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Pharmacokinetic analysis of plasma drug level data obtained from a transdermal therapeutic system with a complex absorption model

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Summary

The phenomenon of a pseudo steady state in the plasma drug level vs time curve observed after the administration of drugs to human skin with transdermal therapeutic systems (TTS) is analyzed with a complex absorption model. The model is based on the following assumptions: (1) drug disposition in the body may be described by kinetics based on a one-compartment model; (2) the process of drug absorption initially proceeds at a constant rate according to (zero-order) absorption kinetics but after a finite time, T_1, the zero-order absorption rate decreases with time in a first-order manner. This model requires three additional parameters to the conventional pharmacokinetic one-compartment model: namely, k_d (h^{-1}), the first-order decreasing rate constant for zero-order absorption, T_1 (h), the time at which the zero-order absorption process ceases and T_2 (h), the time of removal of TTS from the application site, i.e. the skin. The analysis based on this complex absorption model was performed for the plasma drug concentration vs time data obtained after the administration of TTS containing isosorbide dinitrate (ISDN), nitroglycerin (NTG) or clonidine. Equations describing the plasma drug concentration vs time profile are provided and a 'peeling' method to obtain the initial estimates of the parameters is described. The final pharmacokinetic parameter values were determined via nonlinear regression analysis of the plasma drug level vs time data using the above equations. The convergence and fitting of the data were excellent and the results of fitting are in support of the validity of this complex model analysis.

Introduction

One of the fields of biotechnology which is beginning to have a significant impact on clinical drug therapy is that of a new drug delivery system (Chien, 1982). Recently, exciting progress has been made in drug delivery technology for administering drugs in a rate-controlled fashion (Gardiner, 1987; Tomlinson, 1987) and considerable clinical effectiveness and success have been reported for transdermal therapeutic systems (TTS) (Chien, 1987; Utian, 1988). All of the TTS have been designed and developed based on the concept that the rate of release of the drug in the system is constant, i.e., a zero-order rate of release of the

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contained drug is established throughout therapy using TTS. However, a close inspection of the plasma drug concentration vs time data obtained after the application of TTS containing isosorbide dinitrate (ISDN) (Fig. 2) or nitroglycerin (NTG) (Fig. 3) to the skin of Japanese volunteers during clinical pharmacological studies in Japan, plasma drug levels did not attain a steady-state level (Tanaka et al., 1982; Morimoto et al., 1984). Namely, the plasma drug level decreased with time elapsed after the attainment of a pseudo steady-state plasma level.

In general, the plasma concentration of a drug depends on the balance between the rate of drug input into the systemic circulation and that of elimination from the body. To explain such a pseudo steady-state phenomena in plasma level kinetics of ISDN or NTG administered as TTS, two considerations are possible. One is that the plasma clearance of the drug increases with time after being delivered to the systemic circulation. The other is that the rate of drug absorption from the TTS decreases with time. In pharmacokinetics, the clearance of the administered drug from the body is always assumed to be constant during the experimental period. In a long-term study of patients receiving multiple oral dosing of capsules or tablets, such an assumption may sometimes be inappropriate due to renal insufficiency. However, in the case of a phase I study using healthy human subjects who received TTS, the duration of the experimental period is usually 1 week. Therefore, the assumption of constant clearance always holds true. Furthermore, in the case of another type of TTS containing NTG (TTS-NTG® system), the plasma NTG levels have been reported to attain a real steady-state level at about 3 days after application of the system (Noonan et al., 1986). Therefore, the possibility that the time-dependent nonlinear clearance of NTG may be determined can be excluded. It is more plausible to consider the rate of release or absorption of drug from TTS as decreasing with time after plasma drug levels have attained a pseudo steady-state level.

