BP304T · B.PHARM THEORY

BP304T General Pharmacology

Unit II — Pharmacokinetics

Pills & Python Notes

Absorption · Distribution · Metabolism · Excretion

Syllabus coverage: Unit II (7 hours)

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Chapter 3: Drug Absorption: Mechanisms, Membrane Transporters, Bioavailability, Bioequivalence & Affecting Factors

3.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define drug absorption in your own simple words.
2. Explain why a drug must cross biological membranes to reach its target.
3. Describe the four mechanisms of drug absorption — passive diffusion, facilitated diffusion, active transport, and pinocytosis/phagocytosis.
4. Explain the role of ABC and SLC membrane transporter families at an introductory level.
5. Define bioavailability and bioequivalence and explain why both matter in pharmacy practice.
6. List and explain the physicochemical, physiological, and formulation factors that affect drug absorption.
7. Answer exam questions on absorption with correct simple examples.

3.2 Definitions

Drug absorption — the movement of a drug from its site of administration (for example, the stomach after swallowing a tablet) into the blood circulation. Simple meaning: the drug "enters" the body properly so it can travel to where it is needed. A drug given by injection into a vein (IV) does not need absorption because it is already in the blood.

Biological membrane — a thin wall (made mostly of fats called lipids) that surrounds every cell. A drug must cross this fatty wall to move from one place to another inside the body. Think of it as a border fence with special gates.

Bioavailability (F) — the fraction (percentage) of an administered drug dose that reaches the blood circulation unchanged. Simple meaning: out of 100 mg given, how much actually reaches the blood? If 50 mg reaches the blood, bioavailability is 50%.

Bioequivalence — when two different brands of the same drug (same medicine, same dose) reach the blood at the same rate and to the same extent. Simple meaning: the generic brand works just like the original brand in the body.

3.3 Terminology

- **Passive diffusion** — movement of drug molecules from an area of high concentration to low concentration, crossing the fatty membrane directly, without needing energy or a carrier. Like water flowing downhill.
- **Facilitated diffusion** — movement from high to low concentration with the help of a carrier protein in the membrane, but still without energy. Like going through a revolving door that you push.
- **Active transport** — movement against the concentration gradient (from low to high concentration) using energy (ATP) and a carrier protein. Like pumping water uphill using a motor.
- **Pinocytosis** — the cell membrane folds inward and "drinks" tiny droplets of fluid containing drug particles. "Pino" means drink.
- **Phagocytosis** — the cell membrane folds outward and "eats" large particles, like an amoeba catching food. "Phago" means eat.

- **ABC transporters** — "ATP-Binding Cassette" transporters. A family of membrane pumps that use energy (ATP) to push drugs OUT of cells. The most famous is P-glycoprotein (P-gp), which protects the brain and throws drugs back into the intestine.
- **SLC transporters** — "Solute Carrier" transporters. A family of membrane carriers that help drugs ENTER cells, usually without using energy directly. Examples: OCT (organic cation transporters) and OAT (organic anion transporters) in the kidney and liver.
- **P-glycoprotein (P-gp)** — the most important ABC transporter. It acts like a security guard, pumping foreign substances (including many drugs) out of cells.
- **First-pass effect** — when a drug swallowed orally goes to the liver first and part of it is destroyed before reaching the rest of the body, lowering bioavailability. (Explained in detail in Chapter 5.)
- **Concentration gradient** — the difference in drug amount between two sides of a membrane. Drugs move from "more drug" side to "less drug" side naturally.

3.4 Explanation (Main Teaching)

Why does absorption matter? Imagine you swallow a paracetamol tablet for a headache. The tablet does not work inside your stomach. The drug must leave the stomach/intestine, cross the gut wall, enter the blood, travel through the blood to the head, and then act on pain signals. That first step — leaving the gut and entering the blood — is called absorption. If absorption is poor, the drug cannot work, no matter how good the medicine is.

The basic rule of absorption: Most drugs are small molecules that cross the gut wall by slipping through the fatty cell membranes. Fat-loving (lipophilic) drugs cross easily; water-loving (hydrophilic) drugs cross slowly. A drug's nature decides its speed of entry.

The four mechanisms of drug absorption:

1. Passive diffusion (the most common mechanism). No energy needed, no carrier needed. The drug simply moves from where there is a lot of it (inside the intestine after the tablet dissolves) to where there is little of it (the blood, which is constantly flowing and carrying the drug away). This keeps the "downhill" flow going. Properties needed: the drug should be lipophilic (fat-loving) and non-ionized (uncharged). Ionized (charged) drugs cannot cross the fatty membrane — they are repelled, like trying to mix oil and water. Most drugs are weak acids or weak bases, and whether they are ionized depends on the pH around them (stomach is acidic, intestine is alkaline). This pH effect is important for absorption.

2. Facilitated diffusion. Here the drug still moves downhill (high to low concentration, no energy), but it cannot cross the membrane alone — it needs a carrier protein, like a passenger needing a special vehicle. The carrier is selective: it picks up only certain molecules. Example: the absorption of some vitamins and sugars happens this way. It is faster than passive diffusion for those molecules, but it can get saturated (if too many molecules arrive, the carriers are all busy and cannot carry more).

3. Active transport. This moves the drug UPHILL — from low concentration to high concentration — against the natural flow. This needs energy (ATP, the cell's energy currency) and a carrier protein. Example: iron, amino acids, and some drugs like methyldopa are absorbed from the gut by active transport. It is selective and can be saturated, and it can be blocked by similar molecules (competition).

4. Pinocytosis and phagocytosis (endocytosis). In pinocytosis, the cell membrane pinches inward and swallows tiny droplets of fluid containing dissolved drug. In phagocytosis, the membrane reaches out and engulfs larger particles. These mechanisms are less important for most small drug molecules but matter for some large molecules, vaccines, and certain drug delivery systems. Specialized cells (like those in the intestine of newborns, or immune cells) use these.

Membrane transporters — ABC and SLC families (introductory level):

Think of the cell membrane as a building with two kinds of doors:

- **SLC family (Solute Carriers)** — the "entry doors." These are carrier proteins that help drugs and nutrients ENTER the cell. Most work without energy (like facilitated diffusion) or use the natural flow of sodium to pull drugs in. Important examples: OCT1 and OCT2 (organic cation transporters — carry positively charged drugs like metformin), OAT1 and OAT3 (organic anion transporters — carry negatively charged drugs, in the kidney). These transporters decide how much drug enters the liver, kidney, and other organs.
- **ABC family (ATP-Binding Cassette)** — the "exit pumps." These use energy (ATP) to pump drugs OUT of the cell. The star member is **P-glycoprotein (P-gp)**. It sits in the intestine wall, the blood-brain barrier, the liver, and the kidney. Its job: pump foreign chemicals (including drugs) out — back into the gut, or out of the brain. This is protective, but it also reduces absorption of many drugs and keeps some drugs out of the brain. Other ABC members include BCRP (breast cancer resistance protein) and MRP (multidrug resistance proteins).

Why do transporters matter for pharmacists? Because two drugs can fight over the same transporter. Example: if drug A blocks P-gp, drug B (which P-gp normally pumps out) will now be absorbed more — its blood level rises and it may cause toxicity. This is a drug interaction the pharmacist must watch for.

Bioavailability — the "how much reaches the blood" number: When a drug is injected directly into a vein (IV), 100% reaches the blood — bioavailability is 100% (F = 1). When a drug is swallowed, some is lost: it may not dissolve fully, may be destroyed by stomach acid, may not cross the gut wall, or may be destroyed by the liver on first pass. So oral bioavailability is usually less than 100%. Formula: Bioavailability (%) = (amount reaching blood ÷ dose given) × 100. Example: 100 mg tablet given, 40 mg reaches blood unchanged → bioavailability = 40%.

Bioequivalence — "does the generic copy behave the same?" Two products of the same drug (e.g., original brand tablet and generic tablet, same 500 mg strength) are bioequivalent if they deliver the drug into the blood at the same speed (rate) and to the same amount (extent). Regulatory rule of thumb: the generic's peak level and total exposure should fall within 80–125% of the original's. If bioequivalent, the pharmacist can confidently substitute the cheaper generic — the patient gets the same effect.

Factors affecting drug absorption — three big groups:

A. Physicochemical factors (properties of the drug itself):

- **Lipid solubility:** fat-loving drugs cross the fatty membrane easily; water-loving drugs cross slowly.
- **Ionization and pH:** only the non-ionized (uncharged) form crosses the membrane. Weak acids (like aspirin) are non-ionized in the acidic stomach → absorbed there; weak bases are non-ionized in the alkaline intestine → absorbed there.
- **Drug concentration and dose:** higher concentration gradient → faster diffusion.
- **Molecular size:** smaller molecules cross faster.
- **Dosage form:** solutions absorb fastest, then suspensions, then capsules, then tablets, then coated/sustained-release tablets (slowest).

B. Physiological factors (properties of the patient's body):

- **Gastric emptying time:** drugs are mostly absorbed from the small intestine (huge surface area), not the stomach. Faster stomach emptying → faster delivery to intestine → faster absorption.
- **Intestinal motility:** very fast movement (diarrhea) reduces contact time → less absorption.
- **Surface area:** the small intestine has villi and microvilli giving a huge surface (like a tennis court) → main absorption site.
- **Blood flow to the gut:** more blood flow carries absorbed drug away faster → maintains the downhill gradient → faster absorption.

- **Presence of food:** food can delay emptying, bind drugs, or change pH. Some drugs must be taken on an empty stomach; some with food.
- **Disease states:** vomiting, diarrhea, gut surgery, or poor circulation reduce absorption.
- **Age:** infants and elderly may absorb differently (different gut pH, motility).

C. Formulation factors (how the medicine is made):

- **Disintegration and dissolution:** a tablet must first break apart (disintegrate) and dissolve before absorption. Poor dissolution = poor absorption.
- **Excipients (inactive ingredients):** binders, fillers, and coatings can speed up or slow down release.
- **Particle size:** smaller particles dissolve faster (more surface area) — this is why micronization improves absorption of poorly soluble drugs like griseofulvin.
- **Polymorphism:** the same drug can exist in different crystal forms; one form may dissolve faster than another.
- **Coating:** enteric coating protects the drug from stomach acid and releases it in the intestine.

Key takeaway: Absorption is the gateway. The drug's own chemistry, the patient's body, and the tablet's design together decide how much drug enters the blood and how fast — and that decides how well the medicine works.

3.5 Classifications

Classification of absorption mechanisms:

1. **By energy requirement:**
    - No energy needed: passive diffusion, facilitated diffusion, pinocytosis/phagocytosis
    - Energy (ATP) needed: active transport, ABC transporters (P-gp)
2. **By carrier requirement:**
    - No carrier: passive diffusion
    - Carrier needed: facilitated diffusion, active transport, SLC transporters, ABC transporters
3. **By direction relative to gradient:**
    - Downhill (high → low concentration): passive diffusion, facilitated diffusion
    - Uphill (low → high concentration): active transport
    - Bulk movement: pinocytosis, phagocytosis

Classification of factors affecting absorption:

1. Physicochemical factors (drug properties): lipid solubility, ionization/pKa, concentration, molecular size
2. Physiological factors (patient body): gastric emptying, motility, surface area, blood flow, food, disease, age
3. Formulation factors (product design): disintegration, dissolution, excipients, particle size, polymorphism, coating

3.6 Mechanisms

Mechanism 1 — Passive diffusion, step by step:

1. Tablet dissolves in gut fluid → drug molecules spread in the intestine (high concentration).
2. Blood flowing on the other side of the gut wall carries drug away (low concentration).
3. Non-ionized, lipid-soluble drug molecules slip directly through the fatty cell membrane.
4. Movement continues as long as the gradient exists (high in gut → low in blood).

Mechanism 2 — Facilitated diffusion, step by step:

1. Drug molecule binds to a specific carrier protein on the membrane surface.
2. The carrier changes shape and releases the drug on the other side.
3. No energy is used; movement is still downhill (high → low).
4. If all carriers are occupied, transport saturates (cannot go faster).

Mechanism 3 — Active transport, step by step:

1. Drug binds to a carrier protein.
2. The cell spends energy (ATP) to change the carrier's shape.
3. The drug is pushed to the other side AGAINST the gradient (low → high).
4. Selective and saturable; similar molecules compete for the same carrier.

Mechanism 4 — Pinocytosis/phagocytosis, step by step:

1. The cell membrane bulges around fluid droplets (pinocytosis) or solid particles (phagocytosis) containing drug.
2. The membrane pinches off, forming a small sac (vesicle) inside the cell.
3. The vesicle releases its contents inside the cell.

P-glycoprotein (ABC) efflux mechanism:

1. Drug enters the gut wall cell by diffusion.
2. P-gp in the cell membrane catches the drug.
3. Using ATP energy, P-gp pumps the drug back out into the gut lumen.
4. Net effect: less drug absorbed; repeated with each pass.

3.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — The four absorption mechanisms across a cell membrane. Draw a horizontal double line representing the fatty cell membrane. Above it label "Gut side (high drug concentration)"; below it label "Blood side (low drug concentration)". (a) Passive diffusion: draw small dots passing straight through the membrane with a downward arrow. (b) Facilitated diffusion: draw a carrier protein (a rounded shape inside the membrane) catching a dot on top and releasing it below, with a downward arrow. (c) Active transport: draw a carrier protein with a small "ATP" lightning symbol, pushing a dot UPWARD from low (bottom) to high (top) with an upward arrow. (d) Pinocytosis: draw the top membrane dipping down like a pocket around dots, pinching off into a circle inside.

