BP206T · B.PHARM THEORY

BP206T Physical Pharmaceutics

Unit I — Solubility, Distribution & Buffers

Pills & Python Notes

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

Syllabus coverage: Unit I (9 hours).

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Chapter 1: Solubility

Learning objectives

After studying this chapter, you will be able to:

1. Define solubility, solute, solvent, saturated, unsaturated and supersaturated solutions.
2. Describe how solubility is expressed in pharmacopoeias.
3. Explain solute–solvent interactions and why "like dissolves like".
4. Describe the solubility of liquids in liquids, solids in liquids and gases in liquids.
5. State and apply Raoult's law.
6. List and explain factors affecting solubility.
7. Describe the measurement of saturation solubility.
8. Explain how pH affects the solubility of weak acids and weak bases, with calculations.

1.1 Definitions — start here

Solution: A homogeneous (uniform throughout) mixture of two or more substances. Example: sugar dissolved in water — every sip tastes the same.

Solute: The substance that gets dissolved (the smaller amount). Example: sugar.

Solvent: The liquid in which the solute dissolves (the larger amount). Example: water.

Solubility: The maximum amount of solute that can dissolve in a given amount of solvent at a fixed temperature (and pressure, for gases). It is a number, e.g., "10 g per 100 mL".

Saturated solution: A solution that holds the maximum amount of dissolved solute at that temperature. Extra solute just sits at the bottom, undissolved.

Unsaturated solution: A solution that can still dissolve more solute.

Supersaturated solution: A solution holding MORE solute than the maximum, made by dissolving at high temperature and cooling carefully. It is unstable — one shake or one crystal can make the extra solute crash out.

> **Terminology alert:** *Dissolution* = the PROCESS of dissolving (rate — how fast). *Solubility* = the AMOUNT that can dissolve (equilibrium — how much). Exam writers love to swap these. Solubility is "how much"; dissolution is "how fast".

> **Analogy:** Solubility is like the seating capacity of a bus. A 40-seat bus can hold at most 40 passengers (saturated). Fewer passengers = unsaturated. Squeezing in 45 by standing = supersaturated — uncomfortable and unstable.

> **Key takeaway:** Solubility answers "how much can dissolve?", not "how fast".

1.2 Expression of solubility (pharmacopoeial language)

Pharmacopoeias (IP — Indian Pharmacopoeia, USP, BP) describe solubility with standard words instead of numbers. Each word means a fixed range of "parts of solvent needed to dissolve 1 part of solute".

Descriptive term	Parts of solvent for 1 part solute
Very soluble	Less than 1
Freely soluble	From 1 to 10
Soluble	From 10 to 30
Sparingly soluble	From 30 to 100
Slightly soluble	From 100 to 1,000
Very slightly soluble	From 1,000 to 10,000
Practically insoluble	10,000 and over

Terminology alert: "Parts" usually means grams of solute per millilitres of solvent (w/v) for solids, or mL per mL (v/v) for liquids.

Worked example 1 — using the table. A drug dissolves 1 g in 250 mL of water. Express its solubility in pharmacopoeial terms.

Step 1: Parts of solvent per part of solute = 250 mL ÷ 1 g = 250 parts. Step 2: Look at the table. 250 falls between 100 and 1,000. Step 3: Answer: **Slightly soluble**.

Worked example 2. 1 g of a drug needs 40 mL of alcohol to dissolve. Term? 40 parts → between 30 and 100 → **Sparingly soluble**.

Pharmacy relevance: The IP monograph of every drug states its solubility. This single line tells the formulator whether a tablet, syrup or injection is even possible for that drug.

1.3 Solute–solvent interactions: "like dissolves like"

Dissolving happens in three steps: (1) solvent molecules separate from each other, (2) solute particles separate from each other, (3) solute and solvent mix. Steps 1 and 2 need energy; step 3 releases energy. Dissolving happens easily when the energy released ≥ the energy needed.

Polarity: A molecule is **polar** if it has unevenly shared electrons, giving it a positive end and a negative end (like water, H_2O). **Non-polar** molecules share electrons evenly (like oils, fats).

Rule — "like dissolves like": Polar solutes dissolve in polar solvents; non-polar solutes dissolve in non-polar solvents. Why? Polar molecules attract each other strongly (hydrogen bonding, dipole forces). A non-polar molecule cannot break into that attraction, so it stays separate — like oil floating on water.