In this report, we studied the applicability of a complex model for describing such a pseudo steady-state phenomenon in the plasma. In this model, we assume that the zero-order absorption process continues until a finite time T_1 has elapsed, after which the absorption rate decreases with time according to a first-order process until the TTS is removed from the application site on the skin. In other words, after the period of zero-order absorption of the drug, the process of absorption follows behavior consistent with first-order kinetics. Therefore, the model is a complex one where first-order absorption follows an initial zero-order process of absorption. Using this complex model, a pharmacokinetic analysis of the pseudo steady-state phenomenon appearing in the plasma kinetics of three representative TTS drugs such as SDN, NTG and clonidine has been attempted.

Data and Model Used for Analysis

The pharmacokinetic model used in this study is shown in Fig. 1 and embodies the following assumptions: (1) the elimination of drug from the body obeys first-order kinetics, the first-order elimination rate constant being represented as k (h^{-1}); (2) the distribution of drug in the body may be described using a one-compartment model with a distribution volume of V_d (l); (3) zero-order process of absorption proceeding at a constant rate, k_0 (mg/h), until a finite time T_1(h) has elapsed, the rate of absorption subsequently decreasing in first-order fashion until time T_2 (h), when TTS is removed from the site of application on the skin. The first-order rate constant, k_d, represents the rate of decrease with time of the zero-order absorption process. (4) When TTS is removed at time T_2 (h) from the skin, the transfer of drug into the systemic circulation ceases. After T_2, the disposition characteristic of a drug may be described by the kinetics for a one-compartment model.

The different phases of drug absorption and elimination can be characterized as follows:

(1) Phase of continuous absorption ($0 < t \leqq T_1$): The rate of absorption of drug from TTS into the systemic circulation is constant during this period. The equation describing the plasma drug concentration vs time profile is the same as that generally used for describing the plasma kinetics

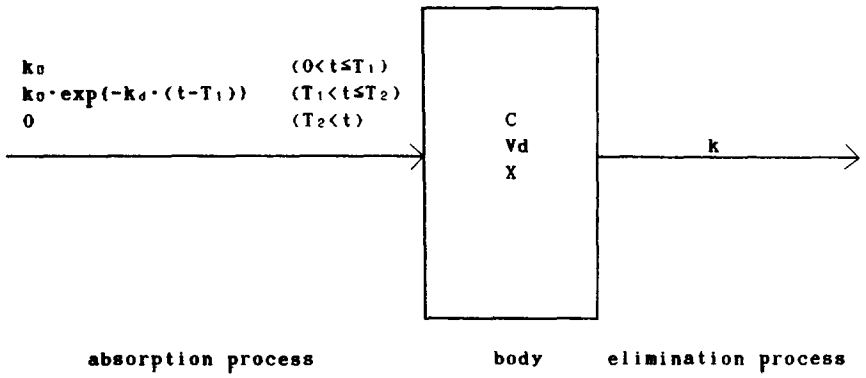

Fig. 1. Pharmacokinetic model for the absorption of drug administered as a transdermal therapeutic system (TTS). The rectangular area represents the body. During the first phase ($0 < t \leqq T_1$), the absorption of drug from TTS obeys zero-order kinetics. At the second phase ($T_1 < t \leqq T_2$), the rate of absorption decreases in a first-order manner and the absorption process continues until the removal of the TTS from human skin at time T_2. C, plasma drug concentration (ng/ml); V_d, volume of distribution (l); k_0, zero-order absorption rate (ng/h); k_d, first-order decreasing rate constant of the zero-order absorption process (h^{-1}); k, first-order elimination rate constant of drug from the body (h^{-1}); T_1, the time at which the zero-order absorption process ceases and the decreasing-rate absorption process begins; T_2, the time of removal of the TTS from the site of application on the skin.

of drug infused at a constant rate of i.v. infusion (Gibaldi et al., 1982). Namely,

$$C = \frac{k_0}{V_d k}\{1 - \exp(-kt)\} \tag{1}$$

where V_d and k are the distribution volume (l) and the first-order elimination rate constant (h^{-1}), respectively. The constant k_0 refers to the zero-order absorption rate (ng/h) of drug.

