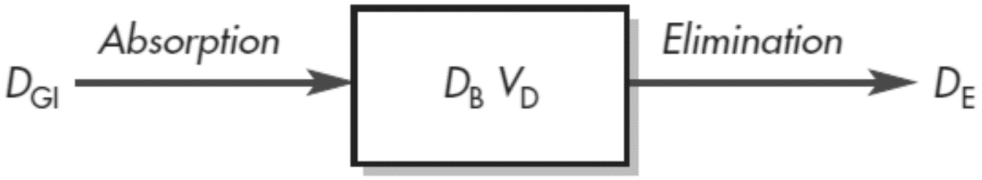
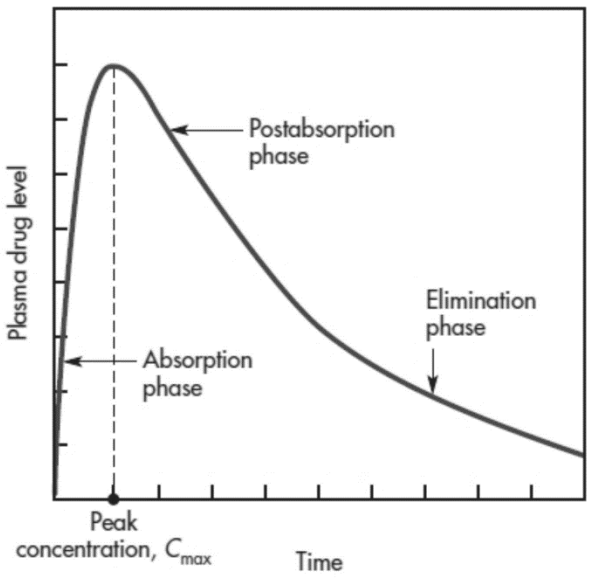
PK of Oral Drug Absorption



The rate of change in the amount of drug in the body, dD_B/dt, is dependent on the relative rates of drug absorption (dD_{GI}/dt) and elimination (dD_E/dt).



At the *absorption phase*
The rate of drug absorption > the rate of drug elimination
$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt}$
At the *peak drug concentration*
$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt}$
At the *postabsorption phase*
$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}$
At the elimination phase
The rate of drug absorption approaches zero $\frac{dD_{GI}}{dt} = 0$
$\frac{dD_B}{dt} = - kD_B$
Where K is the first-order elimination rate constant

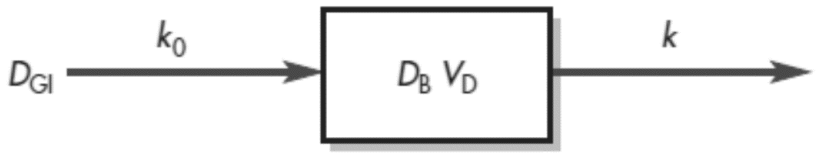
The Absorption Rate Constant

- The overall rate of systemic drug absorption from an orally administered solid dosage (*Ka*) = the net result of rate of dissolution of the drug, rate of GI motility, rate of blood flow, and the rate of transport of the drug across the capillary membranes and into the systemic circulation.
- The actual drug absorption process may be **zero-order, first-order, or a combination of both.**

ZERO-ORDER ABSORPTION MODEL
Zero-order drug absorption from the dosing site into the plasma occurs when either:

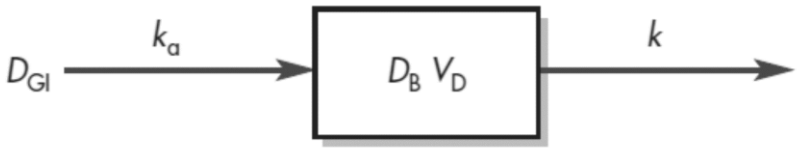
1. The drug is absorbed by a saturable process.
2. Zero-order controlled-release delivery system is used.

