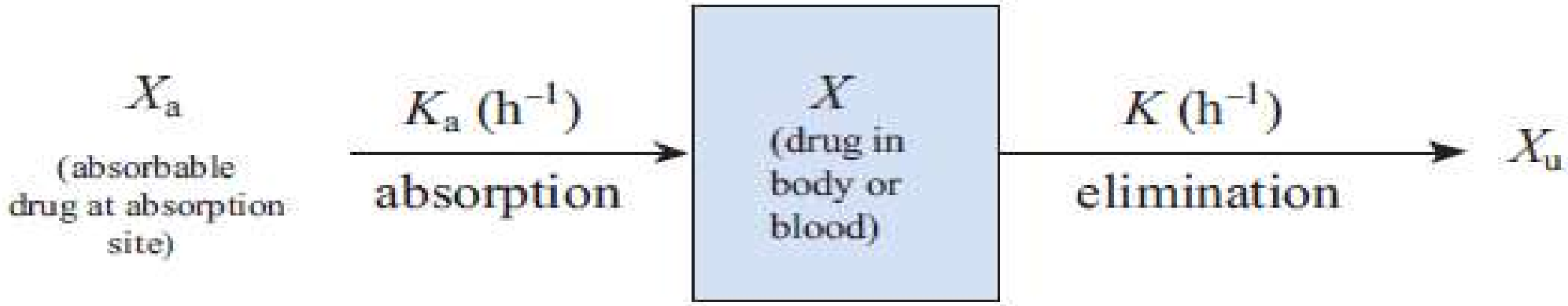
# One compartmental open model Extravascular routes of drug administration

## SCHEME:




## SETUP:


Fig1.1 Absorption of a one-compartment drug with first-order elimination. where Xa is the mass or 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 is the mass or amount of drug in the blood at time, t; Xu is the mass or amount of drug excreted unchanged in the urine at time, t; Ka is the first order
absorption rate constant ($h^{-1}$ or $min^{-1}$); and K (or Kel) is the first-order elimination rate constant ($h^{-1}$ or $min^{-1}$).

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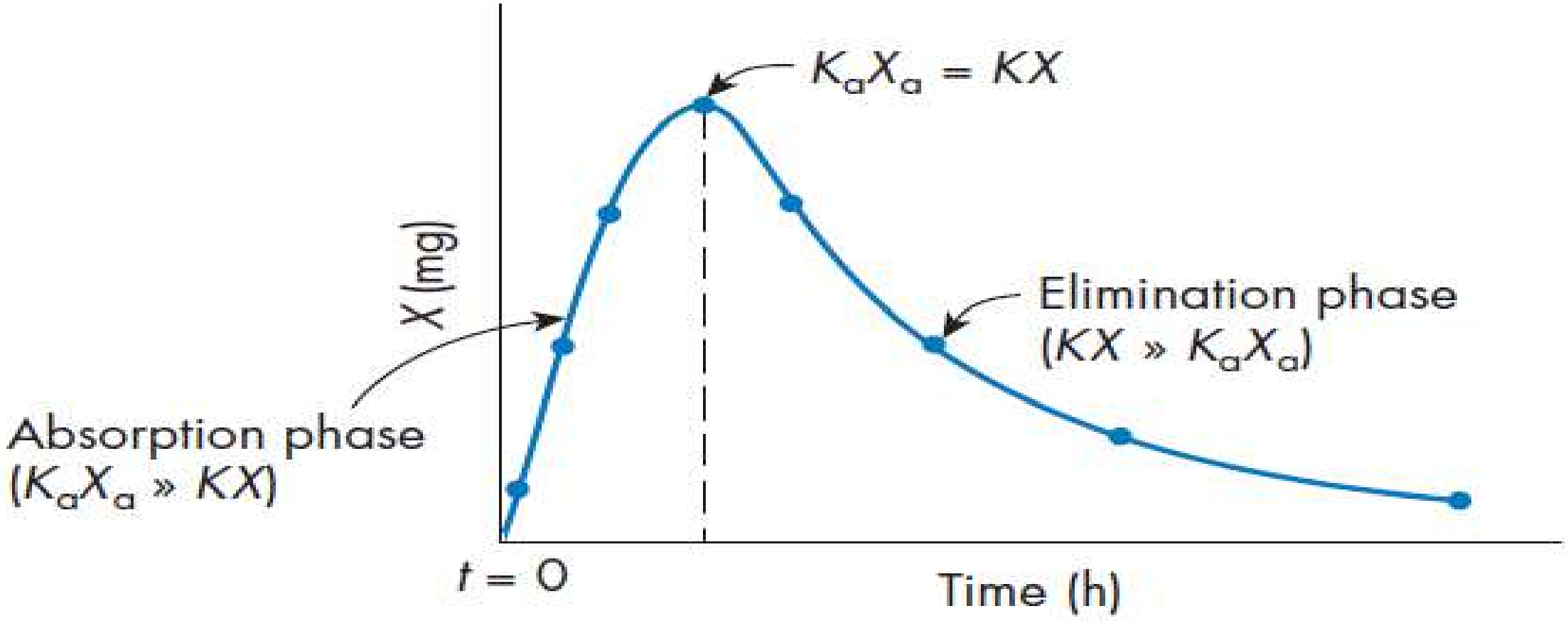



Figure 1.2 Atypical rectilinear profile illustrating amount of drug (X) in blood or body against time. Xa, amount of absorbable drug at the absorption site at time t; Ka and K, first-order absorption and elimination rate constants, respectively; KaXa and KX,first-order rates of absorption and elimination, respectively.