(2) Phase of absorption rate decreasing in first-order fashion ($T_1 < t \leqq T_2$): In this phase, the plasma drug concentration is composed of two fractions: one is the remaining drug concentration, first fraction C_1, due to the cessation of the constant rate absorption process, the other being the drug concentration, fraction C_2, ascribed to the following absorption process of which the absorption rate decreases from k_0 in a first-order manner. The equation representing the first fraction C_1 is expressed as (Gibaldi et al., 1982):

$$C_1 = \frac{k_0}{V_d k}\{1 - \exp(-kT_1)\} \cdot \exp\{-k(t - T_1)\} \tag{2}$$

With respect to the second fraction C_2, the absorption process initiated at T_1 and ceases at T_2. Then, by substituting $(t - T_1)$ for t of Eqn A7 (see the Appendix):

$$C_2 = \frac{k_0}{V_d(k - k_d)}\left[\exp\{-k_d(t - T_1)\} - \exp\{-k(t - T_1)\}\right] \tag{3}$$

Therefore, the plasma drug level in this phase is represented by the sum of the two preceding equations (Eqns 2 and 3):

$$C = C_1 + C_2 = \frac{k_0}{V_d k}\{1 - \exp(-kT_1)\} \cdot \exp\{-k(t - T_1)\} + \frac{k_0}{V_d(k - k_d)}\left[\exp\{-k_d(t - T_1)\} - \exp\{-k(t - T_1)\}\right] \tag{4}$$

(3) Phase after TTS is removed from the skin ($t > T_2$): The plasma drug concentration is also the sum of two fractions. One is the remaining concentration due to the constant rate absorption process, C_1, while the other fraction C_2 is the remaining drug concentration due to the decreas-

ing-rate absorption process. After removing TTS from the skin ($t > T_2$), a new time dimension t' must be introduced.

$$t = t' + T_2 \tag{5}$$

where t' is the post-absorption time.

By substitution of T in Eqn A8 with $(T_2 - T_1)$:

$$C_2 = \frac{k_0}{V_d(k - k_d)}\left[\exp\{-k_d(T_2 - T_1)\} - \exp\{-k(T_2 - T_1)\}\right] \cdot \exp(-kt'). \tag{6}$$

Therefore, the plasma drug concentration in this phase is represented by the sum of Eqns 2 and 6 with the substitution of t' by $(t - T_2)$:

$$\begin{aligned} C &= C_1 + C_2 \\ &= \frac{k_0}{V_d k}\{1 - \exp(-kT_1)\} \cdot \exp\{-k(t - T_1)\} \\ &\quad + \frac{k_0}{V_d(k - k_d)}\left[\exp\{-k_d(T_2 - T_1)\} - \exp\{-k(T_2 - T_1)\}\right]\exp\{-k(t - T_2)\}. \end{aligned} \tag{7}$$

Nonlinear least-squares regression analysis: A nonlinear least-squares regression analysis program based on a simplex algorithm was adopted. The computation was carried out on a desktop digital computer (NEC PC-9801 VM, NEC Corp., Tokyo, Japan). Parameter estimates calculated by the method of peeling were used as the initial values. Data were weighted as the reciprocal of the plasma drug concentration. The efficiency of fitting was assessed using two different methods. One is based on the calculated value for the sum of the squares whereas the other involves the visual inspection of the fits which was performed by plotting the raw data and calculated data values as a best-fit curve on a semilogarithmic scale vs time. These processes were performed automatically by our analytical system.

