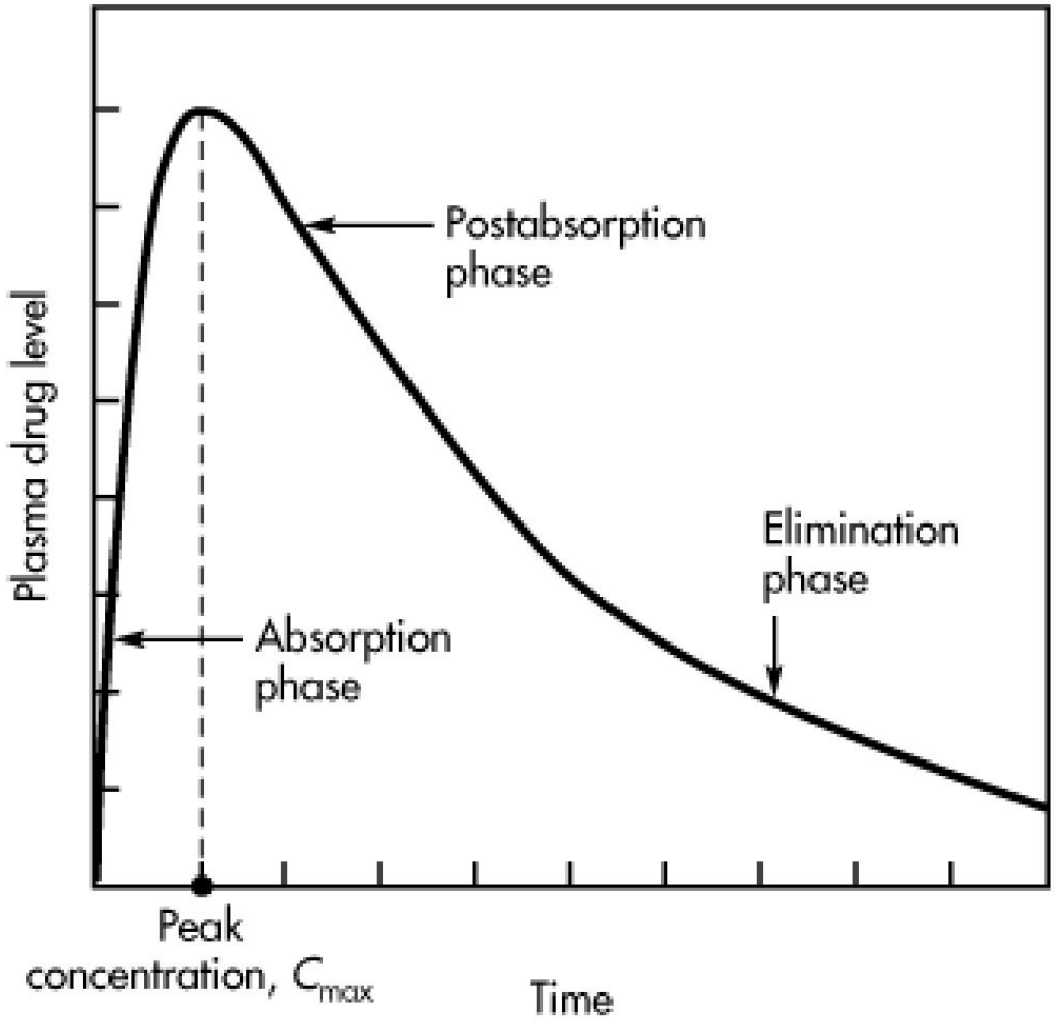
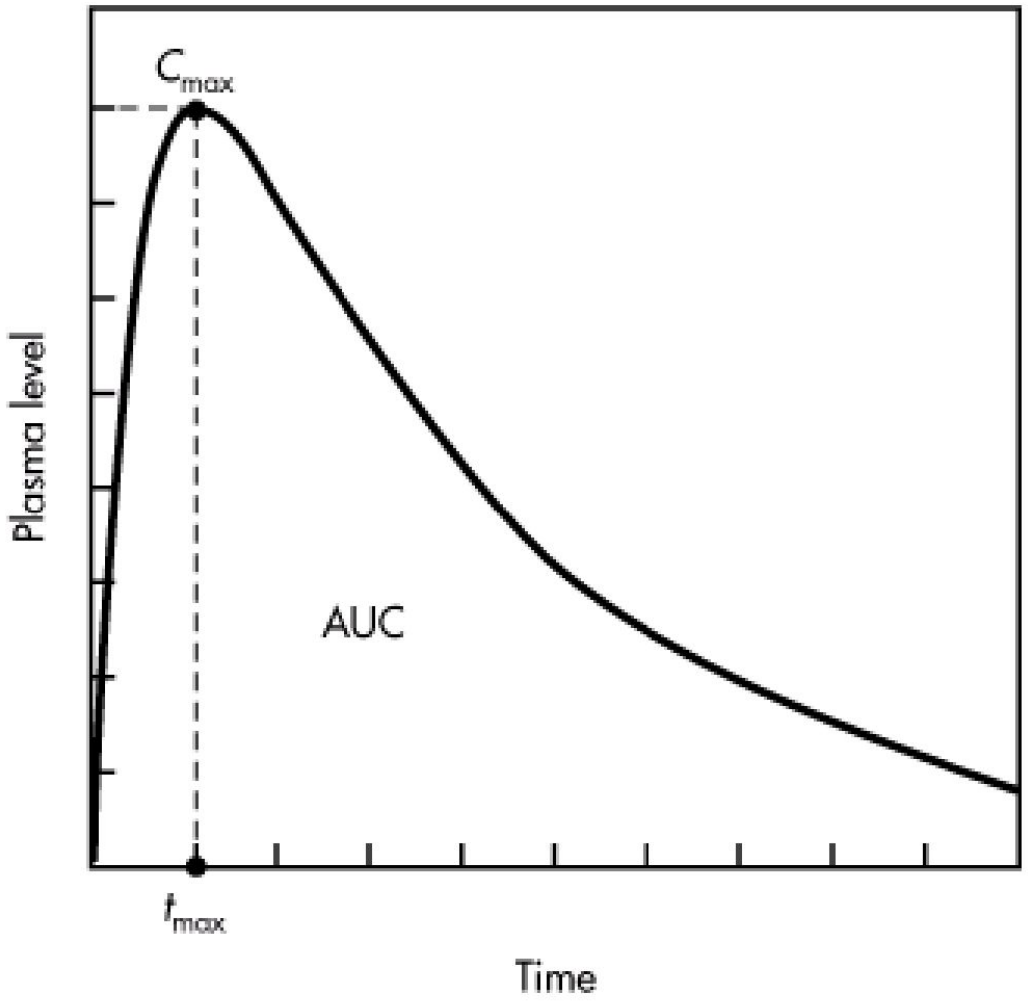
Pharmacokinetics of Drug Absorption

Oral absorption



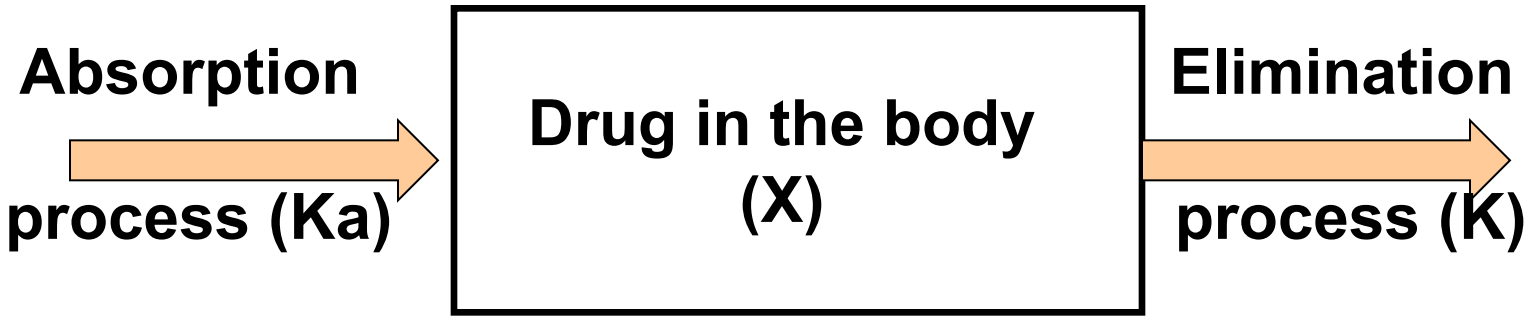
- **Absorption phase:** absorption rate more than elimination rate
- **Postabsorption phase:** elimination rate more than absorption rate
- **Elimination phase:** no significant absorption occur (only elimination process)

Oral absorption



- The t_{max} is independent of dose and is dependent on the rate constants for absorption (*k*a) and elimination (*k*)
- At C_{max}, sometimes called *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
- AUC is a measure of the body's exposure to a drug