- Drug in the gastrointestinal tract, D_{GI}, is absorbed systemically at a constant rate k_0.
- Drug eliminated from the body by a first-order rate process defined by a first-order rate constant (k).
- Rate of drug change in the body $\frac{dD_B}{dt} = K_0 - kD_B$



FIRST-ORDER ABSORPTION MODEL

Systemic drug absorption after oral administration of a drug product (eg, tablet, capsule) is usually assumed to be a first-order process. This model assumes a first-order input across the gut wall and first-order elimination from the body



The rate of disappearance of drug from the gastrointestinal tract is described by
$\frac{dD_{GI}}{dt} = - k_a D_{GI} F$
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.*
$\frac{dD_B}{dt}$ = rate in – rate out
$\frac{dD_B}{dt} = F k_a D_{GI} - k D_B$

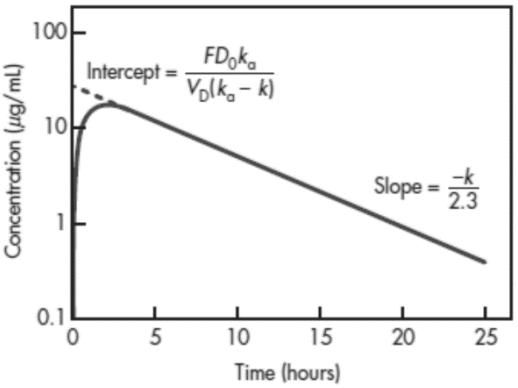
$$C_P = \frac{F k_a D_0}{V_D(k_a - k)} \left(e^{-kt} - e^{-k_a t}\right)$$

The maximum plasma concentration after oral dosing is C_{max} (*peak concentration)* and the time needed to reach maximum concentration is t_{max}
At C_{max} $\quad k e^{-kt} = k_a e^{-k_a t}$
$t_{max} = \frac{2.3 \log (k_a/k)}{(k_a - k)}$
The t_{max} is independent of dose and is dependent on the rate constants for absorption (k_a) and elimination (k)
For the calculation of C_{max}, t_{max} is calculated first and then substituted in the equation above

Determination of *K* and k_a from plasma concentration-time curve

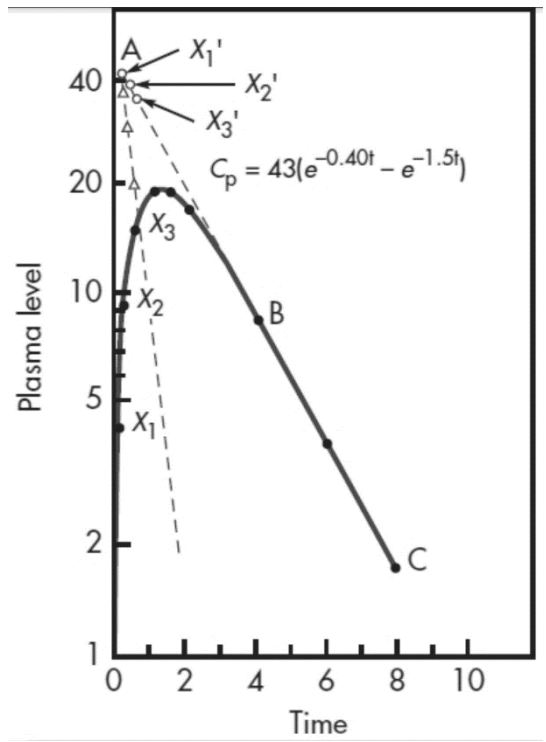
- **Determination of k**
  - A graph constructed by plotting C_p versus time on a semilog paper will yield a straight line with a slope of -k/2.3

- The points used for the calculation of k should be from the elimination phase in the graph.



- **Determination of k_a from Oral Absorption Data by Method of Residuals**

1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis.
2. Obtain the slope of the terminal phase by extrapolation.
3. Take any points on the upper part of the extrapolated line (eg, *x*′1, *x*′2, *x*′3, …) and drop vertically to obtain corresponding points on the curve (eg, *x*1, *x*2, *x*3, …).
4. Read the concentration values at *x*1 and *x*′1, *x*2 and *x*′2, *x*3 and *x*′3, and so on. Plot the values of the differences at the corresponding time points Δ1, Δ2, Δ3, … . A straight line will be obtained with a slope of **-*ka*/2.3**.
5. When using the method of residuals, a minimum of three points should be used to define the straight line.

