جامعة المستقبل
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Biopharmaceutics

Pharmacokinetics of extravascular administration of drugs

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Introduction

- Drugs are most frequently administered extravascularly.
- The majority of these drugs are intended to act systemically
  - For this reason $\Rightarrow$ absorption is important for pharmacological effects
- Delays or drug loss during absorption may contribute to variability in drug response and, occasionally, may result in a failure of drug therapy.
- For oral administration, the gastrointestinal membrane separates the absorption site from the blood.

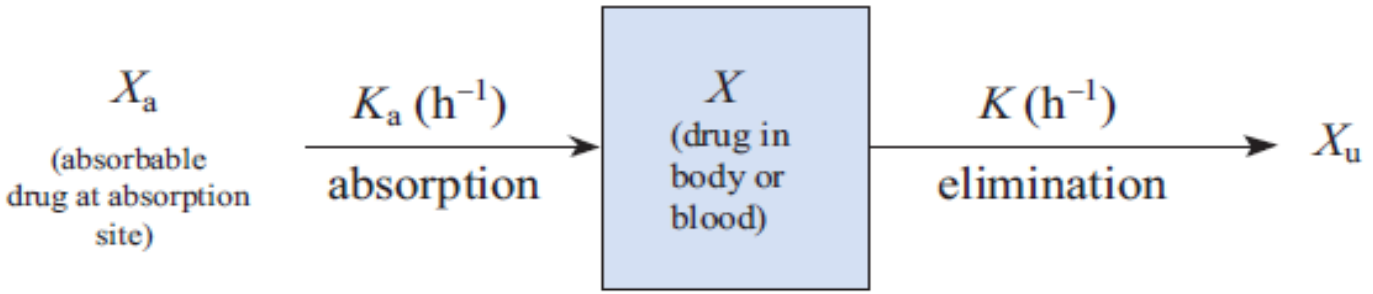
- Therefore, passage of drug across the membrane is a necessary for absorption.
  - For this reason, drug must be in a solution form and dissolution becomes very critical for the absorption of a drug.
  - Any factor influencing dissolution of the drug is likely to affect the absorption of a drug.
  - And any factor influence passage of drug across the membrane, affect the overall absorption of a drug.
  - The physicochemical properties of the drug molecule: pKa of the drug, partition coefficient of the drug, drug solubility, etc.
  - pH at the site of drug administration
  - Nature of the membrane.
  - Physiological factors (fed or fast state)

- The following assumptions are made:
  - Drug exhibits the characteristics of one compartment model
  - Absorption and elimination of a drug follow the first-order process and passive diffusion is operative at all the time.
  - Drug is eliminated in unchanged form (i.e. no metabolism occurs).
  - Drug is monitored in the blood

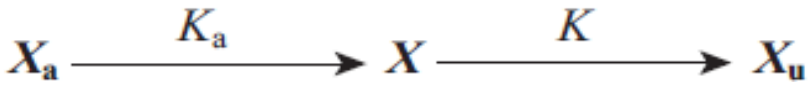
Monitoring drug in the blood (plasma/serum)

- The following scheme represents the Absorption of a one-compartment drug with first-order elimination

SCHEME:



SETUP:



where,

- X_a: the amount of absorbable drug remaining in the gut, or at the site of administration, at time t (i.e. drug available for absorption at time t).

$$(X_a)_0 \neq X_0 \qquad \text{but } (X_a)_0 = FX_0$$

- X: the amount of drug in the blood at time t.
- X_u: the amount of drug excreted unchanged in the urine at time t.
- K_a: the first order absorption rate constant
- K (or K_{el}) is the first-order elimination rate constant