Diagram 2 — P-glycoprotein efflux pump. Draw a gut wall cell as a rectangle. Inside the rectangle near the top edge, draw a pump shape labeled "P-gp (ABC transporter)". Draw arrows showing drug dots entering the cell from the top (gut lumen) and then being pumped BACK out to the top by P-gp, with an "ATP" energy symbol next to the pump. Label: "Result: reduced absorption."

Diagram 3 — Bioavailability concept. Draw a 100 mg tablet on the left. Draw an arrow to a blood drop on the right labeled "blood". Along the arrow, show losses falling off: "not dissolved (10 mg)", "destroyed by acid (10 mg)", "lost in first-pass through liver (40 mg)". Only 40 mg reaches the blood drop: label "Bioavailability = 40%".

Diagram 4 — Factors affecting absorption (mind-map style). Draw a central circle labeled "Drug Absorption". Draw three big branches: "Drug factors (lipid solubility, ionization, size, dose)", "Body factors (stomach emptying, food, blood flow, disease, age)", "Tablet factors (dissolution, particle size, coating, excipients)".

3.8 Flowcharts (Step-by-Step Text Flowcharts)

Flowchart 1 — Journey of an oral tablet to the blood:

```
Swallowed tablet
      ↓
Reaches stomach → tablet disintegrates (breaks apart)
      ↓
Drug dissolves in gut fluid
      ↓
Stomach empties contents into small intestine
      ↓
Drug molecules contact intestinal wall (huge surface area)
      ↓
Cross the gut wall by diffusion / carriers / transporters
      ↓
Enter tiny blood vessels (capillaries) of the gut
      ↓
Travel via portal vein to the LIVER first
      ↓
Some drug destroyed in liver (first-pass effect)
      ↓
Surviving drug enters general blood circulation
      ↓
ABSORPTION COMPLETE → drug now available to reach its target
```

Flowchart 2 — How to decide which mechanism a drug uses:

```
Is the drug lipid-soluble and non-ionized?
   YES → Passive diffusion (most common)
   NO ↓
Does it use a carrier but move downhill without energy?
   YES → Facilitated diffusion
   NO ↓
Does it move uphill using ATP energy?
   YES → Active transport
   NO ↓
Is it a large particle or droplet engulfed by the membrane?
   YES → Pinocytosis / Phagocytosis
```

Flowchart 3 — Bioequivalence decision:

```
Generic tablet vs Original brand tablet (same drug, same dose)
      ↓
Both tested in human volunteers → blood levels measured over time
      ↓
Compare rate (how fast peak is reached) and extent (total drug absorbed)
      ↓
Generic's values within 80–125% of original's?
   YES → BIOEQUIVALENT → pharmacist may substitute safely
   NO  → NOT bioequivalent → do NOT substitute
```

3.9 Infographic Concept Box

ABSORPTION AT A GLANCE

🟢 **Definition:** Drug moves from site of administration → blood.

🟢 **4 Mechanisms:** Passive diffusion (downhill, no help) | Facilitated diffusion (downhill + carrier) | Active transport (uphill + ATP) | Pinocytosis/Phagocytosis (cell "drinks/eats").

🟢 **Transporter families:** SLC = entry doors (OCT, OAT) | ABC = exit pumps (P-gp pushes drugs OUT).

🟢 **Bioavailability:** % of dose reaching blood unchanged. IV = 100%.

🟢 **Bioequivalence:** Generic = Original in speed + amount (80–125% rule).

🟢 **3 Factor groups:** Drug factors (lipid solubility, ionization, size) | Body factors (stomach emptying, food, blood flow, disease) | Tablet factors (dissolution, particle size, coating).

🟢 **Golden rule:** Only non-ionized, lipid-soluble drugs cross membranes easily by diffusion.

🟢 **Main absorption site:** Small intestine (huge surface area).

3.10 Tables

Table 1 — Comparison of the four absorption mechanisms:

Feature	Passive Diffusion	Facilitated Diffusion	Active Transport	Pinocytosis/Phagocytosis
Direction	High → low (downhill)	High → low (downhill)	Low → high (uphill)	Bulk movement into cell
Energy (ATP) needed	No	No	Yes	Yes (cellular energy)
Carrier protein needed	No	Yes	Yes	No (membrane engulfs)
Saturable	No	Yes	Yes	Limited
Selectivity	Low (any lipophilic drug)	High (specific carriers)	High (specific carriers)	Low
Common example	Most drugs (e.g., aspirin)	Vitamins, sugars	Iron, methyldopa	Large molecules, particles

Table 2 — ABC vs SLC transporter families:

Feature	ABC Family	SLC Family
Full name	ATP-Binding Cassette	Solute Carrier
Energy use	Uses ATP (active efflux)	Mostly no ATP (entry help)
Direction	Pumps drugs OUT of cells	Helps drugs ENTER cells
Key members	P-glycoprotein (P-gp), BCRP, MRP	OCT1/2, OAT1/3
Main locations	Intestine, brain barrier, liver, kidney	Liver, kidney, intestine
Effect on drug	Reduces absorption, protects brain	Increases uptake into organs

Table 3 — Factors affecting drug absorption:

Category	Factor	Effect on Absorption
Physicochemical	High lipid solubility	Increases absorption
Physicochemical	Ionized (charged) form	Decreases absorption
Physicochemical	Large molecular size	Decreases absorption
Physiological	Fast gastric emptying	Increases absorption
Physiological	Food in stomach	May delay or reduce absorption
Physiological	Diarrhea / fast motility	Decreases absorption

Category	Factor	Effect on Absorption
Physiological	High gut blood flow	Increases absorption
Formulation	Fast dissolution	Increases absorption
Formulation	Small particle size (micronized)	Increases absorption
Formulation	Enteric coating	Delays release to intestine

3.11 Examples

1. **Aspirin (a weak acid):** In the acidic stomach (pH ~1–2), aspirin stays non-ionized → easily absorbed from the stomach by passive diffusion. This is why aspirin acts relatively fast.
2. **Iron tablets:** Iron is absorbed from the intestine by active transport (needs energy and a carrier). This is why only a limited amount is absorbed at a time, and why iron is best absorbed on an empty stomach.
3. **Griseofulvin (antifungal):** A poorly water-soluble drug. When made into very small particles (micronized), its dissolution and absorption improve greatly — a formulation factor in action.
4. **Digoxin and P-gp:** Digoxin is pumped out by P-glycoprotein. If a patient also takes a P-gp blocker (like verapamil), digoxin absorption increases and blood levels can rise to toxic levels — a clinically important transporter interaction.
5. **Metformin:** Taken up into liver cells by OCT1 (an SLC transporter). Differences in this transporter can change how well metformin works.
6. **Oral vs IV bioavailability:** A drug given IV has 100% bioavailability. The same drug swallowed may have only 40–50% bioavailability because of incomplete absorption and first-pass liver metabolism — so oral doses are often larger than IV doses.

3.12 Analogies

1. **Passive diffusion = water flowing downhill.** Water naturally flows from a high tank to a low tank through a pipe. No pump needed. Drug molecules flow from high concentration (gut) to low concentration (blood) the same way.
2. **Facilitated diffusion = revolving door.** You still walk through on your own (no motor), but you need the door to pass. The carrier protein is the revolving door — it helps specific people (molecules) through.
3. **Active transport = pumping water uphill with a motor.** To move water from a low tank to a high tank, you need a pump and electricity. The cell uses ATP (electricity) and a carrier (pump) to push drugs uphill.
4. **P-glycoprotein = a strict security guard.** Imagine a guard at a building gate who catches intruders and throws them back outside. P-gp catches drug molecules inside the gut wall cell and throws them back into the intestine.
5. **Bioavailability = salary after deductions.** Your salary is ₹10,000, but after tax and deductions you receive ₹7,000 in hand. The tablet's dose is the "salary"; what reaches the blood is the "in-hand" amount. Bioavailability is the in-hand percentage.
6. **Bioequivalence = two brands of the same sugar.** Whether you buy Brand A sugar or Brand B sugar, 1 kg is 1 kg — both sweeten tea the same. Bioequivalent generics work the same as the original brand.

3.13 Pharmacy Relevance

- **Generic substitution:** The pharmacist's daily decision — "can I give the cheaper generic instead of the prescribed brand?" — rests on bioequivalence. Only bioequivalent products are safely interchangeable.
- **Counseling on food:** "Take on an empty stomach" or "take with food" instructions come directly from absorption science. Example: tell patients that some antibiotics are absorbed poorly with milk or antacids (they bind the drug).
- **Spotting interactions:** A pharmacist who knows P-gp and SLC transporters can predict dangerous interactions (e.g., P-gp blockers raising digoxin levels) and warn the doctor.
- **Formulation understanding:** Knowing why micronization, enteric coating, or sustained-release matters helps the pharmacist explain to patients why they must not crush or chew certain tablets (crushing a sustained-release tablet dumps the whole dose at once — dangerous).
- **Route selection advice:** When a patient cannot swallow or has severe vomiting, the pharmacist understands why an injection or alternative route is needed — absorption from the gut is unreliable.

3.14 India Context

- **Generic medicines and Jan Aushadhi:** India is the world's largest supplier of generic medicines. The Jan Aushadhi scheme provides low-cost generics to Indian patients. These generics must prove bioequivalence to the original brands — that is why patients can trust that a ₹10 Jan Aushadhi tablet works like a ₹100 branded tablet of the same drug and dose.
- **CDSCO bioequivalence requirement:** India's drug regulator (CDSCO) requires bioequivalence studies for approval of generic products, protecting Indian patients from substandard copies.
- **Food habits matter:** Indian meals are often heavy and oily, which delays stomach emptying. Pharmacists should counsel patients that "empty stomach" means 1 hour before or 2 hours after such meals, and that some drugs (like certain antifungals) are actually absorbed BETTER with fatty food.
- **Antacids and traditional practices:** Frequent self-use of antacids (for acidity) can reduce absorption of drugs like iron and some antibiotics — a common counseling point in Indian pharmacies. Herbal products like St. John's wort (and some Ayurvedic preparations) can induce P-gp and metabolic enzymes, lowering drug levels — patients must be asked about ALL products they take.

3.15 Key Points

1. Absorption = drug movement from administration site into blood.
2. Four mechanisms: passive diffusion (most common), facilitated diffusion, active transport, pinocytosis/phagocytosis.
3. Passive diffusion needs NO energy and NO carrier; works downhill for lipid-soluble, non-ionized drugs.
4. SLC transporters help drugs ENTER cells (OCT, OAT); ABC transporters pump drugs OUT (P-gp).
5. P-gp in gut, brain, liver, kidney reduces absorption of many drugs and causes interactions.
6. Bioavailability = % of dose reaching blood unchanged; IV = 100%.
7. Bioequivalence = generic matches original in rate + extent (80–125% rule) → safe substitution.
8. Factors: drug properties (lipid solubility, ionization, size), body factors (emptying, food, blood flow, disease), tablet factors (dissolution, particle size, coating).
9. Small intestine is the main absorption site (huge surface area).
10. Only the non-ionized form crosses membranes by passive diffusion.

3.16 Common Confusions (with Corrections)

1. **Confusion:** "Absorption and adsorption are the same." **Correction:** No. AbSorption = drug entering the blood (going inside). ADsorption = molecules sticking to a surface (like activated charcoal adsorbing poison in the stomach — it stays on the surface, it does not enter blood).
2. **Confusion:** "All of the swallowed dose reaches the blood." **Correction:** No. Only the bioavailable fraction reaches the blood. Losses happen through poor dissolution, acid destruction, poor permeation, and first-pass liver metabolism.
3. **Confusion:** "Active transport and facilitated diffusion are the same because both use carriers." **Correction:** Both use carriers, but facilitated diffusion moves DOWNHILL without energy, while active transport moves UPHILL using ATP energy.
4. **Confusion:** "P-gp helps absorb drugs." **Correction:** Opposite. P-gp is an EFFLUX pump — it pushes drugs OUT of cells, REDUCING absorption.
5. **Confusion:** "Bioavailability and bioequivalence are the same." **Correction:** Bioavailability = how much of ONE product reaches blood. Bioequivalence = comparison showing TWO products (generic vs original) behave the same.
6. **Confusion:** "Ionized drugs cross membranes easily." **Correction:** No. Only NON-ionized (uncharged), lipid-soluble drugs cross the fatty membrane easily by passive diffusion. Ionized drugs are repelled.

3.17 Common Mistakes (with Corrections)

1. **Mistake:** Writing "drugs are absorbed mainly from the stomach." **Correction:** Most absorption happens in the SMALL INTESTINE because of its enormous surface area. The stomach absorbs only a few drugs (like aspirin, alcohol).
2. **Mistake:** Saying "IV drugs need absorption." **Correction:** IV drugs are injected directly into blood — absorption is zero step; bioavailability is 100% by definition.
3. **Mistake:** Forgetting that food can both increase AND decrease absorption. **Correction:** Food delays most drugs but INCREASES absorption of some (fatty food helps griseofulvin). Always check the specific drug.
4. **Mistake:** Advising patients to crush sustained-release tablets to "make them work faster." **Correction:** NEVER crush sustained-release or enteric-coated tablets — crushing destroys the slow-release design and can dump a toxic dose at once.
5. **Mistake:** Thinking a higher dose always fixes poor absorption. **Correction:** For carrier-mediated transport (saturable), increasing the dose beyond saturation does NOT increase absorption proportionally — carriers are already full.

