

# Pharmacokinetics Modelling Course:

## 2. Absorption, Metabolization, PK Parameters

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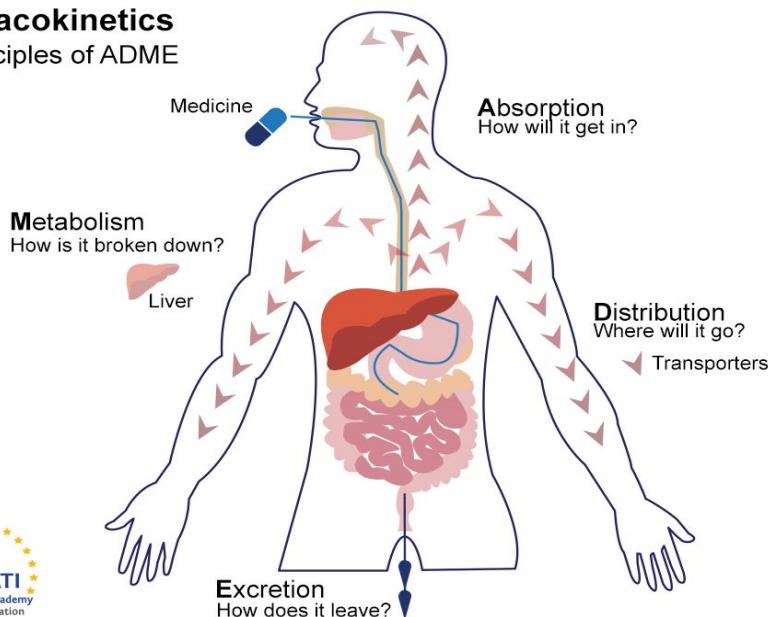
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# ADME

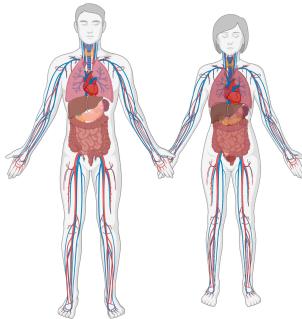
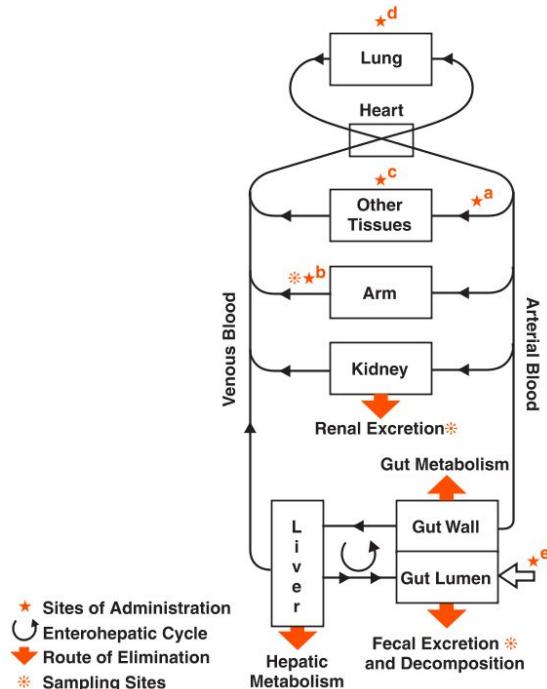
## Pharmacokinetics The principles of ADME



ADME processes determine pharmacokinetics

- **Absorption**
- **Distribution**
- **Metabolization**
- **Elimination**

# ADME



**FIGURE 2-2** Once absorbed from any of the many sites of administration, drug is conveyed by blood to all sites within the body, including the eliminating organs. Sites of administration include: **a**, artery; **b**, peripheral vein; **c**, muscle and subcutaneous tissue; **d**, lung; and **e**, gastrointestinal tract, the most common route (denoted by open arrow). When given intravenously into an arm vein, the opposite arm should then be used for blood sampling. The movement of virtually any drug can be followed from site of administration to site of elimination.

- many sites of administration
  - a) artery
  - b) peripheral vein (iv)
  - c) muscle and subcutaneous tissue
  - d) lung
  - e) gastrointestinal tract (oral)
- sampling sites
  - venous blood, urine, feces
- elimination
  - hepatic metabolism
  - renal excretion/metabolism
  - gut metabolism
  - fecal excretion
- distribution via blood flow and systemic circulation

# Absorption

Various factors can influence drug absorption, including:

**1. Route of Administration:** The route of administration significantly impacts how a drug is absorbed. For instance, drugs administered intravenously bypass the absorption process as they are introduced directly into the bloodstream. However, orally administered drugs must pass through the stomach and intestines, where they are absorbed into the bloodstream. This can be influenced by factors such as pH levels, presence of food, and gastrointestinal motility.

**2. Drug Formulation:** The physical and chemical properties of the drug can influence how well it is absorbed. For example, drugs formulated in a liquid solution are often absorbed more rapidly than those in a tablet or capsule.

**3. Physiological Factors:** Individual characteristics like age, sex, genetic factors, and health status can also influence drug absorption. For example, certain conditions like malabsorption syndromes or diseases affecting the liver or kidney can alter the absorption of drugs.

**4. Drug Interactions:** Certain drugs can interact in the body and affect absorption. For instance, some medications can increase stomach acidity, which can affect the absorption of other drugs.

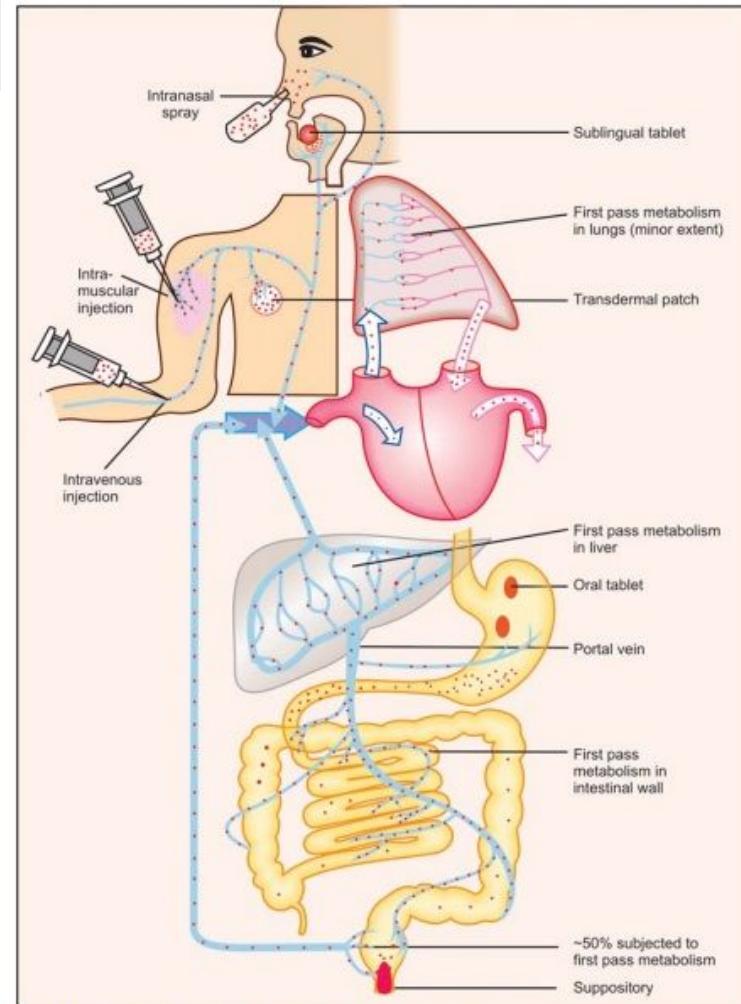


Fig. 1.1: Vascular pathway of drugs absorbed from various systemic routes of administration and sites of first pass metabolism

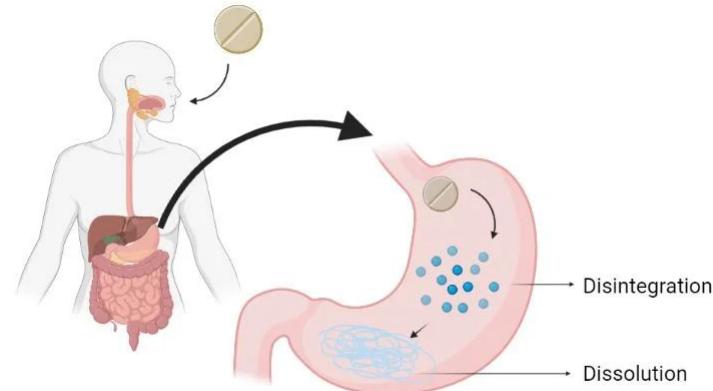
# Dissolution

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Dissolution is the process by which a solid drug disintegrates and dissolves in a solvent (like gastrointestinal fluids) to form a solution that can be absorbed into the body.

- Dissolution is crucial for drug absorption in solid dosage forms.
- The dissolution rate depends on the drug's solubility.
- Drug formulation can significantly impact dissolution rate.
- The rate of dissolution can influence drug bioavailability.
- In vitro dissolution testing is used to estimate how a drug will dissolve and be absorbed in the body.
- Physiological conditions like pH, motility, and the presence of food can affect drug dissolution.

