Biopharmaceutics
Lecture-11 & 12

Pharmacokinetics of oral absorption

PHARMACOKINETICS OF DRUG ABSORPTION

- The systemic drug absorption from the gastrointestinal (GI) tract or from any other extravascular site is dependent on
- 1.
- 2.
- 3.

- In the pharmacokinetics, the overall rate of drug absorption may be described as either a---------- ---------- input process.
- Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.
- The rate of change in the amount of drug in the body, dD_B/dt, is dependent on the relative rates of ---------- and ----------

  as shown in (Fig. 7-1)

Figure 7-1.

Model of drug absorption and elimination

- The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption less the rate of ---------- regardless of whether absorption is zero-order or first-order.

$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt} \qquad (7.1)$$

- Where D_{GI} is amount of drug in the gastrointestinal tract and D_E is amount of drug eliminated.

- A plasma-time-level curve showing drug adsorption and elimination rate processes is given in Fig. 7-2.
- During the absorption phase of plasma level-time curve (Fig. 7-2), the rate of drug absorption is grater than the rate of drug elimination.
- Note that during the absorption phase, elimination occurs whenever drug is present in the plasma, even though absorption predominates.

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt} \qquad (7.2)$$

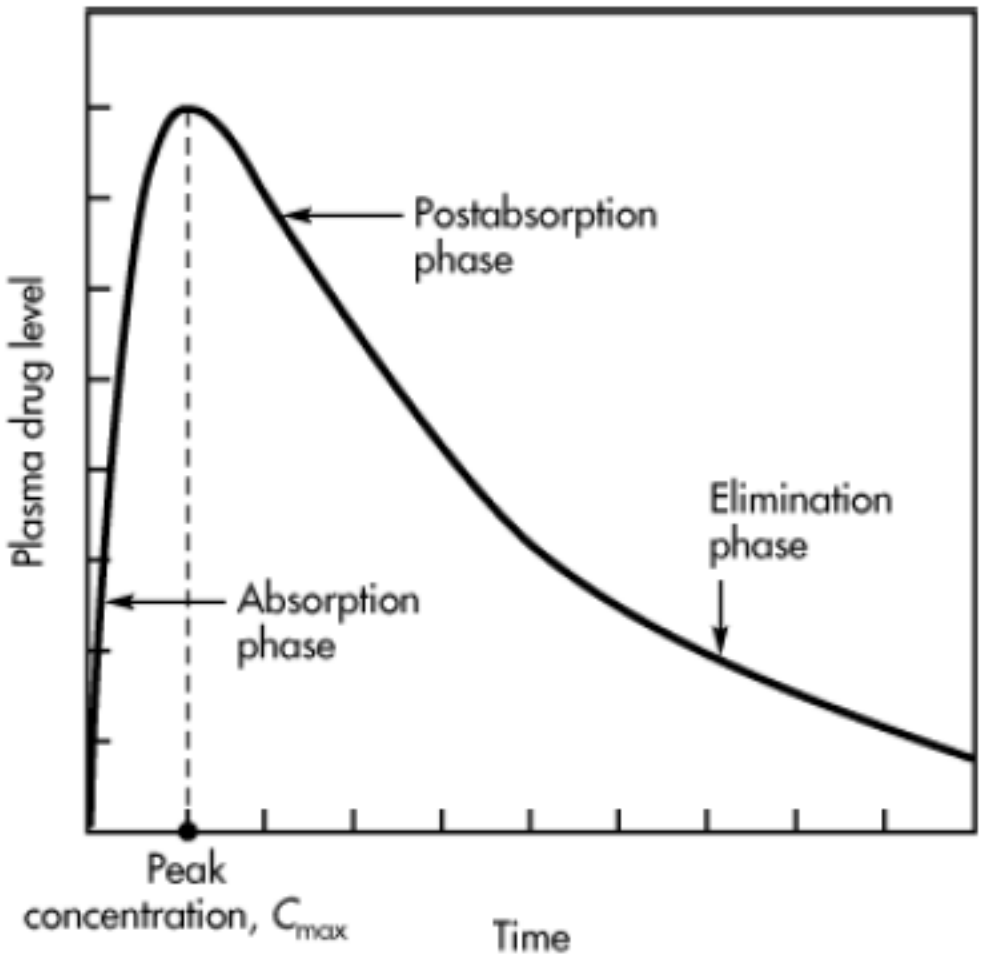


Fig. 7-2 Plasma level-time curve for a drug given in a single oral dose. The drug absorption and elimination of the curve are shown.

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt} \qquad (7.2)$$

At the *peak drug concentration* in the plasma () the rate of drug absorption just equals the rate of drug elimination, and there is no net change in the amount of drug in the body.

