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Research Article

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Feasibility of cardiovascular drugs to transdermal delivery: Prediction of plasma levels using a pharmacokinetic model

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ABSTRACT

Transdermal delivery of drugs has become the viable and successful dosage form due to its clinical benefits. It might be the most efficient, safest and convenient dosage form for drug delivery. In order to consider the feasibility of a number of cardiovascular drugs to transdermal delivery, a pharmacokinetic approach to predict plasma drug levels was applied. The kinetic and biological parameters, identified as important to transdermal delivery, of the drugs studied were either collected from literature or determined experimentally. The analysis demonstrated that the steady-state concentrations (C_{ss}) predicted by the kinetic model in μg/ml of propranolol, procainamide, verapamil, methyldopa, disopyramide and quinidine were 0.434, 5.999, 0.108, 2.322, 2.508 and 2.585, respectively. A linear relationship was found between the predicted and target C_{ss} (r = 0.974). In conclusion, the findings presented are promising for further in vitro and in vivo studies on the transdermal delivery of verapamil and seem to be a reasonable candidate. Increasing the surface area of the device for propranolol, procainamide, disopyramide and methyldopa will accelerate the attainment of effective plasma levels but will eventually lead to an acceptably large device. In addition, the including of penetration enhancer factor may clear the feasibility of the drugs studied and is highly recommended.

Keywords: Cardiovascular drugs, transdermal delivery, pharmacokinetics, propranolol, procainamide, verapamil, methyldopa, disopyramide, quinidine.

INTRODUCTION

Transdermal delivery of drugs is a major area of interest to medical and pharmaceutical scientists. The aim is to provide systemic therapy for acute and chronic conditions in a more convenient and effective way than methods available such as parenteral or oral therapy. Several advantages of these transdermal delivery medications are well known [1]. Transdermal delivery systems, also called transdermal therapeutic systems (TTS), are new dosage forms designed for sustained delivery of drugs through the skin by releasing the drug at a constant rate and slowly absorbed into the underlying blood vessels. In general, transdermal drug delivery is suitable only for drugs for which the daily dose is of the order of a few milligrams [2]. To identify potential drug candidates for transdermal delivery, it is first necessary to examine the feasibility of delivering enough active agents across the skin. At the present study, a number of cardiovascular agents were selected for the prediction of plasma drug concentration using a pharmacokinetic model in order to investigate their feasibility for transdermal delivery before being subject to further studies.

EXPERIMENTAL SECTION

The cardiovascular drugs chosen for this study are: propranolol, procainamide, verapamil, methyldopa, disopyramide and quinidine.

Pharmacokinetic model:

A pharmacokinetic model [3] for percutaneous absorption was used at this study. The scheme of the model is shown in Fig (1). The model kinetic drug criteria, in more simplified way, may be predicted from basic physicochemical properties [4,5]. The model kinetic parameters are associated with the following significance [5]: $f(k_i)$, describes input kinetics from transdermal device where for a membrane controlled system $f(k_i)$ consists of both first-order (k_i) and zero-order (k^o) components. The former represents drug release from the contact adhesive; the latter signifies the membrane limited leaching of drug from the reservoir. k^o can be calculated from;