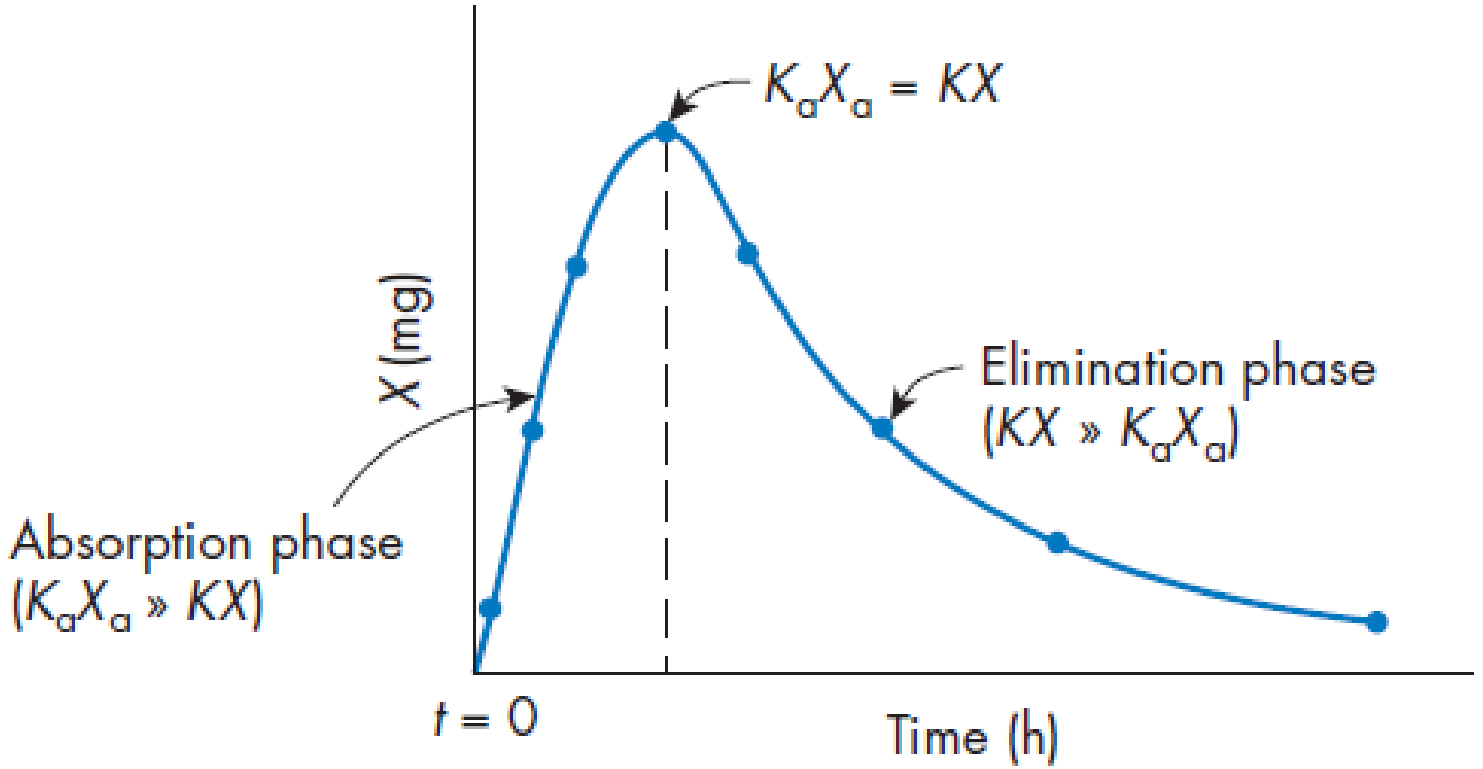
- The differential equation that relates changes in drug concentration in the blood with time to the absorption and the elimination rates is:

$$\frac{dX}{dt} = K_a X_a - KX$$

- This differential equation clearly indicates that the rate of change in drug in the blood reflects the difference between the absorption and the elimination rates .

- Most of the time, the absorption rate constant is greater than the elimination rate constant.

- Furthermore, immediately following the administration of a dose of drug, the amount of (absorbable) drug present at the site of administration will be greater than the amount of drug in the blood.
- Consequently, the rate of absorption will be greater than the rate of elimination up to a certain time (prior to peak time).
- Then, exactly at peak time, the rate of absorption will become equal to the rate of elimination.
- Finally, the rate of absorption will become smaller than the rate of elimination (post peak time).
- This is simply the result of a continuous change in the amount of absorbable drug remaining at the site of administration and the amount of drug in the blood.
- Also, note that rate of absorption and the rate of elimination change with time (first-order process), whereas the absorption and the elimination rate constants do not change.



Atypical rectilinear profile illustrating amount of drug (X) in blood or body against time

$$\frac{dX}{dt} = K_a X_a - KX$$

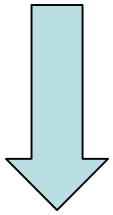
Integration of this equation will give

$$(X)_t = \frac{K_a F X_0}{K_a - K}(e^{-Kt} - e^{-K_a t})$$

where

- $(X)_t$: the amount of drug in the body at time t;
- X_0: the amount of drug at the site of administration at t = 0 (the administered dose).
- F is the absorbable fraction of drug.
- FX_0: the amount of administered dose that is available to reach the general circulation

