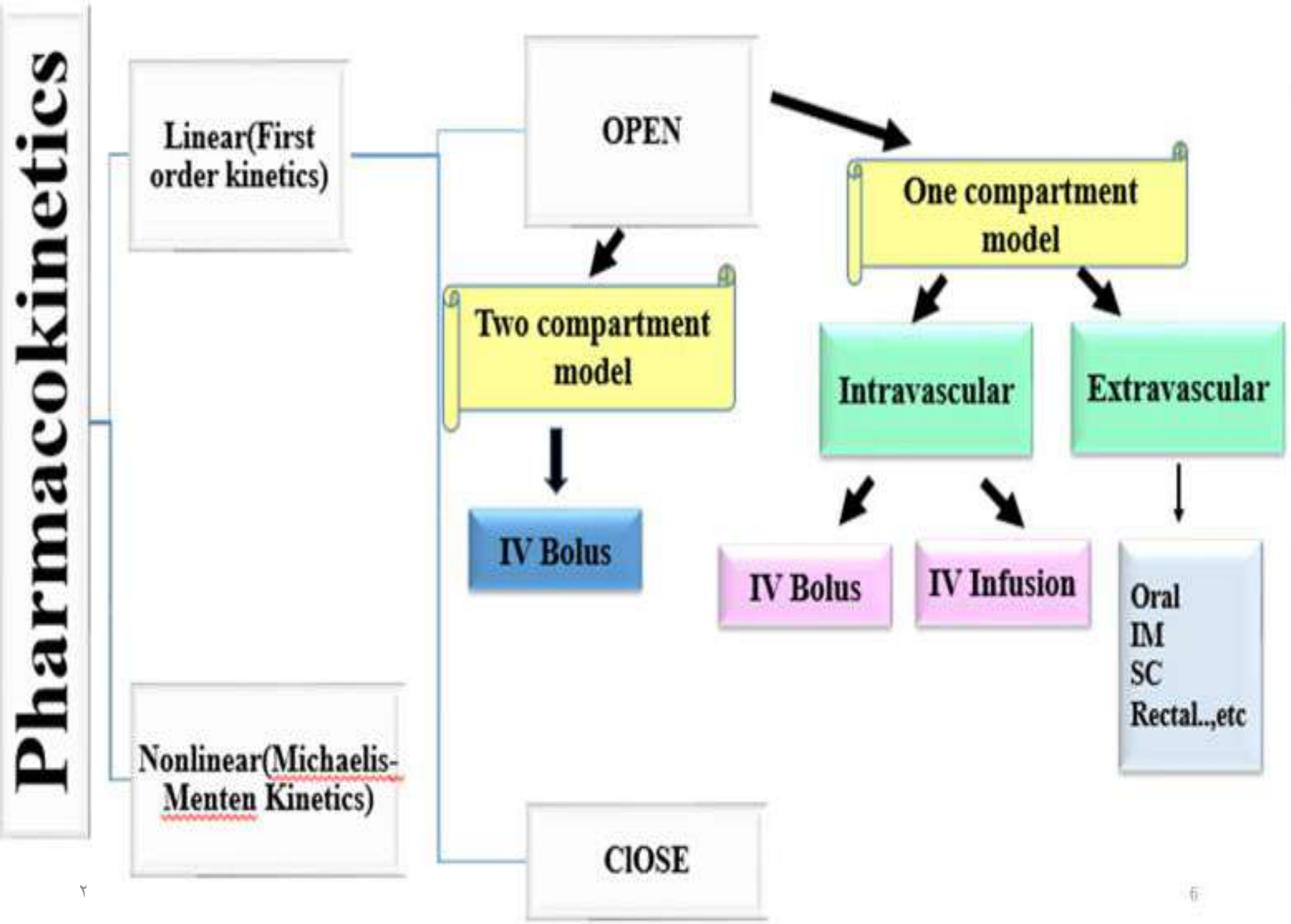
Non linear Pharmacokinetics


Pharmacokinetics
Linear(First order kinetics)
Nonlinear(Michaelis-Menten Kinetics)
OPEN
CIOSE
Two compartment model
IV Bolus
One compartment model
Intravascular
Extravascular
IV Bolus
IV Infusion
Oral
IM
SC
Rectal..,etc

