BP602T · B.Pharm Semester VI · Theory Notes

Biopharmaceutics and Pharmacokinetics

Unit II — Bioavailability and Bioequivalence

Unit II (10 hours)

Pills & Python Notes

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

Syllabus coverage: Unit II (10 hours).

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CHAPTER 4: Bioavailability and Bioequivalence — How Much Reaches the Blood (Unit II)

4.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define bioavailability and state its objectives.

2 Distinguish absolute from relative bioavailability with the equations.

3 Measure bioavailability using plasma data (AUC method) and urinary excretion data (cumulative and sigma-minus methods).

4 Describe the protocol of bioavailability/bioequivalence studies (design, washout, statistics).

5 Define bioequivalence and explain the 80–125% acceptance rule.

6 Solve numericals on absolute/relative bioavailability and urinary excretion kinetics.

4.2 What Is Bioavailability? (Start From Zero)

Technical concept: Bioavailability (F) is the rate and extent to which the active drug reaches the systemic circulation unchanged. Objectives: (a) to know how much of the dose actually works, (b) to compare formulations (generic vs innovator), (c) to design correct doses.

Simple explanation: You swallow 100 mg, but first-pass metabolism destroys 70 mg in the liver — only 30 mg reaches blood. Bioavailability = 30%. It answers: *"How much of what I gave actually arrived?"*

Analogy: You send 100 letters; 30 reach the destination. Delivery success rate = 30%. The post office losing letters = first-pass metabolism + poor absorption.

Why is F less than 100%? Poor dissolution, poor permeability, first-pass metabolism, degradation in gut (acid, enzymes), efflux transporters (P-glycoprotein pumping drug back out).

Terminology box:

Term	Meaning
Absolute bioavailability	Compares oral (or any extravascular) route with IV (F = AUCoral/Dose ÷ AUCiv/Dose)
Relative bioavailability	Compares a test formulation with a reference formulation by the same route
Bioequivalence (BE)	Two products are bioequivalent if their rate AND extent of absorption do not differ significantly

Term	Meaning
Pharmaceutical equivalence	Same drug, same dose, same dosage form (but may still differ in absorption)
Therapeutic equivalence	Pharmaceutical equivalents that are also bioequivalent → same effect

4.3 Absolute vs Relative Bioavailability — Derivations

Absolute bioavailability

Derivation:

Step 1: For IV, F = 1 (100%) by definition, so AUCiv = (F × Doseiv)/CL with F = 1 → AUCiv = Doseiv/CL. Step 2: For oral, AUCev = (F × Doseev)/CL. Step 3: Divide: AUCev/AUCiv = (F × Doseev)/Doseiv. Step 4: **F = (AUCev / Doseev) ÷ (AUCiv / Doseiv)**

(Dose normalisation is needed because the IV and oral doses may differ.)

Relative bioavailability

Frel = (AUCtest / Dosetest) ÷ (AUCref / Doseref)

If both doses are equal, Frel = AUCtest / AUCref — a simple ratio.

Key takeaway: Absolute F needs an IV reference; relative F compares two non-IV products (e.g., generic vs brand).

4.4 Methods of Measurement of Bioavailability

A. Plasma data method

Measure plasma concentration vs time after test and reference doses → calculate AUC by trapezoidal rule → apply the F equations above. Cmax and Tmax give the *rate* of absorption.

B. Urinary excretion data method

Technical concept: For drugs substantially excreted unchanged in urine, the amount in urine mirrors the amount in the body.

Method 1 — Cumulative amount: Collect all urine, measure total unchanged drug excreted (Xu∞). Then: **F = (Xu∞)ev / (Xu∞)iv** (dose-normalised if doses differ)

Method 2 — Sigma-minus (amount remaining to be excreted):

Derivation:

Step 1: Xu∞ = total ever excreted; Xut = excreted up to time t. Amount remaining = Xu∞ − Xut. Step 2: This remaining amount declines by first-order kinetics: Xu∞ − Xut = Xu∞ × e^(−ke×t). Step 3: Take log: **log(Xu∞ − Xut) = log Xu∞ − (ke × t)/2.303** Step 4: Plot log(Xu∞ − Xut) vs t →

straight line, slope = −ke/2.303. Same ke as from plasma!

