B.PHARM SEMESTER IV · BP402T

# BP402T Medicinal Chemistry

## Unit I — Fundamentals of Medicinal Chemistry

Chapters 1–2 · Physicochemical Properties and Drug Metabolism
From-zero learning · Exam-oriented explanations · Worked examples

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# Chapter 1: Physicochemical Properties in Relation to Biological Action

**Subject:** BP402T Medicinal Chemistry | **Unit I** | **B.Pharm Semester IV**

## Learning Objectives

After studying this chapter, you should be able to:

1. Define medicinal chemistry and explain its scope with a brief outline of its history.
2. Define ionization and pKa, and use the Henderson–Hasselbalch equation to calculate the % ionization of weak acids and weak bases at a given pH.
3. Explain why only the unionized form of a drug crosses cell membranes and how this affects absorption.
4. Explain the meaning of solubility and partition coefficient (log P) and their roles in drug action.
5. Define hydrogen bonding and chelation and give drug examples of each.
6. Define bioisosterism and list classical and non-classical bioisosteres with examples.
7. Explain plasma protein binding, the difference between bound and free drug, and drug displacement interactions.
8. Apply these concepts to predict how a drug's structure influences its absorption, distribution, and activity.

## Definitions

- **Medicinal chemistry:** The science that studies how the chemical structure of a drug (its atoms and how they are joined) decides its biological action in the body.
- **Ionization:** The process by which a neutral (uncharged) molecule gains or loses a charged particle called a proton ($H^+$) and becomes a charged particle called an ion. A molecule with a positive charge is a **cation**; a molecule with a negative charge is an **anion**.
- **pKa:** A number that tells you how easily an acid gives away its proton. A **low pKa** means a **strong acid** (gives away its proton easily). A **high pKa** means a **weak acid** (holds on to its proton).
- **Henderson–Hasselbalch equation:** A formula that links pH, pKa, and the ratio of ionized to unionized drug. For a weak acid: **pH = pKa + log([ionized form] / [unionized form])**.
- **Solubility:** How much of a substance can dissolve (mix fully) in a liquid such as water at a given temperature.
- **Partition coefficient (P):** A number that shows how a drug divides itself between two liquids that do not mix — usually **oil** (or octanol) and **water**. **log P** is simply the logarithm of this number.
- **Hydrogen bond:** A weak attraction (pull) between a hydrogen atom attached to an electronegative atom (like O or N) and a nearby electronegative atom (like O or N) on another molecule.
- **Chelation:** The process in which one molecule uses two or more of its atoms to grip (hold) a metal ion like a claw.
- **Bioisostere:** An atom or group of atoms that can replace another in a drug molecule while keeping the drug's biological action nearly the same.
- **Protein binding:** The attachment of a drug to proteins in the blood (mainly albumin). Only the **free** (unbound) drug can act on its target.

# Terminology Word Bank

| Term | What it means (in plain words) |
|---|---|
| Medicinal chemistry | The branch of chemistry that designs and studies drugs |
| Magic bullet | Paul Ehrlich's idea of a drug that hits only the disease and harms nothing else |
| Receptor | A protein on or inside a cell where a drug fits and produces its effect — like a lock that the drug key opens |
| Ligand | Any small molecule that binds to a receptor |
| QSAR | Quantitative Structure–Activity Relationship — maths that links a drug's structure features to its activity |
| Drug design | The planned creation of new drug molecules |
| Acid | A substance that gives away protons ($H^+$) |
| Base | A substance that accepts protons ($H^+$) |
| Weak acid / weak base | An acid or base that only partly gives away or accepts protons — most drugs are weak acids or weak bases |
| Unionized | The neutral, uncharged form of the drug — this is the form that crosses cell membranes |
| Ionized | The charged form of the drug — it dissolves well in water but cannot easily cross membranes |
| pH | A scale from 0 to 14 that measures how acidic or alkaline a liquid is; 7 is neutral |
| Physiological pH | The normal pH of blood and body fluids, about **7.4** |
| Lipophilic | "Fat-loving" — a molecule that mixes well with fats and oils |
| Hydrophilic | "Water-loving" — a molecule that mixes well with water |
| Donor (H-bond) | The group that gives the hydrogen in a hydrogen bond (e.g., –OH, –NH) |
| Acceptor (H-bond) | The atom that accepts the hydrogen in a hydrogen bond (e.g., O in C=O, N in a ring) |
| Chelating agent | A molecule that grips metal ions with two or more bonds |
| Albumin | The most common protein in blood plasma; it carries many drugs |
| Displacement interaction | When one drug pushes another drug off albumin, raising its free level |
| Free drug | The portion of drug not bound to protein — the only portion that can act |
| Bound drug | The portion of drug stuck to plasma proteins — inactive and stored in the blood |
| Distribution | The movement of a drug through the body to its site of action |
| Absorption | The movement of a drug from its site of entry (e.g., the stomach or intestine) into the blood |

# 1. Introduction: A Brief History and Scope of Medicinal Chemistry

## Technical concept

Medicinal chemistry is the science that connects **chemical structure** (what atoms a drug is made of and how they are joined) with **biological action** (what the drug does in the body). It asks one central question: *if I change the structure of a molecule in a small way, what happens to its effect in the body?*

## Simple explanation

Think of medicinal chemistry as the work of a **drug architect**. A pharmacist knows drugs by their names and doses. A medicinal chemist knows drugs by their **structures** — and uses that knowledge to build better drugs: drugs that work more strongly, cause fewer side effects, and reach the right part of the body.

## Key events in its history

- **Paul Ehrlich (early 1900s) — the "magic bullet".** The German scientist Paul Ehrlich dreamed of a medicine that would work like a **magic bullet**: it would fly straight to the disease-causing germ and destroy it, without harming the patient. This idea led to the first synthetic drug against syphilis (called Salvarsan). The magic bullet idea is the grandfather of modern drug design — we still want drugs that hit only the target.
- **The receptor idea.** Scientists then asked: *where exactly does the drug land on the body?* The answer was the **receptor** — a protein on or inside a cell that has a special pocket where a drug fits, like a key fits a lock. Once the drug sits in the pocket, it switches the cell's activity on or off.
- **QSAR and modern drug design.** Later, scientists began to use **mathematics and computers**. **QSAR (Quantitative Structure–Activity Relationship)** is a method that writes down, in numbers, how small changes in structure change the drug's activity. Today, medicinal chemists design drugs on computers first (computer-aided drug design) and make them in the laboratory afterwards.

**Analogy:** A tailor (masterji) making a sherwani does not cut cloth blindly — he first takes measurements, then cuts. Similarly, a medicinal chemist does not test thousands of random chemicals blindly — she first "measures" what structure features matter (size, charge, oil-liking), then designs the molecule.

## Scope of medicinal chemistry

Medicinal chemistry covers:

1. **Drug discovery** — finding new active molecules from nature (plants, microbes) or from the laboratory.
2. **Lead optimization** — taking a promising molecule (a "lead") and changing it step by step to make it stronger, safer, and easier to absorb.
3. **Structure–activity studies** — recording which parts of the molecule are essential for action and which parts can be changed.
4. **Drug design** — using QSAR and computer models to predict good structures before making them.

## Key takeaway

Medicinal chemistry links **structure → properties → biological action**. Every property in this chapter (ionization, solubility, log P, H-bonding, chelation, bioisosterism, protein binding) is one piece of that link.

# 2. Ionization

## Technical concept

**Ionization** is the process by which a neutral molecule gains or loses a proton ($H^+$, a hydrogen atom without its electron) and becomes a **charged ion**. Most drugs are **weak acids or weak bases**, meaning they only partly ionize, and the amount ionized depends on the pH of the surroundings.

- A **weak acid** (HA) gives away its proton: **$HA \rightleftharpoons H^+ + A^-$** (the charged form $A^-$ is the anion).
- A **weak base** (B) accepts a proton: **$BH^+ \rightleftharpoons B + H^+$** (the charged form $BH^+$ is the cation).

**pKa** is a number that measures how easily an acid gives away its proton. Low pKa = strong acid; high pKa = weak acid. For a base, the pKa of its **conjugate acid** ($BH^+$) tells you how easily the base accepts a proton.

## Simple explanation

Imagine a person (the drug molecule) wearing a shawl (the proton). In some rooms (acidic pH), everyone keeps their shawl on. In other rooms (alkaline pH), everyone takes it off. Whether the drug is "wearing the shawl" (unionized/neutral) or has "taken it off" (ionized/charged) depends on the room — and only the shawl-wearing form can walk through the door of the cell (the cell membrane).

## The Henderson–Hasselbalch equation

For a **weak acid**:

> **$pH = pKa + \log ( [A^-] / [HA] )$**

where $[A^-]$ is the ionized form and [HA] is the unionized form.

For a **weak base**:

> **$pH = pKa + \log ( [B] / [BH^+] )$**

where [B] is the unionized form and $[BH^+]$ is the ionized form.

**Useful % formulas** (derived from the same equation):

- Weak acid: **% ionized = 100 ÷ (1 + 10^(pKa − pH))**
- Weak base: **% ionized = 100 ÷ (1 + 10^(pH − pKa))**

**Quick rule to remember:** if pH differs from pKa by 1 unit, the ratio is 10:1; by 2 units, 100:1; by 3 units, 1000:1. *For a weak acid:* if pH is **above** pKa, the drug is mostly **ionized**; if pH is **below** pKa, mostly **unionized**. *For a weak base*, it is the opposite: if pH is **below** pKa, mostly **ionized**; if pH is **above** pKa, mostly **unionized**.

## Worked Example 1 — a weak acid (aspirin, pKa 3.5)

> **Question:** What % of aspirin is ionized in (a) the stomach (pH 1.5) and (b) blood (pH 7.4)?

**Step-by-step calculation (weak acid formula: % ionized = 100 ÷ (1 + 10^(pKa − pH))):**

(a) Stomach, pH 1.5:

- pKa − pH = 3.5 − 1.5 = **2.0**
- 10^2.0 = **100**
- % ionized = 100 ÷ (1 + 100) = 100 ÷ 101 = **0.99%** (≈ 1%)
- So in the stomach, aspirin is **~99% unionized**.

(b) Blood, pH 7.4:

- pKa − pH = 3.5 − 7.4 = **−3.9**
- 10^(−3.9) = **0.000126** (since 10^3.9 ≈ 7943, and 1 ÷ 7943 ≈ 0.000126)
- % ionized = 100 ÷ (1 + 0.000126) = 100 ÷ 1.000126 = **99.99%**
- So in blood, aspirin is **~100% ionized**.