➢ Introduction:

- Pharmacokinetic parameters, (t1/2), (K),(V) and the systemic clearance (Cl) of most drugs are not expected to change when different doses are administered and/or when the drug is administered via different routes as a single or multiple doses. The kinetics of these drugs is described as ***linear***, or ***dose-independent***, pharmacokinetics and is characterized by the **first-order process.**

- The term linear simply means that plasma concentration at a given time at **steady state** and the area under the plasma concentration versus time curve **(AUC)** will both be **directly proportional** to the **dose** administered, as illustrated in Fig. 1.1.

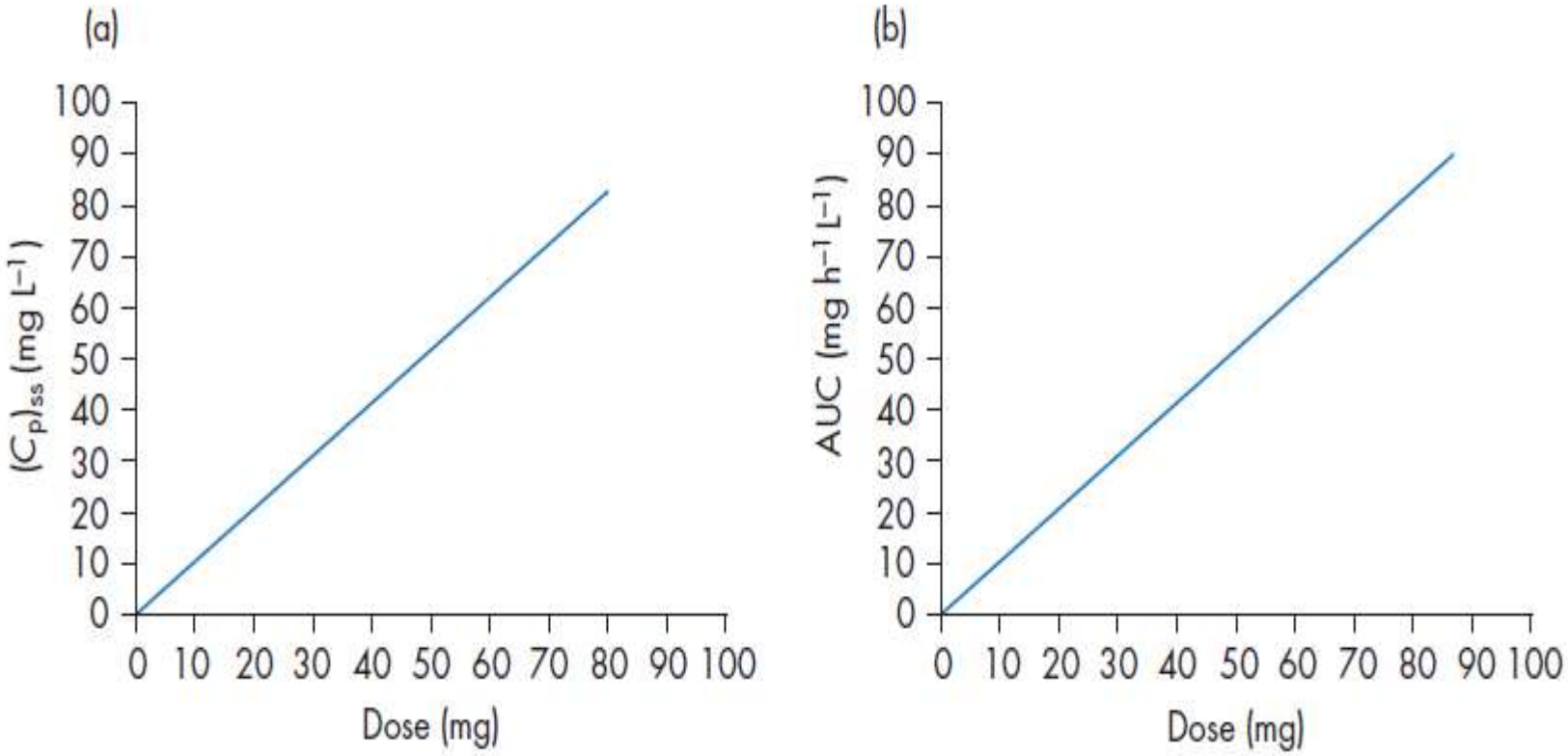


Figure 1.1 Relationship between the plasma concentration (Cp) at a time at steady state (a) and the area under the plasma concentration versus time (AUC) curve (b) against the administered dose for a drug that exhibits dose-independent pharmacokinetics.

- For some drugs, however, the linear P.K may not apply.

  Ex:, when the daily dose of phenytoin is increased by 50%in a patient from 300mg to 450 mg, the average steady-state plasma concentration [(Cp)ss] may increase by as much as 10-fold.

- This dramatic increase in the concentration (greater than directly proportional) is attributed to the ***non-linear kinetics*** of phenytoin.

- For drugs that exhibit ***non-linear*** or ***dose dependent kinetics***, the fundamental pharmacokinetic parameters such as CL, V and the $t_{1/2}$ may vary depending on the administered dose. Why!?
  - because one or more of the kinetic processes (absorption, distribution and/or elimination) of the drug may be occurring via a mechanism other than simple first-order kinetics.

- So, the relationship between the AUC or the plasma concentration at a given time at steady state and the administered dose is **not linear** (Fig. 1.2).