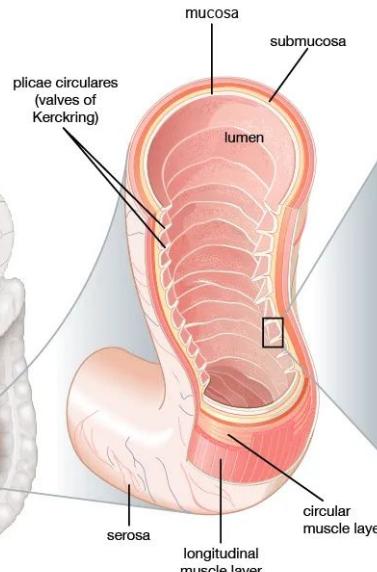
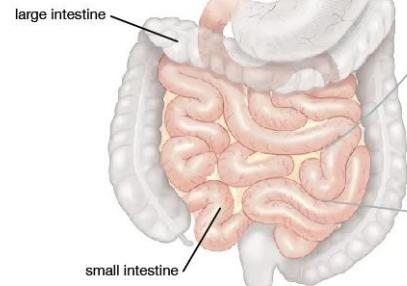
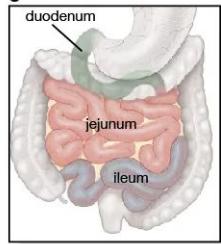
In essence, dissolution is vital in pharmaceutical science to ensure the drug dissolves properly for effective absorption and therapeutic effect.



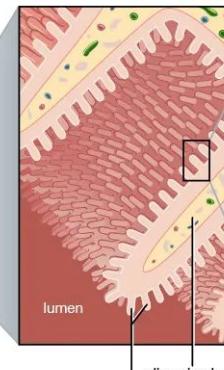
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# Absorption of oral medication in the intestine

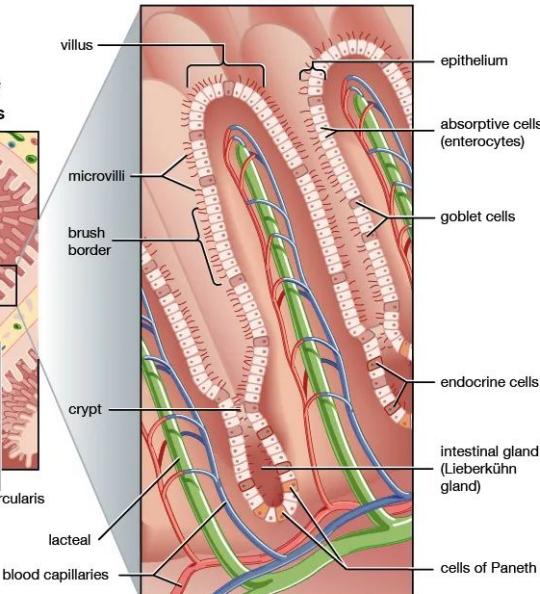
Regions of the small intestine



Enlargement of plicae circulares



Structure of a villus



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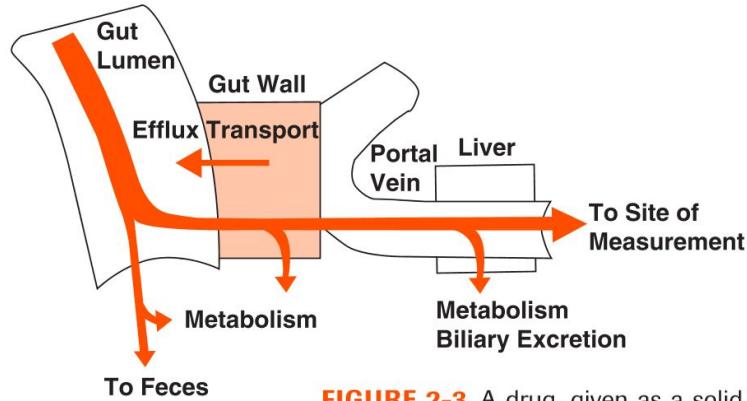
<https://www.pharmacopedia.com/drug-in-pharmacopedia/>  
<https://www.britannica.com/science/small-intestine>

# Bioavailability

- **bioavailability:** due to losses during absorption, intestinal metabolism, efflux and hepatic extraction only a fraction of the drug appears in the systemic circulation

## Clinical implications

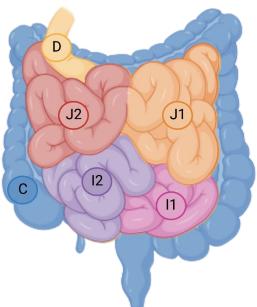
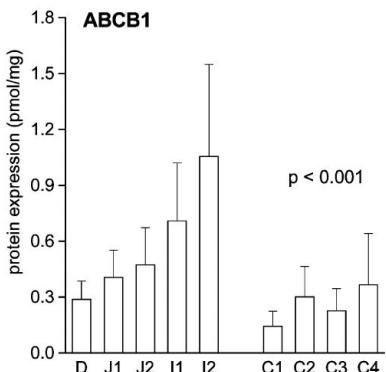
- **Delays or loss of drug during absorption** can introduce a large variability in drug response.
- **Disease conditions and co-medications** may profoundly affect the absorption of certain drugs.



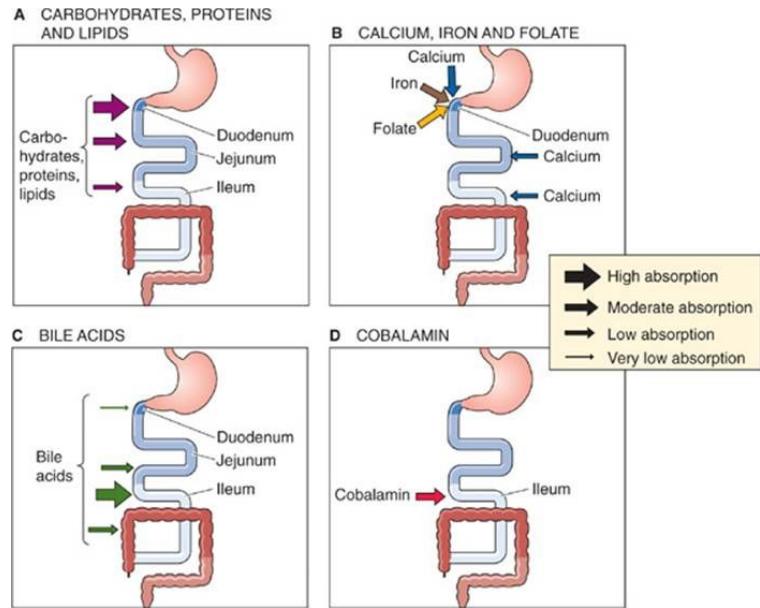
**FIGURE 2-3** A drug, given as a solid, encounters several barriers and sites of loss in its sequential movement (colored arrows) through the gastrointestinal tissues and the liver. Incomplete dissolution, degradation in the gut lumen, metabolism by enzymes, and efflux by transporters, in the gut wall are causes of incomplete input into the systemic circulation. Removal of drug as it first passes through the liver may further reduce systemic input.

# Site-dependent absorption

- transporters/processes specific to certain intestinal segments



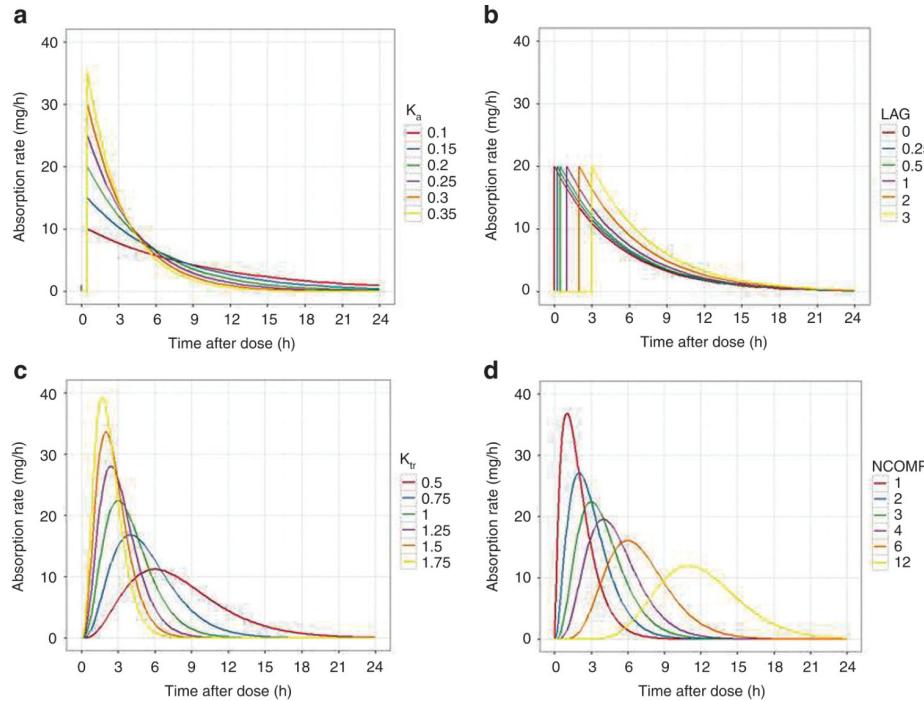
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**Figure 45-2** Sites of nutrient absorption. **A**, The entire small intestine absorbs carbohydrates, proteins, and lipids. However, the absorption is greatest in the duodenum, somewhat less in the jejunum, and much less in the ileum. The thickness of the arrows in the inset indicates the relative magnitude of total absorption at the indicated site *in vivo*. The maximal absorptive capacity of a specific segment under optimized experimental conditions (e.g., substrate concentrations) may be greater. **B**, Some substances are actively absorbed only in the duodenum. **C**, Bile acids are absorbed along the entire small intestine, but active absorption occurs only in the ileum. **D**, The vitamin cobalamin is absorbed only in the ileum.