**Meaning:** Aspirin is absorbed mainly in the stomach (where it is unionized and can cross membranes), but once in the blood (pH 7.4) it becomes ionized and stays dissolved.

## Worked Example 2 — a weak base (propranolol, pKa 9.5)

> **Question:** What % of propranolol is ionized in blood (pH 7.4)?

**Step-by-step calculation (weak base formula: % ionized = 100 ÷ (1 + 10^(pH − pKa))):**

- pH − pKa = 7.4 − 9.5 = **−2.1**
- 10^(−2.1) = **0.00794** (since 10^2.1 ≈ 126, and 1 ÷ 126 ≈ 0.00794)
- % ionized = 100 ÷ (1 + 0.00794) = 100 ÷ 1.00794 = **99.2%**
- So propranolol in blood is **~99% ionized** and only ~1% unionized.

## Why ionization matters for absorption

Cell membranes are made of **fat-like (lipid) layers**. Only the **unionized (neutral)** form of a drug dissolves in fat and passes through. The **ionized (charged)** form is surrounded by water and is blocked at the membrane — but it dissolves very well in body fluids.

This is why pH matters:

| Body region | pH | What happens |
|---|---|---|
| Stomach | ~1.5–2.0 | Weak **acids** are mostly unionized → absorbed here |
| Small intestine | ~6.0–7.0 | Both weak acids and weak bases partly unionized → most absorption happens here (huge surface area) |
| Blood | 7.4 | Most drugs mostly ionized → stay dissolved in blood |

**Analogy:** A dry tea leaf (unionized) can slip through the tiny holes of a tea strainer into the cup; a tea leaf that has swollen up with water (ionized) gets stuck in the strainer. The membrane is the strainer — it lets only the dry, fat-soluble form pass.

## Key takeaway

**Ionization decides where a drug is absorbed.** Unionized = crosses membranes (absorbed). Ionized = stays dissolved in fluids (distributed). The Henderson–Hasselbalch equation lets you calculate exactly how much of each form exists at any pH.

# 3. Solubility

## Technical concept

**Solubility** is the maximum amount of a drug that can dissolve in a liquid (usually water) at a given temperature. For a drug to be absorbed from the gut and carried in the blood, it must first **dissolve** — a solid tablet that never dissolves can never be absorbed.

## Simple explanation

Before the drug can do anything, it must **melt into the body's fluids**, like sugar melting into chai. If the sugar stays as hard crystals at the bottom of the cup, the chai never becomes sweet. Similarly, a drug must dissolve in stomach/intestinal fluid before it can enter the blood.

## Factors affecting solubility

1. **Ionization (pH):** Ionized drugs dissolve much better in water. A weak acid dissolves better at high pH; a weak base dissolves better at low pH. This is why some tablets dissolve only in the intestine, not the stomach.
2. **Crystal form (polymorphism):** The same drug can form different crystal shapes. A loosely packed crystal dissolves faster than a tightly packed one — like crushed jaggery (gur) dissolving faster than a hard jaggery block.
3. **Particle size:** Smaller particles have more surface area, so they dissolve faster. This is why some drugs are **micronized** (ground very fine). Example: the antifungal griseofulvin is micronized to improve its absorption.
4. **Salt formation:** Converting a drug into its salt form (e.g., a basic drug made into its hydrochloride salt) greatly increases water solubility. Example: the base form of many drugs is poorly soluble, but their HCl salts dissolve readily.
5. **Temperature:** Solubility usually increases as temperature rises — like sugar dissolving faster in hot chai than in cold water.

## Key takeaway

**No dissolution = no absorption.** Solubility is the first gate a drug must pass, and chemists control it through salts, crystal forms, and particle size.

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# 4. Partition Coefficient (log P)

## Technical concept

The **partition coefficient (P)** is a number that tells you how a drug divides (partitions) itself between two liquids that do not mix: **octanol** (standing in for body fat/membranes) and **water**. It is defined as:

> **P = [concentration of drug in octanol] ÷ [concentration of drug in water]**

Because P can range from very tiny to very huge, we use its logarithm:

> **$\log P = \log_{10}(P)$**

- **High log P** (e.g., 3–5) → drug prefers oil/fat → **lipophilic**.
- **Low or negative log P** → drug prefers water → **hydrophilic**.

### Simple explanation

Imagine shaking a bottle containing oil and water with a pinch of haldi (turmeric) powder. The haldi colour goes mostly into the oil layer — turmeric is "oil-liking" (lipophilic). Now imagine adding salt — it stays in the water layer — "water-liking" (hydrophilic). **log P is simply a number for this preference.**

### Why it matters for crossing membranes and reaching the target

Cell membranes are fat-like. A drug must be **lipophilic enough** to enter the membrane, but **water-soluble enough** to travel in blood and dissolve at the target. There is a **balance**:

- **Too polar (very low log P):** the drug cannot enter membranes at all — it is excreted without acting. Example: highly polar drugs that stay in the gut or urine.
- **Too lipophilic (very high log P):** the drug gets trapped in fat tissue and never leaves, or it cannot dissolve in blood at all.
- **Just right (moderate log P, roughly 1–3 for many oral drugs):** the drug dissolves in fluids AND crosses membranes — it reaches its target.

### Simple examples

| Drug type | log P behaviour | What happens |
|---|---|---|
| Very polar drug (e.g., a drug with many –OH groups) | Low/negative log P | Stays in water, poor membrane crossing |
| Very lipophilic drug | High log P | Enters membranes easily, but may get stuck in fat and have poor water solubility |
| Balanced drug | Moderate log P | Crosses membranes and dissolves in blood — the ideal for oral drugs |

**Analogy:** A guest who wants to visit every room of a house must pass through both the wet courtyard (water) and the oily kitchen (fat). log P tells you whether the guest is comfortable in both.

### Key takeaway

**log P measures a drug's oil-versus-water preference.** Medicinal chemists tune log P up or down (by adding or removing polar groups) so the drug can both dissolve in body fluids and cross cell membranes.

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## 5. Hydrogen Bonding

### Technical concept

A **hydrogen bond** is a weak attraction between (a) a hydrogen atom attached to an electronegative atom — oxygen (O) or nitrogen (N) — and (b) a nearby electronegative atom (O or N) carrying a lone pair of electrons. The group that **gives** the hydrogen is the **donor**; the atom that **receives** it is the **acceptor**.

- **Donors:** –OH (alcohol, phenol), –NH (amine, amide), –SH (rare).
- **Acceptors:** oxygen in C=O (carbonyl), oxygen in –OH, nitrogen in rings (e.g., pyridine N).

One hydrogen bond is weak, but **many hydrogen bonds together** hold a drug tightly in its receptor pocket.

### Simple explanation

A hydrogen bond is like a **small handshake** between the drug and the receptor. One handshake is weak, but five or six handshakes together hold the two firmly. Drugs use these handshakes to stick exactly into the receptor's pocket.

### Why hydrogen bonding matters

1. **Drug–receptor binding:** The receptor's pocket contains O and N atoms positioned to shake hands with the drug's donors and acceptors. The better the handshake pattern matches, the stronger the drug binds, and the stronger its effect.
2. **Solubility:** Hydrogen bonds with **water** molecules make a drug dissolve better. Drugs with many –OH and –NH groups are usually more water-soluble.
3. **Membrane crossing:** Every hydrogen bond the drug makes with water must be **broken** before it can enter the fatty membrane. Too many H-bond donors/acceptors → the drug cannot leave water → poor absorption. This is why medicinal chemists count donors and acceptors when designing oral drugs.

### Simple examples

- **Paracetamol:** a benzene ring with –OH at position 1 and –$NHCOCH_3$ at position 4. Its –OH and –NH groups are donors; its carbonyl oxygen is an acceptor. These groups help it dissolve and interact with its target proteins.
- **Water itself** is the classic example: each water molecule forms hydrogen bonds with its neighbours — that is why water is a liquid and not a gas.

### Key takeaway

**Hydrogen bonds are the handshakes between drug and receptor.** They decide binding strength, water solubility, and (in excess) can block membrane crossing.

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## 6. Chelation

### Technical concept

**Chelation** (from the Greek *chele*, meaning "crab's claw") is the process in which **one molecule uses two or more of its atoms to grip a single metal ion**, forming a ring-like complex. A molecule that does this is called a **chelating agent** (or ligand), and the product is a **chelate**.

### Simple explanation

A chelating molecule grips a metal ion the way a **crab's claw — or two hands together — grips a laddoo**. One hand might slip, but two hands holding from both sides hold it firmly. The metal ion is trapped inside the grip.

### Drug examples that chelate

1. **Tetracyclines (e.g., tetracycline, doxycycline) + calcium:** Tetracycline antibiotics have several –OH and C=O groups that together grip **calcium ions ($Ca^{2+}$)**. The resulting chelate cannot be absorbed from the gut. This is why patients are told **not to take tetracyclines with milk, antacids, or calcium/iron supplements** — the drug gets locked up and wasted.
2. **Penicillamine:** A drug that chelates **copper** and is used to remove excess copper from the body in Wilson's disease (a condition where copper builds up to toxic levels). It also chelates lead and mercury in metal poisoning.
3. **Deferoxamine / deferiprone:** Chelating agents used to remove excess **iron** from the blood of patients who receive repeated blood transfusions (e.g., thalassemia patients).

### Why chelation matters

- **Can reduce absorption** (tetracycline + calcium → less drug absorbed → treatment fails).
- **Can be used as treatment** (penicillamine and iron chelators deliberately trap and remove toxic metals).
- **Can change drug distribution** — chelated metal complexes behave very differently from the free drug.

### Key takeaway

**Chelation is a molecular double-grip on metal ions.** It can ruin a drug's absorption (tetracycline with milk) or be deliberately used to pull poisonous metals out of the body.

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## 7. Bioisosterism

### Technical concept

**Bioisosterism** is the idea that certain atoms or groups of atoms (**bioisosteres**) have similar size, shape, and electronic character, so one can **replace** the other in a drug molecule while the biological activity stays nearly the same. Medicinal chemists use bioisosteric replacement to improve a drug — for example, to make it last longer in the body, reduce side effects, or get a patent around an existing drug.

### Simple explanation

If a key is slightly too long for a lock, a locksmith files it down a little — the key still opens the lock. Bioisosterism is the same: you **swap one small part of the molecule for a look-alike part**, and the drug still fits the receptor and still works.