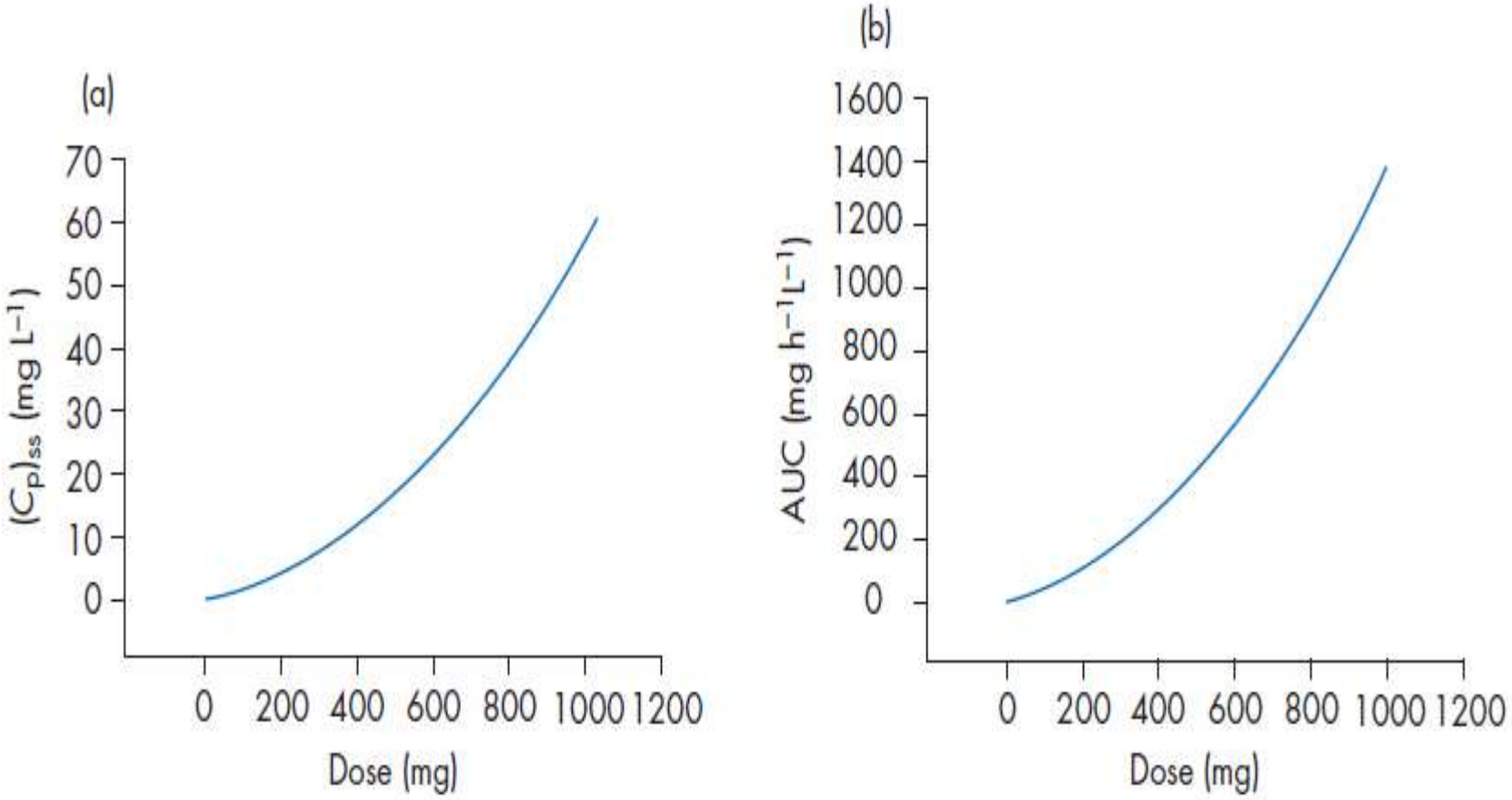


Figure 1.2 Relationship between the plasma concentration (Cp) at a time at steady state (a) and the area under the plasma concentration versus time (AUC) curve (b) against the administered dose for a drug that exhibits dose-dependent pharmacokinetics.

- Furthermore, administration of different doses of these drugs may not result in parallel plasma concentration versus time profiles expected for drugs with linear pharmacokinetics (Fig. 1.3).

