BP405T · B.PHARM THEORY

BP405T Systemic Pharmacology I

Unit III — Drugs Acting on Blood & Kidney

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UNIT III — Pharmacology of Drugs Acting on Blood and Kidney (10 hours)

Chapters 8–10 (numbered within the unit in the source drafts)

CHAPTER 1

Anti-platelet Agents, Coagulants and Anticoagulants

Learning Objectives

After studying this chapter, the student will be able to:

1. Explain why and how blood clots form (platelet plug → coagulation cascade → fibrin clot).
2. Classify anti-platelet drugs with examples and describe their mechanisms of action.
3. Describe the mechanism, uses, adverse effects and monitoring of heparin and warfarin.
4. Explain the newer direct oral anticoagulants (rivaroxaban, apixaban, dabigatran).
5. List coagulants (vitamin K, fibrinogen, anti-haemophilic factors) and their uses.
6. Describe important drug interactions of warfarin and management of bleeding caused by anticoagulants.

Definitions

- **Haemostasis:** The body's natural process of stopping bleeding when a blood vessel is injured. It happens in two steps — a platelet plug forms first (primary haemostasis), then the clotting (coagulation) cascade strengthens it (secondary haemostasis).
- **Thrombosis:** Formation of a harmful clot inside an unbroken blood vessel. It is the same clotting machinery switched on in the wrong place.
- **Anti-platelet agent:** A drug that prevents platelets from sticking together (aggregating), thus preventing the first step of clot formation.
- **Anticoagulant:** A drug that slows or prevents the coagulation cascade (fibrin formation).
- **Fibrinolytic:** A drug that dissolves an already-formed clot.
- **Coagulant:** A drug that promotes clotting (used in bleeding disorders).

Terminology

- **Platelet aggregation:** Platelets clumping together — the main target of anti-platelet drugs.
- **ADP (adenosine diphosphate):** A chemical released by platelets that activates other platelets; blocked by clopidogrel.
- **GP IIb/IIIa receptor:** The final common receptor on platelets that binds fibrinogen and glues platelets together.
- **Thromboxane A2 (TXA2):** A platelet-activating chemical made from arachidonic acid by the COX-1 enzyme; blocked by aspirin.
- **Coagulation factors:** Numbered proteins (II, VII, IX, X, etc.) that activate one another in a chain (cascade).
- **INR (International Normalised Ratio):** A standardised blood test used to monitor warfarin therapy.
- **PT/aPTT:** Prothrombin time / activated partial thromboplastin time — clotting-time tests. aPTT is used to monitor heparin.
- **HIT (Heparin-induced thrombocytopaenia):** A serious immune reaction to heparin causing low platelets and clotting.
- **DOAC:** Direct oral anticoagulant — modern oral drugs that directly inhibit factor Xa or thrombin.
- **Reversal agent:** A drug that cancels the effect of an anticoagulant (e.g., vitamin K for warfarin).

Explanation: Why blood clots — and why we block clotting

Blood must do two opposite jobs: clot quickly when we bleed, and stay liquid while flowing. Clot formation has three stages:

1. **Platelet plug (primary haemostasis):** Injury exposes collagen under the vessel lining. Platelets stick to it, get activated (ADP, thromboxane A2, thrombin), and clump together — the first soft plug.
2. **Coagulation cascade (secondary haemostasis):** A chain reaction of clotting factors produces thrombin, which converts fibrinogen into fibrin threads that cement the plug into a firm clot.
3. **Fibrinolysis:** Later, plasmin dissolves the clot once healing is done.

Drugs target each stage: anti-platelets stop stage 1, anticoagulants stop stage 2, fibrinolytics break the finished clot.

Analogies

- **Traffic jam:** A clot blocking an artery is like a traffic jam blocking a road — anti-platelets stop the cars (platelets) from piling up at the accident spot.
- **Domino chain:** The coagulation cascade is like a row of dominoes; anticoagulants remove one domino so the chain stops.
- **Cement mixer:** Thrombin is the mixer that turns liquid cement (fibrinogen) into solid concrete (fibrin) around the platelets.

Classification (Anti-platelet Agents)

Class	Examples	Mechanism in short
COX-1 inhibitor	Aspirin	Blocks thromboxane A2 formation
ADP (P2Y12) receptor blockers	Clopidogrel, ticagrelor	Block ADP-driven platelet activation
GP IIb/IIIa receptor blockers	Abciximab, tirofiban	Block the final glue receptor (IV use)
Phosphodiesterase-3 inhibitors	Dipyridamole, cilostazol	Raise cAMP, reduce activation
Protease-activated receptor (PAR-1) blocker	Vorapaxar (concept)	Blocks thrombin-mediated activation

1. Aspirin

- **Mechanism:** Irreversibly inhibits the COX-1 enzyme in platelets, so thromboxane A2 cannot be made. Because platelets have no nucleus, they cannot make new enzyme — the effect lasts for the platelet's whole life (7–10 days).
- **Pharmacological effects:** Anti-platelet (at low doses, typically 75–150 mg), analgesic/anti-inflammatory at higher doses.
- **Therapeutic uses:** Prevention of heart attack and stroke in high-risk patients; after coronary stent placement; acute treatment of myocardial infarction; secondary prevention in angina and transient ischaemic attacks.
- **Adverse effects:** Stomach irritation, ulcer, gastric bleeding (low dose reduces but does not remove this risk); increased bleeding in general; allergic reactions in sensitive individuals; Reye's syndrome in children with viral illness — so aspirin is avoided in children.
- **Key point:** Aspirin's anti-platelet effect is IRREVERSIBLE — unlike most drugs, it never comes off the enzyme.

2. Clopidogrel

- **Mechanism:** Blocks the ADP (P2Y12) receptor on platelets, preventing ADP-driven activation and aggregation. It is a prodrug — the liver converts it to the active form (so liver enzyme interactions matter).
- **Uses:** Dual anti-platelet therapy (with aspirin) after stents and acute coronary syndrome; patients who cannot take aspirin; stroke prevention.
- **Adverse effects:** Bleeding; rarely, low blood counts (thrombotic thrombocytopaenic purpura); slow onset (several hours) unless a loading dose is given.

3. Ticagrelor

- **Mechanism:** Also blocks the P2Y12 receptor, but directly (not a prodrug) and reversibly — acts fast and wears off faster.
- **Uses:** Acute coronary syndrome (with aspirin); alternative when clopidogrel's slow onset or variability is a problem.
- **Adverse effects:** Bleeding; breathlessness (dyspnoea) in some patients; slow heart rate; twice-daily dosing.
- **Comparison tip:** Clopidogrel = slow, irreversible, prodrug; Ticagrelor = fast, reversible, direct acting, but more expensive.

4. GP IIb/IIIa Inhibitors — Abciximab, Tirofiban

- **Concept:** These block the GP IIb/IIIa receptor — the final common step where fibrinogen glues platelets together. They are the most powerful anti-platelets.
- **Use:** Given only intravenously in hospital during high-risk angioplasty/PCI or unstable angina.
- **Adverse effects:** Serious bleeding; low platelet counts (thrombocytopaenia).

5. Dipyridamole

- **Mechanism:** Inhibits phosphodiesterase-3, raising cAMP inside platelets, which keeps them calm and inactive. Also dilates coronary vessels.
- **Uses:** Combined with aspirin for stroke prevention (recurrent stroke/TIA); used with warfarin in patients with artificial heart valves.
- **Adverse effects:** Headache, dizziness, flushing; "coronary steal" concern in theory; safe in pregnancy for valve patients (an advantage over warfarin).

