Therapeutic Drug Monitoring

Lecture 1
Dr Atheer Zgair

Therapeutic drug monitoring (TDM) refers to the individualisation of dosage by maintaining plasma or blood drug concentrations within a target range (therapeutic range, therapeutic window).

Major sources of variability between individual patients in drug response

1. **Pharmacodynamic variability:** drug concentration at the receptor and the response.

   This type of variability includes

   - Genetic Variability in Receptors such variability in *μ-opioid receptor, $ß_2$-andrenergic receptor, dopamine receptors, and serotonin receptors*

- Non-genetic variability includes psychological factors - The placebo effect is a phenomenon that a patient's symptoms can be alleviated by giving a placebo drug.

2. **Pharmacokinetic variability:** dose and plasma concentration.

   Major sources of pharmacokinetic variability

1. Compliance
2. Age - neonates, children, elderly
3. Physiology - gender, pregnancy
4. Disease - hepatic, renal, cardiovascular, respiratory.
5. Drug interactions
6. Environmental influences on drug metabolism - diet, alcohol, and tobacco.
7. Genetic polymorphisms of drug metabolism - the less effective Butyrylcholinesterase (Atypical BuCHE, type A) on succinylcholine.

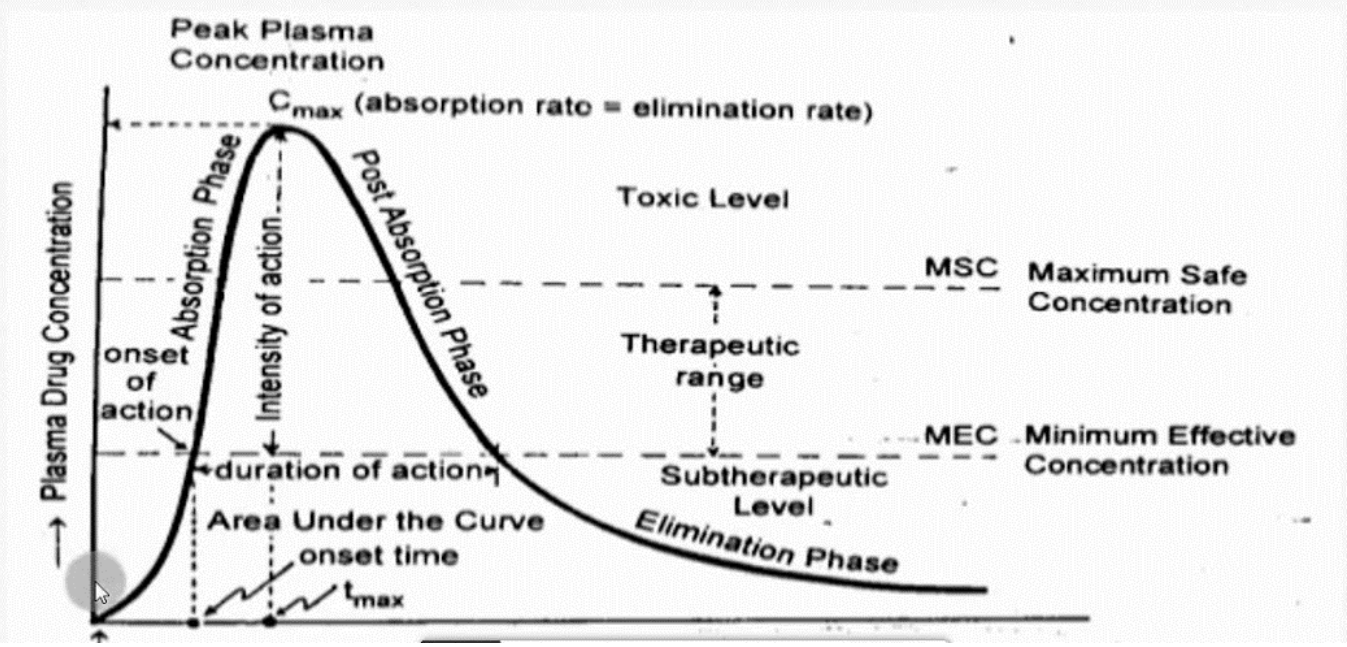
   For which drugs is monitoring helpful?

