Pharmacokinetics of
Oral Drug Absorption

References

- Applied Biopharmaceutics and Pharmacokinetics, *7th Edition*
  - Leon Shargel and Andrew B. C. Yu
- Basic Pharmacokinetics, *2nd Edition*
  - Sunil S. Jambhekar and Philip J. Breen

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Lecture-1

Contents

- Chapter Objectives
- Routes of Drug Administration
- Comparison of Common Routes of Drug Administration
- Sites for Absorption of Orally Administered Drugs

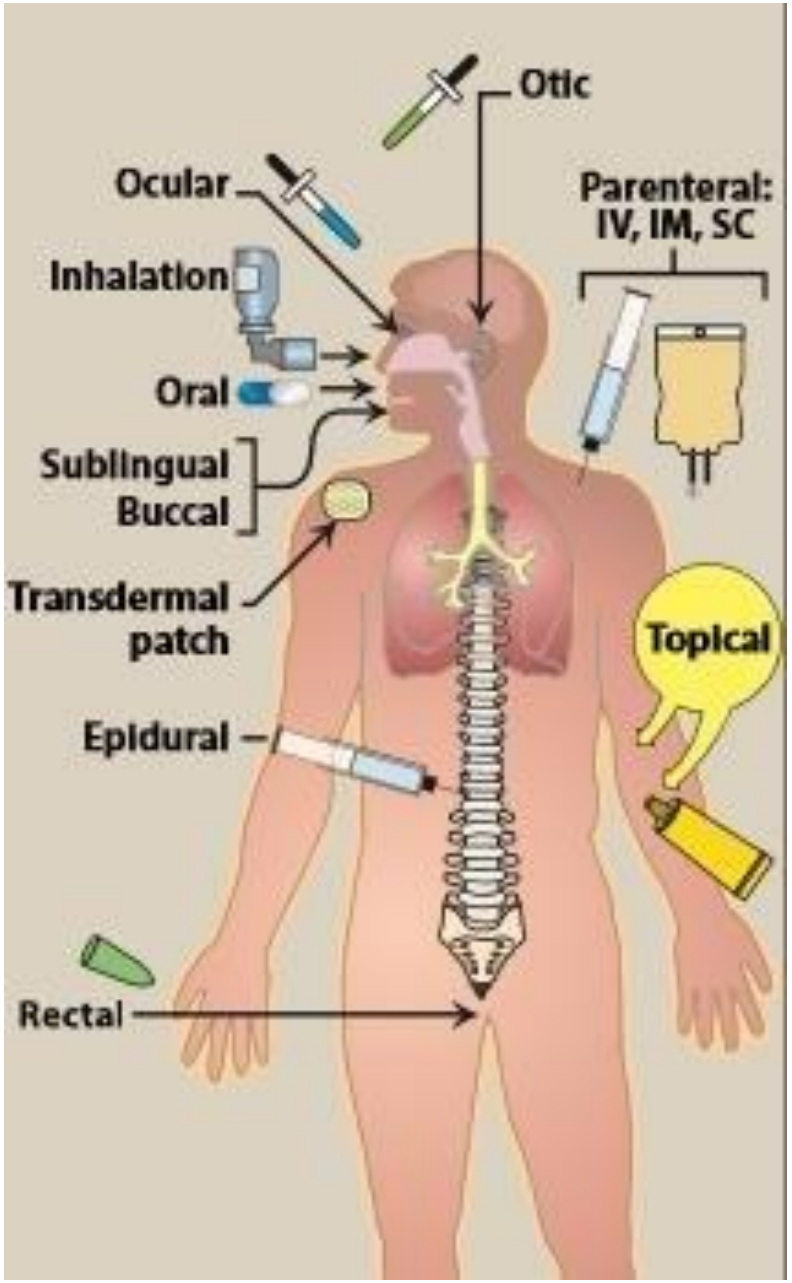
Chapter Objectives

Students will be able to

- Define oral drug absorption and describe the absorption process.
- Introduce two general approaches used for studying absorption kinetics and their similarities and differences.
- Understand the basic principles for physiologically based absorption kinetics.
- Describe the oral one-compartment model and explain how this model simulates drug absorption from the gastrointestinal tract.
- Calculate the pharmacokinetic parameters of a drug that follows the oral one-compartment model.

- Calculate the fraction of drug absorbed in a one-compartment model using the Wagner–Nelson method.
- Calculate the fraction of drug absorbed in a two-compartment model using the Loo–Riegelman method.
- Describe the conditions that may lead to flip-flop of k_a and k during pharmacokinetics (PK) data analysis
- Describe the model parameters that form the foundation of drug absorption and bioavailability of oral dosage forms.
- Discuss how k_a and k may influence C_{max}, t_{max}, and AUC and how changes in these parameters may affect drug safety in a clinical situation.

Routes of Drug Administration



Courtesy: ResearchGate

Comparison of Common Routes of Drug Administration

Route	Bioavailability	Advantages	Disadvantages
Intravenous bolus (IV)	100%	Drug is given for immediate effect.	Increased chance for adverse reaction.
Intravenous infusion (IV inf)	100%	Plasma drug levels more precisely controlled.	Requires skill in insertion of infusion set.
Subcutaneous injection (SC)	Prompt from aqueous solution.	Generally, used for insulin injection.	Rate of drug absorption depends on blood flow and injection volume.

Route	Bioavailability	Advantages	Disadvantages
Intramuscular injection (IM)	Rapid from aqueous solution.	Easier to inject than intravenous injection.	Irritating drugs may be very painful.
Rectal (PR)	Absorption may vary from suppository.	Useful when patient cannot swallow medication.	Absorption may be erratic. Some patient discomfort.
Oral	Absorption may vary. Generally, slower absorption rate compared to IV bolus or IM injection.	Safest and easiest route of drug administration. May use immediate-release and modified-release drug products.	Some drugs may have erratic absorption, be unstable in the gastrointestinal tract, or be metabolized by liver prior to systemic absorption.

Sites for Absorption of Orally Administered Drugs

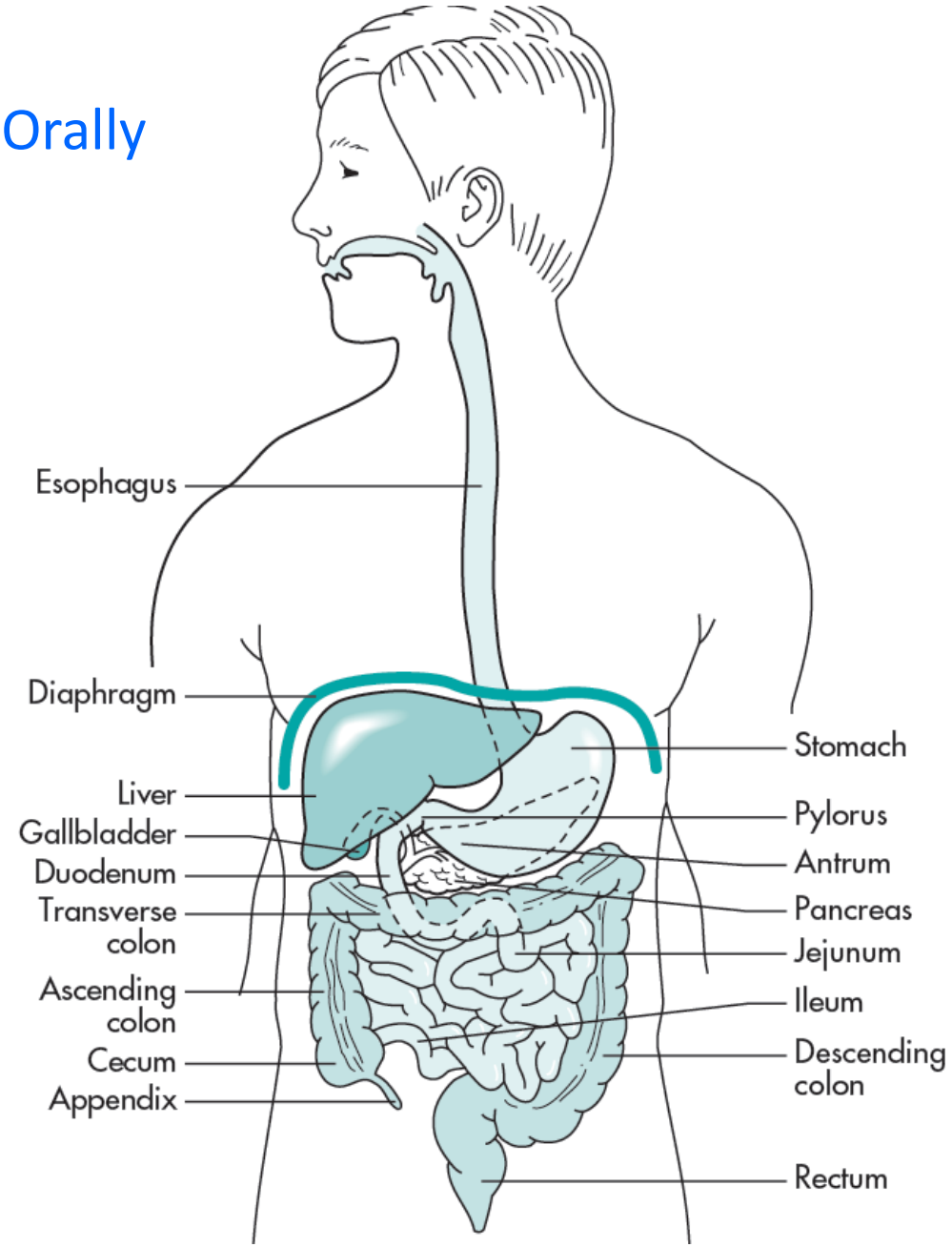
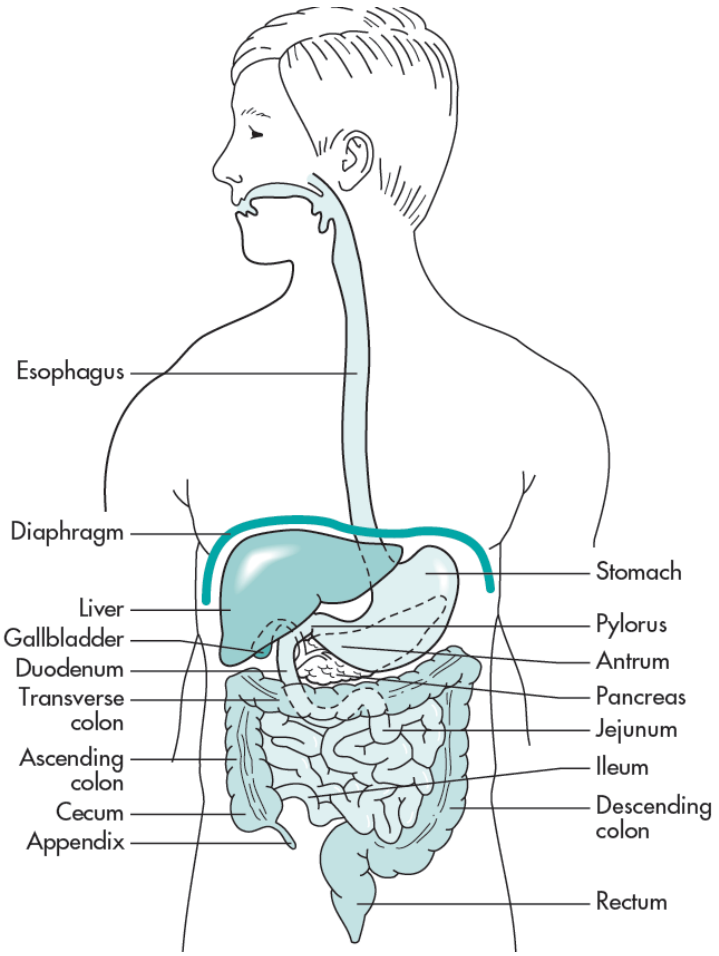


FIGURE 14-12
Gastrointestinal tract.

Ref. Shargel 7th Edn.

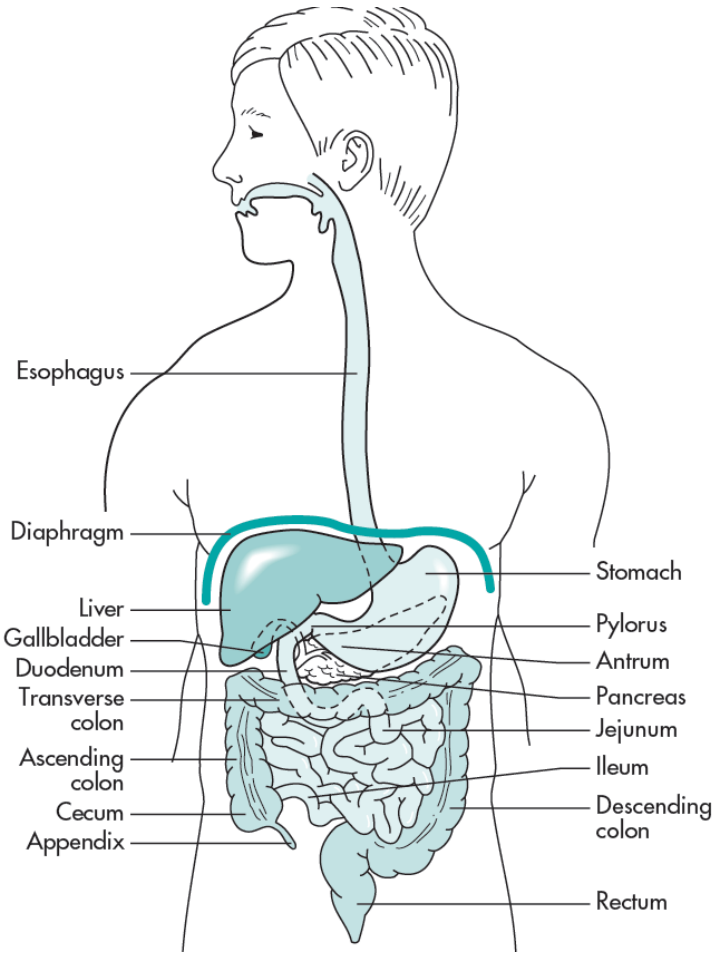
Oral Cavity

- Saliva is the main secretion of the oral cavity, and it has a pH of about 7.
- The oral cavity can be used for the buccal absorption of lipid-soluble drugs.
- Recently, orally disintegrating tablets (ODTs) have become available. These ODTs rapidly disintegrate in the oral cavity in the presence of saliva and the drug is then absorbed from the gastrointestinal tract.