- The following assumptions are made:

1. Drug exhibits the characteristics of one compartment model
2. Absorption and elimination of a drug follow the first-order process and passive diffusion is operative at all the time
3. Drug is eliminated in unchanged form (i.e. no metabolism occurs)
4. Drug is monitored in the blood.

# 1-Drug remaining to be absorbed, or drug remaining at the site of administration

- $\frac{-dXa}{dt} = Ka(Xa)t$ **Equation 1.1**

Where

- -dX/dt is the decrease in the amount of absorbable drug present at the site of administration per unit time (e.g. mgh$^{-1}$);
- $K_a$ is the first order absorption rate constant (h$^{-1}$; min$^{-1}$); and
- (Xa)t is the mass or amount of absorbable drug at the site of administration (e.g. the gastrointestinal tract) at time t.
- Upon integration of Eq. 1.1, we obtain the following:

- $(Xa)t=(Xa)t=o.e^{-kat} = FXo\,e^{-kat}$ *Equation 1.2*

Where

- (Xa)t=0 is the mass or amount of absorbable drug at the site of administration at time t=0 (for extravascular administration of drug,
- (Xa)t=0 equals FX0); and F is the fraction or percentage of the administered dose that is available to reach the general circulation; X0 is the administered dose of drug. If F=1.0, that is, if the drug is completely (100%) absorbed, then

- $(Xa)t=Xao.e^{-kat}$ *Equation 1.3*

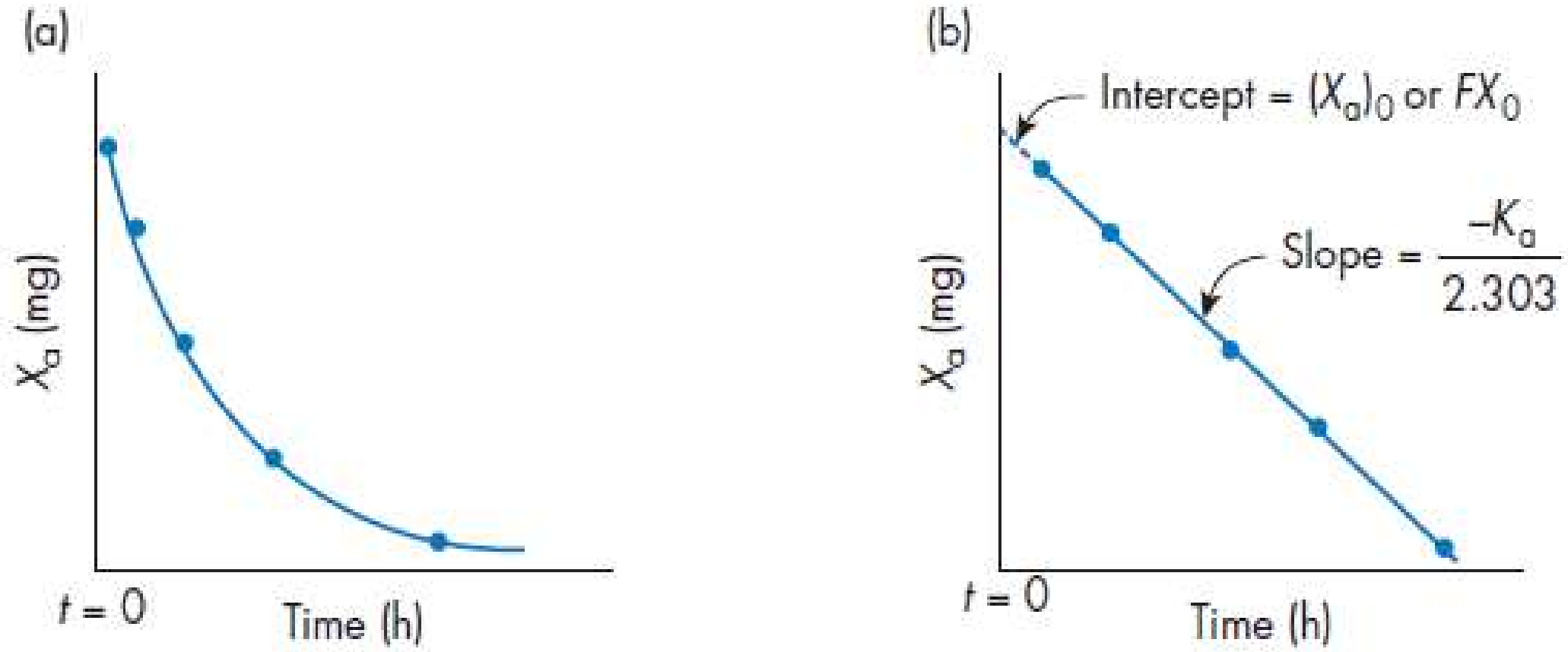



Fig 1.3 Amount of drug remaining at the site of administration against time in a rectilinear plot (a) and a semilogarithmicplot (b). Xa, amount of absorbable drug at the site of administration; $(X_a)_0$, amount of absorbable drug at the site of administration at time t=0; F, fraction of administered dose that is available to reach the general circulation.

