Pharmacokinetics of Oral Extended-Release Dosage Forms. I. Release Kinetics, Concentration, and Absorbed Fraction

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In this study, we derive pharmacokinetic models for oral extended-release (OER) drug products with defined in vivo release kinetics (IVRK) and a compartmental system. Fitting the model to clinical data, we were able to examine the correlation between released and absorbed fractions. Furthermore, we found that absorbed fractions of OER products can be expressed by absorption rate and release duration only. The expression is unchanged in different compartmental systems with the same IVRK, implying that the IVRK drives the pharmacokinetic system of an OER product. The apparent absorption rate constant of an OER product can be estimated by solving an implicit equation using observed concentrations. We also propose a new method for calculating absorbed fractions, which is more accurate than Loo-Riegelman method. Ultimately, these methods may permit optimally designed OER products.

KEY WORDS: extended-release; in vivo release kinetics; pharmacokinetics; absorbed fraction; in vitro/in vivo correlation absorption rate.

INTRODUCTION

Oral administration of a drug in an extended-release dosage form not only reduces the fluctuation in plasma drug concentrations, but also permits the drug to be given less frequently (1,2,3). Although a large number of extended-release drug products are commercially available, the need for fundamental pharmacokinetic models for these products remains.

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NOTATIONS: $X(t)$: amount of drug in the body at time t, $X_a(t)$: amount of drug in the absorption site at time t, $X_r(t)$: cumulative amount of drug released in the absorption site at time t, $X_c(t)$: amount of drug in the central compartment at time t, $X_p(t)$: amount of drug in the peripheral compartment at time t, $X_b(t)$: cumulative amount of drug absorbed at time t, $X_e(t)$: cumulative amount of drug eliminated at time t, D: total dose, F: bioavailability, V: volume of distribution, K: apparent first-order elimination rate constant for a one-compartment model, k_a: apparent first-order absorption rate constant, k_{10}: exit rate constant from the central compartment to the elimination site, k_{12}: exit rate constant from the central compartment to the peripheral compartment, k_{21}: exit rate constant from the peripheral compartment to the central compartment.

With zero-order release and zero-order absorption, the relationship of plasma drug concentration versus time for an oral extended-release drug product should be the same as that for an intravenous infusion of a defined duration (3,4). Similar to immediate-release products, most oral extended-release drug products approximately follow, however, first-order absorption. Many researchers have used conventional models (e.g., one-compartment with instantaneous release and first-order absorption) to fit the plasma drug concentration-time data of extended-release products (3,4,5,6). These models do not, however, explicitly take into account the unique in vivo release kinetics of these products. Deconvolution is a technique that has been used to characterize the in vivo release kinetics (7).

Incorporation of the in vivo release kinetics into the overall pharmacokinetic model is critical because, as we will show, it drives the system. A general class of pharmacokinetic models which incorporates in vivo release kinetics is not available at the present time. The objective of this study is to derive pharmacokinetic models for oral extended-release drug products with defined in vivo release kinetics and a compartmental system. In addition we will explore the relationship of these new models with other descriptors, such as absorbed fraction.

One-Compartment Models

The kinetics for an oral extended-release drug product, assuming first-order absorption and elimination, with a one-compartment system can be described by Eq. (1):

$$\begin{cases} \dfrac{dX(t)}{dt} = k_a X_a(t) - KX(t), \\ \dfrac{dX_a(t)}{dt} = \dfrac{dX_r(t)}{dt} - k_a X_a(t), \end{cases} \tag{1}$$

in which the in vivo release rate, $\dfrac{dX_r(t)}{dt}$, is usually a function of time. In this study, a "divide and conquer" strategy was used to treat the in vivo release profile by separating it into pieces. The two specific cases of in vivo release kinetics, zero-order and two-piece linear, were studied as steps toward a generalized approach.

Zero-Order Release

If a product follows zero-order in vivo release kinetics, i.e.,

$$\frac{dX_r(t)}{dt} = \begin{cases} 0, & t<t_0, \\ r, & t_0 \le t \le T, \\ 0, & t>T, \end{cases} \tag{2}$$

in which r is equal to $\dfrac{DF}{T - t_0}$ and T denotes the time for the completion of in vivo release, the plasma drug concentration, $C(t)$, is therefore given by Eq. (3):

$$C(t) = \begin{cases} 0, & t<t_0, \\ \dfrac{k_a DF}{V(k_a - K)(T - t_0)} \left\{ \dfrac{1}{K}[1 - e^{-K(t - t_0)}] \right. & \\ \left. - \dfrac{1}{k_a}[1 - e^{-k_a(t - t_0)}] \right\}, & t_0 \leq t \leq T, \\ C(T)e^{-K(t - T)} + \dfrac{k_a X_a(T)}{V(k_a - K)}[e^{-K(t - T)} & \\ - e^{-k_a(t - T)}], & t>T, \end{cases} \quad (3)$$

in which

$$X_a(T) = \frac{DF}{k_a(T - t_0)}[1 - e^{-k_a(T - t_0)}]. \quad (4)$$

Piecewise Linear, with Respect to Time, Release

If a product has a piecewise linear in vivo release kinetics, with respect to time, as described by Eq. (5):