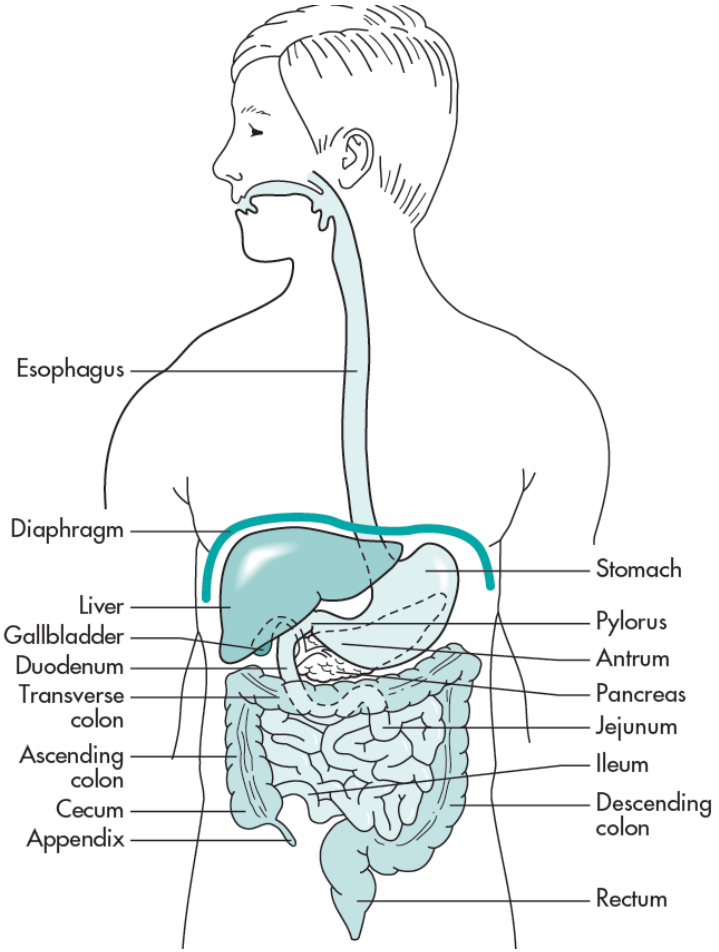
Esophagus

- The esophagus connects the pharynx and the cardiac orifice of the stomach.
- The pH of the fluids in the esophagus is between 5 and 6.
- The lower part of the esophagus ends with the esophageal sphincter, which prevents acid reflux from the stomach.
- Tablets or capsules may lodge in this area, causing local irritation.
- Very little drug dissolution occurs in the esophagus.

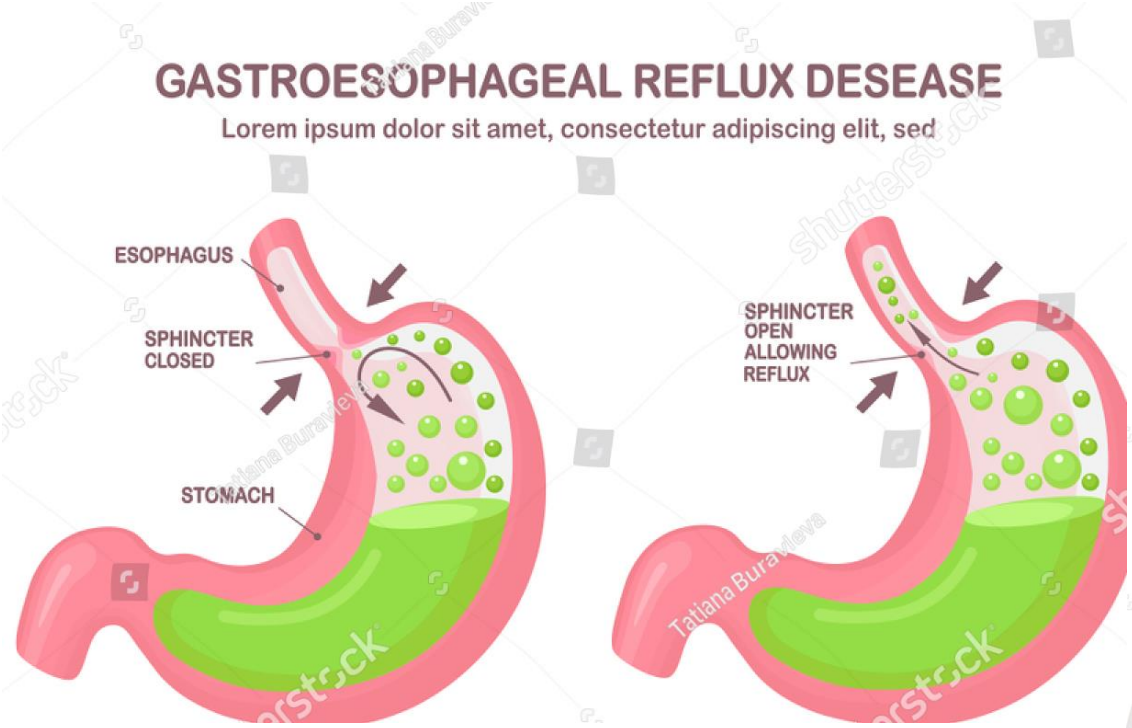


Stomach

- Fasting pH: 2–6, pH in presence of food: 1.5-2
- Basic drugs are solubilized rapidly
- If the stomach pH is too high, the enteric-coated drug product may release the drug in the stomach, thus causing irritation to the stomach.
- A few fat-soluble, acid-stable drugs may be absorbed from the stomach by passive diffusion.



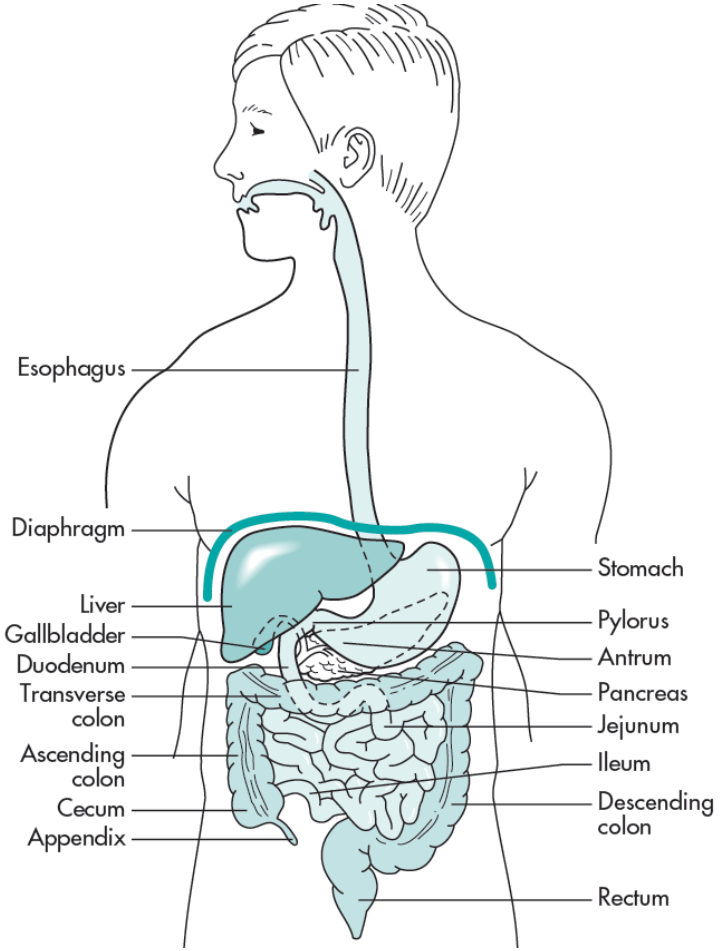
Gastroesophageal Reflux Disease (GERD)



Woman Suffering From Acid Reflux Or Heartburn

Duodenum

- pH is about 6–6.5 due to because of the presence of bicarbonate
- The pH is optimum for enzymatic digestion of proteins, fats and carbohydrates and peptide-containing food.
- The complex fluid medium in the duodenum helps dissolve many drugs with limited aqueous solubility.
- **Major site for passive drug absorption due to high surface area, and high blood flow.**
- Many ester prodrugs are hydrolyzed during absorption.
- Proteolytic enzymes degrade many protein drugs preventing adequate absorption of the intact protein drug.

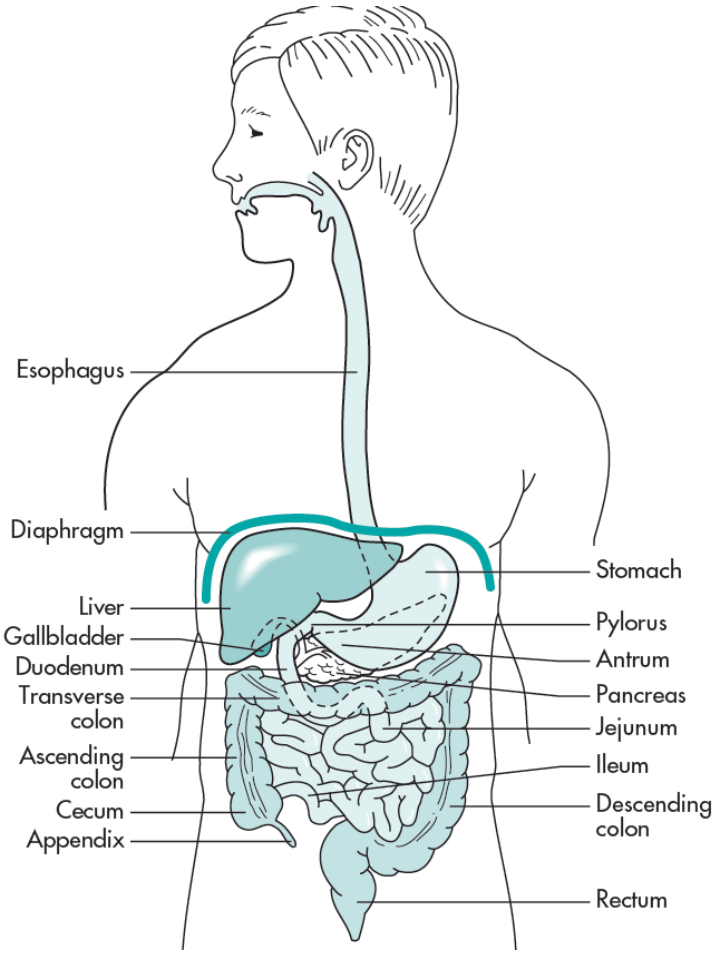


Jejunum

This portion of the small intestine generally has fewer contractions than the duodenum and is preferred for *in vivo* drug absorption studies.

Ileum

The pH is about 7-8. Due to the presence of bicarbonate secretion, acid drugs will dissolve in the ileum. Bile secretion helps dissolve fats and hydrophobic drugs.