3.18 Mnemonics

1. **Mechanisms — "PAFP" (say "paff-p"): P**assive diffusion, **A**ctive transport, **F**acilitated diffusion, **P**inocytosis/Phagocytosis.
2. **Transporter families — "SLC IN, ABC OUT": S**olute **C**arriers bring drugs **IN**; **A**TP-**B**inding **C**assette pumps push drugs **OUT**.
3. **Factors — "D-B-T" (Drug–Body–Tablet): D**rug factors (chemistry), **B**ody factors (physiology), **T**ablet factors (formulation).
4. **Bioavailability vs Bioequivalence — "One vs Two":** Bioavailab**i**l**i**ty = **I** (one product, how much reaches blood); Bio**e**quival**e**nc**e** = **E** (two products compared, are they Equal?).
5. **P-gp locations — "BILK": B**rain barrier, **I**ntestine, **L**iver, **K**idney — where P-gp pumps drugs out.

3.19 Exam Summary

Drug absorption is the transfer of drug from its administration site into blood circulation. Four mechanisms: (1) passive diffusion — downhill, no energy, no carrier, for lipid-soluble non-ionized drugs (most common); (2) facilitated diffusion — downhill with carrier, no energy, saturable; (3) active transport — uphill with carrier + ATP energy, saturable and selective; (4) pinocytosis/phagocytosis — membrane engulfs droplets/particles. Two transporter families: SLC (entry carriers like OCT, OAT) and ABC (efflux pumps like P-glycoprotein, which reduces absorption and causes interactions). Bioavailability is the percentage of dose reaching blood unchanged (IV = 100%). Bioequivalence means a generic matches the original in rate and extent of absorption (80–125%), allowing safe substitution. Absorption is affected by drug factors (lipid solubility, ionization, size), body factors (gastric emptying, food, blood flow, disease, age), and formulation factors (dissolution, particle size, coating). The small intestine is the main absorption site.

3.20 One-Minute Revision

Absorption = drug → blood. 4 mechanisms: passive (downhill, no energy/carrier — most common), facilitated (carrier, downhill), active (carrier + ATP, uphill), pinocytosis/phagocytosis (engulfing). SLC = drug entry doors; ABC/P-gp = exit pumps (reduce absorption). Bioavailability = % reaching blood (IV = 100%). Bioequivalence = generic equals original (80–125%). Factors: drug chemistry, body physiology, tablet design. Main site: small intestine. Only non-ionized, lipid-soluble drugs diffuse easily.

3.21 Exam Questions

Short questions:

1. Define drug absorption and bioavailability.
2. Name the four mechanisms of drug absorption.
3. What is the difference between facilitated diffusion and active transport?
4. What is P-glycoprotein and what does it do?
5. Define bioequivalence and state its importance.
6. Name three physiological factors affecting drug absorption.
7. Why is the small intestine the main site of drug absorption?
8. What is the difference between ABC and SLC transporters?

Long questions:

1. Describe the four mechanisms of drug absorption with suitable examples. Add a note on membrane transporters (ABC and SLC families).
2. Define bioavailability and bioequivalence. Explain the factors affecting drug absorption under three headings with examples.
3. Explain the role of physicochemical, physiological, and formulation factors in drug absorption. How does this knowledge help a pharmacist in patient counseling?

MCQs (answers at the end):

1. The most common mechanism of drug absorption is:
   a) Active transport
   b) Passive diffusion
   c) Pinocytosis
   d) Phagocytosis

2. Passive diffusion of a drug occurs:
   a) Against the concentration gradient using ATP
   b) Along the concentration gradient without energy
   c) Only with a carrier protein
   d) Only in the stomach
3. Which form of a drug crosses the lipid membrane easily by passive diffusion?
   a) Ionized form
   b) Non-ionized, lipid-soluble form
   c) Ionized, water-soluble form
   d) Protein-bound form
4. Active transport is characterized by all EXCEPT:
   a) Requires ATP energy
   b) Moves against concentration gradient
   c) Cannot be saturated
   d) Requires a carrier protein
5. P-glycoprotein belongs to which transporter family?
   a) SLC family
   b) ABC family
   c) Ion channel family
   d) Aquaporin family
6. The function of P-glycoprotein is to:
   a) Pump drugs into cells
   b) Pump drugs out of cells
   c) Dissolve tablets
   d) Bind plasma proteins
7. Bioavailability of a drug given by IV route is:
   a) 0%
   b) 50%
   c) 100%
   d) Variable
8. Two products are bioequivalent if the generic's rate and extent of absorption fall within what range of the original?
   a) 50–150%
   b) 80–125%
   c) 90–110%
   d) 70–130%
9. Which formulation factor improves absorption of poorly soluble drugs?
   a) Larger particle size
   b) Micronization (smaller particle size)
   c) Thicker coating
   d) Larger tablet weight

10. Food generally affects drug absorption by:
    a) Always increasing it
    b) Always decreasing it
    c) Delaying gastric emptying and sometimes binding drugs
    d) Having no effect at all
11. The main site of drug absorption is:
    a) Stomach
    b) Small intestine
    c) Large intestine
    d) Oesophagus
12. Which of the following is an SLC transporter?
    a) P-glycoprotein
    b) BCRP
    c) OCT1
    d) MRP

Answers: 1-b, 2-b, 3-b, 4-c, 5-b, 6-b, 7-c, 8-b, 9-b, 10-c, 11-b, 12-c

Viva questions:

1. What is the difference between absorption and bioavailability?
2. Why can't ionized drugs cross cell membranes easily?
3. Give one example each of active transport and facilitated diffusion in drug absorption.
4. What happens if a P-gp inhibitor is given with digoxin?
5. Why should sustained-release tablets not be crushed?

Application-based questions:

1. A patient takes an iron tablet with a glass of milk and an antacid, and complains the iron "is not working." Explain using absorption principles what went wrong and counsel the patient.
2. A doctor wants to switch a patient from a costly branded tablet to a Jan Aushadhi generic of the same drug and strength. The patient is worried it "won't work as well." How do you explain bioequivalence to reassure them?
3. Two drugs are known: Drug X is a P-gp substrate, Drug Y is a P-gp inhibitor. Predict what happens to Drug X's absorption when both are given together, and state the clinical risk.

3.22 References

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Chapter 4: Drug Distribution: Compartments, Volume of Distribution, Storage Sites & Plasma Protein Binding

4.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define drug distribution in simple words.
2. Describe the body's fluid compartments — intracellular, extracellular, intravascular (plasma) — and central vs peripheral compartments.
3. Explain volume of distribution (Vd) and what high vs low Vd means, using simple numerical logic.
4. Name the major drug storage sites (fat, bone, liver, thyroid) and explain their importance.
5. Explain plasma protein binding — which proteins bind drugs, and why only the free (unbound) drug acts.
6. Describe the therapeutic importance of protein binding, including displacement interactions.
7. Answer exam questions on distribution with correct examples.

4.2 Definitions

Drug distribution — after a drug reaches the blood (absorption), it travels through the blood to different parts (tissues and organs) of the body. Simple meaning: the blood is a delivery truck, and distribution is the truck dropping the drug at different houses (organs).

Compartment — a imaginary "box" used to describe where the drug goes in the body. The body is divided into compartments (like rooms in a house) to understand and calculate drug movement simply.

Volume of distribution (Vd) — a number (in litres) that tells us how widely a drug spreads in the body. It is NOT a real physical space; it is a calculated value. Simple meaning: a small Vd means the drug mostly stays in the blood; a large Vd means the drug has spread deep into tissues.

Storage site (drug reservoir) — a tissue where a drug gets collected and stored (like fat storing fat-soluble drugs), from where it is slowly released back into the blood later.

Plasma protein binding — many drugs stick (bind) to proteins floating in the blood plasma, mainly albumin. The bound drug is "locked" and inactive; only the free (unbound) drug can leave the blood and act on targets.

4.3 Terminology

- **Intracellular fluid (ICF)** — fluid INSIDE the cells (about 60% of body water).
- **Extracellular fluid (ECF)** — fluid OUTSIDE the cells; includes interstitial fluid (between cells) and plasma (in blood vessels).
- **Intravascular compartment** — the fluid inside blood vessels = blood plasma (about 4–5 litres in an adult).
- **Central compartment** — blood plus organs with very high blood flow (heart, liver, kidney, brain) — drug reaches here first and fast.
- **Peripheral compartment** — tissues with lower blood flow (muscle, fat, skin) — drug reaches here slowly.
- **Free drug** — drug molecules NOT bound to plasma proteins; this is the active form that can cross membranes and produce effects.

- **Bound drug** — drug molecules stuck to plasma proteins; inactive, cannot cross membranes, acts as a storage reserve in blood.
- **Albumin** — the main plasma protein that binds drugs (especially acidic drugs). Made by the liver.
- **Alpha-1-acid glycoprotein** — another plasma protein that mainly binds basic (alkaline) drugs.
- **Displacement interaction** — when one drug pushes another drug off its protein binding site, suddenly increasing the free (active) level of the displaced drug — can cause toxicity.
- **Blood-brain barrier (BBB)** — a tight protective wall of cells around brain blood vessels that stops most drugs from entering the brain.
- **Placental barrier** — the barrier between mother and baby in the womb; many drugs can cross it and affect the unborn baby.

4.4 Explanation (Main Teaching)

What happens after absorption? The drug is now in the blood. But the headache is in the head, the infection is in the lungs, the pain is in the knee. The blood must carry the drug to those places. This journey from blood to tissues is called **distribution**. Think of blood as a network of delivery trucks circulating non-stop; every organ is a delivery address.

Step 1 — The drug rides in the blood. As soon as the drug enters the blood, many drug molecules stick to plasma proteins (mainly albumin), like passengers holding handrails in a bus. This is **plasma protein binding**. The bound passengers cannot get off the bus — only free passengers (free drug) can exit at their stop (cross into tissues). This creates a balance: bound drug ⇌ free drug. As free drug leaves the blood and enters tissues, some bound drug lets go of the protein to replace it. So the bound drug acts as a **reserve store** in the blood, releasing drug slowly and making the effect last longer.

Why does protein binding matter therapeutically?

- Only free drug is active. If 99% of a drug is bound, only 1% is free and working.
- **Displacement danger:** Suppose drug A (e.g., warfarin, a blood thinner) is 99% bound. Now drug B (e.g., an NSAID painkiller) is given, which binds to the same protein more strongly and pushes warfarin off. Suddenly warfarin's free level jumps from 1% to 2% — that is DOUBLE the active drug! Bleeding risk shoots up. This is called a **displacement interaction**, and pharmacists must watch for it with highly bound drugs (warfarin, phenytoin).
- **Disease changes binding:** In liver disease or malnutrition, albumin is low → less binding → more free drug → normal doses can become toxic. In kidney disease, waste products push drugs off proteins. Elderly patients often have lower albumin — they need careful dosing.

Step 2 — The drug leaves the blood and enters tissues. Free drug crosses the walls of tiny blood vessels (capillaries) into the fluid between cells, then into cells. How far it goes depends on the drug's properties:

- Small, lipid-soluble drugs go everywhere, even into the brain (if they can cross the blood-brain barrier) and into fat.
- Large or water-soluble drugs stay mostly in the blood and fluid between cells.
- Some drugs cannot cross the blood-brain barrier (a tight security wall protecting the brain) — this is good for drugs we don't want in the brain, but a problem when we need to treat brain infections.
- Many drugs cross the placenta and reach the unborn baby — this is why drug use in pregnancy needs extreme care.

The body's compartments — rooms in the house: To understand distribution, we divide body fluids into compartments:

1. **Intravascular compartment (plasma)** — inside blood vessels; ~4–5 L in an adult. Drugs injected IV start here.
2. **Extracellular fluid (outside cells)** — includes plasma + fluid between cells (interstitial fluid); ~14 L total.
3. **Intracellular fluid (inside cells)** — ~28 L; the biggest compartment.
4. **Central compartment** (conceptual) — blood + highly perfused organs (heart, liver, kidneys, brain). Drug arrives here within minutes.
5. **Peripheral compartment** (conceptual) — muscle, fat, skin (less blood flow). Drug arrives here slowly, over hours.

Total body water is about 60% of body weight (~42 L in a 70 kg adult). These numbers help you judge whether a Vd value is small or large.

Volume of distribution (Vd) — the key number: Vd answers: "If all the drug in the body were dissolved at the same concentration as in the blood, how many litres would it fill?" Formula: **Vd = Total amount of drug in body ÷ Concentration of drug in blood (plasma).**

Simple numerical logic (no heavy math): Imagine 100 mg of drug is in the body, and blood measurement shows 10 mg per litre.

- Vd = 100 mg ÷ 10 mg/L = **10 litres**. The drug seems spread in about 10 L — a small Vd (roughly the extracellular fluid). Meaning: the drug mostly stays in blood and nearby fluid.
- Now imagine the same 100 mg in the body, but blood shows only 1 mg per litre.
- Vd = 100 mg ÷ 1 mg/L = **100 litres**. But the whole body is only ~42 L of water! How can Vd be 100 L? Because most of the drug has LEFT the blood and hidden in tissues (fat, muscle). The blood level is low because the drug is elsewhere. **A large Vd means wide tissue distribution.**

What Vd tells us:

- **Small Vd (~4–8 L):** drug stays mainly in blood/plasma. Example: heparin, warfarin (highly protein-bound drugs stay in blood).
- **Medium Vd (~15–40 L):** drug spreads through body water.
- **Large Vd (>50 L, sometimes hundreds):** drug concentrates in tissues. Example: chloroquine (Vd ~ hundreds of litres — stored hugely in liver and tissues), digoxin (Vd large — goes into heart muscle).
- **Clinical use:** Vd helps calculate the **loading dose** (the first big dose to quickly fill the body): Loading dose = Vd × desired blood concentration. A drug with large Vd needs a bigger loading dose.

