BP805T · B.Pharm Semester VIII · Theory Notes

Sterile Dosage Forms and Novel Drug Delivery System

Unit II — Oral & Mucosal Delivery Systems

Unit II (6 hours)

Pills & Python Notes

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

Syllabus coverage: Unit II (6 hours).

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CHAPTER 3: Oral and Mucosal Drug Delivery Systems

Learning objectives

- Define gastro-retentive drug delivery systems (GRDDS) and explain why medicines sometimes need to stay in the stomach longer.
- Classify floating, mucoadhesive and expandable gastro-retentive systems.
- Explain the three colon-targeting approaches: pH-triggered, microbially-triggered and time-dependent.
- List buccal, nasal and pulmonary carriers: buccal films, nasal sprays, dry powder inhalers (DPIs), liposomes.
- Explain pulmonary deposition mechanisms: impaction, sedimentation and diffusion.
- Define IVIVC, distinguish Levels A, B and C, and explain biorelevant dissolution testing.

Definitions

- **Oral drug delivery system**: a formulation taken by mouth (swallowed or held in the mouth) to deliver medicine.
- **Gastro-retentive drug delivery system (GRDDS)**: a formulation designed to stay inside the stomach for many hours instead of passing quickly into the intestine.
- **Floating (buoyant) system**: a GRDDS lighter than stomach fluid, so it floats on top of stomach contents like a boat.
- **Effervescent**: producing carbon dioxide (CO_2) gas bubbles when ingredients like sodium bicarbonate meet stomach acid.
- **Mucoadhesion (bioadhesion)**: sticking of a formulation to the mucus layer coating the stomach or intestine wall, like a sticker on wet glass.
- **Expandable (swelling) system**: a tablet that swells after swallowing until it is too big to pass the pylorus (the stomach's exit door).
- **Colon-targeted system**: a formulation that releases its drug only on reaching the colon (large intestine).
- **Buccal delivery**: medicine held between cheek and gum, absorbed through the cheek lining into the blood.
- **Nasal delivery**: medicine sprayed into the nose for absorption through the nasal lining.
- **Pulmonary delivery**: medicine inhaled into the lungs as a mist or powder.
- **Dry powder inhaler (DPI)**: a device delivering medicine as a dry powder; the patient's own breath carries it into the lungs.

- **Liposome**: a tiny bubble made of the same lipid (fat) material as cell membranes, used to carry drugs.
- **IVIVC (in-vitro in-vivo correlation)**: a mathematical relationship between drug release measured in the laboratory (in-vitro) and drug behaviour in the human body (in-vivo).
- **Biorelevant dissolution testing**: laboratory drug-release testing in fluids that copy real stomach and intestinal fluids, not plain water.

Terminology

- **Buoyancy**: tendency to float; a floating tablet is less dense than stomach fluid.
- **Floating lag time**: time before a floating tablet starts floating.
- **Mucus / mucosa**: the slippery protective layer / the moist inner lining of the gut.
- **Pylorus**: the narrow stomach-to-intestine opening — the stomach's "exit door."
- **Absorption window**: the gut region where a drug is best absorbed.
- **First-pass metabolism**: partial destruction of a drug by the liver before it reaches the body.
- **Bioavailability**: fraction of the dose reaching the blood in active form.
- **Deposition**: settling of inhaled particles in the airways or lungs.

Explanation

3.1 Why do we need new oral and mucosal systems?

A swallowed ordinary tablet travels mouth → food pipe → stomach → small intestine → colon, pushed by muscle waves called **peristalsis** (like squeezing toothpaste from a tube). The stomach empties in about 2–3 hours, which is a problem for three drug types: (1) drugs absorbed only in the upper stomach — a narrow **absorption window** — so most of the dose is wasted once the tablet moves on; (2) drugs that must act inside the stomach itself, e.g. antibiotics fighting *H. pylori* bacteria that cause ulcers; (3) drugs that must reach the colon for local action, e.g. medicines for ulcerative colitis — if released in the stomach they are destroyed before reaching the colon. Swallowed drugs also meet the liver first (**first-pass metabolism**), which can destroy much of the dose. **Mucosal routes** — buccal, nasal, pulmonary — place drug on moist, blood-rich linings, so it enters blood quickly and partly avoids the liver. **Key takeaway:** these systems put the drug at the right place at the right time.

