BP602T · B.Pharm Semester VI · Theory Notes

Biopharmaceutics and Pharmacokinetics

Unit I — Introduction to Biopharmaceutics and Pharmacokinetics

Unit I (10 hours)

Pills & Python Notes

From-zero teaching standard: every technical term is defined before use.

Syllabus coverage: Unit I (10 hours).

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CHAPTER 1: Introduction to Biopharmaceutics and Pharmacokinetics — The Plasma Curve and Its Parameters (Unit I)

1.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define biopharmaceutics, pharmacokinetics, and pharmacodynamics in simple words.

2 Explain the journey of a drug inside the body using the LADMER sequence.

3 Draw and label the plasma drug concentration vs time curve and identify Cmax, Tmax, AUC, and the onset of action.

4 Define each pharmacokinetic parameter and explain what it tells about a drug.

5 Derive the first-order elimination equation and calculate the elimination rate constant (ke) and half-life (t½).

6 Calculate AUC by the trapezoidal rule from given plasma data.

7 Define pharmacodynamic parameters (EC50, Emax) and the drug delivery index.

8 Solve numericals on Vd, clearance, ke, t½, loading dose, and maintenance dose with every step shown.

1.2 What Are Biopharmaceutics and Pharmacokinetics? (Start From Zero)

Technical concept: Biopharmaceutics is the study of the relationship between the physical and chemical properties of a drug, its dosage form, and the route of administration — and the rate and extent to which the drug reaches its site of action. Pharmacokinetics (PK) is the study of how the body handles the drug over time: absorption, distribution, metabolism, and excretion.

Simple explanation: Biopharmaceutics asks: *"Does the way we make the tablet affect how much drug reaches the blood?"* Pharmacokinetics asks: *"Once the drug is swallowed, where does it go, how fast does it move, and how long does it stay?"* Pharmacodynamics (PD) is the third partner — it asks: *"What does the drug do to the body?"* (the effect).

Example: Two brands of paracetamol 500 mg tablets contain the same drug, but if one tablet dissolves faster, more paracetamol enters the blood quickly, and the headache goes away faster. That difference is biopharmaceutics. The measurement of paracetamol levels in blood over 8 hours is pharmacokinetics. The reduction of fever is pharmacodynamics.

Analogy: Think of the body as a city and the drug as a delivery truck. Biopharmaceutics = how well the truck is packed and which gate it enters. Pharmacokinetics = the truck's route, speed, and how long it stays in the city. Pharmacodynamics = the delivery it makes at the end.

Key takeaway: Biopharmaceutics connects the formulation to drug delivery; pharmacokinetics describes drug movement in the body (ADME); pharmacodynamics describes the drug's effect.

1.3 The LADMER Sequence — The Drug's Journey (Flowchart)

```
Drug administered (tablet swallowed)
        |
        ▼
L – LIBERATION: drug released from the dosage form (disintegration + dissolution)
        |
        ▼
A – ABSORPTION: drug crosses the GI wall into the blood
        |
        ▼
D – DISTRIBUTION: blood carries drug to tissues and organs
        |
        ▼
M – METABOLISM: liver chemically changes the drug (usually to inactive form)
        |
        ▼
E – EXCRETION: unchanged drug + metabolites leave the body (urine, bile, etc.)
        |
        ▼
R – RESPONSE: drug acts on its target → therapeutic effect
```

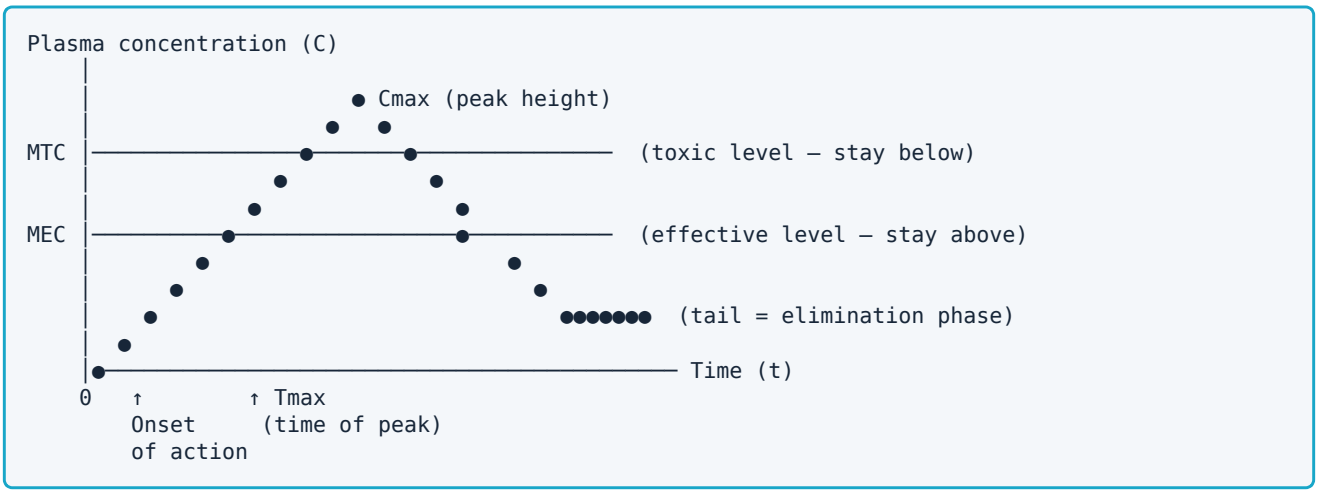
Terminology box:

Term	Simple meaning
ADME	Absorption, Distribution, Metabolism, Excretion — the four PK processes
Bioavailability (F)	Fraction of the given dose that reaches blood unchanged
Onset of action	Time when the drug effect first appears
Duration of action	How long the effect lasts
Minimum effective concentration (MEC)	Lowest blood level that gives a useful effect
Minimum toxic concentration (MTC)	Blood level above which harmful effects begin
Therapeutic range/window	The safe zone between MEC and MTC
Plasma	The liquid part of blood (without cells)
Intravenous (IV) bolus	Drug injected directly into a vein all at once — 100% bioavailable by definition

1.4 The Plasma Concentration vs Time Curve (The Heart of This Chapter)

Technical concept: When a drug is given orally, we draw blood samples at fixed times (0.5 h, 1 h, 2 h, 4 h, 8 h…) and measure the drug concentration in each sample. Plotting concentration (y-axis) against time (x-axis) gives the plasma concentration vs time curve. Every PK parameter is read from this one curve.

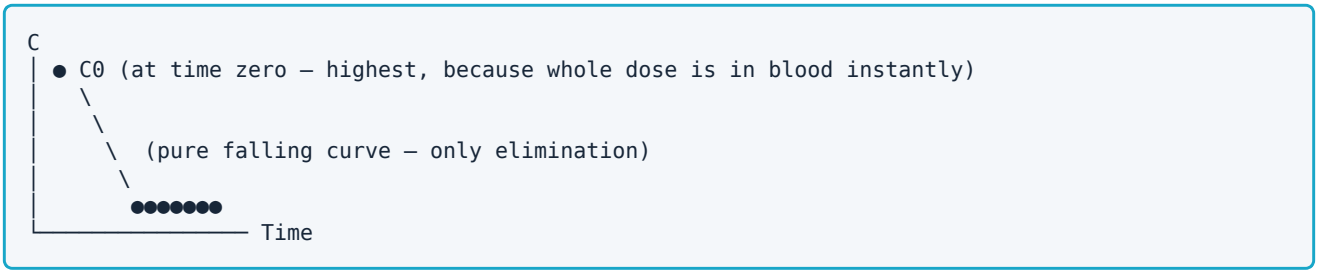
Textual diagram — oral dose curve:



What each part means:

- **Rising part (absorption phase):** absorption is faster than elimination → concentration rises.
- **Peak:** Cmax at Tmax — absorption and elimination rates are equal here.
- **Falling part (elimination/post-absorption phase):** only elimination continues → concentration falls.
- **Onset of action:** the time when the curve first crosses MEC.
- **Duration of action:** the time the curve stays above MEC.