$$(X)_t = \frac{K_a F X_0}{K_a - K}(e^{-Kt} - e^{-K_a t})$$



Divide both side by V

$$(C_p)_t = \frac{K_a F X_0}{V(K_a - K)}(e^{-Kt} - e^{-K_a t})$$

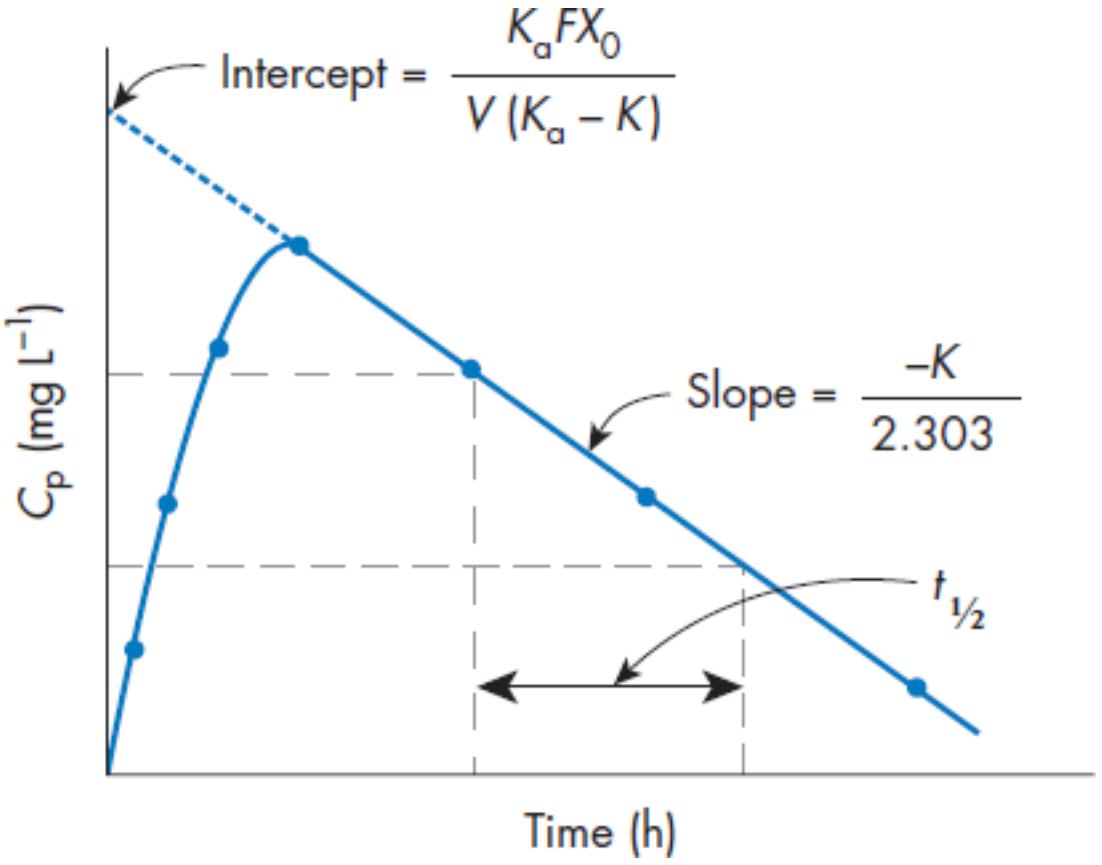
- When a long time has passed,
  - Because of the fact that Ka >> K $\Rightarrow$ e^{-Kat} approaches zero.
  - Therefore, the equation will reduce to reduce to:

$$(C_p)_t = \frac{K_a F X_0}{V(K_a - K)}(e^{-Kt})$$

  - Therefore, on a semilogarithmic paper, the intercept of plasma drug concentration versus time plot will be:

$$\frac{K_a F X_0}{V(K_a - K)}$$

- From graphical methods, the elimination half life and elimination rate constant can be obtained as described in previous chapters