$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt} \qquad (7.3)$$

Immediately after the time of peak drug absorption, some drug may still be at the absorption site (ie, in the GI tract or other site of administration). However, the rate of drug elimination at this time is faster than the rate of absorption, as represented by the *postabsorption phase* in .

$$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt} \qquad (7.4)$$

- When the drug at the absorption site becomes depleted, the rate of drug absorption approaches zero, $dD_{GI}/dt = 0$.
- the plasma level-time curve (now the elimination phase) then represents only the elimination of drug from the body, usually a first-order process.
- Therefore, during the elimination phase the rate of change in the amount of drug in the body is described as a first-order process,

$$\frac{dD_B}{dt} = -kD_B \qquad (7.5)$$

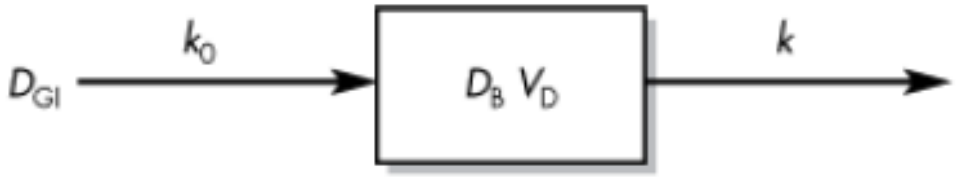
where k is the first-order elimination rate constant.

Zero-order absorption model

- Zero-order drug absorption from the dosing site into plasma usually occurs when the drug is absorbed by a ---------- process or a ---------- is used.
- The pharmacokinetic model assuming zero-order absorption is described in Fig. 7-3.
- In this model, drug in the gastrointestinal tract, D_{GI}, is absorbed systemically at a constant rate, K_0. drug is simultaneously and immediately eliminated from the body by a first-order rate process defined by a first-order rate constant, *k*.
- This model is analogous to that of the administration of a drug by intravenous infusion.

Zero-order absorption model

Figure 7-3.



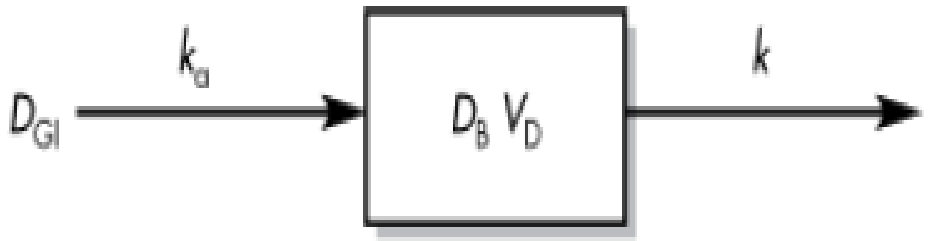
The rate of first-order elimination at any time is equal to D_B K_0.
Therefore, the net change per unit time in the body can be expressed as

$$\frac{dD_B}{dt} = k_0 - kD_B \qquad (7.6)$$

FIRST-ORDER ABSORPTION MODEL

This model assume a first-order input across the gut wall and first-order elimination from the body (Fig. 7-4).
This model applies mostly to the oral absorption of drugs in ---------- or ---------- dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories.
In addition, drugs given by intramuscular or subcutaneous aqueous injections may also be considered using a first-order process.

Figure 7-4.



In the case of a drug given orally, the dosage form first disintegrates if it is given as a solid, then the drug dissolves into the fluids of the GI tract. Only drug in solution is absorbed into the body. The rate of disappearance of drug from the gastrointestinal tract is described by

$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F \qquad (7.8)$$

where k_a is the first-order absorption rate constant from the GI tract, F is the fraction absorbed, and D_{GI} is the amount of drug in solution in the GI tract at any time t. Integration of the differential equation (7.8) gives

$$\frac{dD_{GI}}{dt} = D_0 e^{-k_a t} \qquad (7.9)$$

where D_0 is the dose of the drug.

The rate of drug change in the body, dD_B/dt, is
therefore the rate of drug in, minus the rate of drug out as given by differential equation 7.10:

$$\frac{dD_B}{dt} = \text{rate in} - \text{rate out}$$

$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_B \qquad (7.10)$$

Where F is the fraction of drug absorbed systemically. Since drug in the gastrointestinal tract also follows a first-order decline (i.e., the drug is absorbed across the gastrointestinal wall), the amount of drug in the gastrointestinal tract at any t is equal to

$$D_{GI} = D_o e^{-ka\,t}$$

$$\frac{dD_B}{dt} = Fk_a D_0 e^{-k_a t} - kD_B$$

The value of F vary from 1 for a fully absorbed drug to 0 for a drug that is completely unabsorbed.

This equation can be integrated to give the general oral absorption equation for calculation of drug concentration (Cp) in the plasma at any time t, as shown below

$$C_P = \frac{F k_a D_0}{V_D (k_a - k)} (e^{-kt} - e^{-k_a t}) \qquad (7.11)$$

A typical plot of the concentration of drug in the body after a single oral dose is presented in Figure 7-5.