## 2-Monitoring drug in the blood (plasma/serum) or site of measurement

- $\frac{dX}{dt} = K_a X_a - KeX$ Equation 1.4

Where:

- dX/dt is the rate (mg $h^{-1}$) of change of amount of drug in the blood;
- X is the mass or amount of drug in the blood or body at time, t
- Xa is the mass or amount of absorbable drug at the absorption site at time t;
- Ka and K are the first order absorption and elimination rate constants, respectively (e.g. $h^{-1}$);
- KaXa is the first-order rate of absorption (e.g. mg $h^{-1}$); and
- KX is the first-order rate of elimination (e.g. $mgh^{-1}$).

- Rate of change in drug in the blood reflects the difference between the absorption and the elimination rates (i.e. KaXa and KX, respectively).

- Following the administration of a dose of drug, the difference between the absorption and elimination rates (i.e. $K_aX_a$ - KX) becomes smaller as time increases; at peak time, the difference becomes zero.

- Please note that, most of the time, the absorption rate **constant** is greater than the elimination rate **constant**.

**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, please note that rate of absorption and the rate of elimination change with time, whereas the absorption and the elimination rate constants do not change.

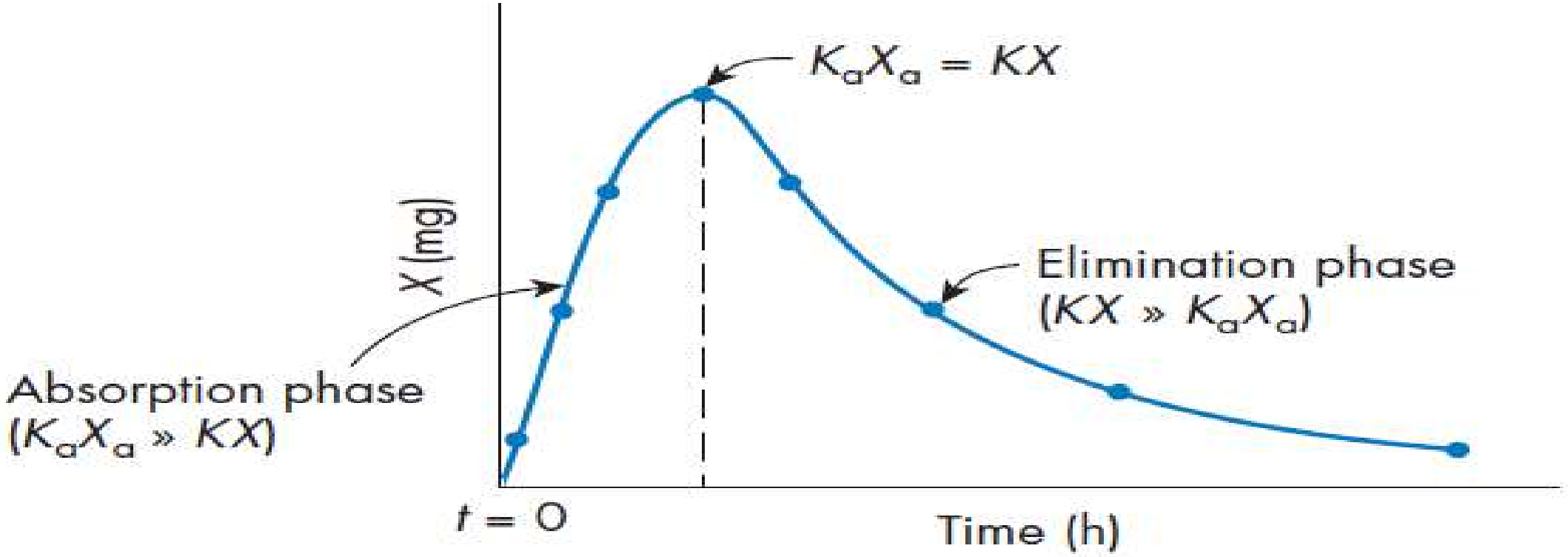
- $\frac{dX}{dt} = K_a X_a - KeX$ Integration of Eq. 1.4 gives:

$$(X)t = \frac{Ka(Xa)t=0}{Ka-K}[e^{-Kt} - e^{-Kat}]$$

$$= \frac{KaFXo}{Ka-K}[e^{-Kt} - e^{-Kat}] \qquad \text{Equation1.5}$$

Where

- (X)t is the mass (amount) of drug in the body at time t;
- X0 is the mass of drug at the site of administration at t=0 (the administered dose);
- F is the fraction of drug absorbed;
- (Xa)=FD0 is the mass of administered dose that is available to reach the general circulation, which is the same as the bioavailable fraction times the administered dose.