### Classical bioisosteres

Classical bioisosteres have the **same number of atoms and similar size/shape**:

| Original group | Bioisosteric replacement | Example idea |
|---|---|---|
| $–CH_3$ (methyl) | –Cl (chloro) | Similar size; chlorine is more lipophilic |
| –OH (hydroxyl) | $–NH_2$ (amino) | Both can donate hydrogen bonds |
| –CH= (in a ring) | –N= (in a ring) | Benzene → pyridine replacement |
| Benzene ring | Thiophene ring (a 5-membered ring with sulfur) | Similar size and flat shape |
| $–CH_2–$ | –O–, –S–, –NH– | Similar single-atom spacers |

### Non-classical bioisosteres

Non-classical bioisosteres have **different numbers of atoms** but behave similarly (same acidity, same H-bonding, similar shape):

| Original group | Bioisosteric replacement | Real drug example |
|---|---|---|
| –COOH (carboxylic acid) | **Tetrazole** (a 5-membered ring with 4 nitrogens) | **Losartan** (blood pressure drug) — the tetrazole is acidic like –COOH but survives longer in the body |
| –COOH | $–SO_2NH_2$ (sulfonamide) | Acidic group with similar properties |
| C=O (carbonyl) | C=S (thiocarbonyl) | Similar shape, different electronics |
| –CH=CH– | –S– | Similar geometry in some scaffolds |

**Losartan example in plain words:** Losartan is a blood-pressure-lowering drug built on a biphenyl scaffold (two benzene rings joined together) with a tetrazole ring (a 5-membered ring containing 4 nitrogen atoms and 1 carbon) attached at one end. The tetrazole behaves like a –COOH group (acidic, can donate/accept H-bonds) but is **more stable in the body** — it is not broken down as quickly. That is bioisosterism in action.

### Why chemists use bioisosterism

1. **Improve metabolic stability** — the replacement survives longer in the body (tetrazole vs –COOH).
2. **Tune lipophilicity** — e.g., $–CH_3 \rightarrow$ –Cl makes the drug more fat-loving.
3. **Reduce toxicity** — remove a group that causes side effects while keeping activity.
4. **Overcome resistance or patent barriers** — a new structure with the same action.

### Key takeaway

**Bioisosterism = swapping a molecular part for a look-alike.** The drug still fits the receptor, but its stability, solubility, or safety can improve.

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## 8. Protein Binding

### Technical concept

When a drug enters the blood, much of it sticks to **plasma proteins** — mainly **albumin** (the most abundant protein in blood plasma). At any moment:

> **Total drug in blood = bound drug + free drug**

- **Bound drug** is stuck to albumin. It is **inactive** — it cannot reach receptors, cannot cross membranes, and cannot be removed by the kidneys. It acts as a **stored reservoir**.
- **Free drug** is dissolved freely in the plasma water. Only the free drug can **leave the blood, reach its target, and produce an effect**.

As free drug is used up or removed, bound drug is released from albumin to replace it — like water flowing out of a tank while a tap refills it.

### Simple explanation

Imagine a bus (albumin) carrying passengers (drug molecules). Passengers **seated inside the bus** (bound) cannot get down and do any work in the town (the body). Only passengers who **step off the bus** (free) can go to the market (the receptor) and do the job. As free passengers leave, seated ones stand up and step off — the bus keeps supplying workers until it is empty.

### Why only free drug acts

Receptors are on cells **outside** the blood. A drug-albumin complex is too big to leave the blood vessels, so only the small, free drug molecules can cross into tissues and meet their receptors.

### Displacement interactions — with one example

**Displacement** happens when a second drug pushes the first drug off albumin, suddenly increasing its free level — which can cause toxicity.

**Example:** The blood-thinner **warfarin** is highly bound to albumin (~99% bound, ~1% free). If a patient on warfarin is given a **sulfonamide antibiotic** (or an NSAID like phenylbutazone), the newcomer competes for the same albumin seats and **pushes warfarin off**. Free warfarin rises → blood becomes too thin → **bleeding risk**. This is a classic, exam-favourite displacement interaction.

### Key takeaway

**Only free drug works; bound drug is stored.** Displacement of one drug by another on albumin can suddenly raise free drug levels and cause toxicity — warfarin displaced by sulfonamides is the classic example.

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## Textual Diagram Descriptions (Sketchable)

**Diagram 1 — The drug's journey (structure → action):** Draw 5 boxes in a row with arrows between them: `[Drug structure] → [Physicochemical properties: ionization, log P, solubility, H-bonding] → [Dissolution in gut fluid] → [Crossing membranes (absorption)] → [Binding to receptor → effect]` Label the arrows: "decides" / "must happen first" / "unionized form only" / "handshakes (H-bonds)".

**Diagram 2 — Ionization at different pH (weak acid, e.g., aspirin):** Draw three beakers labelled "Stomach pH 1.5", "Intestine pH 6.5", "Blood pH 7.4". In the first beaker draw mostly neutral circles (HA, unionized); in the last beaker draw mostly minus-signed circles ($A^-$, ionized). Add an arrow through a wavy membrane line between beakers labelled "only neutral circles pass".

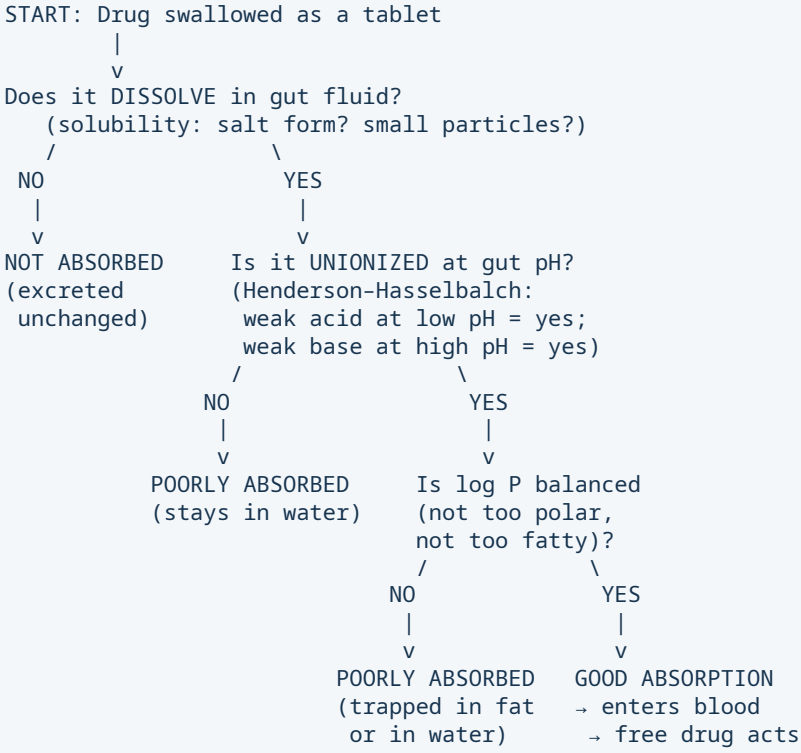
**Diagram 3 — Chelation (crab's claw):** Draw a small filled circle labelled "$Ca^{2+}$" in the centre. Draw a C-shaped claw around it made of two arms labelled "O (from –OH)" and "O (from C=O)" of the tetracycline molecule. Caption: "Two atoms of one molecule gripping one metal ion = chelate".

**Diagram 4 — Protein binding (the bus):** Draw a large rectangle labelled "Albumin (bus)". Inside it draw seated dots labelled "bound drug (inactive, stored)". Outside it draw free dots with arrows pointing to a lock shape labelled "receptor". Caption: "Only dots that leave the bus can open the lock".

**Diagram 5 — Bioisosteric swap:** Draw a hexagon (benzene ring) with "–COOH" attached; draw an arrow to a second hexagon with a pentagon attached, the pentagon labelled "tetrazole ring (4 N atoms)". Caption: "–COOH replaced by tetrazole: still acidic, still active (losartan), but more stable".

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## Flowchart: Will This Drug Be Absorbed Well?




## Infographic Concept Box: "The Five Gates of Drug Action"

*Imagine a drug as a traveller who must pass five gates before reaching the palace (the receptor):*

1. 🚪 **Gate 1 — DISSOLVE** (solubility): melt into the gut fluid like sugar in chai. *Gatekeeper question: "Can you dissolve?"*
2. 🚪 **Gate 2 — UNDRESS** (ionization): drop the electric charge — only the neutral, unionized traveller may pass the membrane. *Gatekeeper question: "Are you unionized at this pH?"*
3. 🚪 **Gate 3 — BALANCE** (log P): be comfortable in both water (blood) and oil (membranes). *Gatekeeper question: "Is your oil–water liking balanced?"*
4. 🚪 **Gate 4 — HANDSHAKE** (H-bonding): shake hands with the receptor's pocket — donors meet acceptors. *Gatekeeper question: "Do your handshakes match?"*
5. 🚪 **Gate 5 — STEP OFF THE BUS** (protein binding): leave albumin — only free travellers reach the palace. *Gatekeeper question: "Are you free, not bound?"*

*Bonus guards on the road:* ⚠️ **Chelators** (tetracycline + milk = locked at Gate 1) and 🔧 **Bioisosteres** (the locksmith's trick to make a better key).

# Real Tables

### Table 1: Summary of physicochemical properties and their effects

| Property | What it measures | Helps absorption when… | Hurts absorption when… |
|---|---|---|---|
| Ionization (pKa) | Charged vs neutral fraction at a given pH | Drug is unionized at gut pH | Drug is fully ionized at gut pH |
| Solubility | Amount dissolving in water | High (dissolves fully) | Very low (never dissolves) |
| log P | Oil-liking vs water-liking | Balanced (moderate) | Too polar or too lipophilic |
| H-bond donors/acceptors | Handshake points | Enough to bind receptor | Too many → cannot leave water |
| Chelation | Metal-gripping ability | Used deliberately (metal removal) | Traps the drug (tetracycline + $Ca^{2+}$) |
| Protein binding | Fraction stuck to albumin | Moderate (acts as reservoir) | Displacement raises free drug → toxicity |

### Table 2: Classical vs non-classical bioisosteres

| Type | Meaning | Examples |
|---|---|---|
| Classical | Same number of atoms, similar size/shape | $-CH_3$ → –Cl; –OH → $-NH_2$; benzene → thiophene; –CH= → –N= |
| Non-classical | Different atoms, similar behaviour | –COOH → tetrazole (losartan); –COOH → $-SO_2NH_2$; C=O → C=S |

# Worked Examples (Numerical — Both Shown in Section 2)

1. **Aspirin (weak acid, pKa 3.5):** stomach pH 1.5 → ~1% ionized (~99% unionized, absorbed); blood pH 7.4 → ~99.99% ionized (stays dissolved).
2. **Propranolol (weak base, pKa 9.5):** blood pH 7.4 → ~99.2% ionized, only ~0.8% unionized.