Results and Discussion

The proposed pharmacokinetic analysis using a complex model was employed in the case of the plasma drug concentration profile obtained after the application of TTS to human subjects. The

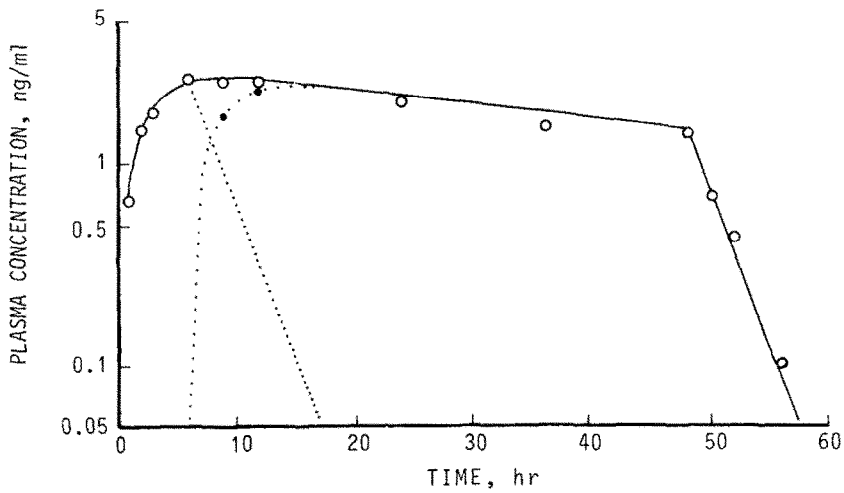

Fig. 2. Time course of the reported mean plasma ISDN concentration following administration from TTS (Frandol® tape) at a dose level of 40 mg for 48 h to six male human volunteers. (○) Data from Tanaka et al. (1982); (●) values calculated using the peeling method. (—) Best-fit curve drawn with the converged parameter values; (· · · · · ·) obtained using the peeling method.

first example concerns published data on ISDN reported by Tanaka et al. (1982). In this study, Frandol® tape (10 × 10 cm) containing 40 mg of ISDN was attached to human skin for 48 h. Subsequently, the tape was removed. The mean plasma ISDN level vs time data obtained via therapy in six subjects are shown in Fig. 2 as open circles. After a single application of the tape to the human breast, the mean plasma ISDN level increased slowly and attained a pseudo steady-state level of 2.7 ng/ml at about 6 h. Thereafter, the plasma ISDN levels declined very slowly to 1.4 ng/ml at 48 h. On removing the tape from the breast, the mean plasma ISDN level declined rapidly with a half-life of about 2.5 h. As the elimination of ISDN from the plasma followed first-order behavior, we may assume that the disposition of ISDN in the body can be represented by a one-compartment model. At first, the initial values of the three main parameters, k_0, k_d and k must be determined. As the four terminal points appear to lie on a straight line, the first-order elimination rate constant, k, may be estimated from the slope by linear regression analysis. In this case, $k = 0.309$ h^{-1} was obtained. The plasma ISDN levels reached a pseudo steady-state level of 2.7 ng/ml at 6 h after the application of TTS to the subjects. Then, by introducing the values, $t = 6$ h, $C = 2.7$ ng/ml and $k = 0.309$ h^{-1}, into Eqn 1, the value for the zero-order absorption rate corrected for the distribution volume (k_0/V_d) may be estimated, our determination yielding a value of $k_0/V_d = 1.05$ ng/h per ml. On the other hand, the mean plasma ISDN concentration attained a pseudo steady-state level at about 6 h after application of the tape to the subjects. With the assumption that the initial constant-rate, i.e., zero-order, absorption process ceases at about 6 h, the fraction of the ISDN level in the plasma, C_1, due to the initial zero-order absorption process decreases in a first-order manner. Therefore, we may draw a line of which the slope is the same as that observed in the final elimination process (after 48 h). This is shown in Fig. 2 as a broken line. By subtracting the calculated values from the observed plasma ISDN levels, the plasma drug concentrations due to the second absorption process can be visualized as shown in Fig. 2. The closed circles in Fig. 2 correspond to the plasma ISDN levels calculated according to this method. As the plasma ISDN level vs time curve due to the second absorption process demonstrates two exponential components as shown in Eqn 3, we can also obtain two linear plots through a conventional peeling technique usually used for the analysis of data on plasma drug levels obtained after oral dosing of drugs (Wagner, 1975; Gibaldi, 1982). As the rate constant k_d representing the decreasing rate of the zero-order absorption process is believed to be extremely low as compared to the elimination rate constant k, the value of k_d may be determined from the slope of the final part of the curve. The values of the two parameters estimated using the peeling technique were $k_d = 0.0167$ h^{-1} and $k = 0.311$ h^{-1}. As the initial zero-order absorption process ceases at about 6 h after dosing, the value of T_1 was estimated as 6 h. Since the time, T_2, at which TTS was removed from the site of application on the skin was clearly evident, we used this value (48 h) as a constant. Employing these values as initial estimates of the parameters, a nonlinear regression analysis was performed, yielding the converged values shown in Table 1. A good fit resulted, as demonstrated by Fig. 3, where the best-fit curve obtained with the converged parameter values is shown as an unbroken line.