Simple explanation: The sigma-minus plot is the urine version of the plasma log plot — it gives ke without drawing blood.

Excretion rate method (alternative): Plot log(dXu/dt) vs midpoint time → slope also = −ke/2.303.

4.5 CALCULATION BOXES

Calculation 1 — Absolute bioavailability

Question: 200 mg oral dose: AUC = 60 µg·h/mL. 100 mg IV dose: AUC = 80 µg·h/mL. Find F.

Solution:

Step 1: Dose-normalise: AUCoral/Dose = 60/200 = 0.3; AUCiv/Dose = 80/100 = 0.8 Step 2: F = 0.3/0.8 = **0.375 = 37.5%**

Common mistake: Dividing AUCs directly (60/80 = 75%) without dose normalisation — wrong when doses differ!

Calculation 2 — Relative bioavailability

Question: Generic tablet 500 mg: AUC = 95 µg·h/mL. Brand tablet 500 mg: AUC = 100 µg·h/mL. Find Frel.

Solution: Doses equal → Frel = 95/100 = **0.95 = 95%** — within the 80–125% BE window.

Calculation 3 — ke from sigma-minus data

Question: Xu∞ = 400 mg. At 4 h, Xut = 300 mg; at 8 h, Xut = 375 mg. Find ke.

Solution:

Step 1: At 4 h: Xu∞ − Xut = 100 mg → log = 2.000. At 8 h: 400 − 375 = 25 mg → log = 1.398. Step 2: Slope = (1.398 − 2.000)/(8 − 4) = −0.602/4 = −0.1505 Step 3: ke = 0.1505 × 2.303 = **0.347 h^{-1}** ($t_{½}$ = 2 h — check: remaining halved twice in 8 h... 400→100 in 4 h is two half-lives → $t_{½}$ = 2 h ✓)

Calculation 4 — Cumulative urinary method

Question: After 500 mg oral, Xu∞ = 150 mg; after 250 mg IV, Xu∞ = 200 mg. Find F.

Solution: Dose-normalise: oral: 150/500 = 0.3; IV: 200/250 = 0.8. F = 0.3/0.8 = **37.5%**.

4.6 Protocol for Bioavailability / Bioequivalence Studies

Element	Standard requirement (simple words)
Design	Randomised, two-period, two-sequence **crossover** — each volunteer takes both test and reference with a gap
Volunteers	Healthy adult volunteers (usually 24+)
Washout period	Gap ≥ 5 half-lives between periods so the first dose is fully gone
Fasting	Usually fasting (food effect studied separately if needed)

Element	Standard requirement (simple words)
Sampling	Blood samples covering absorption, peak, and elimination (up to 3+ half-lives)
Parameters compared	AUC (extent) and Cmax (rate); Tmax descriptively
Statistics	Log-transform AUC and Cmax; 90% confidence interval of test/reference ratio must fall within **80.00–125.00%**
Ethics	Institutional ethics committee approval + informed consent

Why crossover? Each person is their own control — removes between-person differences.

Why 80–125%? On the log scale this range is symmetric (±20%); it is the internationally accepted "no significant difference" window.