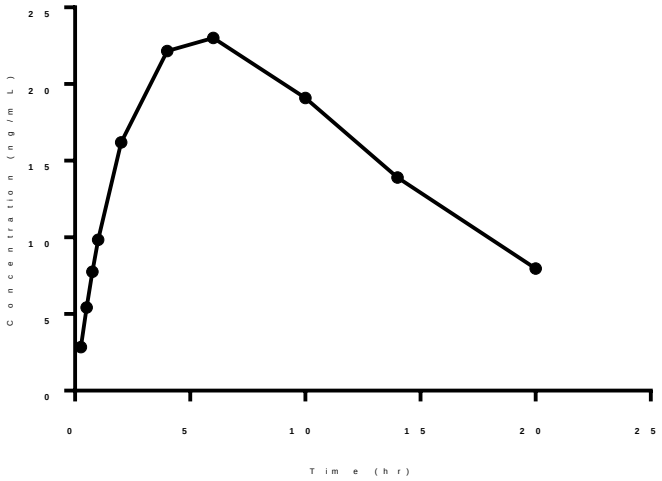


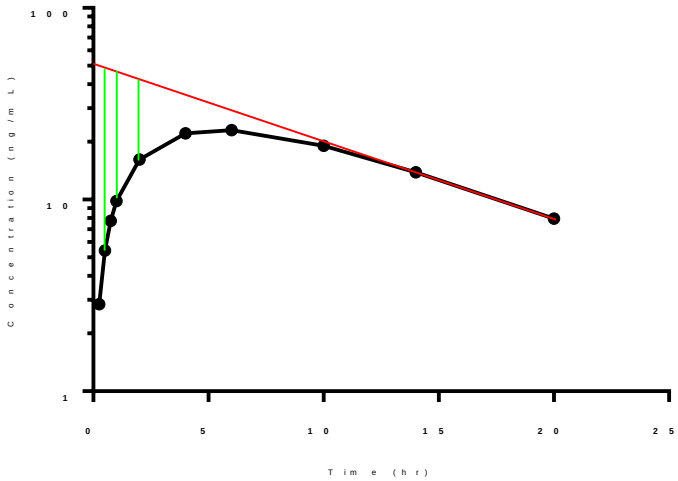
Example:
Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows:

Time (hours)	Concentration (ng/mL)
0.25	2.85
0.50	5.43
0.75	7.75
1.00	9.84
2.00	16.20
4.00	22.15
6.00	23.01
10.00	19.09
14.00	13.90
20.00	7.97

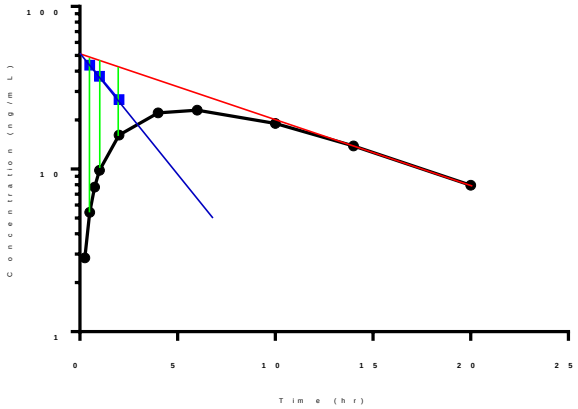
Calculate k, k_a, t_{max} and C_{max}

Note: Assume that the drug in is 80% absorbed





Time (hr)	Observed plasma concentration $(C_p)_{obs}$	Extrapolated plasma concentration $(C_p)_{extrap}$	$(C_p)_{diff} = (C_p)_{extrap}-(C_p)_{obs}$
0.5	5.43	49	43.57
1	9.84	47	37.16
2	16.2	43	26.8