# Analogies Used in This Chapter (Quick Reference)

| Concept | Analogy |
|---|---|
| Medicinal chemistry | The tailor (masterji) who measures before cutting — design before testing |
| Magic bullet | A bullet that hits only the enemy, nobody else |
| Receptor | A lock; the drug is the key |
| Ionization | Wearing or removing a shawl (proton) depending on the room (pH) |
| Membrane crossing | A tea strainer — only dry (unionized) leaves pass through |
| Solubility | Sugar melting in chai — undissolved sugar never sweetens |
| Crystal forms | Crushed jaggery dissolves faster than a hard jaggery block |
| log P | Haldi going into the oil layer, salt staying in the water layer |
| H-bonding | Handshakes between drug and receptor |
| Chelation | A crab's claw — or two hands gripping a laddoo |
| Bioisosterism | A locksmith filing a key slightly — it still opens the lock |
| Protein binding | A bus (albumin); only passengers who step off (free drug) can work |

## Pharmacy Relevance

- **Choosing the salt form:** Pharmacists dispense drugs as salts (e.g., metoprolol tartrate, amlodipine besylate) because salts dissolve better — a direct application of solubility and ionization.
- **Counselling on food–drug interactions:** "Do not take tetracycline with milk" is chelation in practice. Antacids with many drugs is an ionization/pH issue.
- **Understanding why some drugs are injections only:** Highly polar or highly ionized drugs (low log P, fully ionized at gut pH) cannot be absorbed orally and must be injected.
- **Predicting drug interactions:** Displacement from albumin (warfarin + sulfonamides) is a protein-binding concept every pharmacist must watch for.
- **Generic substitution:** Bioisosterism explains how different companies make differently structured but equally acting drugs.

## India Context

- **Iron-deficiency anaemia** is common in India; iron supplements are widely used — and iron, like calcium, **chelates tetracyclines and fluoroquinolones**, reducing their absorption. Counselling patients to separate these medicines by 2–3 hours is everyday Indian pharmacy practice.
- **Milk and curd** are staples of the Indian diet, so the "no milk with tetracycline" counselling point matters in every Indian pharmacy.
- **Thalassemia** patients in India receiving repeated blood transfusions depend on **iron chelators** (deferiprone, deferoxamine) — chelation as life-saving therapy.
- **Wilson's disease** (copper build-up) is treated with **penicillamine**, a chelator — available in Indian hospitals.
- Many Indian generic companies use **bioisosteric design** to develop "me-too" drugs around patented molecules, making medicines affordable.
- **Losartan**, the classic tetrazole-for-COOH bioisostere example, is one of the most widely prescribed blood-pressure drugs in India.

## Key Points

1. Medicinal chemistry links **chemical structure → physicochemical properties → biological action**.
2. Paul Ehrlich's **magic bullet** idea and the **receptor** concept are the historical roots; **QSAR** brought mathematics and computers into drug design.
3. **Ionization:** weak acids are unionized below their pKa; weak bases are unionized above their pKa. Use **Henderson–Hasselbalch** to calculate the exact fractions.
4. **Only the unionized form crosses cell membranes**; the ionized form stays dissolved in body fluids.
5. **Solubility** is the first gate — no dissolution, no absorption. Salts, small particles, and loose crystal forms improve it.
6. **log P** measures oil-vs-water preference; a **balanced** log P gives both solubility and membrane crossing.
7. **Hydrogen bonds** are the handshakes of drug–receptor binding; too many of them block membrane crossing.
8. **Chelation** is a double-grip on metal ions — harmful when it traps the drug (tetracycline + calcium), useful when it removes toxic metals (penicillamine, iron chelators).
9. **Bioisosterism** swaps a group for a look-alike: classical (–$CH_3$ → –Cl; benzene → thiophene) and non-classical (–COOH → tetrazole, as in losartan).
10. **Only free (unbound) drug acts**; albumin-bound drug is an inactive reservoir. Displacement (warfarin + sulfonamides) can cause toxicity.

## Common Confusions

1. **pKa vs pH:** pKa belongs to the **drug** (a fixed property); pH belongs to the **surroundings** (stomach, blood). The equation compares the two — do not mix them up.
2. **Ionized = soluble but blocked; unionized = crossing but poorly soluble.** Students often think ionized is "better" — each form has one advantage and one disadvantage.
3. **Weak acid vs weak base rules are opposites:** For a weak ACID, pH **above** pKa → ionized. For a weak BASE, pH **below** pKa → ionized. Learn one rule and flip it for the other.
4. **log P vs solubility:** A high log P means the drug likes oil — which usually means it does **not** like water. High log P and high water solubility rarely go together.
5. **Bound drug is NOT destroyed:** It is stored and released later. Bound = inactive **for now**, not wasted.
6. **Chelation vs complexation in general:** Chelation specifically needs **two or more** grip points from the **same** molecule forming a ring — a single grip is just binding, not chelation.
7. **Bioisostere ≠ identical:** A bioisostere keeps the **activity** similar, not the structure identical. The structures deliberately differ.

## Common Mistakes (Exam Hall Errors)

1. Writing the Henderson–Hasselbalch equation with [HA]/[$A^-$] upside down for acids — the ionized form goes on **top**.
2. Using the weak-acid % formula for a weak base (and vice versa) — check which formula matches the drug type first.
3. Saying "ionized drugs are absorbed better" — it is the **unionized** form that crosses membranes.
4. Forgetting that stomach pH (~1.5) favours absorption of weak **acids**, not weak bases.
5. Calling any metal binding "chelation" — chelation needs a **claw-like double grip** from one molecule.
6. In displacement interactions, naming the wrong outcome — displacement **increases free drug** (risk of toxicity), it does not decrease the effect.
7. Mixing up donor and acceptor — the **donor gives** the hydrogen (–OH, –NH); the **acceptor receives** it (C=O oxygen, ring nitrogen).

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## Mnemonics

- **"A BUDdy LICks PHarma"** — the five gates: **A**bsorption needs **B**alanced log P, **U**nionized form, **D**issolution (solubility), **L**ow protein **b**inding displacement risk... simpler version below.
- **"S-I-L-H-C-B-P" → "Silly Lions Have Cute Big Paws": S**olubility, **I**onization, **L**og P, **H**-bonding, **C**helation, **B**ioisosterism, **P**rotein binding — the 7 properties in this chapter.
- **"Acid Above = Anion"** (all A's): for a weak acid, pH **a**bove pKa → **a**nion (ionized).
- **"Free is Fee-less to act"**: only the **free** drug acts — bound drug pays no "fee" because it does no work.
- **"Tetra-CALCIUM Trouble"**: **Tetra**cycline + **calcium** = trouble (no absorption with milk).
- **"Warfarin Wobbles When Pushed"**: warfarin is pushed off albumin by sulfonamides → bleeding.

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## Exam Summary

- **Medicinal chemistry** = structure–activity science. History: Ehrlich's **magic bullet** → **receptor** idea → **QSAR**/computer-aided design. Scope: discovery, lead optimization, structure–activity studies, drug design.
- **Ionization:** HA ⇌ $H^+$ + $A^-$ (acid); $BH^+$ ⇌ B + $H^+$ (base). **pH = pKa + log([ionized]/[unionized])**. Weak acid: % ionized = 100/(1 + 10^(pKa−pH)); weak base: % ionized = 100/(1 + 10^(pH−pKa)). Unionized crosses membranes.
- **Solubility:** must dissolve before absorption. Improved by salt formation, small particle size, loose crystal forms; depends on pH/ionization.
- **Partition coefficient:** P = [drug]octanol/[drug]water; **log P** = $\log_{10}$P. Balanced log P → good oral absorption; too polar or too lipophilic → poor.
- **Hydrogen bonding:** donors (–OH, –NH), acceptors (C=O, ring N). Gives receptor binding + solubility; excess blocks membrane crossing.
- **Chelation:** one molecule gripping a metal ion at 2+ points. Tetracycline + $Ca^{2+}$ (don't take with milk); penicillamine chelates copper (Wilson's disease); iron chelators for thalassemia.
- **Bioisosterism:** replace a group with a look-alike, keep activity. Classical: $–CH_3$ → –Cl, –OH → $–NH_2$, benzene → thiophene. Non-classical: –COOH → tetrazole (**losartan**).
- **Protein binding:** albumin binds drugs; **only free drug acts**; bound = reservoir. Displacement: sulfonamides push **warfarin** off albumin → bleeding risk.

## One-Minute Revision

Medicinal chemistry links **structure to action** (Ehrlich → receptors → QSAR). Drugs ionize by pH — **Henderson–Hasselbalch** tells you how much; only the **unionized** form crosses membranes. Drugs must **dissolve** (solubility) first. **log P** balances oil-liking vs water-liking. **H-bonds** are drug–receptor handshakes. **Chelation** = double-grip on metals (tetracycline + milk = bad; penicillamine for copper = good). **Bioisosterism** = swap a part for a look-alike (tetrazole for –COOH in **losartan**). **Only free drug acts** — albumin-bound drug is stored; **warfarin** pushed off albumin by sulfonamides causes bleeding.