One-compartment pharmacokinetic model for first-order drug absorption and first-order drug elimination



$$\frac{dX}{dt} = KaXa - KX$$

X: drug amount in the body, **Xa**: drug amount in the GI available for absorption, **K**: elimination rate constant, and **Ka**: absorption rate constant

Mathematical model

- Assuming first-order absorption and first-order elimination, the amount of drug (*X*) in the body is described by:

$$Cp = \frac{KaFXo}{Vd(Ka - K)}\left[e^{-Kt} - e^{-Kat}\right]$$

Determination of the Model Parameters

- K
- Elimination half life
- Ka
- Absorption half life
- t_{max} and C_{max}
- Clearance
- Volume of distribution
- AUC

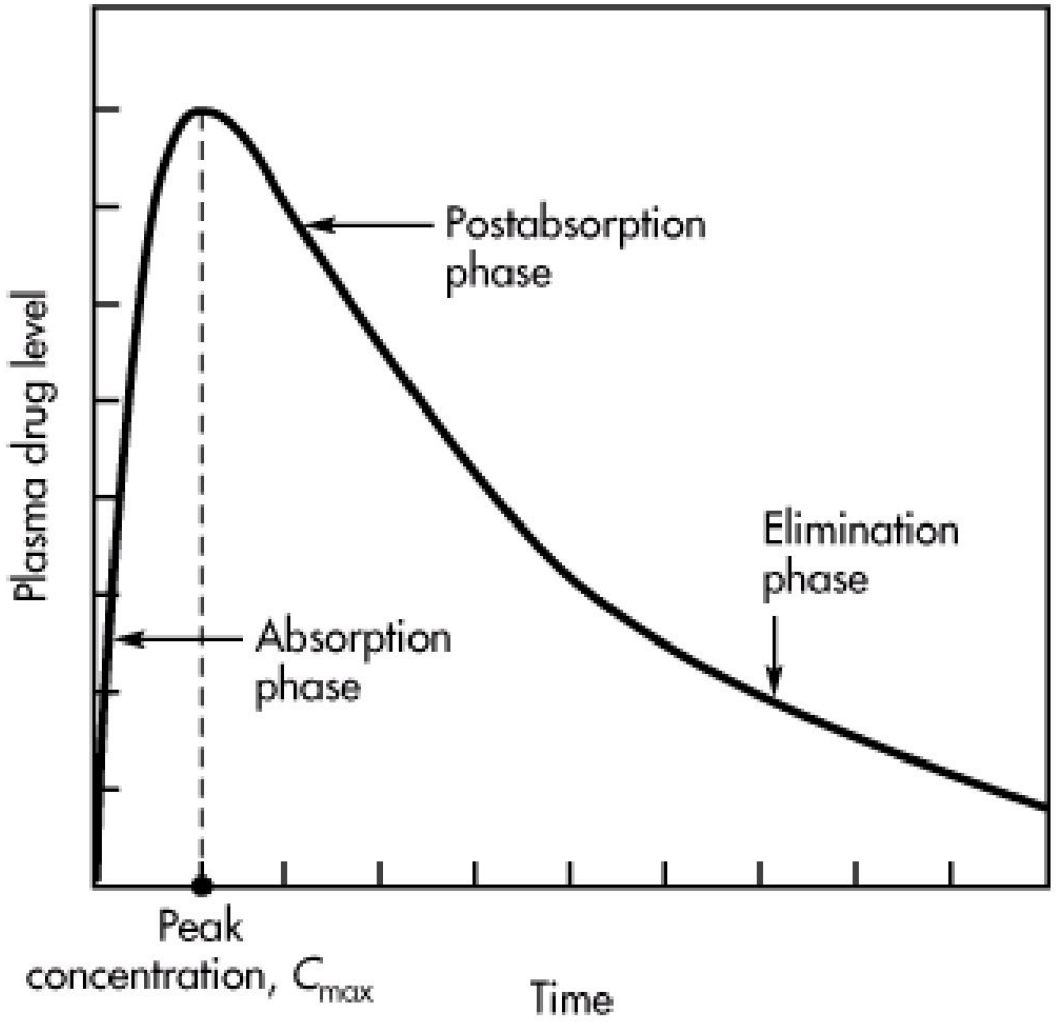
Oral absorption

$$Cp = \frac{KaFXo}{Vd(Ka - K)}\left[e^{-Kt} - e^{-Kat}\right]$$

This portion measure the elimination process

This portion measure the absorption process

Terminal phase (elimination)



- **Because in the Elimination phase** no significant absorption occur (only elimination process), the plasma concentration equation can be simplified into:

$$Cp = \frac{KaFXo}{Vd(Ka-K)}\left[e^{-Kt}\right]$$

method of residuals

- The method of residuals is a graphical method used to determine the drug absorption rate constant and has the following assumptions:
  - The absorption rate constant is larger than the elimination rate constant ,that is, Ka>K.
  - Both drug absorption and elimination follow first-order kinetics
  - The drug pharmacokinetics follow one-compartment model

- The idea of the method of residuals is to characterize the drug elimination rate from the terminal elimination phase of the plasma drug concentration—time profile after a single oral administration. Then the contribution of the drug absorption rate and the drug elimination rate during the absorption phase can be separated

method of residuals

1. The plasma drug concentration is plotted against their corresponding time values on the semi-log scale

2. The slope of the line that represents the elimination phase is calculated. The slope of this line is equal to –k/2.303. The terminal line is back extrapolated to the y-axis

3. At least three Points on the extrapolated line at three different time values during the **absorption Phase** of the drug are taken. Vertical lines from the points on the extrapolated line are dropped to determine the corresponding points (at the same time values) on the plasma drug concentration-time curve

4. The differences between the y-coordinate values of the points on the extrapolated line and corresponding y-coordinate values on the plasma drug concentration-time curve are calculated. The values of these differences are the residuals

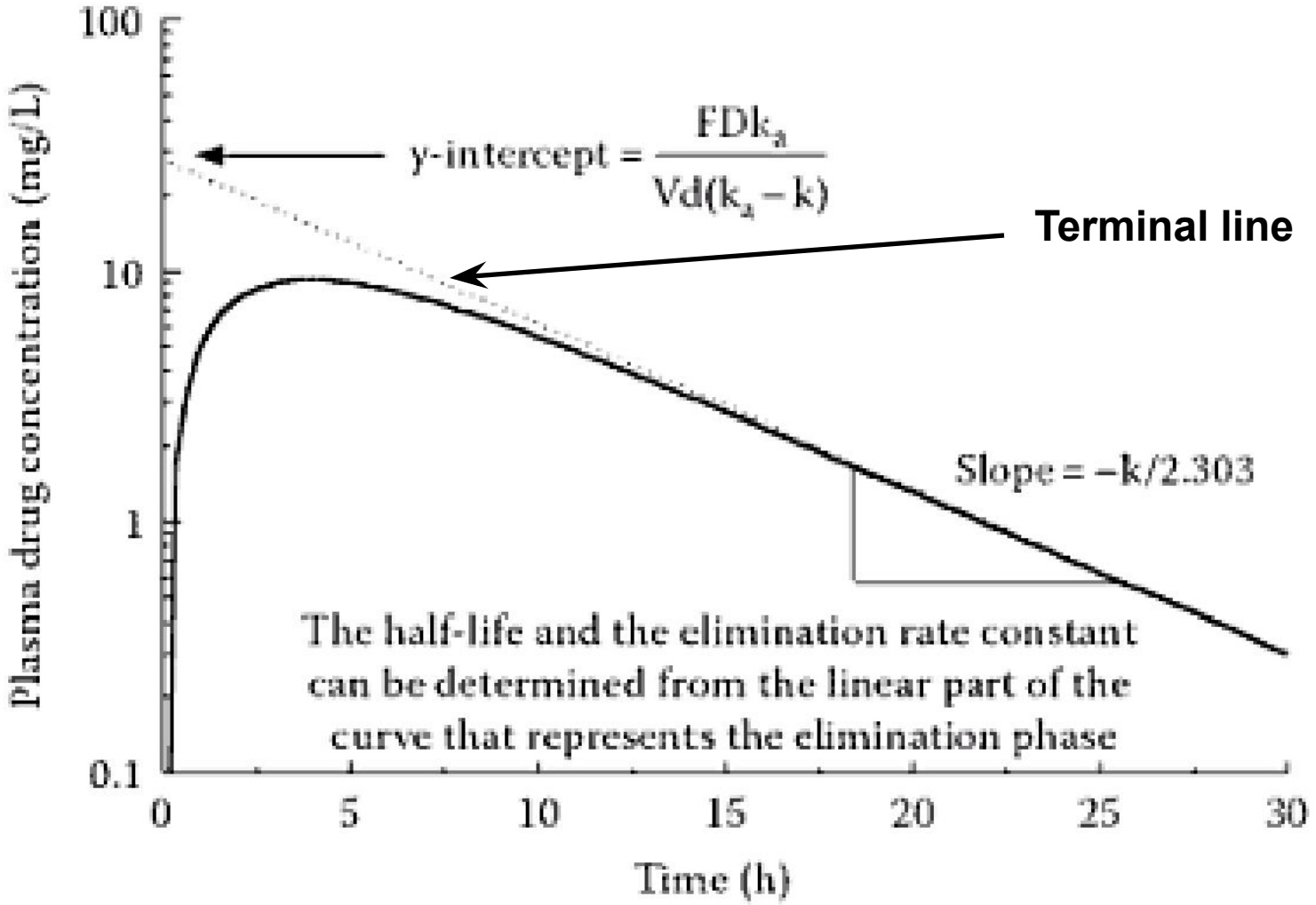
Method of residuals

- The values of the residuals are plotted versus their corresponding time values for each residual on the same graph. A straight line should be obtained with a slope of -ka/2.303.