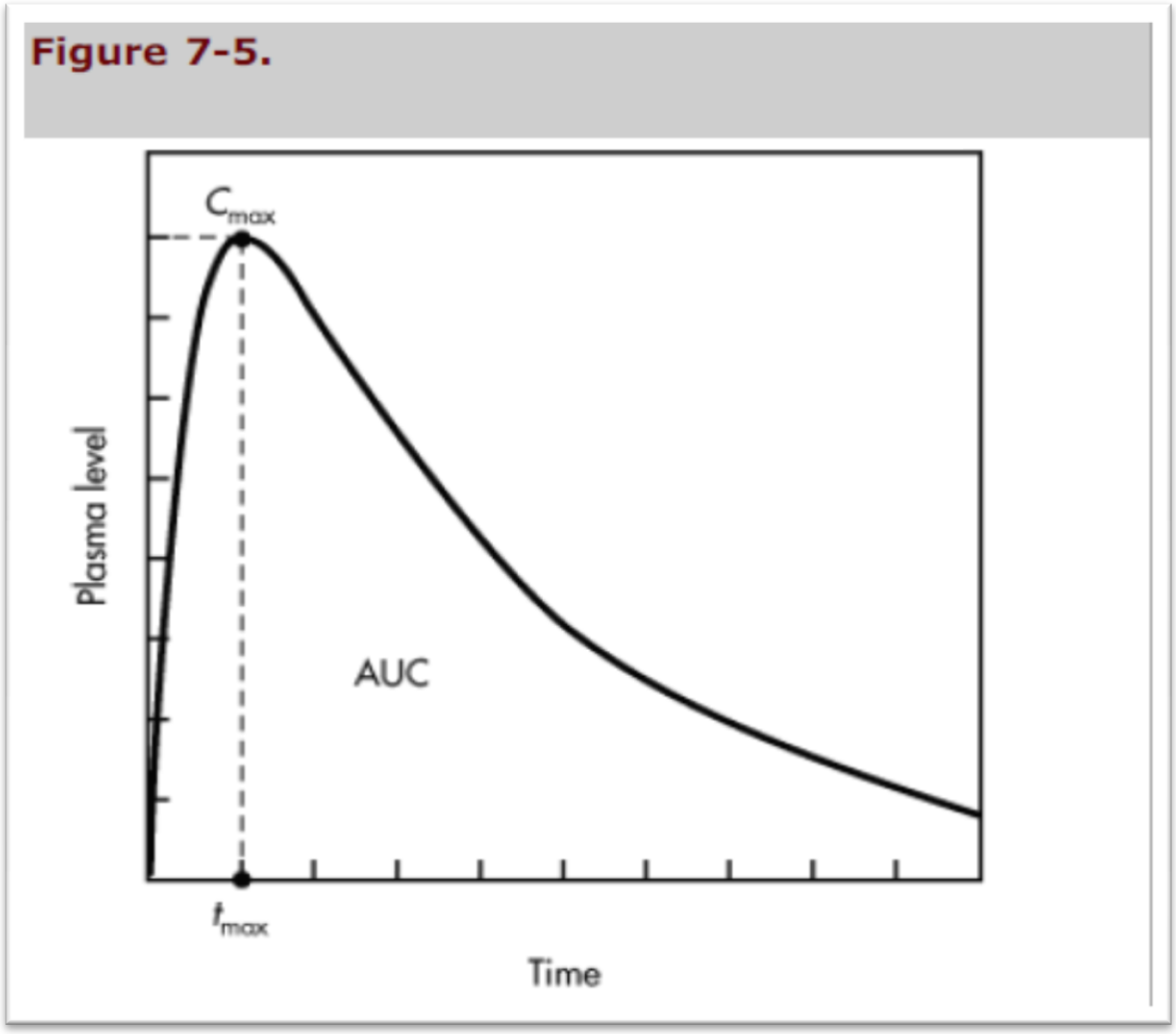


Fig.7-5. Typical plasma level-time curve for a drug in single oral dose

$$dC_p/dt = \frac{k_a D_0 F}{V_D(k_a - k)}\left(-ke^{-kt} + k_a e^{-k_a t}\right) = 0 \qquad (7.12)$$

This can be simplified as follows:

$$-ke^{-kt} + k_a e^{-k_a t} = 0 \quad \text{or} \quad ke^{-kt} = k_a e^{-k_a t} \qquad (7.13)$$

$$\ln k - kt = \ln k_a - k_a t$$

$$t_{max} = \frac{\ln k_a - \ln k}{k_a - k} = \frac{\ln(k_a/k)}{k_a - k}$$

$$t_{max} = \frac{2.3 \log (k_a/k)}{k_a - k} \qquad (7.13a)$$

As shown in Equation 7.13a, the time for maximum drug concentration, t_{max}, is dependent only on the rate constants k_a and k. In order to calculate C_{max}, the value for t_{max} is determined via Equation 7.13a and then substituted into Equation 7.11, solving for C_{max}. Equation 7.11 shows that C_{max} is directly proportional to the dose of drug given (D_0) and the fraction of drug absorbed (F). Calculation of t_{max} and C_{max} is usually necessary, since direct measurement of the maximum drug concentration may not be possible due to improper timing of the serum samples.