Classification (Anticoagulants)

Type	Examples	Route
Unfractionated heparin	Heparin	IV / subcutaneous
Low molecular weight heparins	Enoxaparin, dalteparin	Subcutaneous
Vitamin K antagonists	Warfarin, acenocoumarol	Oral
Direct factor Xa inhibitors	Rivaroxaban, apixaban	Oral
Direct thrombin inhibitors	Dabigatran, (argatroban — IV)	Oral

1. Heparin (Unfractionated)

- **Mechanism:** Works through antithrombin III — it speeds up antithrombin's action about 1000 times. Antithrombin then inactivates thrombin (factor IIa) and factor Xa. Heparin never works without antithrombin present.
- **Pharmacological effects:** Immediate anticoagulation (IV effect in seconds); prevents clot extension; does not dissolve existing clots.
- **Uses:** Acute deep vein thrombosis and pulmonary embolism; during surgery and dialysis; unstable angina; short-term prevention.
- **Monitoring:** aPTT test (heparin prolongs it).
- **Adverse effects:** Bleeding (reversed by protamine sulfate); heparin-induced thrombocytopaenia (HIT); osteoporosis with long-term use.
- **Mnemonic note:** "Heparin = hospital" — IV/SC only, monitored with aPTT.

2. Low Molecular Weight Heparins (Enoxaparin, Dalteparin)

- **Mechanism:** Same antithrombin mechanism, but mainly inhibit factor Xa (less effect on thrombin) because the chains are shorter.
- **Advantages over heparin:** Predictable effect, once-daily subcutaneous dosing, less HIT, no routine aPTT monitoring needed.
- **Uses:** Prevention and treatment of DVT/PE; acute coronary syndrome.
- **Adverse effects:** Bleeding (less than heparin); HIT still possible but rarer.

3. Warfarin

- **Mechanism:** Blocks vitamin K's recycling (inhibits vitamin K epoxide reductase), so the liver cannot make functional clotting factors II, VII, IX and X (and proteins C and S). Effect takes 3–5 days to develop.
- **Monitoring:** INR — typical target range is 2–3 for most indications (confirm against current references for each condition).
- **Uses:** Atrial fibrillation (stroke prevention), artificial heart valves (mechanical valves), DVT/PE treatment and prevention.
- **Reversal:** Vitamin K (slow), fresh frozen plasma or prothrombin complex concentrate (fast).
- **Adverse effects:** Bleeding (major risk); skin necrosis (early, when protein C drops first); purple toe syndrome; teratogenic — NEVER in pregnancy (causes birth defects); hair loss.
- **Interactions (very important):**
- *Increased bleeding risk:* NSAIDs, aspirin, broad-spectrum antibiotics (kill gut vitamin-K-making bacteria), metronidazole, fluconazole, amiodarone, alcohol binge.
- *Reduced effect:* Vitamin K-rich foods (green leafy vegetables) in large amounts, enzyme inducers (rifampicin, carbamazepine), St. John's wort.
- **Patient advice:** Keep diet consistent; report any new medicine to the doctor.
- **Mnemonic for increased effect:** "Many drugs Make Warfarin Mighty" — or remember the rule: anything that kills gut bacteria or blocks liver enzymes raises INR.

4. Direct Oral Anticoagulants (DOACs)

- **Rivaroxaban and Apixaban (factor Xa inhibitors):** Directly block factor Xa, so thrombin cannot be made. Oral, fixed dose, no routine INR monitoring, rapid on/off. Uses: atrial fibrillation, DVT/PE treatment and prevention, post-surgical prevention. Adverse effects: bleeding (no dietary restrictions like warfarin). Specific reversal agent concept: andexanet alfa (confirm availability against current references).
- **Dabigatran (direct thrombin inhibitor):** Directly blocks thrombin (factor IIa). Oral prodrug. Uses: atrial fibrillation, DVT/PE. Adverse effects: bleeding; stomach upset; contraindicated in severe kidney failure (it is cleared by kidneys). Reversal concept: idarucizumab.
- **Advantage over warfarin:** No food interactions, fewer drug interactions, no monitoring, faster action.
- **Disadvantage:** Higher cost; dose depends on kidney function.

Diagram — Coagulation cascade and drug targets (draw as a flow)

> Vessel injury
> ↓
> Platelet plug ← blocked by aspirin, clopidogrel, ticagrelor, GP IIb/IIIa blockers
> ↓
> Factors X → Xa ← blocked by rivaroxaban, apixaban, LMW heparins
> ↓
> Prothrombin → THROMBIN ← blocked by dabigatran, heparin
> ↓
> Fibrinogen → FIBRIN CLOT
> ↓
> Plasmin dissolves clot ← fibrinolytics work here (Chapter 2)

Warfarin acts upstream: it stops the liver from making factors II, VII, IX, X.

Flowchart — Choosing anti-thrombotic therapy (simplified concept)

