Biopharmaceutics

Lec. 8

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Pharmacokinetics of Oral Absorption

Pharmacokinetics of Drug Absorption:

•The systemic drug absorption from the GIT or from any other extravascular site is dependent on: |1| the physicochemical properties of the drug, |2| the type and design of dosage form, and |3| the anatomy and physiology of the drug absorption site. For oral dosing, such factors as |1| surface area of the GI tract, |2| stomach-emptying rate, |3| GI mobility, and |4| blood flow to the absorption site all affect the rate and the extent of drug absorption.

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

$$\frac{dD_B}{dt} = \frac{dD_{GI}}{dt} - \frac{dD_E}{dt} \quad \text{.....(Eq. 1)}$$

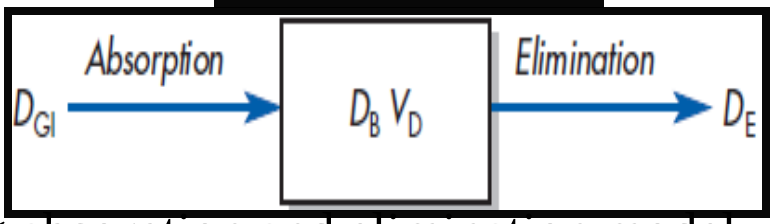


Figure 1: drug absorption and elimination model

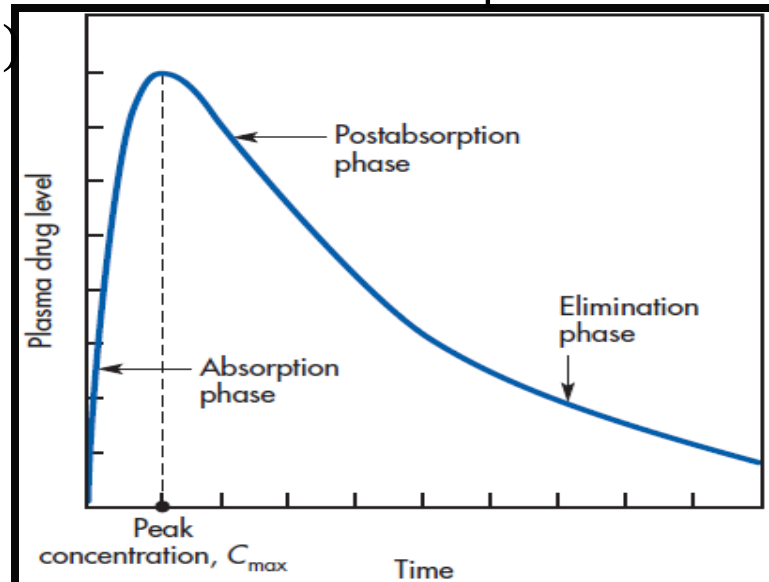


Figure 2: plasma – level time curve for a drug given a single oral dose, note drug absorption and elimination phases

•During the absorption phase of a plasma level–time curve, the rate of drug absorption is greater than the rate of drug elimination. $\frac{dD_{GI}}{dt} > \frac{dD_E}{dt}$ …..(Eq. 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.

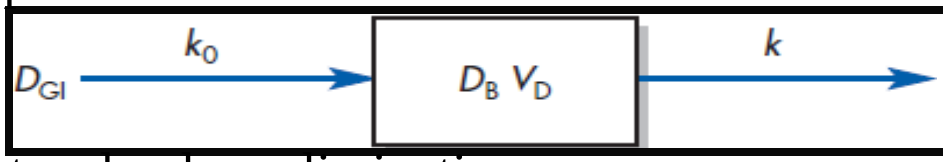
$$\frac{dD_{GI}}{dt} = \frac{dD_E}{dt} \quad \text{…..(Eq. 3)}$$

•Immediately after the time of peak drug absorption, some drug may still be at the absorption site (i.e.; 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. $\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}$ …..(Eq. 4)

•When the drug at the absorption site becomes depleted, the rate of drug absorption approaches zero, or $dD_{GI}/dt = 0$. 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: $\frac{dD_B}{dt} = -kD_B$ …..(Eq. 5)

<u>Zero – Order Absorption Model</u>:

•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.