$$C_P = \frac{F k_a D_0}{V_D (k_a - k)} e^{-kt} \qquad (7.14)$$

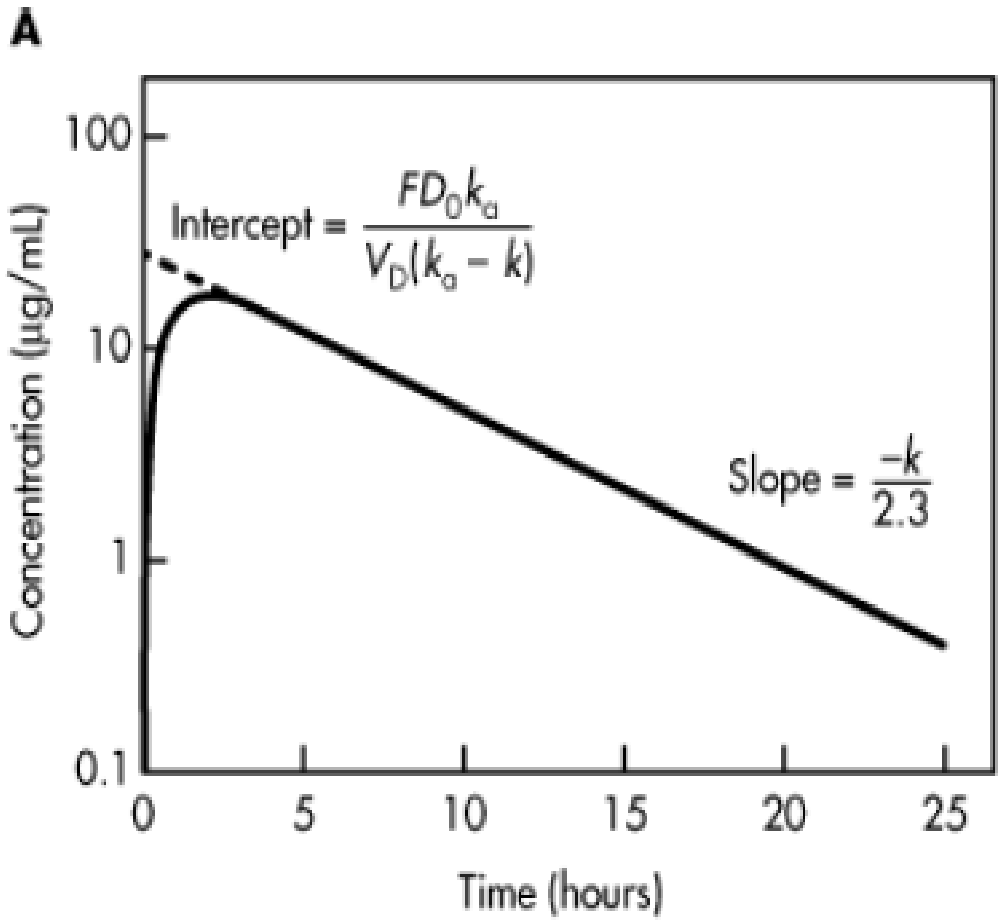
Taking the natural logarithm of this expression,

$$\ln C_P = \ln \frac{F k_a D_0}{V_D (k_a - k)} - kt \qquad (7.15)$$

Substitution of common logarithms gives

$$\log C_P = \log \frac{F k_a D_0}{V_D (k_a - k)} - \frac{kt}{2.3} \qquad (7.16)$$

Figure 7-6.


A
100
10
1
0.1
Concentration (μg/mL)
Intercept = $\frac{FD_0k_a}{V_D(k_a - k)}$
Slope = $\frac{-k}{2.3}$
0
5
10
15
20
25
Time (hours)

Determination of Absorption Rate Constants from Oral Absorption Data

METHOD OF RESIDUALS

Assuming $k_a >> k$ in Equation 7.11

$$C_p = \frac{F k_a D_0}{V_D (k_a - k)} (e^{-kt} - e^{-k_a t}) \qquad (7.11)$$

Equation 7.11 then reduces to Equation 7.22.

$$C_p = \frac{F k_a D_0}{V_D (k_a - k)} e^{-kt} \qquad (7.22)$$

From this, one may also obtain the intercept of the *y* axis

$$\frac{F k_a D_0}{V_D (k_a - k)} = A$$

where A is a constant. Thus, Equation 7.22 becomes

$$C_p = Ae^{-kt} \qquad (7.23)$$

This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper.