Dielectric constant (ε): A number measuring how well a solvent weakens the attraction between charged particles. Water has a very high dielectric constant (~80), so it separates ions easily — that is why salts dissolve in water. Oils have low dielectric constants (~2), so they dissolve non-polar drugs.

Hydration (solvation): When water molecules surround a dissolved ion, it is called **hydration**. This stabilises the ion and releases energy, helping salts dissolve.

Analogy: Mixing at a party. Polar water molecules are like people who only dance in groups holding hands. A non-polar oil molecule is like someone who wants to dance alone — the group will not let them in, so they stay at the edge (separate layer).

> **Key takeaway:** Match polarities. Water dissolves salts and sugars; oils dissolve fats and non-polar drugs.

1.4 Solubility of liquids in liquids

- **Completely miscible:** Mix in all proportions, e.g., alcohol + water.
- **Partially miscible:** Mix only up to a limit, e.g., phenol + water, ether + water. Beyond the limit, two layers form.
- **Immiscible:** Do not mix at all, e.g., oil + water.

For partially miscible pairs, raising the temperature usually increases miscibility. The temperature at which the two liquids become completely miscible in all proportions is the **critical solution temperature (CST)** — covered in detail in Chapter 2.

1.5 Solubility of solids in liquids

Most solids dissolve better when heated (dissolving absorbs heat — the system "welcomes" extra heat). A few, like calcium salts, dissolve worse when heated.

Factors affecting solubility of solids (also see 1.8):

- Temperature (usually increases solubility)
- Particle size (smaller particles dissolve faster AND slightly more — the surface has higher energy)
- Molecular structure (polar groups like –OH, –COOH increase water solubility; long carbon chains decrease it)
- Crystal form (amorphous forms dissolve better than stable crystals; different polymorphs have different solubilities)

1.6 Solubility of gases in liquids — Henry's law

Gases dissolve better at **high pressure** and **low temperature**.

Henry's law: The amount of gas dissolved in a liquid is directly proportional to the pressure of the gas above the liquid.

Formula: $C = k \times P$, where C = concentration of dissolved gas, P = partial pressure of the gas, k = Henry's law constant.

> **Worked example 3.** At 1 atm pressure, 0.15 g of CO_2 dissolves in 100 mL of water. How much dissolves at 3 atm (same temperature)?
>
> Step 1: $C_1/P_1 = C_2/P_2$ (from $C = kP$). Step 2: $0.15/1 = C_2/3$. Step 3: $C_2 = 0.15 \times 3 =$ **0.45 g per 100 mL**.

> **Analogy:** A cold-drink bottle. It is filled under high CO_2 pressure, so lots of gas stays dissolved. Open it (pressure drops to 1 atm) and the gas escapes as fizz. Warm the bottle and even more gas escapes — gases hate hot liquids.

> **Pharmacy relevance:** Effervescent tablets and carbonated preparations rely on Henry's law. Injectable solutions must have dissolved gases controlled, because bubbles in an IV line are dangerous.

1.7 Raoult's law

Statement: In an ideal solution, the vapour pressure of each component equals the vapour pressure of the pure component multiplied by its mole fraction in the solution.

Formula: $P_A = P°_A \times x_A$, where P_A = vapour pressure of A above the solution, $P°_A$ = vapour pressure of pure A, x_A = mole fraction of A.

Terminology alert: Mole fraction = moles of one component ÷ total moles of all components. **Vapour pressure** = the pressure exerted by the vapour (gas) of a liquid sitting above it in a closed container.

Worked example 4. At 25 °C, the vapour pressure of pure water is 23.8 mmHg. A solution has mole fraction of water = 0.90. Find the vapour pressure of water above the solution.

Step 1: $P = P° \times x = 23.8 \times 0.90$. Step 2: 23.8×0.9 = **21.42 mmHg**.

Worked example 5. Mole fraction of water is 0.98. Vapour pressure = 23.8×0.98 = **23.32 mmHg**.

Key takeaway: Dissolved solute LOWERS vapour pressure (fewer solvent molecules escape). This is why salt water boils at a slightly higher temperature — a colligative property.

Pharmacy relevance: Raoult's law underlies distillation (separating alcohol–water mixtures) and the behaviour of volatile oils and tinctures.