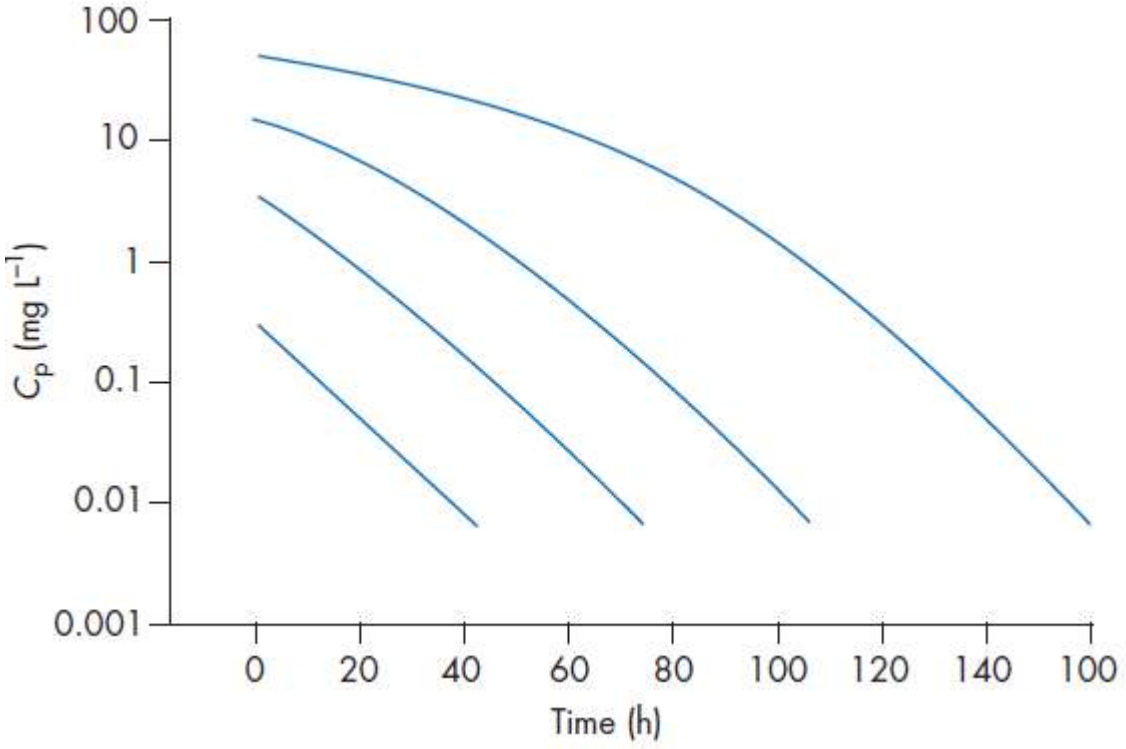


Figure 1.3 The relationship between plasma concentration (Cp) and time following the administration of different doses of a drug that exhibits dose-dependent elimination pharmacokinetics.

- Non-linearity may arise at any one of the various pharmacokinetic steps, such as absorption, distribution and/or elimination.
- Ex:
  - The extent of **absorption** of amoxicillin decreases with an increase in dose.
  - For **distribution**, plasma protein binding of disopyramide is saturable at the therapeutic conc., →an increase in Vd with an increase in dose of the drug.
  - **Renal excretion**, the antibacterial agent dicloxacillin has saturable active secretion in the kidneys → decrease in renal clearance as dose is increased.
  - Both phenytoin and ethanol have saturable **metabolism**, which means an increase in dose → a decrease in hepatic clearance and a more than proportional increase in AUC.

Capacity-limited metabolism

- Capacity-limited metabolism is also called **saturable metabolism**, **Michaelis–Menten** kinetics or **mixed-order** kinetics.
- The process of enzymatic metabolism of drugs may be explained by the relationship depicted below

$$[D] + [E] \underset{k_2}{\overset{k_1}{\rightleftharpoons}} [DE] \xrightarrow{k_{cat}} [M] + [E]$$

[D] is the unbound drug concentration,

[E] is the free enzyme concentration,

[DE] is the concentration of the drug–enzyme complex,

[M] is the metabolite concentration,

k1 and k2 are the forward and backward rate constants for the drug enzyme interaction, and

kcat is the rate constant for the formation of the metabolite.

- First the drug interacts with the enzyme to produce a drug–enzyme intermediate.
- Then the intermediate complex is further processed to produce a metabolite, with release of the enzyme.
- The released enzyme is recycled back to react with more drug molecules.

- According to the principles of Michaelis–Menten kinetics, the rate of drug metabolism changes as a function of drug concentration, as illustrated in Fig. 1.5.