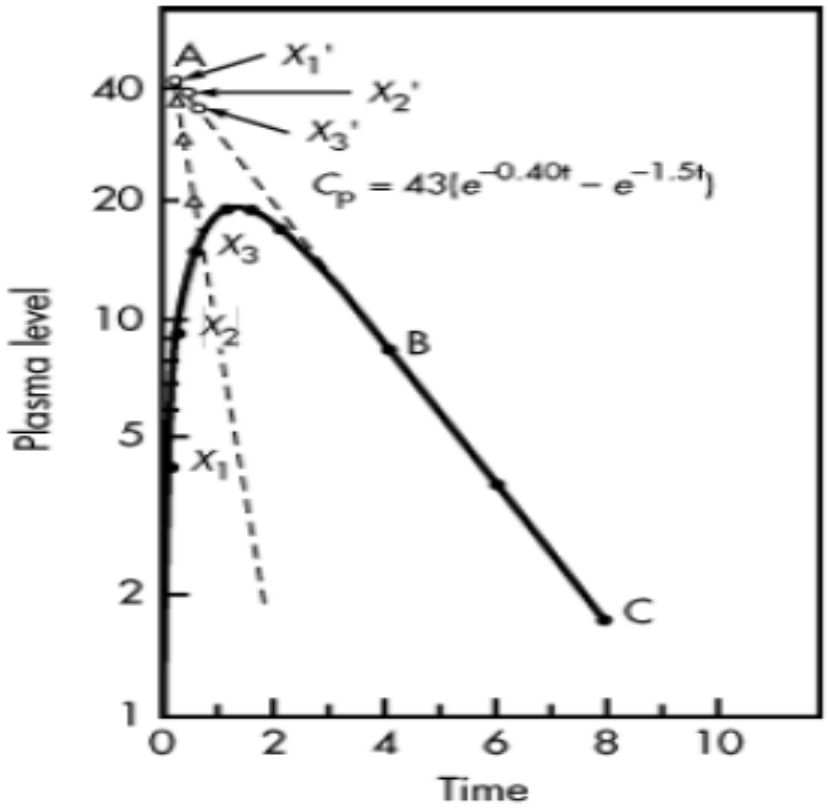


Figure 7-9.

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis (Fig. 7.9).
2. Obtain the slope of the terminal phase (line BC, Fig. 7-9) by extrapolation.
3. Take any points on the upper part of the line BC (e.g. X_1', X_2',X_3'.....) and drop vertically to obtain corresponding points on the curve(e.g., X_1, X_2, X_3 .....).
4. Read the concentration values at X_1 and X_1' and X_2 and X_2' and X_3 and X_3', and so on.
5. Plot the values of the differences at the corresponding time points Δ_1, Δ_2, Δ_3 .....

   a straight line will be obtained with a slope of –ka/2.3 (Fig. 7-9).

Notes

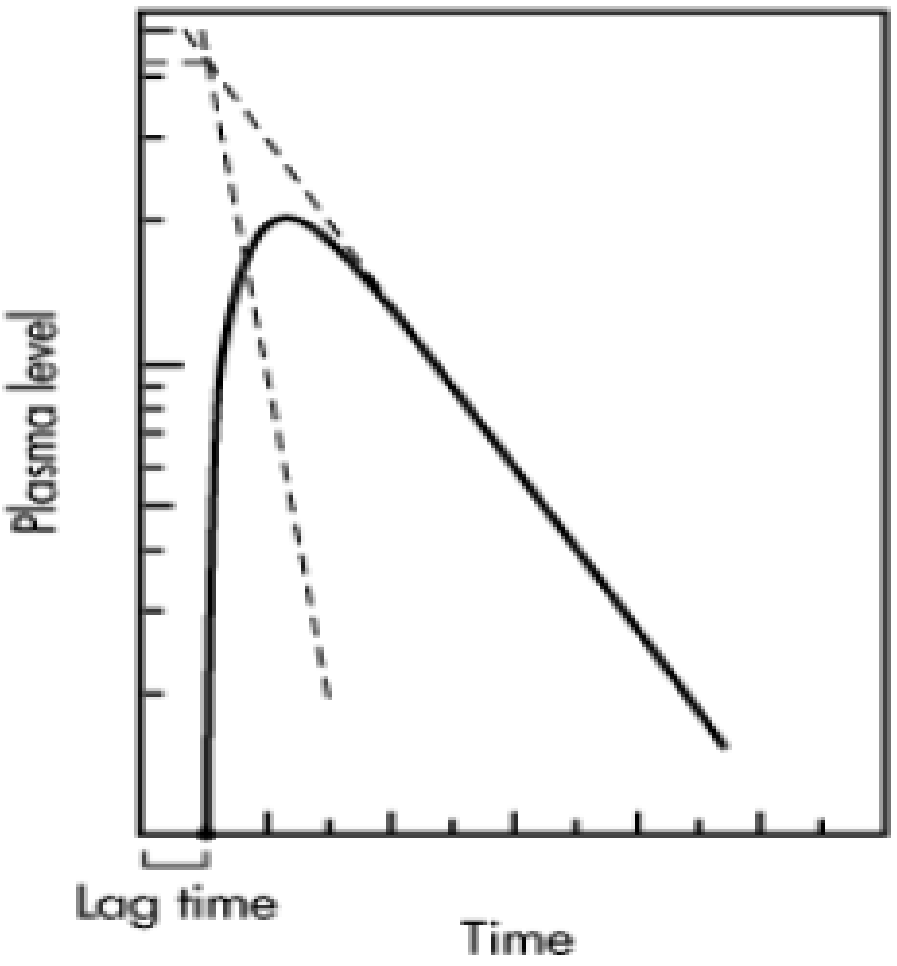
1. When using the method of residuals, a minimum of three points should be used to define the straight line.
2. Data points occurring shortly after t_{max} may not be accurate, because drug absorption is still containing at that time. Because this portion of the curve represents the post absorption phase, only data points from the elimination phase should be used to define the rate of drug absorption as a first-order process.
3. If drug absorption begins immediately after oral administration, the residual lines obtained by feathering the plasma-time curve (as shown in Fig. 7-9) will intersect on the y axis at point A.
4. The value of this y intercept, A, represents a hybrid constant composed of k_a, k, V_D, and FD_0. The value of A has no direct physiologic meaning (see Eq. 7.23).
5. The value for A, as well as the values for k, ka, may be substituted back into Eq. 7.11 to obtain a general theoretical equation that will describe the plasma-time curve.

