BP602T · B.Pharm Semester VI · Theory Notes

Biopharmaceutics and Pharmacokinetics

Unit IV — Multicompartment Models and Multiple Dosage Regimens

Unit IV (9 hours)

Pills & Python Notes

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

Syllabus coverage: Unit IV (9 hours).

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CHAPTER 4: Two-Compartment Open Model — IV Bolus and Oral Administration

Subject: BP602T Biopharmaceutics and Pharmacokinetics (B.Pharm Semester VI) **Unit:** Unit IV

1. Learning Objectives

After studying this chapter, you will be able to:

1 Explain in simple words why a one-compartment model is sometimes not enough, and why we need a two-compartment model.

2 Draw and label the two-compartment open model diagram from zero (central compartment, peripheral/tissue compartment, IV bolus, arrows for k12, k21, k10).

3 Write the meaning of every symbol: A, B, α, β, k12, k21, k10, Vc, Vd_area, Vd_ss, Cl.

4 Derive, step by step, the biexponential equation **C(t) = A·e^(−α·t) + B·e^(−β·t)** for an IV bolus dose.

5 Distinguish between hybrid (macro) constants α, β and micro-constants k12, k21, k10, and state their mathematical relationships.

6 Calculate Vc, Vd_area, Vd_ss, Cl, and t½,β from biexponential data.

7 Perform the method of residuals (feathering) step by step on a set of plasma concentration–time data and obtain A, α, B, β.

8 Explain the triexponential equation for oral (extravascular) administration and the flip-flop phenomenon.

9 Compare one-compartment and two-compartment models in a table and list the advantages of multicompartment modelling.

2. Definitions

- **Compartment:** An imaginary (hypothetical) space inside the body. It is NOT a real organ like the liver or kidney. It is a group of tissues that behave similarly — the drug enters and leaves them at similar speeds.
- **Central compartment:** The imaginary space that includes the blood (plasma) plus those tissues where the drug distributes very quickly (for example, heart, liver, kidneys — the well-blooded organs). We can measure drug concentration here because we can take blood samples.
- **Peripheral (tissue) compartment:** The imaginary space that includes tissues where the drug distributes slowly (for example, muscle, fat, skin, bone). We cannot easily take samples from here; its concentration is only estimated.

- **IV bolus:** A drug dose injected quickly and directly into a vein (all the drug enters the blood at once, in seconds). Think of it as dumping a bucket of water into a tank all at once.
- **Open model:** A model in which the drug can LEAVE the body (it is eliminated — through urine, bile, or metabolism). Contrast with a closed model, in which the drug only moves between compartments and never leaves the body. Almost all pharmacokinetic models used for real drugs are open models.
- **Biexponential equation:** An equation with two exponential terms: C(t) = A·e^(−α·t) + B·e^(−β·t). It describes how drug concentration in blood falls in TWO phases: a fast early fall (distribution phase) and a slower later fall (elimination phase).
- **Hybrid (macro) constant:** A constant obtained from the *shape* of the plasma concentration–time curve. α and β are hybrid constants because each one is a mixture (a combination) of the micro-constants k12, k21, and k10.
- **Micro-constant:** A first-order rate constant describing drug movement in ONE specific direction: k12 (central → tissue), k21 (tissue → central), k10 (central → outside the body, i.e., elimination).
- **Method of residuals (feathering):** A manual, graphical technique to split a curved log-concentration–time plot into two straight lines, giving us the values of A, α, B, and β.
- **Flip-flop:** A situation in oral dosing where the absorption rate constant (ka) is SLOWER than the elimination constant — the terminal slope of the curve then reflects absorption, not elimination.

3. Terminology (Glossary Table)

Symbol / Term	Meaning in simple words	Unit
C(t)	Drug concentration in the blood plasma at time t	mg/L (or µg/mL)
A	Intercept of the fast (distribution) line on the log plot — its contribution at time zero	mg/L
B	Intercept of the slow (terminal) line on the log plot — its contribution at time zero	mg/L
α (alpha)	Hybrid rate constant of the fast DISTRIBUTION phase — slope of the steep early part	hr^{-1} (per hour)
β (beta)	Hybrid rate constant of the slow TERMINAL phase — slope of the shallow late part	hr^{-1}
k12	Micro-constant: rate at which drug moves from central compartment → tissue compartment	hr^{-1}
k21	Micro-constant: rate at which drug moves from tissue compartment → central compartment	hr^{-1}

Symbol / Term	Meaning in simple words	Unit
k10	Micro-constant: rate at which drug is ELIMINATED from the central compartment	hr^{-1}
Vc	Volume of the central compartment = Dose ÷ (A + B)	L
Vd_area	Volume of distribution by area method = Dose ÷ (β × AUC)	L
Vd_ss	Volume of distribution at steady state = Vc × (1 + k12/k21)	L
Cl	Clearance: volume of blood cleared of drug per unit time = Dose ÷ AUC	L/hr
AUC	Area under the plasma concentration–time curve = A/α + B/β	mg·hr/L
$t_{½,\alpha}$	Distribution half-life = 0.693 ÷ α	hr
$t_{½,\beta}$	Terminal (elimination) half-life = 0.693 ÷ β	hr
ka	First-order absorption rate constant (used in oral dosing)	hr^{-1}
L, M, N	Coefficients of the triexponential equation for oral dosing (like A and B, but three of them)	mg/L
Xc	Amount of drug in the central compartment (an amount, not a concentration)	mg
Xt	Amount of drug in the tissue (peripheral) compartment	mg

Key takeaway: Every symbol in this chapter describes either *where* the drug is (compartment), *how fast* it moves (rate constant), or *how much* is there (concentration or amount). When you see a new symbol, ask: "Is it a place, a speed, or an amount?"

4. Explanation — Why Do Multicompartment Models Exist?

4.1 The limitation of the one-compartment model

In the one-compartment model (Unit III of this subject), we assumed that the moment a drug enters the blood, it instantly and uniformly mixes with the whole body. That is a convenient lie.

In reality: When a drug is injected into a vein, it first goes to organs that receive a lot of blood — the heart, liver, kidneys, lungs. Only later does it slowly seep into muscle, fat, skin, and bone. Distribution is NOT instantaneous.

Simple example: Pour a spoon of sugar into a cup of tea and stir — it mixes fast. Now imagine a cup connected by a thin pipe to a second cup. Sugar poured into the first cup reaches the second cup only slowly, through the pipe. The body is like the two cups: blood is the first cup (fast), tissues are the second cup (slow, connected by a thin pipe).

4.2 Central vs peripheral (tissue) compartments

- **Central compartment = the main hall + fast rooms.** It contains the blood and the organs with heavy blood supply. Drug arrives here first and mixes quickly. We take blood samples from here, so we always know its concentration.
- **Peripheral compartment = the slow rooms.** Muscle, fat, skin. The drug enters and leaves these rooms slowly. We cannot sample them directly — we only guess their behaviour from the blood curve.