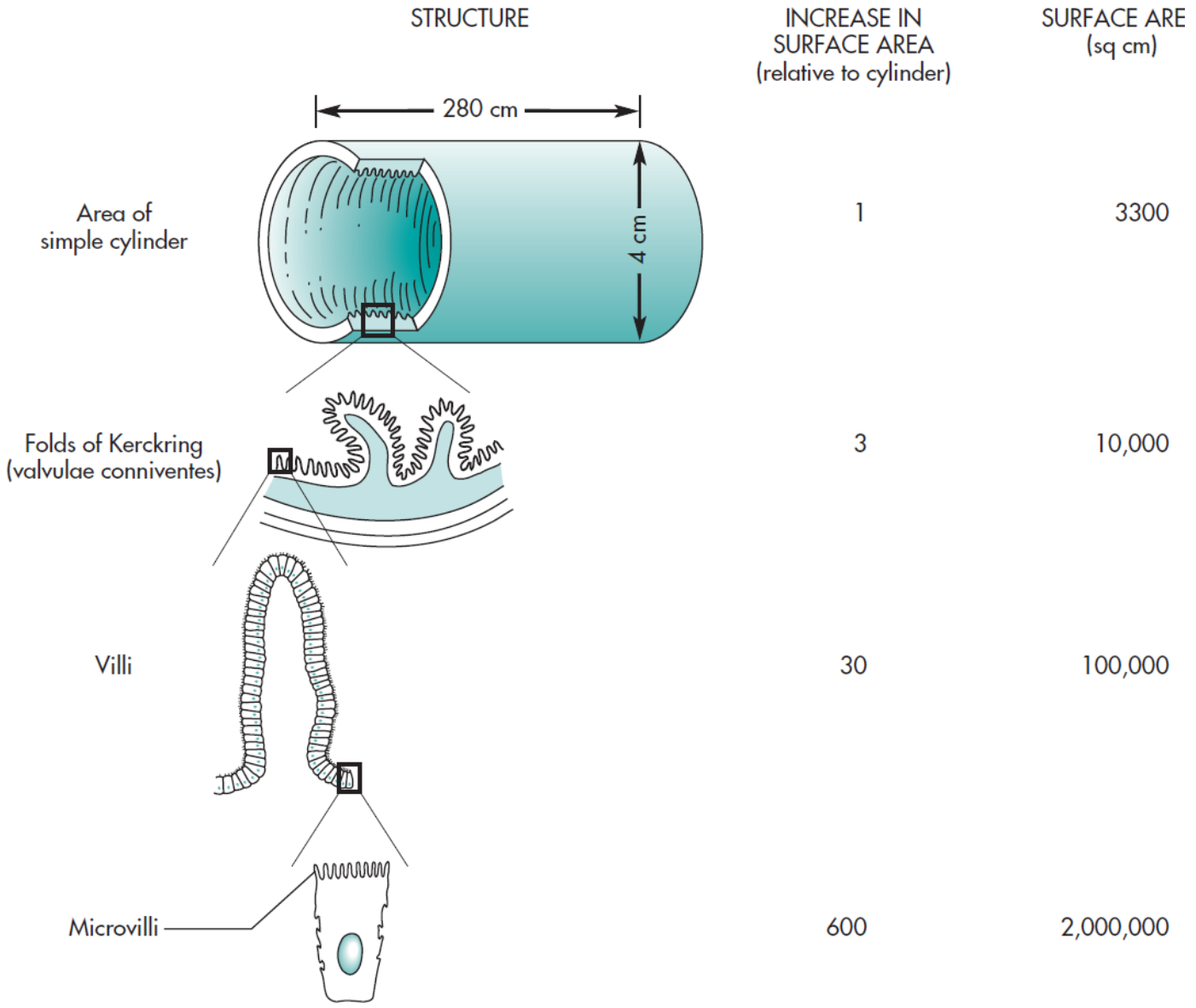


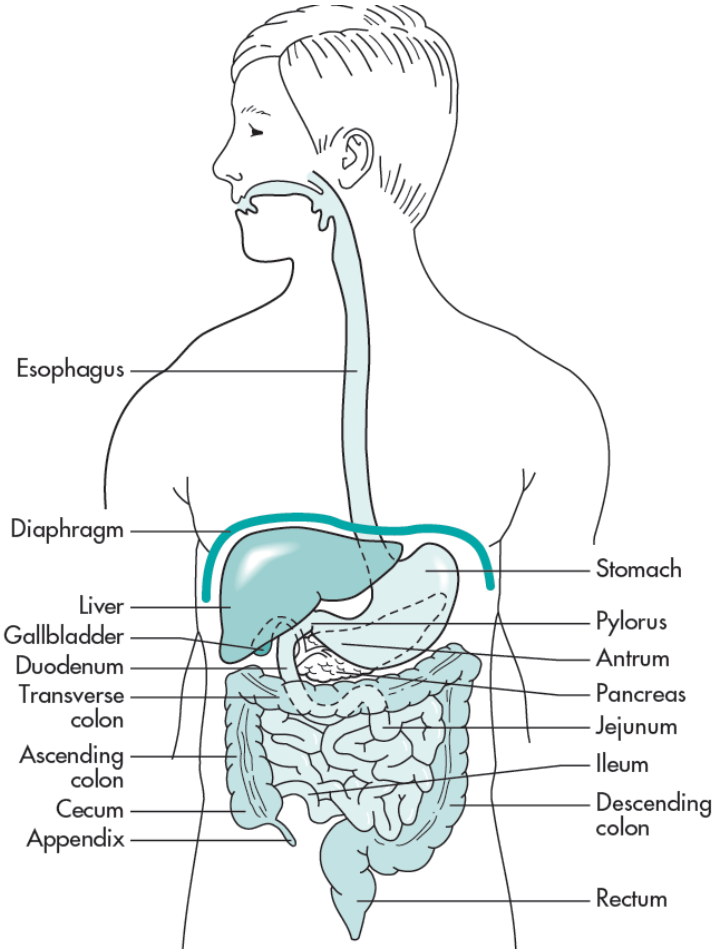
FIGURE 14-13 Three mechanisms for increasing surface area of the small intestine. The increase in surface area is due to folds of Kerkring, villi, and microvilli.

Colon

- The colon lacks villi and has limited drug absorption due to lack of large surface area, blood flow, and the more viscous and semisolid nature of the lumen contents.

Rectum

- The rectum is about 15 cm long, ending at the anus.
- Virtually no buffer capacity; the dissolving drug(s) can have a determining effect
- Drug absorption after rectal administration may be variable, depending on the placement of the suppository or drug solution within the rectum.



Lecture-2

Contents

- Factors Affecting Extravascular Drug Absorption
- Methodologies to study the kinetics of absorption
- Kinetics of Drug Absorption
- Zero-order Absorption Model

Factors Affecting Extravascular Drug Absorption

Drug absorption from the gastrointestinal (GI) tract or any other extravascular site is dependent on-

- the physicochemical properties of the drug and the environment in the small intestine,
- the dosage form used (solution, suspension, capsul, tablet, etc.), and
- the anatomy and physiology of the absorption site, such as surface area of the GI tract, stomach-emptying rate, GI mobility, and blood flow to the absorption site.

Methodologies to study the kinetics of absorption

Two methodologies-

- Pharmacokinetic models can be built based mainly on the observed clinical data ("top-down" approach) or

- Based on the broader understanding of the human body and its mechanisms ("bottom-up" approach)

In a bottom-up approach the elements of the system are first specified in great detail. These elements are then linked together to form larger subsystems, which in turn are linked, sometimes in many levels, until a complete top-level system is formed.

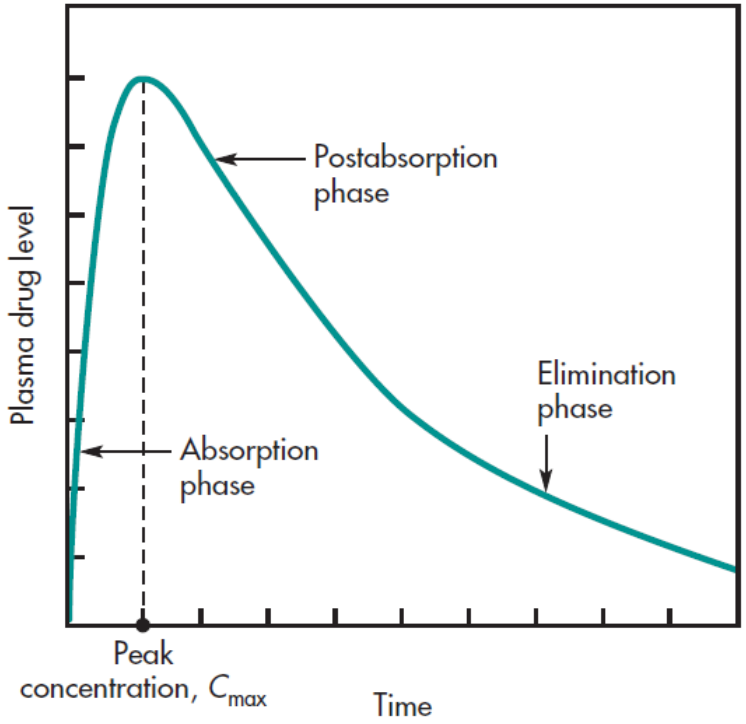
Kinetics of Drug Absorption

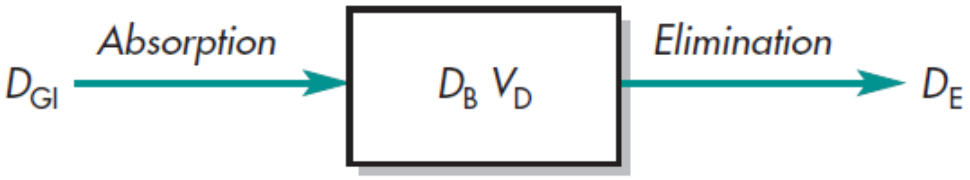
- The overall rate of drug absorption may be described as either a first-order or a zero-order input process.

- Most pharmacokinetic models assume first-order absorption unless an assumption of zero-order absorption improves the model significantly or has been verified experimentally.

The net rate of drug accumulation in the body at any time is equal to the rate of drug absorption minus the rate of drug elimination

$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt}$$





- At absorption phase:

$$\frac{dD_{GI}}{dt} > \frac{dD_E}{dt}$$

- At peak concentration:

$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt}$$

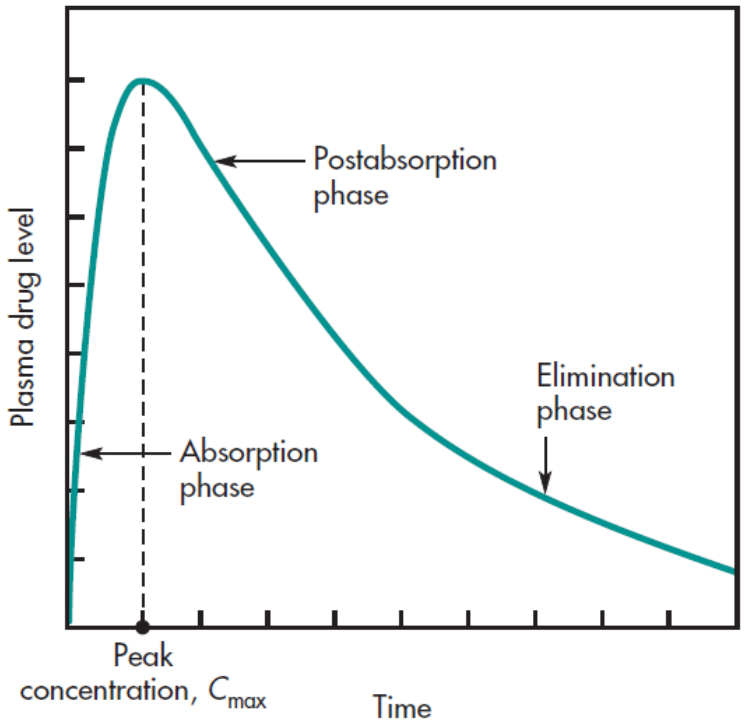
- At post-absorption phase:

$$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}$$

- At elimination phase:

$$\frac{dD_B}{dt} = -kD_B$$

The net rate of drug accumulation in the body at any time is



where *k* is the first-order elimination rate constant.

Significance of Absorption Rate Constants

- The overall rate of systemic drug absorption from an orally administered solid dosage form encompasses many individual rate processes, including dissolution of the drug, GI motility, blood flow, and transport of the drug across the capillary membranes and into the systemic circulation. The rate of drug absorption represents the net result of all these processes.

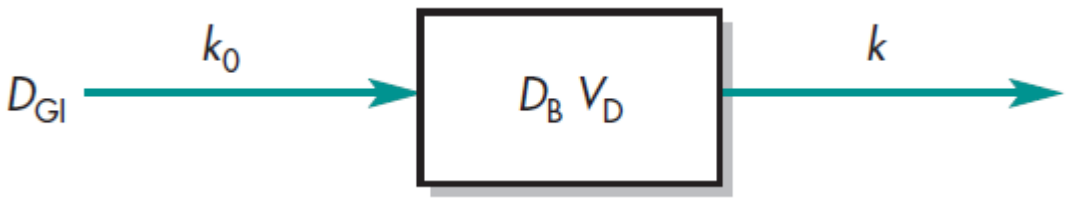
- The calculation of k_a is useful in designing a multiple-dosage regimen. Knowledge of the k_a and k values allows for the prediction of peak and trough plasma drug concentrations following multiple dosing.

Zero-order Absorption Model

- Zero-order drug absorption from the dosing site into the plasma usually occurs when either the drug is absorbed by a saturable process or a zero-order controlled-release delivery system is used.

- 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



Methods for controlled release of drug products

- An *enteric-coated* tablet is one kind of delayed-release type within the modified-release dosage family designed to release drug in the small intestine.
- A *repeat-action tablet* is a type of modified-release drug product that is designed to release one dose of drug initially, followed by a second or more doses of drug at a later time.
- A *prolonged-action drug product* is a formulation whose drug activity can continue for a longer time than conventional drugs.

The rate of first-order elimination at any time is equal to $D_B k$. The rate of input is simply k_0. Therefore, the net change per unit time in the body can be expressed as

$$\frac{dD_B}{dt} = k_0 - kD_B$$

Integration of this equation with substitution of $V_D C_p$ for D_B produces

$$C_p = \frac{k_0}{V_D k}(1 - e^{-kt})$$

Important features of zero-order absorption model

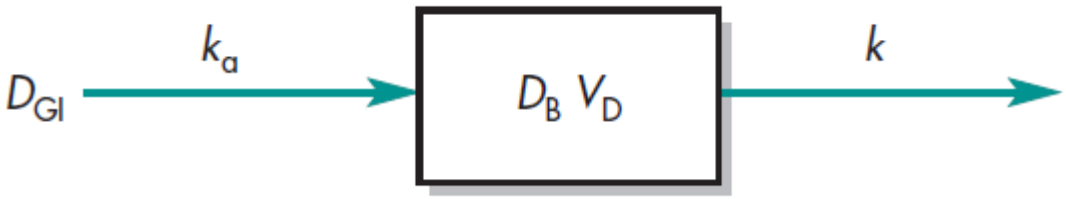
- The rate of drug absorption is constant until the amount of drug in the gut, D_{GI}, is depleted.
- The time for complete drug absorption to occur is equal to D_{GI}/k_0.
- The drug concentration in the plasma subsequently declines in accordance with a first-order elimination rate process.

Lecture-3

Contents

- First-order Absorption Model
- Fraction of drug absorbed, *F*
- First-order rate equation
- Evaluation of t_{max}
- Evaluation of C_{max}
- Determination of Elimination Rate Constant

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.
- This model applies mostly to the oral absorption of drugs in solution or rapidly dissolving dosage (immediate release) forms such as tablets, capsules, and suppositories.
- In addition, drugs given by intramuscular or subcutaneous aqueous injections may also be described using a first-order process.