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Patient at risk of clot
  ├─ Arterial clot (heart attack/stroke) → ANTI-PLATELETS (aspirin ± clopidogrel)
  └─ Venous clot / AF / valves → ANTICOAGULANTS
      ├─ Acute/hospital → heparin (IV) → then
      └─ Long-term oral → warfarin (valves, cheap) or DOACs (AF, DVT)
```

Coagulants

Coagulant	Role
Vitamin K (phytonadione)	Treatment of vitamin K deficiency bleeding; reversal of warfarin overdose
Fibrinogen (concentrate)	Replaces fibrinogen in severe bleeding/disseminated intravascular coagulation
Anti-haemophilic factors	Factor VIII concentrate for haemophilia A; factor IX for haemophilia B; used to stop or prevent bleeding episodes

- **Uses in short:** Bleeding disorders and reversal of excessive anticoagulation.

Infographic Concept Box — "Clot Busters vs Clot Blockers"

REMEMBER: Anti-platelets stop the PLATELET PLUG • Anticoagulants stop the FIBRIN CEMENT • Fibrinolytics (Chapter 2) DISSOLVE the finished clot. Aspirin = irreversible COX-1 blocker. Clopidogrel = ADP blocker (prodrug). Warfarin = vitamin K blocker (slow, INR-monitored, reversed by vitamin K). Heparin = antithrombin booster (fast, aPTT-monitored, reversed by protamine). DOACs = direct Xa or thrombin blockers (no monitoring, no food rules).

Examples

1. A 58-year-old man after a heart stent: aspirin + clopidogrel (dual anti-platelet therapy) for about a year.
2. A 65-year-old woman with atrial fibrillation: warfarin (INR 2–3) or apixaban — prevents stroke.
3. A patient with DVT in hospital: heparin IV infusion (aPTT monitored), then shifted to warfarin or a DOAC.
4. Warfarin patient starts an antibiotic course and notices gum bleeding — INR likely risen; needs a check.

Pharmacy Relevance

- Pharmacists counsel warfarin patients on diet consistency, interacting medicines, and INR schedules.
- Heparin and LMWH dosing is weight-based — pharmacists verify calculations.
- DOACs need kidney-function checks before dispensing (especially dabigatran).
- In an emergency bleed on warfarin, the pharmacist ensures vitamin K or PCC is available.
- Anti-platelet "dual therapy" duration after stents is a frequent counselling point.

India Context

- Rheumatic heart disease still causes valve replacements in India, where warfarin remains the affordable long-term anticoagulant; DOACs are costlier but increasingly used in cities.
- Aspirin and clopidogrel are widely available as low-cost generics (including through Jan Aushadhi stores); several cardiovascular drugs are on the National List of Essential Medicines (NLEM) — confirm current list against official references.
- Pharmacists should promote generic prescribing and counsel in the patient's language about bleeding warning signs (unusual bruising, blood in urine/stool, prolonged bleeding from cuts).

Key Points

1. Anti-platelets act on the platelet plug; anticoagulants act on the fibrin cascade.
2. Aspirin irreversibly blocks COX-1 → no thromboxane A2 → effect lasts 7–10 days.
3. Clopidogrel blocks ADP receptors (prodrug, slow); ticagrelor blocks the same receptor directly and reversibly (fast).
4. GP IIb/IIIa blockers are IV-only hospital drugs — the most potent anti-platelets.
5. Heparin needs antithrombin, acts fast, is monitored by aPTT, and is reversed by protamine.
6. Warfarin blocks vitamin K recycling → factors II, VII, IX, X fall → monitored by INR → reversed by vitamin K.
7. Warfarin has many food and drug interactions; DOACs have almost none.
8. Rivaroxaban/apixaban = factor Xa inhibitors; dabigatran = thrombin inhibitor.
9. Warfarin is teratogenic — never in pregnancy.

Common Confusions

- **Anti-platelet vs anticoagulant:** Both prevent clots but at different stages — arterial clots get anti-platelets, venous clots/AF get anticoagulants.
- **Heparin vs warfarin:** Heparin is fast/IV/monitored by aPTT; warfarin is slow/oral/monitored by INR. They are not interchangeable.
- **Aspirin dose:** Low dose (75–150 mg) is anti-platelet; high dose is analgesic — different jobs.
- **Clopidogrel vs ticagrelor:** Same receptor, different pharmacology (prodrug/irreversible vs direct/reversible).

Common Mistakes

1. Saying aspirin "thins the blood" — it reduces platelet stickiness; it does not thin blood.
2. Forgetting warfarin's slow onset — it takes days; heparin bridges the gap in emergencies.
3. Giving warfarin in pregnancy — it causes birth defects.
4. Ignoring new medicines in a warfarin patient — always recheck INR.

Mnemonics

- **Aspirin — "COX gone, TXA2 gone":** no thromboxane, no aggregation.
- **Clopidogrel — "CLOP the ADP":** blocks the ADP receptor.
- **Warfarin factors — "1972":** factors II, VII, IX, X need vitamin K.
- **Heparin monitoring — "aPTT for Heparin, INR for Warfarin":** H goes with aPTT, W goes with INR (alphabetical pairing trick).
- **Reversal — "Vitamin K kills Warfarin; Protamine punishes Heparin."**

Exam Summary

Anti-platelet drugs (aspirin — irreversible COX-1; clopidogrel — ADP blocker prodrug; ticagrelor — direct reversible ADP blocker; abciximab/tirofiban — IV GP IIb/IIIa blockers; dipyridamole — PDE inhibitor) prevent arterial clots. Anticoagulants (heparin — antithrombin booster, aPTT-monitored, protamine-reversed; LMWH — mainly anti-Xa; warfarin — vitamin K antagonist, INR-monitored, vitamin K-reversed, many interactions, teratogenic; rivaroxaban/apixaban — oral Xa inhibitors; dabigatran — oral thrombin inhibitor) prevent venous clots and stroke in AF. Coagulants (vitamin K, fibrinogen, factor VIII/IX) treat bleeding.

One-Minute Revision

Platelet plug → aspirin/clopidogrel/ticagrelor/GP blockers. Cascade → heparin (aPTT), warfarin (INR), DOACs (no monitoring). 1972 = vitamin-K factors. Reversal: protamine–heparin, vitamin K–warfarin. Never warfarin in pregnancy.

Exam Questions

> **Short-answer:**

1. Why is aspirin's anti-platelet effect irreversible, and how long does it last?
2. State the mechanism of action of clopidogrel. Why is its onset slow?
3. Name two GP IIb/IIIa inhibitors and their route of administration.
4. How does heparin produce its anticoagulant effect? Which test monitors it?
5. Which clotting factors depend on vitamin K? How does warfarin affect them?
6. Name two factor Xa inhibitor DOACs and one direct thrombin inhibitor.

> **Long-answer:**

1. Classify anti-platelet drugs. Describe the mechanism, uses and adverse effects of aspirin, clopidogrel and ticagrelor.
2. Compare heparin, low molecular weight heparins, warfarin and DOACs with respect to mechanism, monitoring, reversal and interactions.
3. Discuss warfarin in detail: mechanism, therapeutic uses, monitoring, adverse effects and important drug interactions.
4. Write short notes on: (a) GP IIb/IIIa inhibitors, (b) coagulants.

> **MCQs (with answer key):**

1. Aspirin produces its anti-platelet effect by inhibiting: a) ADP receptor b) COX-1 enzyme c) GP IIb/IIIa receptor d) Phosphodiesterase — **Answer: b**
2. Which anti-platelet drug is a prodrug requiring liver activation? a) Aspirin b) Ticagrelor c) Clopidogrel d) Dipyridamole — **Answer: c**
3. Heparin acts by: a) Blocking vitamin K b) Potentiating antithrombin III c) Directly inhibiting thrombin d) Dissolving fibrin — **Answer: b**
4. The antidote for heparin overdose is: a) Vitamin K b) Protamine sulfate c) Aminocaproic acid d) Desmopressin — **Answer: b**
5. Warfarin therapy is monitored using: a) aPTT b) Bleeding time c) INR d) Platelet count — **Answer: c**
6. Which drug is a direct thrombin inhibitor? a) Rivaroxaban b) Apixaban c) Dabigatran d) Enoxaparin — **Answer: c**
7. Vitamin K-dependent clotting factors are: a) I, V, VIII, XI b) II, VII, IX, X c) III, IV, V, VI d) II, V, VII, VIII — **Answer: b**
8. Which statement about ticagrelor is TRUE? a) It is a prodrug b) It irreversibly blocks P2Y12 c) It acts directly and reversibly d) It is given IV — **Answer: c**

Viva questions:

1. Why can't aspirin be given to children with viral fever?
2. What is HIT? Why is it paradoxical?
3. Why does warfarin take 3–5 days to act?
4. A warfarin patient eats a large amount of spinach daily — what happens to INR?
5. Which anticoagulant is preferred in pregnancy and why?

Application-based:

1. A patient on warfarin (INR 2.5) is prescribed metronidazole for an infection. What problem may occur and what would you advise?
2. A 70-year-old with AF and poor kidney function needs anticoagulation. Compare warfarin vs dabigatran for this patient.
3. After a coronary stent, why are two anti-platelet drugs given instead of one?

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CHAPTER 2

Fibrinolytics, Plasma Expanders, Haematinics and Anti-hyperlipidaemic Drugs

Learning Objectives

After studying this chapter, the student will be able to:

1. Explain fibrinolysis and the mechanism of streptokinase, alteplase, urokinase and tenecteplase.
2. List plasma expanders, their properties and uses in hypovolaemia.
3. Classify haematinics and explain the difference between iron-deficiency and megaloblastic anaemia.
4. Describe iron preparations, folic acid, vitamin B12 and erythropoietin.
5. Classify anti-hyperlipidaemic drugs and explain statin pharmacology in detail.

Definitions

- **Fibrinolytic (thrombolytic):** A drug that activates plasminogen to plasmin, which dissolves fibrin clots.
- **Plasma expander:** A large-molecule solution given intravenously to restore blood volume in shock or blood loss (a plasma substitute).
- **Haematinic:** A drug that improves the quantity or quality of red blood cells — used to treat anaemia.
- **Anaemia:** Low haemoglobin/red cell count reducing the blood's oxygen-carrying capacity.
- **Hyperlipidaemia:** Abnormally high blood lipids (cholesterol, triglycerides) — a major risk factor for atherosclerosis and heart disease.
- **Atherosclerosis:** Thickening and hardening of artery walls by cholesterol plaques.

Terminology

- **Plasminogen/plasmin:** Inactive precursor / active enzyme that digests fibrin.
- **Streptokinase:** A bacterial protein that activates plasminogen (non-specific, antigenic).
- **tPA (tissue plasminogen activator):** Alteplase and tenecteplase — more clot-specific activators.
- **Hypovolaemia:** Low circulating blood volume (bleeding, burns, dehydration).