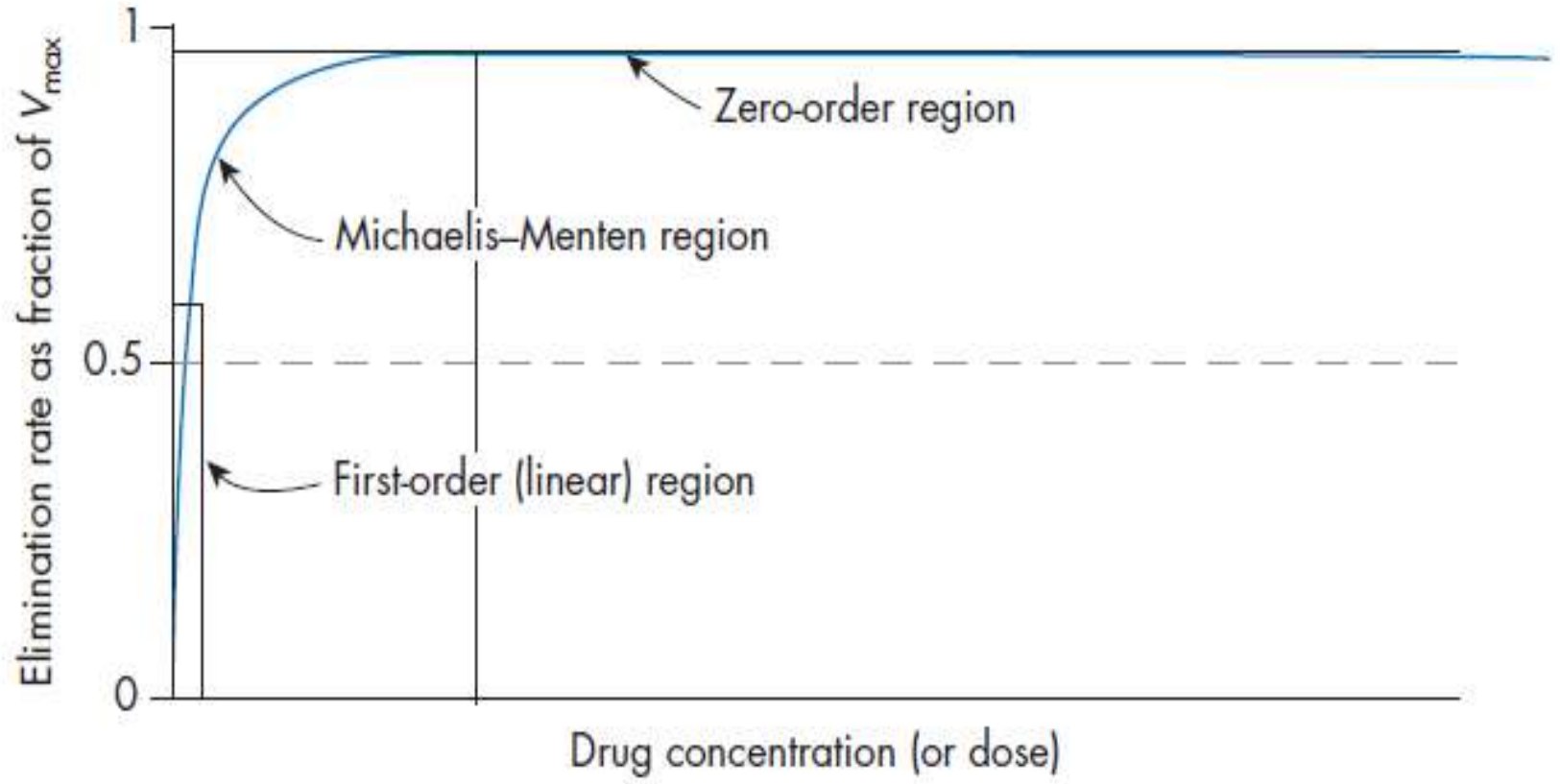