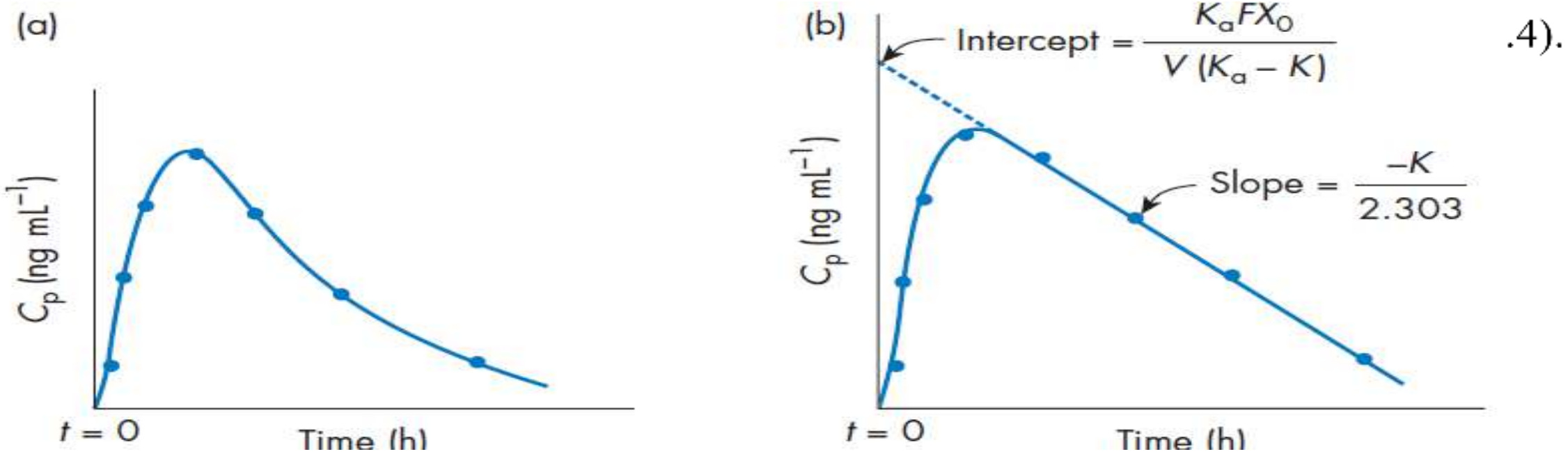



- The mass or amount of drug in the body or blood follows a biexponential profile, first rising and then declining. generally Ka>>K; therefore, the rising portion of the graph denotes the absorption phase.

# 2.1 Determination of elimination half life (t1/2) and elimination rate constant (K or Kel)

- Equation 1.5, when written in concentration (Cp) terms, takes the following form

$$(Cp)t=\frac{KaFXo}{V(Ka-K)}[e^{-Kt}-e^{-Kat}] \qquad \text{Equation 1.6}$$




.4).

Figure 1.4 A plot of plasma concentration (Cp) against time on rectilinear (a) and semilogarithmic (b) paper.$(Xa)_0$, amount of absorbable drug at the site of administration at time t=0; F, fraction of administered dose that is available to reach the general circulation; Ka and K, first-order absorption and elimination rate constants, respectively; V, apparent volume of distribution

## 2.1 Determination of elimination half life (t1/2) and elimination rate constant (K or Kel)

- When time is large, because of the fact that Ka>>K, $e^{-Kat}$ approaches zero, and Eq. 1.6 reduces to:

$$(Cp)t=\frac{KaFXo}{V(Ka-K)}[e^{-Kt}] \qquad \text{Equation1.7}$$

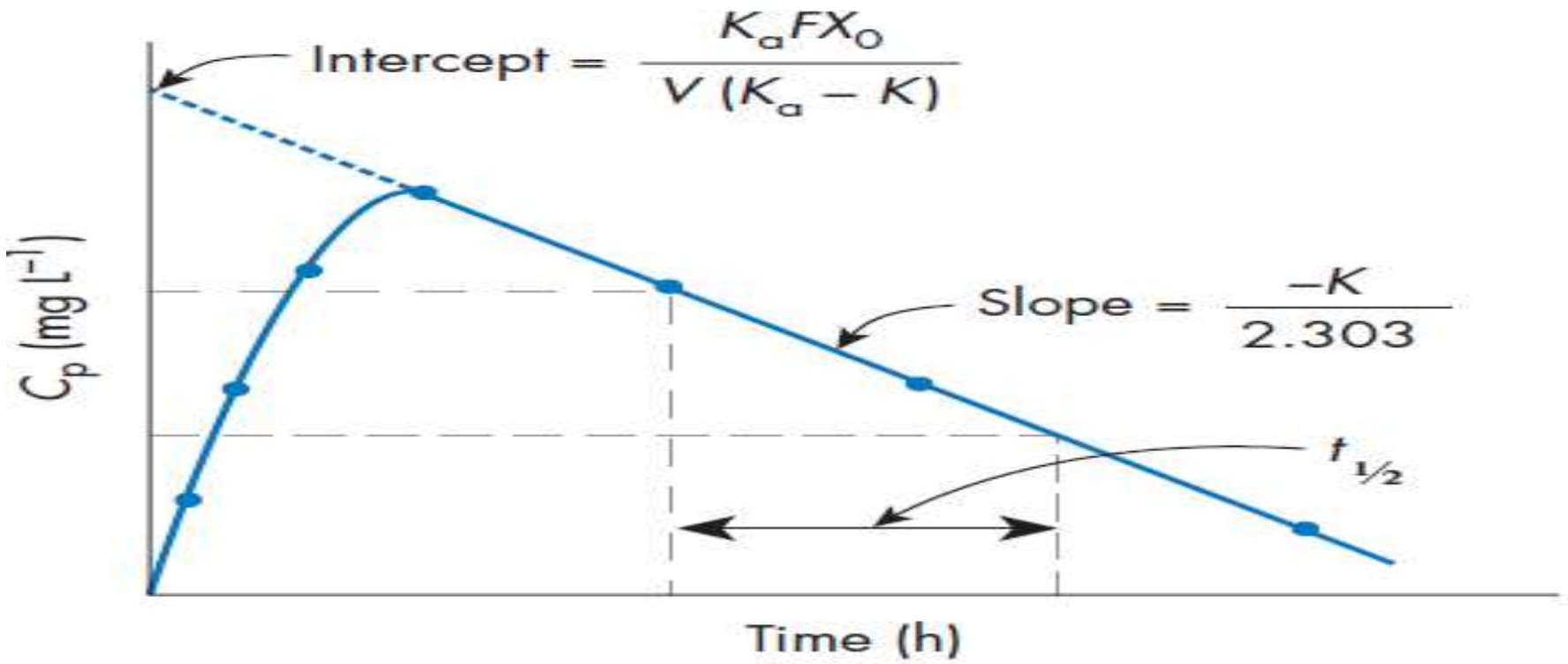



Figure 1.5 Semilogarithmic plot of plasma drug concentration (Cp) versus time of an extravascular dosage form: visualization of elimination half life ($t_{1/2}$)

# 2.2 Absorption rate constant (Ka)

The absorption rate constant is determined by a method known as “feathering, ” “method of residuals” or “curve stripping.”

The method allows the separation of the monoexponential constituents of a biexponential plot of plasma concentration against time.

From the plasma concentration versus time data obtained or provided to you and the plot of the data (as shown in Fig. 1.6) we can construct a table with headings and columns as in Table (next slide) ,for the purpose of determining the absorption rate constant.