# Example absorption models

- A. first-order absorption with different rate of absorption
- B. first-order absorption with different lag-times
- C. Transit chain ( $n=3$ , different rates)
- D. Transit chain (different  $n$ )



**Figure 1** Models of extravascular absorption. The time profile of absorption rate for selected absorption models. (a) A first-order absorption model with different values of the absorption rate constant ( $K_a$ ). Absorption lag was 0.5 h in all cases. (b) A first-order absorption model with different values of the absorption lag (LAG). Absorption rate constant was 0.5/h in all cases. (c) A three-compartment transit chain model with different values of the transit chain rate constant ( $K_{tr}$ ). Note that decreasing the rate constant lowers the overall absorption rate and delays the time of its maximum value. (d) Transit chain models with different numbers of transit chain compartments (NCOMP). The transit chain rate constant was 1/h in all cases. Note that increasing the number of compartments introduces a delay before absorption, and functionally acts as a lag. The dose was 100 mg in all cases (hence the area under the curve should be 100 mg for all models).

Mould DR, Upton RN. Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT Pharmacometrics Syst Pharmacol. 2013 Apr;17(2):e38. doi: 10.1038/psp.2013.14. PMID: 23887688; PMCID: PMC3636497.

# Drug formulation

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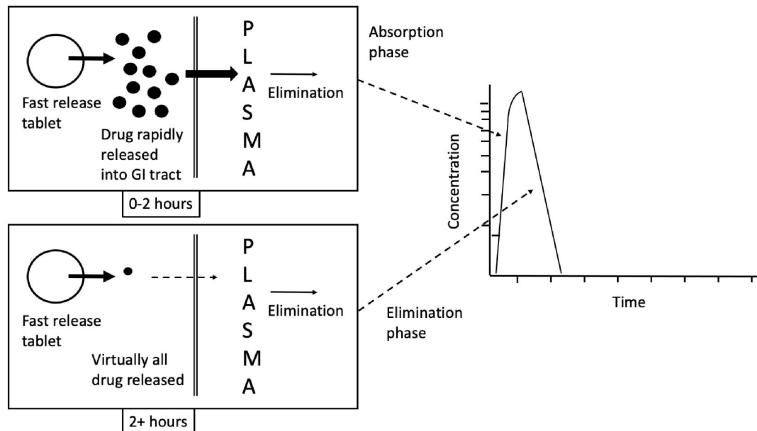


Figure 8: illustration of how the absorption and elimination phases are affected by rapid release of drug into the gastrointestinal tract (GI Tract).

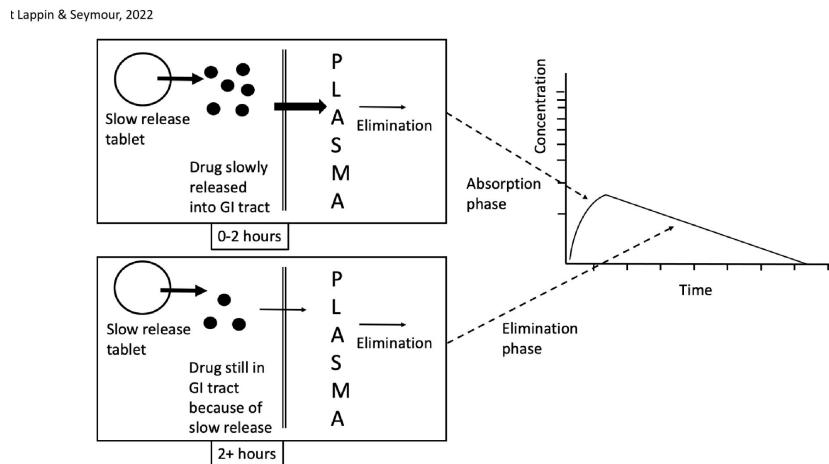
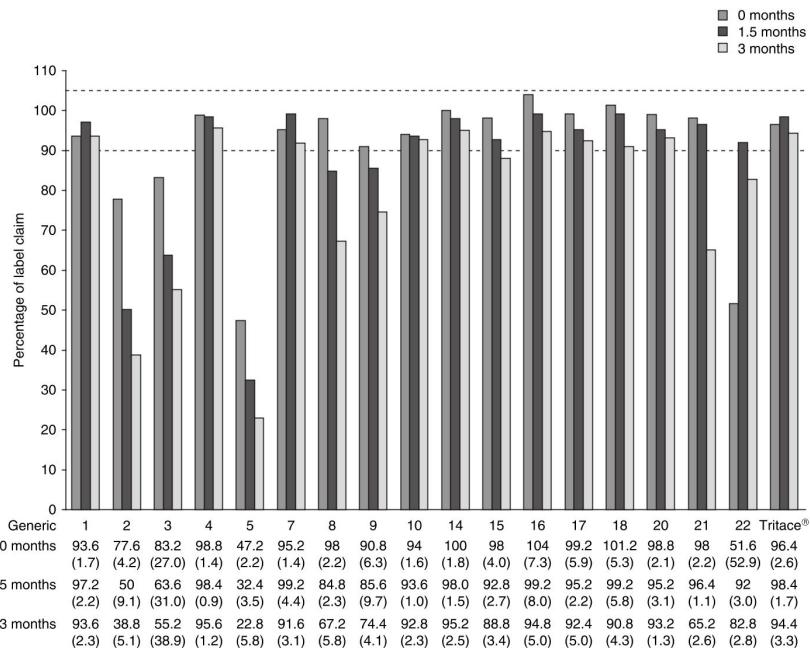
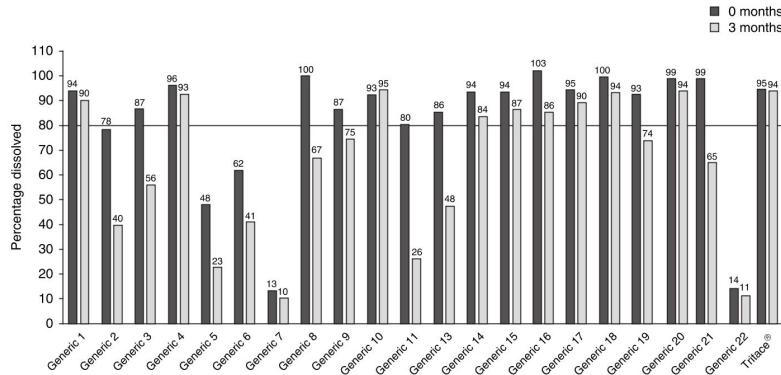


Figure 9: illustration of flip-flop kinetics caused by slow release of drug into the gastrointestinal tract (GI Tract).

# Variability in dose and dissolution



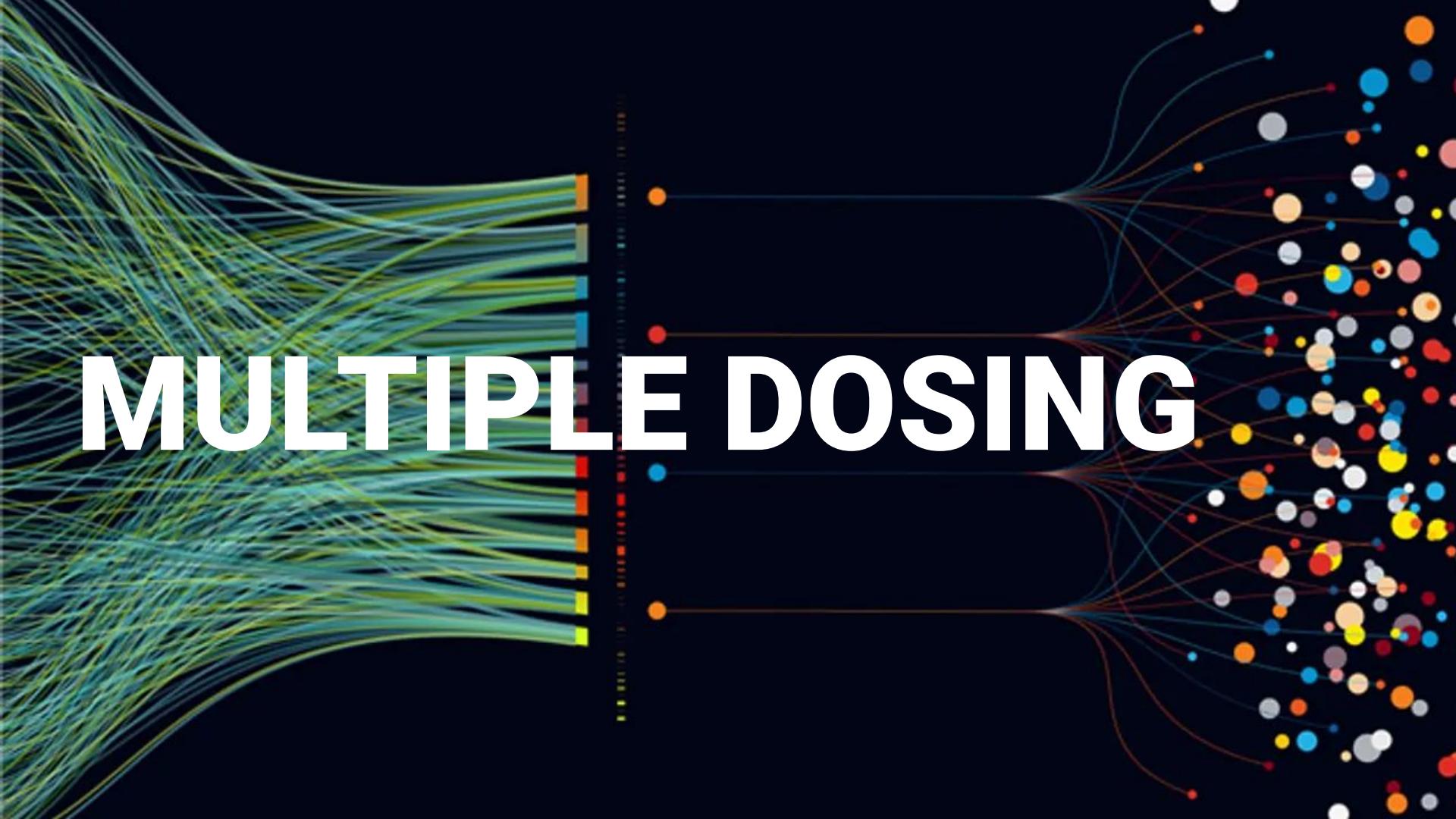
**Fig. 2.** Assay of ramipril levels vs label claim. Percentage of ramipril in 17 ramipril generics/copies vs the reference ramipril product (Tritace<sup>®</sup>) before and after 1.5 and 3 months of temperature-stressed storage, as determined using a validated high-performance liquid chromatography system (see Materials and Methods section for details of the assay).<sup>[16]</sup> Results represent the mean (relative standard deviation) of the average values for ten individual tablets. No data are reported for Generics 6, 11, 12, 13 and 19 as the assays for these were not completed because of a shortage of tablets. Sanofi-Aventis specification limits (within 90–105% of label claim) are illustrated by the dotted lines.



