BP306T · B.PHARM THEORY

BP306T Pharmaceutical Dosage Forms I

Unit I — Fundamentals of Dosage Form Development

Pills & Python Notes

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

Syllabus coverage: Unit I (7 hours).

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Chapter 1 — Pre-formulation Studies: The Birth Report of a Drug (Unit I)

1.1 Learning objectives

After studying this chapter, you will be able to:

1. Define pre-formulation, formulation, and dosage form in your own words.
2. Explain why pre-formulation studies are needed before making a tablet or capsule.
3. Describe how solubility affects drug absorption, with one example.
4. Define pKa and use the Henderson–Hasselbalch equation to decide whether a drug is ionised or unionised at a given pH.
5. Distinguish crystalline, amorphous, and polymorphic forms of a drug solid.
6. Explain how particle size and shape influence dissolution and powder flow.
7. Measure and interpret powder flow using angle of repose, Carr's index, and Hausner ratio.
8. List the main pre-formulation parameters in a logical testing order.

1.2 Definitions

- **Dosage form:** The final, patient-ready form of a drug — e.g., tablet, capsule, syrup, injection. It is the drug *plus* the vehicle/excipients that carry it.
- **Formulation:** The complete recipe and process used to convert a pure drug powder into a dosage form — which excipients, in what amounts, made how.
- **Pre-formulation:** The *investigation stage* before formulation. The drug powder (called the **drug substance** or **API — active pharmaceutical ingredient**) is studied alone for its physical and chemical properties, so that the formulation scientist can choose the right excipients and process.
- **Excipient:** Any substance added to the formulation other than the drug — it helps make, stabilise, or deliver the dosage form (e.g., lactose as filler, starch as disintegrant). Excipients are pharmacologically inactive ("inactive ingredients").
- **API (Active Pharmaceutical Ingredient):** The part of the medicine that actually treats the disease.

Simple explanation: Pre-formulation is like a doctor's full health check-up of the drug *before* designing its medicine. Just as a doctor checks blood pressure, sugar, and weight before prescribing, the formulation scientist checks solubility, pKa, crystal form, particle size, and flow of the drug powder before choosing how to make the tablet.

> **Key takeaway:** Pre-formulation answers the question: *"What is this drug powder like, and what does it need to become a good medicine?"*

1.3 Terminology (word bank — learn these first)

Term	Meaning in one line
Solubility	How much of a substance dissolves in a given amount of solvent (e.g., mg per mL)
Intrinsic solubility	Solubility of the *unionised* form of the drug in water
Ionised	Drug molecule carrying an electrical charge (usually as a salt) — loves water, crosses membranes poorly
Unionised	Drug molecule with no charge — crosses lipid membranes well, dissolves poorly in water
pKa	The pH at which exactly half the drug is ionised and half unionised
Crystalline	Solid with molecules arranged in a regular, repeating pattern (like a tiled floor)
Amorphous	Solid with molecules arranged randomly (like a pile of sand)
Polymorph	A different crystal *form* of the same chemical (same molecule, different packing)
Particle size	Diameter of individual drug particles, usually in micrometres (μm)
Micronisation	Reducing particle size to a few micrometres (usually by milling) to speed up dissolution
Bulk density	Weight of powder divided by the volume it occupies *as poured* (includes air gaps)
Tapped density	Weight of powder divided by the volume *after tapping* the container (air gaps removed)
Angle of repose	Angle of the cone formed when powder is poured — a measure of flow
Compressibility index (Carr's index)	Percentage change from bulk to tapped density — measures how much a powder compresses
Hausner ratio	Tapped density ÷ bulk density — another flow measure

1.4 Concept and need of pre-formulation studies

Technical concept: Pre-formulation is the systematic characterisation of the physicochemical properties of a new drug substance, alone and in simple combinations with common excipients, to guide rational dosage-form design.

Simple explanation: When a new drug molecule is discovered, we only have a powder in a bottle. Before spending crores of rupees making tablets, we must ask: Will it dissolve in the stomach? Will it survive heat and moisture? Will it flow through the tablet machine? Will it react with common excipients? Pre-formulation gives these answers early, when fixing problems is cheap.

Example: A new drug dissolves very slowly. Pre-formulation solubility testing shows the problem early. The team decides to micronise the powder (make particles tiny) — a cheap fix at this stage. If the problem were found only after tablets were made and failed dissolution testing, crores of rupees and months would be wasted.

The "need" of pre-formulation — five reasons (exam favourite):

1. **Right dosage form choice:** Tells whether the drug suits a tablet, capsule, syrup, or injection.
2. **Right excipients:** Shows which excipients are safe partners and which react with the drug.
3. **Right process:** Powder that flows badly needs granulation; powder that flows well can be directly compressed — the process decision comes from pre-formulation.
4. **Stable product:** Identifies how heat, moisture, light, and pH damage the drug, so packaging and storage can be designed.
5. **Bioavailability:** Solubility and particle-size data predict whether the drug will dissolve and be absorbed in the body.

Flowchart — where pre-formulation sits in drug development:

```
New drug molecule discovered (pure powder)
        ↓
PRE-FORMULATION STUDIES  ← (we are here: solubility, pKa, crystal form,
        ↓                        particle size, flow, compatibility)
Formulation development (choose excipients + process)
        ↓
Pilot batches → stability studies → clinical trials
        ↓
Manufacturing + marketing
```

Analogy: Building a house starts with testing the soil — is it sandy, rocky, or marshy? The soil report decides the foundation type. Pre-formulation is the *soil report* of the drug; the formulation is the *house design* built on it.