# 2.2 Absorption rate constant (Ka)

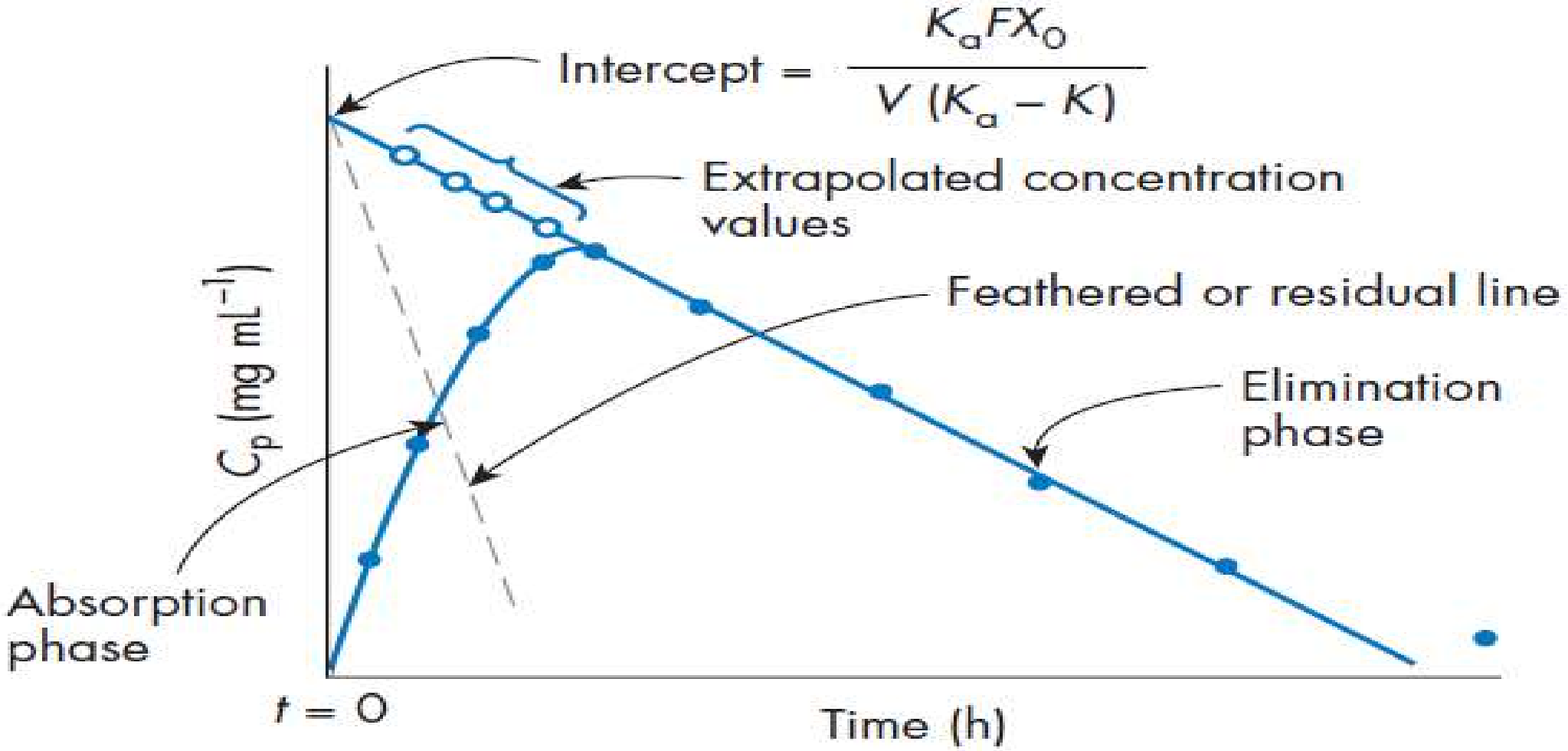



Figure 1.6 Semi logarithmic plot of plasma concentration (Cp) versus time of an extravascular dosage form, showing the method of residuals.

## 2.2 Absorption rate constant (Ka)

Table ■ Illustration of the table created for determination of the first-order absorption rate constant $K_a$

| Time (h) | Observed plasma concentration $(C_p)_{obs}$ | Extrapolated plasma concentration $(C_p)_{extrap}$ | $(C_p)_{diff} = (C_p)_{extrap} - (C_p)_{obs}$ |
|---|---|---|---|
| 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) (units, e.g. $\mu g\,mL^{-1}$) | Values only from the extrapolated portion of the plot of plasma concentration–time (units, e.g. ($\mu g\,mL^{-1}$) | Differences between extrapolated and observed values for each time in the absorption phase (units, e.g. $\mu g\,mL^{-1}$) |

# .2.2 Absorption rate constant (Ka)

$$(Cp)diff=\frac{KaFXo}{V(Ka-K)}[e^{-Kat}] \qquad \text{Equation 1.8}$$

Where $\frac{KaFXo}{V(Ka-K)}$ is the intercept of plasma drug concentration versus time plot.

- A plot of this difference between extrapolated and observed plasma concentrations against time, on semilogarithmic paper (Fig. 1.7), should yield a straight line, which, in turn, should allow determination of:
  - the half life of the feathered or residual line (i.e. the $t_{1/2}$ of absorption phase)
  - the first-order absorption rate constants, using the equation $Ka=0.693/(t_{1/2})abs$, or Ka=_(slope)*2.303