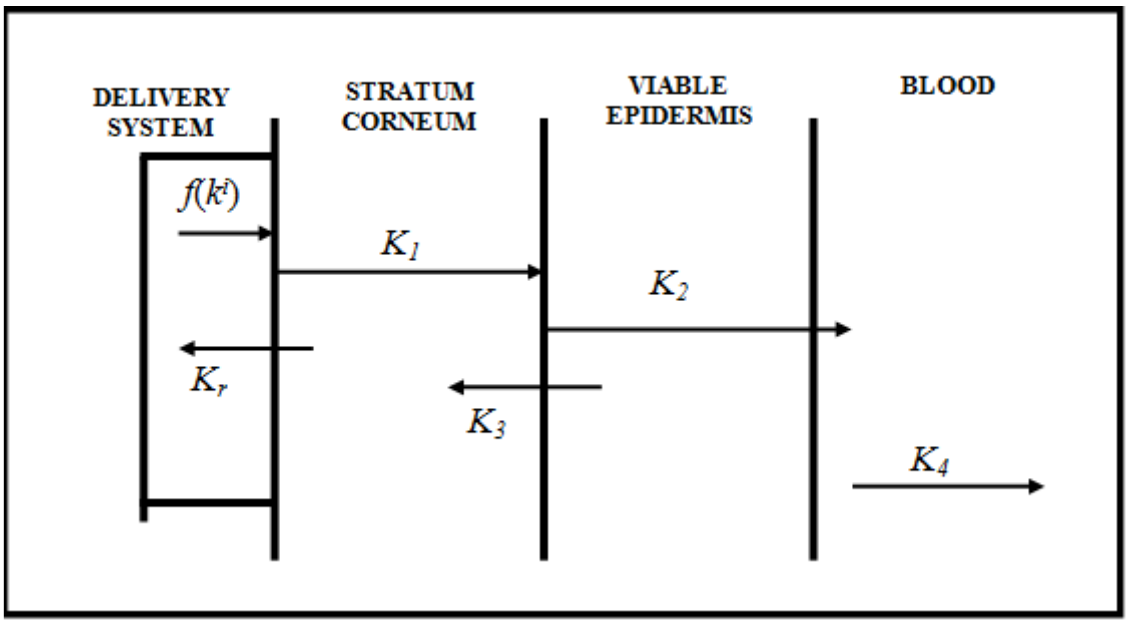

Fig 1: A scheme of pharmacokinetic model for transdermal drug delivery

$$k^o = (V_d\, k_4\, C_{ss})/A \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

where V_d is the volume of distribution, k_4 is the elimination rate constant of drug from blood and A is the surface area. k_r reflects the fact that there will be competition for the drug between the patch and the strateum corneum. k_1 and k_2 are first-order rate constants describing drug transport across the strateum corneum and viable tissue, respectively. They are, therefore, proportional to the corresponding diffusion coefficients through these layers of skin and may be simplistically related to the penetrant molecular weight (M) via Stokes-Einstein equation:

$$D = C \,.\, M^{-1/3} \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (2)$$

where, C is a constant for benzoic acid. k_1 and k_2 values have been established [3], hence the following equations may be used to calculate k_1 and k_2 parameters for the drugs used in the present study:

$$K_1^{BA} = k_1^{BA} (M^{BA} / M^D)^{1/3} \quad \ldots\ldots\ldots\ldots \quad (3)$$

$$K_2^{BA} = k_2^{BA} (M^{BA} / M^D)^{1/3} \quad \ldots\ldots\ldots\ldots \quad (4)$$

where: k_1^{BA} (k_1 of benzoic acid) = 0.184 hr, k_2^{BA} (k_2 of benzoic acid) = 2.90 hr, M^{BA} (Molecular weight of benzoic acid) = 122.1 and M^D is the molecular weight of drug.

K_3 describes the affinity of the penetrant for the strateum corneum compared to the viable epidermis. K_3 compensates for the facile estimation of K_i and allows for greater interaction between penetrant and strateum corneum. The ratio K_3/K_2 may be viewed as an effective partition coefficient between strateum corneum and viable epidermis. The equation: $K_3/K_2 = K/5$ shows that K_3/K_2 appears to be linearly correlated with the corresponding octanol-water partition coefficient (k). K_4 is the elimination rate constant of drug from the blood which cannot be predicted but must be measured following intravenous administration of the drug [6].

The predicted plasma drug concentration values (C_p) for 24 hours were obtained using the following equation:

C_p = { ($A\ k^o\ k_1\ k_2$)/V_d} {1/$\alpha\ \beta\ \varepsilon$ -exp (-$\alpha\ t$)/[α ($\alpha - \beta$)($\alpha - \varepsilon$)]
-exp(-$\beta\ t$)/[β ($\beta - \alpha$)($\beta - \varepsilon$)]
-exp(-$\varepsilon\ t$)/[ε ($\varepsilon - \alpha$)($\varepsilon - \beta$)] }
+ { ($M\ k^i\ k_1\ k_2$)/V_d } {exp(-$\alpha\ t$)/[($\beta - \alpha$)($\alpha - \omega$)($\alpha - \mu$)]
+ exp (-$\beta\ t$)/[($\alpha - \beta$) ($\beta - \omega$)($\beta - \mu$)]
+ exp(-$\omega\ t$)/[($\alpha - \omega$)($\omega - \beta$)($\omega - \mu$)]
+ exp(-$\mu\ t$)/[($\alpha - \mu$)($\mu - \beta$) ($\mu - \omega$)]} …….…..…. (5)

where α, β, ε, ω and μ are defined by: ($\alpha + \beta$) = $k_2 + k_3 + k_4$; $\alpha\ \beta = k_2\ k_4$; $\varepsilon = k_1 + k_r$; ($\omega + \mu$) = $k^i + k_r + k_1$; and $\omega\ \mu = k^i\ k_1$. As it can be seen, equation (5) is difficult to calculate by hand, therefore, software programmed specially for this purpose [7] was used to calculate C_p values for all drugs. Information including partition coefficient, half-life and other derived properties were collected from literature. The partition coefficient (*n*-octanol/water system) of methyldopa, propranolol and verapamil was determined experimentally using the method described by Yalkowsky [8]. The pharmacokinetic parameters (target C_{ss}, V_d, k_4) were either obtained from literature or calculated from the biological half-life of the drug. The values of k^i and k_r were set exactly as those used by Guy and Hadgraft [3] for evaluating the feasibility of other series of compounds.