1.8 Factors affecting solubility — full list

Factor	Effect	Example
Temperature	Usually ↑ solubility of solids; ↓ solubility of gases	Sugar dissolves faster in hot tea
Pressure	↑ solubility of gases (Henry's law); little effect on solids/liquids	Cold drinks bottled under pressure
Nature of solute/solvent	Like dissolves like	Salt in water, not in oil
pH of solvent	Weak acids dissolve better at high pH; weak bases at low pH (§1.10)	Aspirin dissolves better in alkaline medium
Particle size	Very small particles slightly more soluble	Micronised drugs
Crystal form/polymorph	Metastable/amorphous forms more soluble	—
Common ion effect	Decreases solubility (shifts equilibrium back)	AgCl less soluble in NaCl solution
Cosolvents	Water-miscible solvents increase solubility of poorly soluble drugs	Alcohol, glycerin, propylene glycol in syrups/elixirs
Complexation	Soluble complexes increase apparent solubility	Iodine + KI → soluble I_3^- (Lugol's iodine)
Surfactants	Micelles solubilise poorly soluble drugs	— (Chapter 4)

India context: In hot Indian summers, poorly stored syrups can show crystallisation when nights are cooler — solubility falls with temperature, so dissolved drug crystallises out. "Shake well before use" exists partly for this reason.

1.9 Measurement of saturation solubility — the shake-flask method

Procedure:

1. Add EXCESS solid drug to a fixed volume of solvent in a stoppered flask (more than can dissolve).
2. Shake/agitate at constant temperature (usually 25 °C or 37 °C) for 24–72 hours until equilibrium.
3. Let undissolved solid settle; filter the clear liquid.
4. Measure the drug concentration in the filtrate (e.g., by UV spectrophotometry or titration).

That concentration = **saturation solubility** at that temperature.

Diagram to sketch: A conical flask with solid settled at the bottom, clear solution above, labelled "excess solid", "saturated solution", "thermostat/water bath at 25 °C", arrow to a filter funnel, arrow to "analyse filtrate".

> **Key takeaway:** Excess solid + enough time + constant temperature = true equilibrium solubility.

1.10 Effect of pH on solubility

Most drugs are weak acids or weak bases. Only the **unionised** form dissolves well in water... more precisely, the ionised form is far more water-soluble, so TOTAL solubility rises when pH favours ionisation.

For a weak acid ($HA \rightleftharpoons H^+ + A^-$): raising the pH converts $HA \rightarrow A^-$ (ionised, soluble). Total solubility increases with pH.

For a weak base ($B + H^+ \rightleftharpoons BH^+$): lowering the pH converts $B \rightarrow BH^+$ (ionised, soluble). Total solubility increases as pH falls.

Formulas (from Henderson–Hasselbalch):

- Weak acid: S_total = S_0 × (1 + 10^(pH − pKa)), where S_0 = intrinsic solubility of unionised form.
- Weak base: S_total = S_0 × (1 + 10^(pKa − pH)).

> **Worked example 6 — weak acid.** A weak acid has S_0 = 0.10 mg/mL and pKa = 4.0. Find total solubility at pH 6.0.

> Step 1: pH − pKa = 6.0 − 4.0 = 2.0. Step 2: 10^2.0 = 100. Step 3: S_total = 0.10 × (1 + 100) = 0.10 × 101 = **10.1 mg/mL**. Check: at pH two units above pKa, solubility is ~100× the intrinsic — sensible.

> **Worked example 7 — weak base.** A weak base has S_0 = 0.05 mg/mL and pKa = 8.0. Find total solubility at pH 6.0.

> Step 1: pKa − pH = 8.0 − 6.0 = 2.0. Step 2: 10^2.0 = 100. Step 3: S_total = 0.05 × (1 + 100) = 0.05 × 101 = **5.05 mg/mL**.

> **Pharmacy relevance:** This is why the pH of syrups, injections and eye drops is carefully chosen — a small pH shift can make a drug 100× more soluble or make it precipitate. Aspirin (weak acid) dissolves better in the alkaline intestine than in the acidic stomach — which also explains where it is absorbed.

> **Analogy:** A weak acid at low pH is like a person in disguise (unionised, hiding from water). Raise the pH and the disguise comes off (ionised) — water welcomes it.

Common confusions

- **Solubility vs dissolution:** amount vs speed. A drug can have high solubility but slow dissolution (large crystals).
- **"Like dissolves like" exceptions:** some polar drugs dissolve in semi-polar solvents via hydrogen bonding — the rule is a guide, not a law.
- **pH effect direction:** students often reverse it. Remember: **acids like alkali** (weak acid dissolves better at HIGH pH); **bases like acid** (weak base dissolves better at LOW pH).