# 2.2 Absorption rate constant (Ka)

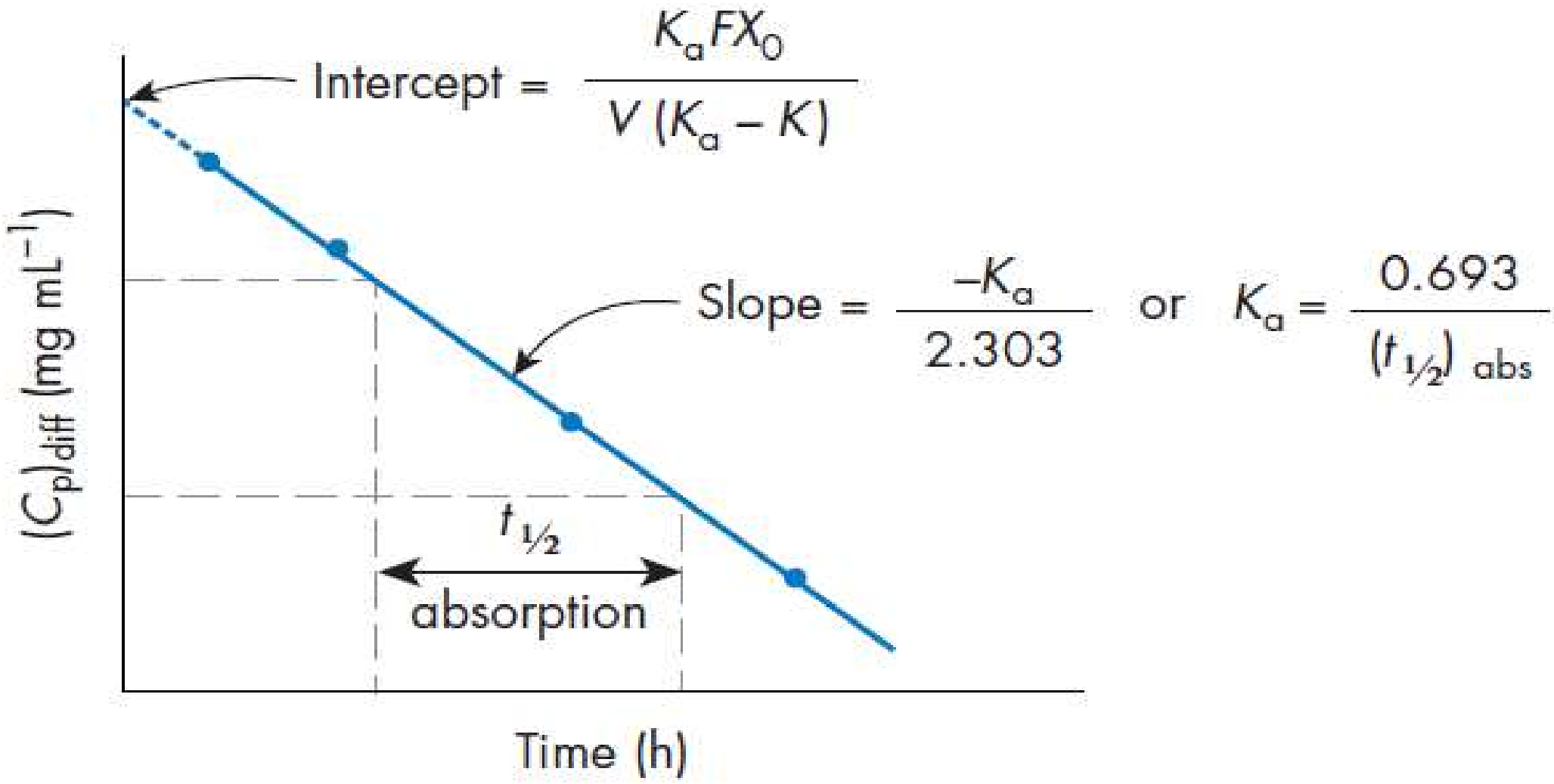



Figure 1.7 Semilogarithmic plots of plasma concentration (Cp)diff. between calculated residual concentrations and measured ones versus time, allowing the calculation of the absorption rate constant. ($t_{1/2}$)abs, absorption half life

# 2.3 The apparent volume of distribution (V)

- The apparent volume of distribution cannot be calculated from plasma drug concentration data alone. The reason is that the value of F (the fraction of administered dose that reaches the general circulation) is not known.

$$\text{Intercept} = \frac{KaFXo}{V(Ka-K)} \qquad \text{Equation 1.9}$$

- In the absence of data for the fraction of administered dose that reaches the general circulation

$$\frac{V}{F} = \frac{KaXo}{(Ka-K)}\left(\frac{1}{Intercept}\right) \qquad \text{Equation 1.10}$$

# 2.4 Time of maximum drug concentration, peak time (tmax)

- The peak time (tmax) is the time at which the body displays the maximum plasma concentration, (Cp)max. It occurs when the rate of absorption is equal to the rate of elimination (i.e. when KaXa=KX). At the peak time, therefore, Ka(Xa)tmax = K(X)tmax.
- **Calculating peak time:**
- According to Eq 1.4 derived above:

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

- When t=tmax, the rate of absorption (KaXa) equals the rate of elimination (KX).Hence, Eq. 1.4 becomes:

$$\frac{dX}{dt} = K_{a(X_a)tmax} - Ke(X)tmax = 0$$

Or: $$K_{a\,(X_a)tmax} = Ke(X)tmax$$ Equation1.11

•• We know from earlier equations (Eqs 1.5 and 1.2) that

$$(X)t=\frac{KaFXo}{Ka-K}\left[e^{-Kt}-e^{-Kat}\right] \qquad \text{Equation 1.5}$$

$$(Xa)t = F\,Xo\,e^{-kat} \qquad \text{Equation 1.2}$$

- When t=tmax, Eqs 1.5 and 1.2 become Eqs 1.12 and 1.13, respectively

$$(X)t_{max}=\frac{KaFXo}{Ka-K}\left[e^{-K\,tmax}-e^{-Ka\,tmax}\right] \qquad \text{Equation1.12}$$

$$(Xa)_{t\,max} = F\,Xo\,e^{-ka\,tmax} \qquad \text{Equation1.13}$$

- Equation 1.11 shows that Ka(Xa)tmax=K(X)tmax. Substituting for (Xa)tmax (from Eq. 1.13) and (X)tmax (from Eq. 1.12) in Eq. 1.11, then rearranging and simplifying, yields:

$$Ka.e^{-Ka\ tmax} = K.e^{-K\ tmax} \qquad \text{Equation1.14}$$

- Taking natural logarithms of Eq. 1.14 yields:

$\ln Ka - Ka \cdot t_{max} = \ln K - K \cdot t_{max}$

$\ln Ka - \ln K = Ka \cdot t_{max} - k \cdot t_{max}$

$\ln(Ka/K) = t_{max}(Ka/K)$

or

$$t_{max} = \frac{\ln(Ka/K)}{Ka-K} \qquad \text{Equation1.15}$$

# 2.4 Time of maximum drug concentration, peak time (tmax)

- Peak time depends on, or is influenced by, only the absorption and elimination rate constants; therefore, any factor that influences the absorption and the elimination rate constants will influence the peak time value.