Key takeaway: Pre-formulation is cheap insurance. It finds problems when they are cheapest to fix.

1.5 Solubility — the first and most important parameter

Technical concept: Solubility is the maximum amount of drug that dissolves in a given volume of solvent at a given temperature, expressed as mg/mL or g/100 mL. It decides how much drug is available in solution at the absorption site.

Simple explanation: For a tablet to work, it must first *dissolve* in the stomach or intestine fluids, because only dissolved drug can be absorbed into the blood. A drug that does not dissolve is like sugar wrapped in plastic inside your tea — it never sweetens the tea. Most new drug molecules are poorly water-soluble, so solubility is the first property checked.

Why it matters (pharmacy relevance):

- Poorly soluble drugs → slow/erratic absorption → poor and variable blood levels → treatment may fail.
- Solubility data guides: choice of dosage form, need for micronisation, use of salts, and the dissolution test method.

Example: Drug X has solubility of 0.01 mg/mL. A 100 mg dose would need 10 litres of water to dissolve — far more than stomach fluid. Pre-formulation flags this; the formulator may use the drug's salt form or micronise it.

How solubility is measured (basic idea): The **shake-flask method** — excess drug powder is shaken in water/buffer at 37 °C until no more dissolves, then the dissolved amount is measured. Solubility is checked at different pH values (stomach pH ~1.2, intestinal pH ~6.8) because many drugs dissolve differently at different pH.

Key takeaway: No dissolution → no absorption → no effect. Solubility is the gatekeeper of oral drug action.

1.6 pKa — the pH at which the drug is half-charged

Technical concept: Many drugs are weak acids or weak bases. In water, they exist in two forms — **ionised** (charged) and **unionised** (neutral). The pKa is the pH at which the drug is exactly 50% ionised and 50% unionised.

Simple explanation: Think of pKa as the drug's "tipping point." Below its pKa, a weak acid is mostly unionised; above its pKa, it is mostly ionised. (For a weak base, it is the reverse.) This matters because:

- **Unionised** drug → no charge → dissolves in fats → **crosses cell membranes easily** → well absorbed.
- **Ionised** drug → has charge → **dissolves in water easily** → crosses membranes poorly.

So the same drug dissolves well in one part of the gut and gets absorbed well in another!

The Henderson–Hasselbalch equation (for a weak acid): > **pH = pKa + log (ionised ÷ unionised)**

> **Worked example:** Aspirin is a weak acid with pKa ≈ 3.5.

- In the stomach (pH ≈ 1.2): pH is *below* pKa → aspirin is mostly **unionised** → well absorbed from the stomach.
- In the intestine (pH ≈ 6.8): pH is *above* pKa → aspirin is mostly **ionised** → dissolves very well here.
- At pH = pKa = 3.5: exactly 50% ionised, 50% unionised.

> **Pharmacy relevance:** pKa helps predict *where* in the gut a drug dissolves and gets absorbed, guides salt selection (salts dissolve faster), and explains why some drugs irritate the stomach.

Common confusion: Students mix up "solubility" and "dissolution rate." **Solubility** = *how much* dissolves (a capacity). **Dissolution rate** = *how fast* it dissolves (a speed). Micronisation increases dissolution *rate* but does not change solubility. Both matter for absorption.

> **Key takeaway:** pKa + gut pH decides the ionised/unionised balance — and that balance decides solubility vs absorption.

1.7 Physical nature: amorphous vs crystalline

Technical concept: "Physical nature" means how the drug's molecules are arranged in the solid state.

Feature	Crystalline	Amorphous
Arrangement	Ordered, repeating lattice (like tiles)	Random, disordered (like a sand pile)
Stability	High (molecules locked in place)	Low (wants to convert to crystalline)
Solubility/dissolution	Lower (lattice energy must be overcome)	Higher (no lattice to break)
Melting point	Sharp, fixed	No sharp melting point
Example behaviour	Most marketed drugs	Used when extra solubility is needed, with stabilisers

Simple explanation: Breaking sugar candy (crystalline) needs more effort than dissolving powdered jaggery (disordered) — similarly, amorphous drugs dissolve faster but can slowly "settle" into crystals during storage, which is a stability risk.

> **Key takeaway:** Crystalline = stable but slower dissolving; amorphous = faster dissolving but less stable. The formulator must balance the two.

1.8 Polymorphism — same drug, different crystal packing

Technical concept: Polymorphism is the ability of a drug to exist in more than one crystal form (polymorphs). Same chemical formula, same molecule — but packed differently in the crystal lattice, like the same bricks arranged into different wall patterns.

Why it matters: Different polymorphs can have very different solubility, dissolution rate, stability, and even bioavailability. One polymorph may work; another may fail. So the formulator must identify, select, and *consistently use* the right polymorph.

Classic examples (textbook cases):

- **Ritonavir:** A more stable but much less soluble polymorph (Form II) appeared during manufacturing; capsules failed dissolution and had to be reformulated — the most famous polymorphism disaster in pharma history.
- **Chloramphenicol palmitate:** One polymorph is well absorbed, another is poorly absorbed — same drug, different blood levels.