$$A = \frac{Fk_a D_0}{V_D (k_a - k)}$$

LAG TIME

- In some individual, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility. The time delay prior to the commencement of first-order absorption is known as lag time.
- The lag time for a drug may be observed if the two residual lines obtained by feathering the oral absorption plasma level-time curve intersect at a point greater than t = 0 on the x axis.
- The time at the point of intersection on the x axis is the lag time (Fig. 7-10).

Figure 7-10.



- The lag time, t_0, represents the beginning of drug absorption and should not be confused with the pharmacologic term onset time, which represents latency, e.g., the time required for the drug to reach minimum effective concentration.
- Two equations can adequately describe the curve in Fig. 7-10

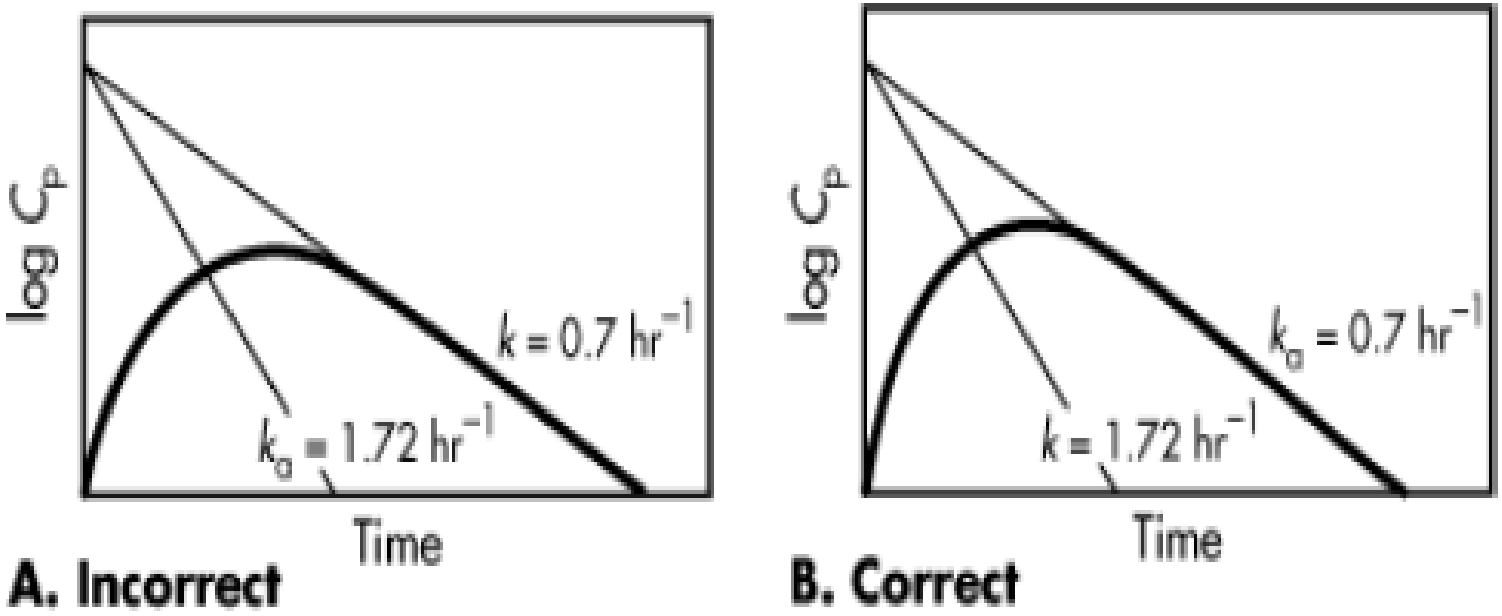
$$C_P = \frac{Fk_a D_0}{V_D(k_a - k)}\left(e^{-k(t-t_0)} - e^{-k_a(t-t_0)}\right) \qquad (7.24)$$

$$C_P = Be^{-kt} - Ae^{-k_a t} \qquad (7.25)$$

FLIP-FLOP OF K_A AND K

- In using the method of residuals to obtain estimates of ka and k, the terminal phase of an oral absorption curve is usually represented by k whereas the steeper slope is represented by ka (fig. 7-11).
- In few cases, the elimination rate constant is obtained from oral absorption data does not agree with that obtained after intravenous bolus injection.
- For example, the k obtained after an intravenous bolus injection of a bronchodilator was 1.72 hr^{-1} whereas the k calculated after oral administration was 0.7 hr^{-1} (Fig. 7-11).

