is given by the first series of terms in the flower bracelets while the first order component is given by the second series of terms in the box brackets.

The significance of the various terms are :

A : Surface area of the delivery system

Mad: Amount of the drug incorporated into the adhesive as a loading dose

Vd : Volume of distribution of the drug

K^1 : First order rate constant for the concentration of the drug in the plasma.

x,y,w and μ are defined by the following Eqn. 8-9

$x+y = K_2+K_3+K_4$ and $xy = K_2K_4$ — (8)

$z = K_1+K_2$ — (9)

$w + \mu = K^1 + K_r + K_1$ and $w\,\mu = K\,\mu = K^1 K_1$ — (10)

The above model was used to determine the feasibility of ketorolac tromethamine as a candidate drug for transdermal delivery. The required physicochemical and pharmacokinetic parameters of ketorolac tromethamine[3] are, molecular weight: 376.41, partition co-efficient ($k_{o/w}$): 0.26, volume of distribution (Vd): 16.8 litres (Taking Average weight of an adult : 70 kg)[5], Area of the patch (A) : 20 cm^2, K^0 : 25 $\mu g/cm^2/h$ and 75 $\mu g/cm^2/h$, K_1 : 0.1236 h^{-1}, K_2: 1.9920 h^{-1}, K_3 : 0.1036 h^{-1}, K_4 : 0.17325 h^{-1}.

Volume of distribution (Vd) : volumes of distribution[6] of ketorolac tromethamine in healthy volunteers have ranged form 0.15-0.33 l/kg. Taking the average body weight of a normal adult as 70 kg, an average value of 16.8 litres was considered here.

Input rate of the drug required from the patch : (K^0):

For a patch of 20 cm^2 area, which can deliver IN : 0.5 mg/h and IN : 1.5 mg/h of drug K^0 is calculated as follows :

$IN = K^0 \times A$ — (11)

Therefore, K^0 : 25 $\mu g/cm^2/h$ when IN : 0.5 mg/h

and K^0 : 75 $\mu g/cm^2/h$ when IN : 1.5 mg/h

Using the known values[4] of Molecular weight of benzoic acid : 122

K_1^{BA} : 0.18/hr

K_2^{BA} : 2.90/hr

$K_{o/w}$: 0.26

Molecular weight of Ketorolac tromethamine (M) : 376.41 the following have been calculated

$K_1 = K_1[M^{BA}/M]^{1/3} = 0.18\ [122/376.41]^{1/3} = 0.1236$

$K_2 = K_2[M^{BA}/M]^{1/3} = 2.90\ [122/376.41]^{1/3} = 1.9920$

$K_3 = K_{o/w}/5 \times K_2 = \{0.26 \times 1.9920\}/5 = 0.1036$

$K_4 = 0.693/t_{1/2} = 0.693/4 = 0.17325$

K_r is the tendency of the drug to diffuse from the stratum corneum to the patch and is assumed to be negligible. Only the zero order component of release is considered for predicting blood levels, since a monolithic system does not contain a drug reservoir or rate controlling membrane and loading dose is not incorporated. The first order component only helps in reaching the steady state faster and it is the zero order release that is more important for predicting blood levels.

Hence,

$C = \{AK^0K_1K_2/Vd\}\ \{1/XYZ - E^{-xt}/x\ (x-y)(x-z) - e^{-yt}/y(y-x)(y-z) - e^{-zt}/z\ (z-x)(z-y)\}$ — 12

Using the above calculated parameters, x, y and z were calculated as follows :

$x+y = K_2+K_3+K_4 = 1.9920+0.1036+0.17325 = 2.26885$

$xy = K_2xK_4 = (1.9920)\ (0.17325) = 0.3452$

Solving using substitution and quadratic equations,

$x = 2.1033$ and $y = 0.1656$

Also, $z = K_1+K_r = 0.1236$

Using all these values in equation (12) one can obtain the values of c at varied times, by solving the exponential terms using logarithm tables or hand held calculators or through a small computer program written for the purpose.

When K^0 : 25 $\mu g/cm^2/h$ then, from equation (12) we have,

$c = (7.3277)\ [23.2284 - 0.12394\ e^{-2.1033t} + 74.1999\ e^{-0.1656t} - 97.3045\ e^{-0.1236t}]$ —— 13

Accordingly at K^0 : 75 $\mu g/cm^2/h$

$c = (21.9831)\ [23.2284 - 0.12394\ e^{-2.1033t} + 74.1999\ e^{-0.1656t} - 97.3045\ e^{-0.1236t}$ — 14

The results obtained on solving the above equations (13) and (14) are graphically depicted in Fig. 2.

The estimated concentration of ketorolac tromethamine required to bring about perceptable decrease in pain has been reported to be 0.1 - 0.3 $\mu g/ml$[3]. The desired concentration to reduce pain will obtained from a transdermal patch that delivers 1.5 mg/h of the drug is 6-8 h whereas in case of a system which delivers 0.5 mg/h, the therapeutic concentration is achieved in 6-8 h if the area of the patch is increased from the considered 20 cm^2 to around 50 cm^2. Using this model it can, therefore, be concluded that ketorolac tromethamine can

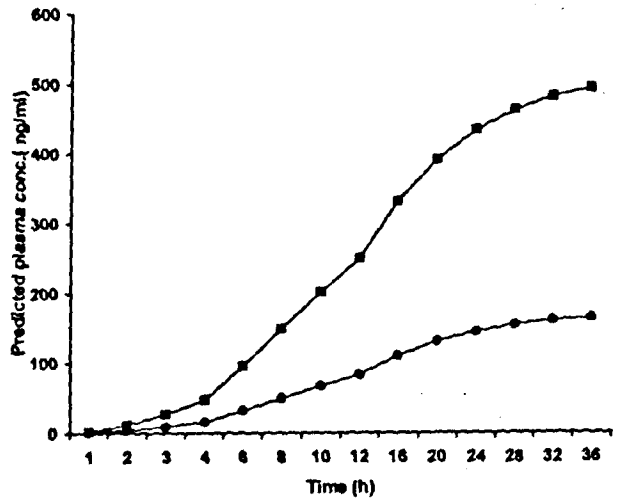

Fig. 2 : Plasma concentrations predicted by mathematical modeling at different rates

K = 25 µg/cm²/h K = 75 µg/cm²/h

be considered to be a candidate suitable for transdermal delivery. Thus the developed mathematical model can be used for any drug to get an idea of its potential to be delivered transdermally, theoretically, saving enormous amount of time, effort and experimental material.

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