Storage sites — where drugs hide: Some tissues collect and store drugs:

- **Fat (adipose tissue):** stores fat-soluble drugs (e.g., thiopental, an anesthetic; DDT pesticide). Fat acts as a reservoir — the drug leaks out slowly, prolonging effect. In obese patients, fat-soluble drugs have very large Vd.
- **Bone:** stores tetracycline antibiotics and heavy metals like lead. Tetracycline deposited in growing bones/teeth of children causes permanent yellow staining — this is why tetracyclines are avoided in children under 8 and in pregnancy.
- **Liver:** stores chloroquine, tetracyclines.
- **Thyroid gland:** stores iodine (used in thyroid treatment).
- **Muscle:** stores digoxin (binds to heart and skeletal muscle).
- **Importance:** storage prolongs drug action (slow release), but also prolongs toxicity — a stored drug keeps leaking out long after dosing stops. Also, a stored drug may be inactive while stored (e.g., drug in fat is not acting on the brain).

Key takeaway: Distribution decides WHERE the drug goes and HOW MUCH reaches each tissue. Vd is the number that summarizes this spread. Protein binding controls how much drug is free to act, and storage sites act as slow-release reservoirs.

4.5 Classifications

Classification of body compartments:

1. **By fluid location:**
    - Intracellular compartment (inside cells, ~28 L)
    - Extracellular compartment (outside cells, ~14 L)
    - Intravascular (plasma, ~4–5 L)
    - Interstitial (between cells, ~10 L)
2. **By blood flow (pharmacokinetic model):**
    - Central compartment (blood + heart, liver, kidney, brain — fast entry)
    - Peripheral compartment (muscle, fat, skin — slow entry)

Classification of Vd values:

1. Small Vd (plasma volume range, ~4–8 L) — drug confined to blood
2. Medium Vd (body water range, ~15–40 L) — drug spreads in body fluids
3. Large Vd (>50 L) — drug extensively stored in tissues

Classification of storage sites:

1. Fat — lipid-soluble drugs (thiopental, DDT)
2. Bone and teeth — tetracyclines, lead, fluoride
3. Liver — chloroquine
4. Thyroid — iodine
5. Muscle — digoxin

Classification of plasma proteins that bind drugs:

1. Albumin — binds mainly acidic drugs (warfarin, phenytoin, NSAIDs)
2. Alpha-1-acid glycoprotein — binds mainly basic drugs (lidocaine, propranolol)
3. Others — lipoproteins, globulins (minor role)

4.6 Mechanisms

Mechanism of distribution from blood to tissues, step by step:

1. Free (unbound) drug in blood reaches the capillary wall of an organ.
2. Free drug crosses the capillary wall into interstitial fluid (between cells).
3. Free drug crosses the cell membrane into the cell (if lipid-soluble and small).
4. Inside the tissue, drug may bind to tissue proteins or dissolve in fat — becoming "stored."
5. Meanwhile, bound drug in blood releases from albumin to replace the free drug that left (bound ⇌ free equilibrium).
6. Net result: drug spreads until its free concentration is balanced across blood and tissues.

Mechanism of a displacement interaction, step by step:

1. Drug A (e.g., warfarin) is 99% bound to albumin; 1% is free and active — patient is stable.
2. Drug B (e.g., an NSAID) is added; it binds albumin more strongly at the same site.
3. Drug B pushes (displaces) drug A off the albumin.
4. Drug A's free fraction jumps (e.g., 1% → 2% or more).
5. Active drug A level suddenly rises → effect/toxicity increases (bleeding with warfarin).
6. Note: the body later compensates by eliminating more free drug, but the sudden spike is dangerous.

How Vd is determined (conceptual mechanism):

1. Give a known dose (amount in body is known).
2. Wait for distribution to complete (drug evenly spread).
3. Measure drug concentration in blood plasma.
4. Calculate: Vd = amount ÷ plasma concentration.
5. Interpret: small Vd = stays in blood; large Vd = hidden in tissues.

4.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — Body fluid compartments. Draw a large rectangle representing total body water (~42 L in a 70 kg adult). Divide it: the biggest section (~28 L) labeled "Intracellular fluid (inside cells)". The remaining section (~14 L) labeled "Extracellular fluid" — subdivide it into "Plasma/intravascular (~4–5 L)" and "Interstitial fluid between cells (~10 L)". Add a small figure of a person beside it for context.

Diagram 2 — Central vs peripheral compartments. Draw a central circle labeled "CENTRAL: blood + heart, liver, kidney, brain (fast, minutes)". Draw arrows from it outward to outer boxes labeled "PERIPHERAL: muscle, fat, skin (slow, hours)". Show a drug dot moving quickly into the central circle and slowly leaking into the outer boxes.

Diagram 3 — Plasma protein binding equilibrium. Draw a blood vessel cross-section. Inside, draw albumin as large oval shapes with small drug dots stuck to them (label "Bound drug — inactive, reserve"). Draw a few free dots floating (label "Free drug — active, can exit"). Draw a two-way arrow between bound and free labeled "equilibrium". Draw an arrow from free drug through the vessel wall into tissue labeled "only free drug crosses".

Diagram 4 — Vd concept (small vs large). Two panels. Panel A: draw a small bucket (10 L) filled with drug dots mostly in liquid labeled "Small Vd — drug stays in blood". Panel B: draw a huge warehouse with most dots stuck to the walls (tissues) and few in the liquid, labeled "Large Vd (100 L) — drug hidden in tissues, blood level low".

Diagram 5 — Storage sites map. Draw a simple human body outline. Mark: brain-area fat deposits and belly fat ("Fat: thiopental, DDT"), bones/teeth ("Bone: tetracycline → yellow teeth in children"), liver ("Liver: chloroquine"), neck thyroid ("Thyroid: iodine"), muscles ("Muscle: digoxin").

4.8 Flowcharts (Step-by-Step Text Flowcharts)

Flowchart 1 — Path of drug distribution:

```
Drug in blood (bound to albumin + free)
      ↓
Blood carries drug to every organ (delivery truck)
      ↓
FREE drug crosses capillary wall → interstitial fluid
      ↓
FREE drug crosses cell membrane → inside cells
      ↓
Some drug binds tissue proteins / dissolves in fat → STORED
      ↓
Bound drug in blood releases more free drug (equilibrium)
      ↓
Drug reaches target tissue → produces effect
```

Flowchart 2 — Interpreting Vd:

```
Calculate Vd = Amount in body ÷ Plasma concentration
      ↓
Is Vd small (~4-8 L)?
   YES → Drug stays mainly in BLOOD (e.g., heparin, warfarin)
   NO ↓
Is Vd medium (~15-40 L)?
   YES → Drug spreads in BODY WATER
   NO ↓
Is Vd large (>50 L)?
   YES → Drug stored deep in TISSUES (e.g., chloroquine, digoxin)
         → needs larger loading dose; effect/toxicity lasts longer
```

Flowchart 3 — Displacement interaction:

```
Drug A highly bound to albumin (99% bound, 1% free) → patient stable
      ↓
Drug B added → binds same albumin site more strongly
      ↓
Drug B DISPLACES Drug A from albumin
      ↓
Free Drug A suddenly rises (1% → 2%+)
      ↓
Effect/toxicity of Drug A increases sharply
      ↓
PHARMACIST ACTION: monitor, adjust dose, warn doctor/patient
```

4.9 Infographic Concept Box

DISTRIBUTION AT A GLANCE

🟣 **Definition:** Blood carries drug → tissues. Blood = delivery truck.

🟣 **Compartments:** Intracellular (~28 L) | Extracellular (~14 L) = Plasma (~4–5 L) + Interstitial (~10 L). Central (fast organs) vs Peripheral (slow tissues).

🟣 **Vd = Amount in body ÷ Blood concentration.** Small Vd = stays in blood. Large Vd = hides in tissues (can exceed body size!).

🟣 **Protein binding:** Albumin binds acidic drugs; α1-acid glycoprotein binds basic drugs. ONLY free drug acts. Bound = reserve.

🟣 **Displacement danger:** New drug pushes old drug off albumin → free level jumps → toxicity (warfarin + NSAID = bleeding risk).

🟣 **Storage sites:** Fat (thiopental) | Bone/teeth (tetracycline → yellow teeth) | Liver (chloroquine) | Thyroid (iodine) | Muscle (digoxin).

🟣 **Barriers:** Blood-brain barrier blocks most drugs; placenta lets many through → care in pregnancy.

🟣 **Loading dose = Vd × target concentration.** Large Vd → bigger first dose.

4.10 Tables

Table 1 — Body fluid compartments (70 kg adult):

Compartment	Location	Approx. Volume
Intracellular fluid	Inside cells	~28 L
Interstitial fluid	Between cells	~10 L
Plasma (intravascular)	Inside blood vessels	~4–5 L
Total body water	All of the above	~42 L (≈60% of body weight)

Table 2 — Interpreting Vd with examples:

Vd Range	Meaning	Example Drugs
Small (~4–8 L)	Confined mainly to blood plasma	Heparin, warfarin
Medium (~15–40 L)	Distributed in body water	Gentamicin, theophylline
Large (>50 L, up to hundreds)	Extensively stored in tissues	Chloroquine, digoxin, thiopental

Table 3 — Major storage sites:

Storage Site	Drugs Stored	Clinical Importance
Fat (adipose)	Thiopental, DDT	Slow release → prolonged effect; larger Vd in obesity
Bone & teeth	Tetracycline, lead, fluoride	Yellow teeth in children; avoid tetracycline <8 yrs & in pregnancy
Liver	Chloroquine	Very large Vd; long tissue half-life
Thyroid	Iodine	Basis of thyroid treatment/diagnosis
Muscle	Digoxin	Large Vd; muscle binding affects blood levels

Table 4 — Plasma protein binding essentials:

Protein	Mainly Binds	Example Drugs
Albumin	Acidic drugs	Warfarin, phenytoin, NSAIDs, sulfonamides
Alpha-1-acid glycoprotein	Basic drugs	Lidocaine, propranolol, quinidine

Table 5 — Free vs bound drug:

Feature	Free Drug	Bound Drug
Bound to protein	No	Yes
Can cross membranes	Yes	No
Pharmacologically active	Yes	No (inactive reserve)

Feature	Free Drug	Bound Drug
Can be filtered by kidney	Yes	No
Affected by displacement	Increases when displaced	Decreases when displaced

4.11 Examples

1. **Warfarin (blood thinner):** 99% bound to albumin. Only 1% is free and active. This is why small dose changes or displacement interactions cause big effects — the active fraction is tiny and sensitive.
2. **Chloroquine (antimalarial):** Vd of hundreds of litres — far bigger than the body. It is massively stored in the liver and tissues, which is why it stays in the body for weeks after stopping.
3. **Digoxin (heart drug):** Large Vd because it binds strongly to heart and skeletal muscle. Muscle mass affects its distribution — dosing differs in muscular vs thin patients.
4. **Tetracycline in children:** Stored in growing bones and teeth, causing permanent yellow-brown staining. Hence contraindicated below age 8 and in pregnancy — a direct storage-site lesson.
5. **Thiopental (anesthetic):** Highly fat-soluble; after injection it first goes to the brain (fast effect, patient sleeps), then redistributes into fat (patient wakes up as brain level falls), then slowly leaks back from fat (prolonged drowsiness). A classic redistribution story.
6. **Phenytoin + valproate:** Valproate displaces phenytoin from albumin → free phenytoin rises → toxicity (drowsiness, unsteady walk) even though total blood level looks "normal." Pharmacists monitor FREE levels here.

4.12 Analogies

1. **Distribution = delivery trucks.** Blood vessels are roads, blood is a fleet of delivery trucks, and organs are houses. Distribution is the trucks dropping parcels (drug) at each house.
2. **Vd = how far the crowd spreads in a hall.** 100 people in a small room = crowded (high concentration, small Vd). The same 100 people spread across a huge stadium = sparse (low concentration, large Vd). Vd measures the "stadium size" the drug spreads into.
3. **Protein binding = passengers holding bus handrails.** Bound passengers (bound drug) can't get off the bus. Only standing-free passengers (free drug) can exit at their stop. When free passengers get off, some holding passengers let go of the rail to replace them (equilibrium).
4. **Displacement = someone stealing your reserved seat.** You reserved a seat (albumin site). A stronger person pushes you off. Suddenly you're standing (free) — exposed. Displaced drug becomes suddenly active.
5. **Fat storage = a sponge soaking water.** Fat soaks up fat-soluble drugs like a sponge soaks water, then slowly squeezes it back out — prolonging the drug's stay in the body.
6. **Blood-brain barrier = a high-security VIP gate.** Most visitors (drugs) are stopped at the gate; only those with special passes (lipid-soluble, small) get into the VIP area (brain).

4.13 Pharmacy Relevance

- **Loading dose calculation:** Vd is used to calculate the loading dose (first dose to quickly reach effective levels). Pharmacists in hospitals use Vd to individualize doses, especially for drugs like digoxin and theophylline.
- **Displacement vigilance:** With highly bound drugs (warfarin, phenytoin), the pharmacist must check every new prescription for displacers (NSAIDs, sulfonamides, valproate) and counsel about bleeding or toxicity signs.