$$\frac{dX_r(t)}{dt} = \begin{cases} 0, & t \leq t_0, \\ r_1(t - t_0), & t_0 < t \leq t_1, \\ r_1\left[(t - t_0) - \dfrac{T - t_0}{T - t_1}(t - t_1)\right], & t_1 < t \leq T, \\ 0, & t>T, \end{cases} \quad (5)$$

in which $r_1 = \dfrac{2DF}{(T - t_0)(t_1 - t_0)}$, the plasma drug concentration is then given by Eq. (6):

$$C(t) = \begin{cases} 0, & t \leq t_0, \\ G(t), & t_0 < t \leq t_1, \\ G(t) - H(t), & t_1 < t \leq T, \\ C(T)e^{-K(t - T)} + \dfrac{k_a X_a(t)}{V(k_a - K)}[e^{-K(t - T)} & \\ - e^{-k_a(t - T)}], & t>T, \end{cases} \quad (6)$$

in which

$$G(t) = \frac{2DF}{VK(k_a - K)(T - t_0)(t_1 - t_0)} \{(k_a - K)(t - t_0) + \frac{K}{k_a}[1 - e^{-k_a(t - t_0)}] - \frac{k_a}{K}[1 - e^{-K(t - t_0)}]\}, \quad (7)$$

$$H(t) = \frac{2DF}{VK(k_a - K)(T - t_1)(t_1 - t_0)} \{(k_a - K)(t - t_1) + \frac{K}{k_a}[1 - e^{-k_a(t - t_1)}] - \frac{k_a}{K}[1 - e^{-K(t - t_1)}]\}, \quad (8)$$

and

$$X_a(T) = \frac{2DF}{k_a^2(t_1 - t_0)} \left\{ \frac{1}{T - t_1}[1 - e^{-k_a(T - t_1)}] - \frac{1}{T - t_0}[1 - e^{-k_a(T - t_0)}] \right\}. \quad (9)$$

Absorbed Fraction

Under the first-order elimination assumption, absorbed fraction for oral extended-release drug products with one-compartment systems follows the Wagner-Nelson model (8, 9) which is given by Eq. (10):

$$A(t) = \frac{C(t) + K \cdot AUC_t}{K \cdot AUC_\infty}, \quad (10)$$

in which $A(t)$ refers to absorbed fraction, at time t, based on the amount of drug absorbed, and $AUC_t = \int_0^t C(u)du$. For extended-release products, however, Eq. (10) has specific implications. Let $C^{(y,z)}(t)$ stand for the concentration function with yth-order in vivo release kinetics and a z-compartment kinetic system, $AUC_t^{(y,z)}$ the corresponding area under the concentration-time curve, and $A^{(y,z)}(t)$ the corresponding absorbed fraction. Based on Eq. (3), it follows that

$$AUC_t^{(0,1)} = \frac{DF}{Kk_aV(T - t_0)}[e^{-k_a(t - t_0)} + k_a(t - t_0) - 1] - \frac{C(t)}{K}, \quad t_0 < t \leq T. \quad (11)$$

Inserting Eq. (11) into Eq. (10) yields Eq. (12):

$$A^{(0,1)}(t) = \frac{1}{k_a(T - t_0)}[e^{-k_a(t - t_0)} + k_a(t - t_0) - 1], \quad t_0 < t \leq T. \quad (12)$$

Similarly, combining Eqs. (6) and (10) yields Eq. (13):

$$A^{(1,1)}(t) = \begin{cases} 0, & t \leq t_0, \\ U^{(1,1)}(t), & t_0 < t \leq t_1, \\ U^{(1,1)}(t) - W^{(1,1)}(t), & t_1 < t \leq T, \end{cases} \quad (13)$$

in which

$$U^{(1,1)}(t) = \frac{1}{k_a^2(T - t_0)(t_1 - t_0)} \{[k_a(t - t_0) - 1]^2 + 1 - 2e^{-k_a(t - t_0)}\}, \quad (14)$$

and

$$W^{(1,1)}(t) = \frac{1}{k_a^2(T - t_1)(t_1 - t_0)} \{[k_a(t - t_1) - 1]^2 + 1 - 2e^{-k_a(t - t_1)}\}. \quad (15)$$

TWO-COMPARTMENT MODELS

The kinetics for an oral extended-release drug product, assuming first-order absorption and elimination, with a two-compartment system, can be described by Eq. (16):

$$\begin{cases} \dfrac{dX_c(t)}{dt} = k_a X_a(t) + k_{21} X_p(t) - k_{12} X_c(t) - k_{10} X_c(t), \\ \dfrac{dX_p(t)}{dt} = k_{12} X_c(t) - k_{21} X_p(t) \\ \dfrac{dX_a(t)}{dt} = \dfrac{dX_r(t)}{dt} - k_a X_a(t). \end{cases} \tag{16}$$