RESULTS AND DISCUSSION

Using the parameters identified in Table (1), equation (5) predicts the plasma drug concentration-time profiles for the drugs studied (Fig. 2). The results demonstrated that the steady-state concentrations (C_{ss}) predicted by the kinetic model in μg/ml of propranolol, procainamide, verapamil, methyldopa, disopyramide and quinidine were 0.434, 5.999, 0.108, 2.322, 2.508 and 2.585, respectively. A comparison between the drugs studied in terms of their ability to achieve the target C_{ss} is given in Table (2). The values of the predicted C_{ss} were calculated from the regression equations corresponding to the curves appearing in Fig (2).

From these findings, one may deduce that for verapamil, propranolol, procainamide, disopyramide and methyldopa there is a reason to believe that their transdermal delivery may be possible. The results were obtained for verapamil (predicted C_{ss} = 0.108, target C_{ss} = 0.038). So, this drug is promising to be good candidate for transdermal delivery. Similar results were obtained for other class of drugs elsewhere [9,10,11]. While with propranolol (predicted C_{ss} = 0.434, target C_{ss} = 0.525), procainamide (predicted C_{ss} = 5.999, target C_{ss} = 7.0), disopyramide (predicted C_{ss} = 2.508, target C_{ss} = 3.5) and methyldopa (predicted C_{ss} = 2.322, target C_{ss} = 3.0), the predicted C_{ss} seems to be so close to the target C_{ss} but not achieved. The results suggest that transdermal delivery for these drugs, at this situation, is unlikely to succeed. However, although one would not, at this time, exclude the possibility of their transdermal delivery on the basis of the present calculations; it is clear that the objective is difficult.

Table 1: Kinetic and biological parameters for the drugs studied

Parameters	Disopyramide	Quinidine	Procainamide	Verapamil	Methyldopa	Propranolol
***MW*[1]**	339.5	360.5	235.3	454.6	238.2	259.3
K_r	0.000001	0.000001	0.000001	0.000001	0.000001	0.000001
***Log P*[2]**	0.32	3.44	0.76	0.014**	3.29**	1.19
K_1	0.13	0.128	0.147	0.118	0.147	0.143
K_2	2.06	2.02	2.33	1.87	2.32	2.25
K_3	0.131	1.39	0.354	0.0053	2.12	0.526
K_4	0.099	0.08	0.231	0.154	0.346	0.173
K^I	1.3	1.3	1.3	1.3	1.3	1.3
V_d*	49	175	140	280	42	280
C_{ss}[3]	3.5	4	7	0.038	3	0.525
***A*[4]**	10	10	10	10	10	10
Dose	50	50	50	50	50	50
K	1.69785	5.6	22.638	0.163856	4.3596	2.5431

*[1]Molecular weight of drugs, [2]Partition coefficient (n-octanol/water), [3]Target steady-state concentration, [4]Surface area, *Assumes 70 kg adult subject, **The log P for these drugs was determined experimentally.*

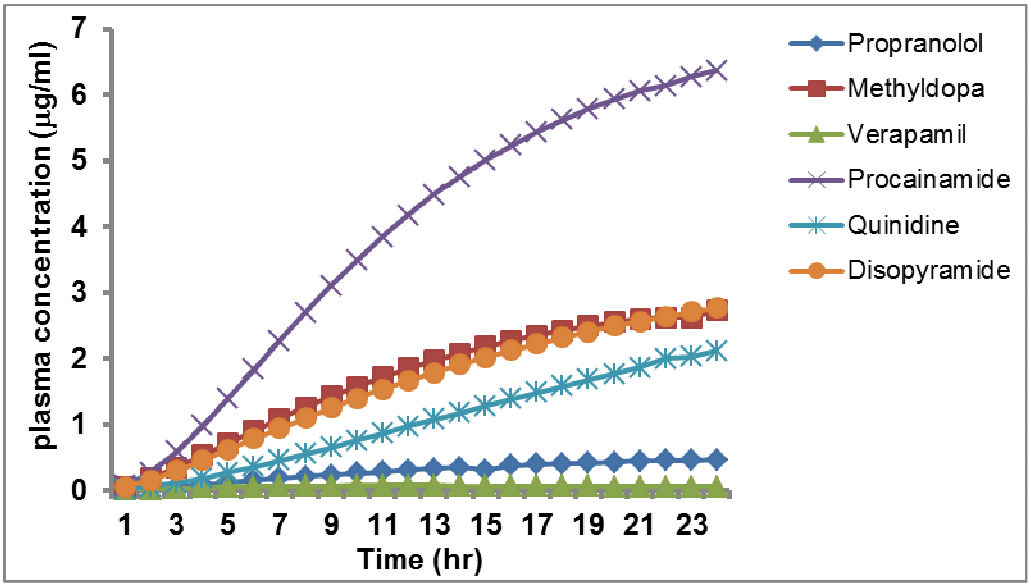

Fig 2: The predicted drug plasma concentration-time profiles for drugs studied. ***Regression equations: Disopyramide (y = 0.1223x + 0.0601), Quinidine (y = 0.0972x + 0.1898), Procainamide (y = 0.2911x + 0.1865), Verapamil (y = 0.0012x + 0.0417), Methyldopa (y = 0.1192x + 0.1979) and Propranolol (y = 0.0202x + 0.0267)***