<u>Figure 3</u>: one-compartment pharmacokinetic model for zero-order drug absorption and first-order drug elimination

•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.

•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: $\frac{dD_B}{dt} = k_0 - kD_B$ …..(Eq. 6). Integration of this equation with substitution of $V_D C_p$ for D_B produces: $C_p = \frac{k_0}{V_D k}(1 - e^{-kt})$ …..(Eq. 7)

•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. After this time, the drug is no longer available for absorption from the gut, and equation 7 no longer holds. The drug concentration in the plasma subsequently declines in accordance with a first-order elimination rate process.

First – Order Absorption Model:

•This model assumes a first-order input across the gut wall and first-order elimination from the body.

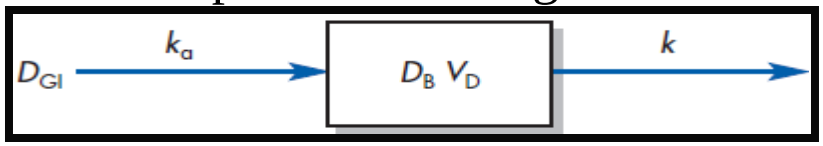


Figure 4: one-compartment pharmacokinetic model for first-order drug absorption and first-order elimination

•After oral administration of a drug product, the drug is released from the drug product and 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: $\frac{dD_{GI}}{dt} = -k_a D_{GI} F$ …..(Eq. 8), where ka 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 8 gives: $\frac{dD_{GI}}{dt} = D_0 e^{-k_a t}$ ..(Eq. 9) where D_0 is the dose of the drug.

•The rate of drug elimination is described by a first-order rate process for most drugs and is equal to $-kD_B$. 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 the differential equation:

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

…..(Eq. 10)

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

where F is the fraction of drug absorbed systemically. Since the drug in the gastrointestinal tract also follows a first-order decline, the amount of drug in the gastrointestinal tract at any time t is equal to $D_0 e^{-kat}$. $\frac{dD_B}{dt} = Fk_a D_0 e^{-k_a t} - kD_B$

The value of F may 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 the drug (C_p) in the plasma at any time t:

$$C_p = \frac{Fk_a D_0}{V_D(k_a - k)}(e^{-kt} - e^{-k_a t})$$ .....(Eq. 11)