Figure 7-11.


log C_p
$k = 0.7\ hr^{-1}$
$k_a = 1.72\ hr^{-1}$
Time
A. Incorrect
log C_p
$k_a = 0.7\ hr^{-1}$
$k = 1.72\ hr^{-1}$
Time
B. Correct

- When ka was obtained by the method of residuals, the rather surprising result was that the ka was 1.72 hr^{-1}.
- Apparently, the ka and k obtained by the method of residuals has been interchanged.
- This phenomenon is called flip-flop of the absorption and elimination rate constants.
- Flip-flop, or the reversal of the rate constants, may occur whenever ka and k are estimated from oral drug absorption data.
- Most of the drugs observed to have flip-flop characteristics are drugs with fast elimination (i.e., k > ka).
- Drug absorption of most drug solutions or fast dissolving products are essentially complete or at least half-complete within an hour (i.e., absorption half-life of 0.5 or 1 hr, corresponding to a ka of 1.38 hr^{-1} or 0.69 hr^{-1}).
- Because most of the drugs used orally have longer elimination half-lives compared to absorption half-lives, the assumption that the smaller slope or smaller rate constant (i.e., the terminal phase of the curve in Fig. 7-11) should be use as the elimination constant is generally correct.

- For drugs that have a large elimination rate constant ($k > 0.69\ hr^{-1}$) the chance for flip-flop of ka and k is much greater.
- The drug isoproterenol, for example, has an oral elimination half-life of only a few minutes, and flip-flop of ka and k has been noted.
- Drugs with a large k are usually considered to be unsuitable for an oral drug product due to their large elimination rate constant, corresponding to a very short elimination half-life.
- An extended-release drug product may slow the absorption of a drug, such that the k_a is smaller than the k and producing a flip=flop situation.

Effect of ka and k on Cmax, tmax, and AUC

Table 7.2 Effects of the Absorption Rate Constant and Elimination Rate[a]

Absorption Rate Constant k_a (hr^{-1})	Elimination Rate Constant k (hr^{-1})	t_{max} (hr)	C_{max} (μg/mL)	AUC (μg hr/mL)
0.1	0.2	6.93	2.50	50
0.2	0.1	6.93	5.00	100
0.3	0.1	5.49	5.77	100
0.4	0.1	4.62	6.29	100
0.5	0.1	4.02	6.69	100
0.6	0.1	3.58	6.99	100
0.3	0.1	5.49	5.77	100
0.3	0.2	4.05	4.44	50
0.3	0.3	3.33	3.68	33.3
0.3	0.4	2.88	3.16	25
0.3	0.5	2.55	2.79	20

Effect of ka and k on C_{max}, t_{max}, and AUC

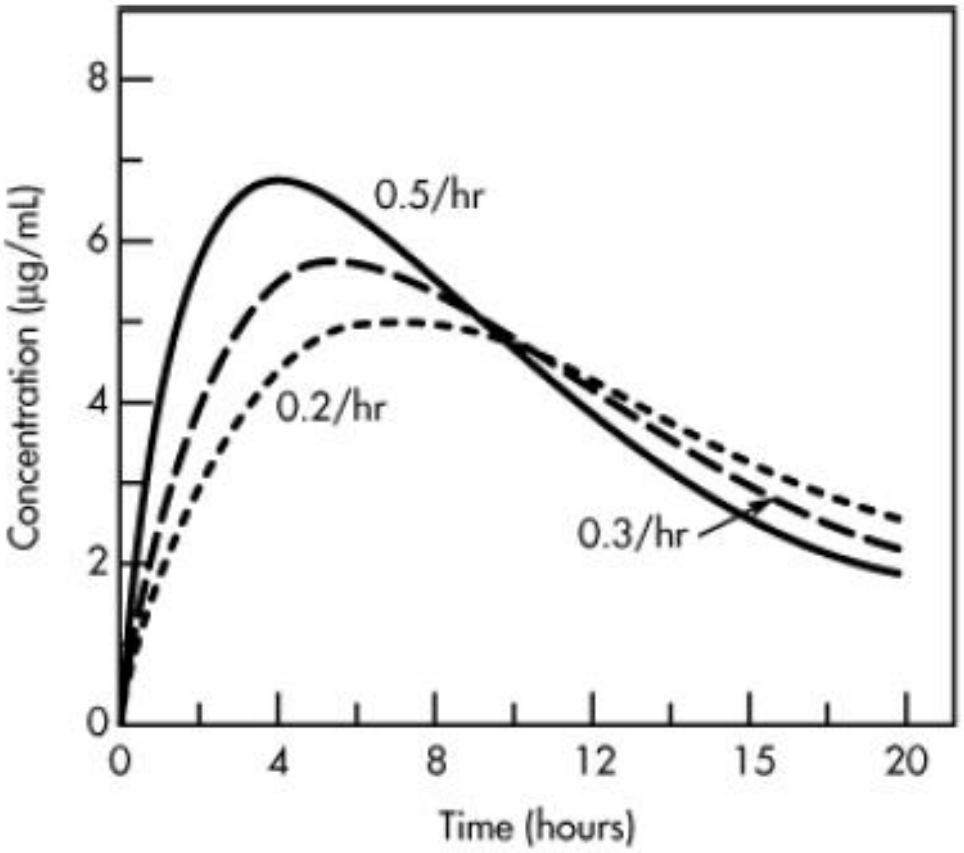
- Changes in ka and k may affect C_{max}, t_{max}, and AUC as shown in Table 7.2.