Zero-Order Release

If a product follows zero-order in vivo release kinetics as described by Eq. (2), the drug concentration in the central compartment is then given by Eq. (17) for a two-compartment system:

$$C(t) = \begin{cases} 0, & t<t_0, \\ \dfrac{k_a DF}{V_c(T-t_0)}\left[\dfrac{k_{21}}{k_a\alpha\beta} - \dfrac{k_{21}-k_a}{k_a(\alpha-k_a)(\beta-k_a)} e^{-k_a(t-t_0)} - \dfrac{k_{21}-\alpha}{\alpha(k_a-\alpha)(\beta-\alpha)} e^{-\alpha(t-t_0)} - \dfrac{k_{21}-\beta}{\beta(k_a-\beta)(\alpha-\beta)} e^{-\beta(t-t_0)}\right], & t_0<\leqslant T \\ C(T)E_1(t) + \dfrac{k_{21}X_p(T)}{V_c(\alpha-\beta)}[e^{-\beta(t-T)} - e^{-\alpha(t-T)}] + \dfrac{k_a X_a(T)}{V_c} E_2(t), & t>T, \end{cases} \tag{17}$$

in which

$$\alpha + \beta = k_{10} + k_{12} + k_{21}, \tag{18}$$

$$\alpha\beta = k_{10}k_{21}, \tag{19}$$

$$E_1(t) = \left[\frac{k_{21}-\alpha}{\beta-\alpha} e^{-\alpha(t-T)} + \frac{k_{21}-\beta}{\alpha-\beta} e^{-\beta(t-T)}\right], \tag{20}$$

$$E_2(t) = \left[\frac{k_{21}-k_a}{(\alpha-k_a)(\beta-k_a)} e^{-k_a(t-T)} + \frac{k_{21}-\alpha}{(k_a-\alpha)(\beta-\alpha)} e^{-\alpha(t-T)} + \frac{k_{21}-\beta}{(k_a-\beta)(\alpha-\beta)} e^{-\beta(t-T)}\right], \tag{21}$$

$$X_p(T) = \frac{k_{12}k_a DF}{T-t_0}\left[\frac{1}{k_a\alpha\beta} - \frac{1}{k_a(\alpha-k_a)(\beta-k_a)} e^{-k_a(T-t_0)} - \frac{1}{\alpha(k_a-\alpha)(\beta-\alpha]} e^{-\alpha(T-t_0)} - \frac{1}{\beta(k_a-\beta)(\alpha-\beta)} e^{-\beta(T-t_0)}\right], \tag{22}$$

and $X_a(T)$ is in the same form as Eq. (4).

Piecewise Linear, with Respect to Time, Release

If a product has piecewise linear in vivo release kinetics as described by Eq. (5), the drug concentration in the central compartment is then given by Eq. (23) for a two-compartment system:

$$C(t) = \begin{cases} 0, & t\leqslant t_0, \\ G(t), & t_0<t\leqslant t_1, \\ G(t) - H(t), & t_1<t\leqslant T, \\ C(T)E_1(t) + \dfrac{k_{21}X_p(T)}{V_c(\alpha-\beta)}[e^{-\beta(t-T)} - e^{-\alpha(t-T)}] + \dfrac{k_a X_a(T)}{V_c} E_2(t), & t>T, \end{cases} \tag{23}$$

in which

$$G(t) = \frac{2k_a DF}{V_c(T-t_0)(t_1-t_0)}\left[\frac{k_{21}}{k_a\alpha\beta}\left(t - t_0 + \frac{1}{k_{21}} - \frac{1}{k_a} - \frac{1}{\alpha} - \frac{1}{\beta}\right) + \frac{k_{21}-k_a}{k_a^2(\alpha-k_a)(\beta-k_a)} e^{-k_a(t-t_0)} + \frac{k_{21}-\alpha}{\alpha^2(k_a-\alpha)(\beta-\alpha)} e^{-\alpha(t-t_0)} + \frac{k_{21}-\beta}{\beta^2(k_a-\beta)(\alpha-\beta)} e^{-\beta(t-t_0)}\right], \tag{24}$$

$$H(t) = \frac{2k_a DF}{V_c(T-t_1)(t_1-t_0)}\left[\frac{k_{21}}{k_a\alpha\beta}\left(t - t_1 + \frac{1}{k_{21}} - \frac{1}{k_a} - \frac{1}{\alpha} - \frac{1}{\beta}\right) + \frac{k_{21}-k_a}{k_a^2(\alpha-k_a)(\beta-k_a)} e^{-k_a(t-t_1)} + \frac{k_{21}-\alpha}{\alpha^2(k_a-\alpha)(\beta-\alpha)} e^{-\alpha(t-t_1)} + \frac{k_{21}-\beta}{\beta^2(k_a-\beta)(\alpha-\beta)} e^{-\beta(t-t_1)}\right], \tag{25}$$

$$X_p(T) = N_1(T) - N_2(T), \tag{26}$$

$E_1(t)$ and $E_2(t)$ are given in Eqs. (20) and (21), $N_1(t)$ and $N_2(t)$ in Eqs. (34) and (35) shown below, and $X_a(T)$ is in the same form as Eq. (9).