- The extrapolated line representing the elimination phase and the residuals versus time line should have the same y-intercept. This is because the equations that describe the two lines have the same coefficient, so substituting time by zero in the two equations should give the same term.

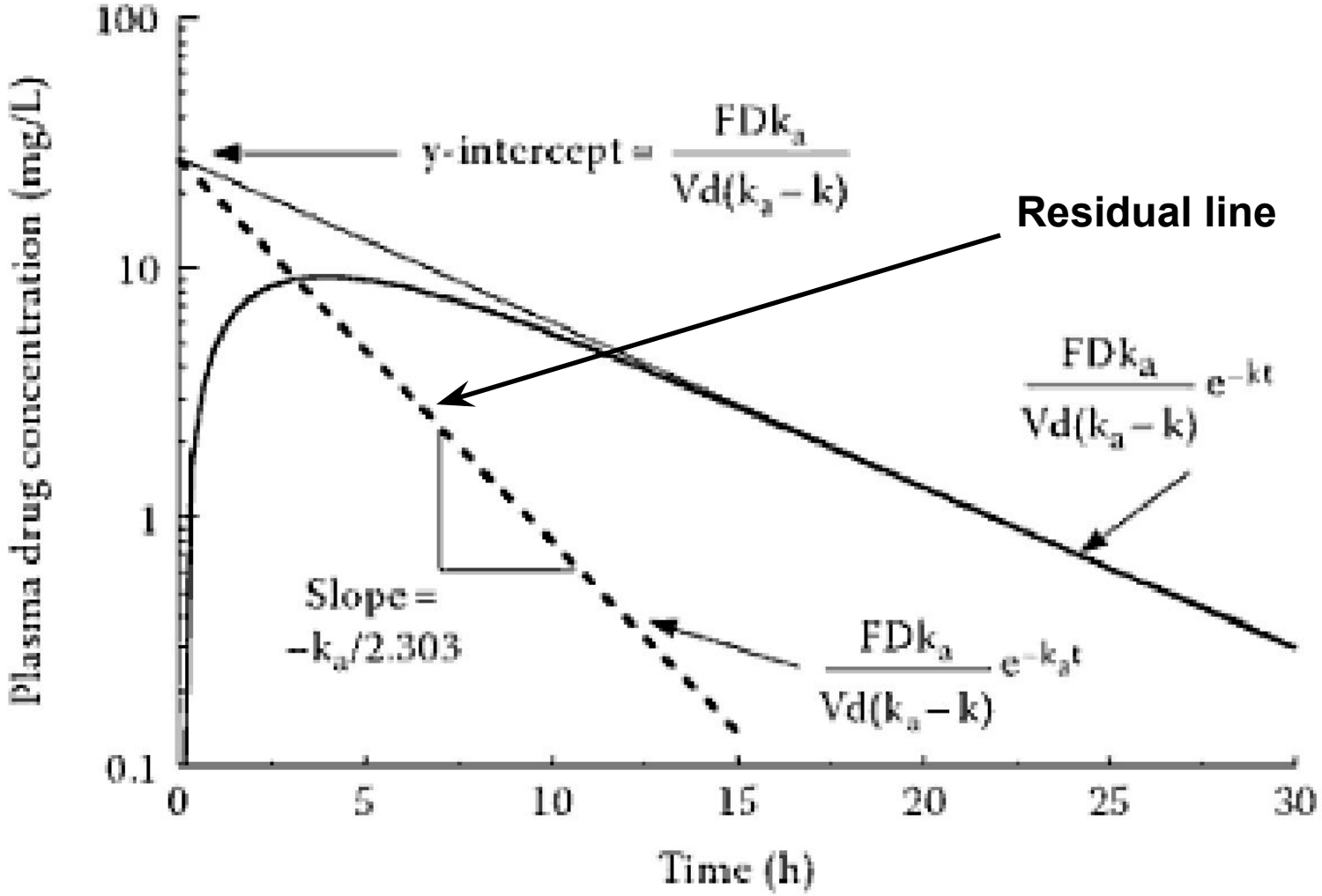
Method of residuals

1- From the terminal phase determine the elimination rate constant



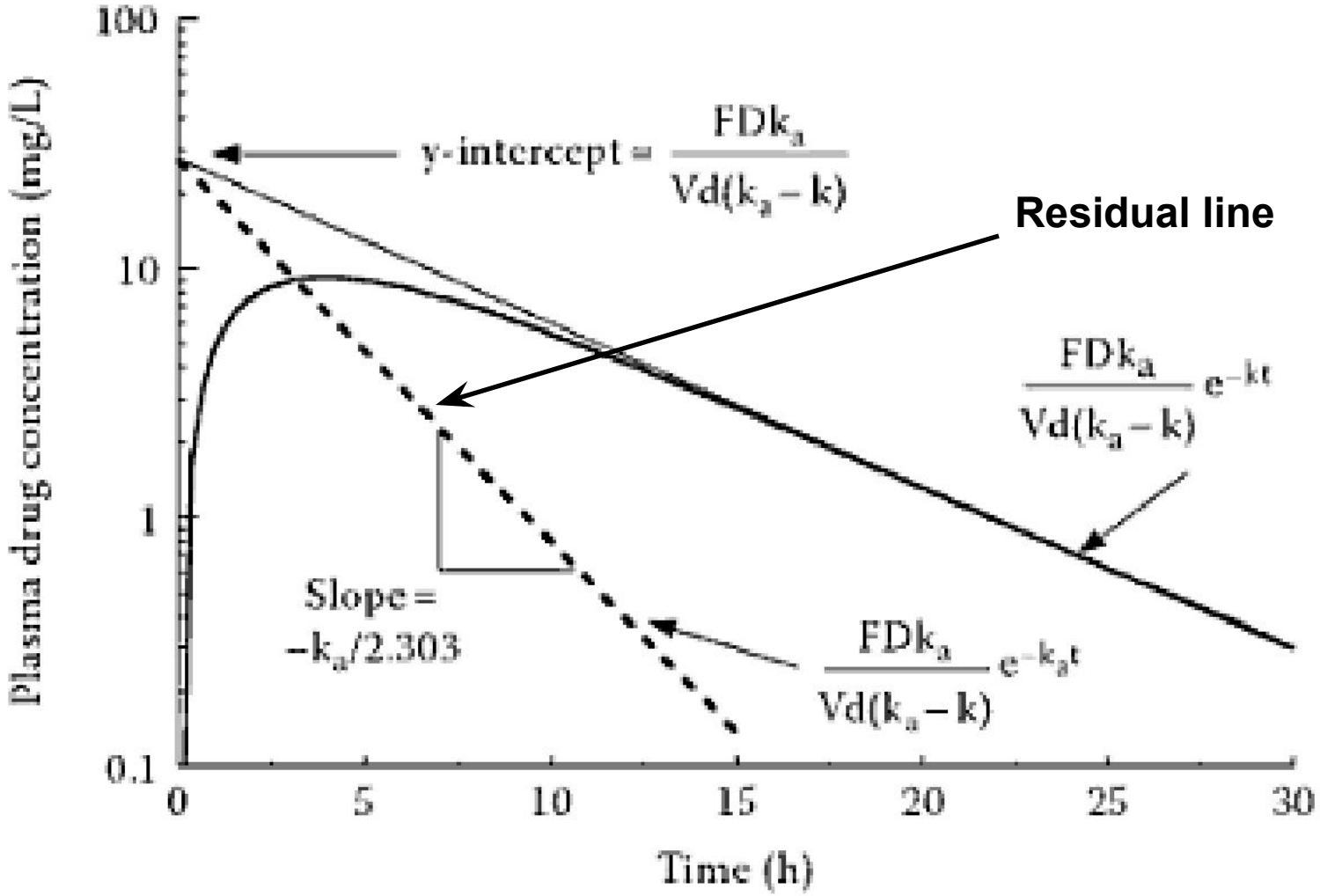
Method of residuals

2- Construct the residual line by taking the difference between the terminal line and the observed conc.



