GPAT Pharmaceutics

Sample Paper – 7

Duration: 36 Minutes **Maximum Marks: 100**

Instructions

- This paper contains **25** Multiple Choice Questions (Single Correct Answer), modelled on the Pharmaceutics portion of **GPAT** entrance.
- Each correct answer carries **+4 marks**. There is **a penalty of −1 mark** for each incorrect answer. Unattempted questions carry no marks.
- Only **one** option is correct per question.
- Syllabus: **GPAT Pharmaceutics — Biopharmaceutics, Drug Absorption and Transport, ADME, Pharmacokinetics, Drug Transporters.**
- Personal calculators, mobile phones, and electronic gadgets are strictly prohibited. A simple on-screen calculator is provided in the CBT interface; rough sheets are supplied at the centre.

Q1. Regarding the Biopharmaceutics Classification System (BCS), which statement CORRECTLY describes the PRIMARY pharmacokinetic difference between a BCS Class II drug and a BCS Class IV drug?

(A) BCS Class IV has high intestinal permeability but low solubility; Class II has both properties low.

(B) BCS Class II has lower permeability than Class IV; both have similarly poor solubility.

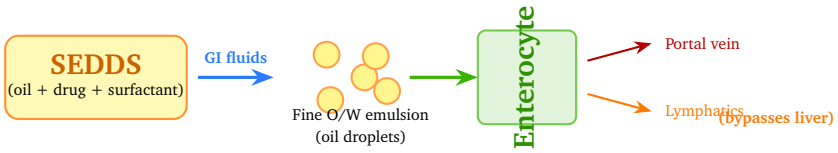
(C) BCS Class II has high permeability but low solubility (dissolution-rate-limited absorption); Class IV has both low solubility AND low permeability (the most challenging class).

(D) BCS Class II and Class IV drugs have equally poor oral bioavailability for identical mechanistic reasons.

Q2. In the "spring and parachute" conceptual framework for amorphous solid dispersions (ASDs), supersaturation generated upon dissolution is termed the "spring." What is the role of the polymer "parachute" in this system?

(A) The polymer "spring" releases supersaturated drug rapidly for immediate systemic absorption.
(B) The "parachute" polymer enhances drug solubility by forming host–guest inclusion complexes, analogous to cyclodextrin.
(C) The polymer "parachute" acts as a disintegrant to fragment ASD particles, releasing drug rapidly.
(D) The polymer "parachute" (e.g., HPMC-AS, PVP-VA) inhibits nucleation and crystal growth on supersaturated drug, sustaining the concentration above equilibrium solubility long enough for absorption.

Q3. Self-emulsifying drug delivery systems (SEDDS) consist of a drug dissolved in a mixture of oil, surfactant, and cosurfactant that spontaneously emulsifies on contact with aqueous gastrointestinal (GI) fluids. The schematic below illustrates the process.



Which mechanism PRIMARILY accounts for the enhanced oral bioavailability of BCS Class II drugs in SEDDS formulations?

(A) Drug pre-dissolved in oil droplets bypasses the dissolution rate-limiting step; lymphatic chylomicron incorporation provides an additional pathway that avoids hepatic first-pass metabolism.
(B) SEDDS prolongs gastric residence time by increasing gastric fluid viscosity, allowing more time for drug dissolution.
(C) SEDDS triggers carrier-mediated active uptake via PEPT1 intestinal transporters, increasing transcellular transport.
(D) SEDDS forms a thermoreversible hydrogel matrix in GI fluid that controls sustained drug release.

Q4. A phase solubility study of a poorly water-soluble drug with 2-hydroxypropyl-β-cyclodextrin (2-HP-β-CD) is conducted according to the Higuchi–Connors method. A linear increase in drug solubility as a function of 2-HP-β-CD concentration is obtained (A_L-type diagram). The apparent stability constant $K_{1:1}$ is calculated from:

$$K_{1:1} = \frac{\text{slope}}{S_0\,(1 - \text{slope})}$$

where S_0 is the intrinsic drug solubility. What drug:cyclodextrin stoichiometry does the A_L-type diagram indicate?

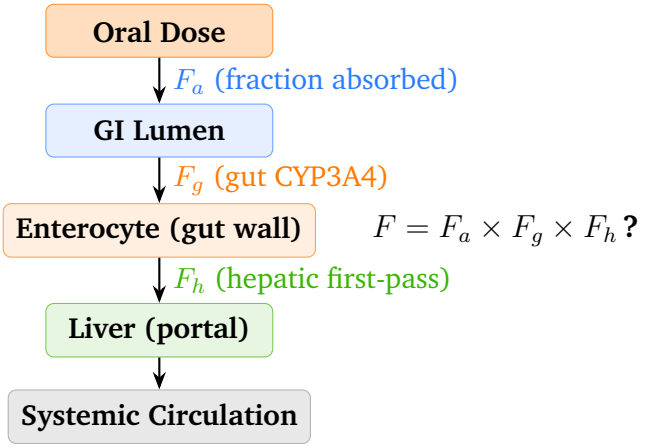
(A) 2:1 drug:CD complex (two drug molecules per one CD cavity)
(B) 1:1 drug:CD complex (one drug molecule per one CD cavity)
(C) 1:2 drug:CD complex with positive cooperativity (one drug in two stacked CDs)
(D) Non-stoichiometric adsorption complex with no defined molar ratio

Q5. P-glycoprotein (P-gp, MDR1, ABCB1) is an ATP-binding cassette (ABC) efflux transporter expressed on the apical membrane of intestinal enterocytes. Which statement BEST describes how P-gp efflux PRIMARILY reduces the oral bioavailability of its substrates?

(A) P-gp chemically degrades the drug within the intestinal lumen by oxidative metabolism.
(B) P-gp inhibits passive transcellular diffusion by incorporating into the lipid bilayer and reducing membrane fluidity.
(C) P-gp uses ATP hydrolysis to pump drug molecules that have entered the enterocyte cytoplasm back into the intestinal lumen, reducing net transcellular flux.
(D) P-gp sequesters absorbed drug in lysosomal vesicles within the enterocyte, preventing its transfer to the basolateral membrane.

Q6. Oral bioavailability is determined not only by the fraction absorbed (F_a) and hepatic first-pass extraction ($F_h = 1 - E_H$), but also by intestinal (gut-wall) first-pass metabolism, characterised by the gut-wall availabil-

ity F_g ($= 1 - E_{\text{gut}}$). The figure below illustrates sequential barriers to oral bioavailability.



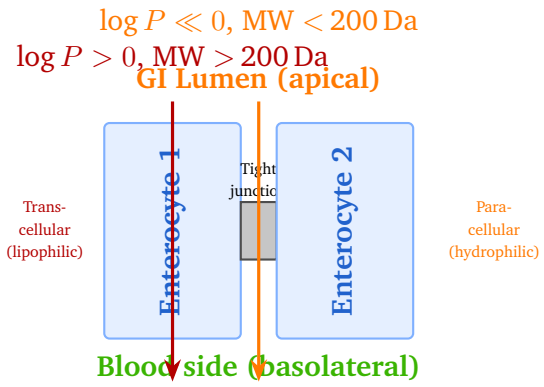
Which formula CORRECTLY expresses oral bioavailability (F) accounting for F_a, gut-wall availability (F_g), and hepatic availability (F_h)?

(A) $F = F_a \times F_h$ (hepatic first-pass only; intestinal first-pass neglected)
(B) $F = F_a \times (1 - F_g) \times F_h$ (incorrect sign convention for F_g)
(C) $F = F_a \times F_g + F_h$ (addition rather than multiplication of barriers)
(D) $F = F_a \times F_g \times F_h$ (all three sequential barriers multiplied)

Q7. Morphine undergoes extensive Phase II glucuronidation catalysed by UDP-glucuronosyltransferase 2B7 (UGT2B7) to produce two glucuronide metabolites. Which statement about UGT-catalysed glucuronidation of morphine is CORRECT?

(A) Morphine-6-glucuronide (M6G) is a more potent μ-opioid agonist than morphine itself; morphine-3-glucuronide (M3G) lacks analgesic activity and is neuroexcitatory.
(B) Both M3G and M6G are pharmacologically inactive; all analgesic activity resides in unchanged morphine.
(C) UGT2B7 glucuronidates morphine exclusively at the 3-position; the 6-hydroxyl group is not conjugated.
(D) M6G is rapidly hydrolysed back to free morphine by intestinal β-glucuronidase within the systemic circulation.