- **Colloid vs crystalloid:** Colloids (albumin, dextran) stay in vessels longer; crystalloids (saline) leak out faster.
- **Ferritin/serum iron:** Tests showing body iron stores.
- **LDL/HDL:** "Bad" cholesterol (deposits in arteries) / "good" cholesterol (removes it).
- **HMG-CoA reductase:** The key enzyme of cholesterol synthesis in the liver — the statin target.
- **PCSK9:** A protein that destroys LDL receptors; blocking it lowers LDL strongly.

PART A — FIBRINOLYTICS

Explanation

Once a clot has formed, the body slowly dissolves it with plasmin. Fibrinolytic drugs speed this up by converting more plasminogen into plasmin. They are used as an emergency — "clot busters" — mainly in heart attack (MI) and ischaemic stroke, where every minute of blocked blood flow kills tissue.

Classification

Type	Examples	Feature
Non-fibrin-specific	Streptokinase, urokinase	Activate plasminogen everywhere (systemic effect)
Fibrin-specific (tPA)	Alteplase, tenecteplase, reteplase (concept)	Prefer clot-bound plasminogen (more targeted)

Individual drugs

- **Streptokinase:** From streptococci bacteria. Forms a complex with plasminogen that activates other plasminogen molecules. Cheap and widely used in India. Antigenic — antibodies form, so it cannot be repeated within about 6–12 months, and allergic reactions occur. Given IV (typical regimens exist — confirm against current references).
- **Alteplase (tPA):** Recombinant human tissue plasminogen activator. Binds fibrin in the clot and activates plasminogen there — more clot-specific, less systemic bleeding risk. Not antigenic; can be repeated. Expensive.
- **Urokinase:** A human enzyme from kidney cells; directly activates plasminogen. Non-antigenic but costly.
- **Tenecteplase:** A modified tPA — longer half-life (single IV bolus), more fibrin-specific, more resistant to inhibitors. Convenient for emergency use.
- **Pharmacological effect:** Rapid clot dissolution, restoring blood flow.
- **Uses:** Acute myocardial infarction (within the "golden hours"), acute ischaemic stroke (alteplase/tenecteplase, within a few hours), massive pulmonary embolism.
- **Adverse effects:** Bleeding (including brain haemorrhage — the main danger); allergic reactions (streptokinase); low blood pressure.
- **Contraindications (concept):** Active bleeding, recent surgery/stroke, uncontrolled hypertension — because dissolving clots in these situations is dangerous.

Analogy

> - **Drain cleaner:** A fibrinolytic is like a chemical drain cleaner poured into a blocked pipe — it dissolves the blockage so flow returns.

Flowchart — Fibrinolysis



PART B — PLASMA EXPANDERS

Explanation

In severe bleeding, burns or shock, blood volume falls (hypovolaemia) and blood pressure collapses. Plasma expanders are large molecules infused IV that hold water inside blood vessels by oncotic pressure, restoring volume until blood transfusion or definitive treatment is possible. They carry no oxygen — they buy time.

Classification and properties

Expander	Type	Key points
Human albumin	Natural protein	Expensive; safe; no infection risk in modern preparations
Dextran (40, 70)	Polysaccharide	Cheap; can interfere with blood cross-matching; allergic reactions possible
Gelatin (e.g., polygeline)	Protein-derived	Shorter action; allergy risk
Hydroxyethyl starch (HES)	Synthetic starch	Longer action; concerns about kidney injury and bleeding with large doses

- **Uses:** Hypovolaemic shock, burns, fluid resuscitation during surgery, plasma replacement.
- **Adverse effects:** Allergic/anaphylactic reactions (dextran, gelatin); fluid overload; HES — kidney injury and coagulation disturbance with heavy use; dextran can coat red cells and confuse blood grouping.
- **Analogy:** Like adding thick syrup to a leaking tank — the thick fluid stays in the tank longer than plain water (saline).

PART C — HAEMATINICS

Explanation: Two main anaemias

- **Iron-deficiency anaemia:** Not enough iron → red cells are small and pale (microcytic). Commonest cause worldwide: blood loss (heavy periods, hookworm), poor diet, pregnancy demand.
- **Megaloblastic anaemia:** Deficiency of vitamin B12 or folic acid → DNA synthesis fails → red cells are large and immature (megaloblasts). Causes: poor diet (B12 in strict vegetarians), pernicious anaemia (no intrinsic factor to absorb B12), pregnancy (folate demand), certain drugs.

Simple rule: Small pale cells = iron problem. Big immature cells = B12/folate problem. Never give folic acid alone when B12 deficiency is possible — it corrects the blood picture but lets nerve damage progress.

Classification of haematinics

1. **Iron preparations** — ferrous sulfate, ferrous fumarate (oral); iron dextran, ferric carboxymaltose (IV, concept)
2. **Folic acid**
3. **Vitamin B12 (cyanocobalamin, hydroxocobalamin)**
4. **Erythropoietin (recombinant human EPO)** — stimulates red cell production in the bone marrow

Individual drugs

- **Ferrous sulfate / ferrous fumarate:** Oral iron of choice. Absorbed best on an empty stomach but that causes nausea — so often taken with food despite lower absorption. Vitamin C improves absorption; antacids, calcium, tea/coffee reduce it. Adverse effects: black stools (harmless — warn the patient!), constipation, nausea, metallic taste. Acute iron poisoning in children is dangerous — keep tablets away from children.
- **Iron dextran (IV):** For patients who cannot tolerate or absorb oral iron, or with major blood loss. Given IV/IM with a test dose (allergy risk). Bypasses gut absorption limits.
- **Folic acid:** Needed for DNA synthesis. Uses: megaloblastic anaemia due to folate deficiency, pregnancy (prevents neural tube defects in the baby), with certain drugs (e.g., methotrexate concept). Very safe; masks B12 deficiency if given alone — always rule out B12 deficiency first.
- **Vitamin B12:** Needed for DNA synthesis and nerve health. Deficiency causes megaloblastic anaemia plus nerve damage (tingling, numbness). Given orally (mild deficiency) or by injection (pernicious anaemia, lifelong). Safe — excess is excreted.
- **Erythropoietin (EPO):** A hormone (made by kidneys) that tells bone marrow to make red cells. Recombinant EPO is used in chronic kidney disease anaemia, chemotherapy-related anaemia, and to reduce transfusions. Given by injection. Adverse effects: high blood pressure, increased clot risk, and misuse in sports doping.

Table — Iron deficiency vs megaloblastic anaemia

Feature	Iron deficiency	Megaloblastic (B12/folate)
Cell size	Small (microcytic)	Large (macrocytic)
Cause	Blood loss, poor intake, pregnancy	B12/folate deficiency
Treatment	Iron	B12 and/or folate
Nerve symptoms	No	Yes (B12 deficiency)
Key warning	—	Folate alone hides B12 nerve damage

PART D — ANTI-HYPERLIPIDAEMIC DRUGS

Explanation

Cholesterol is made mainly in the liver and also absorbed from food. LDL ("bad") cholesterol deposits in artery walls forming plaques (atherosclerosis), causing heart attacks and strokes. Drugs lower lipids by: blocking liver synthesis (statins), blocking gut absorption (ezetimibe), increasing clearance (PCSK9 inhibitors), or lowering triglycerides (fibrates, niacin).

Classification

Class	Examples	Main effect
HMG-CoA reductase inhibitors (statins)	Atorvastatin, rosuvastatin, simvastatin	Lower LDL strongly
Cholesterol absorption inhibitor	Ezetimibe	Lowers LDL modestly
Fibrates	Fenofibrate, gemfibrozil	Lower triglycerides
Niacin (nicotinic acid)	Niacin	Lowers triglycerides, raises HDL
Bile-acid sequestrants	Cholestyramine, colestipol	Lower LDL
PCSK9 inhibitors	Evolocumab, alirocumab (concept)	Lower LDL powerfully (injectable)

1. Statins (Atorvastatin, Rosuvastatin)

- **Mechanism:** Inhibit HMG-CoA reductase — the rate-limiting enzyme of cholesterol synthesis in the liver ("cholesterol factory shutdown"). Liver cells then make more LDL receptors, pulling LDL out of the blood.
- **Pharmacological effects:** Strong LDL reduction; modest triglyceride lowering; slight HDL rise; additional "pleiotropic" benefits — stabilise plaques, reduce inflammation.
- **Uses:** High LDL cholesterol; prevention of heart attack and stroke (primary and secondary); after MI, in diabetes with risk factors. Taken at night for older statins (cholesterol synthesis peaks at night); atorvastatin/rosuvastatin work any time.
- **Adverse effects:** Muscle pain and rarely muscle breakdown (rhabdomyolysis — warn about unexplained muscle pain); raised liver enzymes (monitor); new-onset diabetes risk in predisposed patients; contraindicated in pregnancy.
- **Interactions:** Grapefruit juice and CYP3A4 inhibitors raise statin levels (simvastatin, atorvastatin); gemfibrozil + statin raises muscle-toxicity risk.

2. Ezetimibe

- Blocks cholesterol absorption in the intestine (NPC1L1 transporter). Modest LDL lowering; often added to a statin when targets aren't met. Well tolerated.

3. Fibrates (Fenofibrate)

- Activate PPAR-alpha → lower triglycerides strongly, raise HDL. Used mainly for high triglycerides. Adverse effects: stomach upset, gallstones, muscle issues (especially combined with statins).

4. Niacin (Nicotinic acid)

- Lowers triglycerides and raises HDL the most of any drug, but flushing (red, hot face), itching and liver effects limit use.

5. Bile-acid sequestrants (Cholestyramine)

- Bind bile acids in the gut so they are excreted; the liver uses cholesterol to make more bile acids → LDL falls. Not absorbed — safe in pregnancy and children. Adverse effects: constipation, bloating, and they bind other drugs — take other medicines 1–2 hours apart.

6. PCSK9 inhibitors (concept)

- Monoclonal antibodies (injections every 2–4 weeks) that block PCSK9, so LDL receptors survive longer and clear more LDL. Very powerful LDL lowering; used in familial high cholesterol or when statins aren't enough. Expensive.

Analogy

- **Cholesterol factory shutdown:** Statins switch off the liver's cholesterol factory; the liver then opens more "loading docks" (LDL receptors) to pull cholesterol out of the blood.
- **Sponge in the gut:** Cholestyramine is like a sponge soaking up bile acids so they leave the body, forcing the liver to burn cholesterol making new ones.

Diagram — Where lipid drugs act (draw as a flow)