Textual diagram — IV bolus curve (no absorption phase):



Key takeaway: An oral curve has three phases (absorption → peak → elimination); an IV curve has only the elimination phase because the drug enters blood instantly.

1.5 Pharmacokinetic Parameters — Definitions With Simple Meanings

Parameter	Symbol	Simple meaning	Unit
Peak plasma concentration	Cmax	Highest drug level in blood; tells intensity of effect and risk of toxicity	µg/mL or mg/L
Time of peak	Tmax	Time to reach Cmax; tells how fast the drug is absorbed	hours
Area under the curve	AUC	Total drug exposure of the body; the "total amount of drug work"	µg·h/mL
Elimination rate constant	ke	Fraction of drug removed per unit time (first-order)	h^{-1}
Biological half-life	t½	Time to remove half the drug from the body	hours
Apparent volume of distribution	Vd	"Imaginary tank" — volume that would hold the whole drug at the blood concentration	litres or L/kg
Total body clearance	CL	Volume of blood completely cleared of drug per unit time	L/h or mL/min
Mean residence time	MRT	Average time a drug molecule spends in the body	hours

Analogy for Vd: Imagine you dissolve a spoon of sugar in a cup of tea but the tea tastes as if the sugar were dissolved in a whole bucket of water. The "bucket" is the apparent volume — the drug has spread into tissues, so blood levels look low. Vd is NOT a real body space; it is a proportionality constant.

Analogy for clearance: Think of clearance as the number of buckets of blood the body "cleans" of drug every hour. A clearance of 10 L/h means: every hour, the drug contained in 10 litres of blood is removed.

Pharmacodynamic parameters:

Parameter	Simple meaning
Emax	Maximum possible effect of the drug (the ceiling)
EC50	Drug concentration that produces 50% of Emax — measures potency (lower EC50 = more potent)
Therapeutic index (TI)	TD50 ÷ ED50 — safety margin; bigger TI = safer drug
Drug delivery index	Ratio of drug concentration at the site of action to drug concentration in plasma — tells how well the formulation delivers drug to where it is needed

Key takeaway: PK parameters describe the drug's journey (Cmax, Tmax, AUC, ke, t½, Vd, CL); PD parameters describe the drug's effect (Emax, EC50); the drug delivery index connects the two.

1.6 The Mathematics — Derivations Step by Step

1.6.1 First-order elimination equation

Technical concept: Most drugs are eliminated by first-order kinetics: the rate of elimination is proportional to the amount of drug present. (A constant *fraction* is removed per hour, not a constant amount.)

Derivation (each step shown):

Step 1: Rate of change of drug amount X in the body: $dX/dt = -ke \times X$ (negative sign = amount is decreasing)

Step 2: Divide both sides by X and integrate: $\int(dX/X) = -ke \int dt \rightarrow \ln X = -ke \times t + \text{constant}$

Step 3: At time $t = 0$, $X = X_0$ (initial amount). So constant = $\ln X_0$. $\ln X = \ln X_0 - ke \times t \rightarrow \ln(X/X_0) = -ke \times t \rightarrow X = X_0 \times e^{(-ke \times t)}$

Step 4: Concentration $C = X/Vd$, so dividing both sides by Vd: **$C = C_0 \times e^{(-ke \times t)}$**

Step 5: Convert to base-10 logarithm (easier on graph paper). Recall $\ln x = 2.303 \times \log x$: $\log C = \log C_0 - (ke \times t)/2.303$

This is a straight line ($y = mx + c$) where $y = \log C$, slope $= -ke/2.303$, intercept $= \log C_0$.

Key takeaway: On a semi-log plot (log C vs time), first-order elimination is a straight line; its slope gives ke.

1.6.2 Half-life derivation

Derivation:

Step 1: By definition, at $t = t_{½}$, $C = C_0/2$. $C_0/2 = C_0 \times e^{(-ke \times t_{½})}$

Step 2: Cancel C_0: $1/2 = e^{(-ke \times t_{½})}$

Step 3: Take natural log: $\ln(1/2) = -ke \times t_{½} \rightarrow -0.693 = -ke \times t_{½}$

$t_{½} = 0.693 / ke$

Simple explanation: Half-life depends only on ke. It does NOT depend on dose — doubling the dose does not change $t_{½}$ (first-order rule).

1.6.3 AUC by the trapezoidal rule

Technical concept: AUC = $\int C\,dt$ from 0 to ∞. Since we only have measured points, we approximate the area as a series of trapezoids.

Derivation:

Step 1: Between two time points t_1 and t_2 with concentrations C_1 and C_2, the area of the trapezoid is: Area = $(C_1 + C_2)/2 \times (t_2 - t_1)$ = average height × width

Step 2: Add all trapezoids: AUC(0→last) = $\Sigma [(Ci + Ci_{+1})/2 \times (ti_{+1} - ti)]$

Step 3: Add the tail (from last point to infinity). The tail is a triangle-like area: AUC(tail) = Clast / ke.

Total AUC = Σ trapezoids + Clast/ke

1.6.4 Volume of distribution, clearance, and dose equations

- **$Vd = X_0 / C_0$** (for IV bolus: dose ÷ concentration at time zero). C_0 is found by back-extrapolating the log C vs t line to t = 0.
- **CL = ke × Vd** (clearance links the speed of removal, ke, to the size of the tank, Vd).
- Also **CL = rate of elimination ÷ C** and **CL = Dose ÷ AUC** (for IV).
- **Loading dose = Css × Vd** (fills the tank to the target level).
- **Maintenance dose rate = Css × CL** (replaces what the body removes); for dosing every τ hours: **Maintenance dose = Css × CL × τ**.

1.7 CALCULATION BOXES (Worked Numericals With Every Step)

Calculation 1 — ke and t½ from plasma data

Question: After an IV bolus, plasma concentrations are: 10 µg/mL at 2 h and 2.5 µg/mL at 6 h. Find ke and t½.

Solution:

Step 1: Use log C = log C_0 − ket/2.303. Take $\log_{10}$ of both values: log(10) = 1.000; log(2.5) = 0.398

Step 2: Slope = $(\log C_2 - \log C_1)/(t_2 - t_1)$ = (0.398 − 1.000)/(6 − 2) = (−0.602)/4 = −0.1505 per hour

Step 3: Slope = −ke/2.303, so ke = 0.1505 × 2.303 = **0.347 h^{-1}**

Step 4: t½ = 0.693/ke = 0.693/0.347 = **2.0 hours** ✓ (check: concentration fell from 10 → 2.5, i.e., two half-lives, in 4 hours → t½ = 2 h — matches)

Calculation 2 — AUC by trapezoidal rule

Question: Plasma data after an oral dose: t = 0 h (C = 0), 1 h (C = 8), 2 h (C = 12), 4 h (C = 6), 8 h (C = 1.5) µg/mL. ke = 0.35 h^{-1}. Find AUC(0–∞).