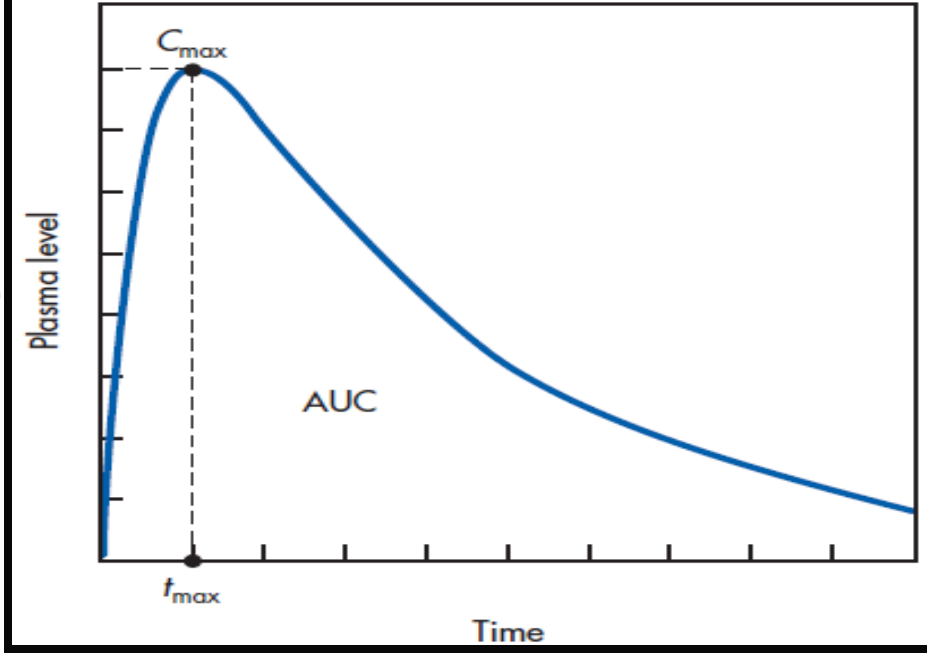


Figure 5: Typical plasma level–time curve for a drug given in a single oral dose

•The maximum plasma concentration after oral dosing is C_{max}, and the time needed to reach maximum concentration is t_{max}. The t_{max} is independent of dose and is dependent on the rate constants for absorption (k_a) and elimination (k), equation 13. At C_{max}, (peak concentration), the rate of drug absorbed is equal to the rate of drug eliminated. Therefore, the net rate of concentration change is equal to zero. At C_{max}, the rate of concentration change can be obtained by differentiating equation 11, as follows:

$$C_p = \frac{k_a D_0 F}{V_D(k_a - k)}(-ke^{-kt} + k_a e^{-k_a t}) = 0$$ .....(Eq. 12)

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

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

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

•This can be simplifies as follows:

$$t_{max} = \frac{2.3 \log (k_a/k)}{k_a - k}$$ ..(Eq. 13)

•Equation 13, 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 13 and then substituted into equation 11, solving for C_{max}. Equation 11 shows that C_{max} is directly proportional to the dose of drug given (D_0) and the fraction of drug absorbed (F).

•The first-order elimination rate constant may be determined from the elimination phase of the plasma level–time curve, figure 2. At later time intervals, when drug absorption has been completed, i.e.; $e^{-kat} \approx 0$, equation 11 reduces to: $$C_p = \frac{Fk_aD_0}{V_D(k_a - k)}e^{-kt}$$ …..(Eq. 14).

•Taking the natural logarithm of this expression, $$\ln C_p = \ln\frac{Fk_aD_0}{V_D(k_a - k)} - kt$$ …..(Eq. 15).

•Substitution of common logarithms gives $$\log C_p = \log\frac{Fk_aD_0}{V_D(k_a - k)} - \frac{kt}{2.3}$$ ……(Eq. 16).

•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:

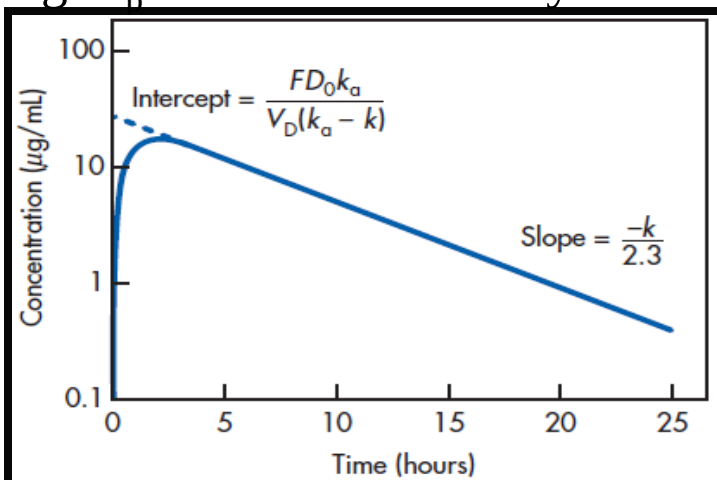


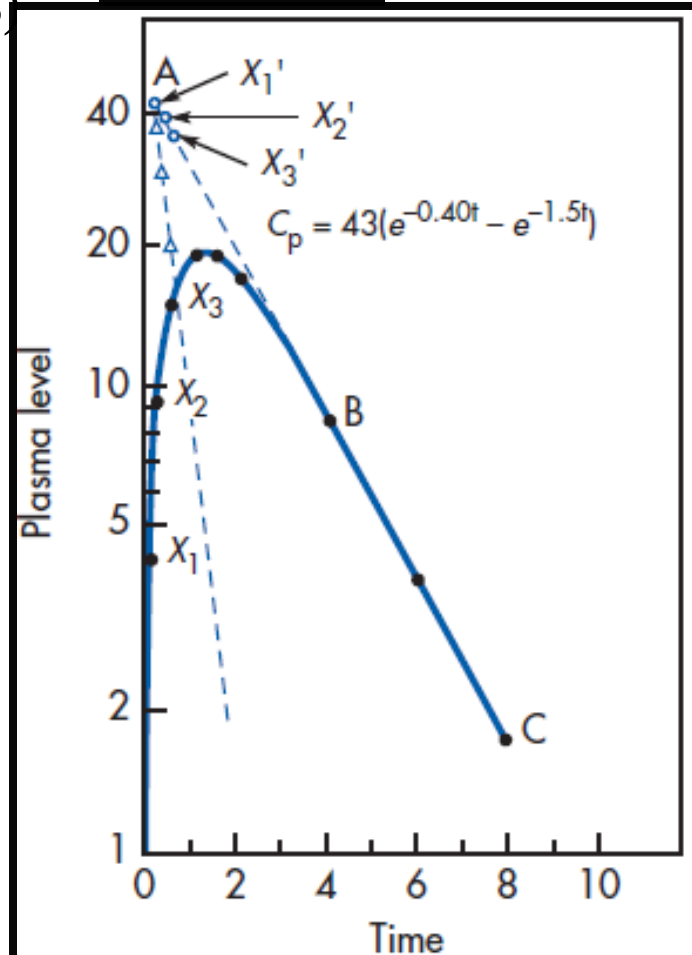
Figure 6: plasma drug concentration versus time, single oral dose

***Determination of Absorption Rate Constants from Oral Absorption Data*:**

Method of Residuals – assuming $k_a >> k$ in equation 11, the value for the second exponential will become insignificantly small with time (i.e.; $e^{-kat} \approx 0$) and can therefore be omitted. When this is the case, drug absorption is virtually complete. Equation 11 then reduces to: $C_p = \frac{Fk_aD_0}{V_D(k_a - k)}e^{-kt}$ …..(Eq. 17).

•From this, one may also obtain the intercept of the *y* axis $\frac{Fk_aD_0}{V_D(k_a - k)} = A$ where A is a constant. Thus, equation 17 becomes: $C_p = Ae^{-kt}$ ..(Eq. 18)

Figure 7: plasma level–time curve for a drug demonstrating first-order absorption and elimination kinetics / the equation of the curve is obtained by the method of residuals



•Equation 18 represents first-order drug elimination, will yield a linear plot on semilog paper. The slope is equal to – k/2.3. The value for ka can be obtained by using the method of residuals or a feathering technique, as described in lecture 5. The value of ka is obtained by the following procedure:

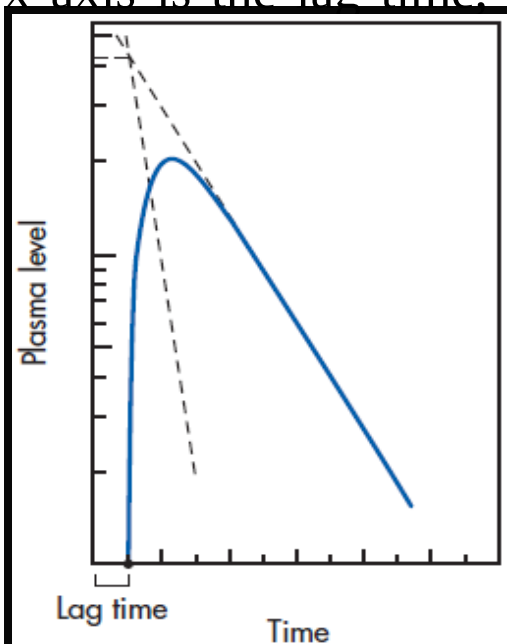
1. Plot the drug concentration versus time on semilog paper, figure 7.