- Marked pharmacokinetic variability
- Concentration related therapeutic and adverse effects
- Narrow therapeutic index
- Defined therapeutic (target) concentration range
- Desired therapeutic effect difficult to monitor

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion.

Clinical Pharmacokinetics is the application of pharmacokinetic principles to the *safe* and *effective* therapeutic management of drugs in an individual patient.

➢ Absorption and Disposition kinetics



Anatomic and physiologic considerations for drug measurement in the body

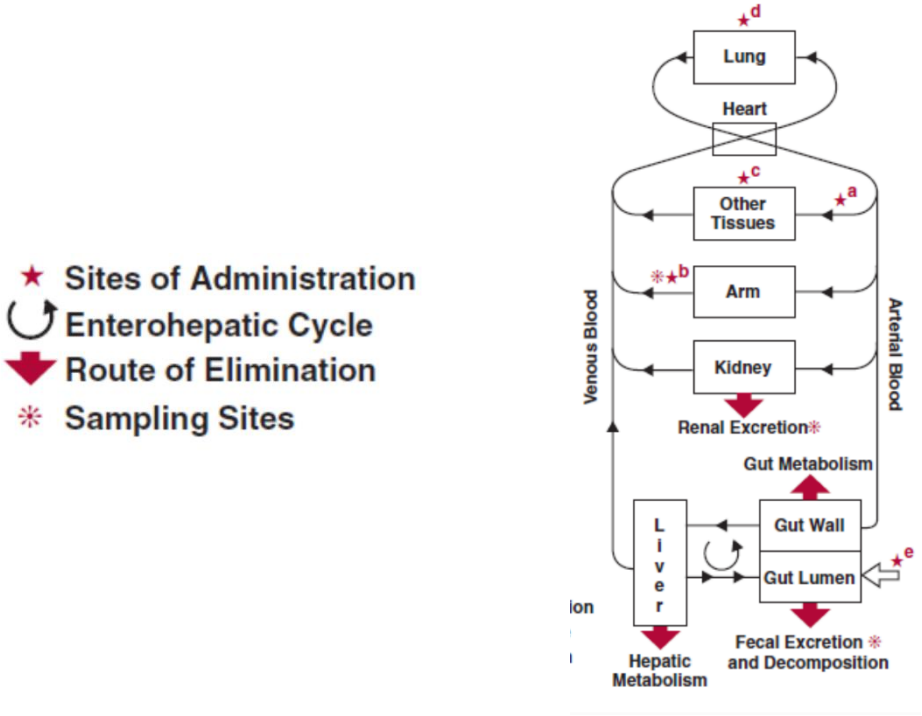
Blood is the most logical site for measurement of drug in the body. Blood receives drug from the site of administration and carries it to all the organs, including those in which the drug acts and those in which it is eliminated

Sites of Administration

There are several sites at which drugs are commonly administered.

1. **Intravascular** administration refers to the placement of a drug directly into the blood—either intravenously or intra-arterially.
2. **Extravascular** modes of administration include the intradermal, intramuscular, oral, pulmonary (inhalation), subcutaneous (into fat under skin), rectal, and sublingual (under the tongue) routes.

   After extravascular administration, an additional step, namely, absorption, is required for drug to reach the systemic site of measurement relative to that required after intravascular administration.

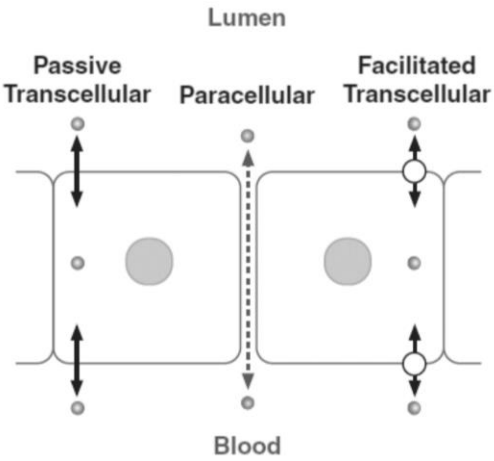


Absorption

Absorption is the process by which unchanged drug proceeds from site of administration to site of measurement within the body, usually plasma in a vein.