Common mistakes

- Forgetting that Henry's law needs constant temperature.
- Using Raoult's law with percentages instead of mole fractions.
- In pH–solubility sums, mixing up (pH − pKa) and (pKa − pH).

Mnemonics

- **"SaUNA"** — **Sa**turated = max, **U**nsaturated = can take more, **N**... supersaturated = **A**bove max (unstable).
- **"Acids like Alkali"** — weak acids dissolve better at high pH.

One-minute revision (Chapter 1)

INFOGRAPHIC SUMMARY

Solubility = max amount dissolved at fixed T. Pharmacopoeia words map to parts of solvent (practically insoluble ≥ 10,000). Like dissolves like; water's high dielectric constant dissolves salts. Henry's law: C = kP (gases: high P, low T). Raoult's law: P = P°·x. Saturation solubility measured by shake-flask with excess solid. Weak acids: solubility ↑ as pH ↑; weak bases: solubility ↑ as pH ↓.

Practice questions — Chapter 1

MCQs

1. "Sparingly soluble" means 1 part of solute dissolves in: (a) 1–10 (b) 10–30 (c) 30–100 (d) 100–1000 parts of solvent.
2. According to Henry's law, doubling the gas pressure: (a) halves solubility (b) doubles solubility (c) no change (d) triples solubility.
3. A weak acid (pKa 5) will have highest solubility at: (a) pH 3 (b) pH 5 (c) pH 7 (d) pH 1.
4. Raoult's law relates vapour pressure to: (a) molality (b) mole fraction (c) molarity (d) normality.

Short answers

1. Distinguish between solubility and dissolution with one example each.
2. State Henry's law and give one pharmaceutical application.
3. Why does a cold drink fizz more when opened warm? Explain using gas solubility principles.

Long answers

1. Discuss the factors affecting solubility of solids in liquids.
2. Describe the shake-flask method for measuring saturation solubility with a labelled diagram.

Numericals

1. A drug: 1 g dissolves in 60 mL water. Give the pharmacopoeial term. (Answer: 60 parts → Sparingly soluble)
2. CO_2 solubility is 0.20 g/100 mL at 2 atm. Find it at 5 atm. (Answer: 0.50 g/100 mL)
3. Pure ethanol vapour pressure = 59 mmHg at 25 °C; mole fraction 0.8 in a mixture. Find its partial vapour pressure. (Answer: 47.2 mmHg)
4. Weak acid, S_0 = 0.2 mg/mL, pKa = 5.0. Total solubility at pH 7.0? (Answer: 0.2 × 101 = 20.2 mg/mL)

Application-based

1. A weakly basic drug precipitates in an IV infusion when mixed with an alkaline fluid. Explain and suggest a fix.

Viva

1. What is the difference between a saturated and a supersaturated solution? Which is stable?

Chapter 2: Partition Coefficient and Critical Solution Temperature

Learning objectives

1. Define partition coefficient and explain its measurement.
2. Calculate P and log P from experimental data.
3. Explain the significance of partition coefficient in pharmacy.
4. Define critical solution temperature and describe the phenol–water system.
5. List applications of CST.

2.1 Partition coefficient — definition

Partition (distribution): When a solute is added to two immiscible liquids (usually oil and water) and shaken, it distributes itself between the two layers.

Partition coefficient (P): The ratio of the drug's concentration in the oil phase to its concentration in the water phase at equilibrium.

Formula: P = C_oil / C_water (at the same temperature, for the UNIONISED form of the drug).

log P: The logarithm (base 10) of P. Used because P values range from tiny to huge; log compresses the scale.

> **Terminology alert:** P uses the unionised form only. If the drug ionises, use the **distribution coefficient (D)**, which counts both ionised + unionised forms. At the exam, unless pH/ionisation is mentioned, P is fine.

> **Analogy:** Two neighbouring tea stalls (oil and water) and customers (drug molecules) distribute themselves between the two. P tells you which stall is more popular.

2.2 Measurement of partition coefficient — shake-flask method

1. Take equal volumes of n-octanol (oil phase) and water (or buffer), mutually saturated.
2. Dissolve a known amount of drug; shake until equilibrium at constant temperature.
3. Separate the layers; measure drug concentration in each (e.g., UV spectrophotometry).
4. P = C_octanol / C_water.

Why n-octanol? It is the international standard "oil" — its polarity roughly resembles biological membranes.

Worked example 8. After shaking, 100 mL octanol contains 0.40 g drug and 100 mL water contains 0.04 g drug. Find P and log P.