Flowchart — BE study:

```
Volunteers recruited → Randomised to Sequence 1 (Test then Ref) or 2 (Ref then Test)
        |                                   |
   Period 1 dosing → blood sampling → Washout (≥5 t½) → Period 2 dosing → sampling
        |
        ▼
Calculate AUC, Cmax for each → 90% CI of ratio → within 80–125%? ──YES──► BIOEQUIVALENT
```

4.7 Infographic Concept Box — "F in One Glance"

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ABSOLUTE F = (AUC ÷ Dose)oral ÷ (AUC ÷ Dose)IV     [needs IV data]
RELATIVE F = (AUC ÷ Dose)test ÷ (AUC ÷ Dose)ref   [generic vs brand]
URINE F    = (Xu∞ ÷ Dose)ev ÷ (Xu∞ ÷ Dose)iv
SIGMA-MINUS: log(Xu∞ − Xut) vs t → slope gives ke
BE RULE: 90% CI of Test/Ref ratio within 80–125% for AUC and Cmax
```

4.8 Pharmacy Relevance, India Context, Key Points

Pharmacy relevance: Pharmacists assure patients that CDSCO-approved generics are bioequivalent — same AUC/Cmax within 80–125% — so switching brands is safe. This chapter is the science behind that assurance.

India context: India is the "pharmacy of the world" — thousands of generic BE studies are conducted in Indian CROs (contract research organisations) following CDSCO/ICH guidelines. The 80–125% rule is applied to every generic approval.

Key points:

1. Bioavailability = rate + extent of unchanged drug reaching blood.
2. Absolute F = dose-normalised AUC ratio vs IV; Relative F = vs reference product.
3. Plasma method: AUC by trapezoid; urine methods: cumulative Xu∞ and sigma-minus.
4. Sigma-minus: log(Xu∞ − Xut) = log Xu∞ − ket/2.303.
5. BE study: crossover, washout ≥ 5 t½, fasting, 90% CI within 80–125% for AUC and Cmax.
6. Objectives of BA studies: compare formulations, set doses, support generic approvals.

Common confusions:

- Bioavailability vs bioequivalence: BA is a property of one product; BE is a comparison of two.
- Pharmaceutical equivalence ≠ bioequivalence (same ingredients can still absorb differently).
- Cmax reflects rate; AUC reflects extent.

Common mistakes:

- Forgetting dose normalisation when IV and oral doses differ.
- Using 5 half-lives washout as "5 hours" — it depends on the drug's t½.

Mnemonic — "80 to 125 Keeps Patients Alive": the BE acceptance window.

4.9 Exam Summary and One-Minute Revision

Exam summary: Define BA, objectives. Absolute/relative derivations. Plasma and urinary methods with sigma-minus derivation. Full BE protocol table + flowchart. 80–125% rule. Numericals.

One-minute revision:

- F = (AUC/Dose)ev ÷ (AUC/Dose)iv.
- Frel = AUCtest/AUCref (equal doses).
- Urine: Xu∞ ratio; sigma-minus gives ke.
- Crossover, washout ≥ 5 t½, fasting, 90% CI 80–125%.

4.10 Exam Questions

MCQs (with answers):

1 Absolute bioavailability compares with: a) oral solution b) IV c) IM d) SC. **Answer: b) IV**

2 BE acceptance range for AUC ratio: a) 70–130% b) 80–125% c) 90–110% d) 75–125%. **Answer: b) 80–125%**

3 Washout period should be at least: a) 2 t½ b) 3 t½ c) 5 t½ d) 10 t½. **Answer: c) 5 t½**

4 Sigma-minus plot gives: a) Vd b) ke c) CL d) F. **Answer: b) ke**

5 Cmax indicates ___ of absorption: a) extent b) rate c) neither d) both equally. **Answer: b) rate**

6 In a crossover study each volunteer receives: a) test only b) reference only c) both formulations d) placebo. **Answer: c) both formulations**

