كلية الصيدلة
College of Pharmacy
University of Basrah

4th year 2016/2017
Biopharmaceutics
Course #414:

PHARMACOKINETICS OF DRUG ABSORPTION

UOBCOP

Department of Pharmaceutics

Malathe Alshawi

-BSc. Pharm (Uni. of Basra College of Pharmacy);
-MSc. IPSci. (Brighton University, School of Pharmacy and Biomedical Sciences; UK)
-Email: malathe.oda@uobasrah.edu.iq

Drug absorption

- Drug administration routes:
  - IV → the drug is directly injected into the plasma.
  - Extravascular via lung, oral…etc.
    - More complicated affected by many variables :

كلية الصيدلة
College of Pharmacy

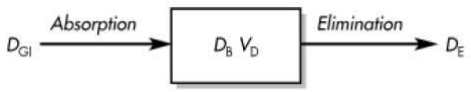
Factors affecting extent and rate of drug absorption via oral route

1. The physicochemical properties of the drug ,
2. The dosage form used,
3. the anatomy and physiology of the absorption site.
4. Surface area of the GI tract,
5. Stomach-emptying rate,
6. GI mobility,
7. and blood flow to the absorption site

PHARMACOKINETICS OF DRUG ABSORPTION via oral route

❑The rate of drug absorption

- ✓ first-order ***(the most common***)
- ✓or zero-order (***in certain cases see next slides***



The net rate of drug accumulation in the body at any time= (the rate of drug absorption)- (the rate of drug elimination (regardless of kinetic of absorption).

كلية الصيدلة College of Pharmacy

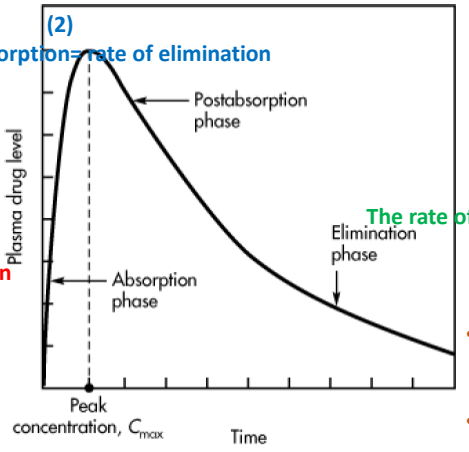
After administration of single oral dose

- Elimination occurs when ever the drug is present in body

(2)

The rate of absorption=rate of elimination

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



(1)

Absorption > elimination

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

(3)

The rate of elimination > rate of absorption

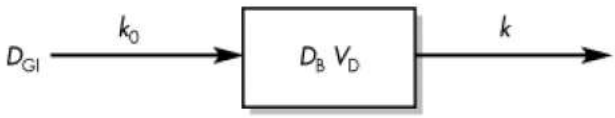
$\frac{dD_{GI}}{dt} < \frac{dD_E}{dt}$

- The rate of absorption is zero as the concentration of the absorbed drug is depleted at site of absorption.
- the elimination phase is 1st order

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

ZERO-ORDER ABSORPTION MODEL

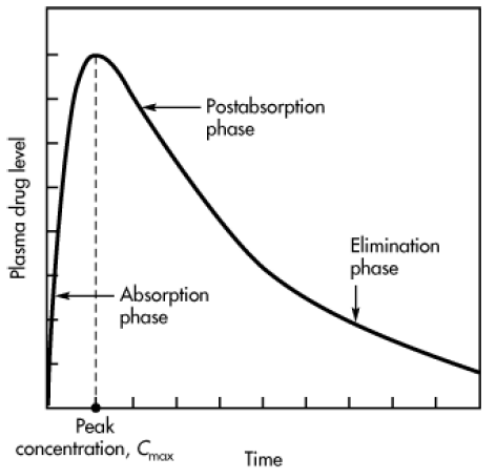
- The absorption of drug from GIT is zero order if:
  - The drug is absorbed by a saturable process (carrier mediated)
  - zero-order controlled-release delivery system is used.