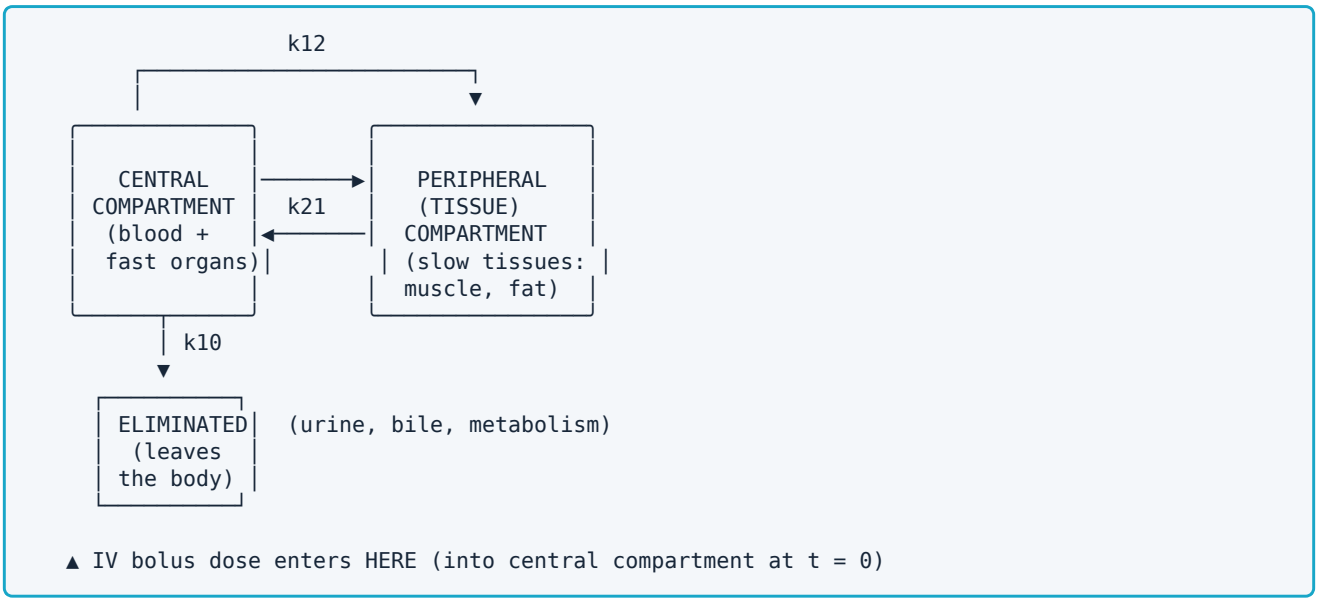
The **two-room house analogy** (memorise this — examiners love it):

Imagine a house with TWO rooms connected by a door. The main room (Room 1, central compartment) has the front door, through which a guest (the drug) enters as an IV bolus. There is also a back door in the main room through which the guest can leave the house (elimination, k10). The guest can walk through the inner door into the second room (k12) and come back (k21). If you watch the main room, you will first see the guest count fall FAST (guests rushing into the second room = distribution phase), and later fall SLOWLY (guests leaving through the back door = elimination phase).

That fast-then-slow fall is exactly why the plasma curve has TWO slopes — and why we need TWO exponential terms.

4.3 Diagram of the two-compartment open model (IV bolus)

Draw this in your exam — it carries marks by itself.



Reading the diagram, arrow by arrow:

1. **IV bolus arrow (into central):** At time zero, the entire dose enters the central compartment instantly. This is the only entry point.
2. **k12 arrow (central → peripheral):** Drug moves from the blood into the slow tissues. This causes the fast early drop in blood concentration (distribution phase).
3. **k21 arrow (peripheral → central):** Drug comes back from the tissues into the blood. At later times, this return slows down the fall of blood concentration.
4. **k10 arrow (central → outside):** Drug is eliminated from the body (only from the central compartment — the kidneys filter the blood, not the fat). This drives the slow terminal decline.

Key takeaway: Drug enters only the central compartment; drug leaves the body only from the central compartment; the tissue compartment only exchanges drug with the central compartment. Memorise these three rules — every derivation below follows from them.

4.4 What the plasma curve looks like

After an IV bolus, if you plot **log C (log of plasma concentration) against time t**, you do NOT get a straight line (as in the one-compartment model). You get a curve that bends — steep at first, then straight and shallow later:

- **Phase 1 — Distribution phase (steep, slope = α):** Drug is rushing out of the blood into the tissues. Blood concentration falls fast.
- **Phase 2 — Terminal (post-distribution) phase (shallow, slope = β):** Distribution is nearly complete (drug entering and leaving tissues is almost balanced). Now the main reason blood concentration falls is elimination. The fall is slow.

β is always smaller than α (β < α), because elimination is slower than distribution.

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5. Classifications

5.1 Mammillary vs catenary models

- **Mammillary model:** Compartments are arranged like the breasts of a mammal — all peripheral compartments connect ONLY to the central compartment, not to each other. The two-compartment model in this chapter is a mammillary model.
- **Catenary model:** Compartments are arranged in a chain (like train bogies) — compartment 1 connects to 2, 2 connects to 3, and so on.

(For B.Pharm exams, you only need the mammillary two-compartment model.)

5.2 Open vs closed models

- **Open model:** Drug is eliminated from the system (k10 exists). Used for real drugs.
- **Closed model:** No elimination; drug only moves between compartments forever. Used only for theoretical exercises.

5.3 Routes covered in this chapter

Route	Equation form	Phases seen
IV bolus	Biexponential: C = A·e^(−αt) + B·e^(−βt)	Distribution + terminal
Oral (extravascular)	Triexponential: C = L·e^(−kat) + M·e^(−αt) + N·e^(−βt)	Absorption + distribution + terminal

Key takeaway: Each "phase" of the curve adds one exponential term. One compartment IV = one exponential; two compartments IV = two exponentials; two compartments oral = three exponentials.

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6. Mechanisms and Derivations

6.1 Setting up the differential equations (IV bolus)

Let us write, in words first, what happens to the AMOUNT of drug in each compartment.

Central compartment (amount = Xc):

- Drug leaves toward tissues at rate k12·Xc (minus — it goes out).
- Drug is eliminated at rate k10·Xc (minus — it goes out).
- Drug returns from tissues at rate k21·Xt (plus — it comes in).

So:

$$dXc/dt = -(k10 + k12)\cdot Xc + k21\cdot Xt \quad \ldots (1)$$

Tissue compartment (amount = Xt):

- Drug arrives from central at rate k12·Xc (plus).
- Drug returns to central at rate k21·Xt (minus).

$$dXt/dt = k12\cdot Xc - k21\cdot Xt \quad \ldots (2)$$

At time zero (IV bolus), all the dose is in the central compartment:

$$Xc(0) = Dose = X0, \text{ and } Xt(0) = 0 \quad \ldots (3)$$

6.2 Converting amounts to concentrations

We measure concentration in blood, C = Xc / Vc, where Vc is the central volume. Divide equation (1) by Vc and define the tissue "concentration" Ct = Xt / Vc (just a scaled amount — keep it simple):

$$dC/dt = -(k10 + k12)\cdot C + k21\cdot Ct \ldots (1a) \quad dCt/dt = k12\cdot C - k21\cdot Ct \ldots (2a)$$

with C(0) = X0/Vc = C0 and Ct(0) = 0.

6.3 Solving with Laplace transforms — every step shown

Step 1 — Take the Laplace transform of both equations.

The Laplace transform converts a differential equation into an algebra problem. Recall: Laplace of dC/dt is s·C − C(0), where C means "Laplace of C".

From (1a):

$$s\cdot C - C0 = -(k10 + k12)\cdot C + k21\cdot C\bar{t} \ldots (4)$$

From (2a):

$$s\cdot C\bar{t} - 0 = k12\cdot C - k21\cdot C\bar{t} \ldots (5)$$

Step 2 — Solve equation (5) for Ct̄.

$$s\cdot C\bar{t} + k21\cdot C\bar{t} = k12\cdot C \quad C\bar{t}\cdot(s + k21) = k12\cdot C \quad C\bar{t} = k12\cdot C / (s + k21) \ldots (6)$$

Step 3 — Substitute (6) into (4).

$$s\cdot C - C0 = -(k10 + k12)\cdot C + k21\cdot[k12\cdot C/(s + k21)]$$

Bring all C terms to one side:

$$C\cdot[s + k10 + k12 - k21\cdot k12/(s + k21)] = C0$$

Multiply through by (s + k21):

$$C\cdot[(s + k10 + k12)(s + k21) - k12\cdot k21] = C0\cdot(s + k21)$$

Step 4 — Expand the bracket.

$$(s + k10 + k12)(s + k21) - k12\cdot k21 = s^2 + s\cdot k21 + s(k10 + k12) + (k10 + k12)\cdot k21 - k12\cdot k21$$
$$= s^2 + s\cdot(k12 + k21 + k10) + k21\cdot k10$$

So:

$$C = C0\cdot(s + k21) / [s^2 + s\cdot(k12 + k21 + k10) + k21\cdot k10] \ldots (7)$$

Step 5 — Factor the denominator.