1. if the values for ka and k are reversed, then the same t_{max} is obtained, but the c_{max} and AUC are different.
2. If the elimination rate constant is kept at 0.1 hr^{-1} and the ka changed from 0.2 to 0.6 hr^{-1} (absorption rate increases), then the t_{max} become --------(from 6.93 to 3.58 hr), the C_{max} ---------- (from 5.00 to 6.99 µg/mL), but the AUC remains constant (100 µg hr/ mL).

3. In contrast, when the absorption rate constant is kept at 0.3 hr^{-1} and k changes from 0.1 to 0.5 hr^{-1} (elimination rate increases), then the t_{max} decreases (from 5.49 to 2.55 hr), the C_{max} decreases (from 5.77 to 2.79 µg hr /mL), and the AUC decreases (from 100 to 20 µg hr/ mL).

- Graphical representations for the relationship of ka and k on the time for peak drug concentrations are shown in Figures 7-13 and 7-14.

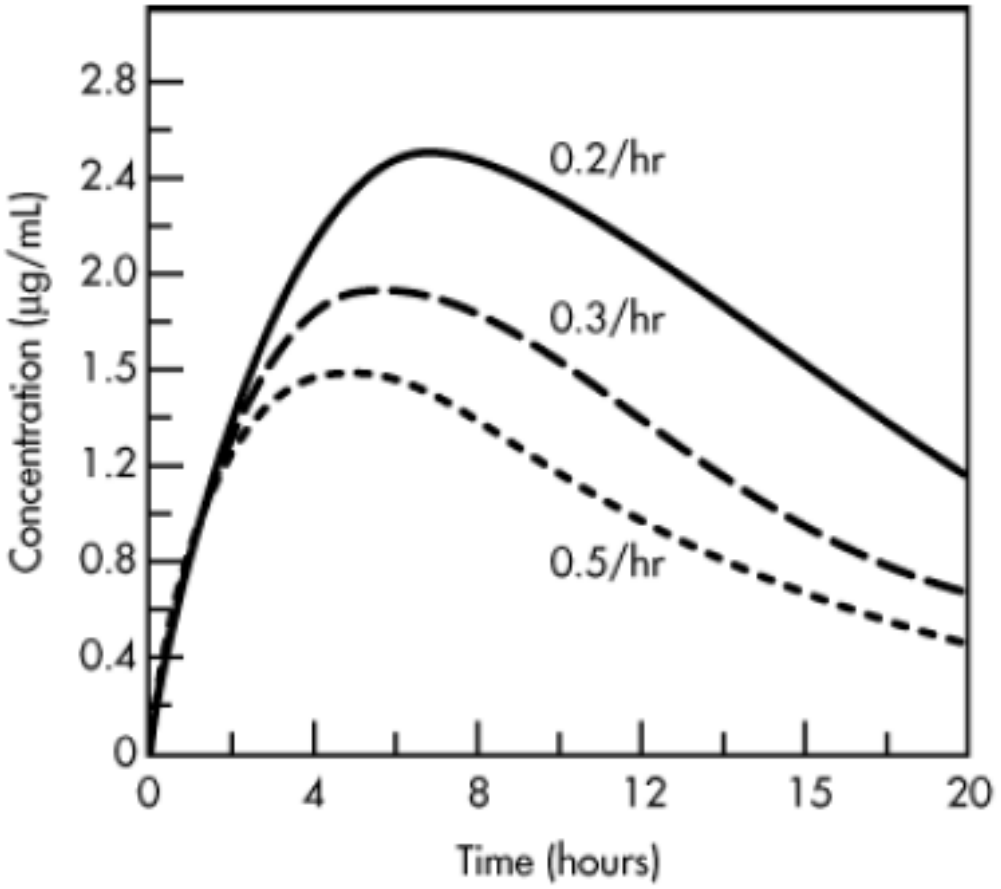
Figure 7-13.



Effect of a change in the absorption rate constant, ka on the plasma drug concentration-time curve, dose of drug is 100mg, V_D is 10 L, and k is 0.1 hr^{-1}

When Ka decrease, C_{max} decrease, t_{max} become longer, and area under the curve remain constant

Figure 7-14.



Effect of a change in the elimination rate constant on the plasma drug concentration-versus-time curve.

Dose of drug is 100 mg, V_D is 10 L, and ka is 0.1 hr^{-1}

Increase rate of elimination will decrease the t_{max}, c_{max} and area under the curve.