**Fig. 4.** Dissolution profiles of 21 ramipril generics/copies vs the reference ramipril product (Tritace<sup>®</sup>). Results from 30-minute dissolution assays conducted at baseline (day 0) and after 3 months' temperature-stressed storage; results are the mean of the average values from six individual tablets. The Sanofi-Aventis specification limit ( $\geq 80\%$  dissolution in 30 minutes) is illustrated by the black line. No data are reported for Generic 12 as the dissolution assay was not completed because of a shortage of tablets. Dissolution assays were conducted according to validated dissolution tests for solid dosage forms using a paddle system (Apparatus 2 as described in the European Pharmacopoeia 6.0<sup>[17]</sup>); dissolved contents were assayed using a validated high-performance liquid chromatography system (see Materials and Methods section for details of the assay).<sup>[16]</sup>

Angeli DG, Trezza C. Quality and stability of ramipril generics/copies versus reference ramipril (Tritace): a 3-month stability comparative study. Clin Drug Investig. 2009;29(10):667-76.  
doi: 10.2165/11315270-000000000-00000. PMID: 19715383.

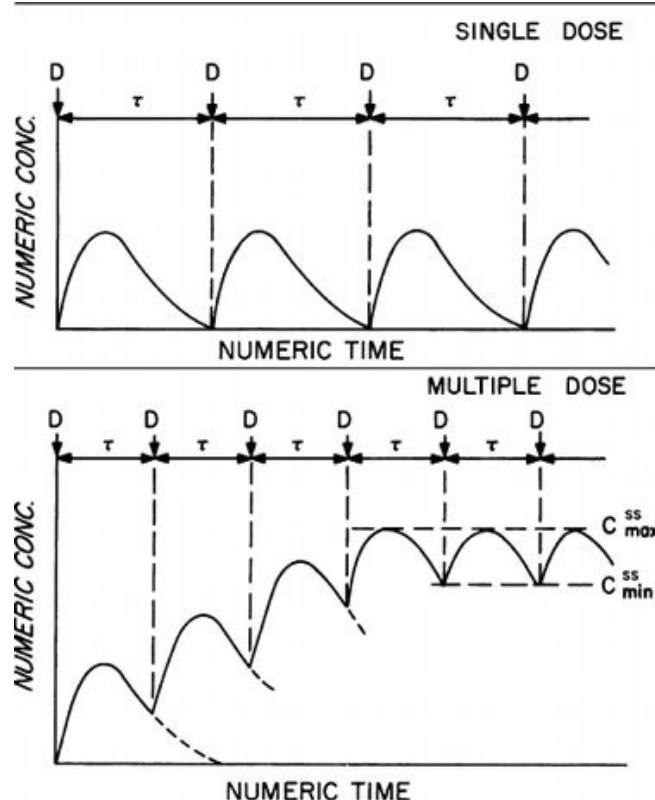
# MULTIPLE DOSING

The background features a complex network of thin, curved lines in various colors (blue, green, yellow, orange) originating from a central vertical axis on the left and converging towards a cluster of larger, semi-transparent circular nodes on the right. The nodes are also colored in a variety of shades, including blue, green, yellow, orange, red, and purple. The overall effect is one of a dynamic, interconnected system.

# Multiple dosing

Multiple dosing in drug therapy refers to the practice of administering multiple doses of a drug or medication

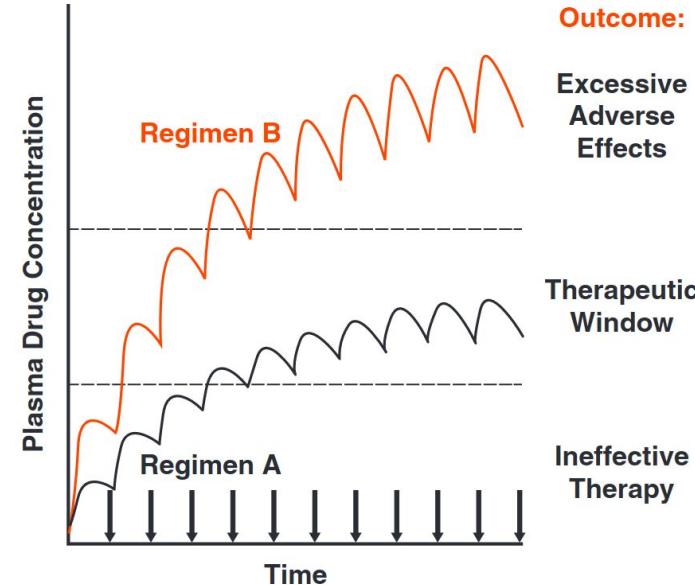
1. **Steady-state Concentration:** Over time, multiple doses of a drug lead to a steady-state concentration in the blood.
2. **Dosing Interval:** The dosing interval is the time between two consecutive doses.
3. **Therapeutic Window:** This is the range of drug concentrations in the blood that provide effective treatment without causing toxicity.
4. **Dose and Frequency:** The size of the dose and frequency of dosing are critical in multiple dosing strategies.
5. **Accumulation and Elimination:** When drugs are administered repeatedly, they can accumulate in the body, leading to higher concentrations than after the first dose.
6. **Interindividual Variability:** There can be a significant difference in how different individuals respond to the same drug and dosage due to genetic factors, age, gender, organ function, and the presence of other diseases or drugs.
7. **Compliance:** Compliance with the dosing regimen is essential for the success of the treatment.



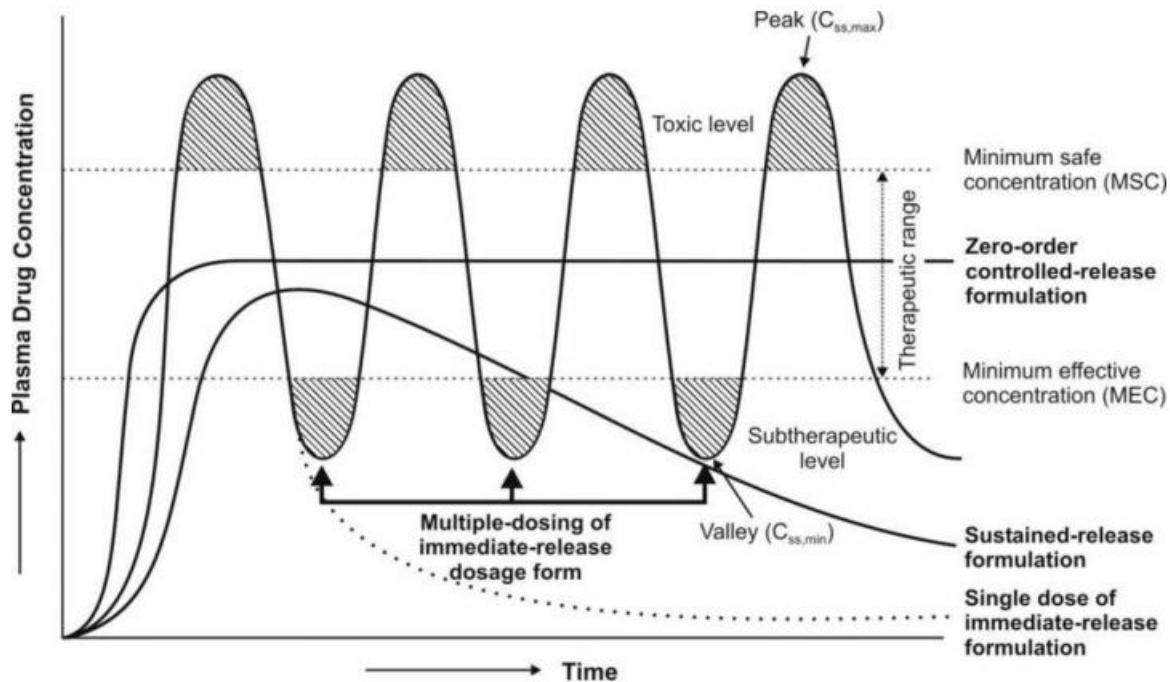
# Optimal dosing regime & Therapeutic window

The therapeutic window is determined by two main factors: **the minimum effective concentration (MEC)** and the **maximum tolerable concentration (MTC)**.