The denominator is a quadratic in s. Its two roots are −α and −β (both negative numbers, so that concentrations decay, not grow):

$$s^2 + s\cdot(k12 + k21 + k10) + k21\cdot k10 = (s + \alpha)(s + \beta)$$

By comparing with the standard quadratic s^2 + (sum)·s + (product):

$\alpha + \beta = k12 + k21 + k10$ ... (8) **$\alpha\cdot\beta = k21\cdot k10$** ... (9)

These two relations are GOLD for exams — α and β are mixtures (hybrids) of the micro-constants.

Step 6 — Partial fractions.

$$C = C0\cdot(s + k21) / [(s + \alpha)(s + \beta)] = A/(s + \alpha) + B/(s + \beta)$$

Multiply out: $C0\cdot(s + k21) = A\cdot(s + \beta) + B\cdot(s + \alpha)$.

- Put $s = -\alpha$: $C0\cdot(k21 - \alpha) = A\cdot(\beta - \alpha)$ → **$A = C0\cdot(\alpha - k21)/(\alpha - \beta)$** ... (10)
- Put $s = -\beta$: $C0\cdot(k21 - \beta) = B\cdot(\alpha - \beta)$ → **$B = C0\cdot(k21 - \beta)/(\alpha - \beta)$** ... (11)

Step 7 — Inverse Laplace transform.

The inverse Laplace of $1/(s + \alpha)$ is $e^{(-\alpha t)}$. Therefore:

$C(t) = A\cdot e^{(-\alpha\cdot t)} + B\cdot e^{(-\beta\cdot t)}$ ... (12)

This is the biexponential equation — derived, not memorised. Note that A + B = C0 = Dose/Vc (put t = 0 in equation 12).

6.4 Meaning of the hybrid constants α and β

- **α (alpha):** The fast hybrid constant. It controls the STEEP early part of the log C vs t plot — the DISTRIBUTION phase. It is "hybrid" because α = a mixture of k12, k21, k10 (see equations 8 and 9). α is always the LARGER number.
- **β (beta):** The slow hybrid constant. It controls the SHALLOW late part of the plot — the TERMINAL (elimination) phase. β is always the SMALLER number.

Memory hook: "**α**lpha is **A**ggressive (fast, early); **β**eta is **B**ehind (slow, late)."

- **k12:** Speed of drug leaving blood for tissues.
- **k21:** Speed of drug returning from tissues to blood.
- **k10:** Speed of drug being eliminated from the blood.

6.5 Macro vs micro constants — relationships (exam favourite)

Given A, B, α, β (the "macro" constants from the curve), we can recover the "micro" constants:

$k21 = (A\cdot\beta + B\cdot\alpha) / (A + B)$ ... (13) **$k10 = (\alpha\cdot\beta) / k21$** ... (14) (from equation 9) **$k12 = \alpha + \beta - k21 - k10$** ... (15) (from equation 8)

Also useful: Vc = Dose / (A + B).

Worked mini-example: A drug gives A = 30 mg/L, B = 10 mg/L, α = 2.0 hr^{-1}, β = 0.2 hr^{-1}.

- k21 = (30×0.2 + 10×2.0)/(30 + 10) = (6 + 20)/40 = 26/40 = **0.65 hr^{-1}**
- k10 = (2.0×0.2)/0.65 = 0.40/0.65 = **0.615 hr^{-1}**
- k12 = 2.0 + 0.2 − 0.65 − 0.615 = **0.935 hr^{-1}**

Check: k12 + k21 + k10 = 0.935 + 0.65 + 0.615 = 2.20 = α + β ✓ (always verify like this in the exam).

6.6 Parameters: Vc, Vd_area, Vd_ss, Cl, t½,β

(a) Vc — volume of the central compartment

Vc = Dose / (A + B) = Dose / C0

Because at t = 0, C(0) = A + B = C0. Simple words: if you know the starting concentration, dividing the dose by it tells you the size of the "first cup".

(b) AUC — area under the curve

Integrate C(t) from 0 to ∞:

AUC = $\int_0^{\infty}$ (A·e^(−αt) + B·e^(−βt)) dt = **A/α + B/β** ... (16)

(Each exponential integrates to its coefficient divided by its rate constant.)

(c) Cl — total body clearance

Cl = Dose / AUC

Clearance is the volume of blood completely cleared of drug per unit time. This formula works for ANY model — one, two, or more compartments.

(d) Vd_area — volume of distribution by the area method

During the terminal phase, C ≈ B·e^(−βt), and by definition Cl = β·Vd_area (elimination rate = β times the volume it acts on). Therefore:

Vd_area = Cl / β = Dose / (β·AUC)

(e) Vd_ss — volume of distribution at steady state

If we could keep the drug concentration constant everywhere (steady state), the total amount in the body divided by the plasma concentration would be:

Vd_ss = Vc·(1 + k12/k21)

Simple words: Vc is the central cup; the tissue cup holds k12/k21 times as much (inflow ÷ outflow at balance); add them.

(f) Terminal half-life

$t_{½,\beta} = 0.693 / \beta$

This is the half-life you report for the drug — the time for plasma concentration to halve during the terminal phase. (There is also a distribution half-life $t_{½,\alpha} = 0.693/\alpha$, but it is rarely used clinically.)

Parameter size order (memorise): For most drugs, **Vc < Vd_ss < Vd_area**. Vc is the smallest (just blood + fast organs); Vd_area is the largest (it is inflated because β is small).

6.7 Method of residuals (feathering) — step by step

This is the standard exam numerical. The idea: peel the curve like an onion — first find the slow outer layer (β, B), subtract it, and what is left is the fast inner layer (α, A).

The steps:

1. **Plot log C vs t** (or ln C vs t — but be consistent; see Common Mistakes). The plot curves early, then becomes straight at late times.
2. **Identify the terminal straight portion** (the last 3–4 points that lie on a straight line).
3. **Extrapolate this line back to t = 0.** Its slope = −β/2.303 (for $\log_{10}$) and its intercept = log B. So:

- β = 2.303 × |slope of terminal line|
- B = antilog(intercept)

1. **Calculate residual concentrations:** For each early time point, Residual = C_observed − C_extrapolated, where C_extrapolated = B·e^(−βt) (the value on the back-extrapolated terminal line at that time).
2. **Plot log(Residual) vs t.** This gives a SECOND straight line (the "feathered" line).
3. **From this line:** α = 2.303 × |slope of residual line|; A = antilog(its intercept).
4. **Verify:** A + B should equal the observed C0 (or Dose/Vc); the residual line must be straight.

Full worked example (exam pattern):

A 500 mg IV bolus dose gives the following plasma concentrations:

t (hr)	0.25	0.5	1	2	4	6	8	12
C (mg/L)	42.0	35.0	27.0	19.0	12.5	9.0	6.6	3.6

Step 1 — Terminal line. The last four points (t = 4, 6, 8, 12) look straight on a log plot. Take the two extreme terminal points to get the slope (exam shortcut; regression is better but this is accepted):

- log C at t=4: log(12.5) = 1.0969
- log C at t=12: log(3.6) = 0.5563
- Slope = (0.5563 − 1.0969)/(12 − 4) = −0.5406/8 = −0.06758 per hr
- β = 2.303 × 0.06758 = **0.1556 hr^{-1}**

Step 2 — Intercept B. Use the line equation through (t=4, log C=1.0969):

- log C = intercept + slope×t → 1.0969 = intercept − 0.06758×4 → intercept = 1.0969 + 0.2703 = 1.3672
- B = antilog(1.3672) = **23.29 mg/L**

Check at t=12: 23.29×e^(−0.1556×12) = 23.29×e^(−1.867) = 23.29×0.1546 = 3.60 ✓ matches observed 3.6.