Q8. Two main passive routes exist for drug absorption across the intestinal epithelium: transcellular (through the lipid membrane of the enterocyte) and paracellular (between enterocytes through tight junctions). The figure below illustrates both pathways.



For a highly polar drug molecule (MW 180 Da, $\log P = -1.5$), which absorption route is MOST likely to predominate?

(A) Active carrier-mediated uptake via the peptide transporter PEPT1
(B) Paracellular diffusion through aqueous tight junction pores
(C) Transcellular passive diffusion through the lipid bilayer
(D) Receptor-mediated endocytosis at clathrin-coated pits

Q9. A new drug candidate is evaluated in the Caco-2 bidirectional permeability assay. The measured apparent permeabilities are: $P_{\text{app}}(\text{A}\rightarrow\text{B}) = 12 \times 10^{-6}$ cm/s and $P_{\text{app}}(\text{B}\rightarrow\text{A}) = 28 \times 10^{-6}$ cm/s. Lucifer Yellow rejection is $> 99\%$ confirming monolayer integrity. What conclusion is MOST appropriate?

(A) Low permeability (BCS Class III or IV) because $P_{\text{app}}(\text{A}\rightarrow\text{B})$ is below 2×10^{-6} cm/s.
(B) The drug is a CYP3A4 substrate because the apparent efflux ratio is elevated.
(C) High permeability (BCS Class I or II) with an efflux ratio of 2.3 (≥ 2), indicating the drug is likely a P-gp or BCRP efflux transporter substrate.
(D) Monolayer integrity is compromised because a high efflux ratio indicates membrane leakage.

Q10. After a single oral dose of an immediate-release tablet, the plasma concentration–time profile shows a distinct lag phase (time T_{lag}) before drug first appears in plasma. Which physiological factor is the PRIMARY cause of T_{lag} in most oral formulations?

(A) Rapid small-intestinal transit driven by high-osmolarity luminal contents
(B) Slow drug dissolution in acidic gastric fluid due to poor aqueous solubility
(C) Extensive pre-systemic metabolism in the gastric mucosal cells
(D) Prolonged gastric retention before the pyloric sphincter opens and drug empties into the duodenum

Q11. A lipophilic BCS Class II drug (log $P = 4.5$, practically insoluble in water) is administered to healthy volunteers in a two-period crossover study under fasted and fed (high-fat breakfast) conditions. What food effect is MOST expected?

(A) Marked increase in both C_{max} and AUC in the fed state, driven by bile salt secretion, micellar solubilisation, and slowed GI motility allowing greater dissolution and lymphatic absorption.
(B) Food delays gastric emptying, reducing C_{max} without a meaningful change in overall AUC.
(C) High-fat meal decreases absorption due to formation of poorly absorbable drug–lipid complexes in the intestinal lumen.
(D) No significant food effect is expected because BCS Class II drugs have high permeability; solubility is the only limiting factor.

Q12. In a Caco-2 bidirectional transport assay, a compound has an efflux ratio (ER) of 8.5. When the dual P-gp/BCRP inhibitor elacridar (GF120918) is added to both chambers, ER falls to 1.2. What does this finding indicate?

(A) The compound is a CYP3A4 substrate, because elacridar also inhibits intestinal CYP3A4.
(B) The compound is a P-gp and/or BCRP efflux transporter substrate,

as confirmed by restoration of symmetrical transport upon inhibitor addition.

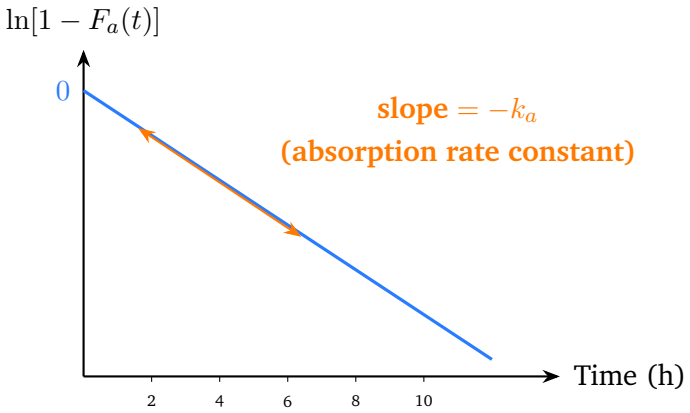
(C) The compound is absorbed paracellularly; elacridar opens tight junctions, allowing bidirectional equilibration.

(D) The compound is a BCS Class I drug with high solubility and high permeability.

Q13. The Wagner–Nelson method is used to calculate the cumulative fraction absorbed $F_a(t)$ from plasma concentration–time data after oral dosing:

$$F_a(t) = \frac{C_p(t) + k_e \, \text{AUC}_{0\to t}}{k_e \, \text{AUC}_{0\to\infty}}$$

A plot of $\ln[1 - F_a(t)]$ versus time (shown below) gives a straight line with slope $= -k_a$.



Wagner–Nelson assumes first-order absorption into a one-compartment body

The Wagner–Nelson method for estimating the in vivo drug absorption rate constant (k_a) assumes which pharmacokinetic model for the body?

(A) Two-compartment open model (central + peripheral compartment)

(B) Non-compartmental analysis (NCA) – model-independent approach

(C) One-compartment open model (drug distributes instantaneously to a single compartment)

(D) Three-compartment mammillary model with deep tissue compartment

Q14. An IVIVC Level A correlation establishes a point-to-point relationship between the in vitro dissolution profile and the in vivo drug absorption

profile. To establish such a correlation, the in vivo absorption profile must be obtained from clinical pharmacokinetic data. How is the in vivo absorption profile TYPICALLY generated?

(A) Monte Carlo simulation of virtual patient plasma profiles using population PK parameters.
(B) Direct rat jejunal perfusion (single-pass intestinal perfusion, SPIP) as a surrogate for human in vivo absorption.
(C) Deconvolution of the in vitro dissolution data using a mathematical reference input function.
(D) Deconvolution of the in vivo plasma concentration–time profile (by Wagner–Nelson or numerical deconvolution) to obtain the cumulative fraction absorbed as a function of time.

Q15. A drug is administered as single oral doses of 25, 50, 100, 200, and 400 mg to separate groups of subjects. AUC values are fitted to the power model:

$$\text{AUC} = \alpha \cdot \text{Dose}^{\,\beta}$$

The best-fit exponent is $\hat{\beta} = 1.85$ with 90% CI (1.70–2.00). If $\hat{\beta} = 1$ represents perfect dose-proportionality, what pharmacokinetic phenomenon MOST likely explains $\hat{\beta} = 1.85$?

(A) Saturable hepatic first-pass extraction: at higher doses, first-pass CYP enzymes become saturated, so a disproportionately greater fraction of dose reaches the systemic circulation ($\beta > 1$).
(B) Saturable renal tubular secretion: reduced elimination at higher dose increases AUC disproportionately.
(C) Strictly linear pharmacokinetics: $\beta = 1.85$ is within the acceptable dose-proportionality range.
(D) Saturable active intestinal carrier-mediated uptake, causing absorption to increase less than proportionally with dose ($\beta < 1$).

Q16. A newly diagnosed epilepsy patient is initiated on carbamazepine 200 mg twice daily. After 3 weeks, trough plasma carbamazepine concentrations

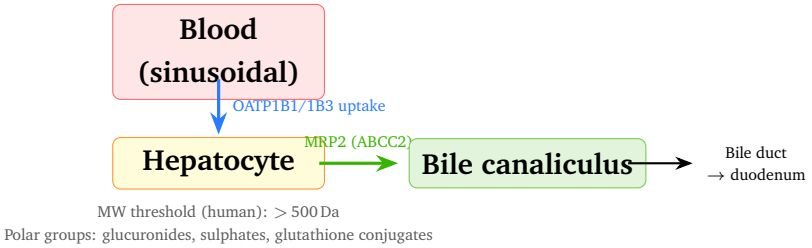
have decreased by approximately 40% compared to concentrations measured at the end of the first week, despite no change in the prescribed dose. The MOST likely pharmacokinetic explanation for this observation is:

(A) Competitive inhibition of intestinal CYP3A4 by a co-administered drug reduces carbamazepine bioavailability.
(B) Autoinduction: carbamazepine progressively induces its own metabolising enzymes (CYP3A4, CYP2C9), increasing its own clearance over 2–4 weeks of therapy.
(C) Decreased oral absorption due to carbamazepine-induced delayed gastric emptying.
(D) Development of pharmacodynamic tolerance to carbamazepine without any change in plasma drug levels.