Solution:

Step 1: Trapezoid 0–1 h: (0 + 8)/2 × (1 − 0) = 4 × 1 = 4 Step 2: Trapezoid 1–2 h: (8 + 12)/2 × 1 = 10 × 1 = 10 Step 3: Trapezoid 2–4 h: (12 + 6)/2 × 2 = 9 × 2 = 18 Step 4: Trapezoid 4–8 h: (6 + 1.5)/2 × 4 = 3.75 × 4 = 15 Step 5: Sum = 4 + 10 + 18 + 15 = 47 µg·h/mL Step 6: Tail = Clast/ke = 1.5/0.35 = 4.29 µg·h/mL Step 7: **AUC(0–∞) = 47 + 4.29 = 51.29 µg·h/mL**

Calculation 3 — Volume of distribution

Question: 500 mg drug given IV bolus. Back-extrapolated C_0 = 25 mg/L. Find Vd.

Solution: Vd = Dose/C_0 = 500 mg ÷ 25 mg/L = **20 L**. Interpretation: 20 L is less than total body water (42 L) but more than plasma (3 L) — the drug distributes into tissues moderately.

Calculation 4 — Clearance, loading dose, maintenance dose

Question: For the drug above, ke = 0.15 h^{-1}. Target steady-state concentration Css = 10 mg/L. Dosing interval τ = 12 h. Find CL, loading dose, maintenance dose.

Solution:

Step 1: CL = ke × Vd = 0.15 × 20 = **3 L/h** Step 2: Loading dose = Css × Vd = 10 × 20 = **200 mg** (given once to fill the tank) Step 3: Maintenance dose = Css × CL × τ = 10 × 3 × 12 = **360 mg every 12 h**

Common mistake: Students calculate the loading dose using clearance — wrong! Loading dose fills the tank (uses Vd); maintenance dose replaces the leak (uses CL).

1.8 Infographic Concept Box — "One Curve, Eight Numbers"

```
              THE PLASMA CURVE — WHAT TO READ FROM IT
┌──────────────────────┬──────────────────────────────────┐
│  PEAK REGION         │  Cmax = how high (effect strength) │
│                      │  Tmax = how fast (absorption speed) │
│  TOTAL AREA          │  AUC  = total exposure (usefulness) │
│  FALLING SLOPE       │  ke   = steepness (removal speed)   │
│                      │  t½   = half-gone time (dosing gap) │
│  STARTING HEIGHT     │  C0   = dose ÷ Vd (tank size)       │
│  WHOLE-BODY MATHS    │  CL   = ke × Vd (cleaning speed)    │
└──────────────────────┴──────────────────────────────────┘
        MEMORISE: "C-T-A-k-h-V-C" → Cmax, Tmax, AUC, ke, half-life, Vd, CL
```

1.9 Pharmacy Relevance, India Context, Key Points

Pharmacy relevance: A pharmacist uses t½ to decide dosing intervals (drug with t½ = 24 h → once daily). Vd tells whether dialysis will remove a drug in poisoning (low Vd = stays in blood = dialysable). Clearance tells how to reduce dose in kidney failure.

India context: Generic drug approval by CDSCO requires showing that the generic's AUC and Cmax match the innovator's — this is the bioequivalence rule you will study in Chapter 4. Indian Pharmacopoeia dissolution tests protect patients from poorly absorbed formulations.

Key points:

1. Biopharmaceutics = formulation → blood; PK = body handles drug (ADME); PD = drug's effect.
2. LADMER: Liberation → Absorption → Distribution → Metabolism → Excretion → Response.
3. Oral plasma curve: absorption phase → Cmax/Tmax → elimination phase.
4. C = C_0e^(−ket); log C = log C_0 − ket/2.303; t½ = 0.693/ke.
5. AUC = Σ trapezoids + Clast/ke.
6. Vd = Dose/C_0; CL = ke × Vd = Dose/AUC.
7. Loading dose = Css × Vd; Maintenance dose = Css × CL × τ.

8 Emax/EC50 are PD parameters; drug delivery index = site concentration ÷ plasma concentration.

Common confusions:

- C_0 vs Cmax: C_0 is the back-extrapolated concentration at time zero after IV bolus; Cmax is the observed peak after oral dosing.
- ke vs CL: ke is a *fraction* per hour (h^{-1}); CL is a *volume* per hour (L/h).
- t½ is independent of dose for first-order drugs.

Common mistakes:

- Forgetting to add the tail (Clast/ke) in AUC — the answer will be too small.
- Using $\log_{10}$ slope directly as ke — must multiply by 2.303.
- Mixing units: keep mg, L, hours consistent.

Mnemonic — "Please Take A Kinder Half-Volumed Cup": Plasma curve gives **T**max, **A**UC, **k**e, **h**alf-life, **V**d, **C**L.

1.10 Exam Summary and One-Minute Revision

Exam summary: Define biopharmaceutics, PK, PD. Draw labelled plasma curve (oral and IV). Derive first-order equation, t½ = 0.693/ke. Trapezoidal AUC + tail. Vd, CL, loading/maintenance dose derivations. PD parameters and drug delivery index. Solve numericals.

One-minute revision:

- LADMER sequence in order.
- Curve: Cmax (height), Tmax (time), AUC (area), ke (slope), t½ = 0.693/ke.
- Vd = Dose/C_0; CL = ke×Vd; AUC tail = Clast/ke.
- Loading = Css×Vd; Maintenance = Css×CL×τ.
- EC50 = potency; Emax = ceiling; drug delivery index = site ÷ plasma.

1.11 Exam Questions

MCQs (with answers):

1 The parameter indicating the rate and extent of absorption is: a) Cmax b) Tmax c) AUC d) ke. **Answer: c) AUC** (extent; rate comes from Cmax/Tmax)

2 t½ = 4 h; ke equals: a) 0.693 b) 0.173 h^{-1} c) 2.77 h^{-1} d) 0.347 h^{-1}. **Answer: b) 0.173 h^{-1}** (0.693/4)

3 Units of clearance: a) h^{-1} b) L/h c) mg/L d) L. **Answer: b) L/h**

4 Loading dose depends on: a) CL b) Vd c) ke d) F. **Answer: b) Vd**

5 On a semi-log plot, first-order elimination gives: a) curve b) straight line c) hyperbola d) sigmoid. **Answer: b) straight line**

6 EC50 measures: a) safety b) potency c) efficacy ceiling d) clearance. **Answer: b) potency**

7 AUC(0–∞) = AUC(0–t) + : a) Ct×ke b) Ct/ke c) ke/Ct d) C_0/ke. **Answer: b) Ct/ke**

8 Which is a PD parameter? a) Vd b) Emax c) CL d) Tmax. **Answer: b) Emax**

Viva questions:

1 Why is the IV bolus curve missing the absorption phase?

2 Why does doubling the dose not change t½ for a first-order drug?

3 What does a very large Vd (e.g., 500 L) tell you about the drug?

4 Define drug delivery index with an example.

Application-based:

1 A drug has t½ = 6 h and is given every 6 h. Explain to a patient in simple words why the dosing gap equals the half-life.

2 Two paracetamol brands show AUC 40 and 42 µg·h/mL but Cmax 8 and 14 µg/mL. Which parameter worries you for toxicity, and why?

Numericals (with worked solutions):

N1. Plasma levels after IV bolus: 20 mg/L at 1 h, 5 mg/L at 5 h. Find ke, t½. *Solution:* log 20 = 1.301, log 5 = 0.699. Slope = (0.699 − 1.301)/4 = −0.1505. ke = 0.1505 × 2.303 = **0.347 h^{-1}**. t½ = 0.693/0.347 = **2 h**.