3.2 Gastro-retentive systems (GRDDS)

Three tricks keep a formulation in the stomach: **(A) Floating systems** — lighter than stomach fluid, they float on top of stomach contents. *Effervescent* types contain sodium bicarbonate + citric acid, which react with stomach acid to make CO_2 bubbles; trapped in the tablet's gel layer, the bubbles lift it (like the fizz in nimbu soda). *Non-effervescent* types use swellable polymers (e.g. HPMC) that form a light gel coat and trap air — floating with no gas. **(B) Bioadhesive/mucoadhesive systems** — sticky polymers (carbopol, chitosan) glue the tablet to the stomach's mucus layer, like a sticker on a wet tile. **(C) Expandable/swelling systems** — swallowed small, then swell until too big to fit through the pylorus; later they break down and leave normally. **Key takeaway:** floating = rises like a boat; mucoadhesive = sticks like a sticker; expandable = grows too big for the door.

3.3 Colon-targeted systems

The drug must survive the acidic stomach and small intestine and release only in the colon. **(A) pH-triggered** — the tablet's coating does not dissolve in acid but dissolves when gut pH rises toward the colon; only then is the drug released. **(B) Microbially-triggered** — the coating is a polysaccharide (e.g. pectin, guar gum) that human enzymes cannot digest, but colonic bacteria produce enzymes that "eat" it — the most colon-specific approach, since only the colon has that bacterial population. **(C) Time-dependent** — a thick coating or plug opens after a fixed delay (roughly the time needed to reach the colon), like an alarm clock. **Key takeaway:** pH-triggered = coating dissolves as pH rises; microbially-triggered = bacteria chew the coating; time-dependent = a timer opens the drug.

3.4 Buccal, nasal and pulmonary carriers

Buccal films are thin films placed between cheek and gum; they stick, dissolve slowly, and drug passes through the cheek lining into blood — useful when stomach acid or the liver would destroy the drug. **Nasal sprays** deliver a fine mist into the nose; the thin, blood-rich lining absorbs drug very fast — useful in emergencies and for nose-to-brain delivery. **DPIs (dry powder inhalers)** — the patient inhales through the device and their own breath carries the powder deep into the lungs; no propellant gas needed. Used for asthma and COPD medicines. **Liposomes** are tiny fat bubbles resembling cell membranes; they carry water-soluble drugs in their core and fat-soluble drugs in their shell, protecting the drug en route. **Key takeaway:** mucosal carriers give fast absorption with less liver loss than swallowing.

3.5 IVIVC and biorelevant dissolution testing

IVIVC is the mathematical bridge between the laboratory release curve (in-vitro) and the blood-level curve in humans (in-vivo). **Level A** — point-to-point match of fraction released vs fraction absorbed at every time point (strongest). **Level B** — compares only single numbers like time to 50% release vs 50% absorption (weaker). **Level C** — one lab value vs one body value, e.g. time to 50% release vs peak blood level (weakest). **Biorelevant dissolution testing** uses fluids copying real stomach/intestinal fluids (pH, bile salts, enzymes) instead of plain water, predicting patient experience far better and supporting a stronger IVIVC. **Key takeaway:** Level A is the full bridge, B and C are partial; body-like fluids make the lab test trustworthy.

Classification

```
Oral & Mucosal Novel Drug Delivery Systems
│
├── GASTRO-RETENTIVE (stay in stomach)
│      ├── Floating — effervescent (NaHCO₃ + acid → CO₂) / non-effervescent (gel polymers)
│      ├── Mucoadhesive — sticky polymers glue to stomach mucus
│      └── Expandable — swells too big to pass the pylorus
│
├── COLON-TARGETED (release in large intestine)
│      ├── pH-triggered (coating dissolves as pH rises)
│      ├── Microbially-triggered (colonic bacteria digest the coating)
│      └── Time-dependent (delay coating opens after a fixed time)
│
└── MUCOSAL CARRIERS
       ├── Buccal films (cheek → blood, avoids liver)
       ├── Nasal sprays (fast absorption, nose-to-brain possible)
       ├── Pulmonary / DPIs (inhaled powder → deep lungs)
       └── Liposomes (tiny fat-bubble carriers)
```

Mechanisms

Mechanism 1 — Buoyancy and effervescence

Stomach fluid has density ≈ 1 g/mL. If the tablet's density is **below 1 g/mL**, buoyancy wins and it floats.

```
Stomach acid + NaHCO₃ (in tablet) → CO₂ bubbles
        → bubbles trapped in tablet's gel layer
        → tablet density falls below 1 g/mL → TABLET FLOATS
```

The delay before floating starts is the **floating lag time** — kept short so the tablet floats before the stomach empties it.