Q17. OATP1B1 (encoded by *SLCO1B1*) is an organic anion transporting polypeptide expressed on the sinusoidal membrane of hepatocytes. Inhibition of OATP1B1 by cyclosporin is MOST likely to produce which clinical drug–drug interaction?

(A) Cyclosporin inhibits CYP3A4, preventing rosuvastatin hepatic metabolism and increasing plasma statin concentrations.
(B) Cyclosporin blocks intestinal P-gp, doubling the oral bioavailability of HMG-CoA reductase inhibitors.
(C) Cyclosporin inhibits OATP1B1-mediated hepatic uptake of statins (e.g., rosuvastatin), increasing systemic statin exposure and the risk of myopathy.
(D) Cyclosporin induces MRP2-mediated biliary efflux, reducing hepatic statin accumulation and lowering plasma levels.

Q18. Biliary excretion is a significant elimination route for certain drugs and metabolites. The figure below shows the hepatic route from blood into bile.



For significant biliary excretion to occur in humans, a drug or metabolite generally requires:

(A) MW $>$ 150 Da and must be ionised across the entire physiological pH range.
(B) MW $>$ 300 Da and must be a monobasic amine with p$K_a > 8$.
(C) MW $>$ 400 Da and must contain a tertiary nitrogen atom for active canalicular secretion.
(D) MW $>$ 500 Da and must possess polar functional groups (e.g., glucuronide, sulphate, glutathione conjugate) for MRP2-mediated canalicular efflux.

Q19. Allometric scaling is used in drug development to predict human pharmacokinetic parameters from preclinical species data. The general allometric relationship for clearance (CL) is:

$$\text{CL} = a \cdot \text{BW}^{b}$$

where BW is body weight and b is the allometric exponent. When predicting paediatric drug clearance using allometric scaling from a 70 kg adult reference, the body weight exponent b for clearance is:

(A) 0.75 (three-quarter power law — the most widely validated allometric exponent for clearance)
(B) 1.0 (linear body weight scaling, more appropriate for volume of distribution)
(C) 0.5 (square-root scaling, derived from surface area in small rodents only)
(D) 0.67 (two-thirds power, based on metabolic body surface area)

Q20. A 75-year-old male patient (body weight 68 kg, serum creatinine $S_{Cr} = 1.5$ mg/dL) is prescribed a renally cleared drug. Dose adjustment is based on creatinine clearance (CrCl) estimated by the Cockcroft–Gault equation:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{BW}}{72 \times S_{Cr}} \qquad (\times 0.85 \text{ for females})$$

His estimated CrCl is closest to:

(A) 28 mL/min
(B) 41 mL/min
(C) 55 mL/min
(D) 68 mL/min

Q21. Certain drugs inhibit cytochrome P450 enzymes through mechanism-based inhibition (MBI), also called time-dependent inhibition (TDI). Examples include clarithromycin (CYP3A4), fluoxetine (CYP2D6), and isoniazid (CYP2E1). Which characteristic BEST distinguishes mechanism-based CYP inhibition from reversible (competitive) inhibition?

(A) MBI requires a much lower inhibitor concentration (smaller K_I) than reversible inhibition to achieve 50% enzyme inhibition at equilibrium.
(B) MBI is fully reversed upon dilution or removal of the inhibitor from the incubation medium.
(C) MBI is time-dependent and effectively irreversible: the inhibitory effect persists after drug removal because a reactive metabolic intermediate covalently inactivates the CYP active site (new enzyme synthesis is required for recovery).
(D) MBI produces steeper concentration–response curves but is otherwise kinetically indistinguishable from competitive inhibition.

Q22. A transplant patient being treated for tuberculosis with rifampicin develops a breakthrough fungal infection despite receiving voriconazole at standard doses. Plasma voriconazole trough concentrations are unde-

tectable. The MOST likely pharmacokinetic mechanism is:

(A) Rifampicin forms a non-covalent complex with voriconazole in plasma, rendering it inactive.
(B) Rifampicin impairs gastrointestinal absorption of voriconazole by altering intestinal motility and pH.
(C) Rifampicin inhibits OATP1B1, diverting voriconazole from hepatic clearance into plasma, paradoxically lowering unbound drug at the site of infection.
(D) Rifampicin activates the pregnane X receptor (PXR), strongly inducing CYP2C19 and CYP3A4 — the principal enzymes metabolising voriconazole — resulting in a $> 90\%$ reduction in voriconazole AUC.

Q23. Probenecid was historically co-administered with penicillin G during World War II to extend its antibacterial action by increasing its plasma half-life. By what mechanism does probenecid increase the plasma half-life of penicillin G?

(A) Inhibiting OAT1/OAT3-mediated renal tubular secretion of penicillin G in the proximal nephron, reducing renal elimination.
(B) Competing with penicillin G for albumin binding sites, increasing the free fraction available for distribution.
(C) Inhibiting glomerular filtration by inducing afferent arteriolar constriction and reducing GFR.
(D) Blocking hepatic CYP3A4-mediated oxidative metabolism of penicillin G.

Q24. A patient on long-term phenytoin therapy (99% albumin-bound at therapeutic concentrations) is started on valproate for adjunct seizure control. Within days, the patient develops phenytoin toxicity (nystagmus, ataxia). Measurement shows total plasma phenytoin concentration is 15 μg/mL, which is within the conventional "therapeutic range" of 10–20 μg/mL. The MOST likely pharmacokinetic explanation is:

(A) Valproate inhibits CYP2C9, increasing total phenytoin concentration

above a toxicity threshold not reflected by the therapeutic range.

(B) Valproate displaces phenytoin from albumin binding sites, increasing the free fraction (f_u) from ∼1% to ∼5–10%; the free (pharmacologically active) phenytoin concentration rises despite total concentration appearing normal.

(C) Valproate acts pharmacodynamically on sodium channels in an additive manner with phenytoin, causing toxicity independent of pharmacokinetics.

(D) Valproate competes with phenytoin for renal tubular secretion, reducing phenytoin elimination.

Q25. Physiologically-based pharmacokinetic (PBPK) models partition the body into tissue compartments (e.g., liver, lung, kidney, muscle, fat) each characterised by tissue:plasma partition coefficients (K_p). The magnitude of K_p for each tissue determines drug distribution into that compartment. In PBPK modelling, tissue:plasma partition coefficients (K_p) are PRIMARILY determined by:

(A) Only observed plasma concentration–time data and the measured volume of distribution from in vivo PK studies.

(B) Hepatic blood flow rates, biliary excretion clearance, and renal GFR exclusively.

(C) Drug physicochemical properties (log P, pK_a, plasma protein binding $f_{u,p}$) combined with tissue-specific composition data (neutral lipid, phospholipid, water, acidic protein content) using methods such as Rodgers–Rowland or Berezhkovskiy.

(D) Only allometric scaling parameters derived from multi-species in vivo pharmacokinetic studies.

Detailed Solutions

Q1.

Solution

Concept — BCS Class II versus Class IV: The Biopharmaceutics Classification System classifies drugs on two axes: aqueous solubility (relative to dose) and intestinal permeability. Class II = high permeability, low solubility; absorption is dissolution-rate-limited. Class IV = low solubility AND low permeability; the most biopharmaceutically challenging class.

Step 1 — Classify each class:

- Class I: high solubility + high permeability (ideal).
- Class II: LOW solubility + HIGH permeability (dissolution-rate-limited absorption).
- Class III: high solubility + LOW permeability (permeability-rate-limited).
- Class IV: LOW solubility + LOW permeability (dual barrier).

Step 2 — Identify the PRIMARY difference: A Class II drug can reach high plasma concentrations if dissolution is optimised (formulation strategy: amorphous solid dispersion, SEDDS, nanosizing). A Class IV drug requires BOTH solubility AND permeability enhancement — formulation is extremely challenging.

Why other options are wrong:

- Option A: Inverts Class II and IV — Class IV has LOW (not high) permeability.
- Option B: Class II has HIGHER permeability than Class IV, not lower.
- Option C: Correctly states that Class II has high permeability/low solubility and Class IV has both properties low. **Correct.**
- Option D: Incorrect — the mechanisms differ; Class II can be "fixed" by dissolution enhancement alone.

Final Answer: Class II = high permeability, low solubility; Class IV = low solubility AND low permeability ⇒ C

Answer: (C) Go Back to Q1

Q2.