Slope = $\frac{log7.9-log13.9}{20-14}$ = **- 0.04**

K = 0.094 hr^{-1} $t_{1/2} = \frac{0.693}{k}$ = **7.37**

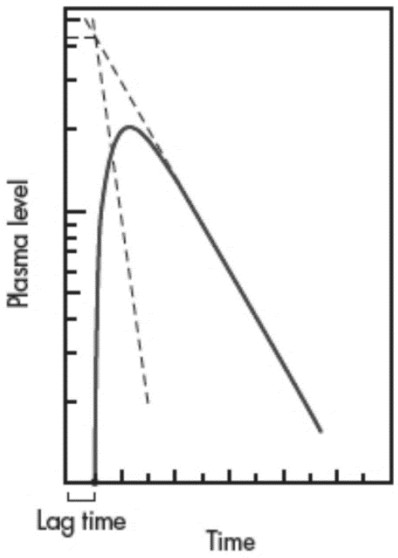
Slope = $\frac{log26.8-log37.16}{2-1}$ = **- 0.142**

K_a = 0.32 hr^{-1}

- $t_{max} = \frac{2.3\ log\ (k_a/k)}{(k_a-k)} = \frac{2.3\ log\ (0.32/0.094)}{(0.32-0.094)} = \frac{1.22}{0.226}$ = 5.4 hr
- **$C_P = \frac{F\ k_a D_0}{V_D(k_a-k)}\ (e^{-kt} - e^{-k_a t})$**
- **$9.84 = \frac{0.8\ x\ 0.32\ x\ 10000000}{V_D(0.32-0.094)}\ (e^{-0.094} - e^{-0.32})$**
- $9.84 = \frac{471}{VD\ 0.226}$
- V_D = 211.8 L
- **$C_{max} = \frac{F\ k_a D_0}{V_D(k_a-k)}\ (e^{-ktmax} - e^{-k_a tmax})$**
- **C_{max} =23 ng/mL**

Lag Time

The time delay prior to the appearance of the drug in the plasma.



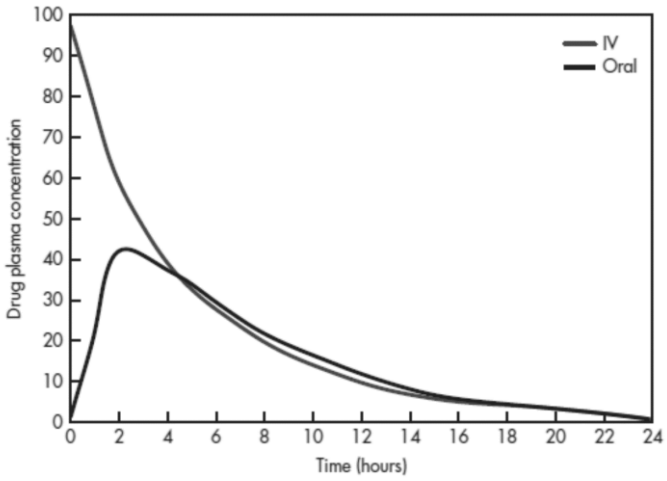
Bioavailability and Bioequivalence

Bioavailability and bioequivalence studies are important in the process of approving pharmaceutical products for marketing.

- *Bioavailability is* the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action
- *Bioequivalence* is the absence of a significant difference in the rate and extent to which the active ingredient becomes available at the site of drug action when administered at the same dose under similar conditions.

Absolute Bioavailability (F_{abs})

Absolute bioavailability compares the bioavailability of the active drug in the systemic circulation following extravascular administration with the bioavailability of the same drug following intravenous administration.



$$F_{abs} = \frac{AUC_{po}\, D_{iv}}{AUC_{iv}\, D_{po}}$$

where

- F_{abs} is the fraction of the dose absorbed;
- AUC_{po} is the AUC following oral administration;

- D_{iv} is the dose administered intravenously;
- AUC_{iv} is the AUC following intravenous administration; and
- D_{po} is the dose administered orally.
- F_{abs}, may be expressed as a fraction or as a percent by multiplying F_{abs} × 100. A drug given by the intravenous route will have an absolute bioavailability of 100% (f = 1). A drug given by an extravascular route may have an F_{abs} = 0 (no systemic absorption) and F_{abs} = 1.0 (100% systemic absorption).