2. Obtain the slope of the terminal phase (line BC, figure 7) by extrapolation.
3. Take any points on the upper part of 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, 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 $-k_a/2.3$, figure 7.

Lag Time – 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 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, figure 8.

Figure 8: the lag time can be determined graphically if the two residual lines obtained by feathering the plasma level–time curve intersect at a point where $t > 0$



•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, i.e.; the time required for the drug to reach minimum effective concentration.

•Two equations can adequately describe the curve in figure 8. In one, the lag time t_0 is subtracted from each time point, as shown in $C_p = \frac{Fk_aD_0}{V_D(k_a - k)}(e^{-k(t-t_0)} - e^{-k_a(t-t_0)})$ …..(Eq.19). where $Fk_aD_0/V_D(k_a - k)$ is the y value at the point of intersection of the residual lines in figure 8.

•The second expression that describes the curve in figure 8 omits the lag time, as follows: $C_p = Be^{-kt} - Ae^{-k_at}$ …..(Eq. 20), where A and B represents the intercepts on the y axis after extrapolation of the residual lines for absorption and elimination, respectively.

Flip-Flop of k_a and k – in using the method of residuals to obtain estimates of k_a and k, the terminal phase of an oral absorption curve is usually represented by k, whereas the steeper slope is represented by k_a, figure 9;

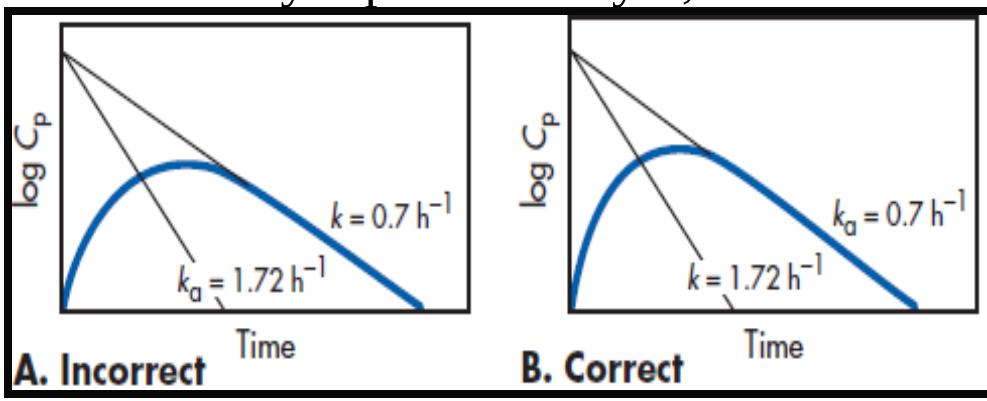


Figure 9: flip-flop of k_a and k, because k > k_a, the right-hand figure and slopes represent the correct values for k_a and k

•In a few cases, the elimination rate constant k obtained from oral absorption data does not agree with that obtained after intravenous bolus injection, e.g.; 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} figure 9. When k_a was obtained by the method of residuals, the rather surprising result was that the k_a was 1.72 h^{-1}.

•Apparently, the k_a and k obtained by the method of residuals have 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 k_a and k are estimated from oral drug absorption data.

•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 figure 9) should be used as the elimination constant is generally correct. For drugs that have a large elimination rate constant ($k > 0.69\ h^{-1}$), the chance for flip-flop of ka and k is much greater.

•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.

Frequently Asked Questions: -

1- If drug absorption is simulated using the oral one compartment model, would a larger absorption rate constant result in a greater amount of drug absorbed?

The fraction of drug absorbed, F, and the absorption rate constant, ka, are independent parameters. A drug in an oral solution may have a more rapid rate of absorption compared to a solid drug product. If the drug is released from the drug product slowly or is formulated so that the drug is absorbed slowly, the drug may be subjected to first-pass effects, degraded in the gastrointestinal tract, or eliminated in the feces so that less drug (smaller F) may be absorbed systemically compared to the same drug formulated to be absorbed more rapidly from the drug product.