Method of residuals

3- Estimate the absorption rate constant from the slope of the residual line



Determination of the Model Parameters

- Elimination half life = 0.693/K
- Absorption half life = 0.693/Ka
- t_{max} (or t_p):

$$t_{\max} = \frac{2.303}{(Ka - K)} \log \frac{Ka}{K}$$

- C_{max} (Conc at t = t_{max})

$$C_{\max} = \frac{KaFXo}{Vd(Ka - K)} \left[e^{-Kt_{\max}} - e^{-Kat_{\max}} \right]$$

Determination of the Model Parameters

- Clearance

$$Cl = \frac{FXo}{AUC}$$

- Volume of distribution

$$Vd = \frac{FXo}{K.AUC}$$

- AUC

$$AUC = \frac{FXo}{KVd}$$

Normal kinetics vs. Flip-flop kinetics

- In a series of two consecutive, irreversible first-order rate processes such as absorption of a drug from the intestine and its subsequent systemic elimination, either step can be rate-limiting in the overall elimination process

- In general, ka of a drug after oral administration is greater than k so that elimination of the drug from the body after oral administration is governed primarily by how fast it can be removed once it enters the systemic circulation

- In this case (e.g., ka > k), a plasma concentration-time profile after oral dosing exhibits a terminal half-life similar to that after intravenous injection

Normal kinetics vs. Flip-flop kinetics

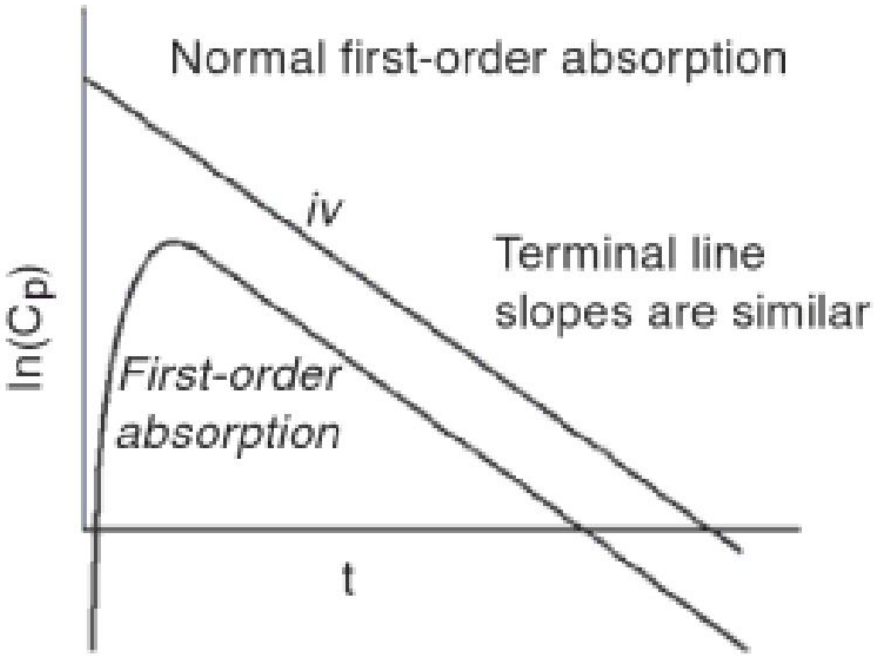
- When ka is much smaller than k (e.g., k > ka) , drug disappearance from the body becomes governed by the rate of absorption rather than by the rate of elimination, and absorption $t_{1/2}$ becomes longer than elimination $t_{1/2}$. This phenomenon is called “flip-flop kinetics”

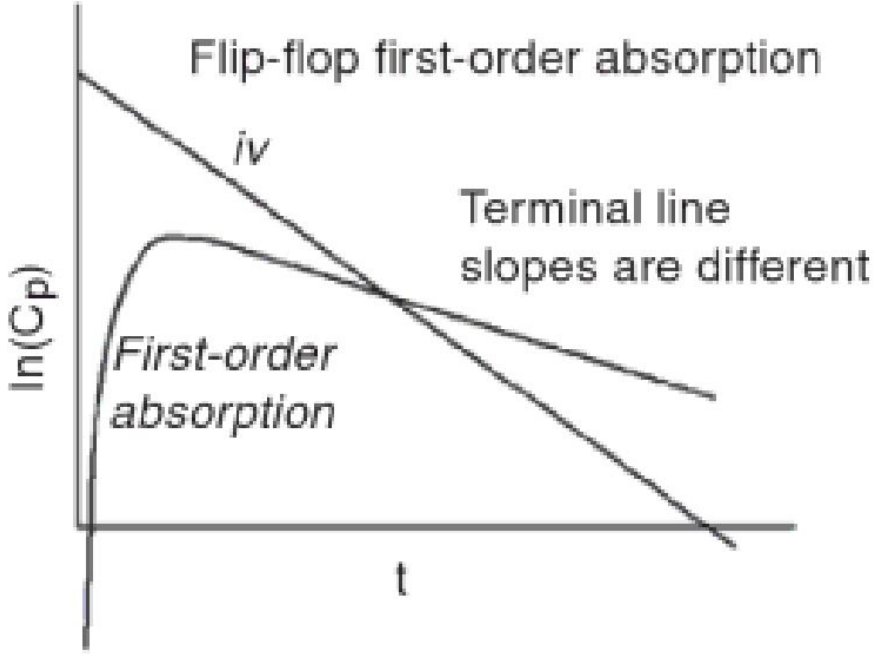
Summary

Ka > K: Normal Kinetics (the slope of the terminal phase represent K)

K > Ka: Flip-Flop Kinetics (the slope of the terminal phase represent Ka)

Distinguishing between Normal and Flip-Flop kinetics

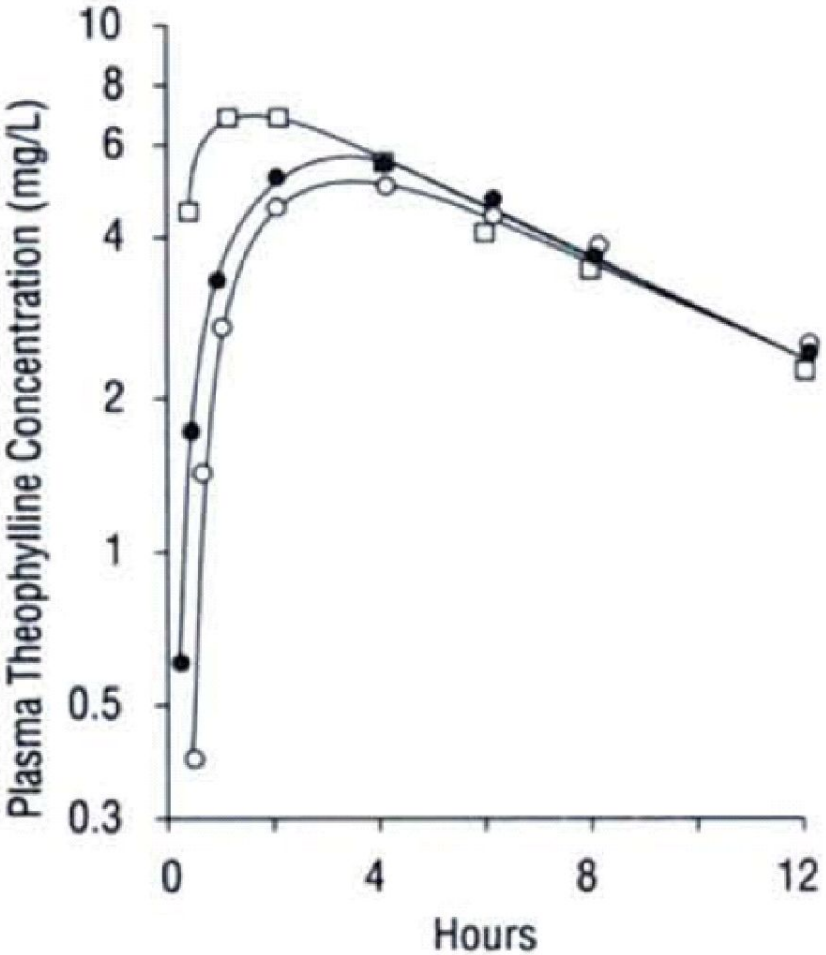




IV bolus data is needed to differentiate between Normal and Flip-Flop kinetics

Normal Kinetics example

Difference observed in the absorption phase Normal kinetics



Theophylline conc-time profile resulting from the administration of two 130 mg tablets:

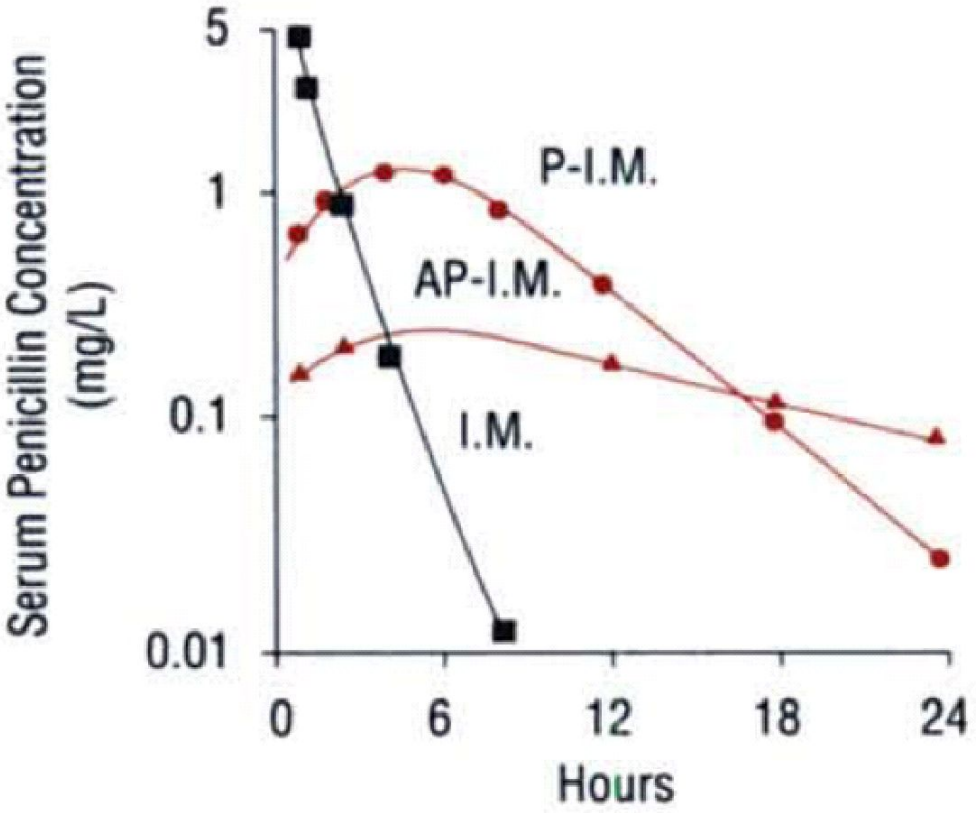
Dissolved in 500 mL water and taken on an empty stomach

Taken on an empty stomach

Taken after meal

Flip-Flop kinetics example

Difference observed in the terminal phase Flip-flop kinetics



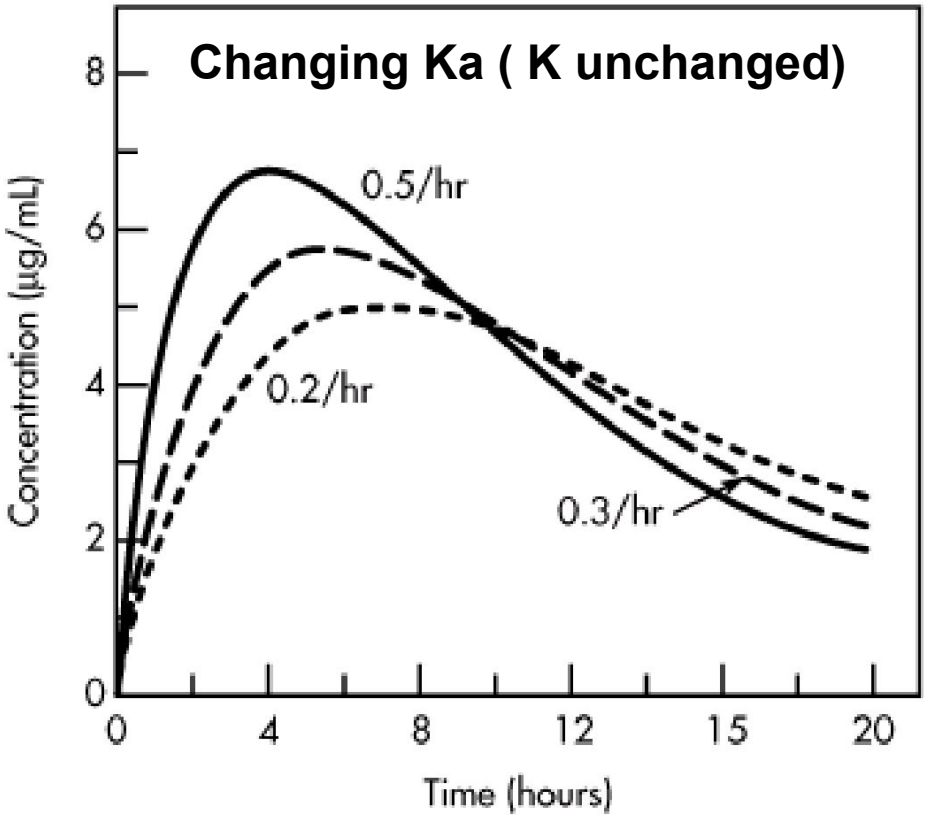
Penicillin G was adminstgered IM as an:

Aqueous solution (I.M)

Procaine penicillin in oil (P-I.M)

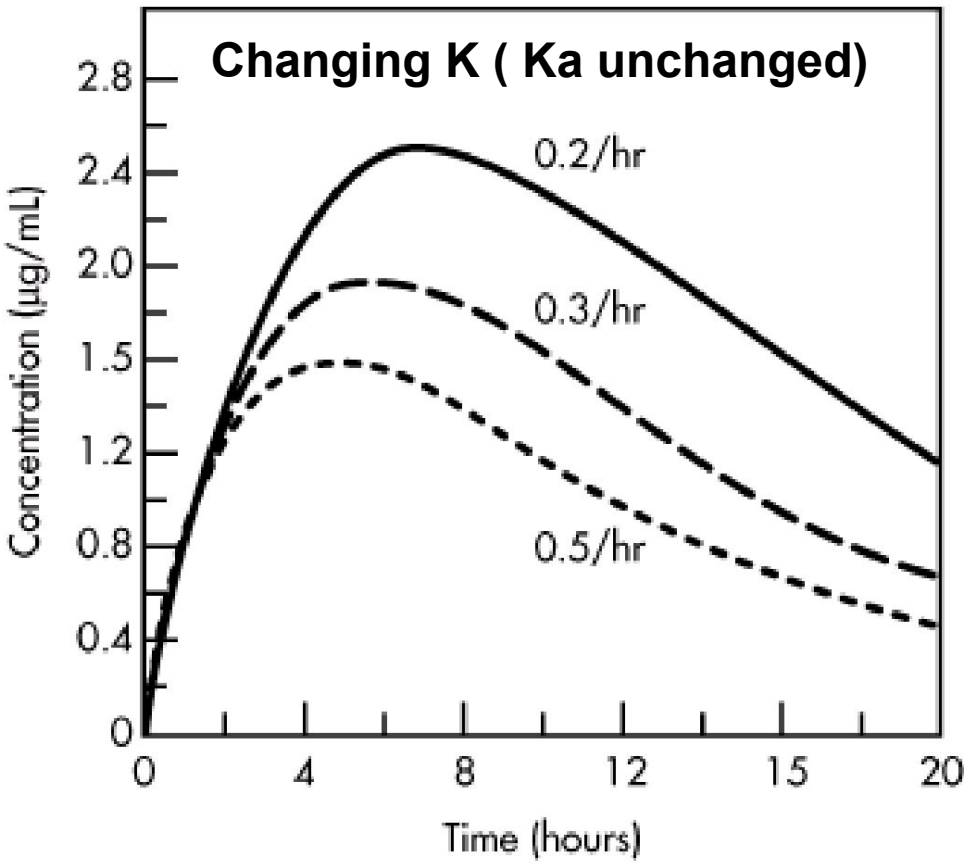
Procaine penicillin in oil with aluminum monostearate (AP-I.M)