```
Food cholesterol → INTESTINE --(ezetimibe blocks here)--> absorbed
                          ↓
LIVER: makes cholesterol --(STATINS block here)--> packaged into LDL
                          ↓
Blood LDL → artery walls (plaque)  ← cleared by LDL receptors
                          ↑ (PCSK9 inhibitors keep receptors alive)
Bile acids → GUT --(cholestyramine binds here)--> excreted
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Infographic Concept Box — "Blood Builders and Fat Fighters"

CLOT BUSTERS: Streptokinase (cheap, allergic, one-time) • Alteplase/tenecteplase (clot-specific, pricey, stroke/MI). **VOLUME:** Albumin, dextran, gelatin, HES — hold water in vessels during shock; carry NO oxygen. **ANAEMIA:** Small pale cells → IRON (warn: black stools, keep from children). Big cells → B12 + FOLATE (never folate alone — nerves!). **CHOLESTEROL:** Statins shut the liver factory (atorvastatin, rosuvastatin); muscle pain = red flag; ezetimibe blocks gut uptake; fibrates cut triglycerides.

Examples

1. A 50-year-old man reaches hospital 2 hours after a heart attack: streptokinase IV to dissolve the clot (if no contraindications).
2. A pregnant woman with Hb 8 g/dL: ferrous sulfate + folic acid tablets (standard antenatal care in India).
3. A strict vegetarian elderly man with numbness in feet and large red cells: vitamin B12 injections (not folate alone).
4. A 55-year-old diabetic with LDL 160 mg/dL: atorvastatin at night; counselled about muscle pain.
5. A road-accident patient in shock: IV fluids + plasma expander while blood is arranged.

Pharmacy Relevance

- Pharmacists dispense iron–folic acid under national anaemia programmes and counsel mothers on compliance (black stools are normal).
- Streptokinase storage, reconstitution and "golden hour" urgency are hospital-pharmacy responsibilities.
- Statin counselling: take regularly, report muscle pain, avoid excess alcohol, continue diet/exercise.
- Cholestyramine must be separated from other drugs — a classic counselling point.
- EPO is a cold-chain injectable used in dialysis units.

India Context

- Anaemia is a massive public health burden in India — a large proportion of women of reproductive age and young children are anaemic (confirm current NFHS figures against official reports). The Anaemia Mukt Bharat programme supplies iron–folic acid through health centres; pharmacists support compliance and deworming advice (hookworm causes iron loss).
- Streptokinase remains the workhorse clot-buster in many Indian hospitals because of its low cost; tenecteplase single-bolus use is growing in better-equipped centres.
- Atorvastatin and rosuvastatin are available as inexpensive generics through Jan Aushadhi stores; statins and iron–folic acid feature in the NLEM (confirm current list).
- Pharmacists should promote generic prescribing and counsel in simple local language.

Key Points

1. Fibrinolytics convert plasminogen → plasmin → dissolve clots; used in MI and ischaemic stroke.
2. Streptokinase is cheap but antigenic (single use); alteplase/tenecteplase are clot-specific and non-antigenic.
3. Plasma expanders restore volume in shock but carry no oxygen.
4. Iron deficiency = small pale cells; B12/folate deficiency = large cells + possible nerve damage.
5. Never give folic acid alone in suspected B12 deficiency.
6. Statins block HMG-CoA reductase; watch for muscle pain and liver effects.
7. Ezetimibe blocks gut cholesterol uptake; fibrates lower triglycerides; cholestyramine binds bile acids.

Common Confusions

- **Streptokinase vs heparin:** Streptokinase dissolves existing clots; heparin only prevents new ones.
- **Plasma expander vs blood transfusion:** Expanders restore volume only; only blood carries oxygen.
- **Iron vs folic acid:** They treat different anaemias — check cell size before choosing.
- **Statins vs fibrates:** Statins mainly lower LDL; fibrates mainly lower triglycerides.

Common Mistakes

1. Repeating streptokinase within months — antibodies make it ineffective and risky.
2. Giving folate alone for B12-deficiency anaemia — nerve damage continues silently.
3. Stopping statins because "cholesterol is normal now" — the drug is keeping it normal.
4. Forgetting cholestyramine binds other drugs — separate dosing times.