- ***Factors affecting Ka:***

1. Liposolubility (1$^{st}$ and 2$^{nd}$ Fick's laws).
2. pH of the media and pKa of the substance (Handerssen Hasselbach equation for weak acids and weak bases).
3. Gastro Intestinal Motility (G.I.T).
4. Gastric emptying Rate (G.E.R).
5. Food.
6. Pathophysiology.

## 2.5 Maximum (peak) plasma concentration (Cp)max

- The peak plasma concentration (Cp)max occurs when time is equal to tmax.
- **How to obtain the peak plasma concentration**
- **Method 1.** Peak plasma concentration obtained from the graph of plasma concentration versus time
- **Method 2**. Peak plasma concentration obtained by using an equation. (Equation 1.6) shows that: $(Cp)t=\frac{KaFXo}{V(Ka-K)}[e^{-Kt}-e^{-Kat}]$
- If tmax is substituted for t in Eq. 1.6:
- $(Cp)max=\frac{KaFXo}{V(Ka-K)}[e^{-K\,tmax}-e^{-Ka\,tmax}]$ Equation 1.16
- We also know from Eqs 1.6 and 1.7 that the intercept (I) of the plasma concentration–time plot is given by:
- $I=\frac{KaFXo}{V(Ka-K)}$
- Hence, substituting for the term $I=\frac{KaFXo}{V(Ka-K)}$ in Eq. 1.16 with I will yield Eq. 1.17:
- $(Cp)max=I[e^{-K\,tmax}-e^{-Ka\,tmax}]$

## 2.5 Maximum (peak) plasma concentration (Cp)max

- Figure 1.8 shows this relationship.

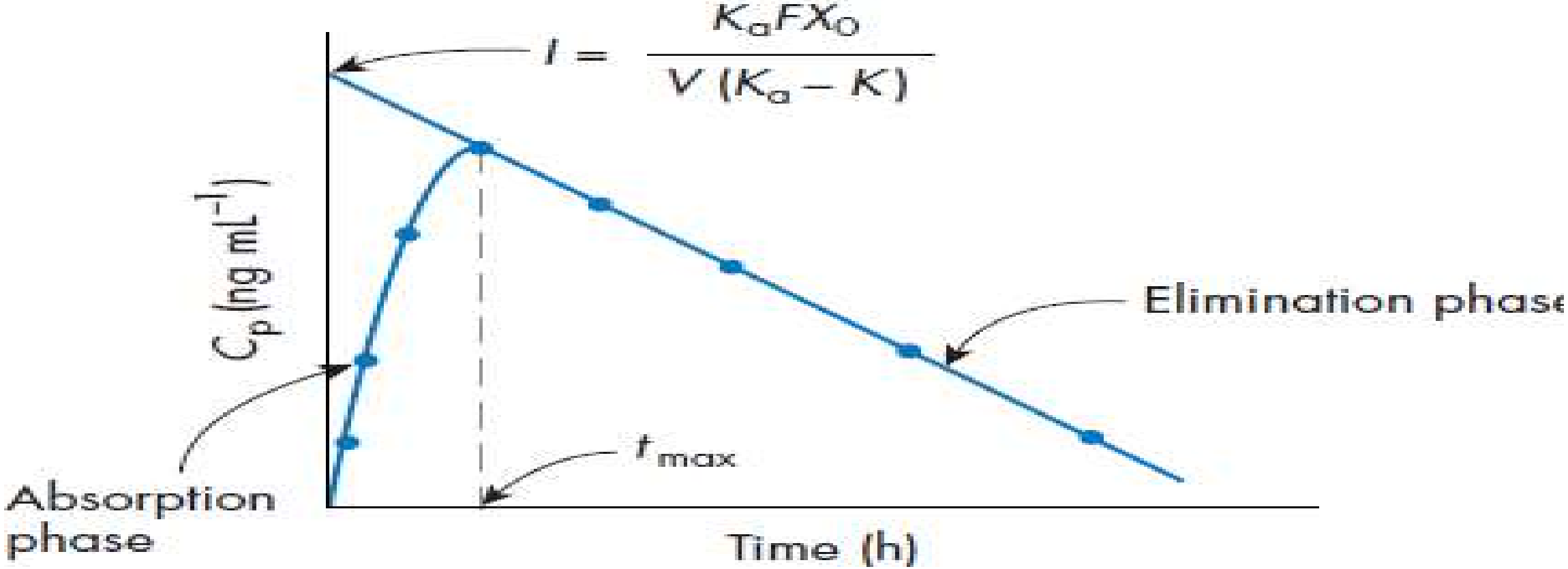



Figure 1.8 Semilogarithmic plot of plasma concentration (Cp) against time following the administration of a drug via the extravascular route, showing the intercept (I) and the the time of peak (tmax).

## 2.5 Maximum (peak) plasma concentration (Cp)max

- Factors affecting Cmax:

1. Dose
2. F
3. Ke
4. Ka
5. Vd

# Other Method to calculate Ct
# Will be discussed in details in the last chapter (Bioavailability)

- **[AUC] Method**

- **Simpson method**