Absorbed Fraction

The kinetics of the cumulative absorbed amount, with a two-compartment model, can be described by Eq. (27):

$$\frac{dX_b(t)}{dt} = \frac{dX_c(t)}{dt} + \frac{dX_p(t)}{dt} + \frac{dX_e(t)}{dt}. \tag{27}$$

Under the first-order elimination assumption, i.e., $\dfrac{dX_e(t)}{dt} = k_{10}X_c$, Eq. (27) yields Eq. (28) and then Eq. (29):

$$X_b(t) = V_c C(t) + X_p(t) + V_c k_{10} AUC_t, \tag{28}$$

$$A(t) = \frac{X_b(t)}{X_b(\infty)} = \frac{C(t) + \frac{1}{V_c} X_p(t) + k_{10}AUC_t}{k_{10}AUC_\infty}. \quad (29)$$

Loo and Riegelman (10) proposed this method and developed an approximate of $X_p(t)$ for calculating absorbed fraction.

With the zero-order in vivo release kinetics, however, solving Eq. (16) with respect to $X_p(t)$ yields Eq. (30):

$$X_p(t) = \begin{cases} 0, & t \leq t_0, \\ L(t), & t_0 < t \leq T, \\ M(T), & t > T, \end{cases} \quad (30)$$

in which

$$L(t) = \frac{k_{12}k_aDF}{T - t_0}\left[\frac{1}{k_a\alpha\beta} - \frac{1}{k_a(\alpha - k_a)(\beta - k_a)} e^{-k_a(t - t_0)} - \frac{1}{\alpha(k_a - \alpha)(\beta - \alpha)} e^{-\alpha(t - t_0)} - \frac{1}{\beta(k_a - \beta)(\alpha - \beta)} e^{-\beta(t - t_0)}\right], \quad (31)$$

and

$$M(t) = \frac{k_{12}V_cC(T)}{\alpha - \beta}[e^{-\beta(t - T)} - e^{-\alpha(t - T)}] + \frac{X_p(T)}{\alpha - \beta}[(k_{21} - \beta)e^{-\alpha(t - T)} - (k_{21} - \alpha)e^{-\beta(t - T)}] + k_{12}k_aX_a(T)\left[\frac{1}{(\alpha - k_a)(\beta - k_a)} e^{-k_a(t - T)} + \frac{1}{(k_a - \alpha)(\beta - \alpha)} e^{-\alpha(t - T)} + \frac{1}{(k_a - \beta)(\alpha - \beta)} e^{-\beta(t - T)}\right]. \quad (32)$$

With the two-piece linear in vivo release kinetics, the solution is given by Eq. (33):

$$X_p(t) = \begin{cases} 0, & t \leq t_0, \\ N_1(t), & t_0 < t \leq t_1, \\ N_1(t) - N_2(t), & t_1 < t \leq T, \\ M(t), & t > T, \end{cases} \quad (33)$$

in which

$$N_1(t) = \frac{2k_{12}k_aDF}{(T - t_0)(t_1 - t_0)}\left\{\frac{1}{k_a\alpha\beta}(t - t_0) + \frac{1}{k_a^2(\alpha - k_a)(\beta - k_a)}[e^{-k_a(t - t_0)} - 1] + \frac{1}{\alpha^2(k_a - \alpha)(\beta - \alpha)}[e^{-\alpha(t - t_0)} - 1] + \frac{1}{\beta^2(k_a - \beta)(\alpha - \beta)}[e^{-\beta(t - t_0)} - 1]\right\}, \quad (34)$$

$$N_2(t) = \frac{2k_{12}k_aDF}{(T - t_1)(t_1 - t_0)}\left\{\frac{1}{k_a\alpha\beta}(t - t_1) + \frac{1}{k_a^2(\alpha - k_a)(\beta - k_a)}[e^{-k_a(t - t_1)} - 1] + \frac{1}{\alpha^2(k_a - \alpha)(\beta - \alpha)}[e^{-\alpha(t - t_1)} - 1] + \frac{1}{\beta^2(k_a - \beta)(\alpha - \beta)}[e^{-\beta(t - t_1)} - 1]\right\}, \quad (35)$$

and $M(t)$ is in the same form as Eq. (32).

By inserting Eqs. (30–35) into Eq. (29), one can obtain a precise formula for calculating absorbed fraction for a two-compartment model, but it is somewhat complicated. A practical method different to Loo-Riegelman's is given in the Discussion.

Inserting Eqs. (17) and (30) into Eq. (29) yields Eq. (36), another precise formula for absorbed fraction:

$$A^{(0,2)}(t) = \frac{1}{k_a(T - t_0)}[e^{-k_a(t - t_0)} + k_a(t - t_0) - 1], \quad t_0 < t \leq T, \quad (36)$$

and inserting Eqs. (23) and (33) into Eq. (29) yields Eq. (37):

$$A^{(1,2)}(t) = \begin{cases} 0, & t \leq t_0, \\ U^{(1,2)}(t), & t_0 < t \leq t_1, \\ U^{(1,2)}(t) - W^{(1,2)}(t), & t_1 < t \leq T, \end{cases} \quad (37)$$

in which

$$U^{(1,2)}(t) = \frac{1}{k_a^2(T - t_0)(t_1 - t_0)}\{[k_a(t - t_0) - 1]^2 + 1 - 2e^{-k_a(t - t_0)}\}, \quad (38)$$

and

$$W^{(1,2)}(t) = \frac{1}{k_a^2(T - t_1)(t_1 - t_0)}\{[k_a(t - t_1) - 1]^2 + 1 - 2e^{-k_a(t - t_1)}\}. \quad (39)$$

It is interesting to note that Eqs. (12) and (36) derived for the zero-order in vivo release kinetics, and Eqs. (13) and (37) derived for the two-piece linear in vivo release kinetics have the same expression. This fact implies that the in vivo release kinetics, associated by compartmental parameters, drives the overall kinetic system of an extended-release product (11,12).