N2. Data: t(h): 0, 2, 4, 6; C(µg/mL): 0, 10, 8, 4. ke = 0.3 h^{-1}. Find AUC(0–∞). *Solution:* Trapezoids: (0+10)/2×2 = 10; (10+8)/2×2 = 18; (8+4)/2×2 = 12. Sum = 40. Tail = 4/0.3 = 13.33. **AUC = 53.33 µg·h/mL**.

N3. Dose 250 mg IV, C_0 = 12.5 mg/L, ke = 0.1 h^{-1}. Find Vd and CL. *Solution:* Vd = 250/12.5 = **20 L**. CL = 0.1 × 20 = **2 L/h**.

1.12 References

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3 Rowland M, Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics*. Wolters Kluwer.

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CHAPTER 2: Absorption — How Drugs Cross the Gut Wall (Unit I)

2.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define absorption and list its mechanisms with examples.

2 Explain passive diffusion using Fick's law and the pH-partition hypothesis.

3 Apply the Henderson–Hasselbalch equation to predict ionisation of weak acids and bases in stomach vs intestine.

4 Classify factors affecting absorption into physicochemical, biological, and dosage-form factors, with examples.

5 Describe methods of assessing GIT absorption (blood level, urinary excretion, in-situ, in-vitro).

6 Solve numericals on Fick's law and Henderson–Hasselbalch ratios.

2.2 What Is Absorption? (Start From Zero)

Technical concept: Absorption is the movement of unchanged drug from its site of administration into the systemic circulation (blood). For an oral tablet, the drug must dissolve in GI fluids and cross the gut wall (a lipid membrane) to reach blood.

Simple explanation: Swallowing a tablet is not enough — the drug must *escape* the tablet, dissolve like sugar in tea, and then *sneak through* the wall of the intestine into the blood. Only the dissolved, free drug can be absorbed.

Analogy: The gut wall is a security gate made of oil (lipid membrane). Water-soluble people cannot pass; oil-soluble people walk through easily. Small, uncharged (non-ionised) drug molecules are the "oil-soluble people".

Key takeaway: Absorption = dissolution first, then crossing the membrane; only dissolved, unionised, lipid-soluble molecules cross easily.

2.3 Mechanisms of Drug Absorption

2.3.1 Passive diffusion (most common)

Technical concept: Drug moves from high concentration (gut) to low concentration (blood) without any carrier or energy, directly through the lipid membrane. Follows Fick's first law of diffusion.

Fick's law: $dQ/dt = (D \times A \times K \times (C_{gut} - C_{blood})) / h$

Symbol	Meaning
dQ/dt	Rate of drug transfer

Symbol	Meaning
D	Diffusion coefficient (how fast the molecule moves)
A	Surface area available for absorption
K	Partition coefficient (lipid solubility)
Cgut − Cblood	Concentration gradient (driving force)
h	Membrane thickness

Simple explanation: Absorption is faster when: the drug is more lipid-soluble (K), the surface area is bigger (A — the intestine has villi giving ~200 m²), the concentration difference is larger, and the membrane is thinner.

Sink condition: Blood constantly carries absorbed drug away, so Cblood ≈ 0. The gradient stays large — that is why absorption continues until the gut is empty.

2.3.2 Pore transport (aqueous channels)

Small water-soluble molecules (urea, small ions) slip through tiny water-filled pores between cells. Only for very small molecules (MW < ~400).

2.3.3 Carrier-mediated transport

Facilitated diffusion: A membrane carrier helps the drug cross, moving down the gradient, no energy needed (e.g., glucose-like drugs). Can be saturated. **Active transport:** Carrier + energy (ATP) moves drug *against* the gradient (e.g., levodopa via amino-acid carrier, iron). Saturable and can be blocked by similar molecules (competition).

Simple explanation: Facilitated diffusion = sliding down a slide with help. Active transport = being carried *up* the stairs — needs energy.

2.3.4 Pinocytosis

The cell membrane engulfs large molecules (proteins, fat droplets) in a vesicle — like the cell "drinking" the drug. Minor route for drugs.

2.3.5 Ion-pair transport

A charged drug pairs with an oppositely charged ion to form a neutral pair that crosses the lipid membrane, then splits. (Used by some quaternary ammonium drugs.)

Flowchart — which mechanism?

```
Is the drug small and lipid-soluble? ──YES──▶ Passive diffusion
        │ NO
Is it very small and water-soluble? ──YES──▶ Pore transport
        │ NO
Does a carrier exist in the gut? ──YES──▶ Facilitated / Active transport
        │ NO
Is it a large molecule? ──YES──▶ Pinocytosis
```

2.4 The pH-Partition Hypothesis and Ion Trapping

Technical concept: Most drugs are weak acids or weak bases, existing in two forms: unionised (HA or B — lipid-soluble, absorbable) and ionised (A^- or BH^+ — water-soluble, NOT absorbable). The pH-partition hypothesis states: only the unionised form crosses the gut wall by passive diffusion. The fraction unionised depends on the drug's pKa and the fluid's pH, given by the Henderson–Hasselbalch equation.

For weak acids ($HA \rightleftharpoons H^+ + A^-$): pH = pKa + log([$A^-$]/[HA]) → [ionised]/[unionised] = 10^(pH − pKa)

For weak bases ($B + H^+ \rightleftharpoons BH^+$): pH = pKa + log([B]/[$BH^+$]) → [unionised]/[ionised] = 10^(pH − pKa)

Simple explanation: A weak acid in acidic stomach (pH 1–3) stays mostly unionised → absorbed from stomach. A weak base in alkaline intestine (pH 6–7.5) becomes unionised → absorbed from intestine. But remember: the intestine's huge surface area means most drugs, acids or bases, are mainly absorbed from the intestine.

Ion trapping: Once the unionised drug crosses into blood (pH 7.4), it may ionise there and get "trapped" — it cannot cross back. This keeps the gradient alive.

Terminology box:

Term	Meaning
pKa	pH at which the drug is 50% ionised and 50% unionised
Unionised	Neutral form — crosses membranes
Ionised	Charged form — stays in water, cannot cross
Partition coefficient	Ratio of drug in oil vs water — measures lipophilicity
pH-partition hypothesis	Only unionised drug is absorbed by passive diffusion

2.5 CALCULATION BOXES

Calculation 1 — Henderson–Hasselbalch for a weak acid

Question: Aspirin is a weak acid with pKa = 3.5. In the stomach (pH = 1.5), what fraction is unionised (absorbable)?

Solution:

Step 1: [ionised]/[unionised] = 10^(pH − pKa) = 10^(1.5 − 3.5) = 10^(−2) = 0.01 Step 2: So for every 1 ionised molecule there are 100 unionised. Step 3: Fraction unionised = 100/101 = **99%** — almost fully absorbable in the stomach.

Calculation 2 — Same drug in the intestine

Question: Aspirin (pKa 3.5) in the small intestine (pH 6.5). Fraction unionised?

Solution:

Step 1: [ionised]/[unionised] = 10^(6.5 − 3.5) = 10^3 = 1000 Step 2: Fraction unionised = 1/1001 ≈ **0.1%** — almost none absorbable here! Step 3: Yet aspirin IS absorbed from the intestine —

because the unionised 0.1% keeps crossing, more unionises to replace it (equilibrium shifts), and the enormous surface area compensates. This is the classic exam trap.

Calculation 3 — Weak base

Question: A weak base drug has pKa = 8.0. In the intestine (pH 6.0), what % is unionised?

Solution:

Step 1: For bases, [unionised]/[ionised] = 10^(pH − pKa) = 10^(6.0 − 8.0) = 10^(−2) = 0.01 Step 2: Fraction unionised = 0.01/1.01 ≈ **1%**.