2- How do you explain that k_a is often greater than k with most drugs?

A drug with a rate of absorption slower than its rate of elimination will not be able to obtain optimal systemic drug concentrations to achieve efficacy. Such drugs are generally not developed into products. However, the apartment *ka for drugs* absorbed from controlled release products may be smaller, but the initial rate of absorption from the GI tract is faster than the rate of drug elimination since, dDGI/dt = -KaDGI.

3- What is the absorption half-life of a drug and how is it determined?
For drugs absorbed by a first-order process, the absorption half-life is 0.693/ka. Although drug absorption involves many stochastic (system based random) steps, the overall rate process is often approximated by a first-order process, especially with oral solutions and immediate-release drug products such as compressed tablets or capsules. The determination of the absorption rate constant, ka, is most often calculated by the Wagner–Nelson method for drugs, which follows a one-compartment model with first-order absorption and first-order elimination.

4- In switching a drug from IV to oral dosing, what is the most important consideration?
The fraction of drug absorbed may be less than 1 (i.e.; 100% bioavailable) after oral administration. In some cases, there may be a different salt form of the drug used for IV infusion compared to the salt form of the drug used orally. Therefore, a correction is needed for the difference in MW of the two salt forms.

5- Drug clearance is dependent on dose and area under the time–drug concentration curve. Would drug clearance be affected by the rate of absorption?
Total body drug clearance and renal drug clearance are generally not affected by drug absorption from most absorption sites. In the gastrointestinal tract, a drug is absorbed via the hepatic portal vein to the liver and may be subject to hepatic clearance.

6- Does a larger absorption rate constant affect C_{max}, t_{max}, and AUC if the dose and elimination rate constant, k remains constant?

Learning Questions: -

1- Plasma samples from a patient were collected after an oral bolus dose of 10 mg of a new benzodiazepine solution as follows, from the table data; a. Determine the elimination constant of the drug, b. Determine ka by feathering, and c. Determine the equation that describes the plasma drug concentration of the new benzodiazepine.

a. The elimination rate constant is 0.1 h^{-1} ($t_{1/2}$ = 6.93 h).

b. The absorption rate constant, k_a, is 0.3 h^{-1} (absorption half-life = 2.31 h).

The calculated $t_{max} = \dfrac{\ln (k_a / k)}{k_a - k} = 5.49$ h.

c. The *y* intercept was observed to be 60 ng/mL. Therefore the equation that fits the observed data is

$$C_p = 60\,(e^{-0.1t} - e^{-0.3t})$$

Time (hour)	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

2- Assuming that the drug in Question 1 is 80% absorbed, find (a) the absorption constant, ka; (b) the elimination half-life, t1/2; (c) the tmax, or time of peak drug concentration; and (d) the volume of distribution of the patient.

By direct observation of the data, the t_{max} is 6 hours and the C_{max} is 23.01 ng/mL. The apparent volume of distribution, V_D, is obtained from the intercept, I, of the terminal elimination phase, and substituting $F = 0.8$, $D = 10{,}000{,}000$ ng, $k_a = 0.3\ h^{-1}$, $k = 0.1\ h^{-1}$:

$$I = \frac{Fk_aD_0}{V_D(k_a - k)}$$

$$60 = \frac{(0.8)\,(0.3)\,(10{,}000{,}000)}{V_D(0.3 - 0.1)}$$

$$V_D = 200\ L$$

3- Contrast the percent of drug-unabsorbed methods for the determination of rate constant for absorption, ka, in terms of (a) pharmacokinetic model, (b) route of drug administration, and (c) possible sources of error.

The percent-of-drug-unabsorbed method is applicable to any model with first-order elimination, regardless of the process of drug input. If the drug is given by IV injection, the elimination rate constant, k, may be determined accurately. If the drug is administered orally, k and ka may flip-flop, resulting in an error unless IV data are available to determine k. For a drug that follows a two-compartment model, an IV bolus injection is used to determine the rate constants for distribution and elimination.