At the completion of release, $t = T$, the absorbed fraction with zero-order in vivo release kinetics can be calculated with Eq. (40):

$$A^{(0,1)}(T) = A^{(0,2)}(T) = \frac{1}{k_a(T - t_0)}[e^{-k_a(T - t_0)} + k_a(T - t_0) - 1]. \quad (40)$$

With the two-piece linear in vivo release kinetics, it becomes Eq. (41):

Table I. Absorbed Fraction at the Completion of Release, $A(T)$, in Percentage

	Zero-Order Release						Two-Piece Linear Release*					
	k_a						k_a					
T	0.5	1.0	1.5	2.0	2.5	3.0	0.5	1.0	1.5	2.0	2.5	3.0
2	36.8	56.8	68.3	75.5	80.1	83.4	38.1	60.0	73.2	81.3	86.5	90.0
4	56.8	75.5	83.4	87.5	90.0	91.7	60.0	81.3	90.0	94.0	96.1	97.2
6	68.3	83.4	88.9	91.7	93.3	94.4	73.2	90.0	95.2	97.2	98.2	98.8
8	75.5	87.5	91.7	93.8	95.0	95.8	81.3	94.0	97.2	98.4	99.0	99.3
10	80.1	90.0	93.3	95.0	96.0	96.7	86.5	96.1	98.2	99.0	99.4	99.6
12	83.4	91.7	94.4	95.8	96.7	97.2	90.0	97.2	98.8	99.3	99.6	99.7
14	85.7	92.9	95.2	96.4	97.1	97.6	92.3	98.0	99.1	99.5	99.7	99.8
16	87.5	93.8	95.8	96.9	97.5	97.9	94.0	98.4	99.3	99.6	99.8	99.8
18	88.9	94.4	96.3	97.2	97.8	98.1	95.2	98.8	99.5	99.7	99.8	99.9
20	90.0	95.0	96.7	97.5	98.0	98.3	96.1	99.0	99.6	99.8	99.8	99.9
22	90.9	95.5	97.0	97.7	98.2	98.5	96.7	99.2	99.8	99.8	99.9	99.9
24	91.7	95.8	97.2	97.9	98.3	98.6	97.2	99.3	99.7	99.8	99.9	99.9

* $t_1 = T/2$.

$$A^{(1,1)}(T) = A^{(1,2)}(T) = \frac{1}{k_a^2(T - t_0)(t_1 - t_0)}\{[k_a(T - t_0) - 1]^2 + 1 - 2e^{-k_a(T - t_0)1}\} - \frac{1}{k_a^2(T - t_1)(t_1 - t_0)}\{[k_a(T - t_1) - 1]^2 + 1 - 2e^{-k_a(T - t_1)}\}. \quad (41)$$

Table I shows $A(T)$, the fraction absorbed at the completion of in vivo release, given k_a and T, with zero-order and two-piece linear in vivo release kinetics. Note that the absorbed fraction is generally smaller than the released fraction at the same time point. We term this phenomenon "absorption delay" (with respect to the corresponding release fraction). In cases where the absorption process is much faster than the in vivo release process, absorption is driven by release (i.e., the absorption delay is ignorable), and the concentration profile of such an oral extended-release product will be similar to that of an intravenous infusion.

If a significant absorption delay is present, the observed fractions listed in Table I should be taken as the upper bound in testing the in vitro/in vivo correlation at level A (13,14), because all released fractions must be 100% after completion. When the in vitro/in vivo correlation is tested at level B (13,14) by comparing mean absorption time with mean dissolution time (15,16), and an absorption delay is present, an appropriate right hand truncation is necessary in the integration for estimating the mean absorption time.

ILLUSTRATION

The data from a six-subject pharmacokinetic study of an oral extended-release product are used to demonstrate the suitability of the derived models. For the product, its in vitro dissolution presents a zero-order pattern, and the corresponding oral immediate-release product presents a pharmacokinetic profile which indicates two-compartment and first-order absorption. Seventeen plasma concentrations collected for each individual during the treatment (0–48 hours) are shown as the dotted lines in Fig. 1. Eq. (17) with 7 parameters, t_0, T, V_c/F, k_a, k_{21}, α and β, was fit to each individual data separately, using the software package NONMEM (17). The estimates of the parameters for each individual are shown in Table II. The excellent goodness-of-fit shown in each individual (Fig. 1) provides support for the model-based applications.