- The **minimum effective concentration (MEC)** is the lowest concentration of a drug in the patient's bloodstream that still produces the desired therapeutic effect. If the concentration falls below this level, the drug may not be effective in treating the condition, leading to ineffective therapy.
- The **maximum tolerable concentration (MTC)** is the highest concentration of a drug that can be tolerated without causing significant toxic effects or side effects. If the drug concentration exceeds this level, the risk of side effects and toxicity increases.

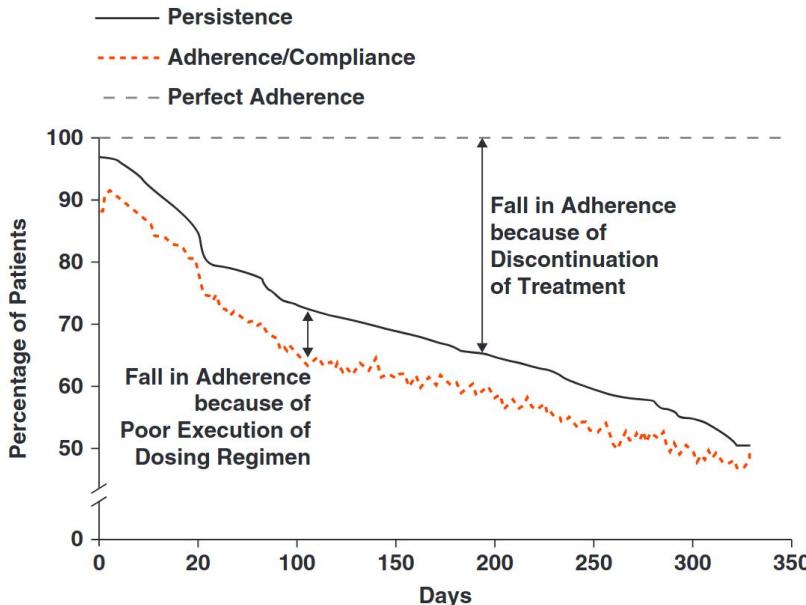


# Controlled release medication



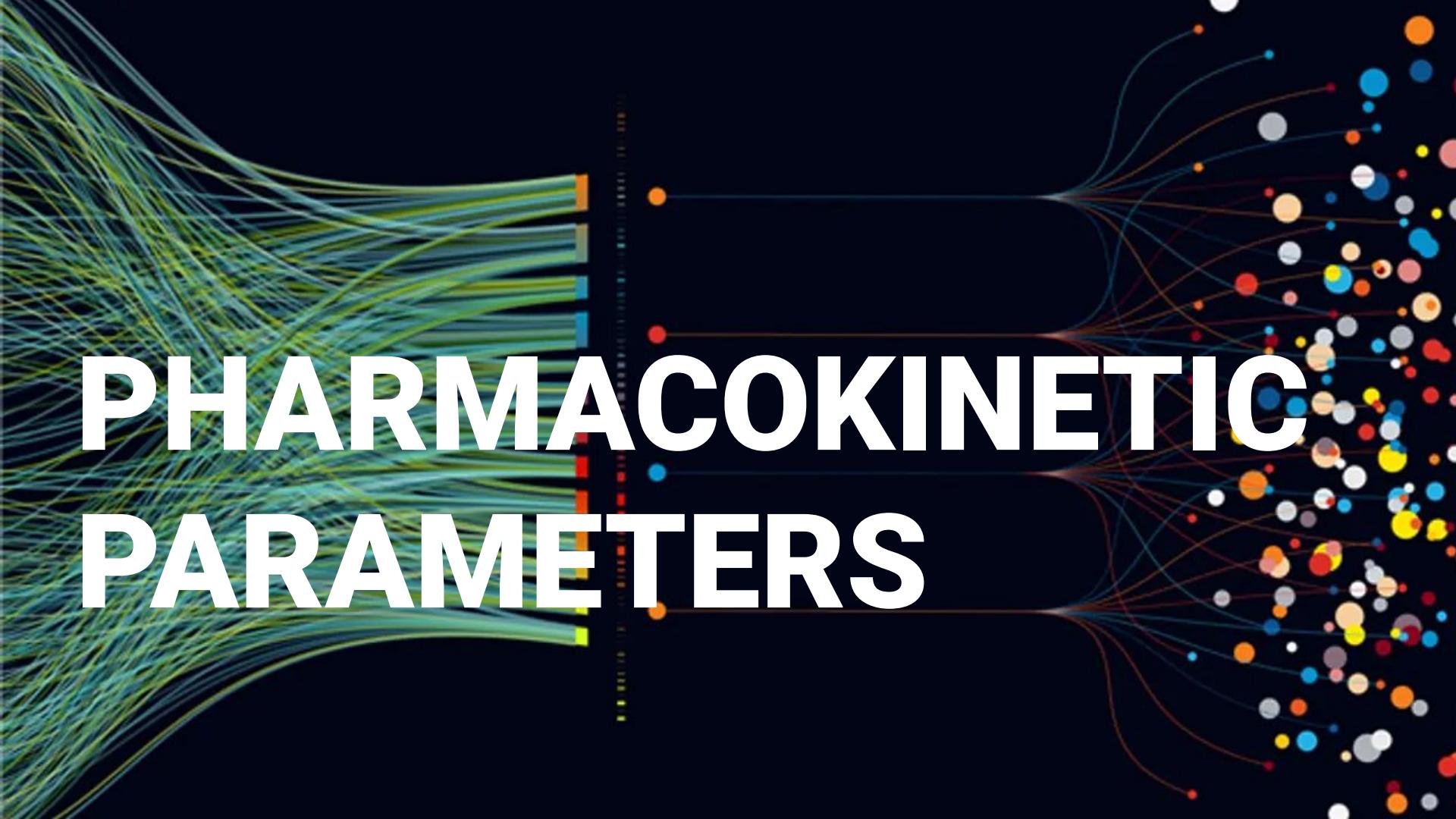
# Compliance

- after the end of first year only ~50% continue to take the prescribed medication
- anti-hypertensive drugs



**FIGURE 1-9** Nonadherence to prescribed medication is a major source of variability in drug therapy. Shown is the gradual but persistent decrease in adherence in the percentage of 4783 patients prescribed a variety of once-a-day antihypertensive therapies due to discontinuation of treatment, such that by the end of the first year only 50% of the patients prescribed the treatment for an indefinite duration continue to take the prescribed medication. The initial 3% drop in adherence is due to some patients never even starting the medication. The data were obtained using an electronic monitoring device that detects and logs each time the container with the medication is opened. (Taken from Vrijens B, Vincze G, Kistanto P, et al. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. *Brit Med J* 2008;18:1-6.)

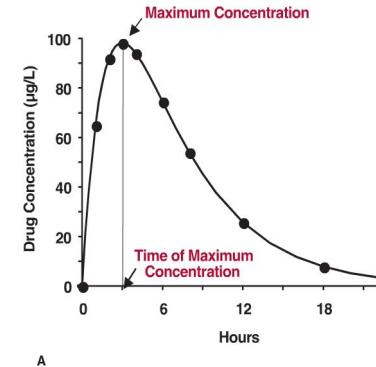
# PHARMACOKINETIC PARAMETERS



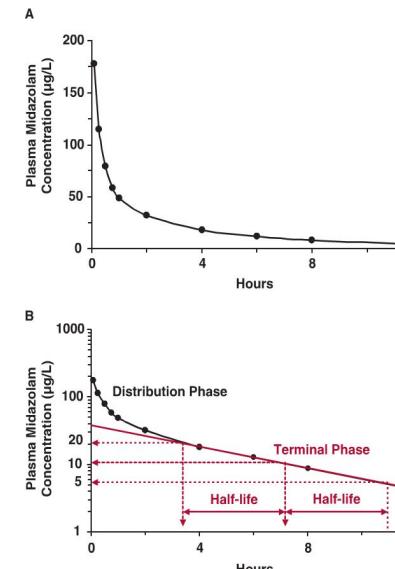
# Pharmacokinetic parameter

Pharmacokinetic parameters are numerical values that describe how a drug behaves in the body. They play a vital role in determining the dosage and frequency of drug administration.

1. **Absorption:** This parameter involves how the drug is absorbed into the bloodstream from the site of administration. The rate and extent of absorption can influence the onset, intensity, and duration of a drug's effect.
2. **Distribution:** This refers to how the drug spreads throughout the body. The volume of distribution ( $V_d$ ) is a key parameter that quantifies the extent to which a drug is distributed in the body's tissues compared to its concentration in the blood.
3. **Metabolism (Biotransformation):** Metabolism is how the drug is chemically modified or broken down in the body, primarily by liver enzymes. This can change the drug's activity and affects how quickly it's cleared from the body.
4. **Elimination (Excretion):** This parameter refers to the removal of the drug from the body, primarily through the kidneys (urine) or liver (bile). The rate of elimination is usually expressed as the drug's half-life ( $t_{1/2}$ ), which is the time it takes for the concentration of the drug in the body to be reduced by half.
5. **Clearance (Cl):** This is a measure of the body's efficiency in eliminating the drug, expressed as volume/time (like mL/min). It's a crucial parameter that determines the steady-state concentration of the drug for a given dosage regimen.
6. **Bioavailability (F):** This is the fraction of the administered dose of a drug that reaches the systemic circulation in an unchanged form. It's a crucial parameter, especially for oral medications.
7. **Area Under the Curve (AUC):** This is a measure of the total exposure of the body to the drug. It's calculated as the integral of the concentration-time curve, from administration to elimination.
8. **Peak Concentration ( $C_{max}$ ) and Time to Reach Peak Concentration ( $t_{max}$ ):**  $C_{max}$  is the highest concentration a drug achieves in the body after administration, and  $t_{max}$  is the time it takes to reach this peak concentration.