Relative Bioavailability (F_{rel})

The systemic exposure of a drug in a formulation (formulation A) is compared with that of the same drug administered in a reference formulation (formulation B). For example assessing F_{rel} of new oral formulation using oral solution of the drug as a reference.

$$F_{rel} = 100 \times \frac{AUC_A D_B}{AUC_B D_A}$$

The value of F_{rel} can be more than 100%

PRACTICE PROBLEM

A new investigational drug was studied. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 50 mg of the drug. AUC_{0-48} values were calculated as follows:

Calculate (a) the relative bioavailability of the drug from the tablet compared to the oral solution and (b) the absolute bioavailability of the drug from the tablet.

Drug Product	Dose (mg)	AUC (μg·h/mL)
Oral tablet	200	89.5
Oral solution	200	86.1
IV bolus injection	50	37.8

- Relative bioavailability = $\frac{89.5}{86.1}$ = 1.04 or 104%
- $F_{abs} = \frac{89.5 \; x \; 50}{37.5 \; x \; 200}$ = 0.592 or 59.2%

Bioequivalence

- Bioequivalence is a type of relative bioavailability study. However, in a bioequivalence study, AUC , peak plasma concentration and peak time are determined for two or more chemically or pharmaceutically equivalent products (**identical dosage forms**) where at least one of them is an innovator product (also known as the Brand Name or Reference Standard).
- $F_{rel} = \frac{AUC_{generic} D_{standard}}{AUC_{standard} D_{generic}}$
- Example: Comparing Propranolol - Inderal® Tablet (innovator product by Wyeth Laboratories) and propranolol HCl tablet (generic brand).

Factors affecting bioavailability

Factors affecting bioavailability may be classified into two general categories:

1. **Formulation factors will include:**

A. Excipients (type and concentration) used in the formulation of a dosage form
B. Particle size of an active ingredient
C. Crystalline or amorphous nature of the drug
D. Hydrous or anhydrous form of the drug
E. Polymorphic nature of a drug.

2. **Physiological factors will include:**

A. Gastric emptying
B. Intestinal motility
C. Changes in gastrointestinal pH
D. Changes in nature of intestinal wall.

Practice Problem

Plasma theophylline concentrations after intravenous and oral administration were described by a one-compartment open model. The doses administered were as follows:

1. Intravenous bolus: 50mg aminophylline (85% theophylline)
2. Oral administration (A): Elixophylline (theophylline, 100mg capsules); administered one capsule
3. Oral administration (C): Aminophylline (aminophylline, 200 mg tablets, 170 mg theophylline); administered one tablet.

Time (h)	Plasma theophylline concentrations ($\mu g\,mL^{-1}$)		
	Intravenous bolus	Oral administration A	Oral administration C
0.25	4.70	0.40	1.65
0.50	4.40	2.40	12.65
0.75	4.10	6.95	14.30
1.00	3.95	11.15	15.70
1.50	3.75	11.15	13.90
2.00	3.60	9.50	14.60
3.00	2.95	8.45	13.75
4.00	2.75	8.15	11.15
6.00	2.05	6.65	10.00
8.00	1.45	4.60	7.30
12.00	0.80	2.90	3.60
24.00	0.25	1.00	0.85

Plot the data and, using the plot, determine the following:

a. The elimination half life ($t_{1/2}$) of theophylline following the administration of intravenous solution, oral capsule and oral tablet doses.

b. The elimination rate constant (K) of theophylline following the administration of intravenous solution, oral capsule and oral tablet doses.

c. The apparent volume of distribution (V) of theophylline from the intravenous bolus data.

d. The absorption rate constant (K_a) for each orally administered theophylline dose.
e. The area under the plasma concentration–time curve, $(AUC)_0^{24}$, by trapezoidal rule for each dose.
f. Using the trapezoidal data for $(AUC)_0^{24}$ determined in (e), calculate the total area under the plasma concentration–time curve $(AUC)_0^{\infty}$for each dose.
g. Determine the absolute bioavailability (i.e. fraction F) of the administered dose reaching the general circulation for the two orally administered (i.e. capsule and tablet) theophylline doses.