7 F = 0.6 means: a) 60% excreted b) 60% reaches blood unchanged c) 60% metabolised d) 60% bound. **Answer: b) 60% reaches blood unchanged**

8 Which parameter is log-transformed in BE statistics? a) Tmax b) AUC and Cmax c) ke d) Vd. **Answer: b) AUC and Cmax**

Viva questions:

1 Why is IV the reference for absolute bioavailability?

2 Why log-transform AUC and Cmax before statistics?

3 What is the purpose of the washout period?

4 When is the urinary method preferred over plasma method?

Application-based:

1 A patient fears switching from a costly brand to a Jan Aushadhi generic. How do you reassure using bioequivalence?

2 A BE study shows Cmax ratio 90% CI = 78–110%. Is the product bioequivalent? Why?

Numericals (with worked solutions):

N1. Oral 400 mg: AUC 120; IV 200 mg: AUC 100. Find F. *Solution:* 120/400 = 0.3; 100/200 = 0.5. F = 0.3/0.5 = **60%**.

N2. Test AUC 88, Ref AUC 100 (same dose). Frel? BE acceptable? *Solution:* Frel = **88%** — inside 80–125% for point estimate, but BE needs the full 90% CI; point estimate alone is not enough.

N3. Xu_∞ oral (500 mg) = 180 mg; Xu_∞ IV (100 mg) = 90 mg. F? *Solution:* 180/500 = 0.36; 90/100 = 0.9. F = 0.36/0.9 = **40%**.

N4. Sigma-minus: Xu_∞ = 500 mg; at 3 h remaining = 250 mg. Find ke and $t_{½}$. *Solution:* Remaining halved in 3 h → $t_{½}$ = **3 h**; ke = 0.693/3 = **0.231 h^{-1}**.

4.11 References

1 Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. McGraw-Hill.

2 Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*. Lea & Febiger.

3 Rowland M, Tozer TN. *Clinical Pharmacokinetics and Pharmacodynamics*. Wolters Kluwer.

4 Brahmankar DM, Jaiswal SB. *Biopharmaceutics and Pharmacokinetics: A Treatise*. Vallabh Prakashan.

CHAPTER 5: BCS, Dissolution Testing, IVIVC, Biowaivers and Bioavailability Enhancement (Unit II)

5.1 Learning Objectives

After studying this chapter, you will be able to:

1 Define the Biopharmaceutics Classification System (BCS) and place drugs in Classes I–IV.

2 Explain the Biopharmaceutics Drug Disposition Classification System (BDDCS).

3 Describe dissolution apparatus I–VII and state the use of each.

4 Explain biorelevant dissolution media (FaSSIF/FeSSIF).

5 Define IVIVC, describe Levels A, B, C, and list applications.

6 State the criteria for biowaivers.

7 List and explain methods of enhancement of bioavailability.

5.2 The Biopharmaceutics Classification System — BCS (Start From Zero)

Technical concept: The BCS (proposed by Amidon and colleagues) classifies drugs by two properties: **solubility** (high/low) and **intestinal permeability** (high/low). A drug has HIGH solubility if its highest dose dissolves in 250 mL of water across pH 1–7.5; HIGH permeability if ≥85–90% is absorbed in humans.

Simple explanation: BCS puts every drug into one of four boxes based on two yes/no questions: "Does it dissolve easily?" and "Does it cross the gut wall easily?" The box predicts what limits its absorption.

The four classes:

Class	Solubility	Permeability	Absorption limited by	Examples
I	High	High	Gastric emptying (dissolves and crosses easily)	Paracetamol, propranolol, metoprolol
II	Low	High	Dissolution (crosses well once dissolved)	Phenytoin, griseofulvin, nifedipine
III	High	Low	Permeability (dissolves but crosses poorly)	Cimetidine, atenolol
IV	Low	Low	Both — poorest absorption	Furosemide, hydrochlorothiazide