Absorption is zero order kinetics
absorbtion rate=k_0

elimination is 1st order kinetic.
Elim rate=kD_B

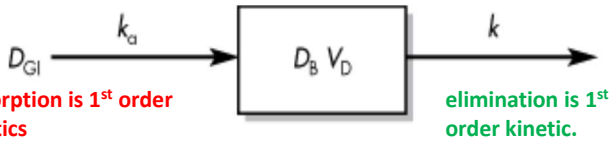
- The net rate of drug accumulation in the body at any time= (the rate of drug absorption)- (the rate of drug elimination)
  - Thus, $\frac{dD_b}{dt}=K_0-kD_B$
  - $C_p=\frac{K_0}{V_D k}*(1-e^{-kt})$---------- in case of zero order absorption



- The time for all drug to be completely absorbed = D_{GI}/k_0
- The drug in GI is depleted until approaches zero
- After this time:
  - $(Cp=\frac{K_0}{V_D k}*(1-e^{-kt}))$ is not applicable
  - The concentration will decline in the body as 1st order kinetic

FIRST-ORDER ABSORPTION MODEL

- Drug absorption and elimination are 1st order process
- This model applies mostly to the oral absorption of:
  - drugs in solution
  - rapidly dissolving dosage (immediate release) forms such as
    - tablets, capsules, and suppositories.



Absorption is 1st order kinetics

ab rate=$\frac{dD_{GI}}{dt}=-K_aD_{GI}F$

elimination is 1st order kinetic.

Elim rate=kD_B

FIRST-ORDER ABSORPTION MODEL

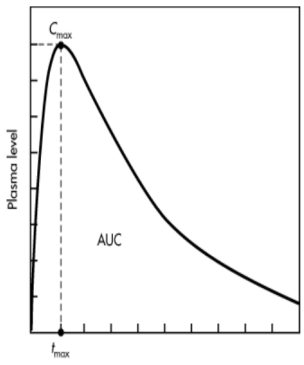
- The rate of drug absorption from GIT ($\frac{dD_{GI}}{dt}$) is:
  - $\frac{dD_{GI}}{dt}=-K_aD_{GI}F$ *or* $\frac{dD_{GI}}{dt}=-D_0\,e^{-k_at}$

  - k_a =the first-order absorption rate constant from the GI tract,
  - F = the fraction absorbed, **range from (1-0)** (1 for fully absorbed drug and 0 for unabsorbed drug).
  - D_{GI} = the amount of drug in solution in the GI tract at any time t.
  - D_0=where D_0 is the dose of the drug.

$$C_p = \frac{Fk_aD_0}{V_D\,(k_a - k)}\,(e^{-kt} - e^{-k_at})$$

After administration of single oral dose following 1st order kinetic

- C_{max} is The maximum plasma concentration after oral dosing sometimes called ***peak concentration***,
  - the rate of drug absorbed= the rate of drug eliminated.
  - Therefore, the net rate of concentration change is ***equal to zero***
- T_{max} is the time needed to reach maximum concentration
  - The t_{max} is dependent on the rate constants for **absorption (k_a)** and **elimination (k)**



The plasma concentration – time curve

A typical plot of the concentration of drug in the body after a single oral dose

FIRST-ORDER ABSORPTION MODEL (C_{max})and (T_{max})

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

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

T max is depended on????

C_{max} can be calculated form the equation:

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

Determination of 1st order elimination rate constant(k)

1-may be determined from the elimination phase of the plasma- plasma concentration