Fig. 3 also displays the plasma drug concentration vs time data after the application of tape containing NTG taken from the report of Morimoto et al. (1984). After attaching three pieces of NTG tape (Millisrol® tape, containing 2.5 mg of NTG) to the breast of five subjects (i.e., the

TABLE 1

Pharmacokinetic parameters for ISDN, NTG and clonidine calculated according to a complex model

Parameter	ISDN	NTG	Clonidine
k_0/V_d (ng/h per l) [a]	1.001	1.219	0.031
k_d (h^{-1})	0.019	0.162	0.0072
k (h^{-1})	0.337	1.017	0.033
T_1 (h)	6.01	2.12	43.1

[a] The zero-order absorption rate k_0 (ng/h) has been corrected for the distribution volume (l) of the drug in the body.

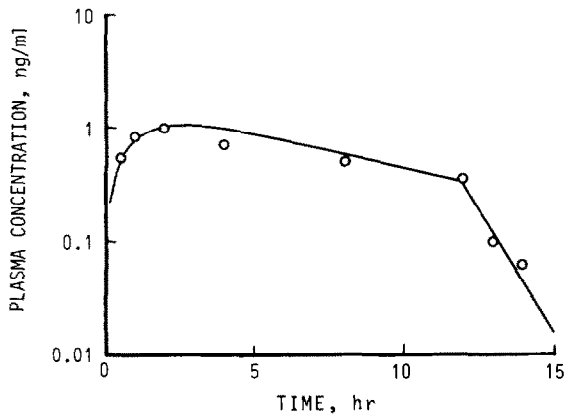

Fig. 3. Time course of the reported mean plasma NTG concentration (Morimoto et al., 1984) following administration with TTS (Millisrol® tape) at a dose level of 7.5 mg for 12 h to five male human volunteers. (—) Drawn with the converged parameter values.

dose was 7.5 mg), the plasma NTG levels were recorded for 12 h. Plasma NTG levels were also monitored after removal of the tape at 12 h. As shown in Fig. 3, plasma NTG levels declined monoexponentially during the terminal phase, although only three sampling points were established. As determined from linear regression analysis, the value of the first-order elimination rate constant k was estimated to be 0.997 h^{-1}. The other two parameters, k_0/V_d and k_d, were also estimated as described above for ISDN, and values of $k_0/V_d = 1.31$ ng/h per l and $K_d = 0.141$ h^{-1} were obtained. In addition, the initial zero-order absorption process is thought to cease at about 2 h after application of the tape to human subjects. Therefore, $T_1 = 2$ h was used as the initial value for this parameter. With these values being taken as initial estimates for the parameters, nonlinear regression analysis was performed. The converged parameter values are listed in Table 1, and the best-fit curve constructed on the basis of these values is also shown in Fig. 3.