Analogy: Class I = sugar in hot tea (dissolves fast, "absorbed" fast). Class II = sand in water (needs stirring = formulation help). Class III = a shy guest (arrives easily but won't enter). Class IV = a rock (hard everywhere).

BDDCS (Biopharmaceutics Drug Disposition Classification System): Uses solubility + **extent of metabolism** instead of permeability. Predicts: highly metabolised drugs → transporter effects less important; poorly metabolised drugs → transporters matter. (Why it exists: metabolism data is easier to get early in development than human permeability data.)

Key takeaway: BCS Class I drugs are the best candidates for biowaivers; Class II needs dissolution help; Class IV is the hardest.

5.3 In-Vitro Dissolution Test Apparatus I–VII

Technical concept: Dissolution testing measures how fast the tablet/capsule releases drug into a standard liquid under controlled conditions — it is the in-vitro predictor of in-vivo absorption for poorly soluble drugs.

Simple explanation: We drop the tablet in a beaker of warm liquid, stir it like the stomach would, and measure how much drug dissolves over time. If it dissolves well here, it will likely absorb well in the patient.

Apparatus	Name	How it works	Used for
I	Basket	Tablet in a rotating wire basket in the medium	Capsules, floating dosage forms
II	Paddle	Rotating paddle stirs medium; tablet sits at bottom	Tablets — the most common
III	Reciprocating cylinder	Cylinders move up-down between media rows	Extended-release; can change pH per row (stomach → intestine)
IV	Flow-through cell	Fresh medium continuously flows past the dosage form	Poorly soluble drugs, implants, powders
V	Paddle over disc	Paddle with a disc holding the dosage form	Transdermal patches
VI	Cylinder (rotating)	Dosage form on a rotating cylinder	Transdermal patches (alternative)
VII	Reciprocating holder	Holders dip in/out of medium	Extended-release, stents, implants

Standard conditions: 900 mL medium, 37 ± 0.5 °C (body temperature), paddle 50–75 rpm or basket 100 rpm.

Mnemonic — "Big People Ride Fast Past Caves Regularly": **B**asket, **P**addle, **R**eciprocating cylinder, **F**low-through, **P**addle-over-disc, **C**ylinder, **R**eciprocating holder.

5.4 Biorelevant Dissolution Media

Technical concept: Simple buffers don't mimic gut fluids. Biorelevant media contain bile salts and phospholipids like real intestinal fluid.

Medium	Mimics	Key contents
FaSSIF	Fasted-state small intestinal fluid	Bile salts + lecithin, pH 6.5
FeSSIF	Fed-state small intestinal fluid	Higher bile salts + fats, pH 5.0
FaSSGF	Fasted-state simulated gastric fluid	Pepsin, low pH

Simple explanation: Testing a tablet in plain water is like testing a raincoat in sunshine — biorelevant media are the "real rain" of the gut, giving predictions that match patients better.

5.5 In-Vitro In-Vivo Correlation (IVIVC)

Technical concept: IVIVC is a mathematical relationship between an in-vitro property (usually dissolution rate) and an in-vivo response (usually absorption rate or plasma levels). If established, dissolution testing can replace human studies for formulation changes.

Levels:

Level	What is correlated	Usefulness
A	Point-to-point: entire dissolution curve vs entire absorption curve	Best — can predict full plasma profile; allows biowaivers for minor changes
B	Mean dissolution time vs mean absorption time (single numbers)	Weak — not predictive of profile