Step 1: C_oil = 0.40 g / 100 mL = 0.004 g/mL. C_water = 0.04 g / 100 mL = 0.0004 g/mL. Step 2: P = 0.004 / 0.0004 = **10**. Step 3: log P = $\log_{10}(10)$ = **1**.

Worked example 9. C_oil = 2.5 mg/mL, C_water = 0.5 mg/mL. P = 2.5 / 0.5 = **5**; log P = log(5) ≈ **0.70**. (Check: 10^0.7 ≈ 5.01 — correct.)

Worked example 10. A drug has log P = 2. What is P? P = 10^2 = **100**. Meaning: 100× more drug in oil than water.

2.3 Significance of partition coefficient

P / log P	Meaning	Pharmacy significance
Very low (log P negative)	Very water-soluble	Poor membrane crossing — stays in gut fluids; good for drugs acting in the GIT
Moderate (log P ~1–3)	Balanced	Best oral absorption — crosses lipid membranes but still dissolves in body fluids
Very high (log P > 5)	Very oil-soluble	Gets trapped in fat; poor aqueous solubility; formulation is difficult

Key uses:

- **Drug absorption:** drugs cross cell membranes (lipid bilayers) by passive diffusion — moderate log P is ideal (this is part of Lipinski's rule of five: log P < 5 for oral drugs).
- **Preservative action:** preservatives must partition into the water phase of emulsions where microbes live — too high P makes them hide in the oil and fail.
- **Formulation:** choosing oil vs water bases, extraction of drugs from plant material (pharmacognosy link).

Common confusion: High log P does NOT always mean better drug. Too high → the drug cannot dissolve in blood at all. Balance is everything.

Mnemonic: "Goldilocks log P" — not too watery, not too oily, just right (~1–3) for oral absorption.

2.4 Critical solution temperature (CST)

Definition: For a pair of partially miscible liquids, the temperature at or above which they become completely miscible in all proportions.

Upper CST: miscibility increases with heating (most common, e.g., phenol–water, ~66–67 °C — the exact value is commonly reported around 66.8 °C for the pure system).

Lower CST: miscibility increases with cooling (rarer, e.g., triethylamine–water).

The phenol–water system (must know):

- At room temperature, phenol and water form two layers: a water-rich layer and a phenol-rich layer.
- Heating increases mutual solubility; the two layers merge into one at the CST.
- Plotting temperature vs composition gives a dome-shaped curve; the top of the dome = CST.

Diagram to sketch: Y-axis temperature, X-axis % phenol. A dome (parabola-like) curve. Below the dome: two regions labelled "two layers". Above the dome: "one homogeneous layer". Mark the peak: "CST ≈ 66.8 °C (phenol–water)". This is called the **miscibility curve** or **consolute curve**.

Effect of impurities: Impurities CHANGE the CST — that is the whole point of its applications:

- Impurities soluble in only ONE component → raise the CST.
- Impurities soluble in BOTH → lower the CST.

Applications:

1. **Purity testing:** a shifted CST reveals impurities (classic test for phenol purity).
2. **Nicotine–water CST** used to check nicotine purity.
3. **Formulation:** knowing CST helps design liquid mixtures and extraction processes that must stay single-phase.

> **Analogy:** CST is like the temperature at which two quarrelling neighbours (phenol and water) finally agree to live in one house. Any gossip (impurity) changes the temperature at which they reconcile.

One-minute revision (Chapter 2)

INFOGRAPHIC SUMMARY

P = C_oil/C_water (unionised drug); log P compresses the scale. Measured by shake-flask with n-octanol. Moderate log P (1–3) = best oral absorption. CST = temperature where partially miscible liquids become fully miscible; phenol–water ≈ 66.8 °C; impurities shift CST → used for purity testing.

Practice questions — Chapter 2

MCQs

1. Partition coefficient is the ratio of drug concentration in: (a) oil/water (b) water/oil (c) solid/liquid (d) gas/liquid.
2. log P = 0 means: (a) all drug in oil (b) all drug in water (c) equal distribution (d) no distribution.
3. CST of phenol–water is approximately: (a) 25 °C (b) 66.8 °C (c) 100 °C (d) 0 °C.
4. An impurity soluble in only one component will: (a) lower CST (b) raise CST (c) not affect CST (d) remove CST.

Short answers

1. Why is n-octanol used as the standard oil phase?
2. Distinguish between partition coefficient (P) and distribution coefficient (D).