Mnemonics

- **Fibrinolytics — "SAT Urgent":** Streptokinase, Alteplase, Tenecteplase (and Urokinase) — urgent clot busters.
- **Anaemia cells — "Small = Steel (iron); Big = B (B12)":** microcytic = iron, macrocytic = B12/folate.
- **Statin names — "A ROSe for cholesterol":** Atorvastatin, Rosuvastatin.
- **Folate warning — "Folate hides, B12 dies":** folate masks the blood picture while nerves suffer.

Exam Summary

Fibrinolytics (streptokinase — cheap, antigenic; alteplase/tenecteplase — fibrin-specific; urokinase) dissolve clots in MI/stroke. Plasma expanders (albumin, dextran, gelatin, HES) restore volume in shock without carrying oxygen. Haematinics: oral/IV iron for microcytic anaemia; B12 + folate for megaloblastic anaemia (never folate alone); EPO for kidney-disease anaemia. Lipid drugs: statins (HMG-CoA blockers, LDL↓), ezetimibe (gut uptake↓), fibrates (triglycerides↓), niacin (HDL↑), cholestyramine (bile-acid binder), PCSK9 inhibitors (powerful LDL↓, injectable).

One-Minute Revision

Clot busters: SAT-U (streptokinase cheap/one-time; alteplase/tenecteplase specific). Volume: albumin/dextran/gelatin/HES — no oxygen. Anaemia: small cells = iron (black stools OK); big cells = B12 + folate (folate alone = nerve danger). Lipids: statins shut factory (muscle pain = alert); ezetimibe gut; fibrates triglycerides; cholestyramine sponge.

Exam Questions

> **Short-answer:**

1. How do fibrinolytic drugs dissolve a clot? Name two with one difference between them.
2. Why can't streptokinase be repeated within a year?
3. Name four plasma expanders and state one use.
4. Differentiate iron-deficiency anaemia from megaloblastic anaemia (any four points).
5. Why should folic acid not be given alone in vitamin B12 deficiency?
6. Explain the mechanism of action of statins.
7. What is the mechanism of ezetimibe? When is it used?

> **Long-answer:**

1. Classify fibrinolytic drugs. Describe streptokinase and alteplase (mechanism, uses, adverse effects) and compare them.
2. Classify haematinics. Discuss iron preparations, folic acid, vitamin B12 and erythropoietin with therapeutic uses and adverse effects.
3. Classify anti-hyperlipidaemic drugs. Discuss statins in detail (mechanism, effects, uses, adverse effects, interactions).

> **MCQs (with answer key):**

1. Streptokinase acts by: a) Inhibiting thrombin b) Activating plasminogen to plasmin c) Blocking platelets d) Binding fibrinogen — **Answer: b**
2. Which fibrinolytic is most fibrin-specific? a) Streptokinase b) Urokinase c) Alteplase d) Heparin — **Answer: c**
3. A plasma expander is used for: a) Carrying oxygen b) Restoring blood volume in shock c) Dissolving clots d) Raising haemoglobin — **Answer: b**
4. Black stools in a patient on iron therapy indicate: a) GI bleeding — stop drug b) Normal harmless effect c) Iron poisoning d) Drug interaction — **Answer: b**
5. Megaloblastic anaemia is caused by deficiency of: a) Iron b) Vitamin B12 or folic acid c) Vitamin K d) Calcium — **Answer: b**
6. Statins lower cholesterol by inhibiting: a) Lipoprotein lipase b) HMG-CoA reductase c) Pancreatic lipase d) NPC1L1 — **Answer: b**
7. Which drug mainly lowers triglycerides? a) Atorvastatin b) Fenofibrate c) Ezetimibe d) Cholestyramine — **Answer: b**
8. Cholestyramine should be taken apart from other drugs because it: a) Increases their absorption b) Binds them in the gut c) Destroys them in blood d) Speeds their excretion by kidneys — **Answer: b**

> **Viva questions:**

1. What is the "golden hour" concept in MI thrombolysis?
2. Why is a test dose given before iron dextran?
3. A patient on EPO develops high BP — explain.
4. Why are statins contraindicated in pregnancy?
5. Which anaemia shows neurological symptoms and why?

> **Application-based:**

1. A rural hospital has only streptokinase for a heart-attack patient who received it 4 months ago. What is the problem and the alternative?
2. A pregnant woman (Hb 9 g/dL) is prescribed iron tablets but stops due to constipation. Counsel her.
3. A patient on simvastatin starts drinking large amounts of grapefruit juice and develops muscle pain. Explain.

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CHAPTER 3

Diuretics and Anti-diuretics

Learning Objectives

After studying this chapter, the student will be able to:

1. Describe the nephron segments and what each reabsorbs.
2. Classify diuretics by site of action with examples.
3. Explain the mechanism of each diuretic class at its nephron site.
4. List therapeutic uses and adverse effects of each class.
5. Explain anti-diuretics (vasopressin, desmopressin) and the paradoxical use of thiazides in diabetes insipidus.

Definitions

- **Diuretic:** A drug that increases urine output by increasing sodium and water excretion by the kidneys.
- **Nephron:** The kidney's functional unit — a tiny filter (glomerulus) plus a tubule that reabsorbs what the body needs.
- **Anti-diuretic:** A drug that reduces urine output (e.g., vasopressin/ADH and desmopressin).
- **Diabetes insipidus:** A condition of passing large volumes of dilute urine due to lack of ADH (central) or kidney resistance to ADH (nephrogenic).
- **GFR:** Glomerular filtration rate — how much fluid the kidneys filter per minute.

Terminology

- **Proximal convoluted tubule (PCT):** First tubule segment; reabsorbs ~65% of filtered sodium and water.
- **Loop of Henle (thick ascending limb):** Reabsorbs ~25% via the Na^+-K^+-$2Cl^-$ co-transporter — the loop diuretic target.
- **Distal convoluted tubule (DCT):** Reabsorbs ~7% via the Na^+-Cl^- co-transporter — the thiazide target.
- **Collecting duct:** Final segment; aldosterone-controlled Na^+ reabsorption in exchange for K^+ — the potassium-sparing target.
- **ADH (vasopressin):** Hormone that inserts water channels (aquaporins) in the collecting duct to conserve water.
- **Carbonic anhydrase:** Enzyme in the PCT that helps reabsorb bicarbonate.
- **Ototoxicity:** Ear damage causing hearing loss — a risk of rapid IV loop diuretics.
- **Gout:** Joint disease from high uric acid — worsened by thiazides and loop diuretics.

Explanation: The nephron as a water-filtering factory

Imagine the nephron as a factory assembly line. About 180 litres of fluid are filtered daily at the glomerulus, but only 1–2 litres leave as urine — the tubule reclaims the rest:

1. **PCT:** Reclaims ~65% of sodium/water + bicarbonate (carbonic anhydrase helps).
2. **Loop of Henle (thick ascending limb):** Reclaims ~25% via the Na^+-K^+-$2Cl^-$ pump.
3. **DCT:** Reclaims ~7% via the Na^+-Cl^- pump.
4. **Collecting duct:** Fine-tunes the last few percent — aldosterone swaps Na^+ for K^+; ADH opens water channels.

Diuretics block reabsorption at one of these stations, so more salt and water escape as urine. **Simple rule: the earlier the blockade, the stronger the diuresis** — loop diuretics (25% station) are the most powerful.

Analogy

- **Factory assembly line:** Each nephron segment is a workstation reclaiming water. Diuretics are workers who go on strike at one station — whatever that station would have reclaimed flows out as urine.
- **Leaky bucket brigade:** Blocking the big early buckets (loop) spills far more water than blocking the small late ones (collecting duct).