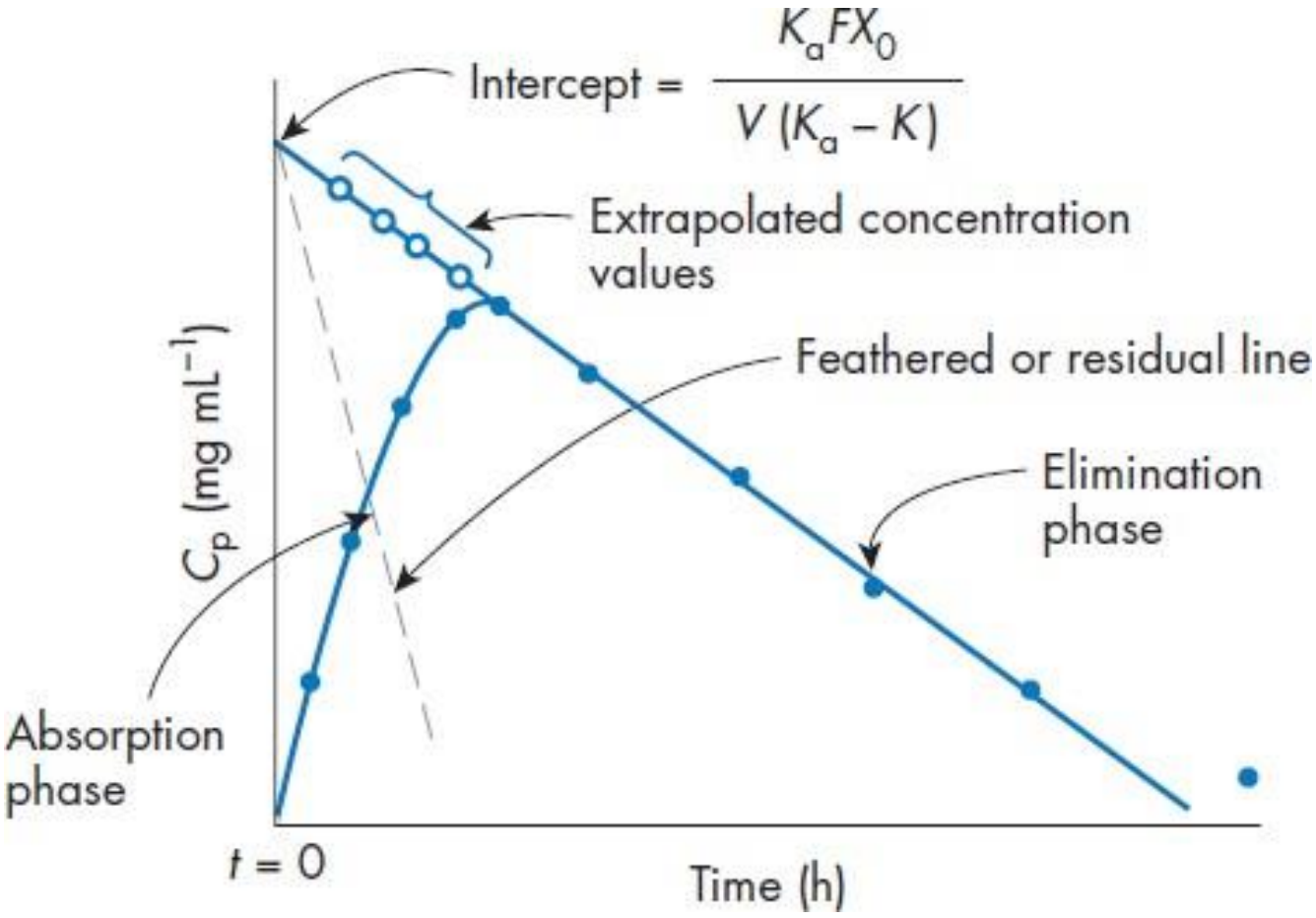


Semilogarithmic plot of plasma drug concentration (Cp) versus time of an extravascular dosage form

Determination of absorption rate constant (K_a)

- The absorption rate constant is determined by the method of residuals (feathering or curve stripping method)
- The absorption half life = 0.693/ Ka
- This method allows the separation of the monoexponential constituents of a biexponential plot of plasma concentration against time.
- In this method, we need to construct a table with headings and columns as described next page, for the purpose of determining the absorption rate constant.

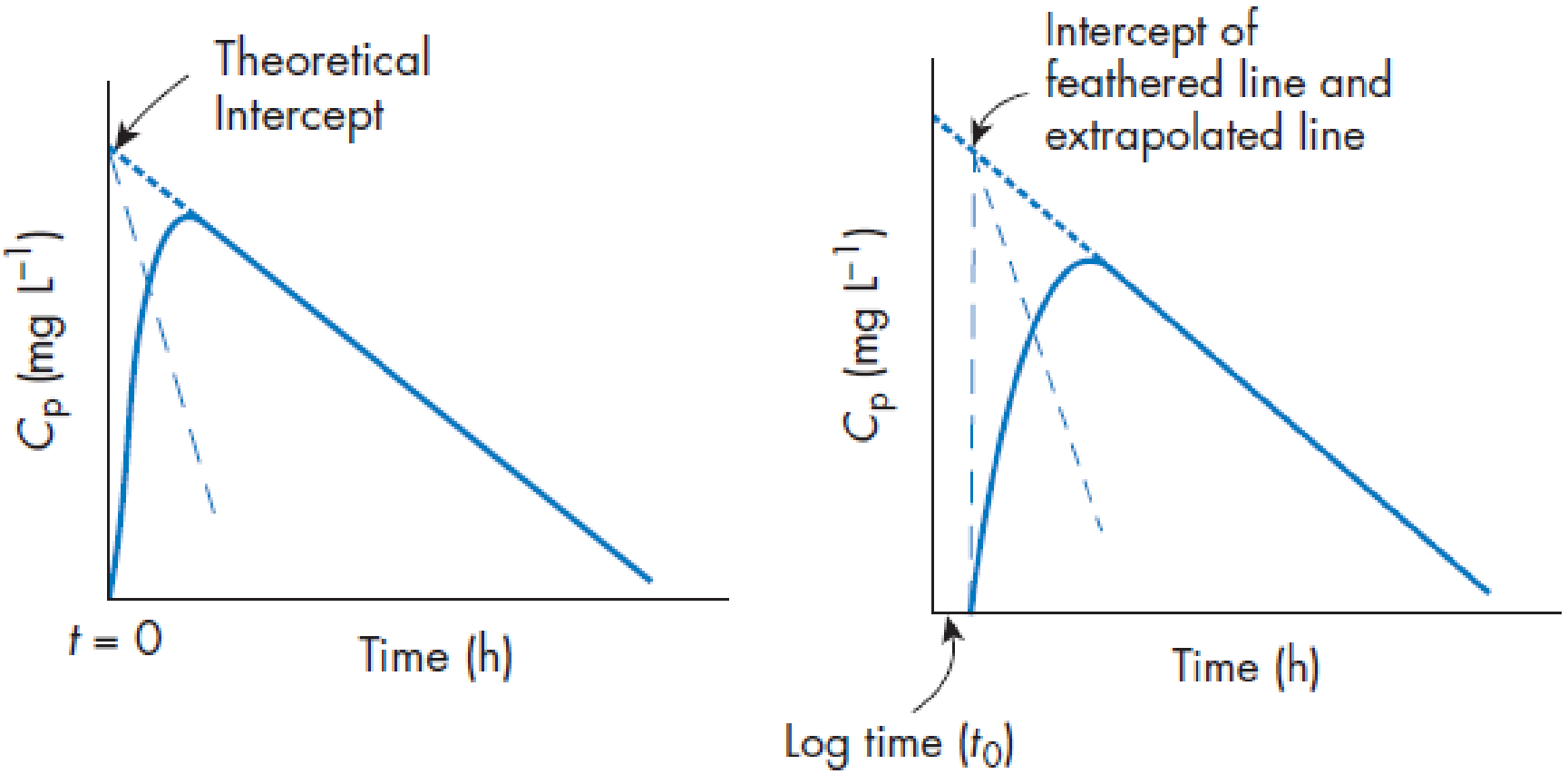
Time (h)	Observed plasma concentration $(C_p)_{obs}$	Extrapolated plasma concentrations $(C_p)_{extrap}$	$(C_p)_{diff} = (C_p)_{extrap} - (C_p)_{obs}$
Time values corresponding to observed plasma concentrations for absorption phase only	Values only from the absorption phase (i.e. all values prior to reaching maximum or highest plasma concentration)	Values only from the extrapolated portion of the plot of plasma concentration–time	Differences between extrapolated and observed values for each time in the absorption phase



Semilogarithmic plot of plasma concentration (C_p) versus time of an extravascular dosage form, showing the method of residuals.