Fig. 2 shows the profiles of mean absorbed fraction and mean released fraction versus time, based on the parameter estimates. The excellent correlation between mean absorbed fraction and mean released fraction (as shown) enables the use of the existing relationship between absorption and in vitro dissolution to represent the relationship between in vivo release and in vitro dissolution. Note also, an absorp-

Table II. Individual Estimates of Pharmacokinetic Parameters Based on Model (17)

Subject ID	Parameter						
	t_0 (h)	T (h)	k_{21} (h^{-1})	k_a (h^{-1})	α (h^{-1})	β (h^{-1})	V_c/F (L)
1	0.464	4.42	0.184	0.634	0.507	0.0747	756
2	0.449	4.40	0.296	1.49	1.34	0.0958	189
3	0.214	3.84	0.319	1.03	0.931	0.0810	760
4	0.587	4.10	0.108	0.522	0.394	0.0595	1184
5	0.230	4.78	0.110	0.470	0.422	0.0650	621
6	0.247	4.72	0.566	1.01	0.611	0.0800	1130

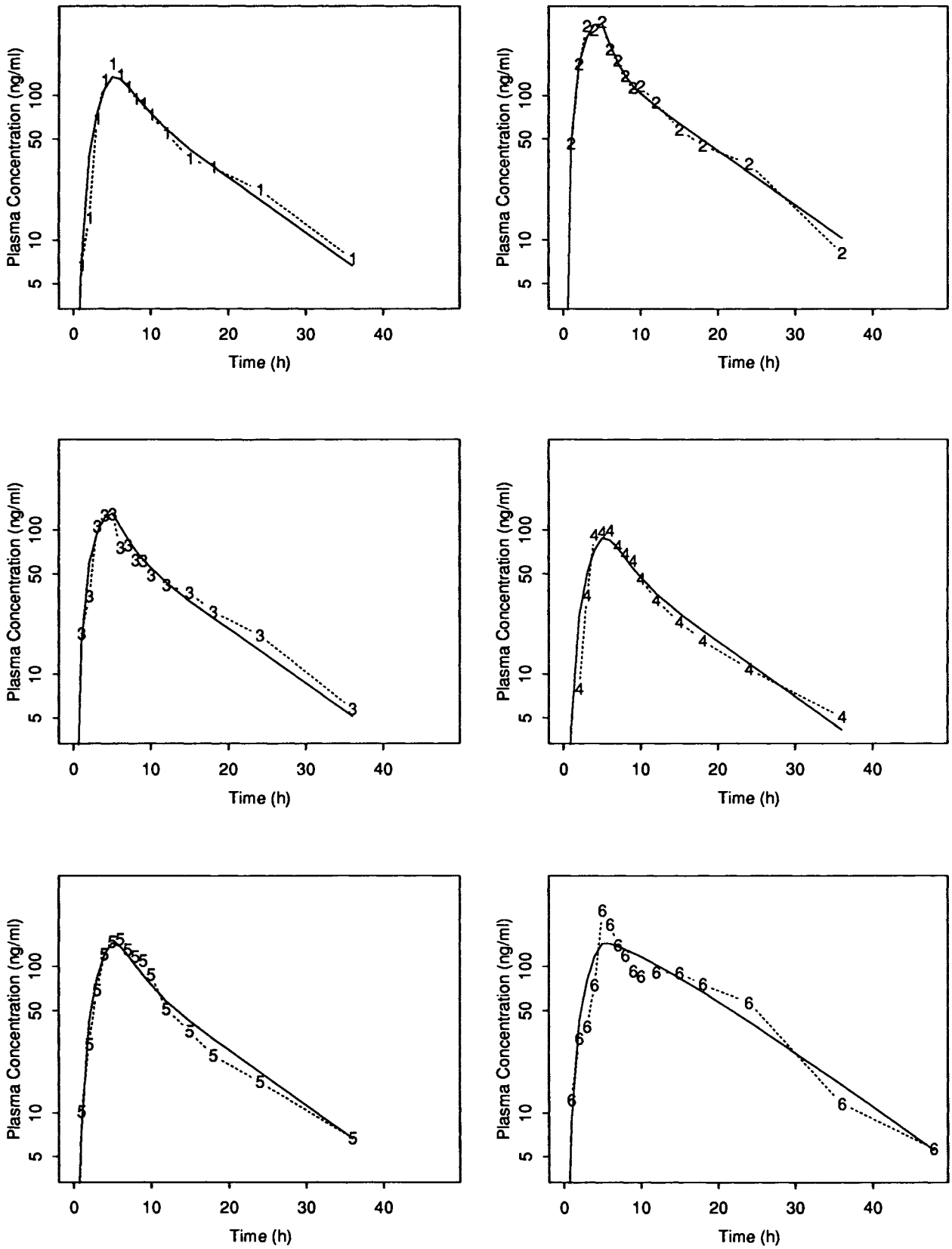

Fig. 1. Model (17) was fit separately to six individuals' plasma drug concentrations. In each panel, the solid line indicates the predictions, and the dotted line connects the data (indicated by the numbers, the value of which is the individual's identification).