C	One dissolution point (e.g., % at 2 h) vs one PK parameter (e.g., Cmax)	Weakest — single point only

Applications: (1) justify dissolution specifications, (2) support minor formulation/process changes without new human studies, (3) reduce BE study burden, (4) guide formulation development.

Deconvolution: The math that extracts the in-vivo absorption curve from plasma data (e.g., Wagner–Nelson method for one-compartment drugs) so it can be compared with dissolution.

Key takeaway: Level A IVIVC is the gold standard — full curve against full curve.

5.6 Biowaivers

Technical concept: A biowaiver is regulatory permission to SKIP the human bioequivalence study, granted when in-vitro evidence is strong enough.

Criteria (simplified):

1 BCS Class I (high solubility, high permeability) — and in some guidelines Class III.

2 Rapid dissolution: ≥85% dissolved in 30 min in standard media.

3 No narrow therapeutic index (not for critical-dose drugs like warfarin, digoxin).

4 Excipients must not affect absorption; same dosage form and strength.

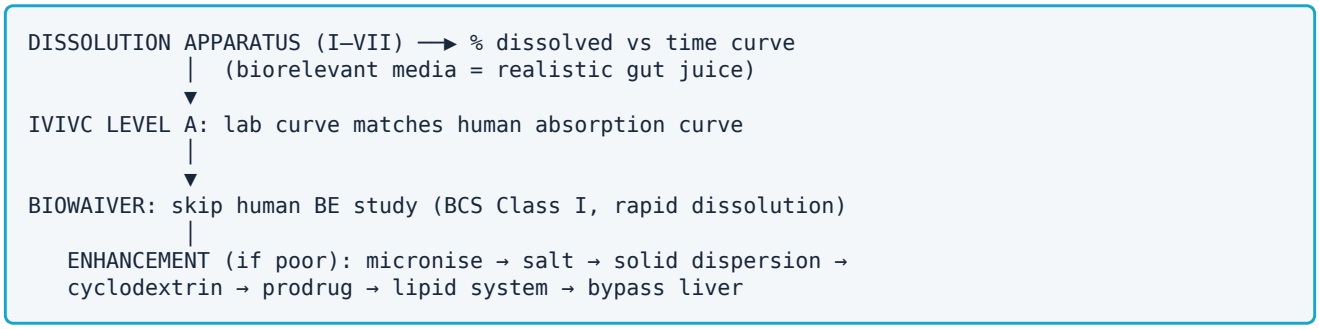
Simple explanation: If the drug dissolves like sugar and crosses like a VIP (Class I), and the tablet releases it fast, regulators trust the lab test and waive the human trial — saving time, money, and volunteers.

5.7 Methods of Enhancement of Bioavailability

Strategy	How it works	Example
Micronisation / nanosizing	Smaller particles → larger surface area → faster dissolution (Noyes–Whitney)	Griseofulvin, fenofibrate
Salt formation	More soluble salt form	Diclofenac sodium
Solid dispersions	Drug dispersed in water-soluble carrier (PEG)	—
Complexation (cyclodextrins)	Drug sits inside a soluble molecular "bucket"	Itraconazole
Prodrug approach	Inactive lipophilic form → converted in body	Enalapril → enalaprilat
Lipid-based systems (SEDDS)	Drug dissolved in oil/surfactant that emulsifies in gut	Cyclosporine microemulsion
Permeation enhancers	Open tight junctions temporarily	—
Avoid first-pass	Sublingual, transdermal, rectal routes bypass liver	Nitroglycerin sublingual
Efflux inhibition	Block P-glycoprotein that pumps drug back out	—
pH adjustment	Buffered formulation keeps drug unionised	—

Key takeaway: Match the fix to the BCS class — Class II needs dissolution help; Class III needs permeability help; first-pass victims need alternative routes.

5.8 Infographic Concept Box — "From Lab Beaker to Patient"



5.9 Pharmacy Relevance, India Context, Key Points

Pharmacy relevance: Dissolution failure is why some cheap tablets don't work — pharmacists should prefer brands with proven quality. Counselling "take with fatty food" for griseofulvin uses the enhancement principle.

India context: Indian Pharmacopoeia includes dissolution tests for many tablets — a key quality gate for the domestic market. CDSCO grants biowaivers per national guidelines aligned with international norms, speeding affordable generics to patients.

Key points:

1 BCS: solubility × permeability → Classes I–IV; Class I best for biowaivers.

2 High solubility = highest dose in 250 mL across pH 1–7.5.

3 Apparatus: I basket, II paddle (commonest), III reciprocating cylinder, IV flow-through, V paddle-over-disc, VI cylinder, VII reciprocating holder.

4 Biorelevant media: FaSSIF (fasted), FeSSIF (fed).