## Exam Questions

### MCQs (10) — Answer key at the end

**Q1.** Who gave the "magic bullet" concept in drug therapy? a) Alexander Fleming b) Paul Ehrlich c) Louis Pasteur d) Gertrude Elion

**Q2.** According to the Henderson–Hasselbalch equation for a weak acid, when pH is 2 units ABOVE the pKa, the ratio of ionized to unionized drug is approximately: a) 1:100 b) 10:1 c) 100:1 d) 1:1

**Q3.** Which form of a drug crosses the lipid cell membrane most easily? a) Ionized form b) Unionized form c) Protein-bound form d) Chelated form

**Q4.** A weak acid with pKa 4.5 is placed in blood at pH 7.4. It will be mostly: a) Unionized b) Ionized c) Precipitated d) Destroyed

**Q5.** A high log P value indicates that the drug is: a) Highly water-soluble b) Highly lipophilic (fat-loving) c) Highly ionized d) Highly protein-bound

**Q6.** Which of the following is a hydrogen-bond DONOR? a) Carbonyl oxygen (C=O) b) Pyridine nitrogen c) Hydroxyl group (–OH) d) Ether oxygen (–O–)

**Q7.** Tetracycline should not be taken with milk because: a) Milk destroys the antibiotic b) Tetracycline chelates calcium in milk, forming an unabsorbable complex c) Milk increases stomach acid d) Tetracycline causes milk allergy

**Q8.** In losartan, the tetrazole ring is a bioisostere of which group? a) $–CH_3$ b) –OH c) –COOH d) $–NH_2$

**Q9.** Which plasma protein binds the largest fraction of drugs in blood? a) Globulin b) Fibrinogen c) Albumin d) Haemoglobin

**Q10.** Displacement of warfarin from albumin by a sulfonamide will: a) Decrease warfarin's effect b) Increase free warfarin and raise bleeding risk c) Have no effect on warfarin d) Convert warfarin to an inactive metabolite

**Answer key:** Q1–b, Q2–c, Q3–b, Q4–b, Q5–b, Q6–c, Q7–b, Q8–c, Q9–c, Q10–b

### Viva Questions (5) with Short Answers

**V1. What is the Henderson–Hasselbalch equation?** For a weak acid: pH = pKa + log([ionized form]/[unionized form]). It links the pH of the medium, the drug's pKa, and the ratio of its ionized to unionized forms.

**V2. Why is only the unionized form of a drug absorbed across membranes?** Cell membranes are made of lipids (fats). The neutral, unionized form dissolves in lipids and passes through; the charged, ionized form is surrounded by water and is blocked.

**V3. What is log P?** The logarithm of the partition coefficient — the ratio of a drug's concentration in octanol (oil) to that in water. It measures whether the drug prefers fat or water.

**V4. Give one example each of useful and harmful chelation.** Useful: penicillamine chelating excess copper in Wilson's disease. Harmful: tetracycline chelating calcium from milk, which prevents the antibiotic's absorption.

**V5. What is a bioisostere? Give one example.** A group that can replace another in a drug while keeping the activity nearly the same. Example: the tetrazole ring replacing –COOH in losartan.

### Application-Based Questions (3)

**A1.** A patient takes tetracycline capsules every morning with a large glass of milk and her infection does not improve. Explain what is happening at the molecular level and what counselling you would give. *(Expected: tetracycline's –OH and C=O groups chelate $Ca^{2+}$ in milk, forming an unabsorbable chelate → less free drug absorbed → treatment failure. Counsel: take tetracycline 2–3 hours apart from milk, antacids, and iron/calcium supplements, with water on an empty stomach.)*

**A2.** Drug X is a weak acid with pKa 5.0. Using the Henderson–Hasselbalch relationship, explain whether it will be better absorbed from the stomach (pH 2.0) or from the blood-side environment (pH 7.4), and why. *(Expected: at pH 2.0, pH is 3 units below pKa → ratio ionized:unionized = 1:1000 → almost fully unionized → crosses stomach membranes well. At pH 7.4, pH is 2.4 units above pKa → mostly ionized → stays dissolved but cannot cross. Hence absorbed better from the stomach.)*

**A3.** A patient stabilized on warfarin is prescribed a sulfonamide antibiotic for a urinary infection. What interaction do you anticipate, what is its mechanism, and what would you monitor? *(Expected: the sulfonamide displaces warfarin from albumin → free warfarin level rises → blood clotting time increases → bleeding risk. Monitor for bleeding signs and clotting time; the prescriber may need to adjust the warfarin dose.)*

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# BP402T — Medicinal Chemistry

## Unit I, Chapter 2: Drug Metabolism — Phase I and Phase II Reactions

## Learning Objectives

After studying this chapter, you will be able to:

1. Define **drug metabolism** and explain in simple words why the body metabolizes drugs.
2. Name the **site** of drug metabolism and describe the **cytochrome P450 (CYP450)** enzyme family in simple terms.
3. Define **Phase I** and **Phase II** reactions and state the key difference between them.
4. List and explain each **Phase I reaction** (oxidation types, reduction, hydrolysis) with one drug example each.
5. List and explain each **Phase II conjugation reaction** with one drug example each.
6. Define **prodrug** and give two to three simple examples.
7. Name the main **factors affecting drug metabolism** (age, genetics, inducers, inhibitors).
8. Explain the difference between **active and inactive metabolites** and describe the **first-pass effect** in simple words.

## Definitions

- **Drug metabolism (biotransformation):** The chemical changes the body makes to a drug molecule after the drug enters the body. "Metabolism" means chemical processing; "biotransformation" means biological transformation. Think of it as the body "processing" the drug before throwing it out.
- **Metabolite:** The new chemical product formed when the body changes a drug. Example: paracetamol is changed by the body into paracetamol-glucuronide — that glucuronide is a *metabolite*.
- **Excretion:** Throwing a substance out of the body, mainly through urine (kidney) and stool/faeces.
- **Water-soluble vs fat-soluble:** A *fat-soluble* substance dissolves in fat/oil; a *water-soluble* substance dissolves in water. Most drugs are fat-soluble, but urine is water — so the body must convert fat-soluble drugs into water-soluble forms to remove them in urine.
- **Enzyme:** A protein in the body that speeds up a chemical reaction. Enzymes are the body's "workers."
- **Cytochrome P450 (CYP450):** A large family of enzymes, mostly found in the liver, that carry out most Phase I oxidation reactions on drugs. They add oxygen atoms to drug molecules.
- **Phase I reaction:** A chemical reaction that *modifies* a drug molecule (adds or removes small groups like oxygen, –CH3) to prepare it for removal or for Phase II.
- **Phase II reaction (conjugation):** A reaction that *joins* the drug (or its Phase I metabolite) to another molecule from the body, making a much bigger, very water-soluble product that is easily excreted.
- **Prodrug:** A drug given in an *inactive* form that the body converts into the *active* form by metabolism.
- **First-pass effect:** When a drug taken by mouth is partly destroyed by the liver *before* it reaches the blood and the rest of the body, so less active drug reaches its target.
- **Inducer:** A substance that *increases* the amount or speed of drug-metabolizing enzymes. **Inhibitor:** A substance that *slows down* or blocks these enzymes.

# Terminology Word Bank

| Term | Simple meaning |
|---|---|
| Metabolism / biotransformation | The body chemically changing a drug |
| Metabolite | The changed product of a drug |
| Conjugation | Joining the drug to a body molecule |
| Oxidation | Adding oxygen (or removing hydrogen) to the drug |
| Reduction | Adding hydrogen (or removing oxygen); opposite of oxidation |
| Hydrolysis | Breaking a bond by adding water |
| Hydroxylation | Adding an –OH (hydroxyl) group to the drug |
| Dealkylation | Removing an alkyl group (like –CH3) from the drug |
| Deamination | Removing an –NH2 (amino) group from the drug |
| N-oxidation | Adding oxygen to a nitrogen atom |
| S-oxidation | Adding oxygen to a sulfur atom |
| Glucuronidation | Joining the drug to glucuronic acid (from the body) |
| Donor molecule | The body molecule that is joined to the drug in Phase II |
| Prodrug | Inactive drug form that the body activates |
| First-pass effect | Liver destroying part of an oral drug before it reaches the body |
| Enzyme inducer | Speeds up metabolism enzymes |
| Enzyme inhibitor | Slows down metabolism enzymes |

## 2.1 Why Does the Body Metabolize Drugs? Where Does It Happen?

### The simple story

> **Technical concept:** Drug metabolism converts lipophilic (fat-soluble) drug molecules into hydrophilic (water-soluble) metabolites so they can be excreted by the kidneys.

> **Simple explanation:** Most drugs are fat-soluble — they dissolve in fat, not in water. But the body's main "waste pipe" is **urine, which is water**. A fat-soluble drug cannot dissolve in urine, so it cannot be thrown out easily. The body therefore *chemically changes* the drug — adding water-loving groups like –OH, or joining it to a water-loving molecule — so the product becomes water-soluble and flows out in urine.

**Example:** Aspirin is fat-soluble. The body joins it to glucuronic acid (a water-loving body molecule) to make salicyl-glucuronide, which dissolves in water and leaves in urine.

> **Key takeaway: Drug metabolism = making the drug water-soluble so it can be excreted. Without metabolism, drugs would stay stuck in the body.**

### Where it happens

**Technical concept:** The liver is the primary site of drug metabolism; extra-hepatic sites include kidney, lung, intestine, and skin.

**Simple explanation:** The **liver** is the body's "chemical factory" — almost all drug metabolism happens there. Small amounts also happen in the **kidney, lungs, intestine, and skin**.

**Key takeaway:** **Liver = the main site. Remember this for every exam answer.**

### Cytochrome P450 — the main Phase I enzyme family

**Technical concept:** Cytochrome P450 (CYP450) is a superfamily of heme-containing enzymes that catalyze oxidative Phase I metabolism of most drugs.

**Simple explanation: Cytochrome P450** (say: "sigh-toe-krome P-450") is a *family* of enzymes sitting mainly in the liver. They are the body's main Phase I workers — they **add oxygen** to drug molecules. One famous member is **CYP3A4**, which handles a very large number of common drugs. Think of CYP450 as a team of carpenters and CYP3A4 as the busiest carpenter on the team.

**Key takeaway:** **CYP450 = the main Phase I enzyme family, mostly in the liver, mainly doing oxidation.**

## Flowchart: The overall fate of a drug

```
Drug taken by mouth
        |
        v
Absorbed from intestine into blood
        |
        v
Reaches the LIVER (first-pass effect — some drug destroyed here)
        |
        v
PHASE I: drug is chemically modified (oxidation / reduction / hydrolysis)
        |   - may become ACTIVE, STAY ACTIVE, or become INACTIVE
        v
PHASE II: drug (or Phase I product) is joined to a body molecule (conjugation)
        |   - product is now very WATER-SOLUBLE and usually INACTIVE
        v
Excreted in URINE (mainly) or bile → faeces
```

**How to sketch this:** Draw 5 boxes in a row with arrows: "Drug" → "Liver" → "Phase I (modify)" → "Phase II (conjugate)" → "Urine/bile out". Label the Phase I box "adds/removes small groups" and the Phase II box "joins a body molecule".