The passage of therapeutic quantities of drug substances through skin into the general circulation for their systemic effects faces the dermal barrier "stratum corneum" as a major problem [12]. Attempts have been made to overcome this barrier by many ways including permeation enhancers and increasing surface area [13,14]. A good penetration enhancer would double the flux [15]. Moreover, taking into account the surface area of the device assumed (A = 10 cm^2), the transdermal delivery of drugs studied is feasible when the surface area is increased and this is another option of improving their transdermal delivery. It have been stated that [4,7], a large k_3 indicates strong penetrant-stratum corneum interaction and slow passage of chemicals into the viable epiderms. This may explain the much slower predicted steady-state rates for quinidine, disopyramide and methyldopa. Nevertheless, the aim of this study was to illustrate the way in which the various drug parameters, identified as important to transdermal delivery, come together to determine the ultimate feasibility of the administration of cardiovascular agents used through the skin. In general, by the interpretation and prediction of drugs studied the inputs kinetic through transdermal route are identified. Fig (3) shows a linear relationship between the target and predicted C_{ss} with a regression coefficient equal to (0.974).

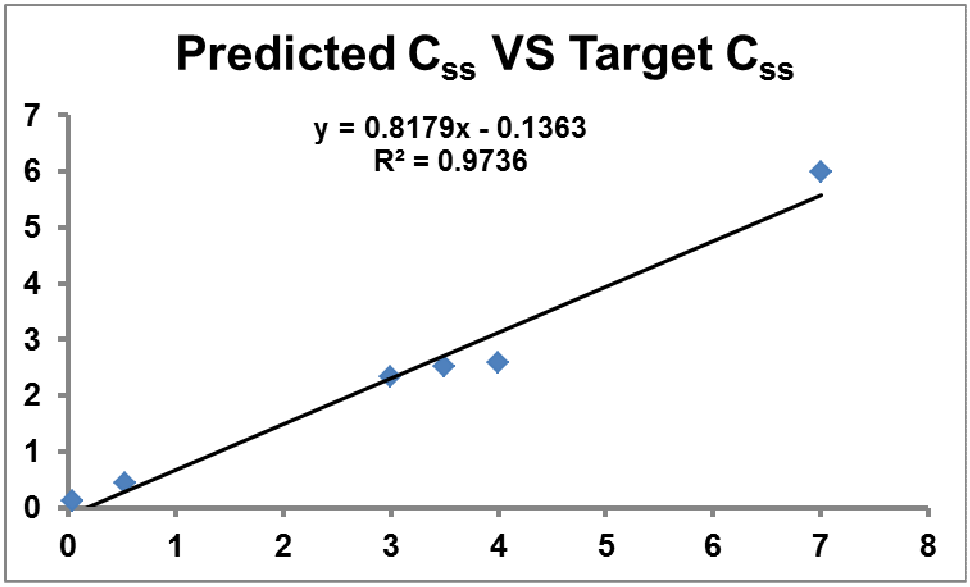

Fig 3: The linear relationship between target and predicted C_{ss}

Table 2: Comparison between the target and predicted C_{ss}

Drug	Target C_{ss} (μg/ml)	Predicted C_{ss} (μg/ml)
Disopyramide	3.5	2.508
Procainamide	7.0	5.999
Quinidine	4.0	2.585
Verapamil	0.038	0.108
Methyldopa	3.0	2.322
Propranolol	0.525	0.434

In conclusion, this study actually places transdermal delivery of the cardiovascular drugs studied in a positive light. Drugs that did not meet the transdermal criteria can be ruled out and concentrate on candidates of high promise. Two points are concluded: 1) the model provide the information required for the initial judgement about the transdermal potentials of drugs studied; and 2) the findings presented are promising for further *in vitro* and *in vivo* studies on the transdermal delivery of verapamil. For propranolol, procainamide, disopyramide and methyldopa increasing the surface area of the device will accelerate the attainment of effective plasma levels but will eventually lead to an unacceptably large device. Including of penetration enhancer factor may clear the feasibility of the cardiovascular drugs studied and is highly recommended.

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