Calculation 4 — Fick's law

Question: Using Fick's law, if the partition coefficient K of a drug is doubled (by making a more lipophilic prodrug), what happens to the absorption rate, all else equal?

Solution: dQ/dt is directly proportional to K. Doubling K → **absorption rate doubles**.

2.6 Factors Affecting Drug Absorption

A. Physicochemical factors (properties of the drug itself)

Factor	Effect	Example
Aqueous solubility	Poor solubility → slow dissolution → slow absorption	Griseofulvin (micronised to improve)
pKa and pH	Decides unionised fraction (see above)	Aspirin vs amphetamine
Lipophilicity (partition coefficient)	Too low → cannot cross membrane; too high → trapped in membrane; ideal log P 1–3	—
Particle size	Smaller particles → larger surface area → faster dissolution	Micronised griseofulvin
Polymorphism	Metastable polymorph dissolves faster than stable form	Chloramphenicol palmitate
Salt form	Salts of weak acids/bases dissolve faster	Sodium salt of phenytoin
Hydrates/solvates	Anhydrous form usually dissolves faster than hydrate	Ampicillin anhydrous vs trihydrate

B. Biological factors (properties of the patient/body)

Factor	Effect
GI pH	Changes ionisation (see Henderson–Hasselbalch)
Surface area	Small intestine (~200 m² with villi/microvilli) absorbs most
GI blood flow	Faster blood flow → better sink condition → faster absorption
GI motility	Faster transit → less time for absorption (diarrhoea reduces absorption)
Food	May delay (gastric emptying slowed), increase (fatty food + griseofulvin), or decrease absorption (tetracycline + milk/calcium)

Factor	Effect
Disease	Malabsorption syndromes, vomiting reduce absorption

C. Dosage-form factors

Factor	Effect
Disintegration time	Tablet must break up first — slow disintegration delays absorption
Dissolution rate	The slowest step for poorly soluble drugs; described by Noyes–Whitney equation
Excipients	Some lubricants (magnesium stearate) are hydrophobic and slow dissolution
Manufacturing	Hard compression → slow disintegration

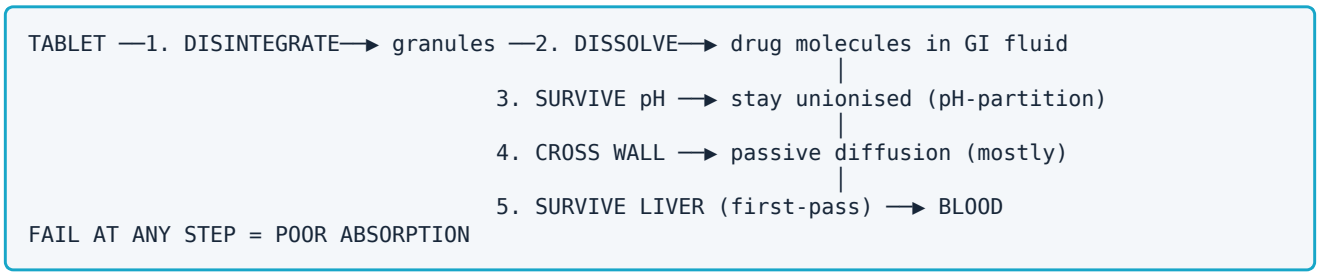
Noyes–Whitney equation (dissolution rate): $dC/dt = (D \times A \times (Cs - C))/h$ — dissolution is faster with larger surface area (A) and higher solubility (Cs).

2.7 Methods of Assessment of GIT Absorption

Method	What is measured	Simple explanation
Blood level method	Plasma concentration vs time; AUC, Cmax	Direct proof the drug reached blood — most reliable
Urinary excretion method	Amount of unchanged drug in urine over time	Useful when drug is excreted unchanged in urine in measurable amounts
In-situ intestinal perfusion	Drug disappearance from a tied-off intestinal loop in anaesthetised animals	Research method — measures absorption across a known gut segment
In-vitro everted gut sac	Drug crossing an inside-out piece of intestine in a lab bath	Screening method — no live animal needed for each test
Caco-2 cell monolayer	Drug crossing a layer of human colon cells in culture	Predicts human intestinal permeability; industry standard screen
Pharmacological/clinical response	Effect measured (e.g., blood sugar fall)	Indirect — used when blood levels are hard to measure

Key takeaway: Blood-level (plasma data) is the gold standard; urinary data is the backup; in-situ/in-vitro methods are for research and screening.

2.8 Infographic Concept Box — "The Absorption Obstacle Course"



2.9 Pharmacy Relevance, India Context, Key Points

Pharmacy relevance: Counselling points come straight from this chapter: "take on empty stomach" (food delays absorption), "do not take tetracycline with milk" (calcium chelation), "do not crush sustained-release tablets" (destroys the dosage-form design).

India context: Many Indian patients take antacids or ayurvedic preparations with allopathic drugs — antacids raise stomach pH and can reduce absorption of weak acids like aspirin and iron. Pharmacists must ask about concurrent antacid use.

Key points:

1 Only dissolved, unionised drug crosses the gut wall by passive diffusion.

2 Fick's law: rate ∝ D × A × K × gradient ÷ thickness.

3 Henderson–Hasselbalch gives the ionised/unionised ratio from pH and pKa.

4 Weak acids absorb better in stomach; weak bases in intestine — but the intestine's area dominates overall.

5 Ion trapping keeps the gradient alive.

6 Factors: physicochemical (solubility, pKa, particle size, polymorph, salt), biological (pH, area, blood flow, motility, food), dosage-form (disintegration, dissolution, excipients).

7 Assessment: blood level (best) > urinary excretion > in-situ > in-vitro (Caco-2, everted sac).

Common confusions:

- Ionised vs unionised: ionised = charged = water-loving = CANNOT cross; unionised = neutral = lipid-loving = CROSSES.
- Absorption vs bioavailability: absorption is crossing the gut wall; bioavailability is what reaches blood *unchanged* after first-pass metabolism.
- Active transport vs facilitated diffusion: active needs ATP and goes against the gradient; facilitated needs no energy.

Common mistakes:

- Saying "weak acids are absorbed only from the stomach" — wrong; most absorption happens in the intestine due to surface area.
- Forgetting sink condition (Cblood ≈ 0) when explaining continued absorption.

Mnemonic — "Please Pass Fatty Food Before Dinner": **P**assive diffusion, **P**ore transport, **F**acilitated diffusion, **F**ood factors, **B**iological factors, **D**osage-form factors. (Mechanisms: "PPFAP"

— Passive, Pore, Facilitated, Active, Pinocytosis.)

2.10 Exam Summary and One-Minute Revision

Exam summary: Define absorption. Five mechanisms with diagrams. Fick's law with each term. pH-partition hypothesis + Henderson–Hasselbalch derivations with stomach/intestine examples. Three factor categories with tables. Four+ assessment methods. Numericals.

One-minute revision:

- Mechanisms: passive diffusion (main), pore, facilitated, active (ATP), pinocytosis, ion-pair.
- Fick: rate ∝ D·A·K·ΔC/h.
- Acid: [I]/[U] = 10^(pH−pKa); Base: [U]/[I] = 10^(pH−pKa).
- Ion trapping in blood (pH 7.4).
- Factors: drug (solubility, pKa, size, polymorph, salt) / body (pH, area, flow, motility, food) / formulation (disintegration, dissolution).
- Assess: blood level > urine > in-situ > in-vitro.