# 2.2 Phase I Reactions

## The big picture

> **Technical concept:** Phase I reactions introduce or expose functional groups (–OH, –NH2, –SH) on the drug molecule through oxidation, reduction, or hydrolysis, usually making the drug slightly more water-soluble and ready for Phase II.

> **Simple explanation:** Phase I = **"preparation work."** The body's workers make small changes to the drug — adding an –OH group, removing a –CH3 group, or cutting the molecule with water. The drug is now "prepared" so that in Phase II a body molecule can be joined to it easily. Sometimes the drug becomes *active* or *inactive* in Phase I itself.

> **Analogy (Indian life):** Think of washing clothes by hand before putting them in the washing machine. Phase I is the hand-scrubbing and soaking (preparation); Phase II is the machine wash with detergent (final cleaning). Just as you scrub collars first, the liver makes small changes first.

> **Key takeaway:** **Phase I = small chemical changes (oxidation, reduction, hydrolysis) that prepare the drug for Phase II.**

## 2.2.1 Oxidation — the main Phase I reaction

> **Technical concept:** Oxidation reactions, catalyzed mainly by CYP450 enzymes, add oxygen to the drug or remove hydrogen from it.

> **Simple explanation: Oxidation** = adding oxygen to the drug (or taking hydrogen away). It is the most common Phase I change. The main types are listed in the table below.

### Phase I oxidation table

| Reaction type | What changes (plain words) | Example drug |
|---|---|---|
| **Aromatic hydroxylation** | An –OH group is added to a benzene ring of the drug: ring–H --CYP450--> ring–OH | **Phenytoin** → para-hydroxyphenytoin (an antiepileptic drug; the ring gets an –OH) |
| **Aliphatic hydroxylation** | An –OH group is added to a straight or branched carbon chain: –CH2– → –CH(OH)– | **Ibuprofen** → hydroxy-ibuprofen (an –OH is added to its side chain) |
| **N-dealkylation** | A –CH3 (methyl) group sitting on a nitrogen is removed and replaced by –H: –N–CH3 → –N–H | **Diazepam** → nordiazepam (the –CH3 on nitrogen is removed) |
| **O-dealkylation** | A –CH3 group sitting on an oxygen is removed and replaced by –H: –O–CH3 → –O–H | **Codeine** → morphine (the –OCH3 becomes –OH; this is how codeine becomes active!) |
| **N-oxidation** | An oxygen atom is added to a nitrogen atom: –N– → –N(=O)– | **Chlorpromazine** → chlorpromazine N-oxide |
| **S-oxidation** | An oxygen atom is added to a sulfur atom: –S– → –S(=O)– | **Cimetidine** → cimetidine sulfoxide (S becomes S=O) |
| **Deamination** | The –NH2 (amino) group is removed and replaced by =O: –CH2–NH2 → –CHO / –COOH | **Amphetamine** → phenylacetone (the –NH2 is removed; then it becomes benzoic acid) |

### Simple reaction schemes (text):

- Aromatic hydroxylation: phenytoin `--CYP450-->` para-hydroxyphenytoin (an –OH added to the ring)
- N-dealkylation: diazepam `--CYP450, –CH3 removed-->` nordiazepam
- O-dealkylation: codeine `--CYP450, –OCH3 becomes –OH-->` morphine
- S-oxidation: cimetidine `--CYP450, +O on sulfur-->` cimetidine sulfoxide

**Worked example — codeine to morphine:** Codeine has an –OCH3 group on its ring. The CYP450 enzyme removes the –CH3 part and leaves –OH behind: codeine `--CYP2D6-->` morphine. Morphine binds pain receptors much more strongly, so codeine actually works *through* this metabolism step — codeine is a prodrug of morphine (more in Section 2.4).

**Key takeaway: Oxidation = adding oxygen or –OH, or removing –CH3/–NH2 groups; CYP450 does most of it; codeine → morphine is the classic exam example.**

### 2.2.2 Reduction — the opposite of oxidation

**Technical concept:** Reduction adds hydrogen (or removes oxygen); it is less common than oxidation and often occurs in the gut by bacterial enzymes.

**Simple explanation: Reduction** = the reverse of oxidation — hydrogen is added (or oxygen removed). It happens less often than oxidation, and some of it is done by bacteria in the intestine.

| Reaction type | What changes (plain words) | Example drug |
|---|---|---|
| **Nitro reduction** | An –NO2 (nitro) group is reduced step by step to –NH2 (amino): –NO2 → –NH2 | **Chloramphenicol** → amino-chloramphenicol (the –NO2 becomes –NH2) |
| **Azo reduction** | An –N=N– (azo) bond is split by adding hydrogen: –N=N– → two –NH2 pieces | **Sulfasalazine** → sulfapyridine + 5-aminosalicylic acid (gut bacteria split the –N=N– bond; the 5-aminosalicylic acid treats ulcerative colitis) |

**Simple reaction schemes:**

- `chloramphenicol (–NO2) --reduction, +H--> amino-chloramphenicol (–NH2)`
- `sulfasalazine (–N=N–) --gut bacteria--> sulfapyridine + 5-aminosalicylic acid`

**Key takeaway: Reduction = adding hydrogen; nitro (–NO2) → amino (–NH2); azo (–N=N–) splits into two amines. Sulfasalazine is the classic azo-reduction example.**

### 2.2.3 Hydrolysis — breaking with water

**Technical concept:** Hydrolysis cleaves ester or amide bonds by adding water across the bond, catalyzed by esterases and amidases (not CYP450).

**Simple explanation: Hydrolysis** = "breaking by water." Water (H2O) splits into H and OH, and these two pieces cut the drug at an **ester** (–COO–) or **amide** (–CONH–) bond, making two smaller pieces. The workers here are **esterases** (cut esters) and **amidases** (cut amides) — not CYP450.

| Reaction type | What changes (plain words) | Example drug |
|---|---|---|
| **Ester hydrolysis** | Water cuts the ester bond: drug–COO–R + H2O → drug–COOH + R–OH | **Aspirin** → salicylic acid + acetic acid (the ester bond is cut by esterases) |
| **Amide hydrolysis** | Water cuts the amide bond: drug–CO–NH–R + H2O → drug–COOH + R–NH2 | **Procainamide** → p-aminobenzoic acid (the amide bond is cut) |

**Simple reaction schemes:**

- `aspirin --esterase, +H2O--> salicylic acid + acetic acid`
- `procainamide --amidase, +H2O--> p-aminobenzoic acid`

**Analogy (Indian life):** Hydrolysis is like tearing a perforated paper coupon in two — the perforation is the ester/amide bond, and water is your hands pulling it apart.

**Key takeaway: Hydrolysis = water cutting ester or amide bonds; esterases and amidases do this work; aspirin → salicylic acid is the classic example.**

### Summary table — all Phase I reactions

| # | Reaction | Change in plain words | Example drug → metabolite |
|---|---|---|---|
| 1 | Aromatic hydroxylation | –OH added to benzene ring | Phenytoin → p-hydroxyphenytoin |
| 2 | Aliphatic hydroxylation | –OH added to carbon chain | Ibuprofen → hydroxy-ibuprofen |
| 3 | N-dealkylation | –CH3 on N removed, replaced by –H | Diazepam → nordiazepam |
| 4 | O-dealkylation | –CH3 on O removed, replaced by –H | Codeine → morphine |
| 5 | N-oxidation | O added to nitrogen | Chlorpromazine → chlorpromazine N-oxide |
| 6 | S-oxidation | O added to sulfur | Cimetidine → cimetidine sulfoxide |
| 7 | Deamination | –NH2 removed | Amphetamine → phenylacetone |
| 8 | Nitro reduction | –NO2 → –NH2 | Chloramphenicol → amino-chloramphenicol |
| 9 | Azo reduction | –N=N– split into two amines | Sulfasalazine → sulfapyridine + 5-ASA |
| 10 | Ester hydrolysis | Water cuts ester bond | Aspirin → salicylic acid |
| 11 | Amide hydrolysis | Water cuts amide bond | Procainamide → p-aminobenzoic acid |

## 2.3 Phase II Reactions (Conjugation)

### The big picture

**Technical concept:** Phase II conjugation reactions attach an endogenous polar molecule (donor) to the drug or its Phase I metabolite, forming a highly water-soluble, usually inactive conjugate that is readily excreted.

**Simple explanation: Conjugation** = "joining together." The body takes the drug (or its Phase I product) and *glues* it to one of its own water-loving molecules — like glucuronic acid, sulfate, or glycine. The joined product is big, very water-soluble, and usually inactive, so it flows out easily in urine or bile.

**Analogy (Indian life):** Think of tying a heavy stone to a balloon — no wait, the opposite! Think of attaching a bright red flag to your luggage at the railway station so it is easy to spot and unload. Phase II attaches a big water-loving "flag" to the drug so the kidney can easily spot and remove it.

**Key takeaway:** **Phase II = joining the drug to a body molecule (donor) → very water-soluble, usually inactive → excreted.**

## Phase II conjugation table

| Conjugate formed | Donor molecule (body's molecule) | Example drug |
|---|---|---|
| **Glucuronide** (glucuronidation) | **Glucuronic acid** (from glucose) | **Paracetamol** → paracetamol glucuronide |
| **Sulfate** (sulfation / sulphate conjugation) | **Sulfate** (PAPS — active sulfate) | **Paracetamol** → paracetamol sulfate |
| **Acetyl** (acetylation) | **Acetyl-CoA** (acetyl group donor) | **Isoniazid** (anti-TB drug) → acetyl-isoniazid |
| **Methyl** (methylation) | **S-adenosylmethionine (SAM)** (methyl donor) | **Adrenaline (epinephrine)** → metanephrine |
| **Glutathione conjugate** (glutathione conjugation) | **Glutathione** (a protective tripeptide) | **Paracetamol's toxic metabolite (NAPQI)** → glutathione conjugate (this detoxifies it) |
| **Glycine conjugate** (amino acid conjugation) | **Glycine** (an amino acid) | **Benzoic acid** → hippuric acid (benzoyl-glycine) |

### Simple reaction schemes (text):

- Glucuronidation: `paracetamol + glucuronic acid --glucuronyl transferase--> paracetamol glucuronide (excreted in urine)`
- Sulfation: `paracetamol + sulfate (PAPS) --sulfotransferase--> paracetamol sulfate`
- Acetylation: `isoniazid + acetyl-CoA --acetyltransferase--> acetyl-isoniazid`
- Methylation: `adrenaline + SAM --methyltransferase--> metanephrine`
- Glutathione conjugation: `NAPQI (toxic) + glutathione --> glutathione conjugate (safe, excreted)`
- Glycine conjugation: `benzoic acid + glycine --> hippuric acid`

**Worked example — paracetamol and glutathione (India-relevant safety story):** A small part of paracetamol is oxidized in Phase I to **NAPQI**, a toxic metabolite that can damage the liver. Normally, **glutathione** (the donor) quickly joins NAPQI and makes it harmless. But in **paracetamol overdose**, glutathione runs out, NAPQI attacks the liver, and liver failure follows. The antidote **N-acetylcysteine (NAC)** works by restoring glutathione. This is why pharmacists must counsel patients: never exceed the paracetamol dose.