Mechanism 2 — Mucoadhesion (four steps)

1 **Wetting** — tablet surface contacts the mucus and absorbs moisture. 2. **Chain interpenetration** — polymer chains spread and tangle with mucin chains, like two brushes pressed together. 3. **Bond formation** — hydrogen bonds and van der Waals forces grip the mucin. 4. **Retention** — the tablet stays glued while drug releases slowly.

Mechanism 3 — Swelling / expansion

```
Small swallowed capsule → absorbs stomach fluid
→ polymer chains uncoil and expand (2–3× size)
→ TOO BIG for the pylorus → RETAINED IN STOMACH
```

Mechanism 4 — pH-dependent coating dissolution

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Stomach (acidic): coating INTACT, no release
→ small intestine (pH rising): still intact
→ colon (pH threshold crossed): coating DISSOLVES → drug released
```

Mechanism 5 — Enzymatic degradation by colonic bacteria

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Polysaccharide coating (pectin/guar gum)
→ stomach & small intestine: human enzymes cannot digest it — passes safely
→ colon: bacterial enzymes digest the coating → DRUG RELEASED where bacteria live
```

Mechanism 6 — Pulmonary deposition (particle size decides the landing site)

- **Impaction** (>5 µm): heavy, fast particles cannot turn at airway branches and crash into upper-airway walls — like a speeding car missing a sharp turn.
- **Sedimentation** (1–5 µm): particles settle slowly under gravity during a breath-hold, like dust settling in a still room — reaching the deep lungs; the ideal DPI target.
- **Diffusion** (<1 µm): tiny particles wander randomly and mostly get exhaled — least efficient.

Diagrams and flowcharts

Diagram 1 — Floating tablet

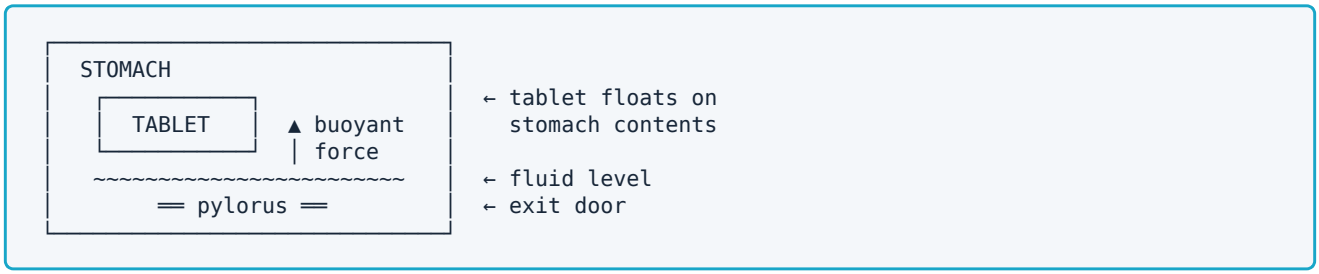


Diagram 2 — Colon-targeting choice

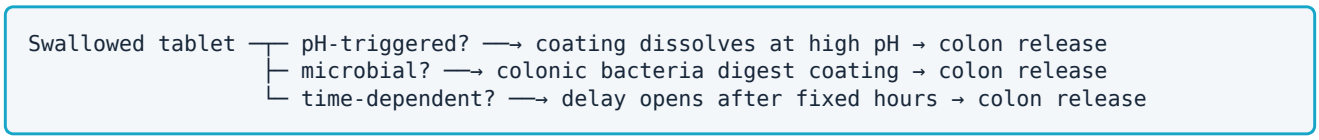


Diagram 3 — IVIVC ladder

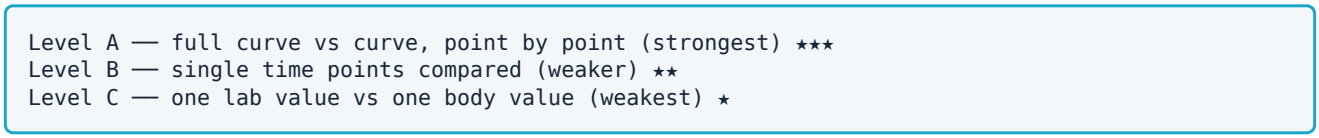
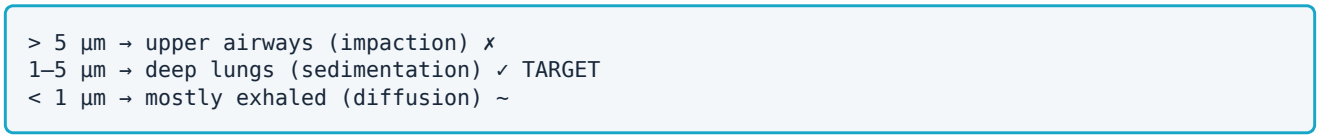


Diagram 4 — DPI particle size vs landing site



Infographic concepts

1 **"Three stay-back tricks"** — three panels: a boat floating (floating), a sticker on a tile (mucoadhesive), a balloon too big for a door (expandable); 5-word caption under each.