Lag time (t_0)

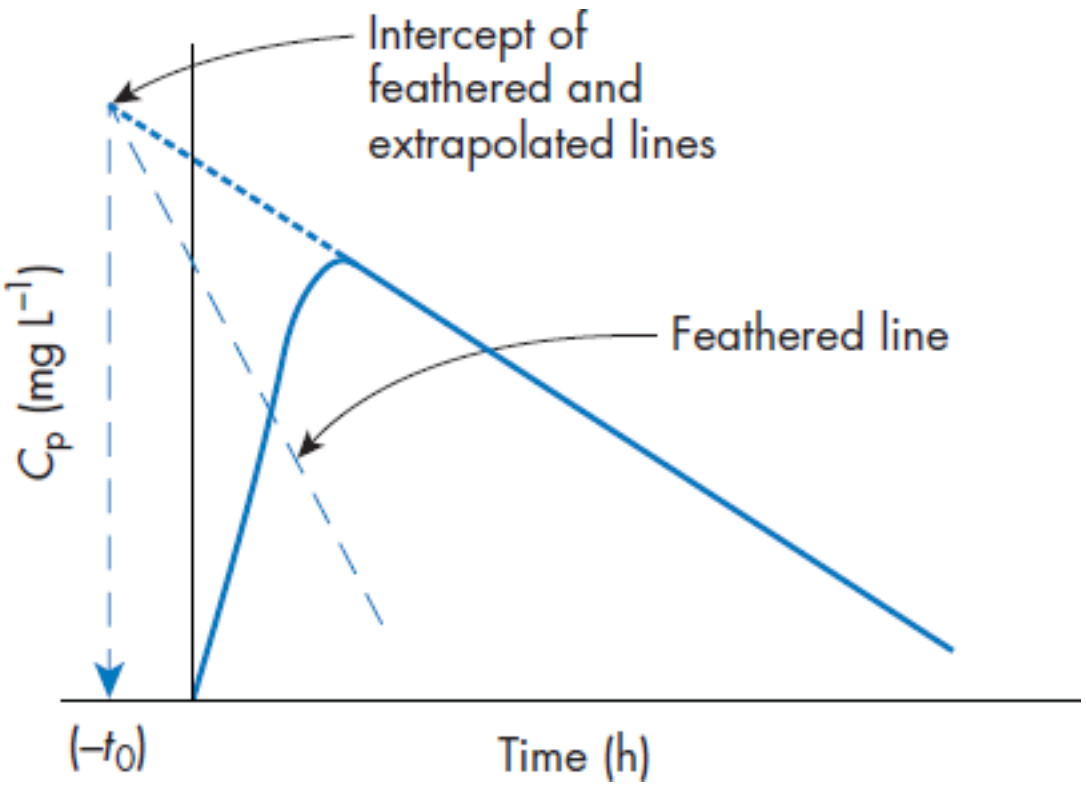
- Theoretically, intercepts of the terminal linear portion and the feathered line should be the same.
- However, sometimes, these two lines do not have the same intercepts (Figure next slide)
- A plot showing a lag time (t_0) indicates that absorption did not start immediately following the administration of drug by the oral or other extravascular route.



Semilogarithmic plots of the extrapolated plasma concentration (C_p) versus time showing the lag time (t_0).

- This delay in absorption may be attributed to some formulation-related problems, such as:
  - Slow tablet disintegration
  - Slow and/or poor drug dissolution from the dosage form
  - Incomplete wetting of drug particles (large contact angle) owing to the hydrophobic nature of the drug or the agglomeration of smaller insoluble drug particles
  - Poor formulation, affecting any of the above
  - A delayed release formulation.

Negative lag time ($-t_0$)