Classification (by site of action)

Class	Site	Examples	Strength
Carbonic anhydrase inhibitors	PCT	Acetazolamide	Weak
Loop diuretics	Thick ascending limb of Henle	Furosemide, torsemide, bumetanide	Most powerful
Thiazides & thiazide-like	DCT	Hydrochlorothiazide, chlorthalidone, indapamide	Moderate
Potassium-sparing	Collecting duct	Spironolactone, amiloride, triamterene	Weak
Osmotic diuretics	Whole tubule (non-reabsorbable)	Mannitol	Special uses

1. Carbonic Anhydrase Inhibitors — Acetazolamide

- **Mechanism:** Inhibits carbonic anhydrase in the PCT → bicarbonate (and with it sodium and water) is lost in urine; urine becomes alkaline.
- **Uses:** Glaucoma (reduces eye fluid/aqueous humour), acute mountain sickness, metabolic alkalosis correction, some epilepsies (concept). Weak diuretic — tolerance develops quickly.
- **Adverse effects:** Metabolic acidosis, potassium loss, tingling of fingers/toes, drowsiness, kidney stones with long use.

2. Loop Diuretics — Furosemide, Torsemide, Bumetanide

- **Mechanism:** Block the Na^+-K^+-$2Cl^-$ co-transporter in the thick ascending limb of Henle → massive sodium, chloride, potassium, calcium and magnesium loss with water. Also dilate veins (useful in pulmonary oedema even before diuresis starts).
- **Pharmacological effects:** Most powerful diuretics ("high-ceiling"); rapid onset (IV furosemide acts within minutes); effective even when kidney function is poor.
- **Uses:** Acute pulmonary oedema and heart failure; severe hypertension emergencies; oedema of kidney/liver disease; hypercalcaemia (flushes calcium out).
- **Adverse effects:** Low potassium (hypokalaemia — muscle weakness, cramps, cardiac rhythm risk), low sodium, dehydration, low blood pressure, high uric acid (gout), high blood sugar, hearing loss/ototoxicity (especially rapid IV injection or combined with aminoglycosides), low calcium/magnesium.
- **Key counselling:** Take in the morning (else night-time urination); eat potassium-rich foods or combine with a potassium-sparing diuretic.

3. Thiazides — Hydrochlorothiazide, Chlorthalidone

- **Mechanism:** Block the Na^+-Cl^- co-transporter in the DCT → moderate sodium and water loss; uniquely reduce calcium excretion (urine calcium falls).
- **Uses:** First-line hypertension treatment (chlorthalidone preferred for longer action); mild heart-failure oedema; prevention of calcium kidney stones; paradoxical treatment of diabetes insipidus (see anti-diuretics).
- **Adverse effects:** Low potassium, low sodium, high uric acid (gout), high blood sugar and lipids, impotence in men, allergic rash (sulfonamide-related).
- **Comparison:** Chlorthalidone acts longer than hydrochlorothiazide and is often preferred for blood pressure control.

4. Potassium-Sparing Diuretics — Spironolactone, Amiloride, Triamterene

- **Mechanism:** Act in the collecting duct. Spironolactone blocks the aldosterone receptor (so sodium is not reabsorbed and potassium is not secreted); amiloride/triamterene directly block sodium channels with the same net effect.
- **Pharmacological effects:** Weak diuretics but they SAVE potassium — used to balance the potassium loss of loop/thiazide diuretics.
- **Uses:** Combined with loop/thiazide diuretics; heart failure (spironolactone improves survival — landmark benefit); aldosterone excess (Conn's syndrome); liver cirrhosis with ascites.
- **Adverse effects:** HIGH potassium (hyperkalaemia — dangerous, especially with ACE inhibitors or kidney disease); spironolactone — breast enlargement/tenderness in men (gynaecomastia), menstrual irregularities (anti-androgen effect); amiloride/triamterene — nausea, kidney stones (triamterene).

5. Osmotic Diuretics — Mannitol

- **Mechanism:** Filtered but not reabsorbed; holds water in the tubule by osmosis all along the nephron.
- **Uses:** Reduce brain swelling (raised intracranial pressure) and eye pressure (acute glaucoma); prevent kidney damage from toxins/haemolysis; given IV only.
- **Adverse effects:** Fluid overload initially (it expands blood volume first), dehydration later, electrolyte imbalance, headache.

Diagram — Nephron sites of diuretic action (draw as a tubule map)

GLOMERULUS (filter)
↓
[PCT] ---- Acetazolamide blocks bicarbonate reabsorption here
↓
[Loop of Henle – thick ascending limb] ---- FUROSEMIDE / TORSEMIDE / BUMETANIDE block Na^+-K^+-$2Cl^-$ here (STRONGEST)
↓
[DCT] ---- HYDROCHLOROTHIAZIDE / CHLORTHALIDONE block Na^+-Cl^- here
↓
[Collecting duct] ---- SPIRONOLACTONE / AMILORIDE save K^+ here
↓ (ADH opens water channels here — desmopressin acts here)
URINE OUT
Mannitol works all along the tubule by osmosis.

Flowchart — Choosing a diuretic (simplified concept)

Need diuresis
├— Emergency / severe oedema / poor kidney function → LOOP (furosemide IV)
├— Routine hypertension → THIAZIDE (chlorthalidone/HCTZ)
├— Losing too much K^+ on above → add K^+-SPARING (spironolactone/amiloride)
├— Glaucoma / mountain sickness → ACETAZOLAMIDE
└— Brain swelling → MANNITOL (IV)

Table — Diuretic comparison

Class	K^+ effect	Ca^{2+} effect	Power	Main use
Acetazolamide	Loses K^+	—	Weak	Glaucoma, mountain sickness
Loop	Loses K^+	Loses Ca^{2+}	Strongest	Emergencies, heart failure
Thiazide	Loses K^+	Saves Ca^{2+}	Moderate	Hypertension
K^+-sparing	Saves K^+	—	Weak	With loop/thiazide, heart failure
Mannitol	—	—	Special	Brain swelling

Anti-diuretics

Explanation

Anti-diuretics do the opposite — they reduce urine output. The natural one is ADH (vasopressin) from the pituitary: it inserts water channels (aquaporins) in the collecting duct so water is reabsorbed and urine becomes concentrated.

Vasopressin (ADH)

- **Actions:** V2 receptors in kidney → water reabsorption (anti-diuretic); V1 receptors in vessels → vasoconstriction (raises blood pressure).
- **Uses:** Diabetes insipidus (central type — pituitary fails to make ADH); bleeding oesophageal varices (vasoconstriction); shock (concept).

Desmopressin

- **What it is:** A synthetic ADH analogue — mainly V2 (water) action with little V1 (vessel) action, and longer acting.
- **Mechanism:** Activates V2 receptors → aquaporins inserted → concentrated urine, less volume.
- **Uses:** Central diabetes insipidus (nasal spray/tablet/injection); bed-wetting in children (nocturnal enuresis); mild haemophilia/von Willebrand disease (releases clotting factor VIII — bonus concept).
- **Adverse effects:** Water retention → low sodium (hyponatraemia); headache; nasal irritation (spray). Patients must limit fluid intake.

Paradoxical use of thiazides in diabetes insipidus (concept)

- **The paradox:** Thiazides are diuretics, yet they REDUCE urine volume in diabetes insipidus. How? They cause mild sodium and volume loss → the body compensates by reabsorbing more sodium AND water in the PCT → less fluid reaches the collecting duct → less urine is made.
- **Used in:** Nephrogenic diabetes insipidus (where ADH/desmopressin doesn't work because the kidney ignores ADH).
- **Exam line:** "Thiazides paradoxically reduce polyuria in diabetes insipidus by inducing mild volume depletion, increasing proximal water reabsorption."