Types of polymorphism:

- **Enantiotropic:** The polymorphs can convert into each other reversibly when temperature changes (each is stable in its own temperature range).
- **Monotropic:** One form is always more stable; the unstable form converts to it one-way only.

How polymorphs are detected: X-ray powder diffraction (XRPD — each polymorph gives a different "fingerprint" pattern), DSC (different melting behaviour), and IR spectroscopy.

Diagram — draw it: Two boxes side by side. Left box: molecules drawn in neat rows (label "Polymorph A — stable, less soluble"). Right box: same molecules in a different arrangement (label "Polymorph B — metastable, more soluble"). Arrow between them labelled "heat/moisture can convert B → A during storage."

> **Pharmacy relevance:** Polymorph screening is a routine pre-formulation step for every new solid drug; regulatory filings must state which polymorph is used.

> **Key takeaway:** Same molecule + different packing = different medicine performance. Always lock in the right polymorph.

1.9 Particle size and shape

Technical concept: Particle size (usually in μm) decides surface area. Smaller particles → larger total surface area → faster dissolution (Noyes–Whitney principle: dissolution rate increases with surface area). Particle *shape* (needle, plate, sphere) affects packing, flow, and how particles stick together.

Simple explanation: A whole potato takes long to cook; the same potato cut into tiny pieces cooks fast — more surface touches the water. **Micronisation** (milling drug to a few micrometres) is the "cutting into tiny pieces" trick for poorly soluble drugs.

Why shape matters: Needle-shaped crystals tangle like dry spaghetti and flow badly; spherical particles roll like marbles and flow well. Shape also affects how tightly powder packs into a tablet die.

Measurement idea: Sieving (for coarse particles), microscopy, and laser diffraction instruments give particle-size data. Pre-formulation records the size distribution, not just one average number.

> **Key takeaway:** Small + spherical = fast dissolving and free-flowing. Large + needle-like = slow and troublesome.

1.10 Powder flow parameters

Technical concept: Tablet machines need powder to flow smoothly and uniformly into the die. Poor flow → uneven die filling → tablets of varying weight → varying drug dose. Pre-formulation measures flow with simple, standard tests.

The four standard flow tests (with formulas):

1. **Angle of repose (θ):** Pour powder through a funnel onto a flat surface; it forms a cone. $\theta = \tan^{-1}(\text{height} \div \text{radius of cone})$. Smaller angle = better flow.

Angle of repose	Flow property
< 25°	Excellent
25–30°	Good
30–40°	Passable (may need a glidant)
> 40°	Very poor

(Commonly used textbook ranges; exact interpretation is comparative.)

2. **Bulk density:** Mass ÷ volume of *poured* powder (includes air gaps). Example: 50 g powder occupies 100 mL → bulk density = 0.5 g/mL.
3. **Tapped density:** Mass ÷ volume *after tapping* the cylinder until no further settling (air gaps removed).
4. **Carr's (compressibility) index:** `[(tapped density − bulk density) ÷ tapped density] × 100`. Lower % = better flow. Commonly taught ranges: 5–12% excellent, 12–16% good, 18–21% fair, 23–35% poor, >40% extremely poor.
5. **Hausner ratio:** `tapped density ÷ bulk density`. Values below ~1.25 generally indicate good flow.

> **Worked example:** Bulk density 0.50 g/mL, tapped density 0.62 g/mL.

- Carr's index = (0.62 − 0.50) ÷ 0.62 × 100 = **19.4%** → fair flow (may need granulation or a glidant).
- Hausner ratio = 0.62 ÷ 0.50 = **1.24** → borderline; confirms fair-to-good flow.

How to fix poor flow: Add a **glidant** (e.g., colloidal silicon dioxide), or granulate the powder (make small uniform granules that roll well).

Diagram — draw it: A funnel pouring powder onto paper, forming a cone; label height (h) and base radius (r); write "tan θ = h/r" beside it. Below, two graduated cylinders: one loosely filled (label "bulk volume — air gaps"), one tapped down (label "tapped volume — compacted").

> **Key takeaway:** Flow tests are cheap, quick, and predict whether the powder will run on a tablet machine. Bad flow → granulate or add glidant.

1.11 Infographic concept box — "Pre-formulation at a glance"

(For the designer: a single-page visual with 6 icons in a circle around a central drug-powder bottle.)

- **Solubility** (water drop icon): "How much dissolves? Decides absorption."
- **pKa** (pH strip icon): "Charged or neutral? Decides where it dissolves vs where it is absorbed."
- **Crystal form** (diamond icon): "Ordered or disordered? Polymorph locked in."
- **Particle size** (magnifier icon): "Small = fast dissolving."
- **Flow** (funnel icon): "Angle, Carr's, Hausner — will it run on the machine?"
- **Stability hints** (thermometer icon): "Heat, moisture, light sensitivity noted for later."