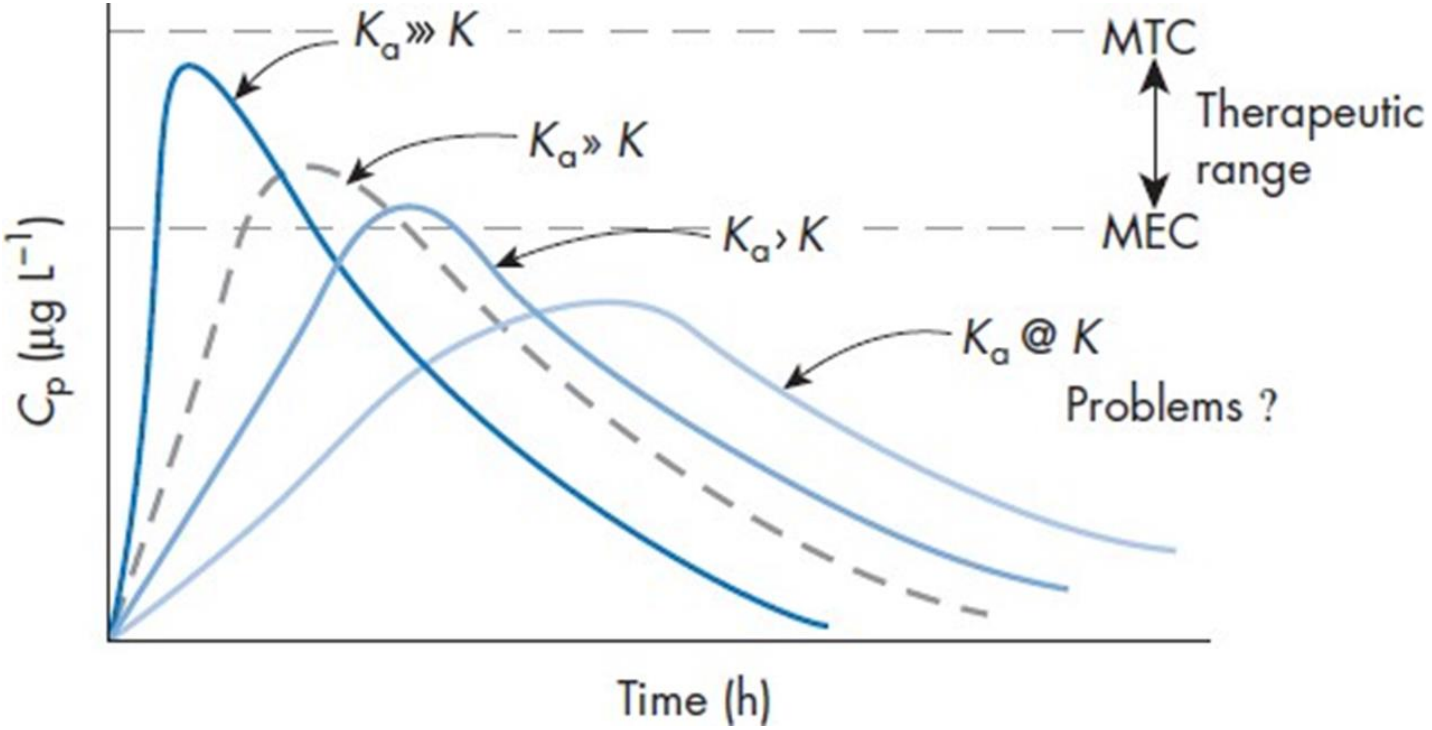
Semilogarithmic plot of plasma concentration (C_p) versus time showing a negative value for the lag time (t_0).

- What does negative lag time mean? Does it mean that absorption has begun prior to the administration of a drug?
  - That cannot be possible unless the body is producing the drug!
- The presence of a negative lag time may be attributed to a deficit (insufficiency) of data points in the absorption as well as in the elimination phase.
- Another possible reason may be that the absorption rate constant is not much greater than the elimination rate constant.

- In such cases $\Rightarrow$ the absorption rate constant obtained by the feathering, or residual, method could be erroneous
- Therefore, for under these conditions $\Rightarrow$ it is advisable to employ some other methods to determine the absorption rate constant such as:
  - Wagner and Nelson method
  - Statistical moment analysis
  - Loo–Rigelman method for a two-compartment model
- Although these methods tend to be highly mathematical and rather complex $\Rightarrow$ they do provide an <u>accurate</u> estimate of the absorption rate constant

- Why do we need an accurate estimate of the absorption rate constant?
- This will permits accurate estimation of other pharmacokinetic parameters such as:
  - Peak time
  - Peak plasma concentration
  - The assessment of bioequivalence
  - The assessment of comparative and/or relative bioavailability.

Some important comments on the absorption rate constant



- The greater the difference between the absorption and the elimination rate constants (i.e. Ka >> K) $\Rightarrow$ the faster is drug absorption and the quicker is the onset of action

- The absorption rate constant for a given drug can change as a result of:
  - Changing the formulation
  - Changing the dosage form (tablet, suspension and capsule)
  - Changing the extravascular route of drug administration (oral, intramuscular, subcutaneous, etc.).
- Administration of a drug with or without food will also influence the absorption rate constant for the same drug administered orally through the same formulation of the same dosage form.