The rate of absorption of drug from the gastrointestinal tract is described by

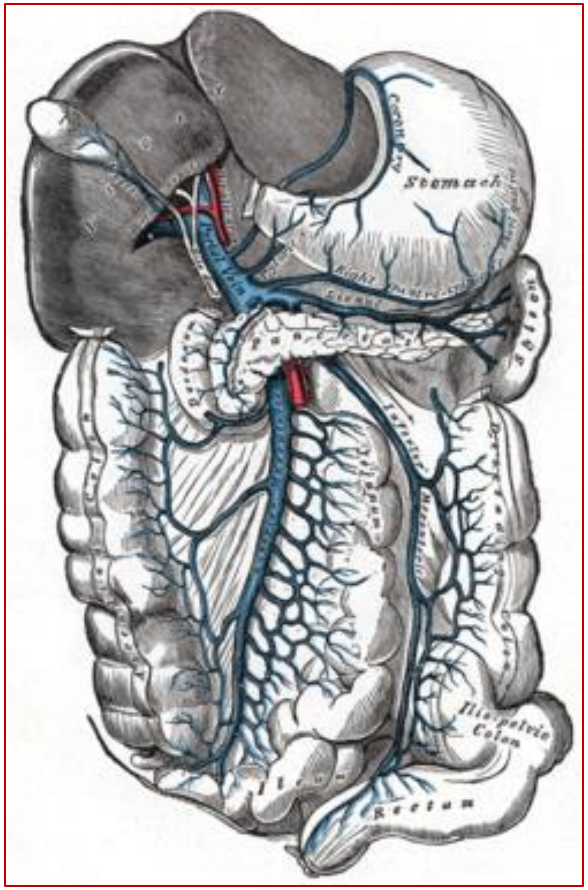
$$\frac{dD_{GI}}{dt} = -k_a D_{GI} F$$

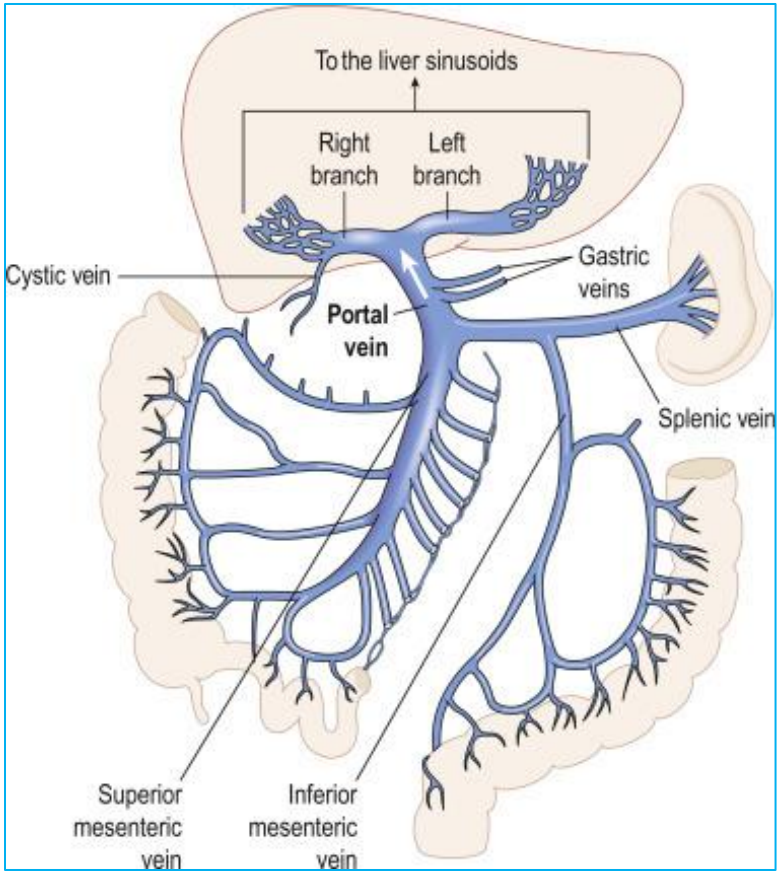
where k_a is the first-order absorption rate constant from the GI tract, F is the fraction absorbed, and D_{GI} is the amount of drug in solution in the GI tract at any time t.

Integration of the differential equation gives

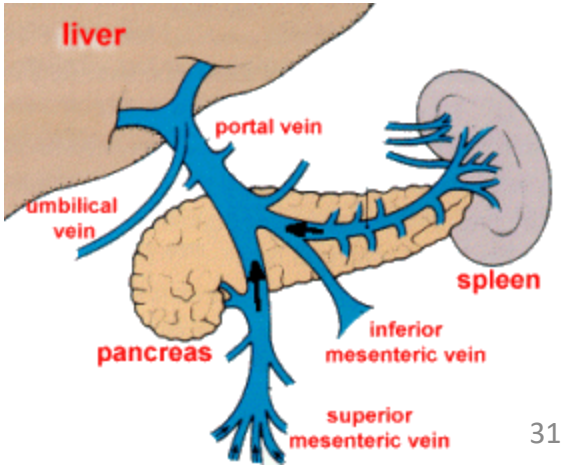
$$D_{GI} = D_0 e^{-k_a t}$$

where D_0 is the dose of the drug.





Portal Vein: A blood vessel that carries blood from the GI tract, gallbladder, pancreas and spleen to the liver. This blood contains nutrients and toxins extracted from digested contents.



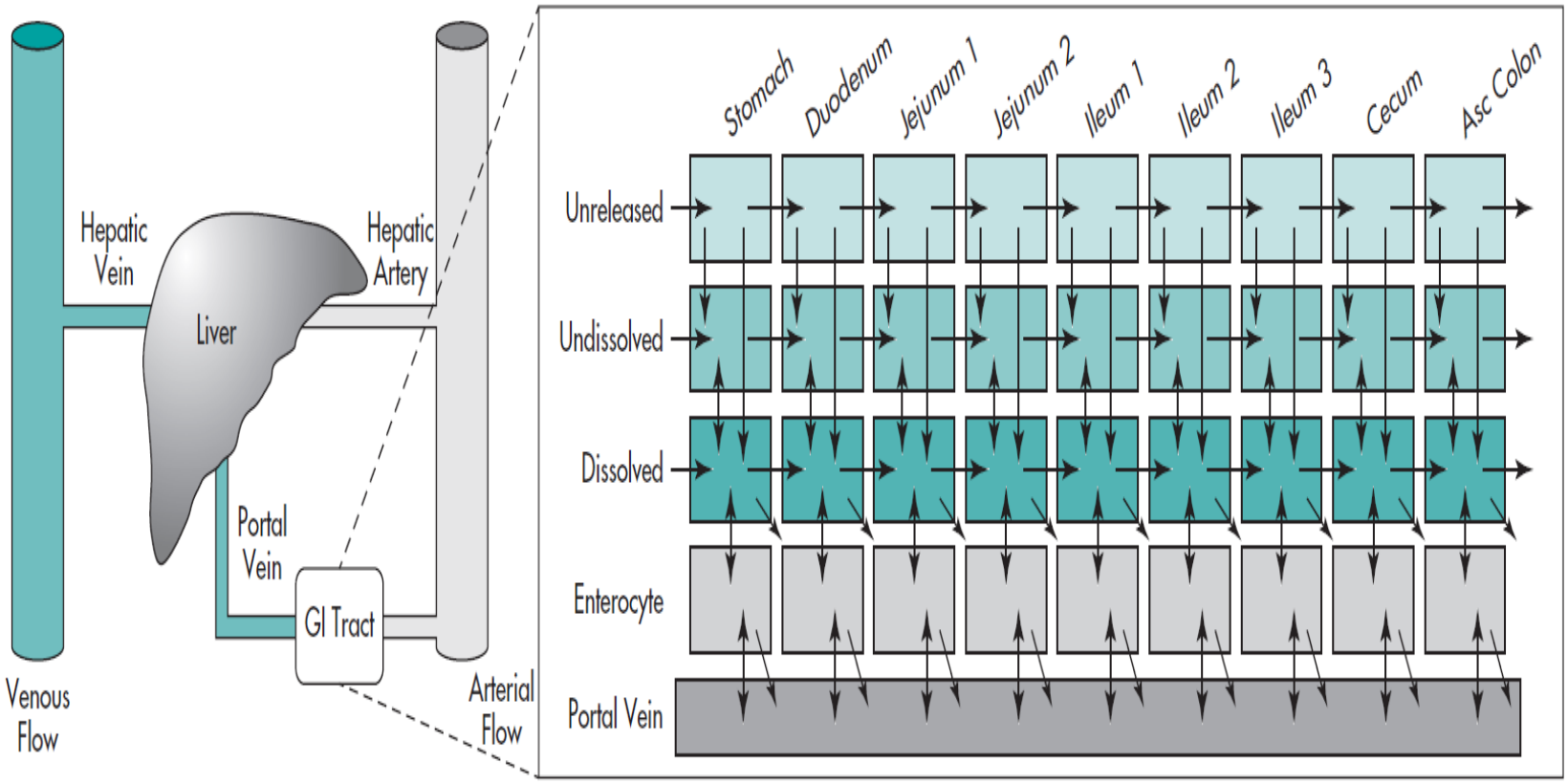
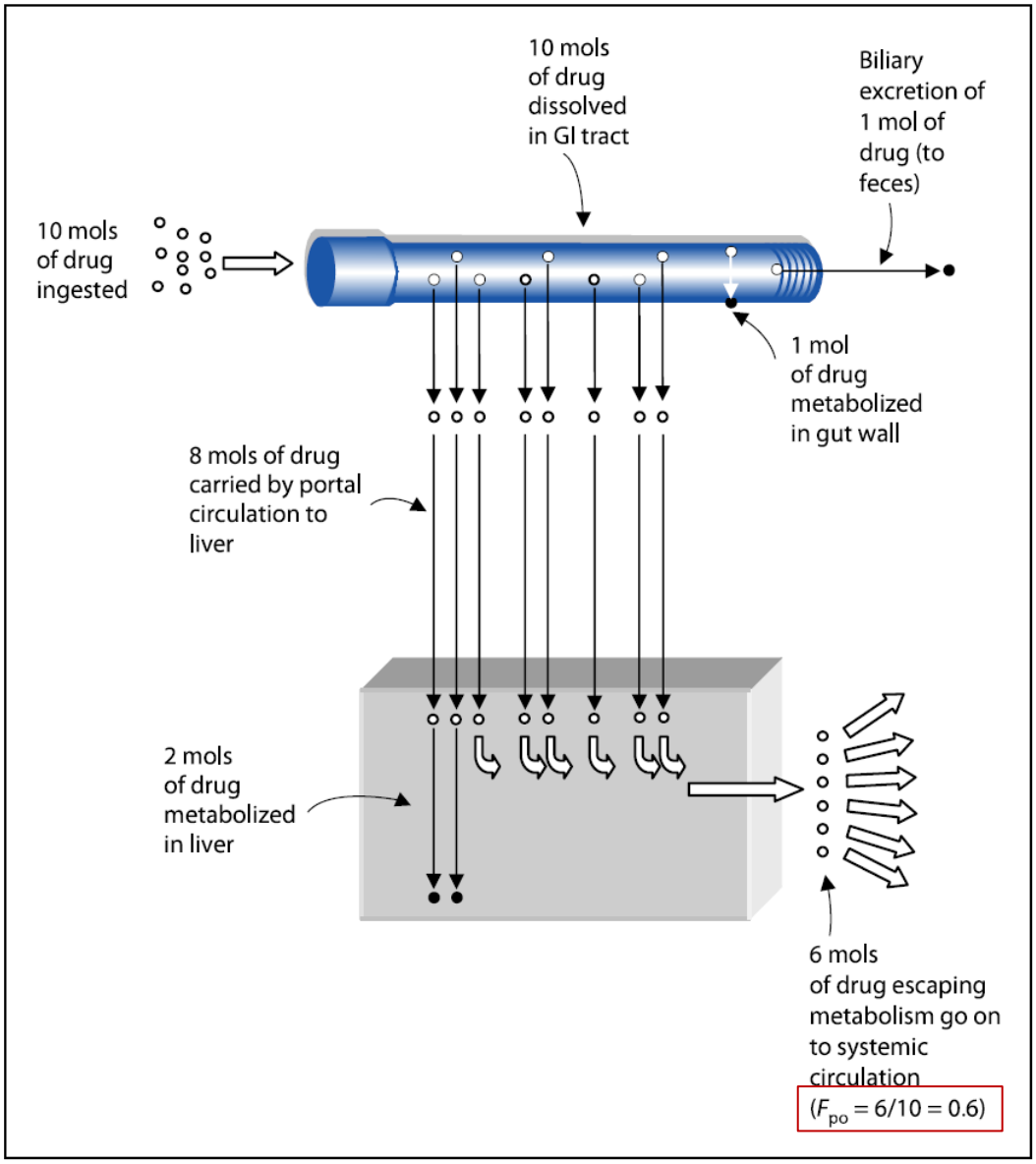


FIGURE 8-1 A graphic representation of drug absorption from the GI tract.

Understanding *F*



The rate of drug elimination = $-kD_B$.