TTS is a unique dosage form from which drug is designed to be released and absorbed into the systemic circulation at a constant rate, i.e., according to a zero-order absorption process. However, close inspection of the data reported for plasma drug levels vs time with TTS containing ISDN or NTG suggests that the zero-order absorption rate decreases with passage of time. In most of the investigations describing the pharmacokinetics of TTS drugs in humans and other animals, the analysis is based on a noncompartmental model (Kondo et al., 1987) of which the main parameters are AUC (area under the plasma concentration vs time curve) and MRT (mean residence time), or a diffusion model (Guy et al., 1985; Kubota et al., 1986). In particular, Tojo (1988) recently carried

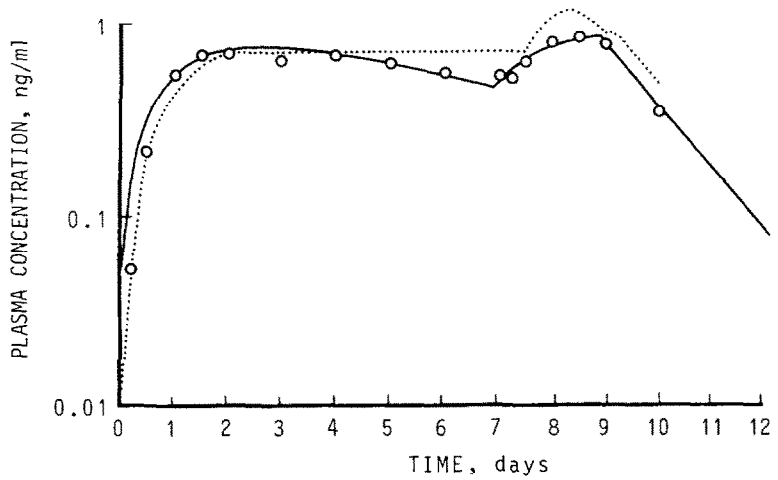

Fig. 4. Reported mean plasma clonidine concentrations vs time data (Arndt et al., 1984) after administration of clonidine as TTS-RP 600679; the first system was applied from days 1 to 8, the second being from days 8 to 10. Nonlinear regression analysis was performed on all the data, the unbroken line representing the best-fit curve resulting from the converged parameter values.

out dynamic mathematical model analysis of the reported pharmacokinetic profile for plasma levels of clonidine (Arndt et al., 1984) measured after transdermal application of TTS. In the case of the plasma profile of clonidine, a pseudo steady-state phenomenon was also observed. Fig. 4 shows plots of the data reported by Arndt et al. (1984) on a semi-logarithmic scale. In this study, the TTS was employed twice, viz., the first system was applied from days 1 to 8, and the second from days 8 to 10. Therefore, two pseudo steady-state levels are observed in the plasma clonidine level vs time curve, and plasma clonidine levels decreased slowly between the two peaks. During this phase, the rate of absorption of clonidine from TTS is believed to decrease with time. The analysis reported by Tojo (1988) was not capable of explaining such pseudo steady-state kinetics of clonidine. Our pharmacokinetic analysis using a complex model was also carried out for data from the two-stage application of clonidine and resulted in the best-fit curve and best-fit parameter values shown in Fig. 4 and Table 1. In Fig. 4, the unbroken line shows the best-fit curve resulting from the analysis with a complex model, while the dotted line refers to the simulation with the model analysis described by Tojo (1988). Clearly, a better fit was obtained with our analysis than that obtained by Tojo (1988). This study strongly supports the suitability of the concept proposed in the present paper, namely, that the zero-order absorption rate decreases with time after a pseudo steady-state has been attained in the plasma clonidine level vs time profile. In a recent paper, Ogiso et al. (1989) proposed a pharmacokinetic model involving two parallel first-order absorption processes for the analysis of the kinetics of plasma indomethacin (IM) after the percutaneous administration of IM. However, the assumption that the absorption of IM through a transdermal route can be described as a first-order absorption process is difficult to accept, since the rate of delivery of the drug is designed to follow zero-order kinetics. Our complex model is generally applicable for the analysis of plasma drug level vs time profiles obtained after the application of TTS. To clarify this contention in more detail, investigation of the situation for dissolution under in vitro conditions is required. Most in vitro dissolution studies have been performed with the aim of determining the amount or the percentage of drug that is dissolved into the medium per unit time. In addition, the time period is usually set to be considerably shorter (at most 10 h) as compared to in vivo availability studies using human subjects. Therefore, from the standpoint of pharmacokinetics, in vitro dissolution should be monitored for considerably longer periods, the results being represented as data on dissolution rate vs time. If the data on dissolution rate vs time are recorded at hourly intervals over a considerable duration of the experimental period, it should be possible to establish whether the dissolution rate of the drug from the TTS decreases with time. We are currently planning such dissolution experiments with the TTS used here.