Long answers

1. Describe the phenol–water system and explain how CST is used in purity testing, with a labelled miscibility curve.

Numericals

1. Octanol phase: 0.9 g/100 mL; water phase: 0.3 g/100 mL. Find P and log P. (Answer: P = 3, log P ≈ 0.48)
2. log P = 1.5. Find P. (Answer: 10^1.5 ≈ 31.6)
3. Two drugs: A has P = 0.1, B has P = 50. Which is more likely to be well absorbed orally, and why? (Answer: B is closer to the ideal range, but 50 (log P ≈ 1.7) is actually good; A (log P = −1) is too hydrophilic.)

Application-based

1. A preservative fails in an o/w cream although it works in simple solution. Explain using partition concepts.

Viva

1. What happens to CST if an impurity dissolves in both liquids?

Chapter 3: Buffers

Learning objectives

1. Define buffer, buffer capacity and buffer equation.
2. Explain buffers in pharmaceutical and biological systems.
3. Describe pH determination by electrometry and colorimetry.
4. Derive and use the Henderson–Hasselbalch (buffer) equation.
5. Explain factors influencing pH and buffer capacity.
6. Describe the general procedure for preparing buffers and the role of indicators.

3.1 Definitions

pH: A scale (0–14) measuring acidity: pH = $-\log_{10}[H^+]$. pH 7 = neutral, below 7 = acidic, above 7 = alkaline.

Buffer: A solution that RESISTS changes in pH when small amounts of acid or alkali are added. Made of a weak acid + its salt (acidic buffer) or a weak base + its salt (basic buffer).

Buffer capacity (β): A NUMBER measuring how good the buffer is — the amount of strong acid/alkali needed to change the pH of 1 litre of buffer by 1 unit. Higher β = stronger resistance.

> **Analogy:** A buffer is like a shock absorber on a scooter. Small bumps (added acid/alkali) are absorbed; the ride (pH) stays smooth. Buffer capacity is how strong the shock absorber is.

How a buffer works (acidic buffer: CH_3COOH + CH_3COONa):

- Add acid (H^+): the salt's anion eats it — $CH_3COO^- + H^+ \rightarrow CH_3COOH$ (weak acid, barely changes pH).
- Add alkali (OH^-): the weak acid neutralises it — $CH_3COOH + OH^- \rightarrow CH_3COO^- + H_2O$.
- Each partner "sacrifices" itself to protect the pH.

> **Key takeaway:** A buffer is a weak acid/base + its salt; the two partners neutralise any added acid or alkali.

3.2 Buffers in pharmaceutical and biological systems

Biological buffers (must know):

System	pH	Buffer pair
Blood	7.4	Carbonic acid / bicarbonate (H_2CO_3/HCO_3^-) — main; also phosphate, proteins, haemoglobin
Tears	~7.4	Bicarbonate, proteins
Gastric fluid	~1.5–3.5	HCl (not a buffer — strongly acidic)
Urine	~6.0 (varies)	Phosphate buffer

Pharmaceutical buffers: Eye drops (must be ~pH 7.4 or tears sting), injections (blood pH 7.4; wrong pH causes pain and drug precipitation), syrups (pH controls drug solubility and stability), antacid formulations.

> **India context:** ORS (oral rehydration salts) contains citrate, which gives mild buffering; many Indian-made eye drops are labelled "buffered to pH 7.4". In summer, improperly stored liquid medicines can drift in pH as CO_2 dissolves — another reason buffers are added.

3.3 pH determination methods

A. Electrometry (pH meter) — the standard method

- Uses a **glass electrode** (sensitive to H^+) + a reference electrode (calomel or Ag/AgCl).
- The voltage between them changes with $[H^+]$; the meter converts voltage to pH.
- **Procedure:** calibrate with standard buffers (pH 4.0 and 7.0 — or 9.2), rinse electrode, dip in sample, read.
- Accurate to ±0.01 pH. Used in every QC lab.

B. Colorimetry (indicators / pH paper)

- **Indicators** are weak acids/bases whose ionised and unionised forms have DIFFERENT COLOURS.
- Example: phenolphthalein — colourless in acid, pink in alkali (range ~8.3–10).
- Universal indicator / pH paper gives approximate pH by colour matching. Less accurate (±0.5) but cheap and fast.

Diagram to sketch (pH meter): Beaker with sample; glass electrode + reference electrode dipped in; wires to a box labelled "pH meter — reads voltage → pH"; note "calibrate with pH 4.0 & 7.0 buffers first".