Drug transport across physiological membranes

Drug transport can be divided into **transcellular** and **paracellular** processes.



Factors influencing absorption

1. **Effect of pH and the extent of ionisation**

- Weak electrolytes exist in both unionised and ionised form, the ratio of the two forms varying with pH.
- The ionized form of the drug contains a charge and is water soluble and has very low lipid solubility.
- The non-ionised form of the drug is more lipid soluble and in most cases this lipid solubility is sufficient for membrane permeation.
- The extent of ionisation depends on the pKa of the drug and the pH of the medium according to ***Henderson and Hasselbalch*** **equation.**
- For weak acids, For weak bases,

$$AH \overset{Ka}{\rightleftharpoons} A^- + H^+ \qquad BH^+ \overset{Ka}{\rightleftharpoons} B + H^+$$

At a pH equals to the pK_a the drug is 50% ionised. Thus, a weakly acidic drug (e.g. aspirin) in a medium of low pH (e.g. stomach) will be mainly in its undissociated form; whereas a weakly basic drugs (e.g. amphetamines) in a medium of high pH (e.g. small intestine) will be mainly in its undissociated form.

When medium is same, drugs can cross the membrane

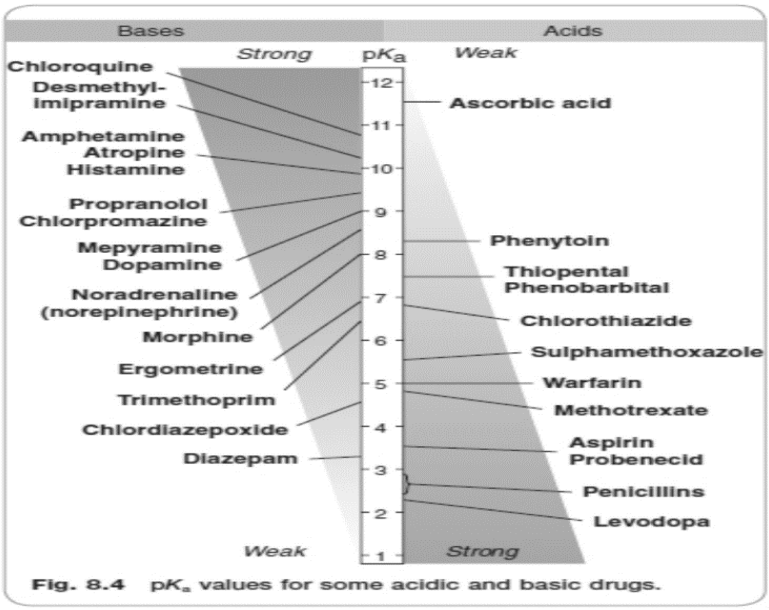
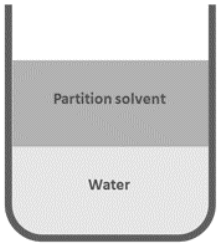


Fig. 8.4 pK_a values for some acidic and basic drugs.

Measurement of Lipid solubility - Log *P* value

$$\text{P = Partition Coefficient} = \frac{\text{Concentration dissolved in partition solvent}}{\text{Concentration dissolved in water}}$$



Conditions:
The solvents are "immiscible"
The system must be at equilibrium
All the solute must be dissolved
Temperature should be constant

Log p	-1.0	0	1.0	2.0	3.0	4.0	5.0	6.0
	Polar compounds Good aq. Solubilty Poor liquid solubility Poor adsorption and distribution.			Compound of intermediate polarity Good balance between aq. And lipid solubility. Good absorption and distribution.			Non polar compounds Poor aq. Solubility Good lipid solubility Slow excretion	

Fig:Effect of log p values on solubility absorption and distribution of drug sunstances.