5 IVIVC Level A (point-to-point) > B > C; applications include spec-setting and avoiding repeat BE studies.

6 Biowaiver needs: BCS I (sometimes III), ≥85% in 30 min, no narrow-TI drug.

7 Enhancement: micronisation, salts, solid dispersions, cyclodextrins, prodrugs, lipid systems, bypass routes.

Common confusions:

- BCS vs BDDCS: BCS uses permeability; BDDCS uses metabolism.
- Dissolution vs disintegration: disintegration = breaking into granules; dissolution = molecules entering solution. Dissolution is the absorption-relevant step.
- Biowaiver ≠ no testing — it replaces human testing with strict lab testing.

Common mistakes:

- Calling Apparatus II the basket (it's the paddle; basket is I).
- Thinking Class III drugs need dissolution help — they need permeability help.

5.10 Exam Summary and One-Minute Revision

Exam summary: BCS four classes with examples; BDDCS difference. Apparatus I–VII table with uses. Biorelevant media. IVIVC levels + applications + deconvolution concept. Biowaiver criteria. Enhancement methods table.

One-minute revision:

- BCS: I high/high, II low/high, III high/low, IV low/low.
- I basket, II paddle, III recip. cylinder, IV flow-through, V paddle-disc, VI cylinder, VII recip. holder.
- FaSSIF fasted, FeSSIF fed.
- IVIVC A = full curve vs full curve.
- Biowaiver: Class I, 85% in 30 min, no narrow TI.
- Enhance: micronise, salt, solid dispersion, cyclodextrin, prodrug, lipids, bypass liver.

5.11 Exam Questions

MCQs (with answers):

1 BCS Class II: a) high sol/high perm b) low sol/high perm c) high sol/low perm d) low/low. **Answer: b) low sol/high perm**

2 Most commonly used dissolution apparatus: a) I b) II c) IV d) VII. **Answer: b) II (paddle)**

3 Basket apparatus is number: a) I b) II c) III d) IV. **Answer: a) I**

4 FeSSIF mimics: a) fasted stomach b) fed intestine c) fasted intestine d) colon. **Answer: b) fed intestine**

5 Best IVIVC level: a) A b) B c) C d) D. **Answer: a) A**

6 Biowaiver NOT allowed for: a) BCS I b) rapid dissolution c) narrow TI drugs d) same strength. **Answer: c) narrow TI drugs**

7 Cyclodextrin complexation improves: a) permeability b) solubility c) stability only d) taste only. **Answer: b) solubility**

8 Sublingual nitroglycerin avoids: a) dissolution b) first-pass metabolism c) distribution d) excretion. **Answer: b) first-pass metabolism**

Viva questions:

1 Why is Class II absorption dissolution-limited?

2 What is the difference between FaSSIF and FeSSIF?

3 What does Level A IVIVC allow a company to skip?

4 Name two enhancement methods for a BCS Class II drug.

Application-based:

1 A company's BCS Class I generic dissolves 95% in 20 min. Argue for a biowaiver.

2 Griseofulvin absorption doubles with fatty food and micronisation. Explain both using Noyes–Whitney and BCS.

Numericals (with worked solutions):

N1. Highest dose 500 mg dissolves fully in 250 mL at all pH 1–7.5; 95% absorbed in humans. BCS class? *Solution:* High solubility + high permeability → **Class I**.

N2. Dissolution: 90% in 25 min; BCS Class I; wide TI. Biowaiver eligible? *Solution:* Yes — Class I, >85% in 30 min, wide TI → **eligible**.

5.12 References

1 Shargel L, Yu ABC. *Applied Biopharmaceutics and Pharmacokinetics*. McGraw-Hill.

2 Gibaldi M. *Biopharmaceutics and Clinical Pharmacokinetics*. Lea & Febiger.

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