Solution

Concept — Spring and Parachute in Amorphous Solid Dispersions: When an ASD dissolves, the amorphous drug generates a supersaturated solution above the equilibrium (crystalline) solubility — this is the "spring" effect. Without additional protection, the supersaturated drug rapidly crystallises and the concentration falls back to the equilibrium value. The "parachute" role refers to polymer-mediated precipitation inhibition.

Step 1 — Define "spring": The amorphous drug (higher free energy state) dissolves rapidly to concentrations exceeding $C_s^{\text{equilibrium}}$. This transient supersaturation constitutes the "spring."

Step 2 — Define "parachute": Precipitation inhibitor polymers (HPMC-AS, PVP-VA, HPMC) adsorb onto nascent drug crystal nuclei, sterically inhibiting crystal growth. This sustains the supersaturated drug concentration in the GI lumen for an extended time, providing a concentration gradient for absorption.

Why other options are wrong:

- Option A: Confuses the roles; the "spring" is not the polymer — it is the amorphous drug itself.
- Option B: Cyclodextrin-type inclusion complexation is distinct from ASD parachute mechanisms.
- Option C: A disintegrant breaks tablets apart; HPMC-AS acts as a precipitation inhibitor, not a disintegrant.
- Option D: Correct — HPMC-AS/PVP-VA inhibits nucleation and crystal growth to sustain supersaturation. **Correct.**

Final Answer: The "parachute" polymer inhibits nucleation/crystal growth, maintaining supersaturation for absorption $\Rightarrow$ $\boxed{\text{D}}$

Answer: (D) Go Back to Q2

Q3.

Solution

Concept — SEDDS Bioavailability Enhancement Mechanism: SEDDS (Self-Emulsifying Drug Delivery Systems) are isotropic mixtures of oil, hydrophilic surfactant, cosurfactant, and dissolved drug. Upon contact with aqueous GI fluids and gentle peristaltic agitation, they spontaneously form fine oil-in-water (O/W) emulsions with droplet sizes typically 100–300 nm.

Step 1 — Primary mechanism (dissolution bypass): BCS Class II drugs often have very slow intrinsic dissolution from solid dosage forms. In SEDDS, the drug is already dissolved in the oil phase of each droplet — no dissolution step is needed. The enormous interfacial area of the fine emulsion ensures rapid transfer of drug from oil droplets to the intestinal aqueous phase adjacent to the epithelium.

Step 2 — Secondary mechanism (lymphatic absorption): Lipophilic drugs ($\log P > 5$, MW > 400 Da) can incorporate into chylomicrons formed during fat digestion. Chylomicrons are exported from enterocytes via mesenteric lymphatics, bypassing the portal vein and hepatic first-pass metabolism entirely.

Why other options are wrong:

- Option A: Correct on both counts — dissolution bypass and lymphatic uptake. **Correct.**
- Option B: SEDDS emulsification occurs in the GI fluid, not by increasing gastric fluid viscosity; gastric retention is not the primary mechanism.
- Option C: PEPT1 transports di/tripeptides and some peptidomimetics; lipophilic BCS Class II drugs are not PEPT1 substrates.
- Option D: SEDDS is not a hydrogel matrix; it is a self-emulsifying liquid or semisolid system.

Final Answer: SEDDS pre-dissolves drug in oil droplets (no dissolution step) and enables lymphatic uptake $\Rightarrow$ A

Answer: (A) Go Back to Q3

Q4.

Solution

Concept — Phase Solubility Analysis (Higuchi–Connors): Phase solubility studies plot drug solubility (S) as a function of cyclodextrin concentration [CD]. The shape of the curve reveals the stoichiometry of the inclusion complex formed.

Step 1 — Interpret the A_L-type diagram: A_L (A = solubility increase; L = linear) indicates that S increases linearly with [CD]. This linear relationship is diagnostic of a simple 1:1 (host:guest) inclusion complex in which one drug molecule occupies one cyclodextrin cavity.

Step 2 — Calculate $K_{1:1}$: For an A_L curve: $K_{1:1} = \text{slope}/[S_0(1 - \text{slope})]$. The linearity reflects that additional CD molecules do not form higher-order complexes under the experimental conditions.

Step 3 — Distinguish from other types: A_P (positive curvature) = higher-order complex (1:2 or 2:1). A_N (linear then plateau) = limited stoichiometry or solubility limit of complex.

Why other options are wrong:

- Option A: 2:1 (drug:CD) would give AP-type with concave-up curvature, not linear.
- Option B: 1:1 complex produces the A_L (linear) diagram. **Correct.**
- Option C: 1:2 complex (two CDs per drug) would also show AP curvature.
- Option D: Non-stoichiometric adsorption does not give the predictable linear relationship described.

Final Answer: A_L-type linear phase solubility diagram indicates 1:1 drug:CD inclusion complex $\Rightarrow$ B

Answer: (B) Go Back to Q4

Q5.

Solution

Concept — P-glycoprotein (P-gp/MDR1/ABCB1) Efflux Mechanism: P-gp is an ABC (ATP-binding cassette) transporter located on the apical (luminal) membrane of intestinal enterocytes, the luminal surface of brain capillary endothelium (BBB), and biliary canalicular membranes of hepatocytes. It uses ATP hydrolysis to actively translocate substrates from the intracellular environment back into the intestinal lumen (or bile, or blood in the BBB).

Step 1 — Mechanism at the intestinal epithelium: Lipophilic drug molecules enter enterocytes by passive transcellular diffusion. P-gp on the apical membrane captures these molecules before they reach the basolateral surface and pumps them back into the gut lumen. Net transcellular (A→B) flux is thus reduced, lowering the fraction absorbed.

Step 2 — Net effect: The counter-transport creates a futile cycle that limits effective drug absorption. P-gp and CYP3A4 act synergistically — CYP3A4 metabolises drug that repeatedly re-enters the enterocyte after efflux.

Why other options are wrong:

- Option A: P-gp does not degrade drugs chemically; CYP enzymes perform oxidative metabolism.
- Option B: P-gp is a transmembrane protein that transports substrates; it does not alter lipid bilayer fluidity.
- Option C: Correctly describes ATP-driven efflux from enterocyte cytoplasm back to the lumen. **Correct.**
- Option D: Lysosomal sequestration is a separate cellular mechanism not attributed to P-gp.

Final Answer: P-gp pumps intracellular drug back into gut lumen via ATP-dependent efflux ⇒ C

Answer: (C) Go Back to Q5

Q6.

Solution

Concept — Sequential Barriers to Oral Bioavailability: Oral bioavailability F is the product of three sequential probabilities of a drug molecule surviving each barrier:

(a) F_a = fraction of dose absorbed from GI lumen across intestinal wall.
(b) F_g = fraction escaping gut-wall (enterocyte) first-pass metabolism by CYP3A4 ($= 1 - E_{\text{gut}}$).
(c) F_h = fraction escaping hepatic first-pass metabolism ($= 1 - E_H$).

Step 1 — Derive the formula: Each barrier acts independently and multiplicatively:

$$F = F_a \times F_g \times F_h$$

For example, midazolam: $F_a \approx 1.0$, $F_g \approx 0.57$ (gut CYP3A4 removes $\approx 43\%$),

$F_h \approx 0.55$ (liver removes $\approx 45\%$), giving $F \approx 0.31$ (31% oral bioavailability).

Step 2 — Check each option: Option A ($F = F_a \times F_h$) neglects gut-wall first-pass; overestimates F for high-CYP3A4 enterocyte drugs. Options B and C apply incorrect arithmetic.

Why other options are wrong:

- Option A: Omits the gut-wall extraction term F_g; underestimates total first-pass loss.
- Option B: $(1-F_g)$ gives the fraction *extracted* by the gut wall, not the fraction escaping; sign error.
- Option C: Addition of F_g and F_h is dimensionally and conceptually incorrect.
- Option D: $F = F_a \times F_g \times F_h$ correctly accounts for all three sequential barriers. **Correct.**

Final Answer: $F = F_a \times F_g \times F_h$ (sequential multiplication of three escape fractions) $\Rightarrow$ D

Answer: (D) Go Back to Q6

Q7.

Solution

Concept — Morphine Glucuronidation by UGT2B7: Morphine undergoes Phase II glucuronidation at both the 3- and 6-hydroxyl positions, catalysed primarily by UGT2B7 (hepatic and intestinal). This generates two structurally distinct and pharmacologically opposite metabolites.

Step 1 — Morphine-6-glucuronide (M6G): M6G retains the correct spatial orientation for μ-opioid receptor binding. It crosses the blood–brain barrier (though slowly) and is a more potent analgesic than morphine (receptor affinity $\approx 4\times$ greater). In renal failure, M6G accumulates and is responsible for prolonged narcosis.