2. **Blood flow to the absorption site**
3. **Total surface area available for absorption**
4. **Contact time at the absorption surface**

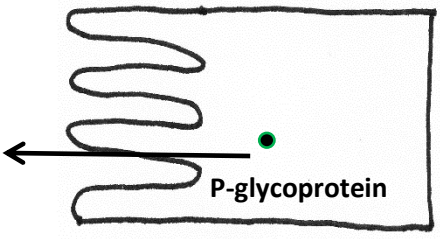
Environment in different parts of the gastrointestinal tract

The GI tract is not a uniform structure, it is composed of several regions differing in anatomy, amount of fluids, biochemical environment, pH, microbial flora, expression of transporters and absorption characteristics

Region	Length (m)	Surface Area (m^2)	pH	Residence Time	Micro-organisms
Oesophagus	0.3	0.02	6.8	>30 seconds	unknown
Stomach	0.2	0.2	1.8-2.5	1-5 hours	$\leq 10^2$
Duodenum	0.3	0.02	5-6.5	>5 minutes	$\leq 10^2$
Jejunum	3	100	6.9	1-2 hours	$\leq 10^2$
Ileum	4	100	7.6	2-3 hours	$\leq 10^7$
Colon	1.5	3	5.5-7.8	15-48 hours	$\leq 10^{11}$

5. **Efflux Transporters: P-Glycoprotein**

P-glycoprotein is an ATP-dependent transporter that is capable of transportation of an extremely wide variety of drugs OUT of the cell

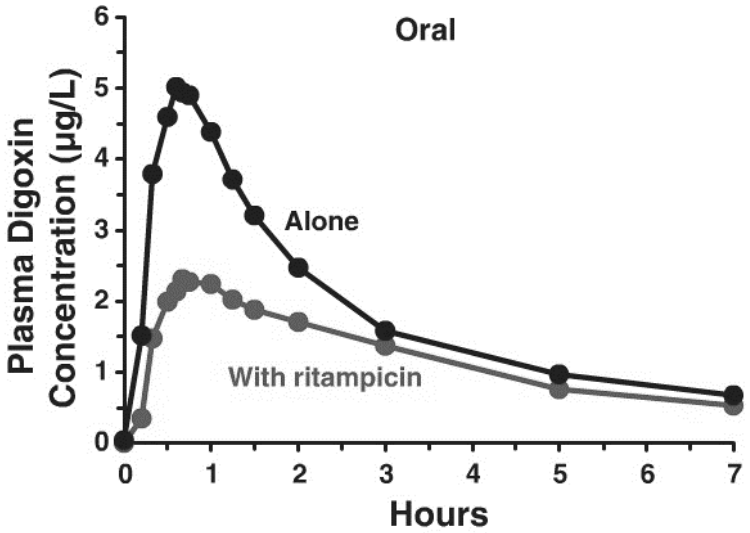


- P-glycoprotein is one of the most important barriers in intestinal absorption of drugs that are substrates to p-glycoprotein
- Most of P-glycoprotein substrates are lipophilic or amphiphilic
- P-glycoprotein is expressed not only in the intestinal epithelium, but also in liver, brain, adrenal gland and kidney
- P-glycoprotein is highly expressed by some cancer cells and is responsible for "multi-drug resistance" of cancer cells

EX Effect of induction of P-glycoprotein on absorption of digoxin

- Digoxin is used in treating heart failure and arrhythmias, and is a substrate for P-glycoprotein.
- Rifampicin is an inducer of P-glycoprotein.

Pre-treatment with rifampicin increases the efflux process from the enterocyte (intestinal epithelial cell) to the intestinal lumen and therefore ***decreases*** the absorption.