1.12 Putting it together — the pre-formulation testing order (flowchart)

```
1. Organoleptic: colour, odour, taste of drug powder
        ↓
2. Solubility at various pH (stomach → intestine)
        ↓
3. pKa determination
        ↓
4. Crystal nature: crystalline/amorphous; polymorph screening (XRPD, DSC)
        ↓
5. Particle size & shape (microscopy / laser diffraction)
        ↓
6. Powder flow: angle of repose, bulk/tapped density, Carr's, Hausner
        ↓
7. Stability hints: effect of heat, moisture, light, pH (stress testing)
        ↓
8. Drug–excipient compatibility (Chapter 2)
        ↓
→ Formulation strategy decided (dosage form, excipients, process)
```

1.13 Pharmacy relevance

Every tablet, capsule, and syrup on a pharmacy shelf passed through pre-formulation. When a pharmacist counsels "take this tablet with water on an empty stomach," the advice often traces back to pre-formulation solubility/pKa data. Generic companies repeat pre-formulation on the innovator's drug to design an equivalent product.

1.14 India context

India's hot, humid climate (ICH Zone IVb — hot and very humid) makes moisture-sensitivity data from pre-formulation extra important; a formulation stable in Europe may cake or degrade in a Chennai monsoon. India's huge generic industry runs pre-formulation on every innovator molecule it copies. The Indian Pharmacopoeia (IP) monographs' dissolution and disintegration tests are built on exactly these physicochemical principles.

1.15 Key points

1. Pre-formulation = studying the pure drug's properties *before* designing the formulation.
2. Need: right dosage form, right excipients, right process, stability, bioavailability.
3. Solubility decides how much drug is available for absorption; measured at gut pH values.
4. pKa decides ionised vs unionised balance; unionised crosses membranes, ionised dissolves.
5. Crystalline = stable, slower; amorphous = faster dissolving, less stable.
6. Polymorphs: same molecule, different packing, different performance — select and lock one.
7. Small particles dissolve faster (Noyes–Whitney); spherical shapes flow better.
8. Flow tests: angle of repose, Carr's index, Hausner ratio — poor flow is fixed by glidants or granulation.

1.16 Common confusions

- **Pre-formulation vs formulation:** Pre-formulation *studies the drug*; formulation *designs the medicine*. Pre comes first.
- **Solubility vs dissolution rate:** Solubility = *how much*; dissolution rate = *how fast*. Micronisation changes the rate, not the solubility.
- **Amorphous vs polymorph:** Amorphous = *no* crystal order. Polymorphs = *different* crystal orders. Both affect solubility, but they are different phenomena.
- **Ionised = water-soluble but poorly absorbed; unionised = poorly water-soluble but well absorbed.** Students often reverse this.

1.17 Common mistakes

1. Saying "the drug is insoluble" without stating *at which pH* — solubility of ionisable drugs changes with pH.
2. Confusing bulk density with true density of the solid — bulk density includes air gaps between particles.
3. Forgetting that Carr's index uses *tapped minus bulk* divided by *tapped* (not bulk).
4. Assuming the first crystal form found is the best one — polymorph screening is mandatory.

1.18 Mnemonics

- **Pre-formulation parameters:** "**S**olubility, **P**Ka, **P**hysical nature, **P**olymorphism, **P**article size, **P**owder flow" → "**S**ome **P**harma **P**eople **P**refer **P**erfect **P**owders."
- **Flow tests:** "**A**ngle, **B**ulk, **T**apped, **C**arr's, **H**ausner" → "**A** **B**ig **T**ablet **C**omes from **H**ealthy flow."

1.19 Exam summary (one page)

Pre-formulation studies investigate the drug substance before formulation to guide dosage-form, excipient, and process selection. Key parameters: (1) **Solubility** — amount dissolving per mL; decides absorption; measured by shake-flask at gut pH. (2) **pKa** — pH of 50% ionisation; Henderson–Hasselbalch (pH = pKa + log ionised/unionised); unionised = membrane-crossing, ionised = water-dissolving. (3) **Physical nature** — crystalline (ordered, stable, slower) vs amorphous (random, faster, less stable). (4) **Polymorphism** — different crystal packings of the same drug with different solubility/stability (e.g., ritonavir, chloramphenicol palmitate); enantiotropic vs monotropic; detected by XRPD/DSC/IR. (5) **Particle size/shape** — smaller = faster dissolution (Noyes–Whitney); spherical flows best. (6) **Powder flow** — angle of repose ($\tan^{-1}$ h/r), Carr's index [(tapped−bulk)/tapped×100], Hausner ratio (tapped/bulk); poor flow fixed by glidants or granulation.

1.20 One-minute revision

Pre-formulation = drug's health check-up before formulation. Check solubility (gatekeeper of absorption), pKa (charged vs neutral balance), crystal form (stable vs fast), polymorph (lock the right one — remember ritonavir), particle size (small = fast), and flow (angle, Carr's, Hausner). Bad flow or slow dissolution found early = cheap fix; found late = crores lost.

1.21 Exam questions

Short questions

1. Define pre-formulation and list any four needs of pre-formulation studies.
2. Distinguish between solubility and dissolution rate with one example each.
3. Define pKa. A weak acid has pKa 4.0 — will it be mostly ionised or unionised in the intestine (pH 6.8)? Why?
4. Differentiate crystalline and amorphous solids (any four points).
5. What is polymorphism? Name two drugs whose polymorphs differ in performance.
6. Write the formulas for Carr's index and Hausner ratio. A powder has bulk density 0.55 and tapped density 0.70 g/mL — calculate both and comment on flow.