3.4 The buffer equation (Henderson–Hasselbalch)

For a weak acid HA: $K_a = [H^+][A^-]/[HA]$. Taking negative logs and rearranging:

$pH = pK_a + \log_{10}([salt] / [acid])$

where [salt] = concentration of conjugate base (A^-), [acid] = concentration of weak acid (HA).

For a weak base buffer: **pOH = pKb + log([salt] / [base])**, then pH = 14 − pOH.

Worked example 11. An acetate buffer has $[CH_3COO^-]$ = 0.10 M and $[CH_3COOH]$ = 0.10 M. pKa of acetic acid = 4.76. Find pH.

Step 1: ratio = 0.10 / 0.10 = 1. Step 2: log(1) = 0. Step 3: pH = 4.76 + 0 = **4.76**. Rule: when salt = acid, pH = pKa. (Maximum buffer capacity point!)

Worked example 12. $[CH_3COO^-]$ = 0.15 M, $[CH_3COOH]$ = 0.05 M, pKa = 4.76.

Step 1: ratio = 0.15 / 0.05 = 3. Step 2: log(3) = 0.477. Step 3: pH = 4.76 + 0.477 = **5.24** (5.237).

Worked example 13. $[CH_3COO^-]$ = 0.05 M, $[CH_3COOH]$ = 0.15 M.

Step 1: ratio = 0.05/0.15 = 0.333. Step 2: log(0.333) = −0.477. Step 3: pH = 4.76 − 0.477 = **4.28**.

Worked example 14 — weak base buffer. Ammonia buffer: $[NH_4^+]$ = 0.10 M (salt), $[NH_3]$ = 0.10 M (base), pKb = 4.75.

Step 1: pOH = 4.75 + log(0.10/0.10) = 4.75 + 0 = 4.75. Step 2: pH = 14 − 4.75 = **9.25**.

Key takeaway: pH depends on the RATIO salt/acid, not on how dilute the buffer is. Diluting a buffer (without adding acid/alkali) does not change its pH.

3.5 Factors influencing the pH of buffer solutions

1. **pKa of the weak acid** — sets the centre of the buffering range.
2. **Ratio [salt]/[acid]** — shifts pH above or below pKa (the log term).
3. **Temperature** — pKa changes slightly with temperature, so pH shifts.
4. **Ionic strength** — high salt concentrations alter activity coefficients, shifting pH slightly.
5. **Dilution** — theoretically no change in pH (ratio unchanged); in practice, tiny shifts.

3.6 Factors influencing buffer capacity

1. **Total concentration** — more buffer molecules = more acid/alkali absorbed. Doubling concentration doubles capacity.
2. **Ratio [salt]/[acid]** — capacity is MAXIMUM when ratio = 1 (pH = pKa); it falls as the ratio moves away. A buffer works well within pKa ± 1.
3. **pKa relative to desired pH** — choose an acid whose pKa is close to the target pH.

Van Slyke equation (for interest): $\beta = 2.303 \times C \times Ka[H^+] / (Ka + [H^+])^2$, where C = total buffer concentration. At pH = pKa, this simplifies to **$\beta_{max} = 2.303 \times C / 4 = 0.576 \times C$**.

> **Worked example 15 — buffer capacity.** Find the maximum buffer capacity of a 0.20 M acetate buffer (at pH = pKa).
>
> Step 1: $\beta_{max} = 0.576 \times C$. Step 2: $0.576 \times 0.20 =$ **0.115**. Meaning: it takes ~0.115 mol of strong acid/alkali per litre to shift pH by 1 unit near pKa.
>
> **Worked example 16 — comparison.** Buffer A: 0.10 M total. Buffer B: 0.40 M total (same ratio). Which has higher capacity? $\beta_{max}(A) = 0.576 \times 0.10 = 0.0576$. $\beta_{max}(B) = 0.576 \times 0.40 = 0.2304$. **B is 4× stronger** — capacity scales directly with concentration.

Diagram to sketch (buffer capacity curve): X-axis pH, Y-axis β. A bell-shaped curve peaking at pH = pKa. Shade the useful range pKa − 1 to pKa + 1. Label: "maximum at pH = pKa".

3.7 General procedure for preparing buffers

1. **Select** the weak acid whose pKa is closest to the desired pH (within ±1).
2. **Calculate** the [salt]/[acid] ratio using Henderson–Hasselbalch.
3. **Weigh** the required amounts of acid and salt (or take acid + strong base to generate the salt in situ).
4. **Dissolve** in ~70% of the final volume of purified water.
5. **Adjust** pH with a pH meter, adding small amounts of acid or alkali dropwise.
6. **Make up** to final volume; **store** in a tightly closed container, labelled with pH and date.