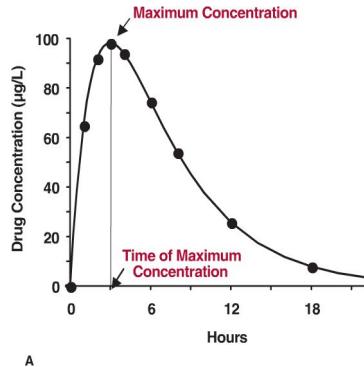
**FIGURE 2-1.** Drug concentration–time curve following a single oral dose showing the maximum systemic exposure ( $C_{max}$ ) and the time of its occurrence ( $t_{max}$ ). The concentration could represent drug in whole blood, plasma, or serum.



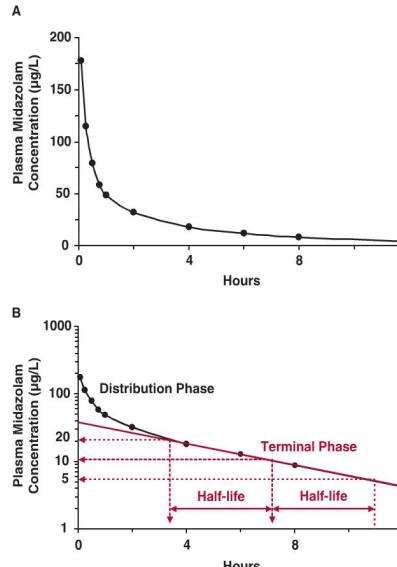
**FIGURE 3-4.** A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Penttiläinen PJ, Väistöalmi L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989;29: 272–277.)

# Pharmacokinetic parameter

- $C_{max}$  : Maximal concentration
- $T_{max}$  : time of maximal concentration
- AUC : area under the curve
- $k_{el}$ : elimination rate fitting linear part of terminal phase (log)
- $t_{1/2}$  : half-life ( $= \ln 2/k_{el}$ ) time for concentration to fall to half
- $Vd$ : volume of distribution ( $= CL/k$ ), dilution space
- $CL$ : clearance ( $= \text{Dose}/\text{AUC}$ ,  $= \text{Dose}/C(0)_{\text{extrapolated}}$ )



**FIGURE 2-1.** Drug concentration–time curve following a single oral dose showing the maximum systemic exposure ( $C_{max}$ ) and the time of its occurrence ( $t_{max}$ ). The concentration could represent drug in whole blood, plasma, or serum.



**FIGURE 3-4.** A. Plasma concentration of midazolam with time in an individual after an 8.35-mg i.v. bolus dose of midazolam hydrochloride (7.5 mg of the base) in a healthy adult. B. The data in A are redisplayed as a semilogarithmic plot. Note the short distribution phase. (From: Pentikäinen PJ, Väistönen L, Himberg JJ, Crevoisier C. Pharmacokinetics of midazolam following i.v. and oral administration in patients with chronic liver disease and in healthy subjects. *J Clin Pharmacol* 1989;29: 272–277.)

# Area under the curve (AUC)

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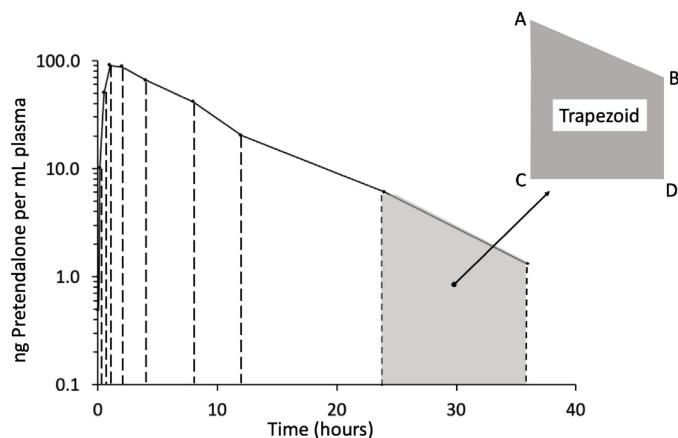


Figure 22: illustration of calculation of area of each trapezoid across the drug-concentration time plot using the linear trapezoidal rule.

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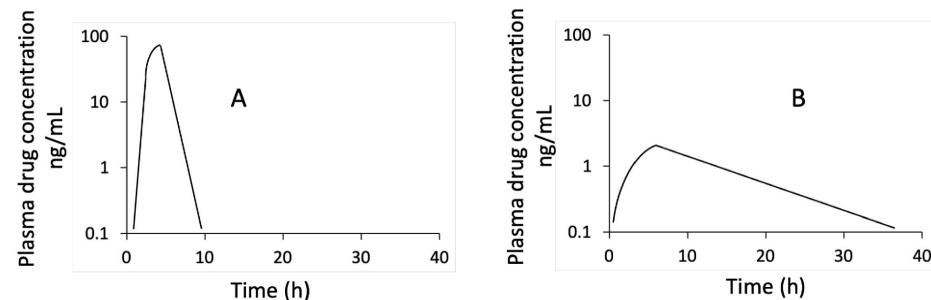


Figure 20: two pharmacokinetic curves of different shape but with the same AUC.

# AUC extrapolation

## Area Under the Curve (AUC):

- It's a pharmacokinetic parameter that represents the total exposure of the body to a drug.
- AUC is calculated as the integral of the drug concentration-time curve, from the time of administration until the drug is eliminated from the body.
- The AUC provides valuable information about the drug's bioavailability and clearance rate.
- It's widely used in therapeutic drug monitoring, dose adjustment, and comparison of generic drugs with original brands (bioequivalence studies).

## AUC Interpolated to Infinity ( $AUC_{0-\infty}$ ):

- This is an extension of the AUC that accounts for the drug amount that remains in the body and has not yet been eliminated at the last measured time point.
- It's calculated by adding the AUC from time zero to the last measurable concentration ( $AUC_{0-t}$ ) and the extrapolated AUC from the last measurable concentration to infinity (Clast/elimination rate constant).
- $AUC_{0-\infty}$  provides a more complete picture of the body's exposure to the drug over an infinite period.
- It is particularly useful when determining the bioavailability of a drug, as it accounts for the total drug exposure from the time of administration onwards.

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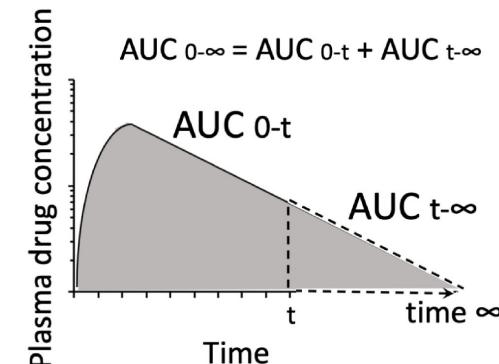
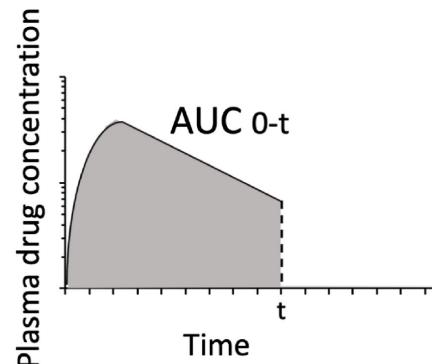


Figure 19: grey areas underneath the drug-concentration versus time curve are diagrammatic representations of areas under the curve with  $AUC_{0-t}$  (on the left) and  $AUC_{0-\infty}$  (on the right) for a typical oral administration. Dotted lines on the right-hand plot represent extrapolation of  $AUC_{0-t}$  to  $AUC_{0-\infty}$ .

# Pharmacokinetic parameters (pretendalone)

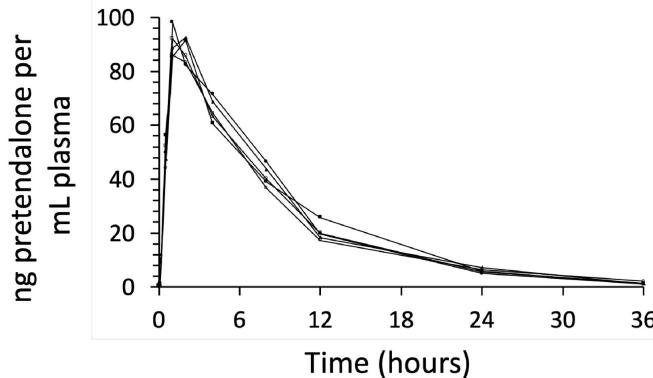


figure 2: plot of time versus concentration (ng Pretendalone per mL plasma) for five subjects following a 50 mg single oral dose.

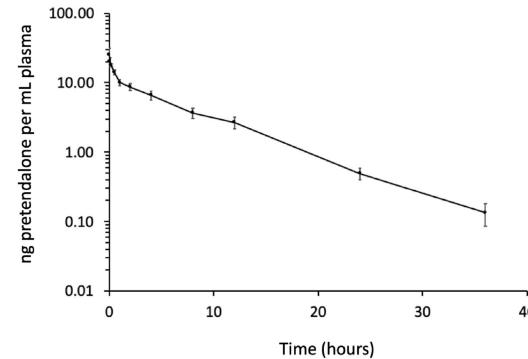


Figure 4: semi-log plot of time versus mean concentration (ng Pretendalone per mL plasma) following a 2 mg single bolus intravenous dose. Error bars are  $\pm$  one standard deviation (n=5).