MCQs (answers at end)

1. Pre-formulation studies are carried out on:

a) Finished tablets b) The pure drug substance c) Packaged products d) Excipients alone

2. At pH = pKa, a weak acid drug is:

a) Fully ionised b) Fully unionised c) 50% ionised, 50% unionised d) Precipitated

3. Which solid form generally dissolves faster?

a) Crystalline b) Amorphous c) Both equal d) Neither dissolves

4. Different crystal packings of the same drug are called:

a) Isomers b) Polymorphs c) Enantiomers d) Tautomers

5. Micronisation mainly increases:

a) Solubility b) Dissolution rate c) pKa d) Melting point

6. An angle of repose of 28° indicates:

a) Excellent flow b) Good flow c) Very poor flow d) No flow

7. Carr's index is calculated from:

a) True and bulk density b) Bulk and tapped density c) Weight and thickness d) pH and pKa

8. The famous polymorphism failure case in pharma history is:

a) Aspirin b) Ritonavir c) Paracetamol d) Lactose

Answers: 1-b, 2-c, 3-b, 4-b, 5-b, 6-b, 7-b, 8-b

Viva questions

1. Why do we study the drug *alone* in pre-formulation instead of directly making tablets?
2. Your drug flows poorly (angle of repose 45°). What two corrective actions will you suggest?
3. Why is solubility tested at pH 1.2 and 6.8?
4. A stable polymorph appears during storage and dissolution slows — explain what happened.

Application-based

1. A new weak-base drug (pKa 8.0) dissolves well in stomach acid but precipitates in intestinal fluid. Using Henderson–Hasselbalch reasoning, explain why, and suggest two formulation approaches the team could consider.
2. Two batches of the same drug show different dissolution profiles; XRPD patterns differ. Diagnose the problem and outline your corrective plan as a pre-formulation scientist.

1.22 References

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7. *British Pharmacopoeia*. British Pharmacopoeia Commission. (Solubility and identification tests.)

Chapter 2 — Drug–Excipient Compatibility, Packaging & ICH Q1 Stability (Unit I)

2.1 Learning objectives

After studying this chapter, you will be able to:

1. Define drug–excipient compatibility and explain why it is studied.
2. Describe physical and chemical methods used to detect drug–excipient interactions.
3. Give two classic examples of drug–excipient incompatibility.
4. Select suitable packaging for tablets, capsules, liquids, and sterile products, with reasons.
5. Explain drug product–container/closure interactions: adsorption, absorption, leaching, and permeation.
6. State the purpose and standard storage conditions of ICH Q1 stability testing.
7. Explain why India uses the 30 °C/65% RH long-term condition.

2.2 Definitions

- **Compatibility:** A drug and excipient are *compatible* if mixing them causes no physical or chemical change that harms the product's quality, safety, or performance.
- **Interaction/incompatibility:** Any undesirable physical or chemical change when drug and excipient meet — e.g., colour change, loss of potency, bad odour, sticky mass.
- **Packaging:** All materials that contain, protect, and present the dosage form — divided into **primary** (touches the product: blister, bottle), **secondary** (outer carton), and **tertiary** (shipping boxes).
- **Container–closure system:** The container plus its cap/lid/stopper taken together as one protective unit (e.g., HDPE bottle + screw cap).
- **Stability:** The ability of the drug product to keep its identity, strength, quality, and purity within specified limits throughout its shelf life.
- **Shelf life (expiry period):** The time during which the product remains within specifications under stated storage conditions.
- **ICH:** The International Council for Harmonisation — it writes common technical guidelines so that one set of stability data is accepted in the USA, Europe, and Japan (and widely followed in India).

Simple explanation: Compatibility testing is like checking whether two new roommates can live together *before* signing a long lease. The drug and excipient are mixed, stressed with heat and humidity, and watched for fights (colour change, degradation). Packaging is the product's "house" — it must keep out moisture, light, and air. ICH Q1 is the *rulebook* that tells every company in the world how to prove their product stays good till expiry.

> **Key takeaway:** A perfect drug + a wrong excipient or wrong pack = a failed medicine. Compatibility, packaging, and stability are designed together.

2.3 Terminology (word bank)

Term	Meaning in one line
Maillard reaction	Browning reaction between a primary amine drug and a reducing sugar (e.g., lactose) — a classic incompatibility
Sorption	General word for drug moving into/onto packaging (includes adsorption + absorption)
Adsorption	Drug sticking *onto the surface* of the container
Absorption	Drug penetrating *into the body* of the container material
Leaching	Chemicals moving *out of* the packaging *into* the product
Permeation	Gases/moisture passing *through* the packaging wall
Accelerated stability	Testing at high heat/humidity (40 °C/75% RH) to predict long-term behaviour quickly
Stress testing	Deliberately harsh conditions (heat, light, acid/base) to find degradation pathways
DSC (Differential Scanning Calorimetry)	Instrument that detects melting-point changes — used to spot physical interactions
Blister pack	Pre-formed plastic cavities sealed with foil, one dose per cavity
Strip pack	Product sealed between two flexible films (often aluminium), cut into strips

2.4 Drug–excipient compatibility studies — concept and need

Technical concept: Even "inactive" excipients can react with drugs. Compatibility studies mix the drug with each proposed excipient (typically 1:1), store under stress, and check for physical changes (colour, odour, caking) and chemical degradation (assay by HPLC/TLC, DSC/ IR changes).