4- What is the error inherent in the measurement of *ka for an orally administered drug* that follows a two-compartment model when a one-compartment model is assumed in the calculation?

After an IV bolus injection, a drug such as theophylline follows a two-compartment model with a rapid distribution phase. During oral absorption, the drug is distributed during the absorption phase, and no distribution phase is observed. Pharmacokinetic analysis of the plasma drug concentration data obtained after oral drug administration will show that the drug follows a one-compartment model.

5- What are the main pharmacokinetic parameters that influence (a) time for peak drug concentration and (b) peak drug concentration?

The equations for a drug that follows the kinetics of a one-compartment model with first-order absorption and elimination are

$$C_p = \frac{FD_0k_a}{V_D(k_a - k)}(e^{kt} - e^{-k_at}) \qquad t_{max} = \frac{\ln(k_a / k)}{k_a - k}$$

As shown by these equations:

a. t_{max} is influenced by k_a and k and not by F, D_0, or V_D.

b. C_p is influenced by F, D_0, V_D, k_a, and k.

6- Name a method of drug administration that will provide a zero-order input.

A drug product that might provide a zero-order input is an oral controlled-release tablet or a transdermal drug delivery system (patch). An IV drug infusion will also provide a zero-order drug input.

7- A single oral dose (100 mg) of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fits a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is $C_p = 45(e^{-0.17t} - e^{-1.5t})$ From the equation above, calculate (a) tmax, (b) Cmax, and (c) t1/2 for the drug in this patient. Assume Cp is in μg/mL and the first-order rate constants are in h–1.

The general equation for a one-compartment open model with oral absorption is

$$C_p = \frac{FD_0k_a}{V_D(k_a - k)}(e^{-kt} - e^{-k_at})$$

From $C_p = 45(e^{-0.17t} - e^{-1.5t})$,

$$\frac{FD_0k_a}{V_D(k_a - k)} = 45$$

$$k = 0.17\ \text{h}^{-1}$$

$$k_a = 1.5\ \text{h}^{-1}$$

a. $$t_{max} = \frac{\ln(k_a/k)}{k_a - k} = \frac{\ln(1.5/0.17)}{1.5 - 0.17} = 1.64\ \text{h}$$

b. $$C_{max} = 45(e^{-(0.17)(1.64)} - e^{-(1.5)(1.64)})$$

$$= 30.2\ \mu\text{g/mL}$$

c. $$t_{1/2} = \frac{0.693}{k} = \frac{0.693}{0.17} = 4.08\ \text{h}$$

8- Two drugs, A and B, have the following pharmacokinetic parameters after a single oral dose of 500 mg; Both drugs follow a one-compartment pharmacokinetic model and are 100% bioavailable. a. Calculate the tmax for each drug, and b. Calculate the Cmax for each drug.

Drug	k_a (h^{-1})	k (h^{-1})	V_D (mL)
A	1.0	0.2	10,000
B	0.2	1.0	20,000

a. Drug A $$t_{max} = \frac{\ln(1.0/0.2)}{1.0-1.2} = 2.01\ \text{h}$$

Drug B $$t_{max} = \frac{\ln(0.2/1.0)}{0.2-1.0} = 2.01\ \text{h}$$

b. $$C_{max} = \frac{FD_0\,k_a}{V_D(k_a-k)}(e^{-kt_{max}} - e^{-k_a t_{max}})$$

Drug A $$C_{max} = \frac{(1)(500)(1)}{(10)(1-0.2)}(e^{-(0.2)(2)} - e^{-(1)(2)})$$

$$C_{max} = 33.4\ \mu\text{g/mL}$$

Drug B $$C_{max} = \frac{(1)(500)(0.2)}{(20)(0.2-1.0)}$$

$$= (e^{-1(2)} - e^{-(0.2)(2)})$$

$$C_{max} = 3.34\ \mu\text{g/mL}$$