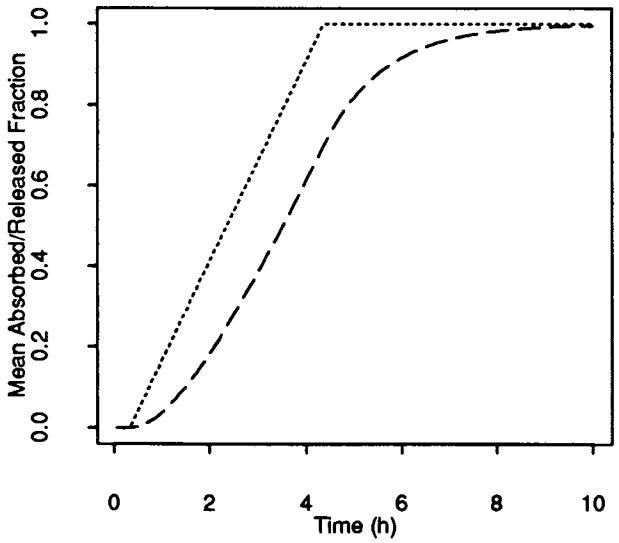

Fig. 2. Mean absorbed fraction (dashed line) and mean released fraction (dotted line) versus time, based on the parameter estimates shown in Table II.

tion delay is present, i.e., the absorbed fraction is below the corresponding released fraction. When the completion of the release (100% released fraction) is reached, the absorbed fraction is about 70%.

DISCUSSION

In Vivo Release Kinetics

In general, the in vivo release kinetics of an oral extended-release drug product can be described approximately by a stepwise zero-order, or a piecewise linear (with respect to time) function, or a mixture of these two. For example, a three-piece linear release rate is given by Eq. (42):

$$\frac{dX_r(t)}{dt} = \begin{cases} 0, & t \le t_0, \\ r_1(t - t_0), & t_0 < t \le t_1, \\ r_1(t - t_0) - r_2(t - t_1), & t_1 < t \le t_2, \\ r_1(t - t_0) - r_2(t - t_1) & \\ \quad - \dfrac{r_1(T - t_0) - r_2(T - t_1)}{T - t_2} & \\ (t - t_2), & t_2 < t \le T, \\ 0, & t > T. \end{cases} \quad (42)$$

By linking an in vivo release kinetics to a defined compartmental system, one can follow the methodology mentioned above to derive the overall pharmacokinetic model for a specific product.

A Practical Method for Calculating Absorbed Fraction Under Two-Compartment Kinetics

By solving Eq. (43):

$$\frac{dX_p(t)}{dt} = k_{12}X_c(t) - k_{21}X_p(t), \quad (43)$$

we can obtain Eq. (44):

$$X_p(t) = k_{12}V_c e^{-k_{21}(t - t_0)} \int_{t_0}^{t} e^{k_{21}u} C(u)du. \quad (44)$$

Eq. (44) is generally true for two-compartment models with any type of in vivo release kinetics. Based on Eq. (44), a practical method for calculating absorbed fraction under two-compartment kinetics can be established with an approximate term for $\frac{X_p(t)}{V_c}$ given by Eq. (45):

$$\frac{X_p(t)}{V_c} \approx k_{12}e^{-k_{21}(t - t_0)} \sum_{i=1}^{n} \frac{e^{k_{21}(t_{(i)} - t_0)}C(t_{(i)}) + e^{k_{21}(t_{(i-1)} - t_0)}C(t_{(i-1)})}{2} \Delta t_{(i)}, \quad (45)$$

in which $t_0 = t_{(0)} < t_{(1)} < \cdots < t_{(n)} = t$ and $\Delta t_{(i)} = t_{(i)} - t_{(i-1)}$.

Table III shows the comparison of the absorbed fractions derived from the precise method (based on the model), our practical method and the Loo-Riegelman method, for the data (provided) with parameter estimates $k_a = 2.5\ h^{-1}$, $\alpha = 1\ h^{-1}$, $\beta = 0.35\ h^{-1}$, $k_{21} = 0.55\ h^{-1}$, $V/F = 10\ l$, $D = 25\ mg$, and zero-order in vivo release kinetics with $t_0 = 0\ h$ and $T = 8\ h$.

This practical method is applicable to any type of product with a two-compartment kinetics.

Absorption Rate

With observed concentrations, $\hat{C}(t)$, the absorbed fraction for a one-compartment system can be estimated using Eq. (46):

$$\hat{A}(t_{(i)}) = \frac{\hat{C}(t_{(i)}) + \hat{K}\sum_{i=1}^{n} \frac{\hat{C}(t_{(i)}) + \hat{C}(t_{(i-1)})}{2} \Delta t_{(i)}}{\hat{K} \cdot A\hat{U}C_{\infty}}. \quad (46)$$

Table III. Comparison of Different Methods for Calculating Absorbed Fraction Under Two-Compartmental Kinetics

Time (*h*)	Concentration (*ng/ml*)	True Value Based on Model	Our Method	Loco-Riegelman Method
0.5	58.3	0.027	0.028	0.034
1.0	149	0.079	0.080	0.095
1.5	226	0.139	0.140	0.163
2.0	285	0.200	0.201	0.232
3.0	361	0.325	0.325	0.373
4.0	406	0.450	0.450	0.511
6.0	451	0.700	0.702	0.787
8.0	472	0.950	0.952	1.06

The absorbed fraction for a two-compartment system can be estimated using Eq. (47):

$$\hat{A}(t_{(i)}) = \frac{\hat{C}(t_{(i)}) + \frac{\hat{X}_p(t_{(i)})}{V_c} + \hat{k}_{10}\sum_{i=1}^{n} \frac{\hat{C}(t_{(i)}) + \hat{C}(t_{(i-1)})}{2}\Delta t_{(i)}}{\hat{k}_{10} \cdot A\hat{U}C_{\infty}}, \tag{47}$$

in which

$$\frac{\hat{X}_p(t_{(i)})}{V_c} = \hat{k}_{12}e^{-\hat{k}_{21}(t - t_0)} \sum_{i=1}^{n} \frac{e^{\hat{k}_{21}(t_{(i)} - t_0)}\hat{C}(t_{(i)}) + e^{\hat{k}_{21}(t_{(i-1)} - t_0)}\hat{C}(t_{(i-1)})}{2}\Delta t_{(i)}. \tag{48}$$