Step 3 — Residuals at early times. C_extrapolated = 23.29×e^(−0.1556t):

t (hr)	C_obs	C_extrapolated	Residual = C_obs − C_ext
0.25	42.0	22.40	19.60
0.5	35.0	21.55	13.45
1	27.0	19.93	7.07
2	19.0	17.06	1.94

Step 4 — Residual line. log(Residual) vs t using first and last residual points:

- log(19.60) = 1.2923 at t=0.25; log(1.94) = 0.2878 at t=2
- Slope = (0.2878 − 1.2923)/(2 − 0.25) = −1.0045/1.75 = −0.5740 per hr
- α = 2.303 × 0.5740 = **1.322 hr⁻¹**
- Intercept: 1.2923 = intercept − 0.5740×0.25 → intercept = 1.2923 + 0.1435 = 1.4358
- A = antilog(1.4358) = **27.28 mg/L**

Step 5 — Verify. C0 = A + B = 27.28 + 23.29 = 50.57 mg/L. Vc = 500/50.57 = 9.89 L — a sensible central volume (roughly blood + well-perfused organs). ✓

Final answer: A ≈ 27.3 mg/L, α ≈ 1.32 hr⁻¹, B ≈ 23.3 mg/L, β ≈ 0.156 hr⁻¹.

6.8 Two-compartment model with oral (extravascular) administration

When the drug is given ORALLY, it must first be ABSORBED from the gut into the central compartment (rate constant ka) before it can distribute and be eliminated. That adds a THIRD process — and a third exponential term:

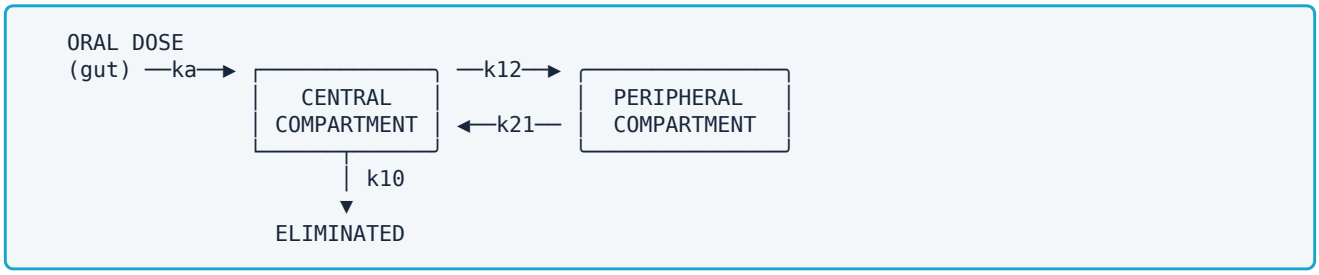
C(t) = L·e^(−ka·t) + M·e^(−α·t) + N·e^(−β·t) … (17)

What each phase means, from zero:

1. **Absorption phase (term L·e^(−kat), the fastest-decaying part of the RISING curve):** Drug is moving from the gut into the blood. Blood concentration RISES because absorption is faster than elimination at first. On the curve, this is the uphill part before the peak.
2. **Distribution phase (term M·e^(−αt)):** After the peak, drug rushes into tissues — the steep downhill part.
3. **Terminal phase (term N·e^(−βt)):** Distribution is balanced; the slow downhill tail is driven by elimination.

Note: L, M, N are just numbers (like A and B); one of them is typically negative so that C(0) = 0 (no drug in blood at time zero — correct for oral dosing!).

Diagram (oral):



The only change from the IV diagram: a "gut box" is added BEFORE the central compartment, connected by ka.

6.9 Absorption complications — the flip-flop phenomenon

Normally, absorption is fast and elimination is slow (ka > β). The terminal tail of the curve then shows elimination (slope = β).

Flip-flop: Sometimes absorption is SLOWER than elimination (ka < β) — for example, with sustained-release tablets or drugs absorbed very slowly. Then the roles REVERSE: the terminal slope reflects the slow ABSORPTION rate (ka), not elimination. The curve looks "flipped."

Simple analogy: A bucket (blood) is filled by a thin pipe (slow absorption) and drained by a wide pipe (fast elimination). The water level falls at the speed of the thin filling pipe — the slow step controls what you see. Whatever is slower — absorption or elimination — dominates the terminal phase.

Why it matters in pharmacy: If you mistake a flip-flop terminal slope for elimination, you will calculate a wrongly LONG half-life and may overdose the patient on repeat dosing. For sustained-release products, always check: is the terminal slope really elimination?

Key takeaway: Count the exponentials to know the model: IV one-compartment = 1, IV two-compartment = 2, oral two-compartment = 3. And remember — the slowest process always shows up in the terminal tail.

7. Diagrams (Textual — Practice Drawing These)

Diagram 1 — Two-compartment open model, IV bolus (see Section 4.3 — the box-and-arrow diagram with k12, k21, k10).

Diagram 2 — Log C vs t plot after IV bolus (biexponential):

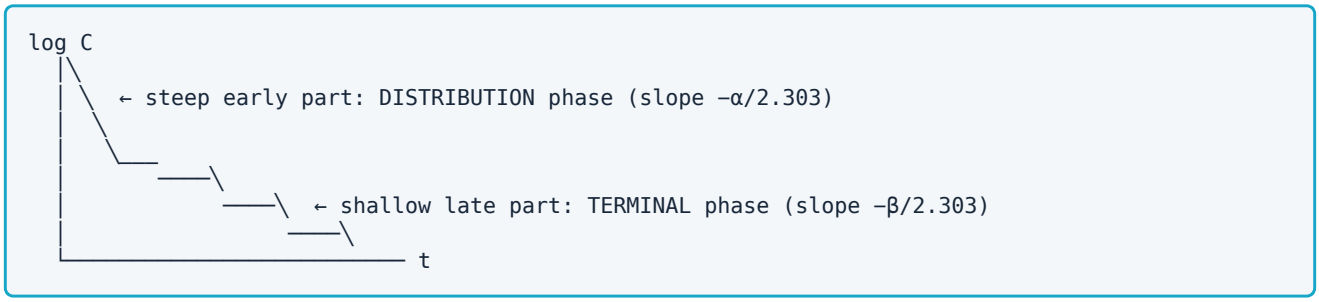


Diagram 3 — Method of residuals (feathering):