- **Special populations:** Low albumin (liver disease, malnutrition, elderly) → more free drug → toxicity at "normal" doses. The pharmacist should recommend dose reduction or monitoring in such patients.
- **Pregnancy counseling:** Because many drugs cross the placenta, the pharmacist must warn pregnant women and check every drug's pregnancy safety.
- **Pediatric caution:** Tetracycline–teeth staining is the classic example pharmacists quote to refuse/redirect tetracycline prescriptions for young children.

4.14 India Context

- **Malnutrition and albumin:** Protein-energy malnutrition is still seen in parts of India. Low albumin → higher free drug levels → standard doses of highly bound drugs (phenytoin, warfarin) can become toxic. Indian pharmacists should be alert in undernourished patients.
- **Warfarin + NSAID self-medication:** Self-medication with painkillers (NSAIDs) is extremely common in India. A patient on warfarin who self-medicates with an NSAID faces a double danger: displacement (more free warfarin) PLUS the NSAID's own bleeding risk. Pharmacists must ask about OTC painkiller use.
- **Chloroquine legacy:** India used chloroquine massively against malaria for decades. Its enormous Vd and tissue storage (weeks-long stay) is why it was given weekly for prophylaxis — a fact older Indian pharmacists remember from national malaria programs.
- **Iodine and thyroid:** Iodine deficiency (goitre) was historically common in India's sub-Himalayan belt; the thyroid's iodine storage is the basis of iodized salt programs and thyroid treatment — familiar context for Indian students.

4.15 Key Points

1. Distribution = drug travel from blood to tissues.
2. Compartments: intracellular (~28 L), extracellular (~14 L) = plasma (~4–5 L) + interstitial (~10 L).
3. Central compartment (blood + vital organs, fast) vs peripheral (muscle, fat, skin, slow).
4. Vd = amount in body ÷ plasma concentration. Small Vd = stays in blood; large Vd = stored in tissues.
5. Only FREE (unbound) drug crosses membranes and acts; bound drug is an inactive reserve.
6. Albumin binds acidic drugs; alpha-1-acid glycoprotein binds basic drugs.
7. Displacement interactions (e.g., NSAID displacing warfarin) suddenly raise free drug → toxicity.
8. Storage sites: fat, bone/teeth, liver, thyroid, muscle — prolong action and toxicity.
9. Blood-brain barrier blocks most drugs; placenta allows many through.
10. Loading dose = Vd × desired plasma concentration.

4.16 Common Confusions (with Corrections)

1. **Confusion:** "Vd is a real space inside the body." **Correction:** No. Vd is a CALCULATED, imaginary volume. It can be 100 L even though the body holds only ~42 L of water — it just means the drug is mostly in tissues, not blood.
2. **Confusion:** "Bound drug is active." **Correction:** No. Only FREE drug is active. Bound drug cannot cross membranes or reach targets; it is a reserve.
3. **Confusion:** "A large Vd means high blood levels." **Correction:** Opposite. Large Vd means the drug has LEFT the blood for tissues, so blood levels are LOW.
4. **Confusion:** "Protein binding always reduces drug effect." **Correction:** Not exactly. Binding creates a reserve that releases drug slowly, which can PROLONG the effect. The danger is sudden displacement, not binding itself.

5. **Confusion:** "All drugs enter the brain easily." **Correction:** No. The blood-brain barrier blocks most drugs; only small, lipid-soluble ones (or those with special transporters) enter well.
6. **Confusion:** "Distribution and absorption are the same." **Correction:** Absorption = drug entering the BLOOD. Distribution = drug leaving the blood for TISSUES. Two different steps.

4.17 Common Mistakes (with Corrections)

1. **Mistake:** Calculating Vd using the DOSE instead of the amount actually in the body at the time of measurement. **Correction:** Vd uses the amount present in the body AFTER absorption/distribution equilibrium, divided by plasma concentration — not the raw swallowed dose.
2. **Mistake:** Ignoring albumin levels when dosing highly bound drugs. **Correction:** In low-albumin patients (liver disease, elderly, malnourished), reduce dose or monitor free levels — "normal" total levels can mask toxic free levels.
3. **Mistake:** Prescribing tetracycline to a 5-year-old for a simple infection. **Correction:** Tetracycline stains growing teeth permanently — avoid under age 8; choose a safer antibiotic.
4. **Mistake:** Assuming a drug stored in fat is acting while stored. **Correction:** Stored drug is INACTIVE until released back into blood. Fat storage delays and prolongs, but does not intensify, the effect.
5. **Mistake:** Forgetting the placenta when dispensing to pregnant women. **Correction:** Always check pregnancy safety — many drugs cross the placenta and harm the baby.

4.18 Mnemonics

1. **Compartment volumes — "28-14-5": 28** L inside cells, **14** L outside cells, **5** L plasma (approx). Total ~42 L.
2. **Vd formula — "AViD": A**mount ÷ **V**... think "**A** over **C**": **A**mount in body ÷ **C**oncentration in plasma = Vd.
3. **Storage sites — "FBLTM" (say "fibble-tim"): F**at, **B**one, **L**iver, **T**hyroid, **M**uscle.
4. **Protein binding — "A for Acidic": A**lbumin binds **A**cidic drugs; **A**lpha-1-acid glycoprotein binds b**A**sic (alkaline) drugs.
5. **Free vs bound — "Free is the Fee":** Only the **free** drug pays the **fee** (produces the effect); bound drug just rides along.

4.19 Exam Summary

Drug distribution is the movement of drug from blood into tissues. Body fluids form compartments: intracellular (~28 L), extracellular (~14 L), including plasma (~4–5 L). Pharmacokinetically: central compartment (blood + vital organs, fast) and peripheral compartment (muscle, fat, skin, slow). Volume of distribution (Vd) = amount of drug in body ÷ plasma concentration; small Vd means drug stays in blood (heparin), large Vd means extensive tissue storage (chloroquine, digoxin) and needs a larger loading dose (loading dose = Vd × target concentration). Storage sites — fat, bone/teeth, liver, thyroid, muscle — act as reservoirs prolonging action and toxicity (tetracycline stains children's teeth). Plasma protein binding: albumin binds acidic drugs, alpha-1-acid glycoprotein binds basic drugs; only free drug is active and crosses membranes. Displacement interactions (e.g., NSAIDs displacing warfarin) suddenly raise free drug levels causing toxicity. The blood-brain barrier restricts brain entry; the placenta allows many drugs through, requiring caution in pregnancy.

4.20 One-Minute Revision

Distribution = blood → tissues. Compartments: ICF 28 L, ECF 14 L, plasma ~5 L. Central (fast) vs peripheral (slow). Vd = amount ÷ plasma concentration: small = stays in blood, large = hides in tissues. Only free drug acts; albumin binds acidic drugs. Displacement (warfarin + NSAID) = toxicity risk. Storage: fat, bone (tetracycline → yellow teeth), liver, thyroid, muscle. BBB blocks; placenta passes. Loading dose = Vd × target level.

4.21 Exam Questions

Short questions:

1. Define drug distribution and volume of distribution.
2. What is the formula of Vd? What does a large Vd indicate?
3. Name the body fluid compartments with approximate volumes.
4. Distinguish between central and peripheral compartments.
5. Which plasma protein binds acidic drugs? Give two examples.
6. Why is only free drug pharmacologically active?
7. What is a displacement interaction? Give one example.
8. Name four drug storage sites with one drug example each.

Long questions:

1. Define volume of distribution. Explain its significance with simple numerical examples. How is it used to calculate the loading dose?
2. Describe plasma protein binding and its therapeutic importance, including displacement interactions with examples.
3. Explain the various compartments of drug distribution and the major storage sites, with their clinical significance.

MCQs (answers at the end):

1. Volume of distribution is calculated as:
   a) Plasma concentration ÷ amount in body
   b) Amount in body ÷ plasma concentration
   c) Dose ÷ bioavailability
   d) Clearance × half-life
2. A very large Vd (e.g., 200 L) indicates:
   a) Drug is confined to blood
   b) Drug is extensively stored in tissues
   c) Drug is poorly absorbed
   d) Drug is rapidly excreted
3. The approximate plasma volume in a 70 kg adult is:
   a) 28 L
   b) 14 L
   c) 4–5 L
   d) 42 L

4. Which protein mainly binds acidic drugs like warfarin?
   a) Alpha-1-acid glycoprotein
   b) Albumin
   c) Lipoprotein
   d) Fibrinogen
5. Only which form of drug can cross membranes and produce effect?
   a) Bound drug
   b) Free drug
   c) Metabolized drug
   d) Ionized drug
6. Displacement of warfarin from albumin by an NSAID causes:
   a) Decreased warfarin effect
   b) Increased free warfarin and bleeding risk
   c) No change
   d) Faster excretion of NSAID
7. Tetracycline is avoided in children below 8 years because it:
   a) Causes liver damage
   b) Stains growing teeth and deposits in bone
   c) Causes deafness
   d) Stops growth completely
8. Which organ stores iodine?
   a) Liver
   b) Thyroid gland
   c) Kidney
   d) Spleen
9. The blood-brain barrier:
   a) Allows all drugs into the brain
   b) Restricts entry of most drugs into the brain
   c) Is absent in adults
   d) Pumps drugs into the brain
10. Loading dose is calculated as:
    a) Vd × desired plasma concentration
    b) Dose ÷ Vd
    c) Clearance × Vd
    d) Half-life × dose
11. Which drug has a very large Vd due to extensive tissue storage?
    a) Heparin
    b) Chloroquine
    c) Warfarin
    d) Gentamicin
12. Alpha-1-acid glycoprotein mainly binds:
    a) Acidic drugs
    b) Basic drugs
    c) Neutral drugs
    d) Metals

Answers: 1-b, 2-b, 3-c, 4-b, 5-b, 6-b, 7-b, 8-b, 9-b, 10-a, 11-b, 12-b

Viva questions:

1. Can Vd be larger than the total body volume? Explain.
2. Why does a drug with large Vd need a larger loading dose?
3. What happens to highly bound drugs in a patient with low albumin?
4. Why does thiopental's anesthetic effect wear off quickly even though it stays in the body long?
5. Name the barrier that protects the brain and the one relevant in pregnancy.

Application-based questions:

1. A 70-year-old malnourished patient with low albumin is prescribed a normal dose of phenytoin (90% protein-bound). Explain why toxicity may occur and what the pharmacist should do.
2. A patient stable on warfarin starts self-medicating with ibuprofen for joint pain. Explain the displacement interaction risk and counsel the patient.
3. A mother asks why the doctor refused tetracycline for her 5-year-old's infection and gave another antibiotic instead. Explain using storage-site concepts.

4.22 References

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Chapter 5: Drug Metabolism (Biotransformation) & Drug Excretion

5.1 Learning Objectives

By the end of this chapter, you will be able to:

1. Define biotransformation (drug metabolism) in simple words and state why the body does it.
2. Distinguish between microsomal and non-microsomal metabolism.
3. Explain the cytochrome P450 enzyme system and its importance.
4. Describe Phase I reactions (oxidation, reduction, hydrolysis) and Phase II reactions (glucuronidation, sulfation, acetylation, glutathione conjugation, methylation).
5. Explain first-pass metabolism and entero-hepatic cycling.
6. Define prodrugs and give 2–3 classic examples (enalapril, levodopa, chloramphenicol palmitate).
7. Describe drug excretion through kidney (filtration, secretion, reabsorption), bile, lungs, saliva, milk, and sweat/skin.
8. Explain clearance and half-life in simple form without heavy math.
9. Answer exam questions on metabolism and excretion confidently.

5.2 Definitions

Biotransformation (drug metabolism) — the chemical changing of a drug by the body's enzymes, mainly in the liver, into a different substance called a metabolite. Simple meaning: the liver "processes" the drug, usually converting a fat-soluble drug into a water-soluble form so the kidney can throw it out in urine.

Metabolite — the new substance formed when the body chemically changes a drug. Metabolites are usually inactive and water-soluble (easy to excrete), but sometimes they are active or even toxic.

Microsomal metabolism — drug metabolism carried out by enzymes located in the microsomes (tiny fragments of the endoplasmic reticulum) of liver cells. The cytochrome P450 system lives here. This is the main drug-metabolizing machinery.

Non-microsomal metabolism — drug metabolism by enzymes NOT in microsomes, but floating free in the cell fluid (cytosol) or in mitochondria or blood plasma. Examples: esterases in blood, monoamine oxidase in mitochondria.

Cytochrome P450 (CYP450) — a large family of liver enzymes (with names like CYP3A4, CYP2D6) that carry out most Phase I oxidation reactions. "Cytochrome" = colored cell protein; "P450" = it absorbs light at 450 nm. Think of it as the liver's main chemical-processing factory.

Phase I reactions — the first set of metabolic changes: oxidation, reduction, hydrolysis. They ADD or EXPOSE a chemical handle (like –OH) on the drug molecule, making it slightly more water-soluble and ready for Phase II.

Phase II reactions — the second set: conjugation reactions where a large water-soluble molecule (like glucuronic acid, sulfate) is ATTACHED to the drug, making it very water-soluble and ready for excretion in urine or bile.

First-pass metabolism — when a swallowed drug goes from the gut through the portal vein to the LIVER FIRST, and the liver destroys part (sometimes most) of it before it reaches the rest of the body. This reduces bioavailability.