2.11 Exam Questions

MCQs (with answers):

1 Passive diffusion follows: a) Michaelis–Menten b) Fick's law c) Noyes–Whitney d) Henderson–Hasselbalch. **Answer: b) Fick's law**

2 Which form of drug crosses the lipid membrane? a) ionised b) unionised c) protein-bound d) conjugated. **Answer: b) unionised**

3 Aspirin (pKa 3.5) is best absorbed from: a) intestine b) stomach c) colon d) rectum. **Answer: b) stomach** (mostly unionised at pH 1–3)

4 Active transport requires: a) gradient only b) carrier + ATP c) pores d) pinocytosis. **Answer: b) carrier + ATP**

5 Sink condition means: a) Cgut = 0 b) Cblood ≈ 0 c) no absorption d) saturation. **Answer: b) Cblood ≈ 0**

6 Tetracycline absorption decreases with milk because of: a) pH change b) chelation with calcium c) faster motility d) enzyme induction. **Answer: b) chelation with calcium**

7 Caco-2 model measures: a) dissolution b) intestinal permeability c) protein binding d) metabolism. **Answer: b) intestinal permeability**

8 Noyes–Whitney equation describes: a) diffusion b) dissolution rate c) ionisation d) clearance. **Answer: b) dissolution rate**

Viva questions:

1 Why is the intestine the main absorption site even for weak acids?

2 What is ion trapping? Give one example.

3 Differentiate facilitated diffusion from active transport.

4 Why must a drug dissolve before it can be absorbed?

Application-based:

1 A patient takes iron tablets with morning tea and complains they don't work. Explain using absorption factors.

2 Why should sustained-release tablets not be crushed? Link to LADMER.

Numericals (with worked solutions):

N1. Weak acid pKa = 4.5. Calculate % unionised in stomach (pH 2.5) and intestine (pH 7.5). *Solution:* Stomach: [I]/[U] = 10^(2.5−4.5) = 10^−2 = 0.01 → %U = 100/101 ≈ **99%**. Intestine: [I]/[U] = 10^(7.5−4.5) = 10^3 = 1000 → %U = 1/1001 ≈ **0.1%**.

N2. Weak base pKa = 9.0. % ionised in blood (pH 7.4)? *Solution:* [U]/[I] = 10^(7.4−9.0) = 10^−1.6 = 0.0251. % ionised = 1/1.0251 ≈ **97.5%** — mostly ionised (trapped) in blood.

N3. If membrane thickness h is halved and surface area A doubled, by what factor does absorption rate change (Fick's law)? *Solution:* Rate ∝ A/h → (2A)/(h/2) = 4×. **Rate increases 4 times.**

2.12 References

1 Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. McGraw-Hill.

2 Brahmankar DM, Jaiswal SB. *Biopharmaceutics and Pharmacokinetics: A Treatise*. Vallabh Prakashan.

3 Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*. Lea & Febiger.

4 Rowland M, Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics*. Wolters Kluwer.

CHAPTER 3: Distribution, Protein Binding, Metabolism and Excretion (Unit I)

3.1 Learning Objectives

After studying this chapter, you will be able to:

1 Explain tissue permeability and the barriers to distribution (blood–brain, placental).

2 Define apparent volume of distribution and interpret its values.

3 Describe plasma and tissue protein binding of drugs with examples.

4 List factors affecting protein–drug binding and explain Scatchard kinetics.

5 Explain the clinical significance of protein binding (displacement interactions).

6 Describe Phase I and Phase II metabolic pathways with examples.

7 Explain the three renal excretion processes and derive renal clearance.

8 Calculate creatinine clearance by Cockcroft–Gault and adjust doses.

9 List non-renal routes of excretion.

3.2 Distribution — The Drug Travels (Start From Zero)

Technical concept: Distribution is the reversible transfer of drug from blood to tissues and organs. It depends on tissue permeability (blood flow to the tissue, ability to cross capillary walls and cell membranes) and binding.

Simple explanation: Blood is the highway; tissues are the towns. Well-vascularised towns (liver, kidney, brain) get the drug fast; poorly vascularised towns (fat, bone) get it slowly. Some towns have walls (blood–brain barrier) that keep most drugs out.

Barriers:

Barrier	What it blocks	Example
Blood–brain barrier (BBB)	Ionised, large, water-soluble drugs kept out of brain	Penicillin barely enters brain (good for body infections, bad for meningitis — needs inflamed meninges)
Placental barrier	Partial — lipid-soluble drugs cross to the foetus	Thalidomide tragedy — lesson: pregnancy safety matters
Blood–testis barrier	Similar protective role	—

Tissue permeability factors: blood flow rate, capillary structure, lipid solubility of drug, protein binding (only free drug crosses).

Apparent volume of distribution — interpretation table

Vd value	Meaning	Example drugs
~3 L (plasma volume)	Drug stays in blood (highly protein-bound or large molecule)	Heparin, warfarin (low Vd)
~14 L (extracellular fluid)	Distributed in extracellular water	Aminoglycosides
~42 L (total body water)	Distributed throughout body water	Ethanol
> 42 L (e.g., 200–500 L)	Concentrated in tissues/fat — blood level is only the tip	Digoxin (~500 L), chloroquine (very high)

Key takeaway: Small Vd = drug stays in blood (dialysable in poisoning); huge Vd = drug hides in tissues (dialysis useless).

3.3 Protein Binding of Drugs

Technical concept: In blood, drug exists in two forms: free (unbound — active, can cross membranes, can be eliminated) and protein-bound (inactive reservoir). Only the FREE drug acts.

Simple explanation: Plasma proteins (mainly albumin) are like buses — drug molecules ride the bus (bound, inactive) or walk free (unbound, active). Only the walking ones can enter tissues and work.

Proteins involved:

Protein	Binds mainly	Example drugs
Albumin (most abundant)	Acidic drugs	Warfarin, phenytoin, aspirin
α1-acid glycoprotein (AAG)	Basic drugs	Propranolol, lidocaine
Lipoproteins	Lipophilic drugs	—
Tissue proteins	—	Digoxin (muscle), tetracycline (bone/teeth)

Degree of binding: % bound = (Cbound / Ctotal) × 100. Warfarin is ~99% bound — only 1% free!

Factors affecting protein–drug binding:

Factor	Effect
Drug concentration	Binding sites saturate at high doses → free fraction rises
Albumin level	Low albumin (liver disease, malnutrition, elderly) → more free drug → toxicity at "normal" doses
Displacement	A second drug kicks the first off albumin → sudden rise in free drug
Disease	Renal failure → accumulated toxins displace drugs
Age	Neonates and elderly have less albumin

Kinetics of protein binding — Scatchard plot

Technical concept: Binding follows the law of mass action: P + D ⇌ PD. Define r = moles of drug bound per mole of protein, Cf = free drug concentration, n = number of binding sites, Ka = association constant.

Derivation:

Step 1: Ka = [PD]/([P][D]) = r / ((n − r) × Cf) Step 2: Rearrange: r/Cf = Ka × (n − r) = nKa − rKa Step 3: Plot r/Cf (y) vs r (x): straight line with slope = −Ka and x-intercept = n.

The Scatchard equation: r/Cf = nKa − rKa

Simple explanation: The Scatchard plot is a straight-line graph that tells you how many seats (n) the protein bus has and how tightly passengers hold on (Ka).