Simple explanation: Excipients are called "inactive," but that only means they don't treat disease — chemically, some are quite reactive. Lactose looks innocent, but it can brown with amine drugs. Checking compatibility early avoids discovering a brown, degraded tablet after crores are spent.

Why it is needed:

1. Excipients form the bulk of a tablet — the drug sits surrounded by them for years.
2. Reactions can reduce potency, create toxic impurities, or change appearance.
3. Regulatory filings must include compatibility data — no data, no approval.

Methods to detect interaction (classification):

Type	What it detects	Common methods
Physical observation	Colour, odour, caking, liquefaction	Visual inspection after storage at stress conditions (e.g., 40 °C/75% RH for 4 weeks)
Thermal analysis	Disappearance/shift of the drug's melting peak = interaction	DSC/DTA — the drug's sharp melting endotherm vanishes or shifts if it interacts
Spectroscopy	Changes in molecular vibrations	IR spectroscopy — new or shifted peaks suggest interaction
Chromatography	Chemical degradation, new impurity peaks	TLC, HPLC — the gold standard for *chemical* incompatibility
Microscopy	Crystal changes	Hot-stage microscopy

Flowchart — compatibility screening:

```
Drug + each excipient (1:1 mix) in sealed vials
        ↓
Store: room temp (control) + stress (40 °C/75% RH, 4 weeks)
        ↓
Check: colour/odour/caking (physical) → DSC/IR (thermal) → HPLC (chemical)
        ↓
No change → excipient ACCEPTED
Change/degradation → excipient REJECTED or used with caution
```

Classic textbook examples of incompatibility:

1. **Primary amine drug + lactose → brown Maillard reaction** (the most quoted example — this is why amine drugs avoid lactose).
2. **Aspirin + magnesium stearate → accelerated degradation** of aspirin (a classic lubricant incompatibility taught in every pharmaceutics text).

Common confusion: "Excipients are inactive, so they can't react." Wrong — *pharmacologically* inactive does not mean *chemically* inert.

> **Key takeaway:** Screen every excipient against the drug with physical + chemical methods under stress. Reject the fighters.

2.5 Packaging selection for various dosage forms

Technical concept: Packaging must protect the product from moisture, oxygen, light, and mechanical damage; be compatible with the product; be convenient and tamper-evident; and meet regulatory labelling rules.

Simple explanation: Packaging is the medicine's raincoat, sunglasses, and bodyguard in one. A moisture-sensitive tablet in a cheap pack will go soft in one monsoon.

Selection table — match the pack to the dosage form:

Dosage form	Common primary packaging	Why this pack
Tablets (ordinary)	Strip (aluminium), blister (PVC/PVDC or alu-alu), HDPE bottles	Unit-dose protection; alu-alu for moisture-sensitive drugs
Capsules	Blister, HDPE bottles with desiccant	Capsules absorb moisture and become brittle — need dry packs
Oral liquids/syrups	Amber glass or PET bottles with measuring cap	Amber glass blocks light; plastic is lighter/cheaper
Powders/granules (sachets)	Laminated foil sachets	Total moisture barrier for single doses
Sterile injections	Glass ampoules, vials with rubber stoppers	Hermetic seal, sterility maintained
Eye drops	Plastic dropper bottles (LDPE)	Squeezable, sterile, single-patient use

Factors in packaging selection (exam favourite):

1. **Barrier needs** — moisture/oxygen/light sensitivity of the product.
2. **Compatibility** — pack must not react with the product (see §2.6).
3. **Patient convenience** — easy to open (but child-resistant where needed), unit-dose aids compliance.
4. **Cost** — alu-alu blisters protect best but cost more than PVC blisters.
5. **Regulatory** — labelling space, tamper-evidence, light-protection statements.

Analogy: Choosing packaging is like choosing footwear — slippers for home (cheap strip pack for stable tablets), rain boots for monsoon (alu-alu blister for moisture-sensitive drugs), sports shoes for running (dropper bottle for eye drops). Wrong footwear for the weather = failure.

Key takeaway: No single pack suits all products. Match barrier, compatibility, convenience, and cost to the product's needs.

2.6 Drug product and container–closure interaction

Technical concept: The product and its container can affect each other in four ways:

1. **Adsorption:** Drug molecules stick *onto the inner surface* of the container → dose lost on the wall.

- *Classic example:* Nitroglycerin (a heart drug) adsorbs onto PVC plastic — so it is packed in glass, not plastic.

2. **Absorption:** Drug or preservative penetrates *into* the container material itself.

- *Classic example:* Preservatives (e.g., benzalkonium chloride) can be absorbed by rubber closures, leaving an eye drop under-preserved.

3. **Leaching (extractables):** Chemicals migrate *from* the packaging *into* the medicine.

- *Classic example:* Plasticisers (like DEHP) can leach from PVC into liquid products.

4. **Permeation:** Moisture, oxygen, or volatile drug components pass *through* the container wall.

- *Classic example:* Moisture entering through a thin plastic bottle softens hygroscopic tablets; volatile oils escape through poor seals.

Simple explanation: The container is not an invisible wall — things move both ways. Medicine can stick to the pack or soak into it (patient gets less drug), and pack chemicals can leak into the medicine (patient gets impurities). Testing these interactions is a regulatory expectation.