The rate of drug change in the body,

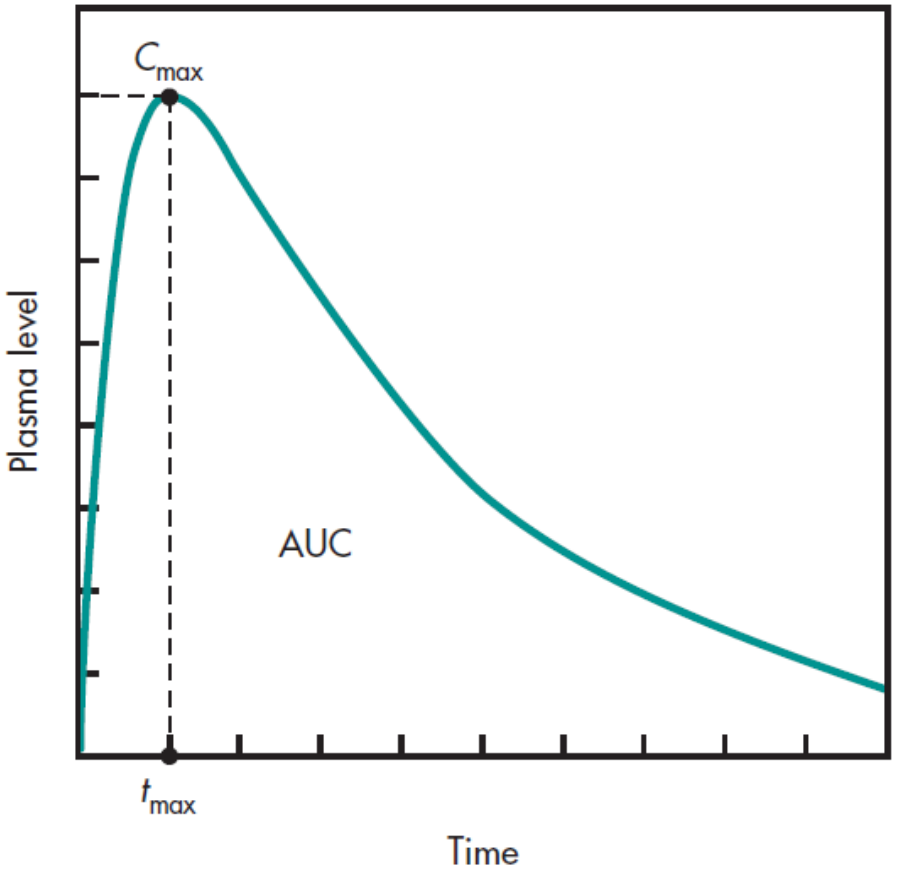
$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_B$$

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

Integration of this equation with substitution of $V_D C_p$ for D_B produces

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

Typical plasma level–time curve for a drug given in a single oral dose



- C_{max} = The maximum plasma concentration or peak concentration

- t_{max} = the time needed to reach maximum concentration

Evaluation of t_{max}

At C_{max}, the net rate of concentration change is equal to zero. Therefore,

$$\frac{dC_p}{dt} = \frac{Fk_a D_0}{V_D(k_a - k)}(-ke^{-kt} + k_a e^{-k_a t}) = 0$$

This can be simplified as follows:

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

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

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

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

The time for maximum drug concentration, t_{max}, is dependent only on the rate constants k_a and k.

Evaluation of C_{max}

In order to calculate C_{max}, the value for t_{max} is determined by the Equation

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

Then substituted into the following Equation to obtain C_{max}.

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

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.

Determination of Elimination Rate Constant

The first-order elimination rate constant may be determined from the elimination phase of the plasma level–time curve.

When drug absorption has been completed,

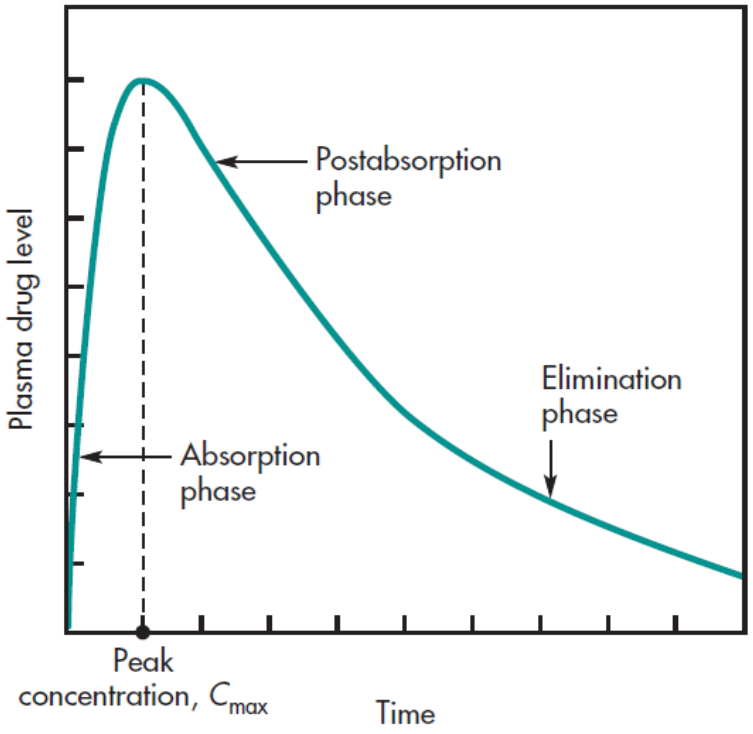
$$e^{-k_a t} \approx 0$$

Then,

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

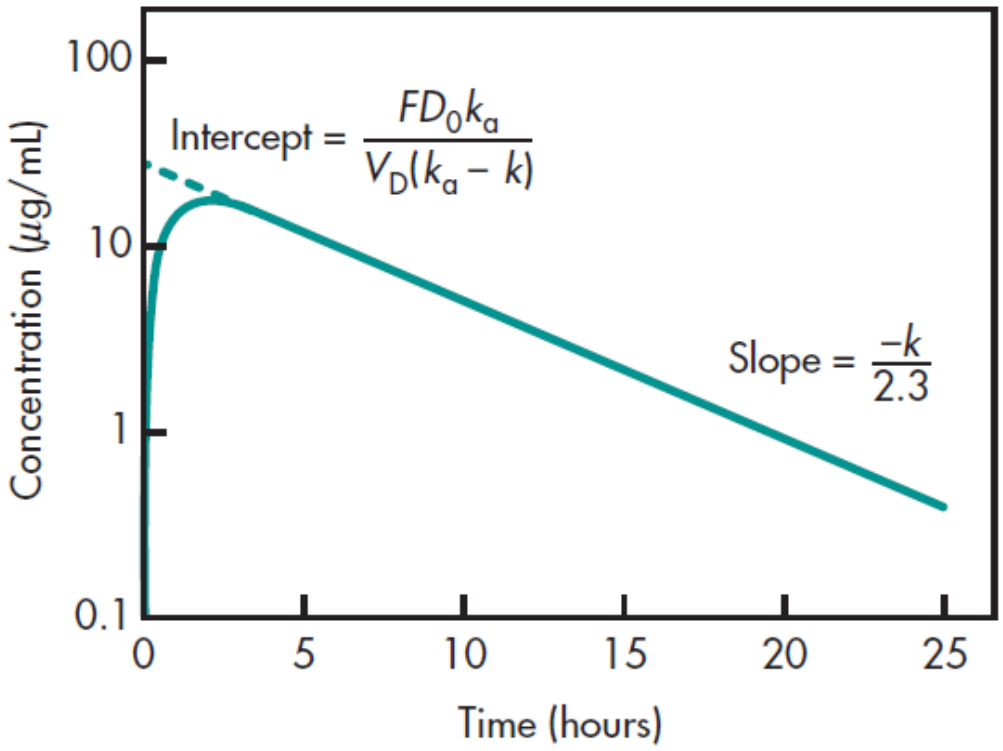
Taking the natural logarithm of this expression,

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



Substitution of common logarithms gives

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



With this equation, a graph constructed by plotting log C_p versus time will yield a straight line with a slope of -k/2.3

Lecture- 4

Contents

- Elimination Rate Constant from Urinary Drug Excretion Data
- Determination of Absorption Rate Constants from Oral Absorption Data
    - Method of residuals
    - Lag Time
    - Flip-flop of k_a and k
    - Elimination of Flip-flop of k_a and k

Elimination Rate Constant from Urinary Drug Excretion Data

The rate of drug excretion after a single oral dose of drug is given by

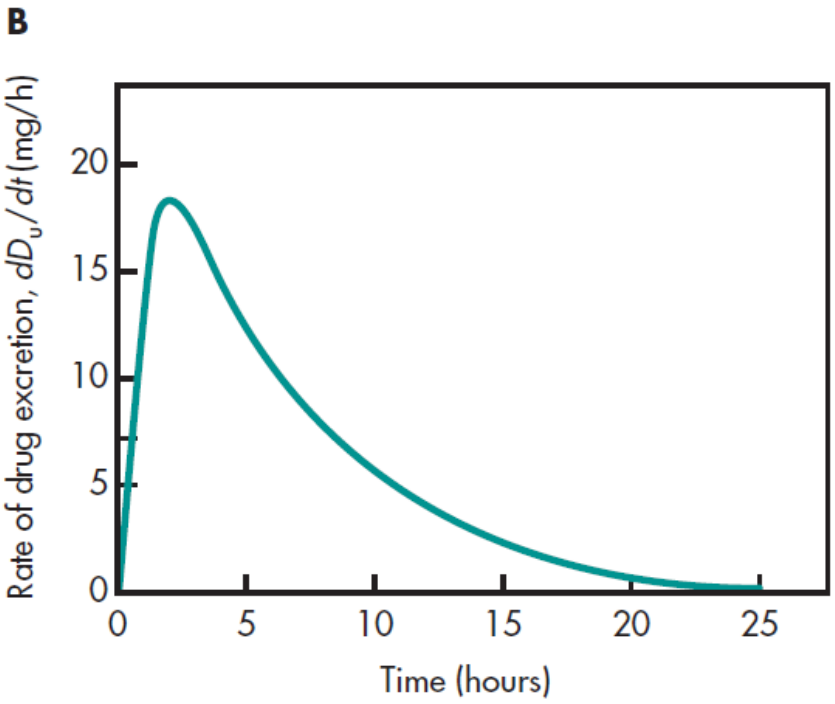
$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k}(e^{-kt} - e^{-k_a t})$$

where dD_u/dt = rate of urinary drug excretion,

k_e = first-order renal excretion constant, and

F = fraction of dose absorbed.

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



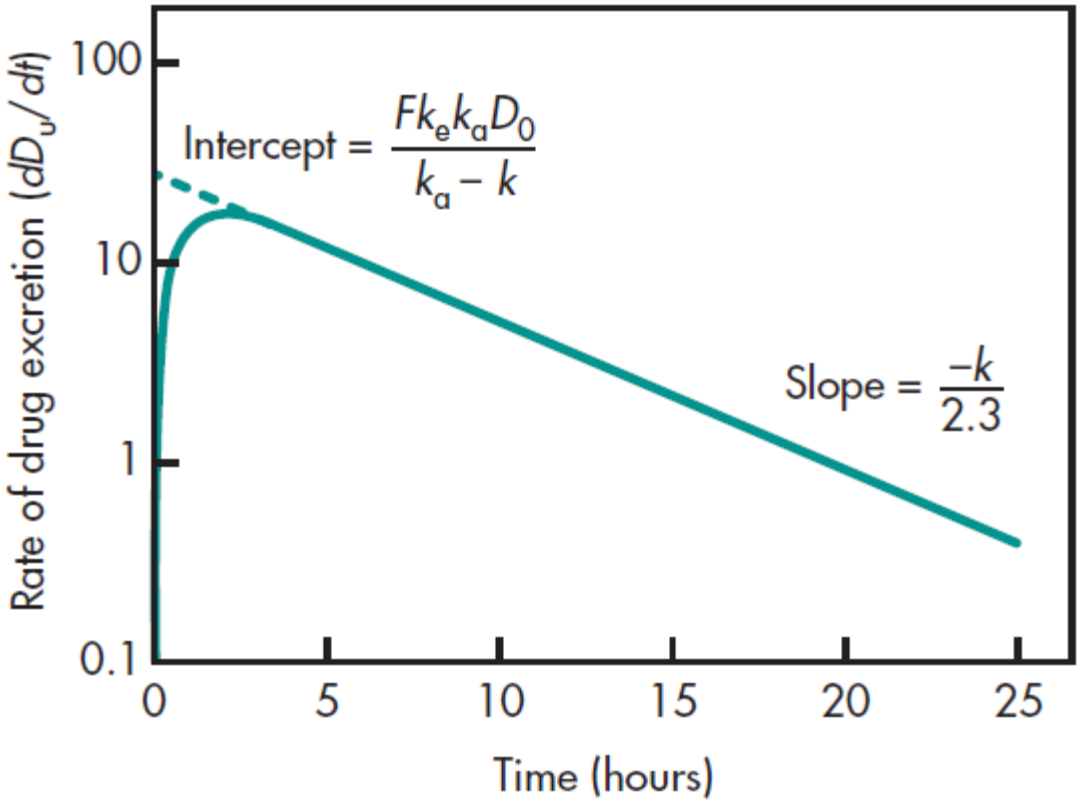
After drug absorption is virtually complete, $-e^{-k_a t}$ approaches zero, and the Equation reduces to

$$\frac{dD_u}{dt} = \frac{Fk_a k_e D_0}{k_a - k} e^{-kt}$$

Taking the natural logarithm of both sides of this expression and substituting for common logarithms,

$$\log \frac{dD_u}{dt} = \log \frac{Fk_a k_e D_0}{k_a - k} - \frac{kt}{2.3}$$

When log(*dDu/dt)* is plotted against time, a graph of a straight line is obtained with a slope of -*k*/2.3.



Determination of Absorption Rate Constants from Oral Absorption Data

Method of Residuals

Consider the Equation, $$C_p = \frac{F k_a D_0}{V_D (k_a - k)} (e^{-kt} - e^{-k_a t})$$

Assuming $k_a >> k$ in the Equation, the value for the second exponential will become insignificantly small with time and can therefore be omitted.