Appendix

As generally pointed out by Benet (1972), the Laplace transform for the concentration of drug in the systemic circulation, $c(s)$, is given by the product of the input function, $\mathrm{in}(s)$, and disposition function, $\mathrm{dis}(s)$:

$$c(s) = \mathrm{in}(s) \cdot \mathrm{dis}(s) \tag{A1}$$

In the case of the zero-order absorption process, the input function, $\mathrm{in}(s)$, has been derived (Benet, 1972; Gibaldi and Perrier, 1982). In our complex model, the zero-order absorption rate begins to decrease at time T and diminishes in a first-order manner. Therefore, we must first derive the input function representing such a process of decreasing zero-order absorption. According to the assumptions described above, the rate of absorption, $\mathrm{d}A/\mathrm{d}t$, of drug from TTS into the systemic circulation is expressed as:

$$\begin{aligned} \frac{\mathrm{d}A}{\mathrm{d}t} &= k_0 \cdot \exp(-k_\mathrm{d} t) \quad (0 < t \leqq T) \\ \frac{\mathrm{d}A}{\mathrm{d}t} &= 0 \quad (t > T) \end{aligned} \tag{A2}$$

where T is the time at which the decrease in the zero-order absorption process ceases, i.e., the time

when the TTS is removed from the site of application on the skin. The Laplace transform of dA/dt is

$$L\left\{\frac{dA}{dt}\right\} = \int_0^T k_0 \cdot \exp(-K_d t) \cdot \exp(-st)dt + \int_T^\infty 0 \cdot \exp(-st)\, dt = \frac{k_0[1-\exp\{-(s+k_d)T\}]}{(s+k_d)} \quad (A3)$$

Eqn A3 expresses the input function representing the decreasing zero-order absorption process. The constant, k_d (h^{-1}), corresponds to the rate at which the zero-order absorption rate, k_0 (ng/h), decreases.

The disposition function for the central compartment, dis(s), is given on assuming a one-compartment disposition model (Benet L.Z., 1972; Gibaldi M., 1982) by:

$$\text{dis}(s) = \frac{1}{s+k} \quad (A4)$$

where k is a first-order elimination rate constant (h^{-1}). Substituting Eqns A3 and A4 into Eqn A1 yields:

$$c(s) = \frac{k_0[1-\exp\{-(s+k_d)T\}]}{(s+k_d)(s+k)} \quad (A5)$$

By performing inverse Laplace transformation of Eqn A5 according to the method of Benet and Turi (1971) and Benet (1972), we obtain the following expression describing the plasma drug concentration:

$$C = \frac{k_0[1-\exp(k-k_d)T]}{V(k_d-k)}\exp(-kt) \quad (A6)$$

During the phase in which drug absorption continues ($0 < t \leqq T$), we may introduce $T = t$ into Eqn A6. Then

$$C = \frac{k_0}{V(k-k_d)}\{\exp(-k_d t) - \exp(-kt)\} \quad (A7)$$

After the absorption process ceases ($t > T$), a new time scale t', $t' = t - T$, is introduced. The following equation is then obtained from Eqn A6:

$$C = \frac{k_0\{\exp(-k_d T) - \exp(-kT)\}}{V(k-k_d)}\exp(-kt') \quad (A8)$$

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