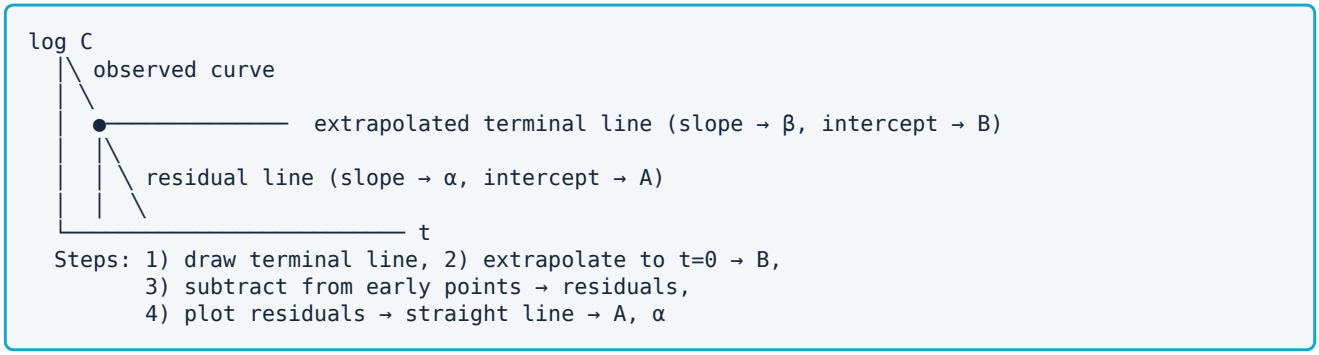
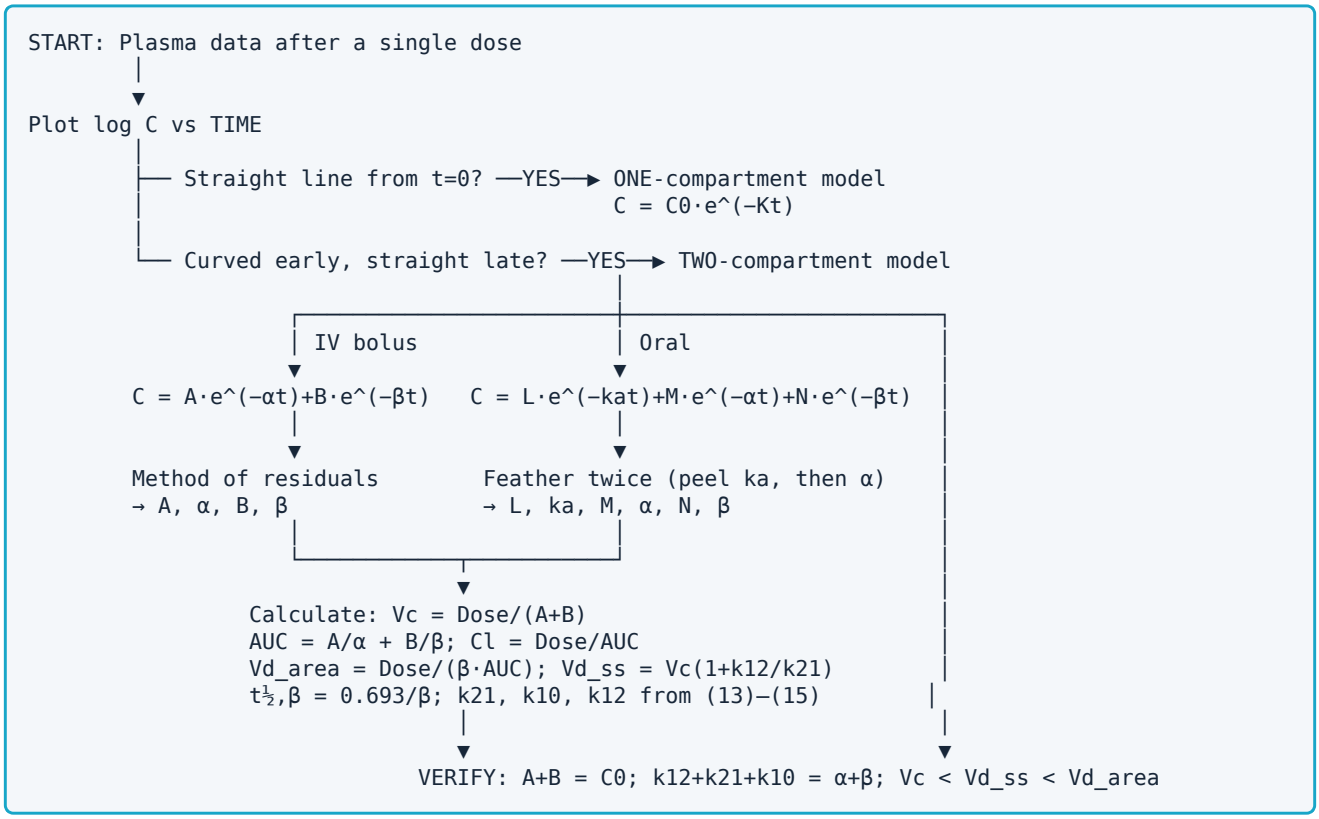
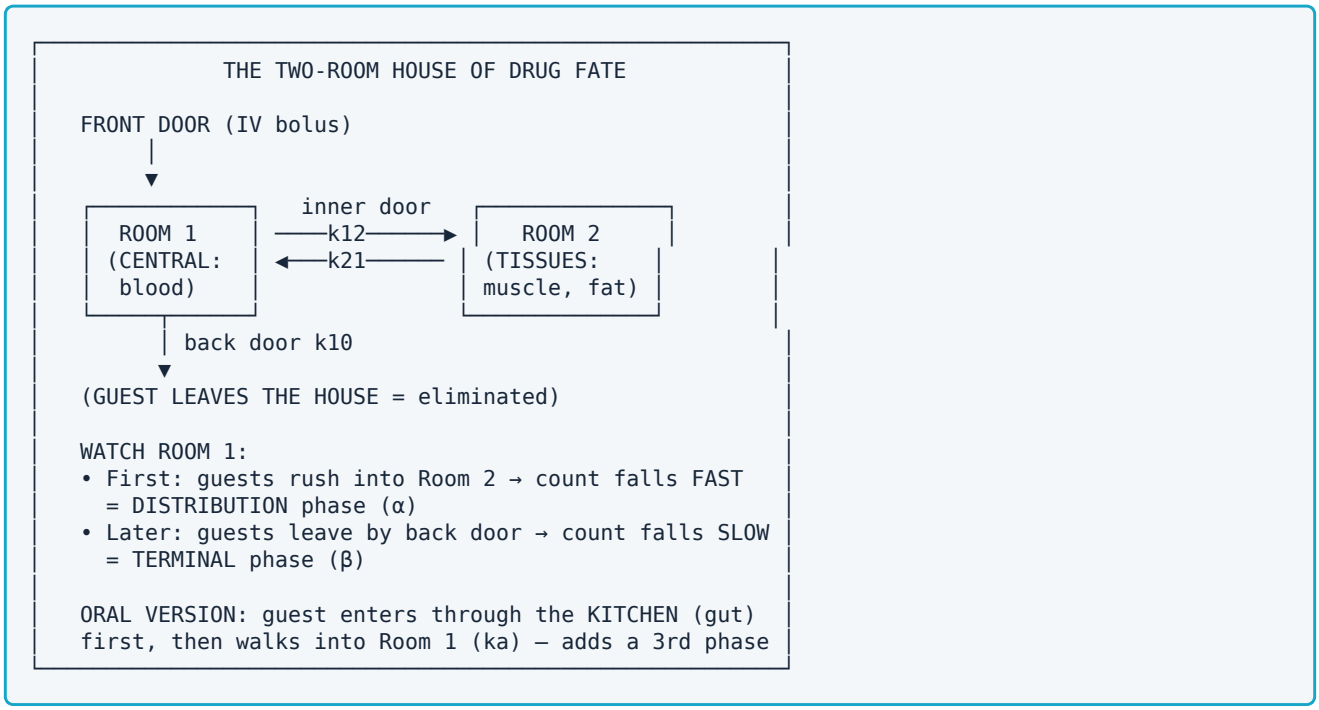


Diagram 4 — Oral two-compartment model (see Section 6.8 — gut box + ka arrow added before the central compartment).