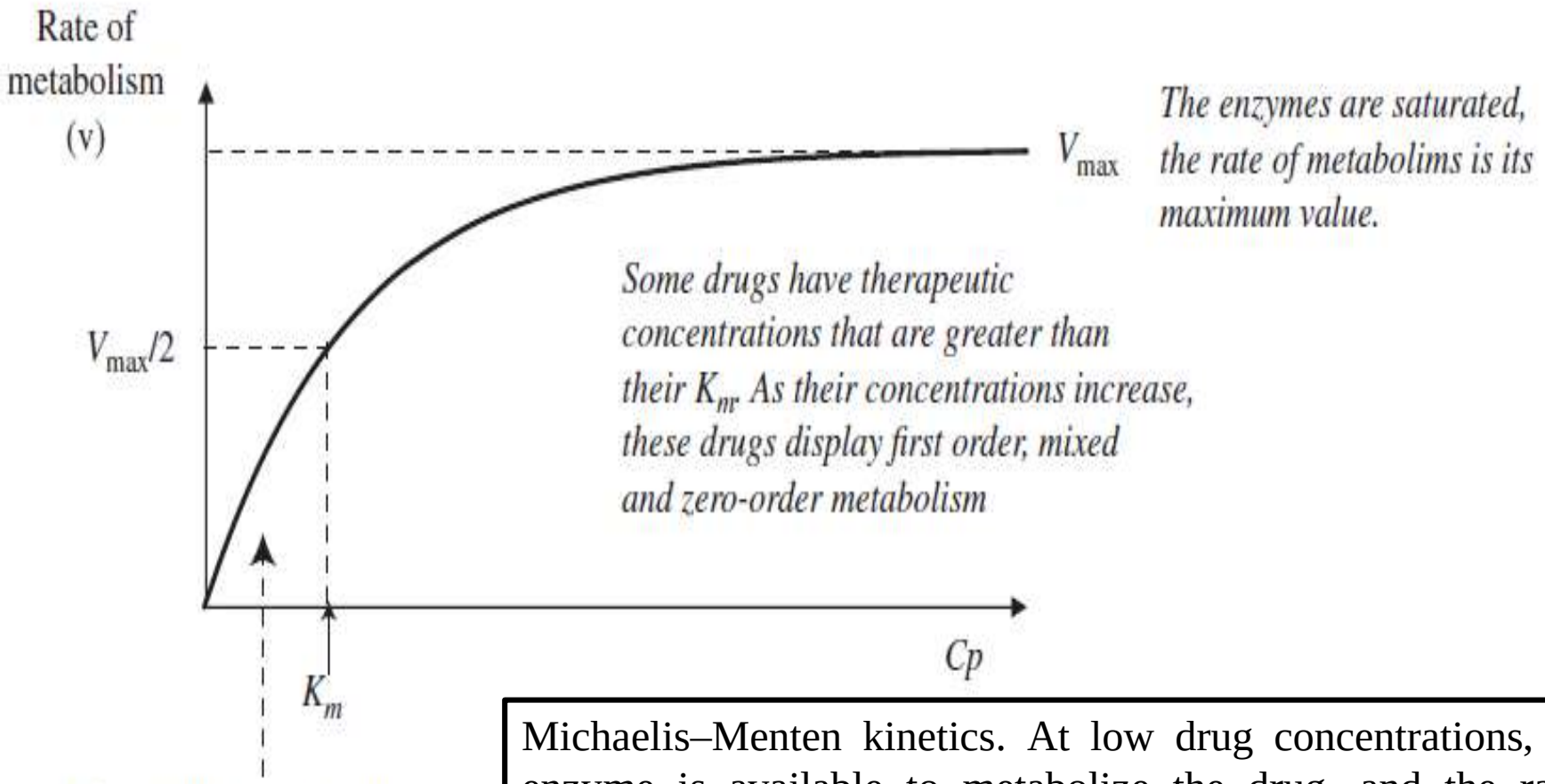