2 **"Journey to the colon"** — a road map mouth → stomach → intestine → colon with three vehicles: a pH-key unlocking the colon gate, bacteria eating a wrapper, an alarm clock ringing at the colon.

3 **"Where does the inhaled drug land?"** — branching airways with particles colour-coded: red large (crashes early), green medium (reaches deep), grey tiny (floats out).

Tables

Table 1 — Gastro-retentive approaches compared

Feature	Floating	Mucoadhesive	Expandable
How it stays	Floats on stomach contents	Sticks to stomach wall	Too big for the pylorus
Key ingredient	$NaHCO_3$ (effervescent) or gel polymers	Sticky polymers (carbopol, chitosan)	Swelling polymers
Main risk	Fails if stomach is empty	Mucus sheds and renews	Must degrade afterwards

Table 2 — Colon-targeting approaches compared

Feature	pH-triggered	Microbially-triggered	Time-dependent
Trigger	pH rise in colon	Colonic bacterial enzymes	Fixed time delay

Feature	pH-triggered	Microbially-triggered	Time-dependent
Specificity	Moderate (pH varies)	High (only colon has these bacteria)	Moderate (transit varies)
Failure risk	Early release if pH rises early	Needs normal gut bacteria	Fails if transit is faster/slower

Table 3 — Pulmonary deposition

Mechanism	Size	Lands in	Picture
Impaction	> 5 μm	Upper airways	Car missing a turn
Sedimentation	1–5 μm	Deep lungs ✓	Dust settling in a still room
Diffusion	< 1 μm	Mostly exhaled	Smoke drifting

Table 4 — IVIVC levels

Level	Compared	Strength
A	Full curve vs full curve, point by point	Highest — predicts body from lab
B	Single time points	Medium — limited prediction
C	One lab value vs one body value	Lowest — rough guide

Worked examples and calculations

Example 1 — Floating lag time and extra stomach time. A floating tablet starts floating 4 minutes after swallowing and floats for 8 hours. Ordinary tablets empty from the stomach in 2.5 hours. Extra stomach time gained?

- Step 1: lag time in hours = 4 ÷ 60 = 0.067 h ≈ 0.07 h.
- Step 2: effective floating time = 8 − 0.07 = 7.93 h.
- Step 3: extra time = 7.93 − 2.5 = **5.43 h ≈ 5.4 extra hours**.

Example 2 — Release rate of a floating tablet. A floating tablet holds 500 mg drug, releasing steadily over 8 hours. Release rate per hour?

- Step 1: rate = total drug ÷ total time = 500 ÷ 8 = **62.5 mg/hour**.

Example 3 — Will it float? Tablet mass 0.80 g, volume 1.0 cm^3 after gelling. Stomach fluid ≈ 1.0 g/mL.

- Step 1: density = 0.80 ÷ 1.0 = **0.80 g/mL**.
- Step 2: 0.80 < 1.0 → **yes, it floats**.

Example 4 — Time-dependent colon tablet. Tablet taken 8:00 AM; coating opens 5.5 h later; colon arrival takes ~5 h.

- Step 1: release at 8:00 AM + 5.5 h = **1:30 PM**; arrival ≈ 1:00 PM.
- Step 2: release is after arrival → **drug releases in the colon** (but if transit were faster, it would open too early — the weakness of time systems).

Analogies

1. **Floating tablet = a boat** — lighter than the fluid it sits in, so it rides on top and avoids the exit.
2. **Effervescence = nimbu soda** — baking-soda fizz lifts things up; trapped CO_2 bubbles lift the tablet.
3. **Mucoadhesion = sticker on a wet tile** — press and it grips the slippery surface.
4. **Expandable system = inflated balloon at a doorway** — deflated it passes; inflated it cannot.
5. **Microbial coating = parcel wrapped in food** — only the colon's bacteria can "eat" the wrapper, so it opens only at their address.