Step 2 — Morphine-3-glucuronide (M3G): M3G lacks analgesic activity at μ-opioid receptors and actually antagonises the analgesic effect of morphine and M6G. It is neuroexcitatory and associated with hyperalgesia and allodynia.

Why other options are wrong:

- Option A: Correctly identifies M6G as more potent analgesic and M3G as neuroexcitatory/inactive analgesic. **Correct.**

- Option B: Incorrect — M6G is pharmacologically active (potent agonist); only M3G lacks analgesia.
- Option C: UGT2B7 glucuronidates BOTH the 3- and 6-positions of morphine; both metabolites are formed.
- Option D: Glucuronides are not hydrolysed significantly in the systemic circulation; M6G is excreted renally.

Final Answer: M6G is more potent than morphine; M3G is neuroexcitatory and analgesically inactive $\Rightarrow$ A

Answer: (A) Go Back to Q7

Q8.

Solution

Concept — Transcellular vs Paracellular Drug Absorption: Two principal passive routes exist for drug permeation across the intestinal epithelium: (1) Transcellular: drug partitions into and diffuses through the enterocyte lipid membrane; favoured by lipophilicity ($\log P > 0$) and moderate MW. (2) Paracellular: drug passes through aqueous tight junction channels between adjacent enterocytes; restricted to small, hydrophilic molecules (MW < 200 Da, $\log P \ll 0$).

Step 1 — Evaluate the drug properties: The drug has MW = 180 Da and $\log P = -1.5$. Log $P = -1.5$ indicates a strongly hydrophilic molecule with very poor lipid membrane partitioning. MW = 180 Da is small enough to fit through tight junction pores.

Step 2 — Select the predominant route: Transcellular passive diffusion requires $K_{\text{membrane/water}} > 1$, which is not satisfied for $\log P = -1.5$. The paracellular route accommodates small hydrophilic molecules and is the predominant pathway.

Why other options are wrong:

- Option A: PEPT1 is substrate-selective (recognises di/tripeptide backbone); not relevant to a generic polar small molecule unless it is a peptide mimetic.
- Option B: Paracellular diffusion through tight junction pores — correct for this hydrophilic, low-MW molecule. **Correct.**
- Option C: Transcellular passive diffusion requires lipophilicity; $\log P = -1.5$ precludes efficient membrane partitioning.
- Option D: Receptor-mediated endocytosis operates for macromolecules (proteins, nanoparticles), not small molecules.

Final Answer: MW 180 Da, $\log P = -1.5 \Rightarrow$ paracellular diffusion through tight

junctions predominates $\Rightarrow$ B

Answer: (B) Go Back to Q8

Q9.

Solution

Concept — Caco-2 Bidirectional Permeability and Efflux Ratio: The Caco-2 assay provides: (a) P_{app}(A→B) — apparent permeability in the absorptive direction, used to classify BCS permeability; (b) Efflux ratio (ER) = P_{app}(B→A)/P_{app}(A→B) — used to identify efflux transporter substrates.

Step 1 — Classify permeability: $P_{app}(\text{A}\rightarrow\text{B}) = 12 \times 10^{-6}$ cm/s $> 10^{-6}$ cm/s (BCS high permeability threshold); propranolol reference $\approx 30 \times 10^{-6}$ cm/s. Drug is classified as HIGH permeability.

Step 2 — Calculate efflux ratio:

$$\text{ER} = \frac{P_{app}(\text{B}\rightarrow\text{A})}{P_{app}(\text{A}\rightarrow\text{B})} = \frac{28}{12} = 2.33$$

ER ≥ 2 indicates the drug is a substrate for an efflux transporter (P-gp, BCRP, MRP2). To confirm, the experiment should be repeated with a specific inhibitor (e.g., elacridar for P-gp/BCRP).

Why other options are wrong:

- Option A: Incorrect — $P_{app} = 12 \times 10^{-6}$ cm/s is well above the low-permeability threshold.
- Option B: CYP3A4 metabolism is not assessed by bidirectional permeability; ER reflects efflux transporter activity.
- Option C: High permeability + ER ≥ 2 = P-gp/BCRP substrate. **Correct.**
- Option D: Monolayer integrity is confirmed by Lucifer Yellow rejection $> 99\%$; ER is not an integrity marker.

Final Answer: $P_{app}(\text{A}\rightarrow\text{B}) = 12 \times 10^{-6}$ cm/s (high permeability); ER $= 2.33 \geq 2$ (efflux substrate) $\Rightarrow$ C

Answer: (C) Go Back to Q9

Q10.

Solution

Concept — Gastric Emptying and Oral Absorption Lag Time (T_{lag}): After oral ingestion, a tablet or capsule first enters the stomach. Dissolution may begin in the stomach, but the small intestine (duodenum/jejunum) is the primary absorption site for most drugs due to its large surface area. The pyloric sphincter regulates the rate of gastric emptying into the duodenum.

Step 1 — Define T_{lag}: T_{lag} is the apparent time before drug first appears in plasma after oral dosing. It appears as a horizontal plateau near zero on the plasma concentration–time curve.

Step 2 — Primary cause: The most common cause is gastric retention: the dosage form (and dissolved drug) must wait in the stomach until gastric emptying delivers it to the absorptive mucosa of the small intestine. Fed state prolongs gastric emptying half-life from $\sim$ 20–30 min (fasted) to 2–4 h (fed), markedly increasing T_{lag}.

Why other options are wrong:

- Option A: High osmolarity can actually accelerate or retard gastric emptying; it is not the primary cause of T_{lag}.
- Option B: Low solubility can slow dissolution but not create a true lag on the plasma profile independent of absorption site delivery.
- Option C: Gastric mucosal metabolism is negligible for most drugs compared to intestinal CYP3A4.
- Option D: Prolonged gastric retention before pyloric emptying is the PRIMARY and most physiologically understood cause of T_{lag}. **Correct.**

Final Answer: T_{lag} primarily reflects gastric residence time before pyloric emptying into the absorptive small intestine $\Rightarrow$ $\boxed{\text{D}}$

Answer: (D) Go Back to Q10

Q11.

Solution

Concept — Positive Food Effect for BCS Class II Lipophilic Drugs: For BCS Class II drugs (low solubility, high permeability), oral bioavailability is limited by dissolution rate in the GI fluid. A high-fat meal dramatically increases absorption through multiple mechanisms.

Step 1 — Mechanisms of positive food effect:

- Bile salt secretion: fat ingestion stimulates cholecystokinin release, causing the gallbladder to contract and deliver bile acids into the duodenum. Bile acids micellise lipophilic drugs, dramatically increasing their apparent solubility ($\uparrow C_s$).
- Slowed GI motility: fed state prolongs intestinal transit, allowing more contact time for dissolution and absorption.
- Lymphatic absorption: fat-stimulated chylomicron formation carries highly lipophilic drugs ($\log P > 5$) via lymphatics, bypassing hepatic first-pass.
- Gastric lipase activity: partial digestion of dietary triglycerides generates fatty acids and monoglycerides that act as solubilisers.

Why other options are wrong:

- Option A: Marked increase in both C_{max} and AUC is the expected positive food effect for this drug. **Correct.**
- Option B: While fed state can reduce C_{max} for some drugs (delayed absorption), the overall AUC typically increases for BCS Class II due to improved dissolution.
- Option C: Drug–lipid complexes in SEDDS/lipid formulations enhance (not reduce) absorption; poorly absorbable complexes are not formed for most drugs.
- Option D: High permeability cannot compensate for poor dissolution; BCS Class II is dissolution-rate-limited.

Final Answer: High-fat meal $\rightarrow$ bile salt micellar solubilisation + lymphatic uptake $\rightarrow$ markedly increased AUC and $C_{\text{max}} \Rightarrow \boxed{\text{A}}$

Answer: (A) Go Back to Q11

Q12.

Solution

Concept — Efflux Ratio and Transporter Substrate Identification: The efflux ratio (ER) in Caco-2 cells identifies efflux transporter substrates:

$$\text{ER} = \frac{P_{\text{app}}(\text{B}\rightarrow\text{A})}{P_{\text{app}}(\text{A}\rightarrow\text{B})}$$

$\text{ER} \geq 2$ is the standard threshold indicating likely P-gp or BCRP efflux. Elacridar (GF120918) is a potent dual inhibitor of both P-gp (ABCB1) and BCRP (ABCG2).