The apparent volume of distribution

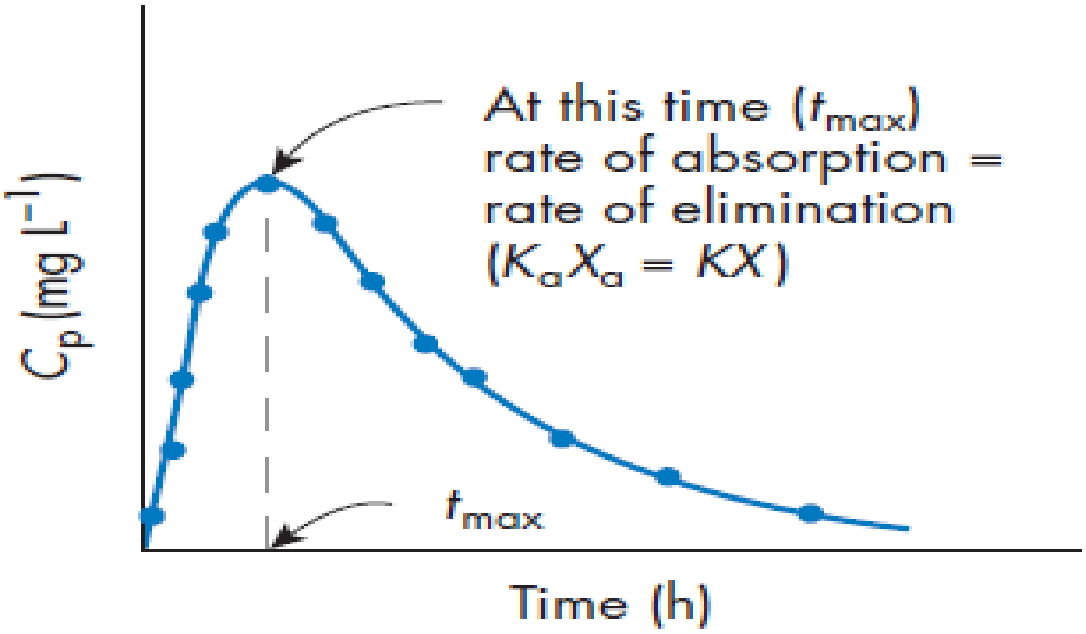
- For a drug administered by the oral, or any other extravascular route of administration $\Rightarrow$ the apparent volume of distribution cannot be calculated from plasma drug concentration data alone.
- The reason is that the value of F is not known.
- In the absence of data for the fraction of administered dose that reaches the general circulation, the best one can do is to obtain the ratio of V/F:

$$Y - \text{intercept} = \frac{K_a F X_0}{V(K_a - K)}$$

Time of maximum drug concentration, peak time (t_{max})

- The peak time (t_{max}) is the time at which the body displays the maximum plasma concentration [$(C_p)_{max}$].
- It occurs when the rate of absorption is equal to the rate of elimination (i.e. when $K_aX_a = KX$).
- It can be calculated using:

$$t_{\max} = \frac{\ln(\frac{K_a}{K})}{K_a - K}$$



- This equation indicates that peak time depends on (or is influenced) by only the absorption and elimination rate constants.
- Therefore, any factor that influences the absorption (ex : poor oral formulation) and the elimination (ex: renally impaired patient) rate constants will influence the peak time value.
- On the other hand, the peak time is always independent of the administered dose of a drug

Significance of peak time

- The peak time can be used:
  - To determine comparative bioavailability and/or bioequivalence
  - To determine the preferred route of drug administration and the desired dosage form for the patient.
  - To assess the onset of action.

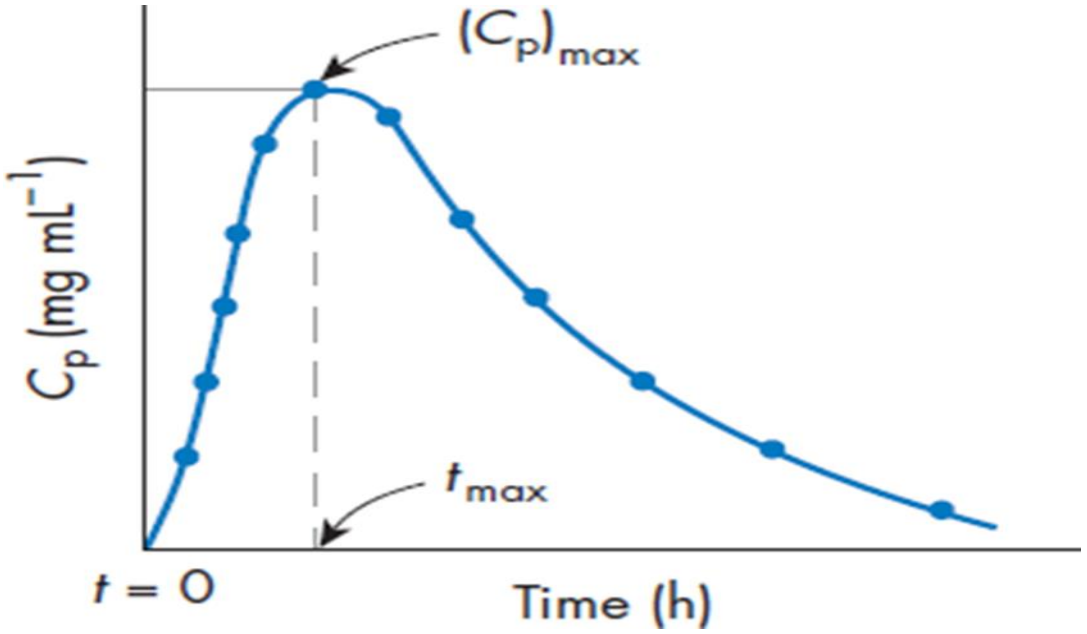
- Differences in onset and peak time may be observed as a result of
- ✓ Administration of the same drug in different dosage forms (tablet, suspension, capsules, etc.)
- ✓ Administration of the same drug in same dosage forms but different formulations

Significance of the peak plasma concentration

The peak plasma concentration $(C_p)_{max}$ occurs when time is equal to t_{max}.

- Is one of the parameters used to determine the comparative bioavailability and/or the bioequivalence between two products (same and or different dosage forms) but containing the same chemical entity or therapeutic agent
- May be used to determine the superiority between two different dosage forms or two different routes of administration.
- May correlate with the pharmacological effect of a drug.