Effect of Ka on t_{max}, C_{max}, and AUC



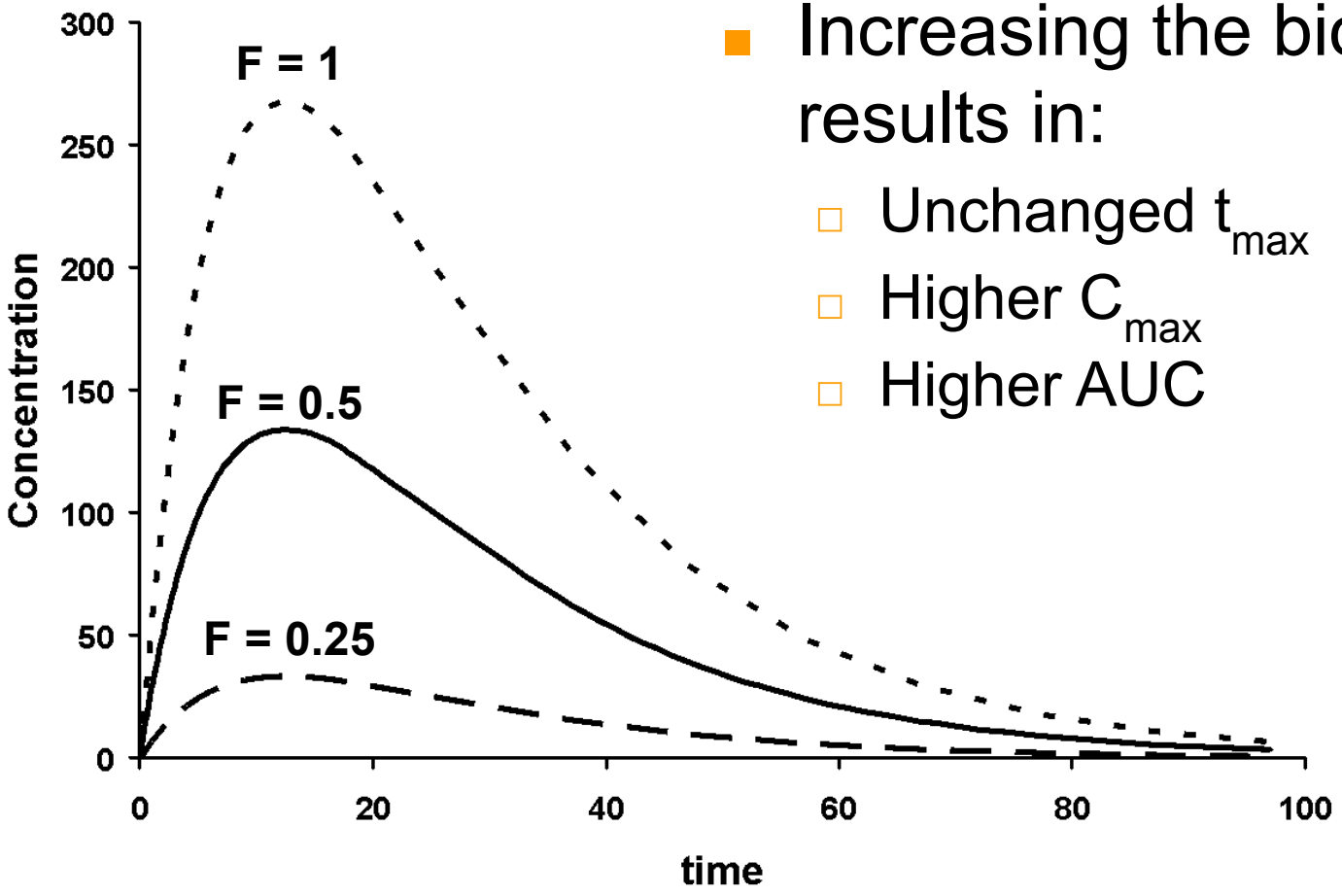
- Increasing the absorption rate constant (Ka) results in:
  - Shorter t_{max}
  - Higher C_{max}
  - Unchanged AUC

Effect of K on t_{max}, C_{max}, and AUC



- Increasing the elimination rate constant (K) results in:
  - Shorter t_{max}
  - Lower C_{max}
  - Lower AUC

Effect F on t_{max}, C_{max}, and AUC



- Increasing the bioavailability results in:
  - Unchanged t_{max}
  - Higher C_{max}
  - Higher AUC

Bioavailability

- Systemic absorption is often incomplete when given extravascularly
- Knowing the extent of absorption (bioavailability) helps to en-sure that the correct dose is given extravascularly to achieve a therapeutic systemic expo-sure
- Although dose is known and area can be determined following an extravascular dose, clearance is needed to estimate bioavailability

Bioavailability

- To determine clearance, a drug must be given intravascularly, as only then is the amount entering the systemic circulation known (the dose, F =1):

$$Dose_{IV} = Cl \cdot AUC_{IV}$$

- After an oral dose:

$$F \cdot Dose_{oral} = Cl \cdot AUC_{oral}$$

- Given that Clearance is unchanged, F is estimated by:

$$F \cdot = \frac{AUC_{oral}}{AUC_{IV}} \cdot \frac{Dose_{IV}}{Dose_{oral}}$$

Bioavailability

- If the IV and oral doses were equal, F can be calculated according to:

$$F \cdot = \frac{AUC_{oral}}{AUC_{IV}}$$

Example 1

- A 500-mg dose of the sulfonamide sulfamethoxazole is administered as an oral tablet to a human subject. Eighty percent of the drug is absorbed, and the balance is excreted unchanged in feces. The drug distributes into an apparently homogeneous body volume of 12 L, and has an absorption half-life of 15 min and overall elimination half-life of 12 h.

1) Calculate the following:
(i) AUC0→∞,(ii) tmax and (iii) C max.

2) Recalculate the values in Problem 1 if all parameter values remained unchanged, but the elimination half-life was increased to 18 h.

Example 1

- Estimate k and ka:

$$k = 0.693 / t_{1/2}^{elimin} = 0.693/12 = 0.058\ hr^{-1}$$

$$k_a = 0.693 / t_{1/2}^{abs} = 0.693/15 = 0.046\ hr^{-1}$$

- Estimate AUC:

$$AUC = \frac{FXo}{KVd} = \frac{0.8 * 500}{0.058*12} = 575\ mg \cdot hr/L$$

Example 1

- Estimate t_{max}:

$$t_{\max} = \frac{2.303}{(Ka - K)} \log \frac{Ka}{K}$$

$$= \frac{2.303}{(0.046 - 0.058)} \log \frac{0.046}{0.058} = 19.32 \ hr$$

Example 1

- Estimate C_{max}:

$$C_{\max} = \frac{KaFXo}{Vd(Ka-K)}\left[e^{-Kt_{\max}} - e^{-Kat_{\max}}\right]$$

$$C_{\max} = \frac{0.046*0.8*500}{12(0.046-0.058)}\left[e^{-0.058*19.32} - e^{-0.046*19.32}\right]$$

$$C_{\max} = 10.9\ mg/L$$

Example 1

Recalculate the values in Problem 1 if all parameter values remained unchanged, but the elimination half-life was increased to 18 h

$$k = 0.039\ hr^{-1}$$

$$t_{\max} = 23.5\ hr$$

$$AUC = 855\ mg \cdot hr/L$$

$$C_{\max} = 13.3\ mg/L$$

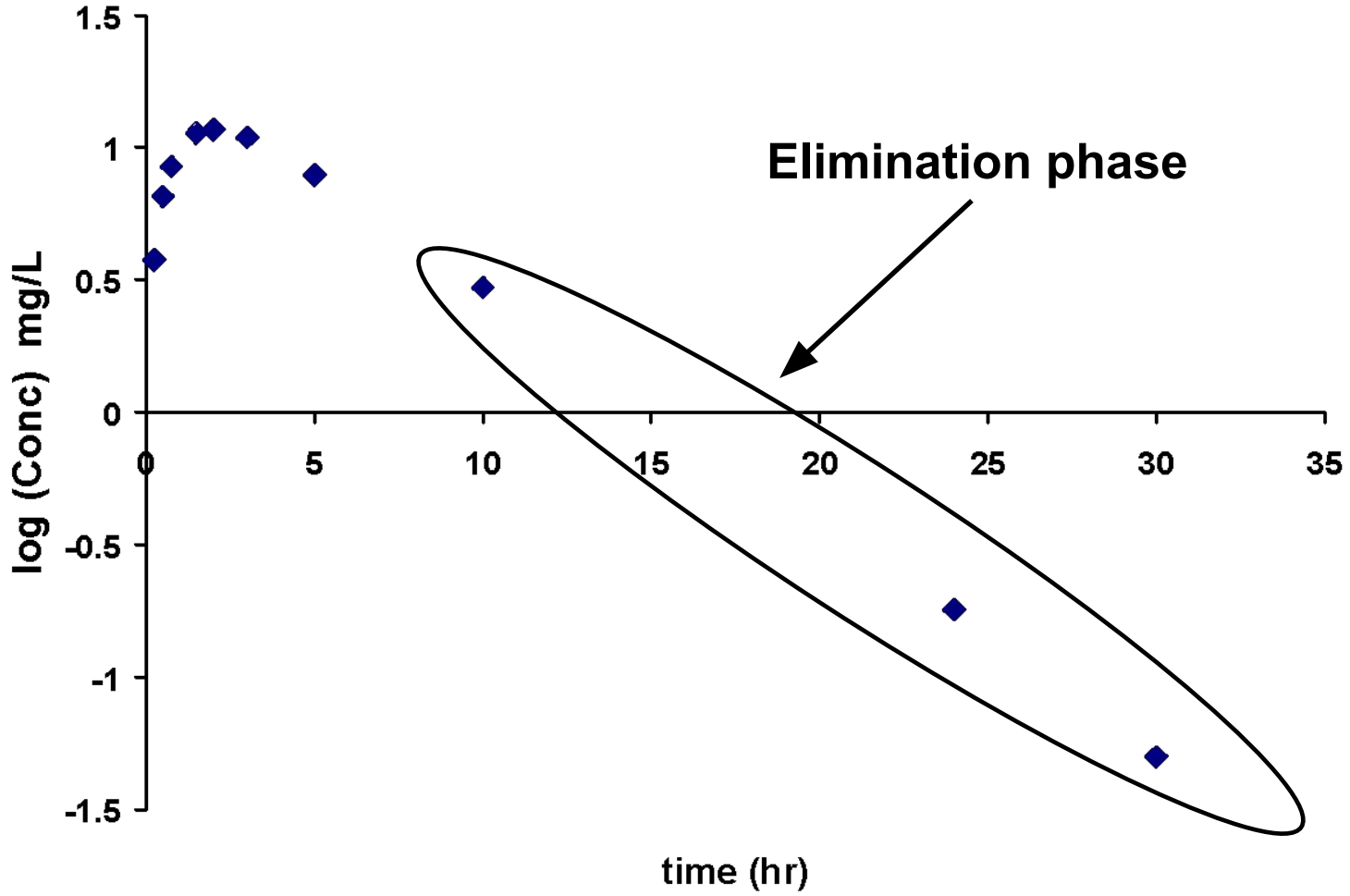
Example 2

- The presented table gives the plasma drug concentrations that were obtained following the oral administration of 500 mg dose of drug X. Assuming that drug X follows normal pharmacokinetics, determine the following:
  - Elimination rate constant
  - Absorption rate constant
  - Volume of distribution (normalized for bioavailability)
  - Bioavailability