Figure 1.5 Relationship between elimination rate and the plasma concentration of a drug that exhibits dose-dependent pharmacokinetics. At high drug concentrations, where saturation occurs, the elimination rate approaches its maximum, Vmax.



Michaelis–Menten kinetics. At low drug concentrations, excess enzyme is available to metabolize the drug, and the rate can increase in direct proportion to increases in concentration (first order). As the drug concentration increases, some saturation is seen and the rate of metabolism can no longer keep up with increases in the drug concentration. At high drug concentrations, the enzyme is completely saturated and the maximum rate of metabolism is observed. At this point, increases in drug concentration are not associated with any further increases in the rate of metabolism.

- Equation 1.1 describes the relationship between the metabolism (or elimination) rate and the concentration over the entire range of concentrations.
- The rate of metabolism, or the rate of elimination if metabolism is the only pathway of elimination, is defined by the Michaelis–Menten equation:

Equation (1.1)

$$\text{Metabolism rate} = \frac{V_{\max} C}{K_m + C}$$

- where V**max** is the maximum rate (mg h-1) of metabolism;
- Km is the Michaelis–Menten constant(mg L-1), (dissociation constant), and is equal to (k2 + kcat)/k1.
- C is the drug concentration(mg L-1)

- The maximum rate of metabolism(i.e. Vmax) is dependent on the amount or conc. of enzyme available for metabolism of the drug

The unit for Vmax of metabolism is the unit of elimination rate and is normally expressed as amount per unit time (e.g. mg.h-1).