Diagram — draw it: A cross-section of a bottle wall. Draw four labelled arrows: (1) arrow from liquid to wall surface — "adsorption: drug sticks on surface"; (2) arrow from liquid into the wall — "absorption: drug soaks into plastic"; (3) arrow from wall into liquid — "leaching: plastic chemicals enter medicine"; (4) arrow through the wall from outside — "permeation: moisture/oxygen passes through."

Additional classic case: Glass vials can shed tiny glass flakes (**delamination**) into injectable products on long storage — a well-known container–closure concern for parenterals.

Key takeaway: Think in both directions — product → pack (sorption losses) and pack → product (leachable impurities).

2.7 Introduction to ICH Q1 — stability guidelines for new drug substances and products

Technical concept: ICH Q1 is the family of guidelines on stability testing. **Q1A(R2)** covers stability testing of new drug substances and products: it defines *what* to test (physical, chemical, microbiological attributes), *how long*, and *under which* temperature/humidity conditions, so that a shelf life and storage label can be justified.

Simple explanation: Every medicine label says "Expiry: 2 years" and "Store below 30 °C." Those claims are not guesses — they are *proven* by stability studies run exactly the way ICH Q1 describes. Without this proof, regulators will not approve the product.

Purpose of stability testing (need):

1. Fix the **shelf life/expiry period**.
2. Decide the **storage statement** on the label ("store below 30 °C", "protect from moisture").
3. Confirm the **packaging** actually protects the product.
4. Detect **degradation products** and ensure they stay within safe limits.

Standard ICH Q1A storage conditions (the famous table — learn it):

Study	Storage condition	Minimum duration
Long-term	25 ± 2 °C / 60 ± 5% RH *or* 30 ± 2 °C / 65 ± 5% RH (for hot/humid climates)	12 months (data for filing)
Intermediate	30 ± 2 °C / 65 ± 5% RH	6 months
Accelerated	40 ± 2 °C / 75 ± 5% RH	6 months

(Standard ICH Q1A(R2) conditions as widely taught; always follow the current guideline text for filings.)

Simple explanation of the three studies: Long-term = "real life" (room conditions, slow). Accelerated = "fast-forward" (hot and humid, 6 months predicts ~2 years). Intermediate = the middle path, used when accelerated data shows significant change.

Testing frequency (typical plan): Accelerated — 0, 3, 6 months. Long-term — 0, 3, 6, 9, 12, 18, 24 months (and yearly after). At each point: appearance, assay, degradation products, dissolution (for tablets), moisture, microbial limits.

India context — Zone IVb: The world is divided into climatic zones. India falls in **Zone IVb (hot and very humid)**, so the long-term condition used for Indian filings is **30 °C/65% RH**, not 25 °C/60% RH. A product stable in Europe (Zone II) can fail in India — this is why tropical stability data is a big deal for Indian companies, and why moisture-proof packaging (alu-alu blisters, desiccants) is so common here.

Flowchart — how stability data becomes a label:

```
Drug product in final pack → place in chambers (long-term, accelerated)
        ↓
Test at intervals (appearance, assay, impurities, dissolution, moisture)
        ↓
No significant change at accelerated 6 months → shelf life 24 months proposed
        ↓
Label: "Expiry 24 months from manufacture. Store below 30 °C. Protect from moisture."
```

Common confusion: "Accelerated testing *replaces* long-term testing." No — accelerated data supports the *initial* shelf-life claim; long-term data must continue and confirm it.

> **Key takeaway:** ICH Q1 turns "how long will it last?" from a guess into measured, regulator-accepted proof.

2.8 Infographic concept box — "From powder to protected product"

(For the designer: a horizontal 4-panel strip.)

- **Panel 1 — COMPATIBILITY** (two puzzle pieces): "Drug + excipient tested together. Fighters rejected."
- **Panel 2 — PACKAGING** (blister/bottle icons): "Match the pack to the product: moisture, light, oxygen — blocked."
- **Panel 3 — INTERACTION** (double-headed arrow through a wall): "Watch both directions: drug lost to pack, pack chemicals into drug."
- **Panel 4 — ICH Q1** (calendar + thermometer): "25/60 or 30/65 long-term; 40/75 accelerated. India = Zone IVb: 30 °C/65% RH."

2.9 Pharmacy relevance

A community pharmacist sees the end of this chain daily: brown-spotted tablets (compatibility failure), soft capsules in monsoon (packaging failure), and "do not use after expiry" counselling (stability data). Understanding this chapter helps pharmacists store medicines correctly and spot defective stock.

2.10 India context

India's generic giants (the "pharmacy of the world") run ICH Q1 stability programmes for every product exported to hot/humid markets. CDSCO expects stability data in Indian filings. The ubiquitous **strip pack** in Indian pharmacies is a cost-effective answer to our climate; **alu-alu blisters** are the premium answer for moisture-sensitive drugs. Desiccant sachets in HDPE bottles are standard Indian practice for hygroscopic products.

2.11 Key points

1. Compatibility = drug + excipient cause no harmful change; tested by physical observation, DSC, IR, HPLC under stress.
2. Classic incompatibilities: amine + lactose (Maillard browning); aspirin + magnesium stearate (degradation).
3. Packaging types: primary/secondary/tertiary; select by barrier need, compatibility, convenience, cost, regulation.
4. Container–closure interactions: adsorption, absorption, leaching, permeation — think in both directions.
5. ICH Q1A(R2) conditions: long-term 25 °C/60% RH (or 30 °C/65% RH), intermediate 30 °C/65% RH, accelerated 40 °C/75% RH.
6. India is Zone IVb → long-term testing at 30 °C/65% RH.