> **Worked example 17 — preparation.** Prepare 1 litre of acetate buffer, pH 4.76, total concentration 0.10 M.
>
> Step 1: pH = pKa → ratio salt:acid = 1:1. Step 2: Total 0.10 M → [salt] = 0.05 M, [acid] = 0.05 M. Step 3: Sodium acetate (anhydrous, MW 82): 0.05 mol × 82 g/mol = **4.1 g**. Acetic acid (MW 60): 0.05 mol × 60 = **3.0 g** (or pipette the equivalent volume of glacial acetic acid). Step 4: Dissolve in ~700 mL water, check/adjust pH to 4.76 with pH meter, make up to 1000 mL.

> **India context:** IP appendices give ready-made "buffer solutions" (e.g., acetate buffer pH 4.5, phosphate buffer pH 7.4) with exact recipes — QC labs across India prepare these daily for dissolution testing and assays.

3.8 Indicators

Definition: Weak organic acids/bases whose ionised and unionised forms have different colours; the colour change happens over a narrow pH range (~2 units).

Indicator	pH range	Colour change (acid → alkali)
Methyl orange	3.1–4.4	Red → yellow
Phenolphthalein	8.3–10.0	Colourless → pink
Litmus	~5–8	Red → blue

Uses: acid–base titrations (choose indicator whose range brackets the end-point pH), rough pH estimation.

Common mistake: Using phenolphthalein for a strong acid vs weak base titration — the end point is acidic, so methyl orange is correct. Match the indicator range to the end-point pH.

One-minute revision (Chapter 3)

INFOGRAPHIC SUMMARY

Buffer = weak acid/base + its salt; resists pH change. Blood pH 7.4 (bicarbonate buffer). pH by glass electrode (accurate) or indicators (rough). Henderson–Hasselbalch: pH = pKa + log(salt/acid). pH = pKa when ratio = 1. Capacity max at pH = pKa, rises with total concentration, useful within pKa ± 1. Prepare: choose acid near target pH → calculate ratio → weigh → dissolve → adjust with pH meter → make up volume.

Practice questions — Chapter 3

MCQs

1. An acidic buffer contains: (a) strong acid + salt (b) weak acid + its salt (c) weak base + salt (d) strong base + salt.
2. Blood pH is maintained mainly by: (a) phosphate (b) bicarbonate (c) acetate (d) citrate buffer.
3. Maximum buffer capacity occurs when: (a) salt >> acid (b) salt = acid (c) acid >> salt (d) no salt present.
4. Phenolphthalein changes colour in the range: (a) 3.1–4.4 (b) 8.3–10.0 (c) 5–8 (d) 1–3.

Short answers

1. Define buffer capacity. On what two main factors does it depend?
2. Why is a buffer's pH unchanged on dilution?
3. Name the electrodes used in a pH meter and the calibration buffers.

Long answers

1. Derive the Henderson–Hasselbalch equation and explain how a buffer resists pH change on addition of acid and alkali.
2. Describe the general procedure for preparing a buffer solution.

Numericals

1. [salt] = 0.2 M, [acid] = 0.1 M, pKa = 4.76. Find pH. (Answer: 4.76 + log 2 = 4.76 + 0.301 = 5.06)
2. [salt] = 0.02 M, [acid] = 0.2 M, pKa = 4.76. Find pH. (Answer: 4.76 + log 0.1 = 4.76 − 1 = 3.76)
3. Maximum buffer capacity of 0.5 M buffer? (Answer: 0.576 × 0.5 = 0.288)
4. Prepare 500 mL of pH 4.76 acetate buffer, 0.2 M total. How much sodium acetate (MW 82) and acetic acid (MW 60)? (Answer: ratio 1:1 → 0.1 M each in 0.5 L = 0.05 mol each → 4.1 g sodium acetate, 3.0 g acetic acid)

Application-based

1. Eye drops at pH 5.0 sting badly. Explain and suggest a formulation fix.

Viva

1. Why must the pKa of the chosen acid be close to the desired buffer pH?

> **Recommended references (as per syllabus):** Sinko, P.J. — Martin's Physical Pharmacy and Pharmaceutical Sciences; Ansel's Pharmaceutical Dosage Forms and Drug Delivery Systems; Remington: The Science and Practice of Pharmacy; Aulton, M.E. — Pharmaceutics: The Science of Dosage Form Design.