壹、單選題（每題 2 分，共 20 分） ※ 注意：請於試卷內之「選擇題作答區」依序作答。

1. After a single IV dose of a drug, the distribution phase is complete. Concentration–time data are extracted from the elimination phase at two different concentration ranges in the **same subject**:

High-concentration range

Time (hr)	**0**	**2**	**4**	**6**
Concentration (mg/L)	40	35	30	25

Low-concentration range

Time (hr)	**0**	**2**	**4**	**6**
Concentration (mg/L)	8	4	2	1

Which statement best describes the elimination kinetics across these concentration ranges?

[A] Both ranges show first-order elimination; the half-life is the same at high and low concentrations.

[B] The high-concentration range approximates zero-order elimination, while the low-concentration range shows first-order elimination; this pattern is consistent with capacity-limited (Michaelis–Menten) elimination.

[C] The high-concentration range shows first-order elimination, and the low-concentration range shows zero-order elimination, suggesting an acute decline in renal function.

[D] The order of elimination cannot be determined without knowing the volume of distribution (V) and clearance (Cl).

2. A drug is given as a single oral immediate-release dose. Its disposition is adequately described by a one-compartment model with linear (first-order) elimination. An independent estimate of the elimination rate constant (k_{el}) is available from the terminal log-linear phase (or from an IV study). Plasma concentration-time data after the oral dose are collected densely.

Which of the following is the primary quantity that the Wagner–Nelson method is used to estimate from these data?

[A] The time course of the cumulative fraction absorbed, Fa(t), after oral dosing (and related absorption-rate information)

[B] The time to maximum concentration (T_{max})

[C] Apparent volume of distribution (V/F)

[D] Renal clearance (Clr)

[E] Absolute bioavailability (F) without any elimination information

3. For a **one-compartment model** after a **single IV bolus** dose, assume **linear (first-order) elimination**. Dose is in mg, concentration is in mg/L, and time is in hr. Which statement is **correct**?

[A] $AUC_{0\text{-}inf}$ = Dose x CL

[B] CL = Dose / $AUC_{0\text{-}inf}$

[C] V = K / CL

[D] $t_{1/2} = 0.693 \times K$

4. In **capacity-limited (Michaelis–Menten) non-linear pharmacokinetics**, which pair represents the **two fundamental parameters** of Michaelis–Menten elimination?

[A] K_a and K

[B] V and CL

[C] K_M and V_{max}

[D] α and β

[E] k_{12} and k_{21}

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5. For a drug given at a constant dosing interval tau under linear pharmacokinetics, the **average steady-state concentration ($C_{ss,avg}$)** over one dosing interval is defined as the **time-averaged concentration** from t = 0 to t = τ at steady state. Which expression is most appropriate?
[A] $(C_{ss,max} + C_{ss,min})/2$
[B] $AUC\tau/\tau$
[C] $C_{ss,max}/C_{ss,min}$
[D] $(C_{ss,max} \times C_{ss,min})^{1/2}$

6. A drug is administered at a fixed dosing interval tau. Assume **linear pharmacokinetics** and that **τ and systemic clearance (CL) remain unchanged**. You want to **decrease the average steady-state concentration ($C_{ss,avg}$) by 20%**.
Which change is the **most direct** way to achieve this target?
[A] Decrease the dose by 20%
[B] Prolong the infusion duration
[C] Increase the absorption rate constant (K_a)
[D] Increase the volume of distribution (V)

7. In standard bioequivalence (BE) assessments for most orally administered drug products, BE is typically concluded by constructing a **90% confidence interval** for the **test/reference ratio of geometric means** using **log-transformed** pharmacokinetic metrics. Which two PK metrics are **most commonly** used for this purpose?
[A] AUC and C_{max}
[B] T_{max} and $t_{1/2}$
[C] CL and V
[D] K_a and K
[E] AUC and CL

8. Compared with older children and adults, which factor is **most likely** to **prolong a drug's elimination half-life in neonates**?
[A] Higher protein binding fraction
[B] Immature glomerular filtration and immature drug-metabolizing enzyme activity
[C] Faster gastric emptying leading to more rapid absorption
[D] Neonates always have a smaller volume of distribution
[E] Complete absence of enterohepatic recirculation

9. After a single **oral** dose, a concentration-time profile shows **two distinct peaks** (a "double-peak" phenomenon). Which of the following is **NOT** a common cause of double peaks?
[A] Enterohepatic recirculation
[B] Delayed or variable gastric emptying
[C] Absorption occurring from different gastrointestinal sites (site-dependent absorption)
[D] Sampling or analytical error (e.g., mislabeled time points, assay variability)
[E] The elimination rate constant (K) suddenly becomes negative

10. A drug is administered by **intermittent IV infusion** with a fixed dose given every dosing interval tau. Assume **linear pharmacokinetics** and that **steady state** has been reached. Which statement is **correct**?
[A] $C_{ss,max}$ occurs at the instant the infusion begins.
[B] $C_{ss,min}$ occurs at the instant the infusion ends.
[C] $C_{ss,avg} = Dose / (CL \times \tau)$.