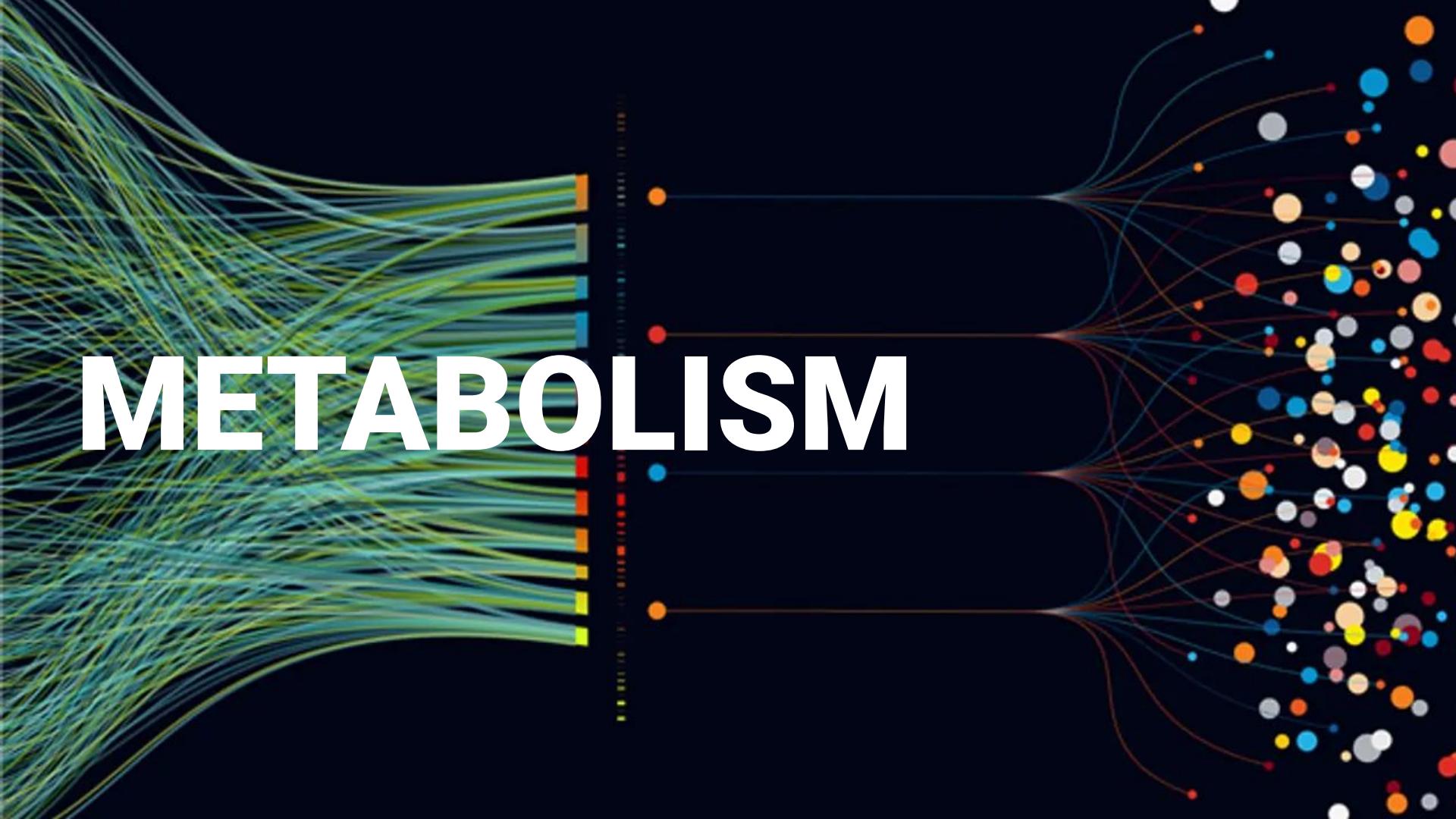
Pharmacokinetic parameter	Symbol	Unit	Mean	Standard Deviation
Maximum plasma drug concentration	$C_{\max}$	ng/mL	92.08	4.31
Time to $C_{\max}$	$t_{\max}$	h	1.4	0.55
Elimination rate constant	$k$	$h^{-1}$	0.123	0.009
Elimination half-life oral	$t_{1/2}$	h	5.64	0.46
Area under the plasma drug concentration time curve between zero and 36 hours	$AUC_{0-36}$	ng/mL.h	789.76	26.66
Area under the plasma drug concentration time curve between zero and infinite time	$AUC_{0-\infty}$	ng/mL.h	800.67	22.59
Absolute oral bioavailability	$F$	Ratio, no unit	0.35	0.02

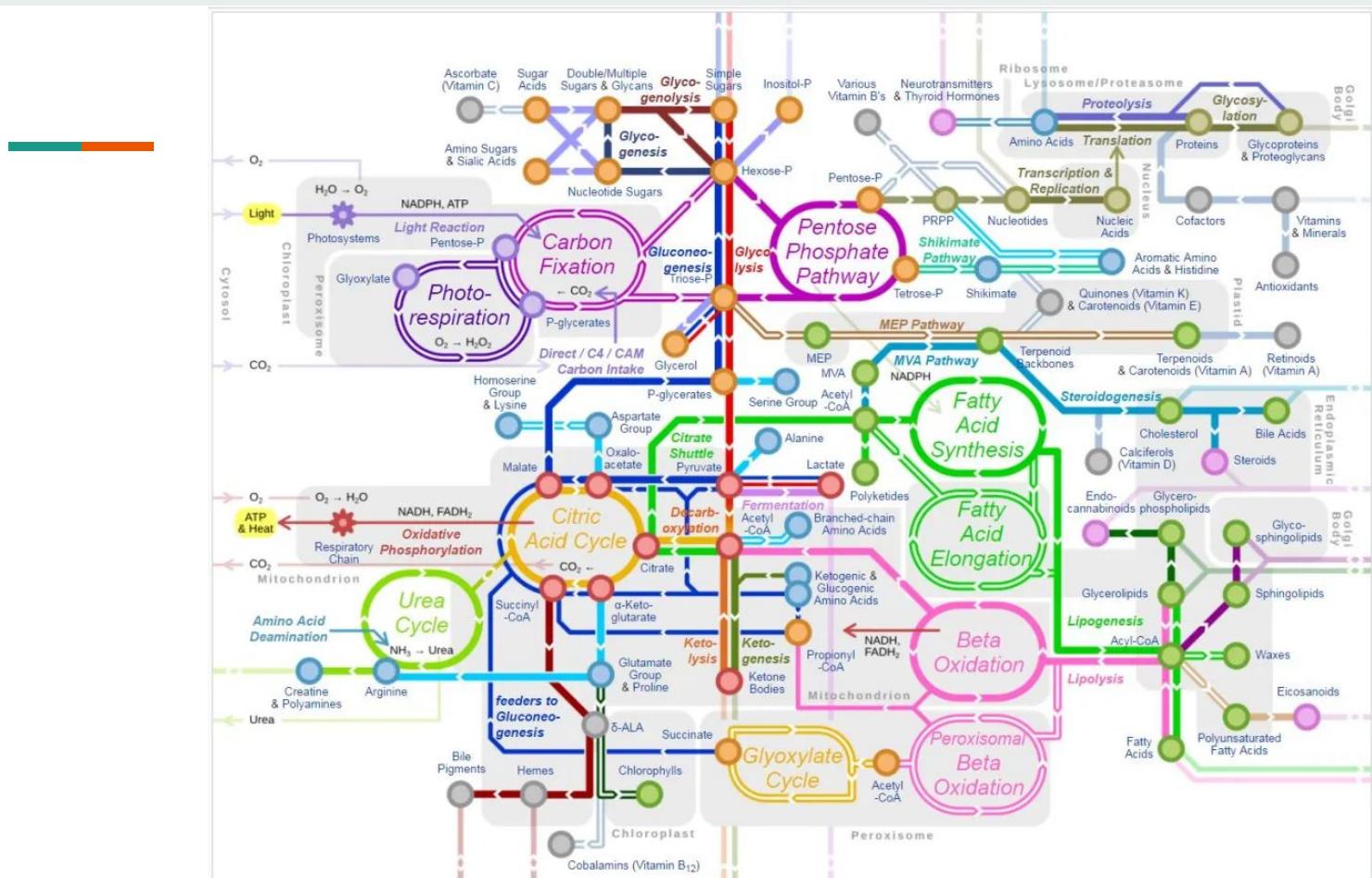
Appendix 1: summary of pharmacokinetic parameters for the imaginary drug Pretendalone following a 50 mg single oral dose.

Pharmacokinetic parameter	Symbol	Unit	Mean	Standard Deviation
Elimination rate constant	$k$	$h^{-1}$	0.123	0.008
Elimination half-life	$t_{1/2}$	h	5.65	0.38
Area under the plasma drug concentration time curve between zero and 36 hours	$AUC_{0-36}$	ng/mL.h	90.00	4.76
Area under the plasma drug concentration time curve between zero and infinite time	$AUC_{0-\infty}$	ng/mL.h	91.15	5.05
Volume of distribution	$V$	L	179.11	10.10
Clearance	$CL$	L/h	22.00	1.23

Appendix 1: summary of pharmacokinetic parameters for the imaginary drug Pretendalone following a 2 mg single intravenous dose.