2- urinary excretion data

Using elimination phase to determine 1st elimination constant (k)

$$C_p = \frac{Fk_aD_0}{V_D(k_a - k)}(e^{-kt} - e^{-k_at})$$

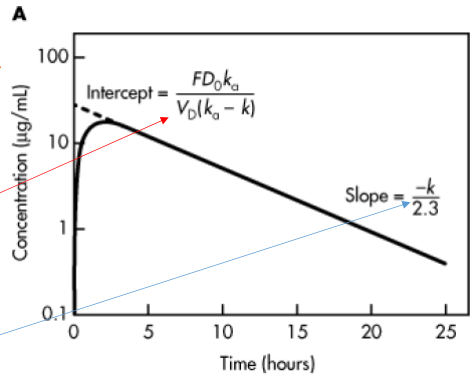
~ zero (when drug absorption has been completed t~0) at the elimination phase

$$C_p = \frac{Fk_aD_0}{V_D(k_a - k)}e^{-kt}$$

$$\ln C_p = \ln \frac{Fk_aD_0}{V_D(k_a - k)} - kt$$

Substitution of common logarithms gives

$$\log C_p = \log \frac{Fk_aD_0}{V_D(k_a - k)} - \frac{kt}{2.3} \qquad (7.16)$$



Plasma drug concentration versus time, single oral dose.

using urinary drug excretion data to determine the 1st order elimination constant form elimination phase

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

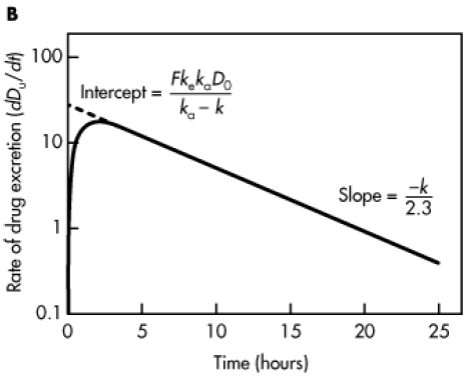
After drug absorption is virtually complete, $-e^{-k_a t}$ ~ zero,

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

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

$$D_u = \frac{Fk_a k_e D_0}{k_a - k}\left(\frac{e^{-k_a t}}{k_a} - \frac{e^{-kt}}{k}\right) + \frac{Fk_e D_0}{k}$$

dD_u/dt = rate of urinary drug excretion,
k_e = first-order renal excretion constant,
F = fraction of dose absorbed

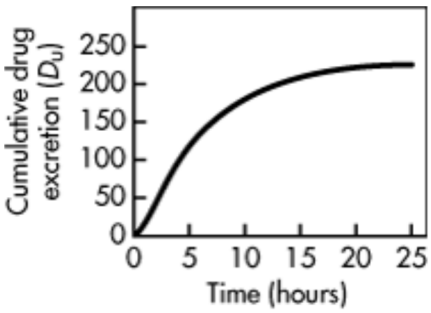


Rate of urinary drug excretion versus time, single oral dose

- . After all of the drug has been excreted, at $t = \infty$.

$$D_u^{\infty} = \frac{Fk_e D_0}{k} \qquad (7.21)$$

where D_u^{∞} is the maximum amount of active or parent drug excreted.



Determination of Absorption Rate Constants from Oral Absorption Data (ka)

Determination of Absorption Rate Constants from Oral Absorption Data

1. **DETERMINATION OF Ka BY PLOTTING PERCENT OF DRUG UNABSORBED VERSUS TIME (WAGNER–NELSON METHOD)**
2. **ESTIMATION OF KA FROM URINARY DATA**
3. **Determination of Absorption Rate Constants from Oral Absorption Data**

1-DETERMINATION OF KA BY PLOTTING PERCENT OF DRUG UNABSORBED VERSUS TIME (WAGNER–NELSON METHOD)

- After a single oral dose of a drug,
- the total dose (D0)=(the amount present in the body)+ (the amount present in the urine)+ (and the amount present in the GI tract)

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

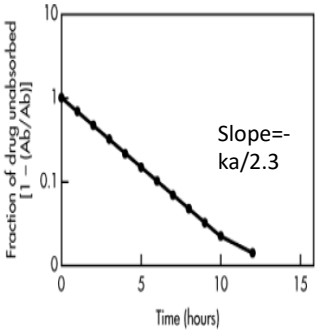
$$\frac{Ab}{Ab^{\infty}} = \frac{C_p + k[AUC]_0^t}{k[AUC]_0^{\infty}}$$