Clinical significance of protein binding

1. **Displacement interactions:** Phenylbutazone displaces warfarin from albumin → free warfarin suddenly rises → bleeding risk. Aspirin displaces methotrexate → toxicity.
2. **Restricted distribution and elimination:** Only free drug crosses membranes and is filtered by the kidney — high binding prolongs t½.
3. **Hypoalbuminaemia:** In malnutrition/liver disease, "normal" total drug levels can hide toxic free levels — monitor free drug or clinical effect.

Key takeaway: Protein binding is a double-edged sword — a reservoir that prolongs action, but displacement or low albumin can suddenly cause toxicity.

3.4 CALCULATION BOXES

Calculation 1 — Free drug after displacement

Question: Phenytoin is 90% bound at total concentration 20 µg/mL. After displacement by valproate, binding falls to 80%. Find free concentration before and after.

Solution:

Step 1: Before: free fraction = 10% → free = 0.10 × 20 = **2 µg/mL** Step 2: After: free fraction = 20% → free = 0.20 × 20 = **4 µg/mL** Step 3: Free (active) drug **doubled** with no dose change — toxicity risk!

Calculation 2 — Scatchard parameters

Question: A Scatchard plot of r/Cf vs r gives slope = -2×10^5 M^{-1} and x-intercept = 2. Find Ka and n.

Solution: Slope = −Ka → Ka = **2×10^5 M^{-1}**. x-intercept = n → n = **2 binding sites**.

Calculation 3 — Vd interpretation

Question: Digoxin dose 0.5 mg IV, C_0 = 1 µg/L. Find Vd and interpret.

Solution: Convert: 0.5 mg = 500 µg. Vd = 500 µg ÷ 1 µg/L = **500 L**. Interpretation: far above body water — digoxin concentrates heavily in tissues (heart muscle); dialysis will NOT remove it in overdose.

3.5 Elimination — Metabolism (Biotransformation)

Technical concept: Metabolism (biotransformation) is the chemical alteration of drugs, mainly in the liver, usually converting lipid-soluble drugs into water-soluble metabolites that the kidney can excrete.

Simple explanation: The liver is the body's chemical factory — it attaches water-soluble "handles" to drugs so the kidney can flush them out in urine.

Phase I reactions (functionalisation — add/change a reactive group):

Reaction	What happens	Example
Oxidation	Add oxygen / remove hydrogen (mainly by CYP450 enzymes)	Phenytoin → hydroxylated
Reduction	Add hydrogen	Chloramphenicol
Hydrolysis	Split by water	Aspirin → salicylic acid

Phase II reactions (conjugation — attach a bulky water-soluble molecule):

Conjugation	Attached group	Example
Glucuronidation	Glucuronic acid (most common)	Morphine, paracetamol
Sulphation	Sulphate	Paracetamol
Acetylation	Acetyl group	Isoniazid (slow/fast acetylators — genetic!)
Glutathione conjugation	Glutathione	Paracetamol toxic metabolite NAPQI detoxified

Key CYP facts: CYP3A4 metabolises ~50% of drugs. **Inducers** (rifampicin, carbamazepine, smoking) speed metabolism → drug effect falls. **Inhibitors** (ketoconazole, erythromycin, grapefruit juice) slow metabolism → drug effect/toxicity rises.

First-pass metabolism: Oral drugs pass through the liver before reaching systemic blood — part is destroyed on this "first pass" (e.g., propranolol, morphine have high first-pass → low oral bioavailability).

3.6 Renal Excretion of Drugs

Three processes in the nephron:

```
GLOMERULUS: filtration — free (unbound) drug + water filtered out
     │  (GFR ≈ 120 mL/min; protein-bound drug NOT filtered)
     ▼
PROXIMAL TUBULE: active secretion — transporters pump drugs (acids AND bases)
     │  into urine (penicillin, furosemide); can be blocked (probenecid)
     ▼
DISTAL TUBULE: passive reabsorption — unionised, lipid-soluble drug
     │  reabsorbed back to blood; ionised drug stays in urine
     ▼
URINE
```

Net renal excretion = filtration + secretion − reabsorption

Factors affecting renal excretion:

Factor	Effect
Urine pH	Alkaline urine → weak acids ionised → trapped in urine → excreted faster (used in aspirin/barbiturate poisoning: give sodium bicarbonate!)
Urine flow	High flow → less time for reabsorption → faster excretion
Protein binding	Only free drug is filtered
Competition for secretion	Probenecid blocks penicillin secretion → prolongs penicillin action

Factor	Effect
Kidney disease	GFR falls → drug accumulates → reduce dose

Renal clearance — derivation

Technical concept: Renal clearance (CLr) = volume of plasma completely cleared of drug by the kidney per unit time.

Derivation:

Step 1: Rate of urinary excretion = (dXu/dt) = CLr × C (clearance × plasma concentration) Step 2: Rearrange: **CLr = (dXu/dt) / C**

Interpretation: If CLr ≈ GFR (120 mL/min) → drug is only filtered. If CLr > GFR → secretion also occurs. If CLr < GFR → reabsorption occurs.

Total clearance = renal clearance + non-renal (mainly hepatic) clearance: CL = CLr + CLh

Creatinine clearance — Cockcroft–Gault equation

Technical concept: Creatinine is produced steadily by muscles and filtered freely — its clearance estimates GFR, telling us how well the kidneys work.

Cockcroft–Gault: CLcr (mL/min) = (140 − age) × weight (kg) / (72 × serum creatinine (mg/dL)) For females: multiply by 0.85.

Dose adjustment rule: If CLcr < 50 mL/min, reduce dose or extend interval for renally cleared drugs (aminoglycosides, digoxin).

3.7 CALCULATION BOXES (continued)

Calculation 4 — Renal clearance from urine data

Question: Urinary excretion rate of a drug = 60 mg/h; plasma concentration = 10 mg/L. Find CLr and interpret (GFR = 7.2 L/h).

Solution:

Step 1: CLr = (dXu/dt)/C = 60 mg/h ÷ 10 mg/L = **6 L/h** = 100 mL/min Step 2: 100 mL/min < 120 mL/min (GFR) → some **reabsorption** occurs.

Calculation 5 — Cockcroft–Gault

Question: 65-year-old male, 70 kg, serum creatinine 1.4 mg/dL. Find CLcr.

Solution:

Step 1: CLcr = (140 − 65) × 70 / (72 × 1.4) = 75 × 70 / 100.8 Step 2: = 5250 / 100.8 = **52.1 mL/min** Step 3: Normal is ~120 — kidneys working at ~43%; reduce doses of renally excreted drugs.

Calculation 6 — Urine pH and excretion (concept numerical)

Question: Aspirin (weak acid, pKa 3.5) poisoning. Why does sodium bicarbonate (alkaline urine) help?

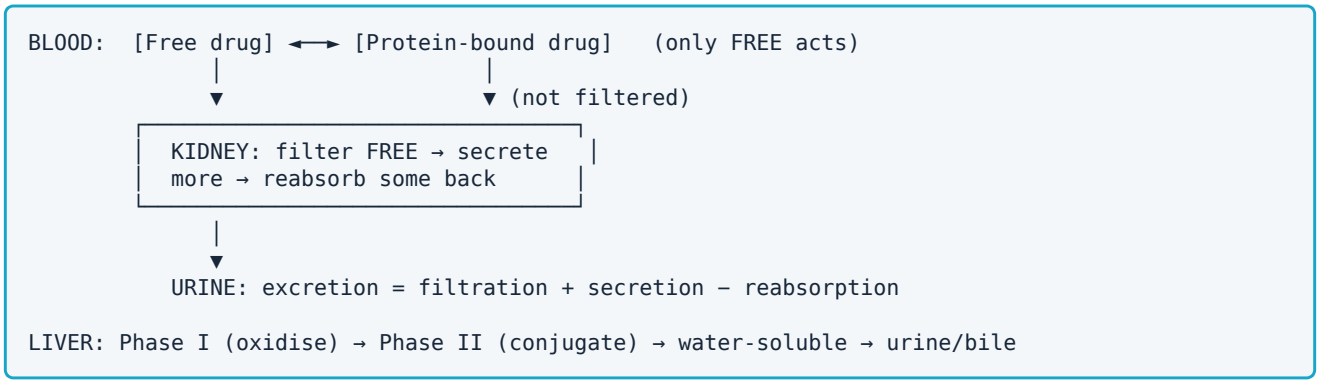
Solution:

Step 1: Alkaline urine (pH ~8): [I]/[U] = 10^(8−3.5) = 10^4.5 ≈ 31,600 → virtually all ionised. Step 2: Ionised drug cannot be reabsorbed → **trapped in urine → flushed out**. This is "ion trapping" used as treatment.