Step 1 — Interpret ER = 8.5: A very high ER ($8.5 \gg 2$) strongly suggests active efflux transport. This would reduce the oral bioavailability of P-gp/BCRP substrates and limit CNS penetration.

Step 2 — Interpret reversal by elacridar: When ER falls from 8.5 to 1.2 (near unity = symmetric transport = passive diffusion) upon elacridar addition, this confirms that the observed efflux is mediated by P-gp and/or BCRP. If MRP2 (ABCC2) were responsible, elacridar would NOT reduce ER (elacridar does not inhibit MRP2).

Why other options are wrong:

- Option A: Elacridar does not inhibit CYP3A4 at the concentrations used in transporter assays; and CYP3A4 would not affect an efflux ratio.
- Option B: Correct interpretation — P-gp and/or BCRP substrate confirmed by elacridar sensitivity. **Correct.**
- Option C: Paracellular absorption would give $\text{ER} \approx 1$ (symmetric); a high ER implies active transporter involvement.
- Option D: BCS Class I drugs have high permeability and $\text{ER} < 2$; ER 8.5 contradicts this classification.

Final Answer: ER 8.5 reduced to 1.2 by elacridar $\Rightarrow$ confirmed P-gp/BCRP efflux substrate $\Rightarrow$ $\boxed{\text{B}}$

Answer: (B) Go Back to Q12

Q13.

Solution

Concept — Wagner–Nelson Method and Its Underlying PK Model: The Wagner–Nelson method (1963) uses plasma concentration–time data from an oral dose to back-calculate the cumulative fraction of dose absorbed $F_a(t)$ as a function of time. The equation is:

$$F_a(t) = \frac{C_p(t) + k_e \, \text{AUC}_{0\to t}}{k_e \, \text{AUC}_{0\to\infty}}$$

where k_e is the apparent first-order elimination rate constant and $\text{AUC}_{0\to t}$ is the trapezoidal area up to time t.

Step 1 — Critical assumption: The equation assumes that at any time t, the amount of drug in the body is distributed in a SINGLE compartment (one-compartment open model): Amount in body $= C_p(t) \times V_d$. Drug elimination follows first-order kinetics with constant k_e. If the drug follows a two-compartment model, the Wagner–Nelson method yields incorrect F_a values; the Loo–Riegelman method must be used instead.

Step 2 — Application: Plotting $\ln[1 - F_a(t)]$ vs time gives a straight line with slope $= -k_a$ during the absorption phase (if first-order absorption is assumed), from which the absorption rate constant is obtained.

Why other options are wrong:

- Option A: Two-compartment model requires the Loo–Riegelman method, not Wagner–Nelson.
- Option B: NCA (non-compartmental) does not provide k_a; Wagner–Nelson is explicitly model-dependent.
- Option C: One-compartment open model is the correct underlying assumption. **Correct.**
- Option D: Three-compartment models are rare and require the Loo–Riegelman extension; Wagner–Nelson is not applicable.

Final Answer: Wagner–Nelson assumes a one-compartment open model for the body $\Rightarrow$ C

Answer: (C) Go Back to Q13

Q14.

Solution

Concept — IVIVC Level A: In Vivo Absorption Profile by Deconvolution: An IVIVC Level A correlation is the most stringent and regulatory valuable form of IVIVC. It requires a point-to-point correlation between:

- **In vitro:** fraction dissolved $f_{\text{diss}}(t)$ from the dissolution apparatus.
- **In vivo:** fraction absorbed $F_a(t)$, obtained from clinical pharmacokinetic data.

Step 1 — How is the in vivo absorption profile obtained? The plasma concentration–time profile after oral administration contains information about both absorption and post-absorption disposition (distribution, elimination). To extract the pure absorption signal (F_a vs t), the plasma data must be deconvoluted:

- *Wagner–Nelson method* (one-compartment drugs).
- *Loo–Riegelman method* (two-compartment drugs).
- *Numerical deconvolution* using an IV reference (impulse response function).

Why other options are wrong:

- Option A: Monte Carlo simulation generates virtual profiles but does not extract real in vivo absorption data.
- Option B: Rat SPIP directly measures jejunal permeability, not the systemic in vivo absorption profile.
- Option C: Deconvolution is applied to in vivo PLASMA data, not to in vitro dissolution data; convolution of in vitro data with a unit impulse response is a different operation.
- Option D: Deconvolution of plasma C_p–t data using Wagner–Nelson or numerical deconvolution yields $F_a(t)$. **Correct.**

Final Answer: In vivo absorption profile obtained by deconvolution (Wagner–Nelson / numerical) of plasma C_p–t data $\Rightarrow$ D

Answer: (D) Go Back to Q14

Q15.

Solution

Concept — Power Model and Greater-Than-Dose-Proportional Pharmacokinetics: The power model AUC $= \alpha \cdot \text{Dose}^{\beta}$ characterises the dose–AUC relationship:

- $\beta = 1$: perfect dose-proportionality (linear PK).
- $\beta < 1$: less-than-dose-proportional (e.g., saturable absorption: carrier-mediated uptake saturates at high dose).
- $\beta > 1$: greater-than-dose-proportional (AUC increases more steeply than dose).

Step 1 — Interpret $\hat{\beta} = 1.85$: $\beta > 1$ means that doubling the dose more than doubles the AUC. The pharmacokinetic mechanism consistent with this pattern is saturable first-pass extraction: at low doses, a large fraction is extracted by CYP enzymes (high E); as dose increases, the enzymes become saturated, extraction ratio falls, and a disproportionately larger fraction reaches the systemic circulation.

Step 2 — Classic examples: Propranolol, verapamil, and several other high-extraction drugs show $\beta > 1$ due to saturable hepatic (or gut-wall) CYP metabolism. Phenytoin shows $\beta > 1$ due to saturable Michaelis–Menten elimination (zero-order at toxic concentrations).

Why other options are wrong:

- Option A: Saturable first-pass extraction explains $\beta > 1$ correctly. **Correct.**
- Option B: Saturable renal tubular secretion would reduce elimination at high doses, increasing AUC — this can also give $\beta > 1$, but saturable first-pass is the more common and classical explanation for the magnitude seen ($\beta = 1.85$).
- Option C: If PK were strictly linear, $\beta = 1.0$; $\beta = 1.85$ is far outside the dose-proportionality range ($\beta \in 0.8$–1.2).
- Option D: Saturable intestinal uptake (carrier-mediated absorption saturates) would give $\beta < 1$, not $\beta > 1$.

Final Answer: $\beta = 1.85 > 1 \Rightarrow$ greater-than-dose-proportional AUC $\Rightarrow$ saturable hepatic first-pass extraction $\Rightarrow$ A

Answer: (A) Go Back to Q15

Q16.

Solution

Concept — Autoinduction of Drug-Metabolising Enzymes: Autoinduction occurs when a drug acts as an inducer of the very enzymes responsible for its own metabolism. Carbamazepine is a prototype autoinducer: it activates the nuclear receptor PXR (pregnane X receptor) and CAR (constitutive androstane receptor), leading to transcriptional upregulation of CYP3A4 and CYP2C9.

Step 1 — Time course of autoinduction: When carbamazepine therapy begins, plasma concentrations reflect only the initial metabolic capacity. Over 2–4 weeks, progressive CYP3A4 and CYP2C9 induction increases intrinsic clearance by 2–3 fold. As a result, the same dose yields lower steady-state concentrations, and initial dose titrations must be revisited.

Step 2 — Clinical implications: Carbamazepine starting doses are lower; after 4–6 weeks, doses frequently need to be increased due to autoinduction. This also affects co-administered drugs (oral contraceptives, warfarin, valproate) metabolised by CYP3A4/CYP2C9.

Why other options are wrong:

- Option A: There is no mention of a co-administered CYP3A4 inhibitor; autoinduction (self-induction) explains the time-dependent decrease.
- Option B: Autoinduction by carbamazepine of its own CYP3A4/2C9 metabolism is the correct explanation. **Correct.**
- Option C: Carbamazepine does not cause significant gastric dysmotility affecting its own absorption.
- Option D: Pharmacodynamic tolerance is a receptor-level adaptation; it does not cause a decrease in plasma drug concentrations.

Final Answer: Carbamazepine autoinduces CYP3A4/CYP2C9 $\rightarrow$ increased clearance $\rightarrow$ falling plasma concentrations over 2–4 weeks $\Rightarrow$ $\boxed{\text{B}}$

Answer: (B) Go Back to Q16

Q17.