**Key takeaway:** **Each Phase II reaction joins the drug to a specific donor molecule; the product is water-soluble and usually inactive; glutathione protects the liver from NAPQI.**

# 2.4 The Prodrug Concept

## Definition

> **Technical concept:** A prodrug is a pharmacologically inactive compound that is converted in the body (usually by metabolism) into the active drug.

> **Simple explanation:** A **prodrug** is a drug given in a "sleeping" (inactive) form. After you take it, the body wakes it up — metabolism converts it into the active form that actually works. It is like sending a sealed letter: the envelope (prodrug) is useless until opened (metabolized) to reveal the letter (active drug) inside.

**Why are prodrugs made?** Three simple reasons:

1. **Better absorption:** The inactive form may pass through the intestine wall more easily (e.g., a fat-soluble prodrug absorbed better, then activated in blood/liver).
2. **Better delivery to the target:** The prodrug can reach places the active drug cannot (e.g., cross the blood-brain barrier).
3. **Fewer side effects / better taste:** The inactive form may irritate the stomach less.

**Simple examples:**

| Prodrug (inactive, given) | Converted by | Active drug (works) | Why it is a prodrug |
|---|---|---|---|
| **Enalapril** | Ester hydrolysis in liver | **Enalaprilat** | Enalaprilat is poorly absorbed by mouth, so the ester prodrug enalapril is given instead |
| **Levodopa** | Decarboxylation in brain | **Dopamine** | Dopamine cannot cross into the brain; levodopa crosses and then becomes dopamine (Parkinson's disease treatment) |
| **Codeine** | O-dealkylation (CYP2D6) | **Morphine** | Codeine itself is weak; the body converts it to morphine, the real painkiller |

**Reaction schemes:**

- `enalapril --esterase (liver)--> enalaprilat (active ACE inhibitor)`
- `levodopa --decarboxylase (brain)--> dopamine (active)`
- `codeine --CYP2D6 (liver)--> morphine (active)`

**Pharmacy relevance:** When dispensing enalapril, remember the patient is really being treated with enalaprilat — the conversion happens in the liver, so severe liver disease can reduce its effect.

> **Key takeaway:** **Prodrug = inactive form given, body activates it; enalapril → enalaprilat, levodopa → dopamine, codeine → morphine.**

## 2.5 Factors Affecting Drug Metabolism

Each factor gets one line plus one example:

1. **Age:** Newborn babies and elderly people metabolize drugs **more slowly** because their liver enzymes are immature (babies) or weaker (elderly) — *example: chloramphenicol can build up to toxic levels in newborns ("grey baby syndrome") because they cannot metabolize it well.*
2. **Genetics:** People's genes decide how fast their enzymes work — some are "fast metabolizers" and some are "slow metabolizers" — *example: some people lack the CYP2D6 enzyme and get almost no pain relief from codeine (because they cannot convert it to morphine).*
3. **Enzyme inducers:** Some drugs/chemicals **speed up** metabolism enzymes, so other drugs are destroyed faster and work less — *example: rifampicin (anti-TB drug) induces CYP450 enzymes and reduces the effect of oral contraceptive pills.*
4. **Enzyme inhibitors:** Some drugs/chemicals **slow down** metabolism enzymes, so other drugs build up and can become toxic — *example: ketoconazole inhibits CYP3A4, raising blood levels of many drugs to dangerous levels.*

**India context:** Tuberculosis treatment with **rifampicin** is extremely common in India, and rifampicin is one of the strongest enzyme inducers known. A pharmacist in India must always check: is the patient on rifampicin plus any other drug (contraceptives, antiretrovirals, antiepileptics)? The inducer can make the other drug fail. Similarly, **isoniazid** (also in TB treatment) can *inhibit* some enzymes — TB drug combinations are a classic exam case of inducer/inhibitor interactions.

> **Key takeaway:** Age, genes, inducers (speed up), and inhibitors (slow down) change how fast drugs are metabolized — always check for interactions.

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## 2.6 Consequences of Drug Metabolism

### Active vs inactive metabolites

> **Technical concept:** Metabolism can produce metabolites that are pharmacologically active, inactive, or toxic.

> **Simple explanation:** The metabolite is not always "dead." Three possibilities:

- **Inactive metabolite (most common):** The changed drug no longer works — it is just waste waiting to be excreted. *Example: diazepam's later metabolites are inactive.*
- **Active metabolite:** The changed drug still works — sometimes even better than the original. *Example: codeine → morphine; diazepam → nordiazepam (still active, long-acting).*
- **Toxic metabolite (rare but dangerous):** The changed drug harms the body. *Example: paracetamol → NAPQI damages the liver in overdose.*

> **Key takeaway:** Metabolites can be inactive (waste), active (still working), or toxic (harmful) — know one example of each.

### First-pass effect — one short paragraph

**Technical concept:** Orally administered drugs pass through the intestinal wall and liver via the portal circulation before reaching systemic circulation, and hepatic metabolism can substantially reduce bioavailability.

**Simple explanation:** When you swallow a tablet, it is absorbed from the intestine into blood vessels that go **first to the liver** (through the portal vein) — before reaching the rest of the body. The liver, doing its metabolism job, destroys **part of the drug** on this first pass. So only a fraction of the swallowed dose reaches the blood and the target organ. This is the **first-pass effect**: the liver takes its "tax" before the drug reaches the body. *Example: propranolol and morphine undergo heavy first-pass metabolism, which is why their oral doses are much larger than their injected doses.* Drugs given by injection, under the tongue, or as skin patches partly or fully **bypass** the first pass.

**Analogy (Indian life):** The first-pass effect is like a toll plaza on a highway — every truck (drug dose) must pass the toll booth (liver), and the booth keeps a share of the goods before the truck continues to the city (the body).

**Key takeaway:** **First-pass effect = liver destroys part of an oral drug before it reaches the body; oral doses are therefore larger than injected doses for such drugs.**

## Infographic Concept Box — "Drug Metabolism at a Glance"

*Design brief for the illustrator: a single A4 infographic, left-to-right flow.*

- **Title banner:** "DRUG METABOLISM: From Fat-Soluble Drug to Water-Soluble Waste"
- **Panel 1 — WHY:** Icon of a fat droplet (drug) that cannot enter a water tap (urine); caption: "Fat-soluble drug cannot dissolve in urine."
- **Panel 2 — WHERE:** Liver icon labelled "Main factory"; small icons for kidney, lung, intestine labelled "small contribution"; CYP450 shown as worker figures with "adds oxygen" tools.
- **Panel 3 — PHASE I (prepare):** Three mini-icons: oxidation (O atom added), reduction (H atom added), hydrolysis (water scissors cutting a bond); caption: "Small changes — prepare the drug."
- **Panel 4 — PHASE II (conjugate):** Drug icon joined by a chain link to donor icons (glucuronic acid, sulfate, glycine); caption: "Join to a body molecule — big, water-soluble, inactive."
- **Panel 5 — OUT:** Water tap/urine icon; caption: "Excreted in urine."
- **Side strip — PRODRUG:** Sleeping pill icon → alarm clock → awake pill icon; "Inactive in, active out: enalapril → enalaprilat."
- **Warning strip:** Red panel: "Paracetamol overdose → glutathione runs out → NAPQI damages liver."
- **Footer strip:** Mnemonic "G-SAM-GG" for Phase II donors (Glucuronic acid, Sulfate, Acetyl-CoA, SAM, Glutathione, Glycine).

## Textual Diagram Descriptions (sketchable)

**Diagram 1 — Phase I vs Phase II (two-box diagram):** Draw two boxes side by side. Left box: "PHASE I — Functionalization" with three bullet icons: "+O (oxidation)", "+H (reduction)", "+H2O (hydrolysis)". Right box: "PHASE II — Conjugation" with "drug + donor → conjugate (water-soluble)". Draw an arrow from Phase I to Phase II labelled "prepared product moves on". Below, write: "Phase I: small changes. Phase II: joining."

**Diagram 2 — The prodrug journey:** Draw a road with three stops. Stop 1: "Tablet swallowed (enalapril — inactive)". Stop 2: "Liver — esterase cuts the ester". Stop 3: "Blood — enalaprilat (active) lowers blood pressure". Draw a sleeping face at Stop 1 and an awake face at Stop 3.

**Diagram 3 — First-pass effect:** Draw the intestine (a tube) with an arrow to the liver (a wedge shape) with an arrow to the heart/body. At the liver, draw a "toll booth" taking a cut: label "100 mg swallowed → 25 mg destroyed in liver → 75 mg reaches body" (illustrative numbers).

## Worked Examples

**Worked Example 1 — Trace aspirin's metabolism.** *Question:* Aspirin is an ester. What Phase I reaction acts on it, and what are the products? *Answer:* Ester hydrolysis. The esterase enzyme adds water across the ester bond: `aspirin + H20 --esterase--> salicylic acid + acetic acid`. Salicylic acid is then conjugated in Phase II (glycine/glucuronic acid) and excreted.

**Worked Example 2 — Why does codeine fail in some patients?** *Question:* A patient gets no pain relief from codeine. Which enzyme and reaction are involved? *Answer:* Codeine is a prodrug activated by **O-dealkylation** (CYP2D6) to morphine. Patients with poor CYP2D6 genes ("poor metabolizers") cannot make morphine, so codeine does not work for them.

**Worked Example 3 — Paracetamol overdose.** *Question:* Why is N-acetylcysteine given in paracetamol poisoning? *Answer:* In overdose, Phase I makes too much toxic **NAPQI**, and the **glutathione** donor runs out. N-acetylcysteine restores glutathione, which conjugates NAPQI into a harmless product.