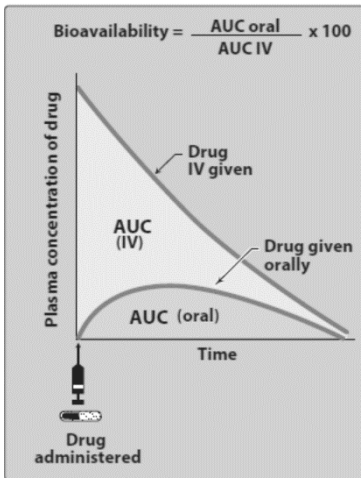


Aliases	Tissue	Drug Substrate	Inhibitor	Inducer
P-gp, MDR1	Intestine, liver, kidney, brain, placenta, adrenal, testes	Digoxin, fexofenadine, indinavir, vincristine, colchicine, topotecan, paclitaxel	Ritonavir, cyclosporine, verapamil, erythromycin, ketocoanzole, itraconazole, quinidine, elacridar (GF120918) LY335979 valspodar (PSC833)	Rifampin, St John's wort

Bioavailability (F)

- ***Bioavailability*** is the rate and extent to which an intact administered drug reaches the systemic circulation
- The fraction of the dose which reaches the systemic circulation as intact drug
- In most cases bioavailability is going to be less than 100%

Determination of bioavailability



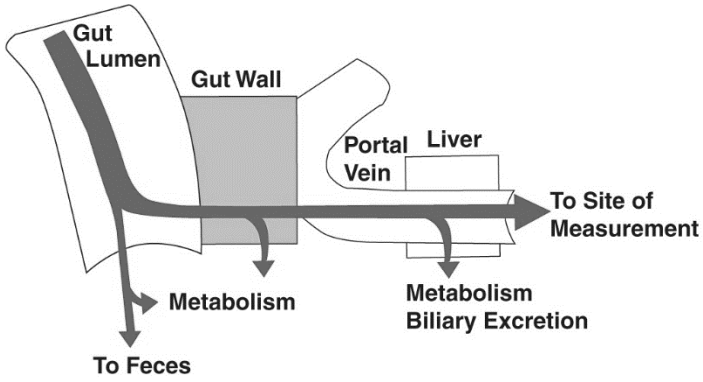
Factors that influence bioavailability

1. **First-pass hepatic metabolism**

Ex More than 90% of *nitroglycerin* is cleared during first-pass metabolism

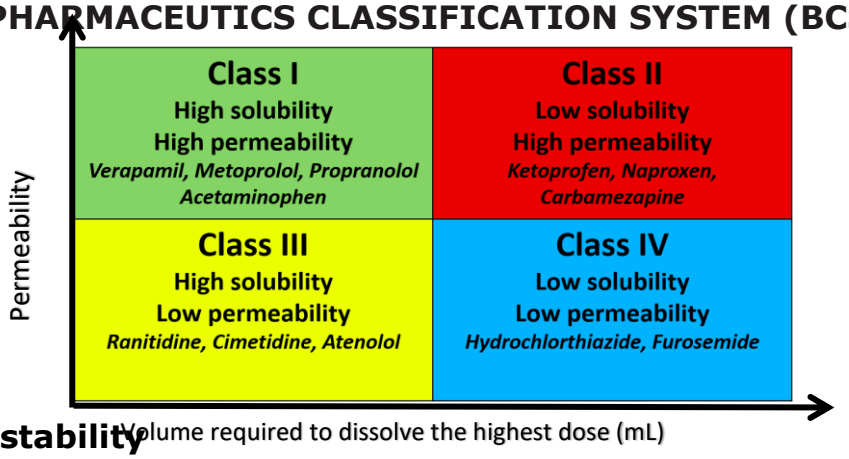
Drugs with High First pass Metabolism

Nitrates	-	Nitrates
Have	-	Hydrocortisone
Large	-	Lignocaine
Pre	-	Propanolol
Systemic	-	Salbutamol
Metabolism	-	Morphine



2. **Solubility of the drug**

THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)



3. **Chemical instability**

Penicillin G -------- unstable in the pH of the gastric contents

Insulin ---------- destroyed in the GI tract by degradative enzymes

4. **Nature of the drug formulation**

- Particle size
- Salt form
- Crystal polymorphism
- Enteric Coatings
- Excipients (such as binders and dispersing agents)

Disposition

Disposition may be defined as all the kinetic processes that occur to a drug subsequent to its systemic absorption. The components of disposition are **distribution** and **elimination**.