Entero-hepatic cycling — when a drug (or its metabolite) is excreted by the liver into bile, enters the intestine, and gets REABSORBED back into blood — going round in a liver → gut → blood → liver cycle. This prolongs the drug's stay in the body.

Prodrug — an INACTIVE form of a drug given to the patient; the body converts it into the ACTIVE form. Simple meaning: a "sleeping" medicine that wakes up inside the body.

Drug excretion — the removal of drugs and their metabolites from the body, mainly through urine (kidney), and also through bile/faeces, lungs, saliva, breast milk, and sweat/skin.

Clearance — the volume of blood completely cleared of drug per unit time (e.g., mL/min). Simple meaning: how fast the body's "cleaning system" removes the drug.

Half-life (t½) — the time taken for the drug's blood level to fall to HALF its value. Simple meaning: if blood level is 100 units now, after one half-life it is 50, after two half-lives 25, and so on. Roughly 4–5 half-lives remove almost all drug from the body.

5.3 Terminology

- **Oxidation** — Phase I reaction adding oxygen (or removing hydrogen) to the drug; the most common metabolic reaction, done by CYP450.
- **Reduction** — Phase I reaction adding hydrogen (or removing oxygen); opposite of oxidation.
- **Hydrolysis** — Phase I reaction breaking a drug apart using water (e.g., esters split by esterases).
- **Glucuronidation** — Phase II reaction attaching glucuronic acid to the drug; the most common conjugation reaction.
- **Sulfation** — Phase II attaching a sulfate group.
- **Acetylation** — Phase II attaching an acetyl group (important for isoniazid — fast vs slow acetylators).
- **Glutathione conjugation** — Phase II attaching glutathione; a detox pathway (protects against paracetamol poisoning when NAC restores glutathione).
- **Methylation** — Phase II attaching a methyl group.
- **Glomerular filtration** — kidney's first excretion step: blood filtered through the glomerulus; free (unbound), small drug molecules pass into urine.
- **Tubular secretion** — kidney's second step: kidney tubule cells ACTIVELY pump drugs from blood into urine (uses transporters like OAT/OCT).
- **Tubular reabsorption** — kidney's third step: some drug in urine is REABSORBED back into blood (mainly lipid-soluble, non-ionized drugs); this reduces excretion.
- **Enzyme induction** — when a drug increases the amount/activity of metabolizing enzymes → faster metabolism of other drugs → reduced effect.
- **Enzyme inhibition** — when a drug blocks metabolizing enzymes → slower metabolism → higher drug levels → toxicity risk.
- **Biliary excretion** — liver excreting drugs/metabolites into bile → intestine → out in faeces (or reabsorbed in entero-hepatic cycling).

5.4 Explanation (Main Teaching)

PART A — DRUG METABOLISM (BIOTRANSFORMATION)

Why does the body metabolize drugs? Most drugs are fat-soluble (lipid-soluble) — that is how they crossed membranes to get absorbed. But the kidney can only throw out WATER-soluble substances in urine; fat-soluble drugs get reabsorbed back from kidney tubules instead of leaving. So the body faces a problem: how to remove fat-soluble drugs? Solution: the **liver chemically converts fat-soluble drugs into water-soluble metabolites** — like converting oil into soap so it washes away with water. That conversion is biotransformation. Main site: the **liver** (also gut wall, kidney, lungs, skin to a lesser extent).

Microsomal vs non-microsomal metabolism:

- **Microsomal:** enzymes sit in the microsomes (pieces of endoplasmic reticulum) of liver cells. The **cytochrome P450 (CYP450)** family lives here and handles MOST drug oxidations. Other microsomal enzymes do glucuronidation. This system is "inducible" — some drugs can increase its amount (enzyme induction).
- **Non-microsomal:** enzymes floating in cell fluid (cytosol), mitochondria, or blood plasma. Examples: esterases in plasma (split ester drugs like aspirin, succinylcholine), monoamine oxidase (MAO) in mitochondria, alcohol dehydrogenase in cytosol. These are generally NOT inducible and handle specific drugs.

The cytochrome P450 system — the star of metabolism: CYP450 is not one enzyme but a FAMILY with many members, named like CYP3A4, CYP2D6, CYP2C9, CYP1A2 (the numbers/letters are family codes). Key facts:

- **CYP3A4** metabolizes the LARGEST number of drugs (about half of all medicines).
- Different people have different CYP activity (genetic differences) — e.g., some are "poor metabolizers" of CYP2D6 drugs and get toxicity from normal doses.
- **Grapefruit juice** blocks CYP3A4 in the gut wall → drugs normally destroyed there now flood into blood → toxicity. Pharmacists warn patients about this.
- **Drug interactions:** one drug can INDUCE (speed up) or INHIBIT (slow down) CYP enzymes, changing other drugs' levels. Example: rifampicin induces enzymes → makes contraceptive pills fail; erythromycin inhibits CYP3A4 → raises levels of certain statins.

Phase I reactions — "prepare the drug": Three types:

1. **Oxidation** (most common): CYP450 adds oxygen. Example: phenytoin oxidized in liver.
2. **Reduction**: adds hydrogen. Example: chloramphenicol reduced.
3. **Hydrolysis**: water splits the molecule. Example: aspirin hydrolyzed by esterases to salicylic acid; procaine split by plasma esterases.

   Result of Phase I: the drug now has a chemical "handle" (–OH, –NH2) and is slightly more water-soluble. The metabolite may be active, inactive, or (rarely) toxic.

Phase II reactions — "attach and flush": A big water-soluble molecule is conjugated (attached) to the drug or its Phase I metabolite:

1. **Glucuronidation** (most common): glucuronic acid attached. Example: morphine → morphine glucuronide; paracetamol is largely glucuronidated.
2. **Sulfation**: sulfate attached (paracetamol also sulfated).
3. **Acetylation**: acetyl group attached. Example: isoniazid (TB drug) — people are genetically "fast" or "slow" acetylators, affecting dose response.
4. **Glutathione conjugation**: glutathione attached — a DETOX pathway. Example: paracetamol's toxic metabolite (NAPQI) is neutralized by glutathione; in overdose glutathione runs out → liver damage; antidote NAC restores glutathione.

5. **Methylation**: methyl group attached. Example: adrenaline/noradrenaline metabolized.

   Result of Phase II: very water-soluble, usually INACTIVE metabolite, easily excreted in urine or bile. (Exception: morphine-6-glucuronide is active.)

Order note: Most drugs go Phase I → Phase II, but some go directly to Phase II (e.g., paracetamol largely conjugated directly).

First-pass metabolism: A swallowed tablet dissolves, is absorbed from the gut into portal blood, and the portal vein carries it STRAIGHT TO THE LIVER before anywhere else. The liver is a strict customs checkpoint: it metabolizes part (sometimes 70–90%) of the drug on this first pass. Only the surviving fraction reaches general circulation. Consequences:

- Oral bioavailability is reduced (e.g., propranolol, morphine have heavy first-pass).
- To bypass first-pass, use other routes: sublingual (under tongue → straight to blood), IV, transdermal, rectal (partly).
- Example: nitroglycerin for chest pain is given SUBLINGUALLY — if swallowed, the liver would destroy most of it before it works.

Entero-hepatic cycling: Some drugs/metabolites are excreted by the liver into BILE, flow into the intestine — and then get REABSORBED from the intestine back into blood, returning to the liver. Round and round: liver → bile → gut → blood → liver. Each cycle returns drug to the body, PROLONGING its action and half-life. Examples: oral contraceptive estrogens, digitoxin. Note: antibiotics that kill gut bacteria can interrupt this cycle (bacteria help release the drug for reabsorption) — another interaction pharmacists watch.

Prodrugs — "sleeping medicines": A prodrug is inactive when given; the body converts it to the active drug. Why make prodrugs?

- To improve absorption (active form absorbs poorly).
- To reduce side effects (e.g., stomach irritation).
- To target delivery (activate only at the needed site).

  Classic examples:

  1. **Enalapril → enalaprilat:** Enalapril (BP medicine) is inactive; liver esterases convert it to active enalaprilat which lowers blood pressure.

  2. **Levodopa → dopamine:** Dopamine itself cannot cross the blood-brain barrier, so Parkinson's patients get levodopa, which crosses into the brain and converts to dopamine there.

  3. **Chloramphenicol palmitate → chloramphenicol:** Chloramphenicol tastes extremely bitter; the palmitate ester prodrug is tasteless (good for children's syrup) and gut enzymes release active chloramphenicol.

PART B — DRUG EXCRETION

The kidney — the main exit (urine): Three processes handle drugs in the kidney:

1. **Glomerular filtration:** Blood arrives at the glomerulus (a tiny filter ball). Water, salts, and SMALL, FREE (unbound) drug molecules are filtered into the kidney tubule. Bound drugs (stuck to albumin — too big) and large molecules are NOT filtered. This is passive — no energy.
2. **Tubular secretion:** As fluid flows through the tubule, tubule cells ACTIVELY PUMP additional drug molecules from blood into the urine using transporters (OAT for acidic drugs like penicillin; OCT for basic drugs). This needs energy and can be saturated. It removes even protein-bound drugs (as free drug is secreted, bound drug releases to replace it). Competition here causes interactions: e.g., probenecid blocks penicillin secretion → penicillin stays longer in blood (used deliberately to prolong penicillin action).

3. **Tubular reabsorption:** As urine flows down the tubule, FAT-SOLUBLE, NON-IONIZED drugs slip back through tubule walls into blood — escaping excretion. Water-soluble, ionized drugs stay in urine and leave the body. This is why metabolism (making drugs water-soluble) is essential before excretion! Doctors can manipulate this: making urine alkaline increases excretion of acidic drugs (aspirin poisoning treatment — "alkaline diuresis") because ionized aspirin cannot be reabsorbed.

Other excretion routes:

- **Biliary excretion (bile → faeces):** Liver pumps some drugs/metabolites into bile → intestine → out in faeces. Large, conjugated metabolites favor this route. (Links to entero-hepatic cycling.)
- **Pulmonary (lungs):** Volatile/gaseous drugs leave in exhaled air — e.g., general anesthetics, alcohol (basis of the breathalyzer test).
- **Salivary:** Some drugs appear in saliva (e.g., lithium, some antibiotics) — usually small amounts.
- **Mammary (breast milk):** Many drugs pass into breast milk → can affect the nursing baby. Lipid-soluble, non-ionized drugs pass most. Nursing mothers need drug safety checks.
- **Sweat and skin:** Small amounts of some drugs (e.g., griseofulvin) leave in sweat.

Clearance and half-life — simple form:

- **Clearance:** how efficiently the body removes the drug = volume of blood fully cleared of drug per minute (mL/min). High clearance = fast removal. Total clearance = kidney clearance + liver clearance + others.
- **Half-life (t½):** time for blood drug level to drop by HALF. Example: drug level 100 → after one half-life 50 → after two 25 → after three 12.5. After about 4–5 half-lives, ~95% of drug is gone. Uses: deciding dose timing (how often to repeat), knowing when a drug is fully out of the body, and understanding why some drugs are given once daily (long half-life) vs four times daily (short half-life). Simple relationship (no heavy math): half-life is LONGER when Vd is large or clearance is low.

Key takeaway: Metabolism (liver) converts fat-soluble drugs to water-soluble metabolites; excretion (mainly kidney) throws them out. Phase I prepares, Phase II attaches-and-flushes. First-pass reduces oral bioavailability; entero-hepatic cycling prolongs stay; prodrugs wake up inside the body. Clearance = cleaning speed; half-life = time to halve the level.

5.5 Classifications

Classification of biotransformation:

1. **By enzyme location:**
    - Microsomal (endoplasmic reticulum): CYP450 oxidations, glucuronidation — main system, inducible
    - Non-microsomal (cytosol, mitochondria, plasma): esterases, MAO, alcohol dehydrogenase — specific, non-inducible
2. **By reaction phase:**
    - Phase I: oxidation, reduction, hydrolysis (functionalization — adds/exposes handle)
    - Phase II: glucuronidation, sulfation, acetylation, glutathione conjugation, methylation (conjugation — attaches bulky water-soluble group)

Classification of excretion routes:

1. Renal (urine) — main route: filtration, secretion, reabsorption
2. Biliary (bile → faeces)
3. Pulmonary (exhaled air) — volatile drugs
4. Salivary (saliva) — minor

5. Mammary (breast milk) — important for nursing mothers
6. Sweat/skin — minor

Classification of CYP interactions:

1. Enzyme inducers (speed up metabolism → less drug effect): rifampicin, carbamazepine, smoking
2. Enzyme inhibitors (slow metabolism → more drug/toxicity): erythromycin, ketoconazole, grapefruit juice

5.6 Mechanisms

Mechanism — Phase I oxidation by CYP450, step by step:

1. Fat-soluble drug enters liver cell and binds to CYP450 enzyme in microsomes.
2. The enzyme uses oxygen and energy to add an oxygen atom (–OH group) to the drug.
3. The drug now has a chemical "handle" and is slightly more water-soluble.
4. The handled drug passes to Phase II enzymes for conjugation.

Mechanism — Phase II glucuronidation, step by step:

1. Drug (or Phase I metabolite) with a handle (–OH) meets glucuronyl transferase enzyme.
2. The enzyme attaches glucuronic acid (a large, water-soluble sugar acid) to the handle.
3. The conjugate is now very water-soluble and inactive.
4. It is excreted in urine (or bile if large).