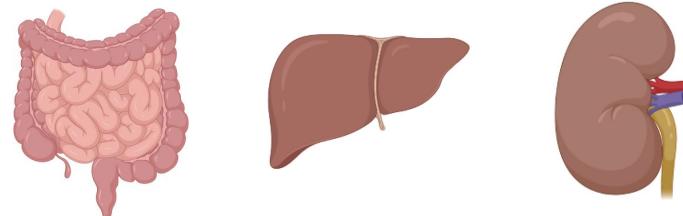
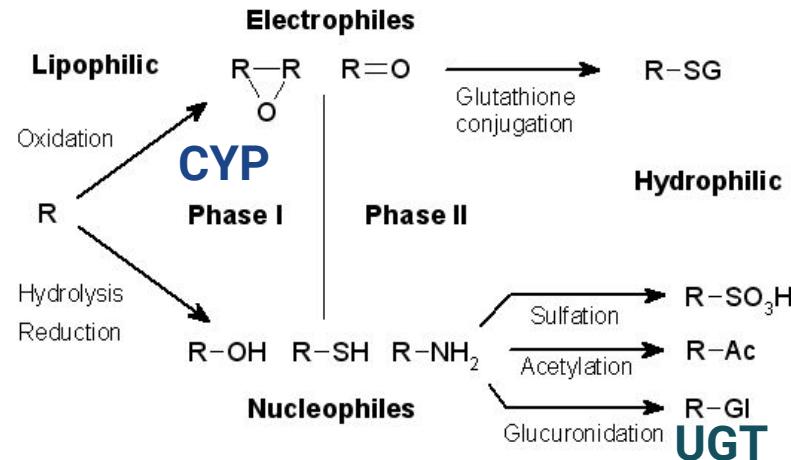
# METABOLISM





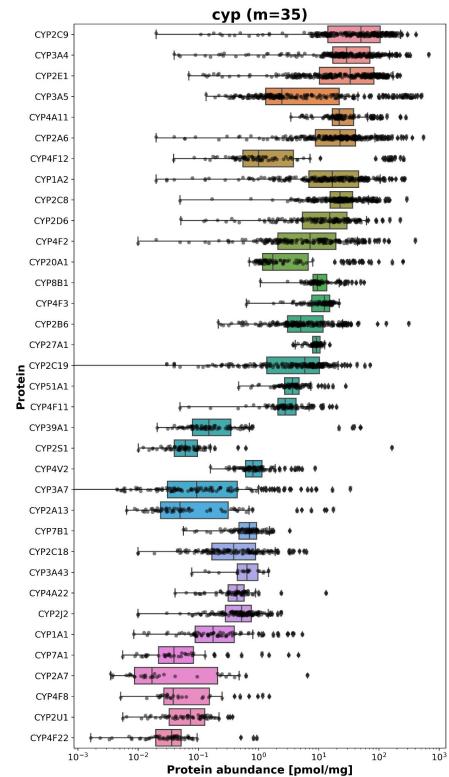
# Drug metabolism in a nutshell

- metabolism of xenobiotics is often divided into 3 phases: **modification, conjugation, and excretion**.
- Cytochrome P450 (CYP)** main players in phase I (modification)
- UDP-glucuronosyltransferases (UGT)** main players phase II (conjugation)
- ATP-binding cassette (ABC)** and **Solute Carrier (SLC)** transporters are main drug transporters
- Multiple isoforms** of CYP, UGT, ABC and SLC with different substrate specificity
- Multiple organs**
  - Intestine:** often metabolism during absorption
  - Liver:** main organ of **drug metabolism**
  - Kidneys:** minor metabolism & **excretion** of (modified) compounds in the urine

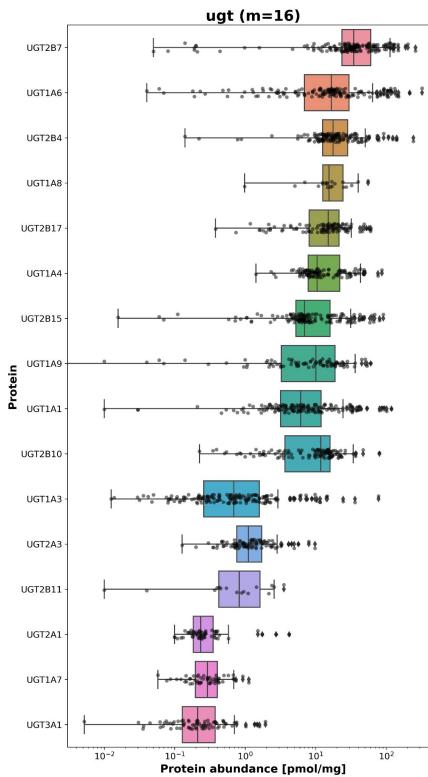


# Large variability & multitude of isoforms (Human Liver)

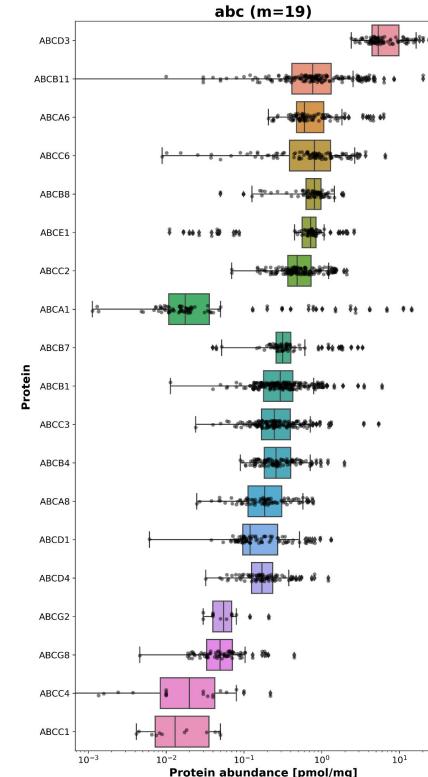
## Cytochrome P450 (CYP)



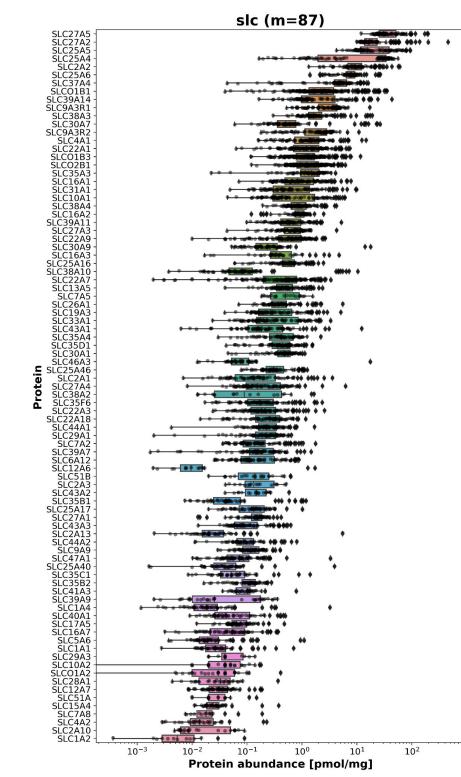
## **UDP-glucuronosyltransferases (UGT)**



## ATP-binding cassette (ABC)



## Solute Carrier (SLC)



Afruja Hossain, Sophie Silberhorn, Matthias König. **Protein distributions of drug metabolizing and transporting enzymes in the Human Liver.** In preparation.

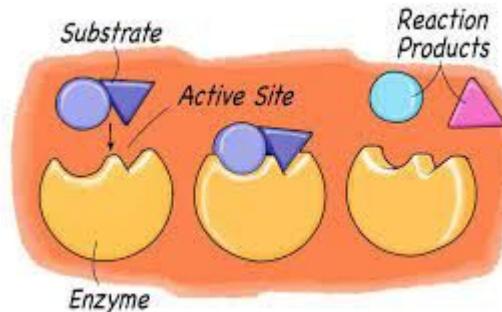
# Metabolic reaction rates

In pharmacokinetics and enzymology, the rate at which reactions occur is crucial. Different mathematical models are used to describe these rates, with some of the most common being the Mass-Action model, the Michaelis-Menten model, and the Hill equation. Here's a brief summary of each:

**1. Mass-Action Model:** This model is one of the simplest and is based on the principle that the rate of a reaction is directly proportional to the concentration of the reacting substances. For a reaction  $A + B \rightarrow C$ , the rate would be expressed as Rate =  $kAB$ , where  $k$  is the rate constant, and  $A$  and  $B$  are the concentrations of  $A$  and  $B$ .

**2. Michaelis-Menten Model:** This model is used to describe enzyme-catalyzed reactions, particularly when enzyme concentrations are much lower than substrate concentrations.  $V_{max}$  is the maximum rate,  $A$  is the substrate concentration, and  $K_m$  is the Michaelis constant (the substrate concentration at which the reaction rate is half of  $V_{max}$ ).

**3. Hill Equation:** This model is often used when there is cooperativity or interaction between multiple binding sites on a molecule (like a protein or enzyme). The Hill coefficient  $n$  represents the degree of cooperativity.



$$v = k \cdot A \cdot B$$

$$v = \frac{V_{max} \cdot A}{K_m + A}$$

$$v = \frac{V_{max} \cdot A^n}{Kd^n + A^n}$$

# Inhibition and activation

Inhibition and activation also play crucial roles in metabolic models:

- **Inhibition:** This occurs when a molecule binds to an enzyme and decreases its activity
  - **competitive** (bind to the active site and compete with the substrate)
  - **non-competitive** (bind to a separate site and change the enzyme's shape)
  - **uncompetitive** (bind to the enzyme-substrate complex).
  - Each type of inhibition changes the parameters ( $V_{max}$ ,  $K_m$ ) in distinctive ways.
- **Activation:** This is when a molecule binds to an enzyme and increases its activity. This can lead to an increase in the maximum reaction rate ( $V_{max}$ ) or a decrease in the  $K_m$  value, indicating an increased affinity of the enzyme for its substrate.