Distribution

- Distribution is the process of reversible transfer of a drug to and from the site of measurement and the peripheral tissues. An example is distribution between blood and muscle.
- The pathway for return of drug might not be the same as that leaving the circulation. An example is the **enterohepatic circulation**

The volume of distribution

The volume of distribution (V_D) is a hypothetical volume that relates drug plasma concentrations to the amount of drug in the body.

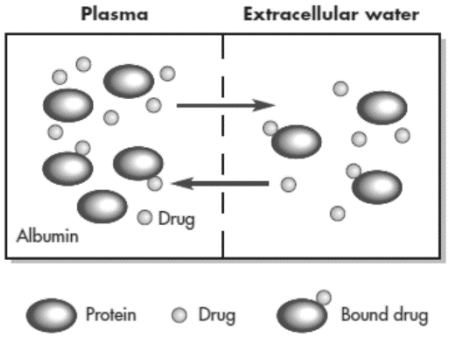
V_D in a pharmacokinetic model, is used to estimate the extent of drug distribution in the body.

$$\mathbf{Vd} = \frac{\mathbf{Amount\ of\ drug\ in\ body\ (D)}}{\mathbf{Concentration\ in\ Plasma (Cp)}}$$

PROTEIN BINDING OF DRUGS

Many drugs interact with plasma or tissue proteins to form a drug–protein *complex*. Drug–protein binding may be

1. Reversible (most common)
2. Irreversible



The protein-bound drug is a large complex that cannot easily transverse the capillary wall and therefore has a restricted distribution

TABLE 11-6 Major Proteins to Which Drugs Bind in Plasma

Protein	Molecular Weight (Da)	Normal Range of Concentrations (g/L)	Normal Range of Concentrations (mol/L)
Albumin	65,000	35–50	$5–7.5 \times 10^{-4}$
α_1-Acid glycoprotein	44,000	0.4–1.0	$0.9–2.2 \times 10^{-5}$
Lipoproteins	200,000–3,400,000	Variable	

Effect of protein binding on the apparent volume of distribution

- Displacement of drugs from plasma proteins can affect the pharmacokinetics of a drug in several ways:

1. Directly increase the free (unbound) drug concentration as a result of reduced binding in the blood;
2. Increase the free drug concentration that reaches the receptor sites directly, causing a more intense pharmacodynamic (or toxic) response;
3. Increase the free drug concentration, causing a transient increase in V_D and decreasing partly some of the increase in free plasma drug concentration;
4. Increase the free drug concentration, resulting in more drug diffusion into tissues of eliminating organs, particularly the liver and kidney, resulting in a transient increase in drug elimination.

Drugs with high plasma protein binding
- Benzodiazepines
  - *Diazepam*
  - *Chlordiazepoxide*
  - *Midazolam*
- Chlorpropamide
- Tolbutamide
- Cyclosporine
- Fluoxetine
- Imipramine
- Verapamil
- Warfarin

Elimination

- Elimination is the irreversible loss of drug from the site of measurement. Elimination occurs by two processes: excretion and metabolism.
- **Excretion** is the irreversible loss of chemically unchanged drug.
- **Metabolism** is the conversion of one chemical species to another.

➢ DRUG CLEARANCE

Drug clearance is a pharmacokinetic term for describing drug elimination from the body without identifying the mechanism of the process.

Drug clearance is the fixed volume of fluid (containing the drug) removed from the drug per unit of time.