- How to obtain the peak plasma concentration?
  - Graphically: from the graph of plasma concentration versus time
  - Using the following equation:



$$(C_p)_{\max} = \frac{K_a F X_0}{V(K_a - K)} (e^{-Kt_{\max}} - e^{-K_a t_{\max}})$$

General comments

1. The elimination rate constant, the elimination half life and the apparent volume of distribution are constant for a particular drug administered to a particular patient, regardless of the route of administration and the dose administered.

2. It is a common practice to use values of the elimination rate constant, the elimination half life and the apparent volume of distribution obtained from intravenous bolus or infusion data to compute parameters associated with extravascular administration of a drug.

3. The absorption rate constant and the fraction absorbed is a constant for a given drug formulation, dosage form and route of administration. That is, the same drug is likely to have a different absorption rate constant if it is reformulated, if the dosage form is changed and/or if administered by a different extravascular route.

Therefore, if the same dose of the same drug is given to the same subject via different dosage forms, different routes of administration or different formulations $\Rightarrow$ it may yield different peak times, peak plasma concentrations and the area under the plasma concentration–time curve (AUC).

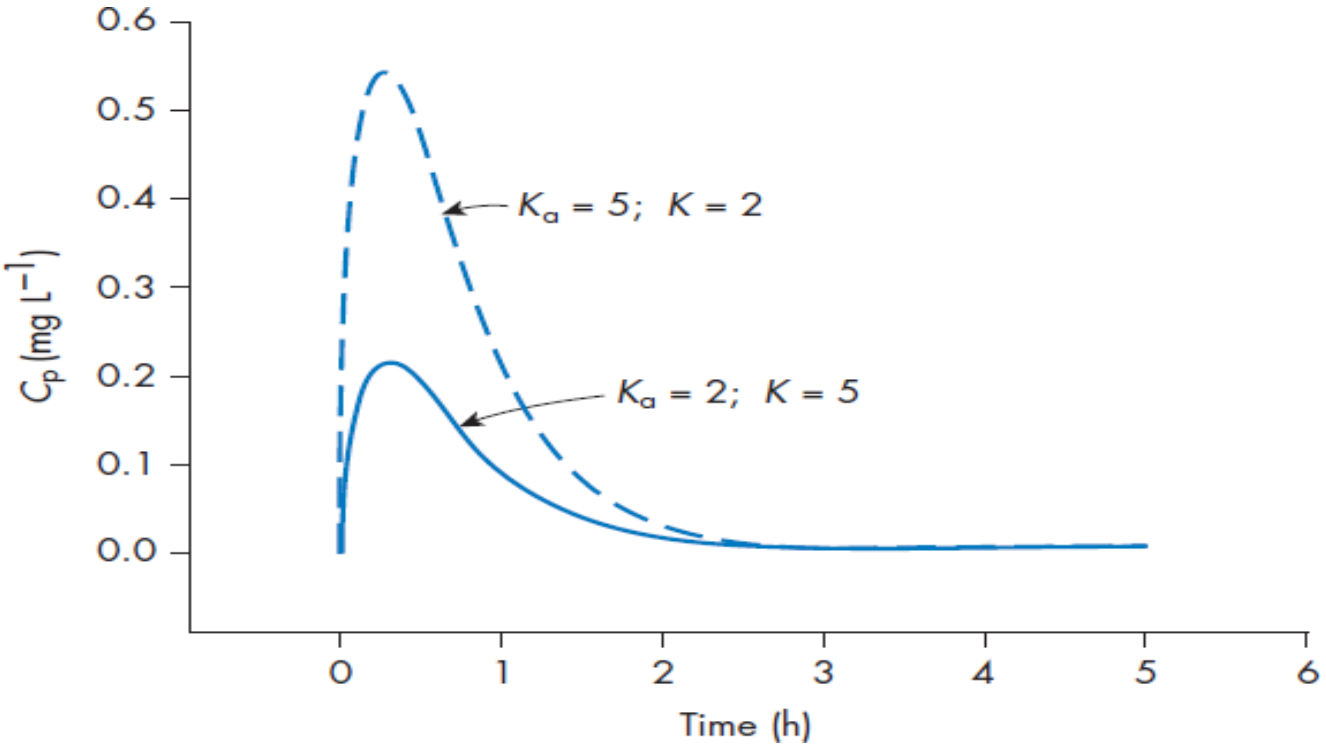
- Peak time characterizes the rate of drug absorption
- AUC characterizes the extent of drug absorption.
- Peak plasma concentration, however, may reflect either or both of these factors.

Flip-flop kinetics

- For a drug absorbed by a slow first-order process, such as depot injection , certain types of sustained release formulations, and dermal administration, the situation may arise where the elimination rate constant is greater than the absorption rate constant (K > Ka).

- For orally or extravascularly administered drugs, generally Ka >> K; therefore, the rising portion of the graph denotes the absorption phase. If K >> Ka (perhaps indicating a dissolution rate - limited absorption) the exact opposite will hold true

- Since the terminal linear slope of plasma drug concentration versus time plotted on semilogarithmic co-ordinates always represents the slower process and related to the absorption rate constant. The slope of the feathered line will be related to the elimination rate constant.



Comparison of a regular (– – –) and a flip-flop (—) oral absorption model.

The flip-flop graph has

A smaller AUC than the normal graph

A smaller (Cp)max than the normal graph.

However, both the regular and flip-flop curves have the same shape and the same tmax

Question

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.

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

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