The fraction unabsorbed at any time t is

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

Therefore, the fraction of drug remaining is

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



2- estimation of Ka from urinary data

The fraction of the absorbed drug at any time (t)

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

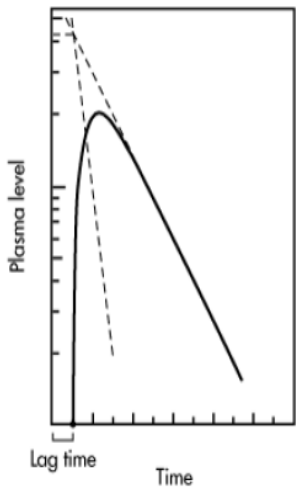
Ab = total amount of drug absorbed—
that is, the amount of drug in the body
plus the amount of drug excreted
D_B = amount of drug in the body
D_u = amount of unchanged drug excreted in the urine
C_p = plasma drug concentration
D_E = total amount of drug eliminated (drug and metabolites)
$Ab = D_B + D_E$

Issues with this method

- If the drug is rapidly absorbed, it may be difficult to obtain multiple early urine samples to describe the absorption phase accurately
- drugs with very slow absorption will have low concentrations, which may present analytical problems.

LAG TIME

- The time delay prior to the commencement of first-order drug absorption is known as *lag time.* The lag time, t_0, represents the beginning of drug absorption.
- Factors control the time of beginning of absorption:
  - physiologic factors as stomach-emptying time and intestinal motility.
- the point of intersection on the *x* axis is the lag time.



- What is the difference between lag time and onset time??
  - Onset of action is the pharmacologic term, which represents latency, eg, the time required for the drug to reach minimum effective concentration.

Therefor, in considering the lag time this equation can be applied

$$C_P = \frac{Fk_aD_0}{V_D(k_a - k)}\left(e^{-k(t-t_0)} - e^{-k_a(t-t_0)}\right)$$

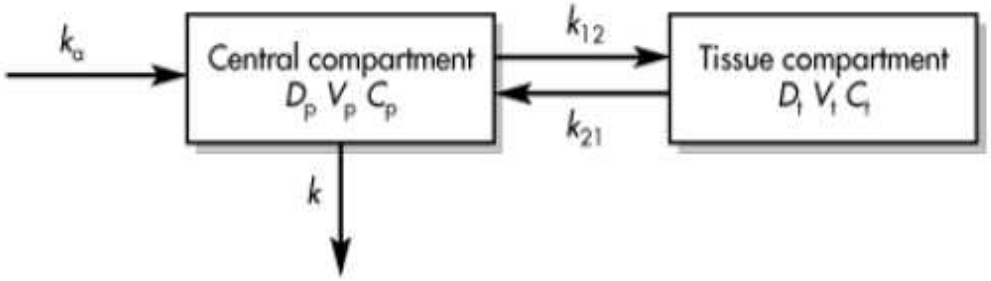
the lag time t_0 is subtracted from each time point, as shown in Equation

DETERMINATION OF Ka FROM TWO-COMPARTMENT ORAL ABSORPTION DATA (LOO–RIEGELMAN METHOD)

DETERMINATION OF Ka FROM TWO-COMPARTMENT ORAL ABSORPTION DATA (LOO–RIEGELMAN METHOD)

- this method does require that the drug be given intravenously as well as orally to obtain all the necessary kinetic constants.
- 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) and in the tissue compartment (*D* t) and the amount of drug eliminated by all routes (*D* u) .

$$\mathrm{Ab} = D_\mathrm{p} + D_\mathrm{t} + D_\mathrm{u}$$



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

SIGNIFICANCE OF ABSORPTION RATE CONSTANTS and T_{max}

- The calculation of *k* a is useful in designing a multiple-dosage regimen.
- Knowledge of the *k* a and *k* allows for the prediction of peak and trough plasma drug concentrations following multiple dosing.
- bioequivalence studies, *t* max, or time of peak drug concentration, can be very useful in comparing the respective rates of absorption of a drug from chemically equivalent drug products.