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

or, $C_p = A e^{-kt}$ where, $\frac{F k_a D_0}{V_D (k_a - k)} = A$

or, $\log C_p = \log A - k/2.3$

This equation, which represents first-order drug elimination, will yield a linear plot on semilog paper. The slope is equal to - *k/2.3.*

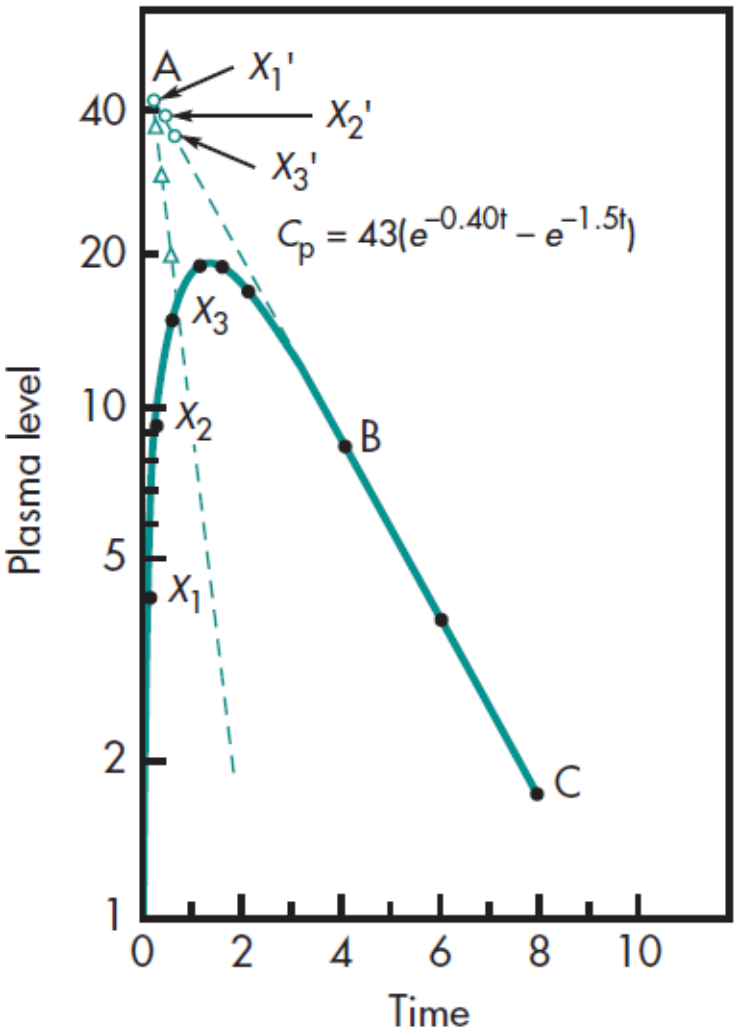
Method of residuals or a feathering technique to obtain k_a

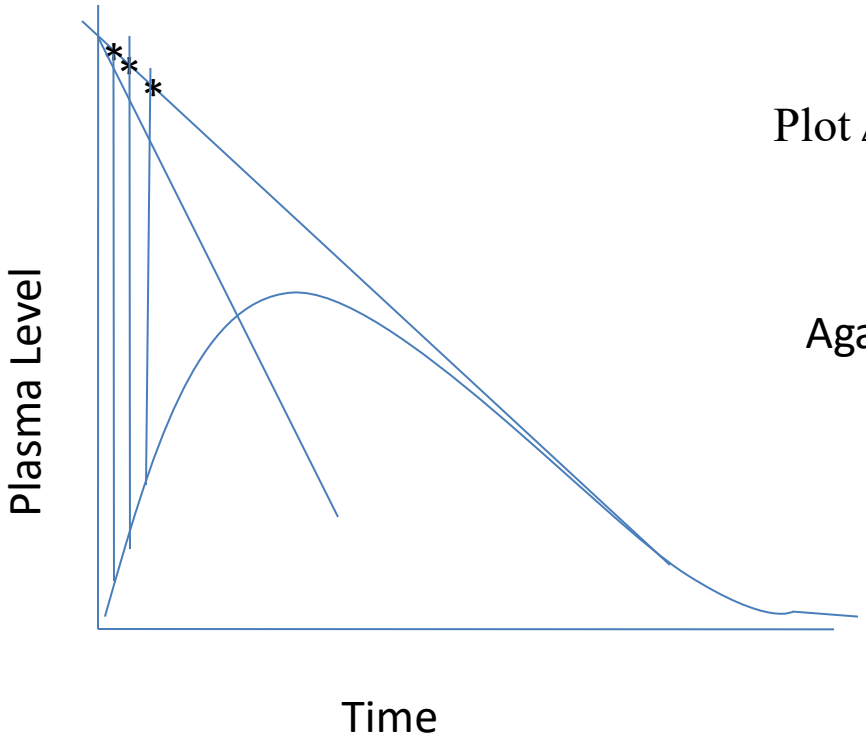
1. Plot the drug concentration versus time on semilog paper with the concentration values on the logarithmic axis.

2. Obtain the slope of the terminal phase (line BC) by extrapolation.

3. Take any points on the upper part of line *BC (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 Δ_1, Δ_2, Δ_3, … . A straight line will be obtained with a slope of $-k_a/2.3$



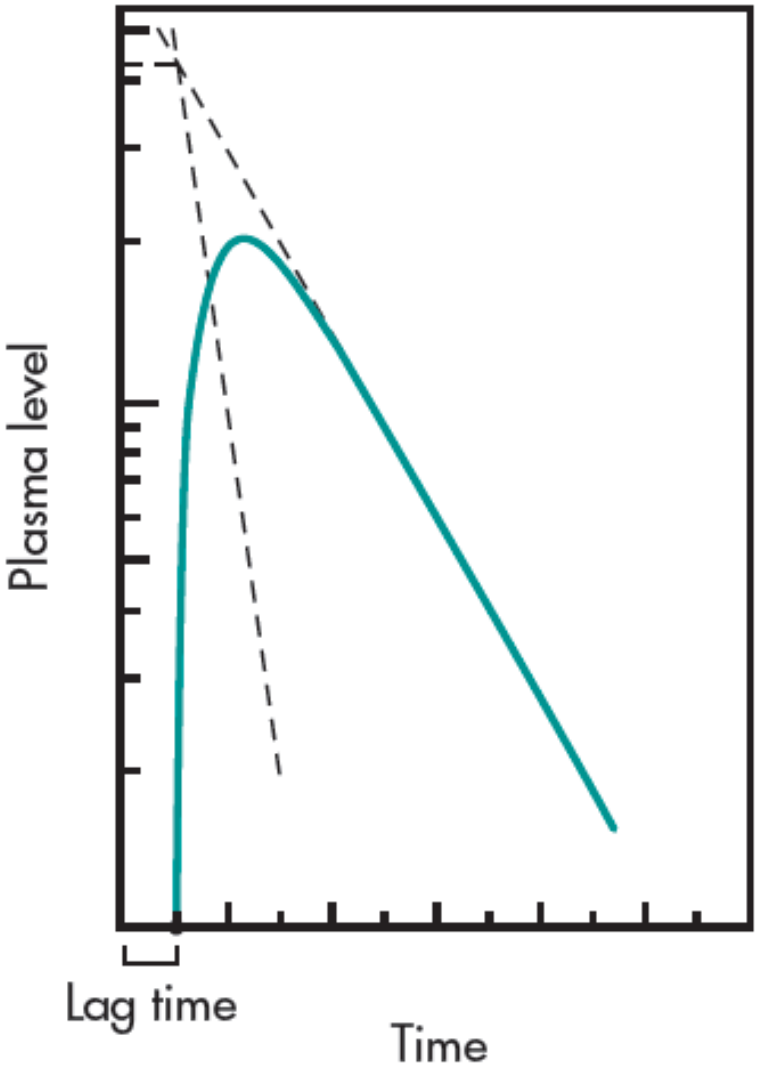


Plot $\Delta_1, \Delta_2, \Delta_3$

Against t

Lag Time

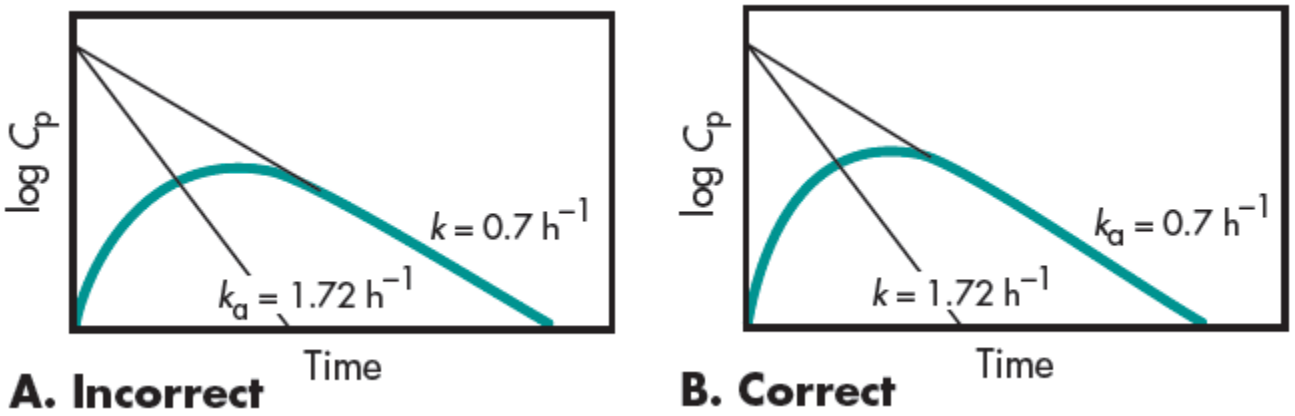
- In some individuals, absorption of drug after a single oral dose does not start immediately, due to such physiologic factors as stomach-emptying time and intestinal motility.
- The time delay prior to the commencement of first-order drug absorption is known as *lag time.*
- The time at the point of intersection on the *x* axis is the lag time.
- The lag time, t_0 is subtracted from each time point, as shown in Equation,



$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)}(e^{-k(t-t_0)} - e^{-k_a(t-t_0)})$$

Flip-Flop of k_a and k

In a few cases, the elimination rate constant *k* 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 h^{-1}, whereas the *k* calculated after oral administration was 0.7 h^{-1}



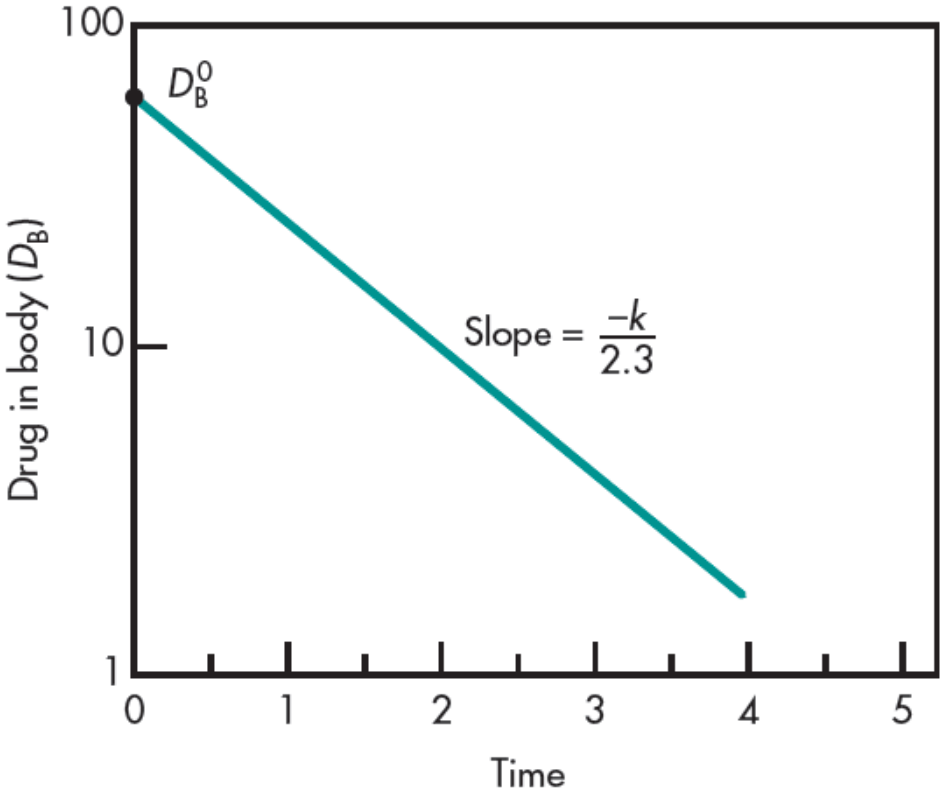
Flip-flop of *ka and k. Because* $k > k_a$

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.

Elimination of Flip-Flop of k_a and k

- In order to demonstrate unambiguously that the steeper curve represents the elimination rate, the drug must be given by intravenous injection into the same patient.

- After intravenous injection, the decline in plasma drug levels over time represents the true elimination rate and the true value of k is obtained from the plasma level-time curve.



Lecture- 5

Contents

- Determination of k_a by Wagner-Nelson method
- Calculation of AUC
- Estimation of ka from Urinary Data

*Determination of k_a by Plotting Percent of Drug Unabsorbed Versus Time (**Wagner–Nelson Method**)*

The Wagner–Nelson method may be used as an alternative means of calculating k_a. This method estimates the loss of drug from the GI over time, whose slope is inversely proportional to k_a.

After a single oral dose of a drug, the total dose should be completely accounted for the amount present in the body, the amount present in the urine, and the amount present in the GI tract.

Therefore, dose (D_0) is expressed as follows:

$$D_0 = D_{GI} + D_B + D_u$$

Let Ab = $D_B + D_u$ = amount of drug absorbed and let Ab^{∞} = amount of drug absorbed at $t = \infty$. At any given time the fraction of drug absorbed is Ab/Ab^{∞}, and the fraction of drug unabsorbed is $1 - (Ab/Ab^{\infty})$.