3.8 Non-Renal Routes of Drug Excretion

Route	Examples / notes
Biliary excretion	Large, conjugated metabolites excreted in bile; may undergo **enterohepatic cycling** (reabsorbed from gut → prolongs action, e.g., oral contraceptives)
Pulmonary (lungs)	Volatile drugs/anaesthetics exhaled (alcohol — basis of breath analyser!)
Saliva	Some drugs secreted (phenytoin — saliva monitoring possible)
Sweat	Minor; griseofulvin reaches skin via sweat (useful for fungal infections!)
Breast milk	Lipid-soluble drugs pass to infant — counselling point for nursing mothers
Faeces	Unabsorbed drug + biliary excretion

3.9 Infographic Concept Box — "Free vs Bound, Filtered vs Secreted"



3.10 Pharmacy Relevance, India Context, Key Points

Pharmacy relevance: Dose reduction in kidney failure is a core pharmacist duty. Displacement interactions (warfarin + NSAIDs) cause bleeding — pharmacists must flag them. Counselling nursing mothers about drugs in breast milk saves infants.

India context: Isoniazid acetylation shows genetic polymorphism — "slow acetylators" are common in some Indian populations, needing dose attention for peripheral neuropathy. High prevalence of CKD (chronic kidney disease) in India makes creatinine-clearance dose adjustment a

daily pharmacy task.

Key points:

1 Only free drug crosses membranes, acts, and is filtered.

2 Vd interpretation: 3 L (blood) → 14 L → 42 L → >42 L (tissue-bound).

3 Albumin binds acidic drugs; AAG binds basic drugs.

4 Scatchard: r/Cf = nKa − rKa (slope = −Ka, x-intercept = n).

5 Displacement (warfarin + phenylbutazone) and low albumin → toxicity.

6 Phase I (oxidation/reduction/hydrolysis) → Phase II (glucuronidation, sulphation, acetylation, glutathione).

7 CYP inducers ↓ effect; inhibitors ↑ effect/toxicity.

8 Renal excretion = filtration + secretion − reabsorption; CLr = (dXu/dt)/C.

9 Cockcroft–Gault estimates GFR; adjust doses when CLcr < 50 mL/min.

10 Non-renal routes: bile (enterohepatic cycling), lungs, saliva, sweat, milk, faeces.

Common confusions:

- Bound drug is INACTIVE — a high total level with high binding can still mean low effect.
- Secretion vs reabsorption: secretion moves drug INTO urine (active); reabsorption moves it BACK to blood (passive).
- First-pass metabolism reduces bioavailability but is NOT the same as poor absorption.

Common mistakes:

- Using total drug concentration instead of free when judging effect in hypoalbuminaemia.
- Forgetting the 0.85 factor for females in Cockcroft–Gault.
- Mixing up units: serum creatinine in mg/dL, weight in kg.

Mnemonic — "Free Fire Burns Bright": **F**ree drug = **F**iltered, **B**inds less = **B**etter effect... simpler: **"Only the FREE are ACTIVE"**.

Mnemonic for Phase II — "Girls Sing And Gossip": **G**lucuronidation, **S**ulphation, **A**cetylation, **G**lutathione.

3.11 Exam Summary and One-Minute Revision

Exam summary: Distribution barriers and Vd interpretation. Protein binding: proteins, factors, Scatchard derivation, displacement significance. Phase I/II tables with examples; CYP inducers/inhibitors. Renal: three processes, factors, CLr derivation, Cockcroft–Gault. Non-renal routes. Numericals.

One-minute revision:

- Free = active; bound = reservoir.

- Albumin–acids; AAG–bases.
- Scatchard: r/Cf = nKa − rKa.
- Phase I = functionalise; Phase II = conjugate (GSAG).
- Kidney: filter + secrete − reabsorb; CLr = rate/C.
- Cockcroft–Gault: (140−age)×wt/(72×SCr), ×0.85 female.
- Alkaline urine flushes weak acids (aspirin poisoning).

3.12 Exam Questions

MCQs (with answers):

1 Only ___ drug crosses membranes: a) bound b) free c) conjugated d) ionised. **Answer: b) free**

2 Albumin mainly binds: a) basic drugs b) acidic drugs c) neutral d) large. **Answer: b) acidic drugs**

3 Scatchard plot slope equals: a) n b) −Ka c) Ka d) nKa. **Answer: b) −Ka**

4 Which displaces warfarin causing bleeding? a) paracetamol b) phenylbutazone c) vitamin K d) heparin. **Answer: b) phenylbutazone**

5 Glucuronidation is a ___ reaction: a) Phase I b) Phase II c) both d) none. **Answer: b) Phase II**

6 CYP3A4 inducer: a) ketoconazole b) rifampicin c) erythromycin d) grapefruit. **Answer: b) rifampicin**

7 CLr > GFR indicates: a) reabsorption b) secretion c) filtration only d) no excretion. **Answer: b) secretion**

8 Enterohepatic cycling prolongs action of: a) penicillin b) oral contraceptives c) insulin d) heparin. **Answer: b) oral contraceptives**

Viva questions:

1 Why is dialysis useless in digoxin poisoning?

2 What is first-pass metabolism? Name two drugs with high first-pass.

3 Why do we alkalinise urine in barbiturate poisoning?

4 What does the 0.85 factor in Cockcroft–Gault account for?

Application-based:

1 An elderly malnourished patient on phenytoin shows toxicity at "therapeutic" total levels. Explain and suggest monitoring.

2 A nursing mother asks if she can take a sedative. What do you check and counsel?

Numericals (with worked solutions):

N1. Drug 95% bound, total 40 µg/mL. Binding drops to 90% after displacement. Free before/after?
Solution: Before: 5% free → 2 µg/mL. After: 10% free → **4 µg/mL** (doubled).

N2. Excretion rate 90 mg/h, plasma 15 mg/L. CLr? (GFR 7.2 L/h) *Solution:* CLr = 90/15 = **6 L/h** = 100 mL/min < GFR → net reabsorption.

N3. 70-year-old female, 60 kg, SCr 1.2 mg/dL. CLcr? *Solution:* (140−70)×60/(72×1.2) = 4200/86.4 = 48.6; ×0.85 = **41.3 mL/min** → dose adjustment needed.

N4. Dose 400 mg IV, C_0 = 10 mg/L, ke = 0.2 h^{-1}. Vd, CL? *Solution:* Vd = 400/10 = **40 L**; CL = 0.2 × 40 = **8 L/h**.

3.13 References

1 Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. McGraw-Hill.

2 Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*. Lea & Febiger.

3 Rowland M, Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics*. Wolters Kluwer.

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