Also,expressed as conc. per unit time (e.g. mgL-1 h-1).

- Km is the conc. of the drug that results in a metabolic rate equal to one half of Vmax (Vmax/2).

Km is inversely related to the affinity of the drug for the metabolizing enzymes (the higher the affinity, the lower the Km value).

Km is not an elimination constant, but is actually a hybrid rate constant in enzyme kinetics, representing both the forward and backward reaction rates.

- Different regions of the Michaelis–Menten curve (Fig. 1.5) can be examined with regard to drug concentrations.

- **<u>At very low drug conc.,</u>** the conc. of available enzymes is much greater than the number of drug molecules or the drug conc.
- Drug conc. < Km.
- So, when the conc of drug is increased, going from left to right in Fig. 1.5, the rate of metabolism is also increased proportionally (linear elimination kinetics).
- In this case, the concentration term may be deleted from the denominator of Eq. 1.1, yielding:

- Equation (1.2) $$\text{Metabolism rate} = \frac{V_{\max} C}{K_m}$$

Because both Vmax and Km are constants, the metabolism rate is proportional to the drug conc. and a constant (i.e. first-order process)→Metabolism rate = KC

K=$\frac{Vmax}{Km}$ Equation(1.3) where units of K are h-1

- However, after a certain point, as the drug plasma concentration increases, the rate of metabolism increases less than proportionally.

- **when the conc. of drug is very high relative to the conc. of available enzyme molecules (**Drug conc. > Km)

  - All of the enzyme molecules are saturated with the drug molecules
  - when conc. is increased →no change in the rate of metabolism of the drug (the maximum rate of metabolism (Vmax)).
  - the term Km deleted from the denominator of Eq. 1.1:

Equation(1.4) $$\text{Metabolism rate} = \frac{V_{max}C}{C} = V_{max}$$

  - Zero-order kinetics

- **<u>At drug concentrations around the Km</u>**
  - A mixed order and nonlinear is observed, which is defined by the Michaelis–Menten equation (Eq. 1.1).
  - The therapeutic concentrations of most drugs are well below their Km values. As a result, the enzymatic metabolism of the majority of drugs used in clinical practice follow apparent first-order kinetics, and their pharmacokinetics are linear.
  - Small number of drugs have therapeutic plasma concentrations that approach or exceed their Km value.
  - For example, the average Km value for phenytoin is 4 mg/L, which compares to a therapeutic range of 10–20 mg/L.

Examples of Drugs Showing Nonlinear Kinetics

Cause[a]	Drug
GI Absorption	
Saturable transport in gut wall	Riboflavin, gebapentin, L-dopa, baclofen, ceftibuten
Intestinal metabolism	Salicylamide, propranolol
Drugs with low solubility in GI but relatively high dose	Chorothiazide, griseofulvin, danazol
Saturable gastric or GI decomposition	Penicillin G, omeprazole, saquinavir
Distribution	
Saturable plasma protein binding	Phenylbutazone, lidocaine, salicylic acid, ceftriaxone, diazoxide, phenytoin, warfarin, disopyramide
Cellular uptake	Methicillin (rabbit)
Tissue binding	Imiprimine (rat)
CSF transport	Benzylpenicillins
Saturable transport into or out of tissues	Methotrexate
Renal Elimination	
Active secretion	Mezlocillin, para-aminohippuric acid
Tubular reabsorption	Riboflavin, ascorbic acid, cephapirin
Change in urine pH	Salicylic acid, dextroamphetamine
Metabolism	
Saturable metabolism	Phenytoin, salicyclic acid, theophylline, valproic acid[b]
Cofactor or enzyme limitation	Acetaminophen, alcohol
Enzyme induction	Carbamazepine
Altered hepatic blood flow	Propranolol, verapamil
Metabolite inhibition	Diazepam
Biliary Excretion	
Biliary secretion	Iodipamide, sulfobromophthalein sodium
Enterohepatic recycling	Cimetidine, isotretinoin