The total body CL of a compound is a summation of the CL contributions of various organs.

$$Cl_T = Cl_{renal} + Cl_{hepatic} + Cl_{other}$$

Renal Drug Excretion

- **Glomerular filtration** is a unidirectional process that occurs for most small molecules (MW < 500), including undissociated (nonionized) and dissociated (ionized) drugs. Protein-bound drugs behave as large molecules and do not get filtered at the glomerulus.
- **Active tubular secretion** is an active transport process. As such, active renal secretion is a carrier-mediated system that requires energy input, because the drug is transported against a concentration gradient. The carrier system is capacity limited and may be saturated. Drugs with similar structures may compete for the same carrier system.
- **Tubular reabsorption** occurs after the drug is filtered through the glomerulus and can be an active or a passive process involving transporting back into the plasma.

Hepatic clearance

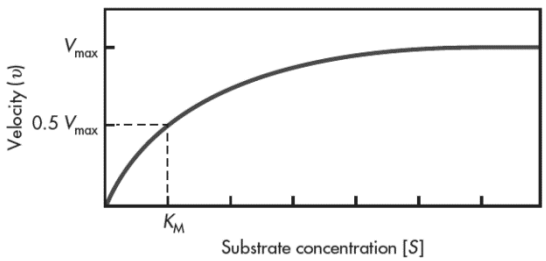
- *Hepatic clearance* may be defined as the volume of blood that perfuse the liver which is cleared of drug per unit of time.

$Cl_T = Cl_{nr} + Cl_r$

$Cl_h = Cl_T - Cl_R$

Metabolism kinetics—michaelis– menten equation

- *biotransformation* or *metabolism* is the enzymatic conversion of a drug to a metabolite.
- the metabolic enzyme concentration is constant at a given site, and the drug (substrate) concentration may vary.
- When the drug concentration is low relative to the enzyme concentration, the rate of metabolism is a first-order process.
- At high plasma drug concentration the rate process then becomes a zero-order process
- The *maximum reaction rate* is known as V_{max}
- The drug concentration at which the reaction occurs at half the maximum rate corresponds to a composite parameter K_M (*Michaelis constant)*.



The relationship between V_{max} and K_M is given by *Michaelis–Menten equation*

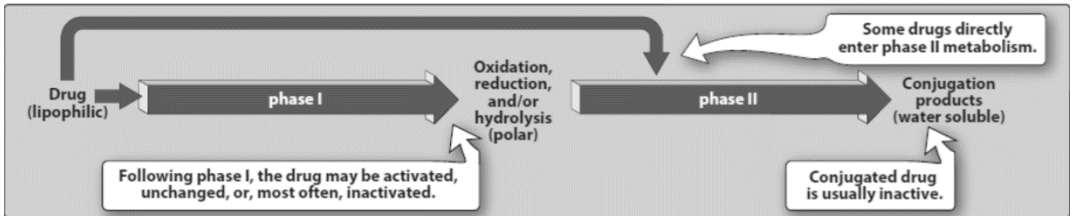
- **1. First-order kinetics**

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{K_m}$$

2. Zero-order kinetics

$$v = \text{Rate of drug metabolism} = \frac{V_{max}[C]}{[C]} = V_{max}$$

Reactions of Drug Metabolism



Some examples of CP450 enzymes, their substrates, inducers, and inhibotors

CYP	Substrate	Inducer	Inhibitor
3A4 (Metabolizes 50% of drugs, most common)	• Astemizole • Cisapride • Terfenadine • Cyclosporine • Tacrolimus • Calcium channel blockers • Protease inhibitors • Estrogens	Barbiturates Rifampicin Phenytion Carbamazepine St. John's wort	Erythromycin Ketoconazole Fluconazole Grapefruit juice Ritonavir
2D6 (Metabolizes 20% drugs)	• Most antidepressants – TCA – SSRI – MAO inhibitors • Most beta blockers • Most antiarrhythmics	No known inducer	Quinidine Paroxetine
2 C 19	• Omeprazole • Clopidogrel	Rifampicin Barbiturates	Fluconazole
2 C 9	• Phenytion • Tolbutamide • Warfarin	Rifampicin Barbiturates	Erythromycin Cimetidine
1 A 2	• Theophylline warfarin	Smoking Rifampicin	Ciprofloxacin
2 E 1	• Acetaminophen • Enflurane • Halothane	Ethanol	Disulfiram