Time (hr)	Conc (mg/L)
0.25	3.77
0.5	6.53
0.75	8.49
1.5	11.32
2	11.7
3	10.92
10	2.96
24	0.18
30	0.05

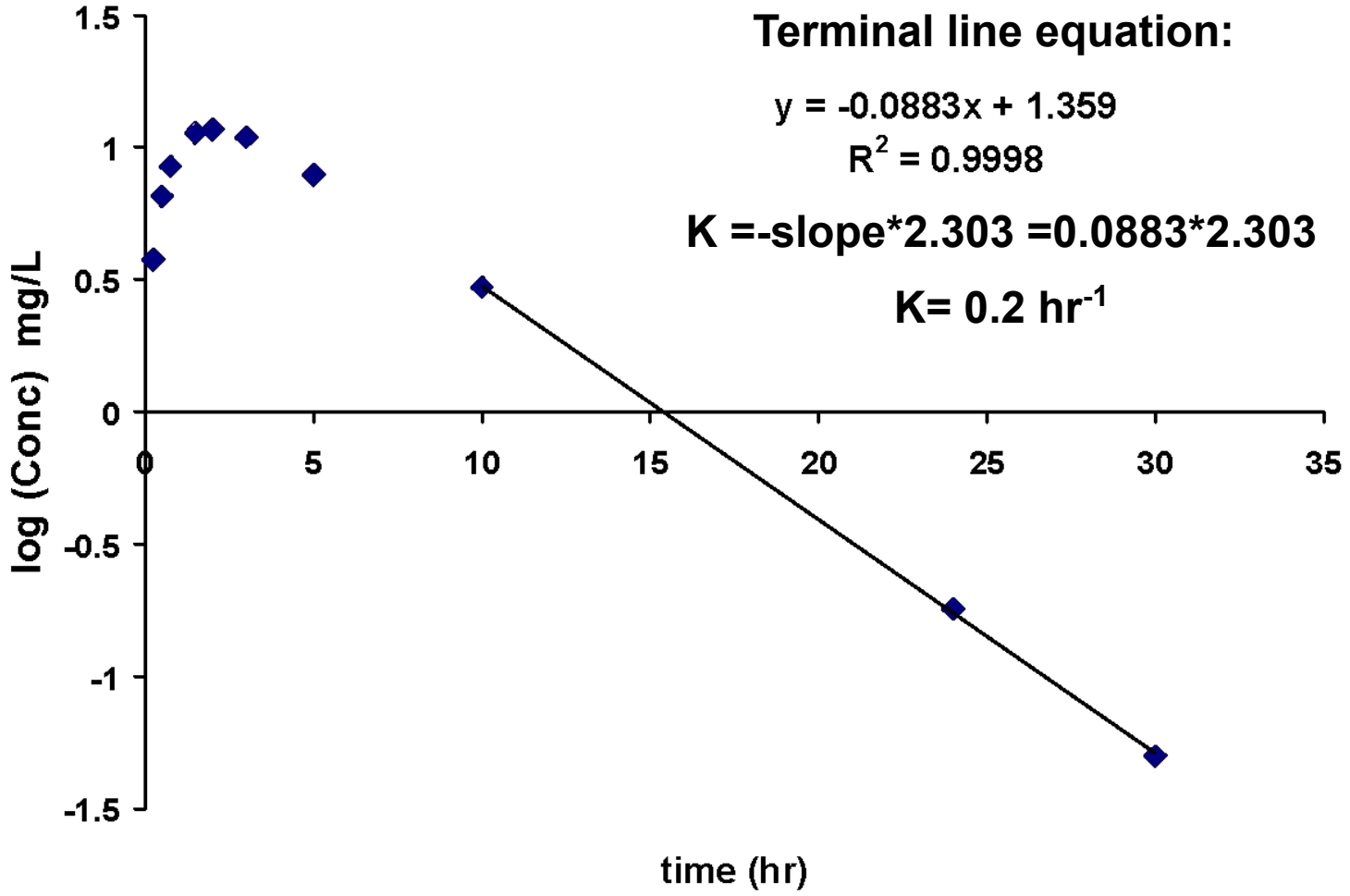
Example 2:

Determine elimination phase



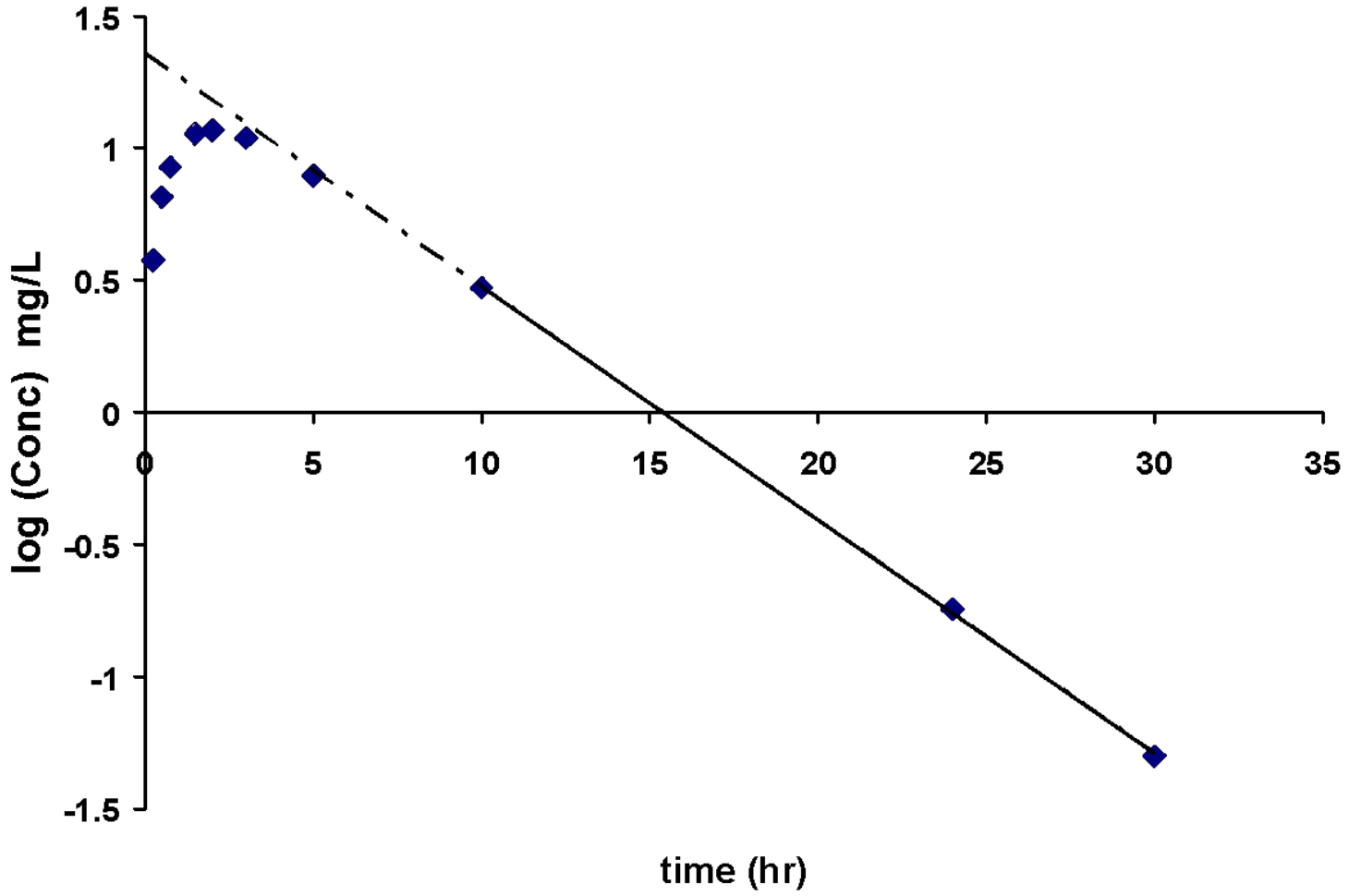
Example 2:

Determine K



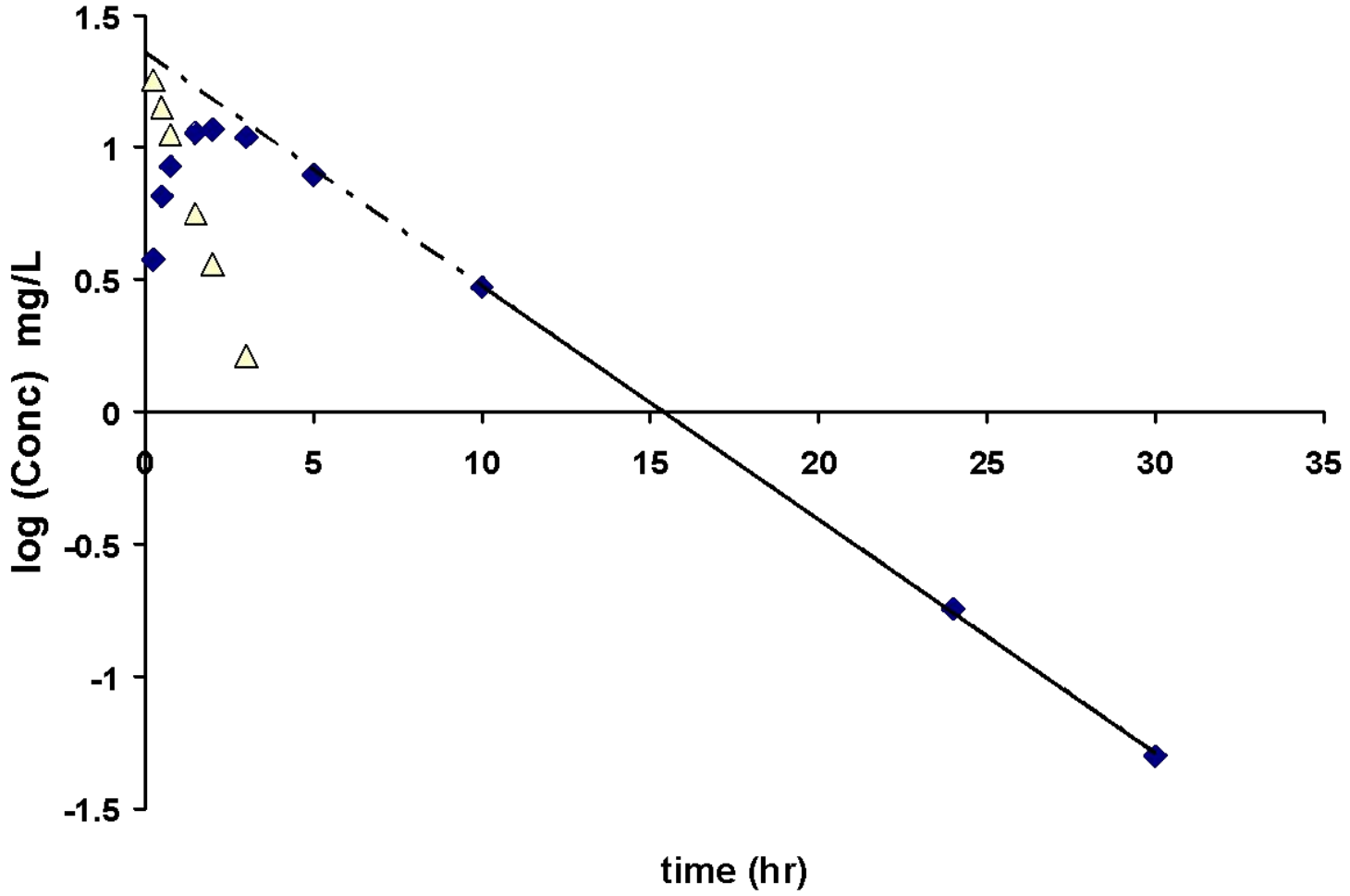
Example 2:

Extrapolate the terminal line to cross the y-axis



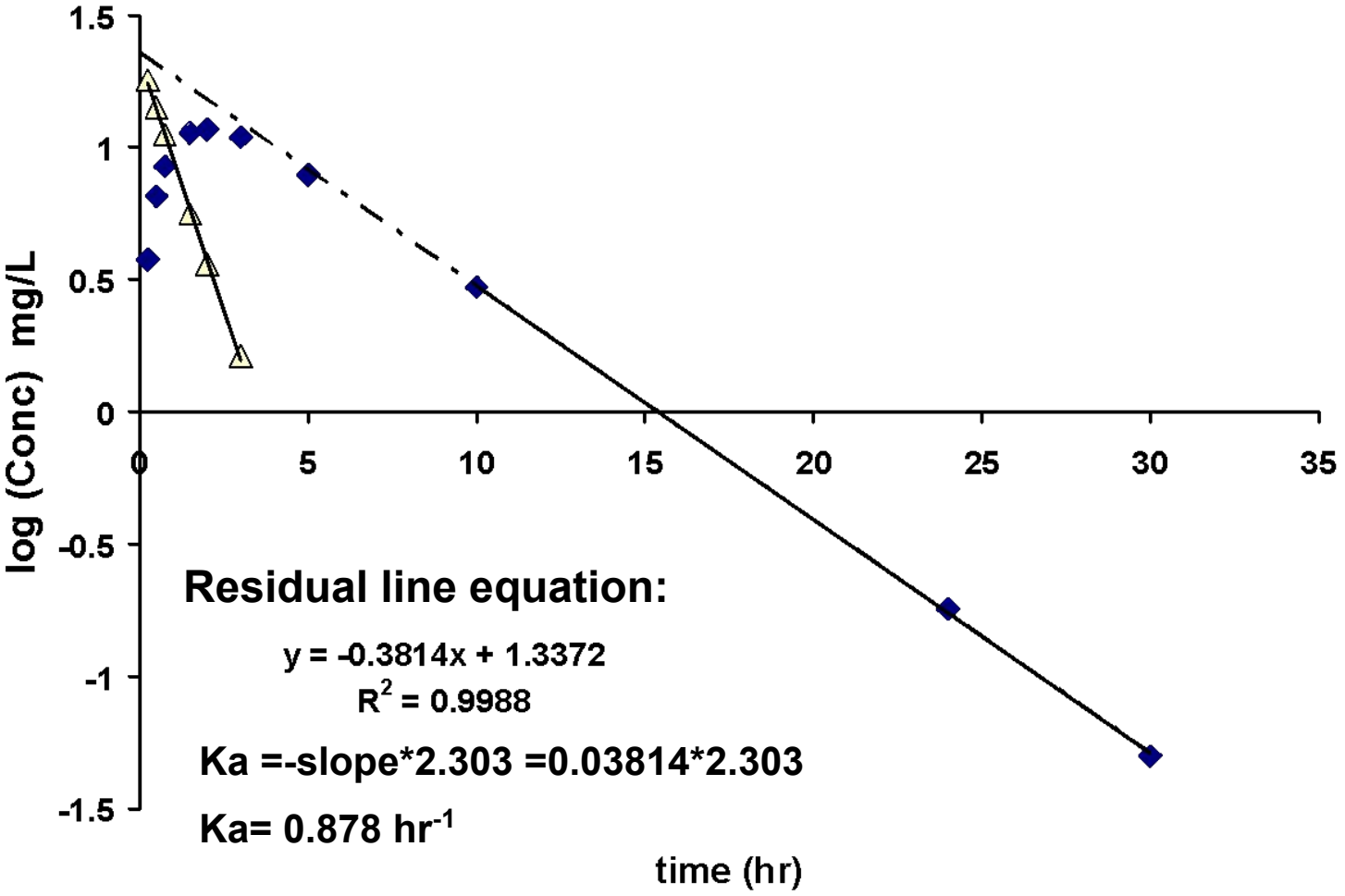
Example 2:

Draw the residual line



Example 2:

Determine Ka



Example 2

- Volume of distribution (normalized for bioavailability):
- From the terminal line best fit line, intercept = 1.359.

$$10^{Intercept} = \frac{Ka \cdot F \cdot D}{Vd(Ka - K)}$$

$$\Rightarrow \frac{Vd}{F} = \frac{Ka \cdot D}{10^{Intercept}(Ka - K)} = \frac{0.878 * 500}{10^{1.359}(0.878 - 0.2)} = 28.3\ L$$

Example 3

- A patient received a single dose of 500 mg erythromycin in the form of a tablet that is known to have 80% bioavailability. Calculate the time to reach the maximum concentration (1.7 hr), the maximum conc (7.11 mg/L), AUC (50) and Clearance (8 L/hr) after this single dose If K is 0.2 hr^{-1}, Ka is 1.3 hr^{-1}, and Vd is 40 liters.