2.12 Common confusions

- **Adsorption vs absorption vs leaching:** Adsorption = *on* the surface; absorption = *into* the material; leaching = *out of* the pack into the drug. Direction and location differ.
- **Primary vs secondary packaging:** Primary *touches* the product (blister); secondary holds primaries (carton).
- **Stability vs compatibility:** Compatibility = drug vs excipient *before* formulation; stability = finished product vs *time and environment*.

2.13 Common mistakes

1. Listing only chemical tests for compatibility and forgetting physical observation (colour/odour changes are often the first signal).
2. Writing "store in a cool place" as a stability conclusion — the label needs ICH-justified conditions.
3. Confusing accelerated (40 °C/75% RH, 6 months) with long-term conditions in answers.
4. Forgetting India-specific 30 °C/65% RH in stability answers.

2.14 Mnemonics

- **Container interactions:** "**A**dsorption, **A**bsorption, **L**eaching, **P**ermeation" → "**A** **A**lways **L**ook at **P**ackaging."
- **ICH conditions:** "**L**ong 25/60, **I**ntermediate 30/65, **A**ccelerated 40/75" → "**L**ow, **I**n-between, **A**ggressive."

2.15 Exam summary (one page)

Drug–excipient compatibility studies check that excipients cause no physical/chemical harm to the drug, using visual inspection, DSC (melting-peak changes), IR, and HPLC under stress (e.g., 40 °C/75% RH). Classic incompatibilities: amine + lactose (Maillard browning), aspirin + magnesium stearate. Packaging (primary/secondary/tertiary) is selected by barrier need, compatibility, convenience, cost, and regulation — strips/blisters/HDPE bottles for tablets, amber glass/PET for liquids, ampoules/vials for steriles. Container–closure interactions work both ways: adsorption (nitroglycerin→PVC), absorption (preservatives→rubber), leaching (plasticisers→product), permeation (moisture through walls); glass delamination affects parenterals. ICH Q1A(R2) stability: long-term 25 °C/60% RH or 30 °C/65% RH, intermediate 30 °C/65% RH, accelerated 40 °C/75% RH; tests at intervals cover appearance, assay, impurities, dissolution, moisture. India is Zone IVb → 30 °C/65% RH long-term.

2.16 One-minute revision

Test drug + excipient together before marriage (compatibility). Dress the product for the weather (packaging). Remember the pack is not invisible — things move both ways (adsorption, absorption, leaching, permeation). Prove expiry with ICH Q1: long 25/60 (India: 30/65), accelerated 40/75. No stability data = no approval.

2.17 Exam questions

Short questions

1. Define drug–excipient compatibility. Name two physical and two chemical methods to detect incompatibility.
2. Explain the Maillard reaction with an example. How is it avoided in formulation?
3. Classify packaging into primary, secondary, and tertiary with one example each.
4. Distinguish adsorption, absorption, leaching, and permeation with one example each.
5. State the ICH Q1A storage conditions for long-term, intermediate, and accelerated studies.
6. Why is 30 °C/65% RH used as the long-term condition for India?

MCQs (answers at end)

1. The browning reaction between a primary amine drug and lactose is called:

a) Hydrolysis b) Maillard reaction c) Oxidation d) Photolysis

2. Disappearance of the drug's melting endotherm in DSC suggests:

a) Higher purity b) Drug–excipient interaction c) Better flow d) Higher solubility

3. A blister pack is an example of:

a) Secondary packaging b) Tertiary packaging c) Primary packaging d) None

4. Nitroglycerin is packed in glass rather than PVC because it:

a) Leaches plasticiser b) Adsorbs onto PVC c) Permeates glass d) Oxidises PVC

5. ICH accelerated stability condition is:

a) 25 °C/60% RH b) 30 °C/65% RH c) 40 °C/75% RH d) 50 °C/90% RH

6. India falls in ICH climatic zone:

a) Zone I b) Zone II c) Zone IVa d) Zone IVb

7. Chemicals migrating from packaging into the product is called:

a) Adsorption b) Leaching c) Permeation d) Sorption

8. The ICH guideline family for stability testing is:

a) Q1 b) Q2 c) Q7 d) E6

Answers: 1-b, 2-b, 3-c, 4-b, 5-c, 6-d, 7-b, 8-a

Viva questions

1. Your tablet turned brown after 3 months at 40 °C/75% RH. The formula contains lactose and a primary-amine drug. What happened, and what will you change?
2. Why can't accelerated stability data alone fix the final shelf life?
3. A moisture-sensitive capsule is packed in a PVC blister in Chennai. Suggest a better pack and justify.
4. What is the difference between a compatibility study and a stability study?

Application-based

1. You must select primary packaging for three products: (a) a hygroscopic uncoated tablet, (b) a light-sensitive syrup, (c) a sterile injectable. Recommend a pack for each with two reasons per choice.
2. A company wants to market a European-approved tablet in India without new stability data. As a regulatory advisor, explain why this is risky and what ICH Q1 expects.

2.18 References

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