8. Flowchart — Choosing and Solving the Model



9. Infographic Concept Box — "The Two-Room House"



10. Tables

Table 1 — One-compartment vs two-compartment model (IV bolus)

Feature	One-compartment	Two-compartment
Assumption	Drug mixes instantly in the whole body	Drug mixes fast in blood, slowly in tissues
Compartments	1 (whole body as one)	2 (central + peripheral)
Log C vs t plot	Straight line from t = 0	Curved early, straight late
Equation	C = C0·e^(−Kt) (monoexponential)	C = A·e^(−αt) + B·e^(−βt) (biexponential)
Rate constants	Single K (elimination)	α, β (hybrid) + k12, k21, k10 (micro)
Half-life	One: t½ = 0.693/K	Two: t½,α (distribution) and t½,β (terminal)
Volume term	Single Vd	Vc, Vd_area, Vd_ss
When to use	Drug distributes very rapidly	Distribution phase clearly visible on the curve
Example behaviour	Like sugar stirred in one cup of tea	Like two cups joined by a thin pipe

Table 2 — The three volume terms

Volume	Formula	Meaning	Typical size order
Vc	Dose/(A+B)	Central compartment only	Smallest
Vd_ss	Vc·(1 + k12/k21)	Body volume at steady state	Middle
Vd_area	Dose/(β·AUC)	Volume from terminal-phase area	Largest

Table 3 — Phase identification cheat-sheet

What you see on log C vs t	Phase	Slope gives	Intercept gives
Steep early decline (IV)	Distribution	α	A
Shallow late decline	Terminal/elimination	β	B
Rising part (oral only)	Absorption	ka	(part of L)
Terminal decline slower than expected (oral SR)	Suspect flip-flop	ka, not β!	—

11. Examples

Example 1 — Reading a curve: A log C vs t plot after IV injection is curved for the first 2 hours and then straight. → Two-compartment behaviour; the curved part is distribution (α), the straight part is terminal (β).

Example 2 — Quick parameter check: Dose = 400 mg, A = 25 mg/L, B = 15 mg/L. Then C0 = 40 mg/L and Vc = 400/40 = 10 L. If someone reports Vc = 200 L from the same data, it is wrong — recheck.

Example 3 — Flip-flop suspicion: An oral sustained-release product shows a terminal half-life of 30 hours, but the same drug given IV has a half-life of 4 hours. → Flip-flop: the 30-hour tail is slow absorption (ka), not elimination.

Example 4 — Tissue trapping: k12 is much larger than k21 (drug rushes into tissues but returns slowly). Then Vd_ss = Vc(1 + k12/k21) becomes large — the drug "hides" in tissues, which explains a long terminal phase even though elimination (k10) is fast.

12. Analogies (For Absolute-Zero Understanding)

1. **Two-room house** (Section 4.2) — the master analogy for the whole chapter.
2. **Two cups and a thin pipe** — pouring sugar water into cup 1; cup 2 fills slowly through the pipe. The level in cup 1 falls fast at first (filling cup 2) and slowly later (evaporation = elimination).
3. **Office and warehouse** — The office (central) receives all couriers (IV doses) and sends out all dispatches (elimination). The warehouse (tissue) only exchanges stock with the office. You can only count stock in the office (blood sampling).

4 **Peeling an onion (method of residuals)** — The outer layer (slow terminal phase) is peeled first; what remains is the inner layer (fast distribution phase).

5 **Thin pipe vs wide pipe (flip-flop)** — The slowest pipe controls the water level, whether it is the filling pipe (absorption) or the draining pipe (elimination).

13. Pharmacy Relevance

- **Dosing decisions:** The terminal half-life t½,β sets the dosing interval. Using the distribution half-life by mistake would lead to dangerously frequent dosing.
- **Loading doses:** Drugs with a large Vd_area need a bigger initial (loading) dose to fill the "tissue cup" quickly — otherwise the blood level stays low for too long.
- **Sustained-release design:** Formulation scientists must check for flip-flop — the product's slow release, not the drug's elimination, may control the tail of the curve.
- **Drug interactions at distribution:** A second drug that displaces the first from tissue binding changes k12/k21 and hence Vd_ss — plasma levels can rise suddenly.
- **Therapeutic drug monitoring:** For drugs with narrow safety margins, knowing whether the measured level is in the distribution or terminal phase changes the clinical interpretation completely.

14. India Context

- In Indian B.Pharm examinations (PCI syllabus), the derivation of the biexponential equation and the method of residuals are among the most frequently asked long-answer and numerical questions in Biopharmaceutics and Pharmacokinetics.
- Generic sustained-release products manufactured in India must demonstrate that their prolonged plasma profile comes from controlled release (formulation) and not from misread flip-flop kinetics — a routine check in bioequivalence evaluation.
- Drugs widely used in Indian practice that show clear two-compartment behaviour include several antibiotics and cardiovascular drugs; pharmacists counselling patients on "why the effect lasts long after the injection" can explain it as the drug slowly returning from tissues (k21) — in simple words, "the medicine stored in the body keeps coming back into the blood slowly."

15. Key Points (Must Memorise)

1 Two compartments: CENTRAL (blood + fast organs, sampled) and PERIPHERAL (slow tissues, not sampled).

2 IV bolus: **C(t) = A·e^(−αt) + B·e^(−βt)** — biexponential.

3 α = fast distribution slope; β = slow terminal slope; always α > β.

4 Micro-constants: k12 (central→tissue), k21 (tissue→central), k10 (elimination).

5 α + β = k12 + k21 + k10; α·β = k21·k10.

6 k21 = (Aβ + Bα)/(A + B); k10 = αβ/k21; k12 = α + β − k21 − k10.

7 Vc = Dose/(A + B); AUC = A/α + B/β; Cl = Dose/AUC.

8 Vd_area = Dose/(β·AUC); Vd_ss = Vc(1 + k12/k21); t½,β = 0.693/β.

9 Size order: Vc < Vd_ss < Vd_area.

10 Method of residuals: terminal line first (β, B) → subtract → residual line (α, A).

11 Oral two-compartment: **C = L·e^(−kat) + M·e^(−αt) + N·e^(−βt)** — triexponential.

12 Flip-flop: if ka < β, the terminal slope measures absorption, not elimination.

16. Common Confusions (Cleared)

Confusion	Correction
"α is elimination and β is distribution"	Opposite! α = distribution (fast, early), β = terminal/elimination (slow, late).
"A and B are concentrations at time zero"	A + B = C0. A and B are the zero-time INTERCEPTS of the two peeled lines, not measured concentrations.
"k10 is the same as β"	No. β is a hybrid (mixture of k12, k21, k10). k10 is pure elimination from the central compartment. They are numerically close only when distribution is much faster than elimination.
"Vd_area and Vd_ss are the same"	No. Vd_area uses the terminal slope (β) and AUC; Vd_ss uses the micro-constants (k12/k21). Vd_area > Vd_ss usually.
"Compartments are real organs"	No — they are mathematical groupings of tissues with similar distribution speed.
"Flip-flop means the drug is eliminated faster"	No — it means ABSORPTION is slower than elimination, so the tail shows absorption.
"The method of residuals works on C vs t directly"	It works on LOG C vs t (the lines must be straight, which needs the log scale).

17. Common Mistakes (Avoid in Exams)

1 **Mixing $\log_{10}$ and ln:** If you plot $\log_{10}$ C, slope = −β/2.303; if you plot ln C, slope = −β directly. Forgetting the 2.303 is the single most common numerical error.

2 **Using early points for the terminal line:** The terminal line must use only the LATE, straight points. Including distribution-phase points bends it and corrupts β and B.

3 **Forgetting to back-extrapolate:** B is the intercept at t = 0 of the EXTRAPOLATED terminal line, not the last measured concentration.

4 **Residuals from the wrong line:** Residual = observed C MINUS the extrapolated terminal-line value at the same time — not minus the neighbouring observed point.

5 **Reporting α < β:** If your calculation gives α smaller than β, you have swapped them — α is always the larger (faster) constant.

6 **Using t½,α for dosing interval:** The clinically reported half-life is t½,β = 0.693/β.

7 **Writing C0 = A or C0 = B alone:** C0 = A + B. Both terms contribute at t = 0.