Pharmacy relevance

- **Stomach infections:** GRDDS keeps antibiotics in the stomach longer against *H. pylori*, improving ulcer therapy.
- **Once-daily dosing:** an 8–12 h floating/expandable tablet can replace 2–3 doses, improving compliance.
- **Colon diseases:** ulcerative colitis medicines delivered straight to the colon give strong local effect with fewer whole-body side effects.
- **Emergencies:** nasal sprays absorb within minutes when a patient cannot swallow.
- **Fewer trials:** a strong Level A IVIVC lets formulators predict human performance from lab tests, saving time, money and animal testing.

India context

- **Stomach infections are widespread in India** — floating antibiotic systems are directly relevant to Indian ulcer/gastritis practice.
- **Asthma/COPD burden:** Rotahaler-type DPIs are widely used and affordable in India; correct inhaler-technique counselling is a core pharmacist skill.
- **Cost sensitivity:** floating tablets use cheap excipients (sodium bicarbonate, citric acid, HPMC), suiting Indian generic manufacturers.
- **Regulatory note:** novel systems are evaluated as per the latest CDSCO/DCGI guidelines — confirm the current edition before filing.

Key points

- Mucoadhesion: wetting → chain entanglement → bonding → retention.
- Colon targeting: pH-triggered, microbially-triggered (most colon-specific), time-dependent.
- Buccal, nasal and pulmonary routes act fast and partly avoid liver first-pass.
- Ideal DPI particle size for deep lungs: 1–5 μm (sedimentation).
- IVIVC: Level A = point-to-point curve match; B and C = single values.

- Biorelevant fluids copy real body fluids for truer lab-to-body prediction.

Common confusions

1 **Floating vs mucoadhesive** — floating rides on stomach fluid; mucoadhesive glues to the stomach wall. Different tricks, same goal.

2 **Effervescent vs non-effervescent floating** — effervescent needs acid + bicarbonate to make gas; non-effervescent floats on a light gel with no gas.

3 **pH-triggered vs microbially-triggered colon delivery** — pH depends on gut pH (varies between people); microbial depends on colon bacteria (more reliable).

4 **DPI vs nasal spray** — DPI is breathed into the lungs as dry powder; nasal spray is sprayed into the nose as mist.

5 **IVIVC vs bioequivalence** — IVIVC links lab release to body behaviour for one formulation; bioequivalence compares two formulations in the body.

Common mistakes

1 Saying a floating tablet "sinks slowly" — its density must be **below** stomach fluid or it will not float.

2 Forgetting effervescent systems need stomach acid — poor gas formation in very low-acid patients.

3 Treating mucoadhesion as permanent — mucus constantly renews and sheds, so the tablet eventually detaches.

4 Using >5 µm particles in a DPI and expecting deep-lung delivery — they impact in the upper airways.

5 Calling any lab-vs-body comparison "Level A" — Level A needs a full point-to-point curve match.

6 Testing dissolution in plain water and claiming it predicts the body — without biorelevant fluids the prediction is weak.

Mnemonics

1 **GRDDS tricks — "FMS": F**loating, **M**ucoadhesive, **S**welling.

2 **Colon triggers — "PMT": P**H-triggered, **M**icrobially-triggered, **T**ime-dependent.

3 **Pulmonary deposition — "ISD": I**mpaction (big, upper), **S**edimentation (medium, deep ✓), **D**iffusion (tiny, exhaled).

4 **IVIVC — "A-B-C, strong to weak": A** = all points match, **B** = both single times, **C** = one comparison.

Exam summary

Gastro-retentive systems prolong stomach stay via floating (effervescent: $NaHCO_3$ + acid → CO_2; non-effervescent: gel polymers), mucoadhesion (wetting → entanglement → bonding → retention) and swelling (too big for the pylorus). Colon targeting uses pH-triggered coatings, microbially-triggered coatings digested by colonic bacteria (most specific), or time-dependent release. Buccal films, nasal

sprays, DPIs and liposomes give fast absorption with less first-pass loss. Inhaled particles deposit by impaction (>5 µm, upper airways), sedimentation (1–5 µm, deep lungs — ideal) or diffusion (<1 µm, exhaled). IVIVC: Level A (point-to-point, strongest), B and C (single values). Biorelevant fluids give a truer lab-to-body prediction.