The amount of drug excreted at any time t can be calculated as

$$D_u = kV_D[AUC]_0^t$$

The amount of drug in the body (D_B) at any time = C_pV_D. At any time t, the amount of drug absorbed (Ab) is

$$Ab = C_pV_D + kV_D[AUC]_0^t$$

At $t = \infty$, $C_p^{\infty} = 0$ (ie, plasma concentration is negligible), and the total amount of drug absorbed is

$$Ab^{\infty} = 0 + kV_D[AUC]_0^{\infty}$$

The fraction of drug absorbed at any time is

$$\frac{\text{Ab}}{\text{Ab}^{\infty}} = \frac{C_p V_D + k V_D [\text{AUC}]_0^t}{k V_D [\text{AUC}]_0^{\infty}}$$

or,

$$\frac{\text{Ab}}{\text{Ab}^{\infty}} = \frac{C_p + k[\text{AUC}]_0^t}{k[\text{AUC}]_0^{\infty}}$$

The fraction unabsorbed at any time *t* is

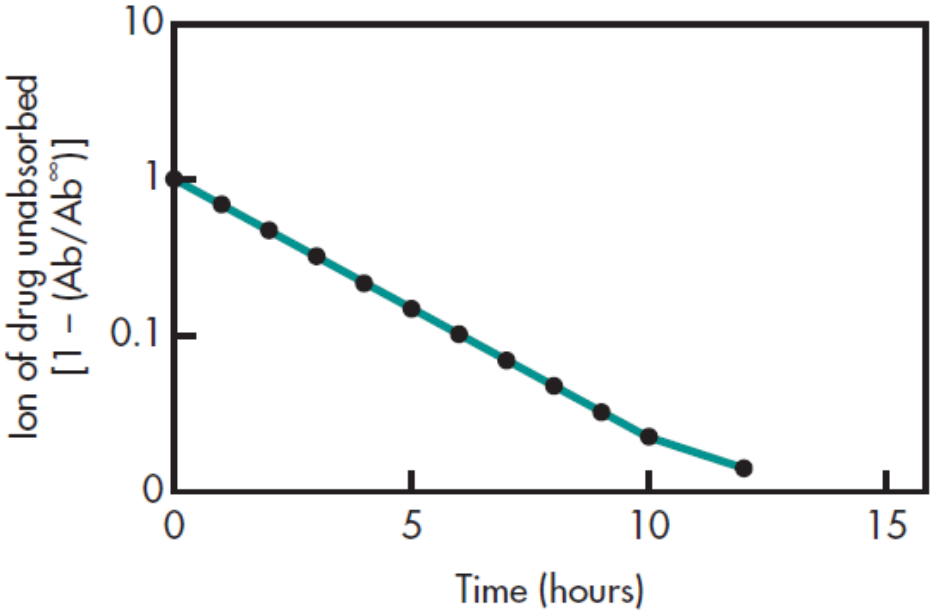
$$1 - \frac{\text{Ab}}{\text{Ab}^{\infty}} = 1 - \frac{C_p + k[\text{AUC}]_0^t}{k[\text{AUC}]_0^{\infty}}$$

The drug remaining in the GI tract at any time t is

$$D_{GI} = D_0 e^{-k_a t}$$

Therefore, the fraction of drug remaining is

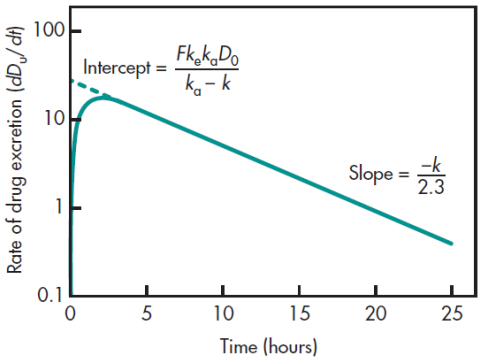
$$\frac{D_{GI}}{D_0} = e^{-k_a t} \qquad \log \frac{D_{GI}}{D_0} = \frac{-k_a t}{2.3}$$

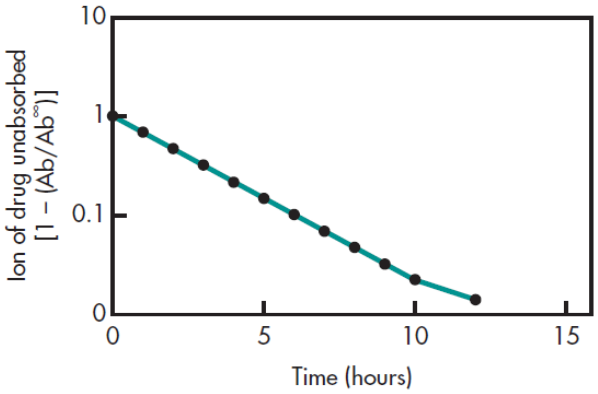


Because D_{GI}/D_0 is actually the fraction of drug unabsorbed—that is, 1 - (Ab/Ab$^\infty$)—a plot of 1 - (Ab/Ab$^\infty$) versus time gives $-k_a/2.3$ as the slope.

The following steps should be useful in determination of k_a:

1. Plot log concentration of drug versus time.
2. Find k from the terminal part of the slope when the slope = $-k/2.3$.
3. Find $[AUC]_0^t$ by plotting C_p versus t.
4. Find $k\,[AUC]_0^t$ by multiplying each $[AUC]_0^t$ by k.
5. Find $k\,[AUC]_0^\infty$ by adding up all the [AUC] pieces, from $t = 0$ to $t = \infty$.
6. Determine the 1 - (Ab/Ab^∞) value corresponding to each time point t
7. Plot 1 - (Ab/Ab^∞) versus time on semilog paper, with 1 - (Ab/Ab^∞) on the logarithmic axis.





The terminal part of the curve is excluded, and only the initial linear segment of the curve is used for the estimate of the slope.

If the fraction of drug unabsorbed, 1 - Ab/Ab^∞, gives a linear regression line on a semilog graph, then the rate of drug absorption, dD_{GI}/dt, is a first-order process.

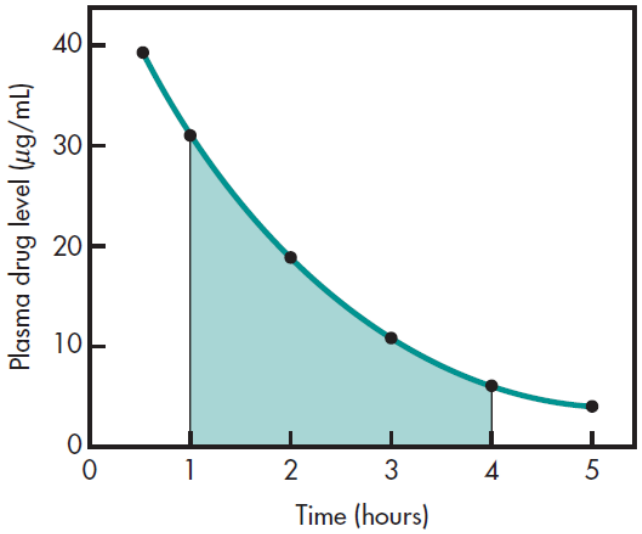
Calculation of AUC

The *trapezoidal rule*

The *trapezoidal rule* is a numerical method frequently used in pharmacokinetics to calculate the area under the plasma drug concentration-versus-time curve, called the *area under the curve* (AUC).

Illustration

Time (hours)	Plasma Drug Level (μg/mL)
0.5	38.9
1.0	30.3
2.0	18.4
3.0	11.1
4.0	6.77
5.0	4.10



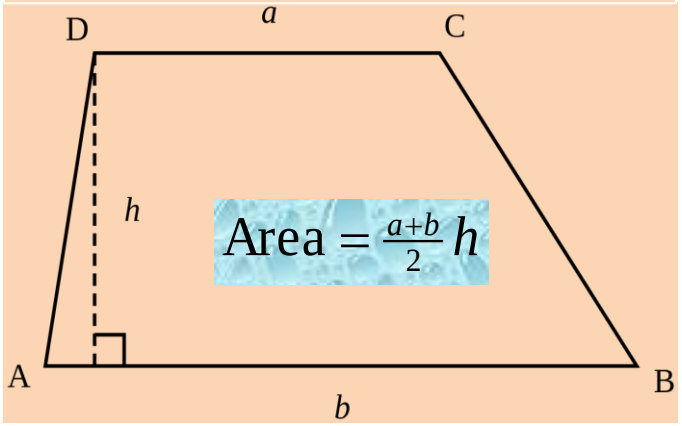
Graph of the elimination of drug from the plasma after a single IV injection.

The area between time intervals is the area of a trapezoid and can be calculated with the following formula:

$$[\mathrm{AUC}]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2}(t_n - t_{n-1})$$

where [AUC] = area under the curve, t_n = time of observation of drug concentration C_n, and t_{n-1} = time of prior observation of drug concentration corresponding to C_{n-1}.

Trapezium (in English outside North America)
Trapezoid (in American and Canadian English)



AUC from 1 to 2 hours

$$[\mathrm{AUC}]_{t_1}^{t_2} = \frac{30.3 + 18.4}{2}(2 - 1) = 24.35\ \mu g \cdot \mathrm{h/mL}$$

PRACTICE PROBLEM

Drug concentrations in the blood at various times are listed in Table 8-1. Assuming the drug follows a one-compartment model, find the k_a value, and compare it with the k_a value obtained by the method of residuals.

TABLE 8-1 Blood Concentrations and Associated Data for a Hypothetical Dru

Time t_n (h)	Concentration C_p (μg/mL)	$[AUC]_{t_{n-1}}^{t_n}$	$[AUC]_0^t$	$k[AUC]_0^t$	$C_p + k[AUC]_0^t$
0	0	0	0		
1	3.13	1.57	1.57	0.157	3.287
2	4.93	4.03	5.60	0.560	5.490
3	5.86	5.40	10.99	1.099	6.959
4	6.25	6.06	17.05	1.705	7.955
5	6.28	6.26	23.31	2.331	8.610
6	6.11	6.20	29.51	2.951	9.061
7	5.81	5.96	35.47	3.547	9.357
8	5.45	5.63	41.10	4.110	9.560
9	5.06	5.26	46.35	4.635	9.695
10	4.66	4.86	51.21	5.121	
12	3.90	8.56	59.77	5.977	
14	3.24	7.14	66.91	6.691	
16	2.67	5.92	72.83	7.283	
18	2.19	4.86	77.69	7.769	
24	1.20	10.17	87.85	8.785	
28	0.81	4.02	91.87	9.187	
32	0.54	2.70	94.57	9.457	
36	0.36	1.80	96.37	9.637	
48	0.10	2.76	99.13	9.913	

Solution

The AUC is approximated by the trapezoidal rule. This method is fairly accurate when there are sufficient data points. The area between each time point is calculated as

$$[\text{AUC}]_{t_{n-1}}^{t_n} = \frac{C_{n-1} + C_n}{2}(t_n - t_{n-1})$$

where C_n and C_{n-1} are concentrations. For example, at $n = 6$, the [AUC] is

$$\frac{6.28 + 6.11}{2}(6 - 5) = 6.20$$

Lecture- 6

Contents

- Estimation of k_a from Urinary Data
- Determination of k_a from Two-Compartment Oral Absorption Data (Loo–Riegelman Method)

Estimation of k_a from Urinary Data

The absorption rate constant may also be estimated from urinary excretion data, using a plot of percent of drug unabsorbed versus time. For a one-compartment model:

Ab = total amount of drug absorbed—that is, the amount of drug in the body plus the amount of drug excreted
D_B = amount of drug in the body
D_u = amount of unchanged drug excreted in the urine
C_p = plasma drug concentration
D_E = total amount of drug eliminated (drug and metabolites)

$$\text{Ab} = D_B + D_E \qquad (1)$$

The differential of Equation 1 with respect to time gives

$$\frac{d\mathrm{Ab}}{dt} = \frac{dD_{\mathrm{B}}}{dt} + \frac{dD_{\mathrm{E}}}{dt} \qquad (2)$$

Assuming first-order elimination kinetics with renal elimination constant k_e,

$$\frac{dD_{\mathrm{u}}}{dt} = k_{\mathrm{e}} D_{\mathrm{B}} = k_{\mathrm{e}} V_{\mathrm{D}} C_{\mathrm{p}} \qquad (3)$$

Assuming a one-compartment model,

$$V_{\mathrm{D}} C_{\mathrm{p}} = D_{\mathrm{B}}$$

Substituting $V_D C_p$ into Equation 2

$$\frac{d\mathrm{Ab}}{dt} = V_{\mathrm{D}} \frac{dC_{\mathrm{p}}}{dt} + \frac{dD_{\mathrm{E}}}{dt} \qquad (4)$$

And rearranging Equation 3,

$$C_{\mathrm{p}} = \frac{1}{k_{\mathrm{e}} V_{\mathrm{D}}} \left(\frac{dD_{\mathrm{u}}}{dt} \right)$$

$$\frac{dC_{\mathrm{p}}}{dt} = \frac{d(dD_{\mathrm{u}}/dt)}{dt\, k_{\mathrm{e}} V_{\mathrm{D}}}$$

Substituting for dC_{p}/dt into Equation 4 and $kD_{\mathrm{u}}/k_{\mathrm{e}}$ for D_{E},

$$\frac{d\mathrm{Ab}}{dt} = \frac{d(dD_{\mathrm{u}}/dt)}{k_{\mathrm{e}}\, dt} + \frac{k}{k_{\mathrm{e}}} \left(\frac{dD_{\mathrm{u}}}{dt} \right)$$

When the above expression is integrated from zero to time *t,*

$$\mathrm{Ab}_t = \frac{1}{k_{\mathrm{e}}} \left(\frac{dD_{\mathrm{u}}}{dt} \right)_t + \frac{k}{k_{\mathrm{e}}} (D_{\mathrm{u}})_t$$

At $t = \infty$, all the drug that is ultimately absorbed is expressed as $Ab\infty$ and $dD_u/dt = 0$. The total amount of drug absorbed is

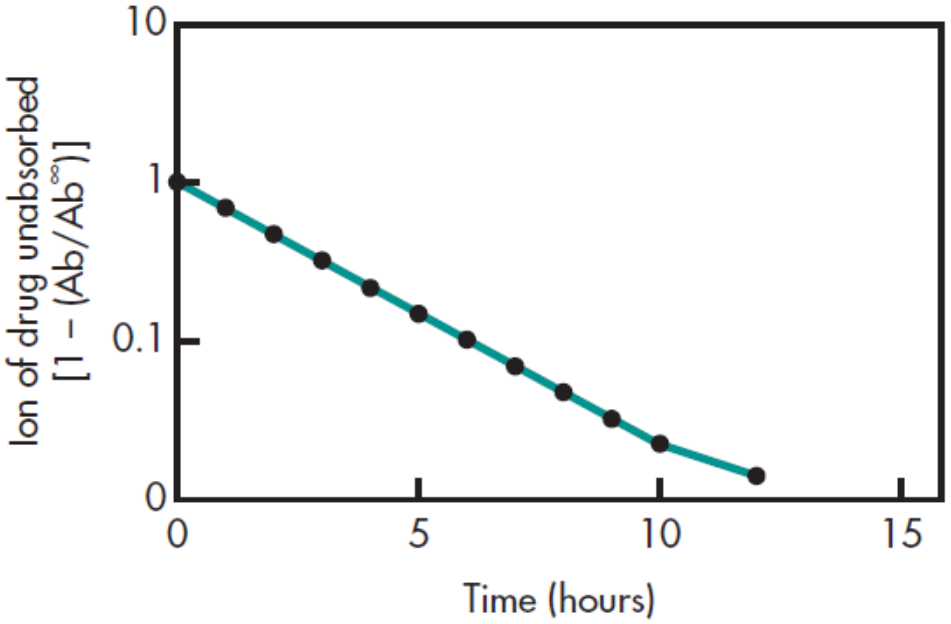
$$\mathrm{Ab}^{\infty} = \frac{k}{k_e} D_u^{\infty}$$

where D_u^{∞} is the total amount of unchanged drug excreted in the urine.