Mechanism — First-pass metabolism, step by step:

1. Tablet swallowed → dissolves → absorbed from intestine.
2. Absorbed drug enters portal vein (not general circulation).
3. Portal vein delivers 100% of absorbed drug to the LIVER first.
4. Liver enzymes metabolize a fraction (sometimes most) immediately.
5. Only the surviving fraction enters general blood circulation.
6. Result: oral bioavailability < 100%.

Mechanism — Entero-hepatic cycling, step by step:

1. Liver conjugates drug and excretes it into bile.
2. Bile carries it into the intestine.
3. Gut bacteria cut off the conjugate, freeing the drug.
4. Free drug is reabsorbed from intestine into portal blood.
5. Blood returns it to the liver — cycle repeats.
6. Result: drug stays in body longer; half-life prolonged.

Mechanism — Renal excretion (three steps):

1. **Filtration:** at the glomerulus, free small drug molecules filter into tubule; bound/large molecules stay in blood.
2. **Secretion:** tubule cells actively pump more drug (acids via OAT, bases via OCT) from blood into tubule fluid.
3. **Reabsorption:** lipid-soluble, non-ionized drug slips back into blood; water-soluble, ionized drug stays and is excreted in urine.

Mechanism — Prodrug activation (enalapril example):

1. Inactive enalapril swallowed and absorbed.
2. Reaches liver; esterase enzymes cut off the ester group.
3. Active enalaprilat is formed.
4. Enalaprilat blocks ACE → blood pressure falls.

5.7 Diagrams (Describe Textually So They Can Be Drawn)

Diagram 1 — Why metabolism is needed. Draw a fat-soluble drug as an oil drop. Show it arriving at the kidney: an arrow loops back labeled "reabsorbed — cannot leave!" Then show the oil drop going to the liver, coming out as a water drop labeled "water-soluble metabolite", then going to the kidney and leaving in urine with an arrow labeled "excreted!" Caption: "Liver converts oil-like drugs to water-like metabolites so kidneys can excrete them."

Diagram 2 — Phase I → Phase II pipeline. Draw three boxes in a row: Box 1 "Fat-soluble DRUG" → arrow "Phase I: oxidation/reduction/hydrolysis (CYP450)" → Box 2 "Metabolite with handle (–OH), slightly water-soluble" → arrow "Phase II: conjugation (glucuronic acid etc.)" → Box 3 "Water-soluble CONJUGATE → urine/bile". Below, a small bypass arrow from Box 1 directly to Phase II labeled "some drugs skip Phase I".

Diagram 3 — First-pass metabolism. Draw the intestine (left), portal vein (pipe going up), liver (center), and general circulation/heart (right). Show drug dots traveling: intestine → portal vein → liver, where half the dots are crossed out (destroyed) labeled "metabolized on first pass", and the surviving dots continue to the heart labeled "reaches body". Add a second small pathway: a tablet under the tongue with dots going directly to the heart labeled "sublingual bypasses first-pass".

Diagram 4 — Entero-hepatic cycle. Draw a circular loop with four stations: LIVER → (bile duct) → INTESTINE → (portal blood) → back to LIVER. Show drug dots circulating around the loop with a small arrow leaking out labeled "some lost in faeces each round". Caption: "Each cycle prolongs the drug's stay."

Diagram 5 — The nephron's three excretion steps. Draw a nephron: glomerulus (filter ball) with an arrow into the tubule labeled "1. FILTRATION: free small drugs filtered"; along the tubule draw pumps pushing dots from blood into tubule labeled "2. SECRETION: active pumping (OAT/OCT)"; further along draw dots slipping back from tubule to blood labeled "3. REABSORPTION: lipid-soluble drugs return"; final arrow out labeled "urine with water-soluble drugs".

Diagram 6 — Half-life decay curve. Draw a graph: vertical axis "drug level", horizontal axis "time". Plot a falling curve starting at 100, marking points: 100 → 50 (1 half-life) → 25 (2) → 12.5 (3) → ~6 (4). Label: "Each half-life halves the level; ~4–5 half-lives ≈ drug gone."

5.8 Flowcharts (Step-by-Step Text Flowcharts)

Flowchart 1 — Fate of an oral drug (full ADME glimpse):

```
Swallowed drug
      ↓
Absorbed from gut → portal vein → LIVER (first-pass: part destroyed)
      ↓
Surviving drug → general circulation → DISTRIBUTED to tissues
      ↓
Liver metabolizes: Phase I (oxidize/reduce/hydrolyze) → Phase II (conjugate)
      ↓
Water-soluble metabolites → KIDNEY → urine (filtration + secretion − reabsorption)
      ↓
Also: bile → faeces; lungs → exhaled air; milk/saliva/sweat (minor)
      ↓
DRUG ELIMINATED (clearance = speed; half-life = time to halve level)
```

Flowchart 2 — Deciding Phase I vs Phase II:

```
Drug enters liver
      ↓
Does it already have a handle (-OH, -NH2) for conjugation?
   YES → May go DIRECTLY to Phase II (e.g., paracetamol → glucuronidation)
   NO ↓
Phase I first: oxidation (CYP450) / reduction / hydrolysis → adds handle
      ↓
Then Phase II: attach glucuronic acid / sulfate / acetyl / glutathione / methyl
      ↓
Water-soluble inactive conjugate → urine or bile
```

Flowchart 3 — What happens in kidney tubule:

```
Blood reaches glomerulus
      ↓
FILTRATION: free + small drugs filtered; bound + large stay in blood
      ↓
Tubule fluid flows on
      ↓
SECRETION: pumps push more drug (acids via OAT, bases via OCT) into tubule
      ↓
REABSORPTION: lipid-soluble/non-ionized drug slips back to blood;
              water-soluble/ionized drug STAYS
      ↓
Remaining drug + water → URINE → out of body
```

5.9 Infographic Concept Box

METABOLISM & EXCRETION AT A GLANCE

🔵 **Why metabolize?** Kidney can't throw out oil-like drugs → liver converts fat-soluble → water-soluble.

🔵 **Two enzyme homes:** Microsomal (CYP450 factory, inducible) | Non-microsomal (esterases, MAO — specific).

🔵 **CYP450 family:** CYP3A4 handles most drugs. Inducers (rifampicin) speed up; inhibitors (grapefruit, erythromycin) slow down.

🔵 **Phase I** = prepare: oxidation, reduction, hydrolysis (adds handle). **Phase II** = attach & flush: glucuronidation, sulfation, acetylation, glutathione, methylation.

🔵 **First-pass:** gut → portal vein → liver destroys part before body sees it → low oral bioavailability. Bypass: sublingual, IV.

🔵 **Entero-hepatic cycle:** liver → bile → gut → blood → liver (round & round) → longer stay.

🔵 **Prodrugs:** inactive → active in body. Enalapril→enalaprilat | Levodopa→dopamine (brain) | Chloramphenicol palmitate→chloramphenicol (tasteless).

🔵 **Kidney 3 steps:** Filtration (free+small) → Secretion (pumps: OAT/OCT) → Reabsorption (lipid-soluble returns).

🔵 **Other exits:** bile/faeces, lungs (alcohol breath), saliva, breast milk (caution!), sweat.

🔵 **Clearance** = cleaning speed (mL/min). **Half-life** = time to halve level; 4–5 half-lives ≈ gone.

5.10 Tables

Table 1 — Phase I vs Phase II reactions:

Feature	Phase I	Phase II
Purpose	Add/expose chemical handle	Attach bulky water-soluble group
Reactions	Oxidation, reduction, hydrolysis	Glucuronidation, sulfation, acetylation, glutathione conjugation, methylation
Main enzymes	Cytochrome P450 (microsomal)	Transferases (e.g., glucuronyl transferase)
Water solubility change	Slight increase	Large increase
Metabolite activity	May be active/inactive/toxic	Usually inactive (morphine-6-glucuronide is an exception)

Table 2 — Phase II conjugation reactions with examples:

Conjugation	Group Attached	Example Drug
Glucuronidation	Glucuronic acid	Paracetamol, morphine
Sulfation	Sulfate	Paracetamol
Acetylation	Acetyl group	Isoniazid (fast/slow acetylators)
Glutathione conjugation	Glutathione	Paracetamol's toxic metabolite NAPQI (detox)
Methylation	Methyl group	Adrenaline, noradrenaline

Table 3 — Microsomal vs non-microsomal metabolism:

Feature	Microsomal	Non-microsomal
Location	Endoplasmic reticulum (microsomes) of liver cells	Cytosol, mitochondria, blood plasma
Key enzymes	Cytochrome P450 family	Esterases, MAO, alcohol dehydrogenase
Inducible by drugs	Yes	Generally no
Handles	Most drugs (oxidations)	Specific drugs (esters, amines, alcohol)

Table 4 — Kidney's three excretion processes:

Process	Where	What Happens	Energy Needed
Glomerular filtration	Glomerulus	Free, small drugs filtered into tubule	No (passive)
Tubular secretion	Tubule cells	Pumps push drugs (OAT/OCT) into urine	Yes (active)
Tubular reabsorption	Tubule walls	Lipid-soluble drugs slip back to blood	No (passive)

Table 5 — Excretion routes:

Route	What Leaves This Way	Example
Urine (kidney)	Most water-soluble drugs/metabolites	Penicillin, paracetamol metabolites
Bile → faeces	Large conjugated metabolites	Oral contraceptive estrogens
Lungs (exhaled air)	Volatile drugs	Anesthetic gases, alcohol

Route	What Leaves This Way	Example
Saliva	Small amounts	Lithium
Breast milk	Lipid-soluble drugs	Many drugs — caution in nursing mothers
Sweat/skin	Small amounts	Griseofulvin

Table 6 — Classic prodrugs:

Prodrug (Inactive)	Active Form	Why a Prodrug?
Enalapril	Enalaprilat	Better absorbed; activated by liver
Levodopa	Dopamine	Dopamine can't cross blood-brain barrier; levodopa can, then converts in brain
Chloramphenicol palmitate	Chloramphenicol	Tasteless (for children's syrup); gut enzymes activate it

5.11 Examples

1. **Paracetamol metabolism:** Mostly conjugated directly (glucuronidation + sulfation) — safe at normal doses. A small part becomes toxic NAPQI, neutralized by glutathione. In overdose, glutathione runs out → liver failure; antidote N-acetylcysteine (NAC) restores glutathione.
2. **Grapefruit juice + felodipine (BP drug):** Grapefruit blocks gut CYP3A4 → much more felodipine absorbed → blood pressure can crash. Pharmacists warn: no grapefruit with certain BP/cholesterol drugs.
3. **Rifampicin + contraceptive pill:** Rifampicin (TB drug) induces liver enzymes → pill hormones metabolized faster → contraceptive failure → unwanted pregnancy. Classic Indian exam example.
4. **Probenecid + penicillin:** Probenecid blocks tubular secretion of penicillin → penicillin stays longer in blood → used deliberately to prolong penicillin's action.
5. **Aspirin poisoning treatment:** Doctors make urine alkaline ("alkaline diuresis") → aspirin becomes ionized in tubule → cannot be reabsorbed → flushed out faster.
6. **Alcohol breath test:** Alcohol is volatile and excreted partly through lungs — the breathalyzer measures it. Simple, memorable proof of pulmonary excretion.
7. **Isoniazid acetylation:** TB patients are genetically fast or slow acetylators — slow acetylators get more side effects from standard doses; fast acetylators may need higher doses.

5.12 Analogies

1. **Metabolism = converting oil to soap.** You can't wash oily hands with water alone; soap converts oil to something water washes away. The liver converts oil-like (fat-soluble) drugs to soap-like (water-soluble) metabolites the kidney can wash out.
2. **CYP450 = a factory with many machines.** The liver is a factory; CYP3A4, CYP2D6 etc. are different machines, each processing certain products (drugs). An inducer hires more workers (faster); an inhibitor switches machines off (slower, products pile up).
3. **Phase I → Phase II = tailor shop.** Phase I is cutting the cloth and adding buttonholes (handles); Phase II is sewing on big buttons (water-soluble groups). The finished garment (conjugate) is ready for delivery (excretion).
4. **First-pass = customs checkpoint.** International passengers (drugs) must pass customs (liver) before entering the country (body). Customs seizes part of the goods — only the rest enters.

5. **Entero-hepatic cycling = a roundabout.** Cars (drug molecules) keep circling the roundabout (liver → gut → blood → liver); a few exit each round (faeces), so traffic clears slowly.
6. **Prodrug = a sealed envelope.** The envelope (prodrug) is useless until opened; inside is the real letter (active drug). The body "opens" it with enzymes.
7. **Half-life = halving a chapati stack.** 16 chapatis → eat half (8 left) → eat half (4 left) → eat half (2 left). Each "half-life" halves the stack; after 4–5 halvings almost nothing remains.
8. **Tubular secretion = bouncers throwing people out.** The kidney tubule's pumps are bouncers actively throwing drug molecules out of the blood-club into the urine.

5.13 Pharmacy Relevance

- **Interaction watchdog:** CYP450 inducers/inhibitors cause the most dangerous drug interactions. The pharmacist must flag rifampicin (kills contraceptives, antiretrovirals), erythromycin/ketoconazole (raise statin levels → muscle damage), and grapefruit juice.
- **Overdose management knowledge:** Understanding NAPQI/glutathione explains why NAC is the paracetamol antidote and why it must be given early — pharmacists in emergency settings use this.
- **Kidney-dose adjustment:** In kidney failure, excretion slows → half-life lengthens → doses must be reduced or intervals extended (e.g., aminoglycosides, digoxin). Pharmacists calculate these adjustments.
- **Nursing mothers:** Because drugs pass into breast milk, the pharmacist checks every prescription for a breastfeeding mother and suggests safer alternatives or timing (feed before the dose).
- **Prodrug counseling:** Patients should know that enalapril "needs the liver to activate it" — in severe liver disease it may work poorly; also why levodopa is given instead of dopamine.
- **Urine pH tricks:** Knowing reabsorption helps pharmacists understand poisoning treatments (alkaline diuresis for aspirin/phenobarbital poisoning).