18. Mnemonics

- **"αlpha Aggressive, βeta Behind"** — α is the fast early (distribution) phase; β is the slow late (terminal) phase.
- **"C-T-E: Comes, Travels, Exits"** — drug COMES into central (IV bolus), TRAVELS to tissues (k12/k21), EXITS from central (k10).
- **"A+B = All at Beginning"** — at t = 0, both exponentials contribute: C0 = A + B.
- **"Peel the Onion"** — method of residuals: outer (slow) layer first, inner (fast) layer second.
- **"Very Small Volumes Ascend: Vc < Vd_ss < Vd_area"** — the size order of the three volumes.
- **"SUM and PRODUCT"** — α + β = sum of micros (k12 + k21 + k10); α·β = product k21·k10.

19. Exam Summary

The two-compartment open model describes drugs whose distribution into tissues is slow enough to be seen as a separate phase. The central compartment (blood + well-perfused organs) receives the IV bolus, exchanges drug with the peripheral tissue compartment (k12, k21), and eliminates drug (k10). Solving the two differential equations by Laplace transforms gives the biexponential equation C(t) = A·e^(−αt) + B·e^(−βt), where α (fast) and β (slow) are hybrid constants with α + β = k12 + k21 + k10 and αβ = k21·k10. Parameters: Vc = Dose/(A+B), AUC = A/α + B/β, Cl = Dose/AUC, Vd_area = Dose/(β·AUC), Vd_ss = Vc(1 + k12/k21), t½,β = 0.693/β. The method of residuals (feathering) extracts A, α, B, β from data: terminal line first, subtract, residual line second. Oral administration adds absorption (ka) giving the triexponential C = L·e^(−kat) + M·e^(−αt) + N·e^(−βt); if ka < β, flip-flop occurs and the terminal slope reflects absorption.

20. One-Minute Revision

Two rooms: central (blood) + tissue (slow). IV bolus → C = A·e^(−αt) + B·e^(−βt). α fast/distribution, β slow/terminal, α > β. Micros: k12 out, k21 back, k10 eliminated. α+β = k12+k21+k10; αβ = k21·k10. Vc = Dose/(A+B); AUC = A/α+B/β; Cl = Dose/AUC; Vd_area = Dose/(β·AUC); Vd_ss = Vc(1+k12/k21); t½,β = 0.693/β. Residuals: peel slow layer first. Oral: three exponentials (add ka). Flip-flop: slow ka controls the tail. Volumes: Vc < Vd_ss < Vd_area.

21. Exam Questions

A. MCQs (with Answer Key)

Q1. In the two-compartment open model after IV bolus, the plasma concentration–time profile on a semilog plot is: (a) A straight line from t = 0 (b) Curved in the early part and straight in the late part (c) Curved throughout (d) A horizontal line **Answer: (b)**

Q2. The hybrid constant α represents: (a) The terminal elimination phase (b) The distribution phase (c) The absorption phase (d) The metabolism rate in the liver **Answer: (b)**

Q3. Which relationship between the hybrid and micro-constants is correct? (a) α + β = k12 + k21 − k10 (b) α·β = k12·k10 (c) α + β = k12 + k21 + k10 (d) α − β = k21·k10 **Answer: (c)**

Q4. In the method of residuals, the FIRST line drawn and extrapolated is the: (a) Residual line giving α (b) Terminal line giving β and B (c) Absorption line giving ka (d) Tangent at t = 0 **Answer: (b)**

Q5. Vd_ss is calculated as: (a) Dose/(A + B) (b) Vc·(1 + k12/k21) (c) Dose/(β·AUC) (d) Cl·β **Answer: (b)**

Q6. Flip-flop phenomenon occurs when: (a) ka > β (b) ka < β (c) k12 > k21 (d) α < β **Answer: (b)**

Q7. The correct size order of the volume terms is: (a) Vd_area < Vd_ss < Vc (b) Vc < Vd_ss < Vd_area (c) Vc = Vd_ss = Vd_area (d) Vd_ss < Vc < Vd_area **Answer: (b)**

Q8. At t = 0 after an IV bolus in a two-compartment model, C0 equals: (a) A only (b) B only (c) A + B (d) A − B **Answer: (c)**

Q9. The oral two-compartment model equation is: (a) Monoexponential (b) Biexponential (c) Triexponential (d) Zero-order **Answer: (c)**

Q10. Clearance (Cl) in a two-compartment model is given by: (a) β·Vc (b) Dose/AUC (c) k10·Vd_area (d) Both (b) and (c) **Answer: (d)**

B. Viva Questions

1 Why is the two-compartment model called "open"? *(Because drug is eliminated from the system via k10.)*

2 What is the difference between a hybrid constant and a micro-constant?

3 Which compartment do we sample, and why can we not sample the other?

4 In the method of residuals, why do we draw the terminal line FIRST?

5 What does it mean if your calculated α is smaller than β?

6 State the formula for Vd_area and explain why it is usually the largest volume term.

7 What is flip-flop, and why is it dangerous to misread it?

8 How many exponential terms appear for oral dosing in a two-compartment model, and why?

9 What is the difference between a mammillary and a catenary model?

10 Why must we use log C (not C) for the method of residuals?

C. Application-Based Questions

1 A new IV antibiotic shows a clearly biexponential decline with β = 0.1 hr^{-1}. The prescriber wants the dosing interval. Which half-life do you use, what is its value, and why not the other one?

2 A sustained-release tablet of a drug shows a terminal half-life of 24 hours orally but 5 hours intravenously. Explain what is happening and what mistake a pharmacist must avoid when counselling on dose timing.

3 Two drugs have the same clearance but Drug X has a much larger Vd_area than Drug Y. Which drug likely distributes more into tissues, and what does this imply for its terminal half-life?

4 During therapeutic drug monitoring, a blood sample taken 30 minutes after IV injection shows a very high level, but a sample at 6 hours is much lower than the one-compartment prediction. Explain using distribution-phase concepts.

D. Numerical Problems (Fully Worked Solutions)

Numerical 1 — Method of residuals: find A, α, B, β.

Problem: A 250 mg IV bolus dose gives the following plasma data. Determine A, α, B, β by the method of residuals.

t (hr)	0.5	1	2	3	5	8	12
C (mg/L)	18.5	14.2	9.8	7.3	4.6	2.7	1.4

Solution:

Step 1 — Terminal line. Last three points (t = 5, 8, 12) are straight on log scale.

- log(4.6) = 0.6628 at t=5; log(1.4) = 0.1461 at t=12
- Slope = (0.1461 − 0.6628)/(12 − 5) = −0.5167/7 = −0.07381 per hr
- β = 2.303 × 0.07381 = **0.170 hr^{-1}**

Step 2 — Intercept B.

- 0.6628 = intercept − 0.07381×5 → intercept = 0.6628 + 0.3691 = 1.0319
- B = antilog(1.0319) = **10.76 mg/L**

Step 3 — Residuals. C_extrapolated = 10.76×e^(−0.170t):

t (hr)	C_obs	C_extrapolated	Residual
0.5	18.5	9.88	8.62
1	14.2	9.07	5.13
2	9.8	7.65	2.15
3	7.3	6.46	0.84

Step 4 — Residual line.

- log(8.62) = 0.9355 at t=0.5; log(0.84) = −0.0757 at t=3
- Slope = (−0.0757 − 0.9355)/(3 − 0.5) = −1.0112/2.5 = −0.40448 per hr

- α = 2.303 × 0.40448 = **0.932 hr⁻¹**
- Intercept: 0.9355 = intercept − 0.40448×0.5 → intercept = 0.9355 + 0.2022 = 1.1377
- A = antilog(1.1377) = **13.73 mg/L**

Step 5 — Verify. C0 = A + B = 13.73 + 10.76 = 24.49 mg/L; Vc = 250/24.49 = 10.2 L ✓ (sensible). α (0.932) > β (0.170) ✓.

Answer: A ≈ 13.7 mg/L, α ≈ 0.93 hr⁻¹, B ≈ 10.8 mg/L, β ≈ 0.17 hr⁻¹.