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[D] The longer the infusion duration, the higher the $C_{ss,avg}$ must be.

[E] Changing only V is sufficient to change $C_{ss,avg}$.

※ 注意：請於試卷內之「非選擇題作答區」依序作答，並應註明作答之大題及小題題號。

貳、簡答題（每題 10 分，共 40 分）

Answer in bullet points. You may include simple equations or schematic sketches if helpful.

1. List **two core assumptions** required when fitting clinical concentration-time data with a **one-compartment model**. For **each** assumption, provide **one clinical scenario** where the assumption may not hold and briefly explain why.
2. A drug has a total clearance such that 70% is due to **renal clearance of the unchanged drug**, and renal clearance is approximately **proportional to creatinine clearance (Cl_{Cr})**. Describe **two different adjustment strategies** to maintain the **same average steady-state concentration ($C_{ss,avg}$)** as Cl_{Cr} decreases (for example, adjusting dose and/or dosing interval). For each strategy, write the **basic proportional relationship** you are using (no full derivation required).
3. Give **two examples of formulation-related factors** and **two examples of physiologic or pathophysiologic factors** that can affect **oral bioavailability (F)**. For each example, state **how** it changes F (increase or decrease) and the **mechanism**.
4. After oral dosing, the **terminal log-linear slope** appears **shallower** than after IV dosing, suggesting possible **flip-flop kinetics**. Please explain:

(1) What flip-flop kinetics means (in terms of absorption vs elimination rate constants), and

(2) One way it can lead to **clinical misinterpretation** (for example, incorrect half-life estimation, incorrect dosing interval decisions, or mistaken conclusions about clearance).

參、計算題（共 40 分）

This section consists of pharmacokinetic calculation problems. Unless otherwise specified, assume a one-compartment model with linear (first-order) kinetics and instantaneous mixing. Clearly show your work, state any formulas used, and label all units of measurement. Answers should be reported with appropriate units and rounded to a reasonable degree of accuracy.

1. A drug is completely absorbed across the gastrointestinal lumen (Fa = 1.0). However, it undergoes presystemic extraction in two sequential sites:

- Intestinal epithelial (gut wall) extraction fraction, **Eg = 0.91**
- Hepatic extraction fraction, **Eh = 0.71**

Assuming these processes act sequentially and independently, and that no other losses occur, what is the expected overall oral bioavailability (F)? Show your calculation and report F as a fraction and as a percent. (8 points)

2. A drug follows first-order elimination and is adequately described by a one-compartment IV bolus model. An adult male (body weight 74 kg) receives a rapid IV injection of 750 mg.

Given:

- Elimination half-life $t_{1/2}$ = 7 hr
- Apparent volume of distribution V = 0.55 L/kg
- Assume instantaneous mixing and linear PK.

(1) What percent of the dose is eliminated by t = 21 hr? (4 points)

(2) What is the expected plasma concentration at 21 hr, Cp_{21h}, in mg/L? (6 points)

(3) At what time (hr) will Cp fall below 2.0 mg/L? (4 points)

3. Tom is an 8-year-old boy (weight 25 kg) receiving **valproic acid (VPA) 250 mg orally every 12 hours** for seizure control.

Assume:

- One-compartment model, linear PK, first-order elimination
- Treat each oral dose as an IV bolus input because F = 1.0
- Pediatric clearance: CL = 13 mL/kg/hr

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- V = 0.14 L/kg
- Therapeutic range: 50 to 100 mg/L
- Toxicity may occur when the concentration is > 200 mg/L
- Normal hepatic and renal function

(1) Predict the steady-state trough concentration Css, min (mg/L). (6 points)

(2) Comment on the adequacy of the current regimen (therapeutic and safety). (4 points)

(3) Propose a revised dose and interval (Dose, τ) such that $\mathbf{C_{ss,\,min} \geq 50\ mg/L}$ and $\mathbf{C_{ss,\,max} < 200\ mg/L}$, and verify both targets using the same steady-state IV bolus equations. (8 points)

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