## Pharmacy Relevance

- **Dose decisions:** Drugs with a high first-pass effect need larger oral doses than injected doses — a pharmacist must never assume "10 mg oral = 10 mg injection."
- **Interaction checking:** Before dispensing, check for inducers (rifampicin) and inhibitors (ketoconazole) that change how fast the patient's other drugs are metabolized.
- **Prodrug counselling:** Tell patients on levodopa that protein-rich meals can reduce its effect, and that the drug needs time to be converted in the brain.
- **Overdose counselling:** Warn every patient buying paracetamol: "Do not exceed the stated dose — overdose damages the liver because the protective glutathione runs out."
- **Genetic awareness:** If codeine does not relieve pain, consider that the patient may be a poor CYP2D6 metabolizer — do not simply keep increasing the dose.

## India Context

- **TB treatment and interactions:** India's huge TB programme uses **rifampicin** (strong inducer) and **isoniazid** (acetylated; also an inhibitor of some enzymes). A patient on TB medicines plus diabetes, epilepsy, or HIV medicines needs interaction review — rifampicin can make those other drugs fail.
- **Paracetamol self-medication:** Paracetamol is India's most common self-medicated fever drug. Pharmacists are the last safety checkpoint against overdose — counsel on maximum daily dose, especially for patients who also drink alcohol (alcohol induces the CYP enzyme that makes toxic NAPQI).
- **Isoniazid and acetylation genetics:** Indians include both fast and slow acetylators of isoniazid; slow acetylators get more side effects (like nerve damage), fast acetylators may get less effect — dose and monitoring are adjusted accordingly.

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## Key Points (one-minute revision list)

1. Drug metabolism makes **fat-soluble drugs water-soluble** so they can be excreted in urine.
2. **Liver** is the main site; **CYP450** is the main Phase I enzyme family (adds oxygen).
3. **Phase I** = small changes: **oxidation, reduction, hydrolysis** — prepares the drug.
4. **Phase II** = **conjugation**: drug + donor molecule → water-soluble, usually inactive product.
5. Phase II donors: **glucuronic acid, sulfate, acetyl-CoA, SAM, glutathione, glycine** (mnemonic: "G-SAM-GG" — Glucuronic acid, Sulfate, Acetyl-CoA, SAM, Glutathione, Glycine).
6. **Prodrug** = inactive form converted by the body to the active drug (enalapril → enalaprilat; levodopa → dopamine; codeine → morphine).
7. Factors: **age** (babies/elderly slower), **genetics** (fast/slow metabolizers), **inducers** (rifampicin speeds up), **inhibitors** (ketoconazole slows down).
8. Metabolites can be **inactive, active, or toxic** (NAPQI from paracetamol).
9. **First-pass effect** = liver destroys part of an oral drug before it reaches the body.

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## Common Confusions

- **Phase I vs Phase II:** Phase I *modifies* (small changes: +O, +H, +H2O). Phase II *conjugates* (joins a whole donor molecule). If the question says "joining to glucuronic acid," that is Phase II, not Phase I.
- **Oxidation vs reduction:** Oxidation adds oxygen or removes hydrogen; reduction adds hydrogen or removes oxygen. They are opposites — do not swap them.
- **N-dealkylation vs O-dealkylation:** N-dealkylation removes –CH3 from **nitrogen**; O-dealkylation removes –CH3 from **oxygen**. The letter tells you which atom.
- **Prodrug vs active metabolite:** A prodrug is *given* inactive and becomes active (enalapril). An active metabolite is the *result* of metabolism that still works (morphine from codeine). Codeine is both a prodrug and an example of an active metabolite — that is fine; the terms describe different viewpoints.
- **Inducer vs inhibitor:** Inducer = speeds up enzymes = other drugs destroyed faster = less effect. Inhibitor = slows enzymes = other drugs build up = more effect/toxicity. Students often reverse these.

## Common Mistakes

1. Writing that CYP450 does Phase II — it does **Phase I** (mainly oxidation).
2. Saying hydrolysis is done by CYP450 — hydrolysis is done by **esterases/amidases**.
3. Calling glucuronidation a Phase I reaction — it is the classic **Phase II** conjugation.
4. Forgetting that Phase II products are usually **inactive** — examiners love asking this.
5. Mixing up the donor molecules — e.g., saying methylation uses acetyl-CoA (it uses **SAM**).
6. Stating that all metabolites are inactive — **active** (morphine) and **toxic** (NAPQI) metabolites are favourite exam traps.

## Mnemonics

- **Phase II donors — "G-SAM-GG": G**lucuronic acid, **S**ulfate, **A**cetyl-CoA (with **M**ethyl from **SAM**), **G**lutathione, **G**lycine. (Read: "G-SAM-GG" — Sam has a double-G.)
- **Phase I types — "ORH": O**xidation, **R**eduction, **H**ydrolysis.
- **Oxidation subtypes — "A-A-N-O-N-S-D": A**romatic hydroxylation, **A**liphatic hydroxylation, **N**-dealkylation, **O**-dealkylation, **N**-oxidation, **S**-oxidation, **D**eamination. (Read: "AANONSD" — "a non-sad" list.)
- **First-pass effect:** "The liver takes its **tax** before the drug reaches the body."

## Exam Summary

Drug metabolism converts fat-soluble drugs into water-soluble metabolites for excretion, mainly in the **liver** by **cytochrome P450** enzymes. **Phase I** (oxidation, reduction, hydrolysis) makes small changes — oxidation subtypes include aromatic/aliphatic hydroxylation, N-/O-dealkylation, N-/S-oxidation, and deamination; reduction covers nitro and azo reduction; hydrolysis covers ester and amide cleavage by esterases/amidases. **Phase II** (conjugation) joins the drug to a donor — glucuronic acid, sulfate, acetyl-CoA, SAM, glutathione, or glycine — giving water-soluble, usually inactive products. **Prodrugs** (enalapril → enalaprilat, levodopa → dopamine, codeine → morphine) are given inactive and activated by metabolism. Metabolism is affected by **age, genetics, inducers** (rifampicin) and **inhibitors** (ketoconazole). Metabolites may be **inactive, active, or toxic** (NAPQI); the **first-pass effect** reduces oral bioavailability because the liver metabolizes part of the dose before it reaches systemic circulation.

## One-Minute Revision

Say it aloud in 60 seconds: "Metabolism makes drugs water-soluble for urine excretion. Liver is the site; CYP450 does Phase I oxidation. Phase I = ORH: oxidation, reduction, hydrolysis — small changes. Phase II = conjugation to six donors: G-SAM-GG. Prodrugs: enalapril→enalaprilat, levodopa→dopamine, codeine→morphine. Factors: age, genes, inducers like rifampicin, inhibitors like ketoconazole. Metabolites: inactive, active, or toxic like NAPQI. First-pass: liver taxes oral drugs before they reach the body."

# Exam Questions

## MCQs (10) — with answer key

**Q1.** The primary site of drug metabolism is the: a) Kidney b) Liver c) Lung d) Skin

**Q2.** Cytochrome P450 enzymes mainly carry out which type of reaction? a) Glucuronidation b) Oxidation c) Glycine conjugation d) Methylation

**Q3.** Codeine is converted to morphine by: a) N-dealkylation b) O-dealkylation c) Ester hydrolysis d) Azo reduction

**Q4.** Sulfasalazine is split by gut bacteria through: a) Nitro reduction b) Azo reduction c) S-oxidation d) Deamination

**Q5.** Aspirin is metabolized by: a) Amide hydrolysis b) Ester hydrolysis c) N-oxidation d) Methylation

**Q6.** The donor molecule in glucuronidation is: a) Acetyl-CoA b) Sulfate c) Glucuronic acid d) Glutathione

**Q7.** Isoniazid undergoes which Phase II reaction? a) Sulfation b) Acetylation c) Methylation d) Glycine conjugation

**Q8.** Which of the following is a prodrug? a) Morphine b) Enalapril c) Enalaprilat d) Dopamine

**Q9.** Rifampicin is an example of an enzyme: a) Inhibitor b) Inducer c) Substrate only d) Cofactor

**Q10.** The toxic metabolite of paracetamol is: a) Paracetamol glucuronide b) Paracetamol sulfate c) NAPQI d) Hippuric acid

**Answer key:** Q1–b, Q2–b, Q3–b, Q4–b, Q5–b, Q6–c, Q7–b, Q8–b, Q9–b, Q10–c

## Viva Questions (5) — with short answers

**V1. Why does the body metabolize drugs?** To convert fat-soluble drugs into water-soluble metabolites that can be excreted in urine.

**V2. What is the difference between Phase I and Phase II reactions?** Phase I makes small chemical changes (oxidation, reduction, hydrolysis) to prepare the drug; Phase II joins the drug to a donor molecule (conjugation), making a water-soluble, usually inactive product.

**V3. Name the six Phase II donor molecules.** Glucuronic acid, sulfate, acetyl-CoA, SAM (S-adenosylmethionine), glutathione, and glycine.

**V4. What is a prodrug? Give one example.** A prodrug is an inactive form of a drug that the body converts into the active form; e.g., enalapril → enalaprilat.

**V5. What is the first-pass effect?** When an oral drug passes through the liver before reaching the rest of the body, the liver metabolizes part of the dose, so less active drug reaches systemic circulation.

## Application-Based Questions (3)

**A1.** A TB patient on rifampicin is also taking oral contraceptive pills and reports contraceptive failure. Explain using drug metabolism concepts, and state what the pharmacist should advise. *Guidance:* Rifampicin is a strong enzyme inducer — it speeds up CYP450 enzymes, so the contraceptive hormones are metabolized faster, blood levels fall, and protection fails. Advise an additional non-hormonal contraceptive method during rifampicin therapy and for a few weeks after stopping it.

**A2.** A patient took a large overdose of paracetamol. Explain why N-acetylcysteine is given, naming the Phase I toxic metabolite and the Phase II donor involved. *Guidance:* Phase I oxidation forms toxic NAPQI; normally glutathione (Phase II donor) detoxifies it, but overdose depletes glutathione, so NAPQI damages the liver. N-acetylcysteine restores glutathione, allowing safe conjugation and excretion.

**A3.** Codeine gives excellent pain relief in one patient but almost none in another, though both took the same dose. Explain using metabolism and genetics. *Guidance:* Codeine is a prodrug activated by O-dealkylation via CYP2D6 to morphine. Genetic differences make some people poor CYP2D6 metabolizers who form little morphine (poor relief), while ultra-rapid metabolizers form too much (toxicity risk).

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