Solution

Concept — OATP1B1 and Hepatic Uptake of Statins: OATP1B1 (organic anion transporting polypeptide 1B1, gene *SLCO1B1*) is expressed exclusively on the sinusoidal (basolateral) membrane of hepatocytes. It is the primary uptake transporter for many anionic drugs entering the liver from portal blood, including HMG-CoA reductase inhibitors (statins: pravastatin, rosuvastatin, atorvastatin).

Step 1 — Role of OATP1B1 for statins: After oral absorption, statins rely on OATP1B1 for hepatic first-pass extraction. This concentrates them in the liver (their pharmacological target) and keeps systemic plasma levels low. When OATP1B1 is inhibited, hepatic uptake is impaired: plasma statin AUC increases dramatically while hepatic concentrations may fall.

Step 2 — Cyclosporin as OATP1B1 inhibitor: Cyclosporin (calcineurin inhibitor) is a potent inhibitor of OATP1B1 (and OATP1B3). Organ-transplant patients on cyclosporin who require statin therapy for hypercholesterolaemia are at greatly elevated risk of statin-induced myopathy (CK elevation, rhabdomyolysis) due to elevated plasma statin concentrations.

Why other options are wrong:

- Option A: CYP3A4 inhibition is not the primary mechanism; rosuvastatin is minimally metabolised by CYP3A4.
- Option B: P-gp at the gut wall is not the dominant interaction mechanism for statins with cyclosporin.
- Option C: OATP1B1 inhibition by cyclosporin increases (not decreases) plasma statin concentration $\rightarrow$ myopathy risk. **Correct.**
- Option D: MRP2 induction by cyclosporin is not established as a clinical interaction mechanism.

Final Answer: Cyclosporin inhibits OATP1B1 $\rightarrow$ reduced hepatic statin uptake $\rightarrow$ elevated plasma statin AUC $\rightarrow$ myopathy risk $\Rightarrow$ C

Answer: (C) Go Back to Q17

Q18.

Solution

Concept — Biliary Excretion Molecular Weight Threshold: Biliary excretion is an active process mediated by canalicular efflux transporters (primarily MRP2/ABCC2, BCRP/ABCG2, and MDR1/P-gp) on the bile canalicular membrane. Not all drugs are excreted in bile: a critical molecular weight threshold exists above which biliary secretion becomes significant.

Step 1 — Species differences in MW threshold:

- Rat: MW threshold ≈ 325 Da.
- Human: MW threshold ≈ 500 Da (higher due to lower canalicular transporter capacity for small molecules).

Step 2 — Required structural features: In addition to MW > 500 Da (human), drugs must possess polar functional groups that facilitate active transport by MRP2 (favours anionic, glutathione, glucuronate, or sulphate conjugates) or P-gp (favours amphipathic cations). Phase II conjugates (glucuronides, sulphates, glutathione adducts) typically exceed 500 Da and are the predominant biliary excretion products.

Why other options are wrong:

- Option A: MW threshold in humans is > 500 Da, not > 150 Da; ionisation alone is insufficient.
- Option B: MW > 300 Da is the rat threshold; monobasic amine is not a universal requirement.
- Option C: MW > 400 Da is below the human threshold; a nitrogen atom is not the defining feature.
- Option D: MW > 500 Da with polar groups (glucuronide, sulphate, glutathione) is the correct human criterion. **Correct.**

Final Answer: Human biliary excretion requires MW > 500 Da and polar conjugate groups for MRP2/BCRP-mediated canalicular efflux $\Rightarrow$ D

Answer: (D) Go Back to Q18

Q19.

Solution

Concept — Allometric Scaling of Drug Clearance: Allometric scaling exploits the empirical observation that many physiological variables (cardiac output, glomerular filtration rate, hepatic blood flow) scale across mammalian species as power functions of body weight: $Y = a \cdot \text{BW}^b$. For drug clearance, the exponent $b = 0.75$ has been validated across multiple species (mouse, rat, rabbit, dog, monkey, human).

Step 1 — Exponent for clearance: $b = 0.75$ for clearance reflects the well-established three-quarter power law (Kleiber's law) originally derived for basal metabolic rate. The same exponent applies to organ blood flows and hepatic microsomal activity across species.

Step 2 — Paediatric dose prediction: For a child of body weight BW_c relative to a 70 kg adult reference:

$$\text{CL}_{\text{child}} = \text{CL}_{\text{adult}} \times \left(\frac{\text{BW}_c}{70}\right)^{0.75}$$

This gives higher per-kg clearance for children than simple linear (per-kg) scaling would predict, which is physiologically consistent with the higher mass-specific metabolic rates of children.

Why other options are wrong:

- Option A: $b = 0.75$ for clearance — the most widely validated exponent. **Correct.**
- Option B: $b = 1.0$ (linear scaling) is more appropriate for volume of distribution (V_d), not clearance.
- Option C: $b = 0.5$ (square-root) is not the standard allometric exponent for clearance in pharmacokinetics.
- Option D: $b = 0.67$ (two-thirds) is sometimes used for surface-area-based metabolic rate calculations but is not the standard for drug clearance allometry.

Final Answer: Allometric exponent for clearance $= 0.75$ (three-quarter power law) $\Rightarrow$ A

Answer: (A) Go Back to Q19

Q20.

Solution

Concept — Cockcroft–Gault Equation for Creatinine Clearance: The Cockcroft–Gault equation estimates glomerular filtration rate (GFR) from serum creatinine in adults:

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times \text{BW (kg)}}{72 \times S_{Cr}\,(\text{mg/dL})} \quad (\times 0.85 \text{ for females})$$

Step 1 — Substitute patient values:

$$\begin{aligned}\text{CrCl} &= \frac{(140 - 75) \times 68}{72 \times 1.5} \\ &= \frac{65 \times 68}{108} \\ &= \frac{4420}{108} \\ &= 40.9 \approx 41 \text{ mL/min}\end{aligned}$$

Step 2 — Interpret in clinical context: CrCl $\approx$ 41 mL/min = moderate renal impairment (Stage G3a, CKD classification). For renally cleared drugs with narrow therapeutic index (digoxin, vancomycin, metformin, aminoglycosides), this level requires dose reduction or interval extension.

Why other options are wrong:

- Option A: 28 mL/min would require approximately $S_{Cr} \approx 2.3$ mg/dL; not consistent with the given values.
- Option B: 41 mL/min is calculated correctly from the Cockcroft–Gault equation. **Correct.**
- Option C: 55 mL/min would require lower S_{Cr} ($\approx$ 1.1 mg/dL) or a younger/heavier patient.
- Option D: 68 mL/min would correspond to a much younger patient or lower S_{Cr}.

Final Answer: CrCl $= (65 \times 68)/(72 \times 1.5) = 4420/108 \approx 41$ mL/min $\Rightarrow$ B

Answer: (B) Go Back to Q20

Q21.

Solution

Concept — Mechanism-Based (Irreversible) CYP Inhibition: Mechanism-based inhibition (MBI), also called suicide inhibition or time-dependent inhibition (TDI), occurs when an inhibitor is metabolically activated by the CYP it inhibits, forming a reactive intermediate (nitroso, carbene, epoxide) that covalently or quasi-irreversibly modifies the enzyme's active site or haem. The CYP is permanently inactivated; recovery requires de novo enzyme synthesis (half-life 24–70 h for CYP3A4).

Step 1 — Key kinetic parameters for MBI:

- k_{inact}: maximum rate of inactivation (min^{-1}).
- K_I: inhibitor concentration producing 50% maximal inactivation rate.
- MBI requires pre-incubation time (time-dependent): the longer the exposure, the greater the inhibition.

Step 2 — Distinguishing from reversible inhibition: Reversible (competitive) inhibition: (a) does not require metabolic activation; (b) inhibition is immediately proportional to inhibitor concentration; (c) completely reversed upon dilution or removal of inhibitor; (d) no time-dependent component. MBI: (a) requires metabolic activation; (b) inhibition increases with pre-incubation time; (c) persists after removal (irreversible); (d) characterised by k_{inact} and K_I rather than K_i.

Why other options are wrong:

- Option A: MBI is not necessarily characterised by a lower K_I than K_i for competitive inhibition; the distinguishing feature is irreversibility and time-dependence.
- Option B: MBI is NOT reversible upon dilution; recovery requires new enzyme synthesis.
- Option C: Time-dependent and irreversible due to covalent active-site modification. **Correct.**
- Option D: MBI and competitive inhibition have fundamentally different kinetics; they are not merely quantitatively but qualitatively distinct.