In order to estimate the apparent absorption rate constant, k_a, of oral extended release drug products, we can solve an implicit equation for k_a, Eq. (12), (13), (36) or (37), corresponding to a specific pharmacokinetic model with estimated $\hat{A}(t)$ and $\hat{T}$ (and the additional $\hat{t}_1$ in the case of the two-piece linear release kinetics).

Suppose that $\hat{k}_{10} = 0.2\,h^{-1}$, $\hat{k}_{12} = 0.4\,h^{-1}$ and $\hat{k}_{21} = 0.6\,h^{-1}$ (as estimated from an intravenous bolus experiment), that an oral extended-release product follows a two-compartment system with zero-order in vivo release kinetics, and that observed concentrations are as listed in the first column of Table IV. Using $\hat{T} = 8\,h$, the corresponding absorbed fraction, $\hat{A}(t)$, and absorption rate, $\hat{k}_{a,t}$, can be estimated (last two columns of Table IV). The apparent absorption rate constant, k_a, can be estimated using Eq. (49):

$$\hat{k}_a = \frac{\sum_{i=1}^{n} \hat{k}_{a,t_{(i)}}\Delta t_{(i)}}{t_{(n)} - t_{(0)}}. \tag{49}$$

In this case, we estimated the apparent absorption rate constant to be $1.58\,h^{-1}$.

The estimates of absorption rate at different times provides researchers a way of testing the null hypothesis, absorption is homogeneous among different site of the gastrointestinal tract.

Table IV. Observed Concentrations, $\hat{C}$ (t), Estimates of Absorbed Fraction, $\hat{A}$ (t), and Absorption Rate, $\hat{k}$

Time (h)	$\hat{C}(t)$ (ng/ml)	$\hat{A}(t)$ (%)	$\hat{k}_{a,t}$ (h^{-1})
1	49.8	6.36	1.63
2	120	17.4	1.57
3	179	29.4	1.53
4	228	41.6	1.48
6	302	66.7	1.52
8	371	92.6	1.69
12	233		
16	149		
20	95.7		
24	61.6		
48	5.49		

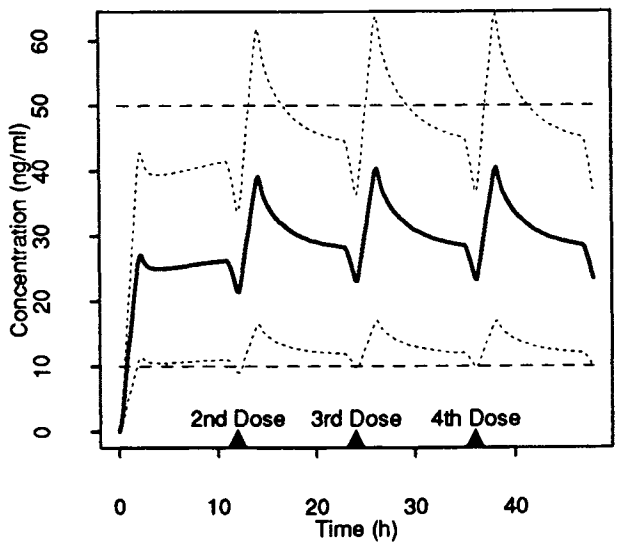

Fig. 3. Predicted concentrations and 0.95 confidence intervals after four successive doses. Solid line indicates predictions, dotted lines the bounds of the 0.95 confidence intervals, and dashed lines the bounds of the therapeutic window.

Design of Oral Extended-Release Products

It is possible to design extended-release products, based on pharmacokinetic knowledge, to meet certain criteria. For instance, there is a need to develop a twice-a-day product for a drug which follows two-compartment kinetics. The drug has a therapeutic window for plasma concentration of 10–50 ng/ml, $V_c/F = 891\,l$, $\hat{k}_{21} = 0.223\,h^{-1}$, $\hat{k}_a = 3.31\,h^{-1}$, $\hat{\alpha} = 0.407\,h^{-1}$, $\hat{\beta} = 0.158\,h^{-1}$, and a coefficient of variation of 30% in plasma concentrations. An ideal in vivo release profile includes two release stages. The first stage is provided by zero-order release of a 36 mg dose within 2 hours starting at the time of administration. The second stage is given by zero-order release of a 60 mg dose starting at 2.5 hours after administration and ending at 11 hours. Fig. 3 shows the expected result with four successive doses.

In summary, we have present several comprehensive models for the pharmacokinetics of oral extended-release products which explicitly recognize the components of the system, namely in vivo release, absorption and compartmental disposition. As illustrated, these models can be used to optimize the design of oral extended-release products. The predictability of the resulting plasma concentrations can be used to test the pharmacokinetic model and, if necessary, redesign the product.

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