Analogy

> - **Tap and plug:** ADH is like pushing the plug into the collecting-duct drain — water stays in the body. Diabetes insipidus is a missing plug (central) or a plug that doesn't fit (nephrogenic).

Infographic Concept Box — "The Nephron Strike Map"

PCT → Acetazolamide (bicarbonate out, weak) • **LOOP** → Furosemide/Torsemide (Na^+-K^+-$2Cl^-$ blocked — STRONGEST, watch K^+ and ears) • **DCT** → Thiazides (Na^+-Cl^- blocked — hypertension's friend, saves calcium) • **COLLECTING DUCT** → Spironolactone/Amiloride (SAVE potassium — watch for HIGH K^+) • **EVERYWHERE** → Mannitol (osmotic — brain swelling). **ANTI:** Desmopressin replaces missing ADH (central DI); thiazides paradoxically help nephrogenic DI.

Examples

1. A 62-year-old with swollen legs and breathlessness (heart failure): furosemide IV, then oral; spironolactone added later.
2. A 50-year-old with newly detected hypertension: chlorthalidone once daily in the morning.
3. A trekker going to high altitude: acetazolamide started a day before ascent (mountain sickness prevention).
4. A head-injury patient with brain swelling: mannitol IV in the ICU.
5. A child passing 6 litres of dilute urine daily with low ADH: desmopressin nasal spray.

Pharmacy Relevance

- Diuretic timing counselling ("morning dose") prevents night-time urination complaints — a top adherence issue.
- Pharmacists monitor potassium: loop/thiazide → supplement or add K^+-sparing; K^+-sparing + ACE inhibitor → watch for hyperkalaemia.
- Furosemide IV must be given slowly to avoid ototoxicity — a nursing/pharmacy coordination point.
- Desmopressin patients must be counselled on fluid restriction to avoid hyponatraemia.

India Context

- Furosemide and hydrochlorothiazide are among the cheapest, most widely used drugs in India — available as low-cost generics including through Jan Aushadhi stores, and listed in the NLEM (confirm current list).
- Hypertension is highly prevalent in Indian adults; thiazides remain a first-line, affordable option in national programme settings.
- Pharmacists should counsel in simple local language about salt restriction, morning dosing, and warning signs (cramps, weakness, dizziness).

Key Points

1. Earlier nephron blockade = stronger diuresis; loop diuretics are the most powerful.
2. Furosemide blocks Na^+-K^+-$2Cl^-$ in the thick ascending limb; watch hypokalaemia and ototoxicity.
3. Thiazides block Na^+-Cl^- in the DCT; first-line for hypertension; reduce urinary calcium.
4. K^+-sparing diuretics (spironolactone, amiloride) save potassium — risk is hyperkalaemia.
5. Acetazolamide: glaucoma, mountain sickness (weak diuretic).
6. Mannitol: IV osmotic diuretic for brain swelling.
7. Desmopressin treats central diabetes insipidus; thiazides paradoxically help nephrogenic DI.

Common Confusions

- **Loop vs thiazide:** Loop = stronger, works in kidney failure; thiazide = milder, fails when GFR is very low.
- **K^+-sparing "weakness":** They are weak diuretics but valuable potassium-savers — never used alone for strong diuresis.
- **Diabetes insipidus vs diabetes mellitus:** Insipidus = water problem (ADH), no sugar; mellitus = sugar problem. Totally different diseases.
- **Why thiazides help DI:** They don't replace ADH — they reduce fluid delivery to the collecting duct.

Common Mistakes

1. Giving furosemide IV too fast — ototoxicity risk.
2. Combining spironolactone with ACE inhibitors without checking potassium — hyperkalaemia danger.
3. Prescribing thiazides in severe kidney failure — they stop working.
4. Dosing diuretics at night — ruins sleep and adherence.

Mnemonics

- **Sites — "P-L-D-C":** Proximal (acetazolamide) → Loop (furosemide) → DCT (thiazide) → Collecting (K^+-sparing).
- **Loop adverse effects — "LOW CaK":** Low K^+, ototoxicity, weak (dehydration); also gout, glucose up.
- **Thiazide — "hyperGLUC":** hyperGlycaemia, hyperLipidaemia, hyperUricaemia (gout), hyperCalcaemia (saves calcium).
- **Spironolactone — "SPIRONO saves K, grows breasts":** K^+-sparing + gynaecomastia warning.

Exam Summary

Diuretics by site: acetazolamide (PCT, carbonic anhydrase — glaucoma, mountain sickness); furosemide/torsemide/bumetanide (loop, Na^+-K^+-$2Cl^-$ — strongest, emergencies); hydrochlorothiazide/chlorthalidone (DCT, Na^+-Cl^- — hypertension); spironolactone/amiloride/triamterene (collecting duct — save K^+); mannitol (osmotic — brain swelling). Anti-diuretics: vasopressin/ADH and desmopressin (V2 → aquaporins) for central diabetes insipidus; thiazides paradoxically reduce urine in nephrogenic DI via proximal compensation.

One-Minute Revision

P-L-D-C: acetazolamide, furosemide (strongest, K^+ loss, ears), thiazide (HTN, saves Ca^{2+}), K^+-sparing (hyperkalaemia risk). Mannitol = brain. Desmopressin = central DI. Thiazide paradox = nephrogenic DI.

Exam Questions

Short-answer:

1. Name the nephron site and transporter blocked by furosemide.
2. Why are loop diuretics called "high-ceiling" diuretics?
3. State two uses of acetazolamide other than diuresis.
4. How does spironolactone spare potassium?
5. What is the paradoxical use of thiazides? Explain briefly.
6. Differentiate central and nephrogenic diabetes insipidus.

Long-answer:

1. Classify diuretics by site of action. Describe the mechanism, uses and adverse effects of loop diuretics and thiazides.
2. Discuss potassium-sparing diuretics and osmotic diuretics with examples.
3. Write short notes on: (a) desmopressin, (b) thiazides in diabetes insipidus.

MCQs (with answer key):

1. Furosemide acts on the: a) PCT b) Thick ascending limb of Henle c) DCT d) Collecting duct — **Answer: b**
2. The transporter blocked by furosemide is: a) Na^+-Cl^- b) Na^+-K^+-$2Cl^-$ c) Aldosterone receptor d) Aquaporin — **Answer: b**
3. Which diuretic reduces urinary calcium excretion? a) Furosemide b) Hydrochlorothiazide c) Spironolactone d) Mannitol — **Answer: b**
4. Gynaecomastia is an adverse effect of: a) Amiloride b) Furosemide c) Spironolactone d) Acetazolamide — **Answer: c**
5. Mannitol is used for: a) Hypertension b) Raised intracranial pressure c) Heart failure d) Gout — **Answer: b**
6. Desmopressin is used in: a) Diabetes mellitus b) Central diabetes insipidus c) Nephrotic syndrome d) Renal stones — **Answer: b**
7. Thiazides paradoxically help diabetes insipidus by: a) Replacing ADH b) Increasing proximal water reabsorption c) Blocking aquaporins d) Increasing GFR — **Answer: b**
8. Ototoxicity is associated with rapid IV injection of: a) Spironolactone b) Furosemide c) Mannitol d) Desmopressin — **Answer: b**

Viva questions:

1. Why should furosemide be taken in the morning?
2. A patient on thiazide develops gout — explain.
3. Why do thiazides fail in severe renal failure?
4. What fluid precaution is needed with desmopressin?
5. Why is mannitol not given orally for diuresis?

Application-based:

1. A heart-failure patient on furosemide complains of muscle cramps and weakness. What is the likely cause and management?
2. A patient on lisinopril is started on spironolactone. What monitoring is essential and why?
3. A trekker to Ladakh asks about preventing mountain sickness. What would you advise?

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