5.14 India Context

- **TB treatment and acetylation:** India has the world's largest TB burden. Isoniazid (a first-line TB drug) is acetylated, and Indians include both fast and slow acetylators — explaining why some patients get more side effects (like nerve tingling) on standard doses. Pharmacists under the national TB program (Nikshay) counsel on completing the full course.
- **Rifampicin interactions in DOTS:** Rifampicin, the backbone of TB treatment, is a powerful enzyme inducer. Indian pharmacists must warn women on oral contraceptives to use additional protection during TB treatment — a frequently examined counseling point.
- **Paracetamol overdose:** Paracetamol is India's most self-used painkiller/fever drug. Overdose (accidental in children, intentional in adults) causes liver failure via NAPQI when glutathione is exhausted. Pharmacists should stock and know about NAC and counsel never to exceed the daily limit.
- **Ayurvedic/herbal enzyme effects:** Some Ayurvedic and herbal products can induce or inhibit liver enzymes, altering allopathic drug levels. Indian pharmacists should always ask patients about concurrent herbal/Ayurvedic use.
- **Breath alcohol checks:** Traffic police breathalyzers across India work on pulmonary excretion of alcohol — a real-life example every Indian student has seen.

5.15 Key Points

1. Biotransformation = liver converts fat-soluble drugs → water-soluble metabolites for kidney excretion.
2. Microsomal (CYP450, inducible — main system) vs non-microsomal (esterases, MAO — specific).
3. CYP3A4 metabolizes the most drugs; inducers (rifampicin) speed up, inhibitors (grapefruit, erythromycin) slow down.
4. Phase I: oxidation, reduction, hydrolysis (adds handle). Phase II: glucuronidation, sulfation, acetylation, glutathione conjugation, methylation (attaches bulky group → very water-soluble, usually inactive).
5. First-pass metabolism: oral drugs pass through liver first → part destroyed → lower bioavailability; bypass via sublingual/IV.
6. Entero-hepatic cycling: liver → bile → gut → blood → liver; prolongs drug stay.
7. Prodrugs: inactive → active in body (enalapril→enalaprilat, levodopa→dopamine, chloramphenicol palmitate→chloramphenicol).
8. Kidney excretion: filtration (free+small) → secretion (active pumps OAT/OCT) → reabsorption (lipid-soluble returns).
9. Other routes: bile/faeces, lungs, saliva, breast milk (caution), sweat.
10. Clearance = volume of blood cleared per minute; half-life = time to halve blood level; ~4–5 half-lives ≈ elimination.

5.16 Common Confusions (with Corrections)

1. **Confusion:** "Metabolism always makes drugs inactive." **Correction:** Usually inactive, but NOT always — some metabolites are ACTIVE (morphine-6-glucuronide) and some are TOXIC (paracetamol's NAPQI). And prodrugs are inactive until metabolized TO the active form.
2. **Confusion:** "Phase I always comes before Phase II." **Correction:** Usually, but some drugs go DIRECTLY to Phase II (e.g., paracetamol largely conjugated without Phase I).
3. **Confusion:** "All excretion happens through urine." **Correction:** Kidney is the MAIN route, but bile/faeces, lungs, saliva, breast milk, and sweat also excrete drugs.
4. **Confusion:** "Enzyme induction and inhibition are the same." **Correction:** Opposite. INDUCTION = more enzyme → faster metabolism → LESS drug effect. INHIBITION = blocked enzyme → slower metabolism → MORE drug → toxicity risk.
5. **Confusion:** "First-pass metabolism happens for IV drugs too." **Correction:** No. IV drugs enter general circulation directly, bypassing the gut-liver first pass. That's why IV bioavailability is 100%.
6. **Confusion:** "Bound drugs are filtered by the glomerulus." **Correction:** No. Only FREE, small molecules are filtered; protein-bound drugs are too big to pass the filter (they can still be secreted by tubule pumps, though).

5.17 Common Mistakes (with Corrections)

1. **Mistake:** Writing "CYP450 is a single enzyme." **Correction:** It is a FAMILY of many enzymes (CYP3A4, CYP2D6, CYP2C9, CYP1A2...), each handling different drugs.
2. **Mistake:** Listing only oxidation as Phase I. **Correction:** Phase I = oxidation AND reduction AND hydrolysis — all three must be named.
3. **Mistake:** Forgetting glutathione conjugation or methylation in Phase II lists. **Correction:** All five must be listed: glucuronidation, sulfation, acetylation, glutathione conjugation, methylation.

4. **Mistake:** Saying "prodrugs are weak drugs." **Correction:** Prodrugs are INACTIVE by design; the body converts them to fully active drugs. Inactive ≠ weak.
5. **Mistake:** Advising a breastfeeding mother that "all medicines are safe because the baby gets only milk." **Correction:** Many drugs pass into breast milk — always check safety and consider timing doses after feeds.
6. **Mistake:** In poisoning, assuming "more water intake flushes all drugs out." **Correction:** Only water-soluble/ionized drugs are excreted well; for acidic drugs like aspirin, URINE ALKALINIZATION (not just water) traps them ionized in tubules for excretion.

5.18 Mnemonics

1. **Phase I — "ORH" (say "orh"): O**xidation, **R**eduction, **H**ydrolysis.
2. **Phase II — "GSAGM" (say "g-sag-m"): G**lucuronidation, **S**ulfation, **A**cetylation, **G**lutathione conjugation, **M**ethylation. Memory hook: "**G**ood **S**tudents **A**lways **G**et **M**arks."
3. **Kidney 3 steps — "FSR" (say "fiss-ur"): F**iltration → **S**ecretion → **R**eabsorption.
4. **Prodrug examples — "ELC" (say "elk"): E**nalapril, **L**evodopa, **C**hloramphenicol palmitate.
5. **Enzyme interactions — "Induce = Increase speed, Inhibit = Increase level": Induc**ers **increase** enzyme speed (drug effect falls); **Inhib**itors **increase** drug level (toxicity risk).
6. **Half-life rule — "4–5 halves = gone":** After **4–5 half-lives**, ~95% of drug eliminated.

5.19 Exam Summary

Biotransformation is the liver's chemical conversion of fat-soluble drugs into water-soluble metabolites for excretion. Microsomal metabolism (cytochrome P450 family in endoplasmic reticulum, inducible) handles most drugs; non-microsomal (esterases, MAO in cytosol/mitochondria/plasma) handles specific ones. CYP3A4 metabolizes the most drugs; inducers (rifampicin) reduce drug effect, inhibitors (erythromycin, grapefruit juice) raise drug levels. Phase I reactions — oxidation, reduction, hydrolysis — add a chemical handle; Phase II conjugations — glucuronidation, sulfation, acetylation, glutathione conjugation, methylation — attach bulky water-soluble groups giving inactive, excretable conjugates. First-pass metabolism destroys part of oral drugs in the liver before systemic circulation, lowering bioavailability (bypassed by sublingual/IV routes). Entero-hepatic cycling (liver → bile → gut → blood → liver) prolongs drug stay. Prodrugs are inactive forms activated in the body: enalapril → enalaprilat, levodopa → dopamine, chloramphenicol palmitate → chloramphenicol. Excretion is mainly renal via glomerular filtration (free, small drugs), tubular secretion (active OAT/OCT pumps), and tubular reabsorption (lipid-soluble drugs return); other routes are bile/faeces, lungs, saliva, breast milk, and sweat. Clearance is the volume of blood cleared of drug per minute; half-life is the time for blood levels to halve, with ~4–5 half-lives eliminating nearly all drug.

5.20 One-Minute Revision

Metabolism: liver converts fat-soluble → water-soluble. Microsomal = CYP450 (inducible); non-microsomal = esterases/MAO. CYP3A4 = busiest. Phase I (ORH: oxidation, reduction, hydrolysis) prepares; Phase II (GSAGM: glucuronidation, sulfation, acetylation, glutathione, methylation) attaches & flushes. First-pass: liver eats part of oral dose (nitroglycerin → sublingual). Entero-hepatic cycle prolongs stay. Prodrugs ELC: enalapril, levodopa, chloramphenicol palmitate. Kidney: filtration → secretion → reabsorption. Clearance = cleaning speed; half-life = halving time; 4–5 halves ≈ gone.

5.21 Exam Questions

Short questions:

1. Define biotransformation. Why is it necessary?
2. Distinguish between microsomal and non-microsomal metabolism.
3. Name the Phase I and Phase II reactions.
4. What is the cytochrome P450 system? Name two important members.
5. Define first-pass metabolism and give one example of bypassing it.
6. What is entero-hepatic cycling? Give one example.
7. Define prodrug with two examples.
8. Name the three processes of renal excretion.
9. Define clearance and half-life in simple words.
10. Why can fat-soluble drugs not be excreted directly by the kidney?

Long questions:

1. Describe Phase I and Phase II biotransformation reactions with examples. Add a note on the cytochrome P450 system and enzyme induction/inhibition.
2. Explain first-pass metabolism, entero-hepatic cycling, and the concept of prodrugs with suitable examples.
3. Describe the mechanisms of renal excretion of drugs (filtration, secretion, reabsorption). Add a note on other routes of excretion, clearance, and half-life.

MCQs (answers at the end):

1. The main organ for drug metabolism is:
   a) Kidney
   b) Liver
   c) Lung
   d) Heart
2. Cytochrome P450 enzymes are located in:
   a) Mitochondria
   b) Microsomes (endoplasmic reticulum)
   c) Blood plasma
   d) Cell nucleus
3. Which CYP enzyme metabolizes the largest number of drugs?
   a) CYP2D6
   b) CYP3A4
   c) CYP1A2
   d) CYP2C9
4. Which of the following is a Phase I reaction?
   a) Glucuronidation
   b) Sulfation
   c) Oxidation
   d) Methylation

5. Which of the following is a Phase II reaction?
   a) Reduction
   b) Hydrolysis
   c) Acetylation
   d) Oxidation
6. Glutathione conjugation is important in detoxifying:
   a) Aspirin
   b) Paracetamol's toxic metabolite NAPQI
   c) Penicillin
   d) Insulin
7. First-pass metabolism primarily reduces:
   a) Drug distribution
   b) Oral bioavailability
   c) Protein binding
   d) Half-life
8. Nitroglycerin is given sublingually to:
   a) Increase first-pass metabolism
   b) Bypass first-pass metabolism
   c) Increase protein binding
   d) Slow absorption
9. Entero-hepatic cycling results in:
   a) Faster drug elimination
   b) Prolonged drug stay in the body
   c) Increased first-pass effect
   d) Reduced absorption
10. Which of the following is a prodrug?
    a) Enalapril
    b) Enalaprilat
    c) Dopamine
    d) Chloramphenicol (active form)
11. Levodopa is useful in Parkinson's disease because:
    a) It is cheaper than dopamine
    b) It crosses the blood-brain barrier and converts to dopamine in the brain
    c) It has no side effects
    d) It acts on muscles directly
12. At the glomerulus, which drugs are filtered?
    a) Protein-bound drugs
    b) Free, small drug molecules
    c) Large molecules
    d) Only water
13. Tubular secretion of acidic drugs like penicillin uses:
    a) OCT transporters
    b) OAT transporters
    c) P-glycoprotein
    d) Passive diffusion

14. Making the urine alkaline increases excretion of:
    a) Basic drugs
    b) Acidic drugs like aspirin
    c) Neutral drugs
    d) Protein-bound drugs
15. Half-life is the time taken for:
    a) The drug to be fully absorbed
    b) Blood drug level to fall to half
    c) The drug to reach the brain
    d) The tablet to dissolve
16. After how many half-lives is nearly all drug eliminated?
    a) 1–2
    b) 2–3
    c) 4–5
    d) 10–12

Answers: 1-b, 2-b, 3-b, 4-c, 5-c, 6-b, 7-b, 8-b, 9-b, 10-a, 11-b, 12-b, 13-b, 14-b, 15-b, 16-c

Viva questions:

1. Why must fat-soluble drugs be metabolized before kidney excretion?
2. What is the difference between enzyme induction and inhibition? Give one example of each.
3. Why is grapefruit juice dangerous with some medicines?
4. Name the antidote for paracetamol poisoning and explain its logic.
5. How does probenecid prolong penicillin's action?
6. Why do nursing mothers need drug safety checks?

Application-based questions:

1. A TB patient on rifampicin-based DOTS therapy is also taking oral contraceptive pills. Explain the interaction risk and counsel her on what to do.
2. A patient took an overdose of paracetamol 6 hours ago. Explain what is happening in the liver (NAPQI, glutathione) and why N-acetylcysteine must be given promptly.
3. A patient on felodipine (a CYP3A4 substrate) starts drinking grapefruit juice daily and develops very low blood pressure with dizziness. Explain the mechanism and advise the patient.
4. In a case of aspirin poisoning, the doctor orders "alkaline diuresis." Explain using tubular reabsorption concepts why this speeds up aspirin elimination.

5.22 References

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