One-minute revision

Stay-back tricks: **FMS** — Floating, Mucoadhesive, Swelling. Colon: **PMT** — pH, Microbial, Time. Inhaled: **ISD** — Impaction (>5 µm), Sedimentation (1–5 µm ✓), Diffusion (<1 µm). IVIVC: A = full curve, B/C = single values. Density below 1 g/mL = floats.

MCQs

1 A floating tablet must have a density: (a) Greater than stomach fluid (b) Equal to stomach fluid (c) Less than stomach fluid (d) Exactly 1.5 g/mL — **Answer: (c)**

2 The gas responsible for floating in effervescent systems is: (a) Oxygen (b) Nitrogen (c) Carbon dioxide (d) Hydrogen — **Answer: (c)**

3 A common gel-forming polymer in non-effervescent floating tablets is: (a) HPMC (b) Lactose (c) Talc (d) Magnesium stearate — **Answer: (a)**

4 Mucoadhesion is sticking of the formulation to: (a) Bone (b) The mucus layer (c) Skin (d) Teeth — **Answer: (b)**

5 An expandable system stays in the stomach because it: (a) Floats (b) Sticks to the wall (c) Becomes too large to pass the pylorus (d) Dissolves instantly — **Answer: (c)**

6 The most colon-specific targeting approach is: (a) pH-triggered (b) Microbially-triggered (c) Time-dependent (d) Sugar-coated — **Answer: (b)**

7 In pH-triggered colon delivery the coating dissolves when: (a) pH falls (b) pH rises to the threshold (c) Temperature falls (d) Light strikes it — **Answer: (b)**

8 A buccal film is placed: (a) Under the tongue (b) Between the cheek and gum (c) In the nose (d) On the skin — **Answer: (b)**

9 The main advantage of buccal/nasal routes over swallowing is: (a) Slower absorption (b) Reduced first-pass liver metabolism (c) Larger dose needed (d) More side effects — **Answer: (b)**

10 In a DPI the powder is carried into the lungs by: (a) Propellant gas (b) The patient's own inhaled breath (c) An electric pump (d) Gravity — **Answer: (b)**

11 Ideal particle size for deep-lung deposition is: (a) Above 10 µm (b) 1–5 µm (c) Below 0.1 µm (d) Above 50 µm — **Answer: (b)**

12 Particles >5 µm deposit in upper airways mainly by: (a) Sedimentation (b) Diffusion (c) Impaction (d) Dissolution — **Answer: (c)**

13 A liposome is best described as: (a) An oil droplet in water (b) A tiny bubble with a lipid bilayer shell (c) A solid metal particle (d) A gas-filled capsule — **Answer: (b)**

14 Level A IVIVC means: (a) One lab value matches one body value (b) Point-to-point match of lab release and body absorption curves (c) Two formulations are identical (d) Full absorption — **Answer: (b)**

Viva and application questions

1 Why do we need GRDDS when ordinary tablets work? — **The stomach empties in 2–3 h, wasting drugs absorbed only in the upper gut or acting in the stomach.**

2 How does an effervescent floating tablet start floating? — **$NaHCO_3$ reacts with stomach acid to form CO_2 bubbles trapped in the gel layer, lowering density.**

3 What is floating lag time? — **The time a floating tablet takes before it begins to float.**

4 Name two mucoadhesive polymers. — **Carbopol and chitosan.**

5 Why can an expandable system not leave the stomach early? — **It swells larger than the pylorus opening and cannot pass through.**

6 Which colon trigger is most reliable and why? — **Microbially-triggered — only the colon has the bacteria that digest the coating.**

7 Why are 1–5 µm particles ideal for DPIs? — **They deposit in deep lungs by sedimentation; larger impact early, smaller are exhaled.**

8 What is the difference between Level A and Level C IVIVC? — **Level A matches full curves point by point; Level C compares only one lab value with one body value.**

9 What are biorelevant dissolution fluids? — **Lab fluids copying real stomach/intestinal fluids (pH, bile salts, enzymes) for truer prediction.**

10 What is the main weakness of time-dependent colon systems? — **Gut transit time varies between patients, so the drug may release too early or too late.**

References

- Vyas, S. P. and Khar, R. K. *Targeted and Controlled Drug Delivery: Novel Carrier Systems* — confirm the current edition.
- Ansel's *Pharmaceutical Dosage Forms and Drug Delivery Systems* — confirm the current edition.
- Aulton's *Pharmaceutics: The Design and Manufacture of Medicines* — confirm the current edition.
- PCI model syllabus and latest CDSCO/DCGI guidance for novel drug delivery systems — as per the latest guidelines, confirm the current edition.