Final Answer: MBI is time-dependent and irreversible (covalent CYP inactivation; recovery needs new enzyme synthesis) $\Rightarrow$ C

Answer: (C) Go Back to Q21

Q22.

Solution

Concept — Rifampicin as a Potent PXR Activator and CYP/P-gp Inducer: Rifampicin is the most potent clinical inducer of drug-metabolising enzymes and transporters. It activates the nuclear receptor PXR (SXR/NR1I2), which translocates to the nucleus and transcriptionally upregulates CYP3A4, CYP2C9, CYP2C19, P-gp (MDR1), and MRP2.

Step 1 — Voriconazole metabolism: Voriconazole is primarily metabolised by CYP2C19 ($\sim$50%), with CYP3A4 and CYP2C9 as minor pathways. Rifampicin induces all three enzymes. Clinical studies show rifampicin reduces voriconazole AUC by $\sim$95% and the mean $C_{\max}$ by $> 90\%$. This interaction is so severe that rifampicin is listed as an absolute contraindication with voriconazole in the SmPC.

Step 2 — Why voriconazole fails: With >90% reduction in voriconazole AUC, plasma concentrations fall below the minimum inhibitory concentration (MIC) for fungi, resulting in treatment failure and potentially life-threatening breakthrough infection.

Why other options are wrong:

- Option A: Rifampicin does not form complexes with voriconazole; it acts via nuclear receptor induction.
- Option B: GI absorption and motility effects are minor compared to the profound CYP induction.
- Option C: Rifampicin inhibits OATP1B1 transiently, but this would increase (not decrease) plasma voriconazole.
- Option D: PXR activation $\rightarrow$ CYP2C19/3A4 induction $\rightarrow$ rapid voriconazole metabolism $\rightarrow$ undetectable plasma levels $\rightarrow$ treatment failure. **Correct.**

Final Answer: Rifampicin activates PXR $\rightarrow$ induces CYP2C19 and CYP3A4 $\rightarrow$ voriconazole AUC reduced >90% $\rightarrow$ treatment failure $\Rightarrow$ $\boxed{\text{D}}$

Answer: (D) Go Back to Q22

Q23.

Solution

Concept — Renal Tubular Secretion via OAT Transporters and Probenecid: Renal elimination of organic anions occurs via three mechanisms: (1) glomerular filtration (passive, proportional to f_u); (2) active tubular secretion (carrier-mediated, can exceed GFR for high-secretion drugs); (3) passive tubular reabsorption. Penicillin G has a short $t_{1/2}$ ($\sim$30 min IV) primarily because it is actively secreted by OAT1 (SLC22A6) and OAT3 (SLC22A8) on the basolateral membrane of proximal tubule cells, then exits via MRP2 (ABCC2) on the apical membrane into the tubular lumen.

Step 1 — Probenecid mechanism: Probenecid is a uricosuric organic acid that competitively inhibits OAT1 and OAT3 at the basolateral membrane of proximal tubular cells. By blocking these transporters, probenecid prevents the uptake of penicillin G from peritubular blood into tubular cells, abolishing active secretion. Only glomerular filtration (of free drug) remains, dramatically reducing total renal clearance and extending $t_{1/2}$.

Step 2 — Historical use: During World War II, penicillin was scarce and expensive. Probenecid co-administration reduced penicillin renal clearance by $\sim$50–80%, allowing lower doses to maintain therapeutic concentrations for longer. This extended $t_{1/2}$ from $\sim$30 min to $\sim$60–90 min.

Why other options are wrong:

- Option A: Inhibiting OAT1/OAT3 tubular secretion is the correct mechanism. **Correct.**
- Option B: Probenecid can displace albumin-bound drugs, but this would increase V_d and shorten $t_{1/2}$, not extend it.
- Option C: Probenecid does not affect GFR or afferent arteriolar tone.
- Option D: Penicillin G is not metabolised by CYP3A4; probenecid is not a CYP inhibitor.

Final Answer: Probenecid inhibits OAT1/OAT3 renal tubular secretion of penicillin G $\rightarrow$ reduced renal CL $\rightarrow$ extended $t_{1/2} \Rightarrow$ A

Answer: (A) Go Back to Q23

Q24.

Solution

Concept — Plasma Protein Binding Displacement and Free Drug Concentration: Phenytoin is ∼90–95% bound to albumin at therapeutic concentrations; the free fraction $f_u \approx 0.01$–0.10. The free (unbound) fraction is pharmacologically active, crosses the blood–brain barrier, and is subject to hepatic metabolism and renal filtration. The conventional therapeutic range (10–20 μg/mL) refers to TOTAL phenytoin.

Step 1 — Effect of valproate displacement: Valproate is an anionic drug that competes with phenytoin for albumin binding sites (Site II). When valproate is added, it displaces phenytoin, increasing f_u from ∼1% to ∼5–10%.

Step 2 — Paradox of toxicity at "therapeutic" total phenytoin:

- If total phenytoin = 15 μg/mL and $f_u = 0.01$: free phenytoin $= 0.15\,\mu$g/mL.
- After displacement ($f_u = 0.07$): free phenytoin $= 15 \times 0.07 = 1.05\,\mu$g/mL.
- A 7-fold increase in free phenytoin causes toxicity despite total concentration appearing "normal."

In the long term, increased free phenytoin also increases its own hepatic clearance (CYP2C9 is saturable; more free drug available), and total phenytoin may eventually fall even as free phenytoin normalises.

Why other options are wrong:

- Option A: Valproate is a weak CYP2C9 inhibitor, which would increase TOTAL phenytoin; here total phenytoin is normal, ruling out inhibition as the cause.
- Option B: Protein binding displacement with increased free phenytoin fraction is the correct explanation. **Correct.**
- Option C: Pharmacodynamic synergism would cause toxicity regardless of PK; the question specifically implicates a PK mechanism.
- Option D: Phenytoin is not significantly secreted renally; its primary elimination is hepatic CYP2C9 metabolism.

Final Answer: Valproate displaces phenytoin from albumin → increased f_u → elevated free phenytoin causing toxicity despite normal total concentration ⇒ $\boxed{\text{B}}$

Answer: (B) Go Back to Q24

Q25.

Solution

Concept — PBPK Tissue:Plasma Partition Coefficients (K_p): In PBPK models, each tissue compartment is characterised by a K_p value that defines the equilibrium ratio of drug concentration in that tissue to concentration in plasma: $K_p = C_{\text{tissue}}/C_{\text{plasma}}$. Accurate K_p values are essential for predicting volume of distribution, tissue accumulation, and site-of-action drug concentrations.

Step 1 — Methods for calculating K_p: Several mechanistic methods combine drug physicochemical descriptors with tissue composition data:

- **Rodgers–Rowland method** (2005): uses $\log P$ (neutral lipid partitioning), pK_a (ion trapping), plasma protein binding ($f_{u,p}$), and tissue composition (neutral lipids, phospholipids, acidic and basic protein content) to predict K_p for acids, bases, and neutrals.
- **Berezhkovskiy method**: extension incorporating additional ionisation parameters.
- **Poulin–Theil method**: uses tissue:buffer and lipid:water partition coefficients.

Step 2 — Why physicochemical + tissue composition? Ion trapping: basic drugs (p$K_a > 7$) accumulate in acidic tissues (lysosomes, muscle). Lipid partitioning: $\log P$ predicts neutral lipid affinity. Protein binding: each tissue has different albumin and lipoprotein content. Without knowing all these factors, K_p cannot be calculated mechanistically.

Why other options are wrong:

- Option A: In vivo V_d data is an aggregate; tissue-specific K_p values require physicochemical + tissue composition inputs.
- Option B: Hepatic flow and renal GFR determine clearance parameters, not tissue partition coefficients.
- Option C: Physicochemical properties ($\log P$, pK_a, $f_{u,p}$) combined with tissue composition — the Rodgers–Rowland or Berezhkovskiy approach. **Correct.**
- Option D: Allometric scaling predicts clearance and V_d but not tissue-specific K_p values.

Final Answer: K_p in PBPK is determined from drug $\log P$, pK_a, $f_{u,p}$ and tissue composition (Rodgers–Rowland / Berezhkovskiy methods) $\Rightarrow$ C

Answer: (C) Go Back to Q25

Answer Key

Q	Ans	Q	Ans	Q	Ans	Q	Ans	Q	Ans
1	C	2	D	3	A	4	B	5	C
6	D	7	A	8	B	9	C	10	D
11	A	12	B	13	C	14	D	15	A
16	B	17	C	18	D	19	A	20	B
21	C	22	D	23	A	24	B	25	C