The fraction of drug absorbed at any time t is equal to the amount of drug absorbed at this time, Ab_t, divided by the total amount of drug absorbed, $Ab\infty$.

$$\frac{\mathrm{Ab}_t}{\mathrm{Ab}^{\infty}} = \frac{(dD_u/dt)_t + k(D_u)_t}{kD_u^{\infty}}$$

A plot of the fraction of drug unabsorbed, (1-Ab/Ab∞), versus time gives -k_a/2.3 as the slope from which the absorption rate constant is obtained



Practical considerations for collecting urine for drug analysis

- Urine is produced at an approximate rate of 1 mL/min and collected in the bladder until voided for collection.
- Thus, the drug urinary excretion rate (dD_u/dt) cannot be determined experimentally for any given instant.
- In practice, urine is collected over a specified time interval, and the urine specimen is analyzed for drug.
- An average urinary excretion rate is then calculated for that collection period.
- Therefore, the average rate of urinary drug excretion, D_u/t, is plotted against the time corresponding to the midpoint of the collection interval, t^*, for the collection of the urine sample.

Time (hours)	D_u (mg)	D_u/t	mg/h	t^* (hours)
0.25	160	160/0.25	640	0.125
0.50	140	140/0.25	560	0.375
1.0	200	200/0.5	400	0.750
2.0	250	250/1	250	1.50
4.0	188	188/2	94	3.0
6.0	46	46/2	23	5.0

Here t^* = midpoint of collection period and t = time interval for collection of urine sample.

Data collected following Intravenous Bolus Administration

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

- Changes in k_a and k may affect t_{max}, C_{max}, and AUC.
- If the values for k_a and k are reversed, then the same t_{max} is obtained, but the C_{max} and AUC are different.

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

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

TABLE 8-2 Effects of the Absorption Rate Constant and Elimination Rate[a]

Absorption Rate Constant, k_a (h^{-1})	Elimination Rate Constant, k (h^{-1})	t_{max} (h)	C_{max} (μg/mL)	AUC (μg · h/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

[a] t_{max} = peak plasma concentration, C_{max} = peak drug concentration, AUC = area under the curve. Values are based on a single oral dose (100 mg) that is 100% bioavailable ($F = 1$) and has an apparent V_D of 10 L. The drug follows a one-compartment open model. t_{max} is calculated by Equation 8.14 and C_{max} is calculated by Equation 8.12. The AUC is calculated by the trapezoidal rule from 0 to 24 hours.

Determination of k_a from Two-Compartment Oral Absorption Data (Loo–Riegelman Method)

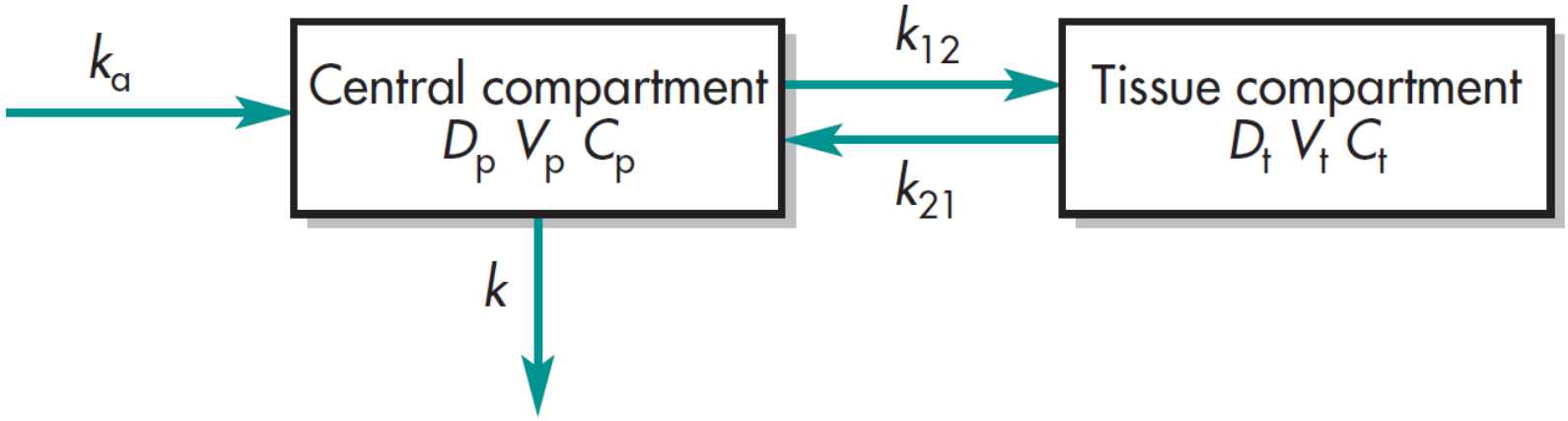


FIGURE 8-18 Two-compartment pharmacokinetic mode. Drug absorption and elimination occur from the central compartment.

Ref. Shargel 7th edition, page196

After oral administration of a dose of a drug that exhibits two-compartment model kinetics, the amount of drug absorbed is calculated as the sum of the amounts of drug in the central compartment (D_p), in the tissue compartment (D_t), and the amount of drug eliminated by all routes (D_u).

$$\mathrm{Ab} = D_p + D_t + D_u$$

The amount of drug absorbed,

$$\mathrm{Ab} = D_\mathrm{p} + D_\mathrm{t} + D_\mathrm{u} \qquad (1)$$

We have,

$$D_\mathrm{p} = V_\mathrm{p} C_\mathrm{p} \qquad D_\mathrm{t} = V_\mathrm{t} C_\mathrm{t}$$

$$\frac{dD_\mathrm{u}}{dt} = kV_\mathrm{p} C_\mathrm{p} \qquad D_\mathrm{u} = kV_\mathrm{p}[\mathrm{AUC}]_0^t$$

Substituting the above expression for D_p and D_u into Equation (1),

$$\mathrm{Ab} = V_\mathrm{p} C_\mathrm{p} + D_\mathrm{t} + kV_\mathrm{p}[\mathrm{AUC}]_0^t \qquad (2)$$

By dividing this equation by V_p to express the equation on drug concentrations, we obtain

$$\frac{\mathrm{Ab}}{V_p} = C_p + \frac{D_t}{V_p} + k[\mathrm{AUC}]_0^t \qquad (3)$$

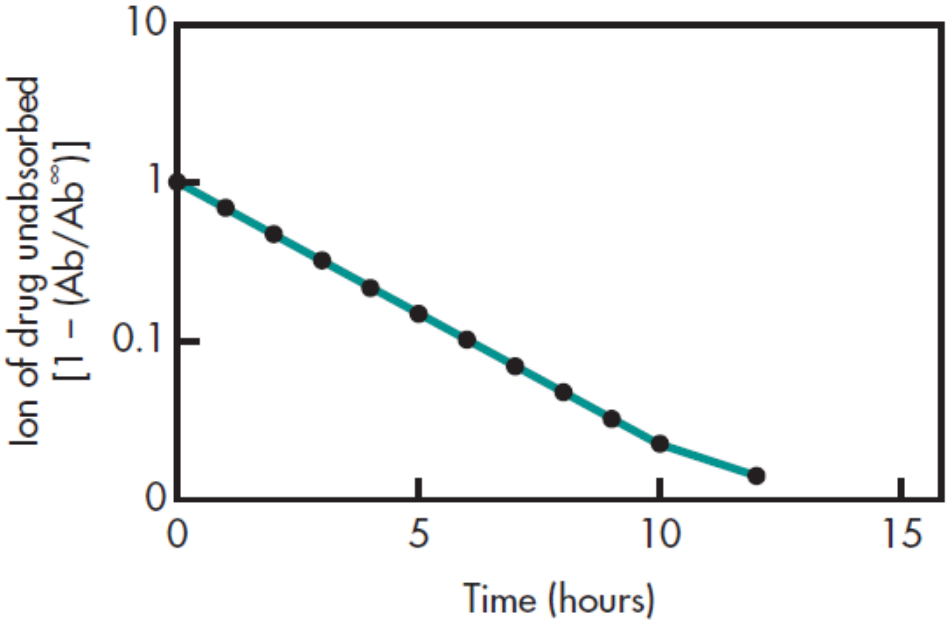
At $t = \infty$, this equation becomes

$$\frac{\mathrm{Ab}}{V_p} = k[\mathrm{AUC}]_0^\infty \qquad (4)$$

Equation (3) divided by Equation (4) gives the fraction of drug absorbed at any time

$$\frac{\mathrm{Ab}}{\mathrm{Ab}^{\infty}} = \frac{C_{\mathrm{p}} + \left(\frac{D_{\mathrm{t}}}{V_{\mathrm{p}}}\right) + k[\mathrm{AUC}]_0^t}{k[\mathrm{AUC}]_0^{\infty}} \qquad (5)$$

A plot of the fraction of drug unabsorbed, 1- Ab/Ab$^{\infty}$, versus time gives -k_a/2.3 as the slope from which the value for the absorption rate constant is obtained.



The values for $k[\mathrm{AUC}]_0^t$ are calculated from a plot of C_p versus time. Values for (D_t/V_p) can be approximated by the Loo–Riegelman method, as follows:

$$(C_t)_{t_n} = \frac{k_{12}\Delta C_p \Delta t}{2} + \frac{k_{12}}{k_{21}}(C_p)_{t_{n-1}}(1 - e^{-k_{21}\Delta t}) + (C_t)_{t_{n-1}} e^{-k_{21}\Delta t}$$

where C_t is D_t/V_p, or apparent tissue concentration; t = time of sampling for sample n; t_{n-1} = time of sampling for the sampling point preceding sample n; and $(C_p)_{t_{n-1}}$ = concentration of drug at central compartment for sample $n - 1$.

TABLE 8-3 Calculation of C_t Values[a]

$(C_p)t_n$	$(t)t_n$	$\Delta(C_p)$	Δt	$\frac{(k_{12}\Delta C_p \Delta t)}{2}$	$(C_p)_{t_{n-1}}$	$(k_{12}/k_{21})\times(1-e^{-k_{21}\Delta t})$	$(C_p)_{t_{n-1}}(k_{12}/k_{21})\times(1-e^{-k_{21}\Delta t})$	$(C_t)_{t_{n-1}}e^{-k_{21}\Delta t}$	$(C_t)t_n$
3.00	0.5	3.0	0.5	0.218	0	0.134	0	0	0.218
5.20	1.0	2.2	0.5	0.160	3.00	0.134	0.402	0.187	0.749
6.50	1.5	1.3	0.5	0.094	5.20	0.134	0.697	0.642	1.433
7.30	2.0	0.8	0.5	0.058	6.50	0.134	0.871	1.228	2.157
7.60	2.5	0.3	0.5	0.022	7.30	0.134	0.978	1.849	2.849
7.75	3.0	0.15	0.5	0.011	7.60	0.134	1.018	2.442	3.471
7.70	3.5	−0.05	0.5	−0.004	7.75	0.134	1.039	2.976	4.019
7.60	4.0	−0.10	0.5	−0.007	7.70	0.134	1.032	3.444	4.469
7.10	5.0	−0.50	1.0	−0.073	7.60	0.250	1.900	3.276	5.103
6.60	6.0	−0.50	1.0	−0.073	7.10	0.250	1.775	3.740	5.442
6.00	7.0	−0.60	1.0	−0.087	6.60	0.250	1.650	3.989	5.552
5.10	9.0	−0.90	2.0	−2.261	6.00	0.432	2.592	2.987	5.318
4.40	11.0	−0.70	2.0	−0.203	5.10	0.432	2.203	2.861	4.861
3.30	15.0	−1.10	4.0	−0.638	4.40	0.720	3.168	1.361	3.891

[a]Calculated with the following rate constants: $k_{12} = 0.29\ h^{-1}$, $k_{21} = 0.31\ h^{-1}$.

Adapted with permission from Loo and Riegelman (1968).

- For calculation of k_a by this method, the drug must be given intravenously to allow evaluation of the distribution and elimination rate constants.
- For drugs that cannot be given by the IV route, the k_a cannot be calculated by the Loo–Riegelman method.

- For drugs that are given by the oral route only, the Wagner– Nelson method, which assumes a one-compartment model, may be used to provide an initial estimate of k_a.
- Therefore, a one-compartment model is frequently used to fit the plasma curves after an oral or intramuscular dose.
- The plasma level predicted from the k_a obtained by this method does deviate from the actual plasma level. However, in many instances, this deviation is not significant.