Numerical 2 — Vd_area, Vd_ss, Cl, t½,β from biexponential parameters.

Problem: A 600 mg IV bolus gives A = 40 mg/L, α = 1.5 hr⁻¹, B = 12 mg/L, β = 0.12 hr⁻¹. Calculate AUC, Cl, Vc, Vd_area, Vd_ss, t½,β, and the micro-constants k21, k10, k12.

Solution:

Step 1 — AUC.

- AUC = A/α + B/β = 40/1.5 + 12/0.12 = 26.67 + 100 = **126.67 mg·hr/L**

Step 2 — Clearance.

- Cl = Dose/AUC = 600/126.67 = **4.737 L/hr**

Step 3 — Central volume.

- Vc = Dose/(A + B) = 600/(40 + 12) = 600/52 = **11.54 L**

Step 4 — Vd_area.

- Vd_area = Dose/(β·AUC) = 600/(0.12 × 126.67) = 600/15.2 = **39.47 L**
- (Check: Cl/β = 4.737/0.12 = 39.48 L ✓)

Step 5 — Micro-constants.

- k21 = (Aβ + Bα)/(A + B) = (40×0.12 + 12×1.5)/52 = (4.8 + 18)/52 = 22.8/52 = **0.4385 hr⁻¹**
- k10 = αβ/k21 = (1.5×0.12)/0.4385 = 0.18/0.4385 = **0.4105 hr⁻¹**
- k12 = α + β − k21 − k10 = 1.5 + 0.12 − 0.4385 − 0.4105 = **0.771 hr⁻¹**
- Verify: 0.4385 + 0.4105 + 0.771 = 1.62 = α + β ✓

Step 6 — Vd_ss.

- Vd_ss = Vc(1 + k12/k21) = 11.54×(1 + 0.771/0.4385) = 11.54×(1 + 1.758) = 11.54×2.758 = **31.83 L**

Step 7 — Terminal half-life.

- t½,β = 0.693/β = 0.693/0.12 = **5.78 hr**

Answers: AUC = 126.7 mg·hr/L; Cl = 4.74 L/hr; Vc = 11.5 L; Vd_area = 39.5 L; Vd_ss = 31.8 L; t½,β = 5.78 hr; k21 = 0.439, k10 = 0.411, k12 = 0.771 hr⁻¹. Note Vc < Vd_ss <

Vd_area ✓.

Numerical 3 — AUC of a biexponential and its meaning.

Problem: After an IV bolus, the plasma curve fits C(t) = 25·e^(−2.0t) + 8·e^(−0.25t) (C in mg/L, t in hr). The dose was 330 mg. (a) Calculate AUC. (b) Calculate Cl. (c) What fraction of the total AUC comes from the terminal phase?

Solution:

(a) Identify A = 25, α = 2.0, B = 8, β = 0.25.

- AUC = A/α + B/β = 25/2.0 + 8/0.25 = 12.5 + 32 = **44.5 mg·hr/L**

(b) Cl = Dose/AUC = 330/44.5 = **7.42 L/hr**

(c) Terminal-phase contribution = (B/β)/AUC = 32/44.5 = **0.719 ≈ 72%**.

- Meaning in simple words: although the terminal phase looks flat and low on the curve, it lasts so long that it contributes nearly three-quarters of the total drug exposure. This is why the terminal phase — not the tall early peak — usually controls total exposure and dosing.

22. References

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End of Chapter 4.

CHAPTER 5: Multiple Dosage Regimens: Accumulation, Loading and Maintenance Doses, Steady State, and Modified Release Products

Learning Objectives

After studying this chapter, you will be able to:

1 Explain why a single dose is not enough for most treatments and why repeated dosing is needed.

2 Define dosing interval (τ) and explain the principle of superposition with a simple example.

3 Derive the accumulation index R = 1 / (1 − e^(−k·τ)) step by step and list the factors that affect drug accumulation.

4 Define steady state, state the rule of 4–5 half-lives, and write the steady-state equations for Cmax,ss, Cmin,ss, and Cave,ss.

5 Explain the difference between fluctuation and swing of drug levels.

6 Derive the loading dose formula DL = Css·Vd/F and the maintenance dose formula DM = Cl·Css·τ/F.

7 State when a loading dose is used (emergencies, drugs with long half-life) and give textbook examples.

8 Summarise multiple-dose PK parameters in a table, and explain missed-dose consequences and how to adjust a regimen.

9 Describe why the pharmacokinetics of modified release products differ (rate-limiting absorption, flip-flop, extended MRT), and explain the basic ideas of Wagner–Nelson, Loo–Riegelman, and in-vitro–in-vivo correlation (IVIVC).

10 Solve numerical problems on accumulation index, steady-state concentrations, loading and maintenance doses, and time to steady state.

Definitions

- **Multiple dosage regimen:** A schedule in which a drug is given repeatedly at fixed intervals of time (e.g., a tablet every 8 hours) to keep the drug's effect going for days or weeks.
- **Dosing interval (τ, "tau"):** The time gap between two successive doses. Example: τ = 8 hours means one dose every 8 hours.
- **Superposition (principle of superposition):** The rule that says the total drug concentration in the body after multiple doses is simply the sum of the concentration contributions of each individual dose, one added on top of the other. (It assumes the body handles each dose the same way — linear pharmacokinetics.)
- **Drug accumulation:** The build-up of drug in the body when doses are repeated before the previous dose has been fully eliminated.
- **Accumulation index (R):** A number that tells how much higher the drug level becomes at steady state compared to the level after a single first dose. R = 1 / (1 − e^(−k·τ)).
- **Steady state (steady-state level):** The condition reached after repeated dosing when the amount of drug going in during each interval equals the amount going out, so the peak and

trough concentrations stay the same from dose to dose. The average level stays constant while it still goes up and down between doses.

- **Cmax,ss:** The maximum (peak) concentration at steady state, just after a dose.
- **Cmin,ss:** The minimum (trough) concentration at steady state, just before the next dose.
- **Cave,ss:** The average concentration at steady state over one dosing interval.
- **Fluctuation:** The size of the ups and downs of drug concentration around the average at steady state (Cmax,ss − Cmin,ss).
- **Swing:** Another name for the relative fluctuation — (Cmax,ss − Cmin,ss) / Cmin,ss or as a ratio Cmax,ss / Cmin,ss.
- **Loading dose (DL):** A large first dose given to quickly raise the drug concentration to the target (therapeutic) level, skipping the long build-up period.
- **Maintenance dose (DM):** The smaller, repeated dose given regularly to replace the amount of drug lost by elimination and keep the level at the target.
- **Modified release (MR) product:** A dosage form (tablet, capsule, injection) designed to release the drug slowly over time, so it does not need to be taken as often — for example, once-daily tablets or monthly depot injections.
- **Flip-flop kinetics:** A situation (common with slow-release products) where absorption of the drug is slower than its elimination, so the absorption rate — not the elimination rate — controls how long the drug stays in the body.
- **In-vitro–in-vivo correlation (IVIVC):** The mathematical relationship between how a modified release product releases drug in a laboratory dissolution test (in-vitro) and how it is absorbed in the body (in-vivo).

Terminology (Glossary Table)

Term	Symbol	Unit	Simple Meaning
Dosing interval	τ (tau)	hours (h)	Time between two doses
Elimination rate constant	k	h^{-1}	How fast the drug leaves the body (fraction per hour)
Half-life	t½	h	Time for drug level to fall by half
Accumulation index	R	no unit	How many times higher the steady-state level is vs the first dose
Peak at steady state	Cmax,ss	mg/L	Highest level reached after each dose at steady state
Trough at steady state	Cmin,ss	mg/L	Lowest level reached just before the next dose at steady state
Average at steady state	Cave,ss	mg/L	Average level during one interval at steady state

Term	Symbol	Unit	Simple Meaning
Volume of distribution	Vd	L	"Size of the tank" — the apparent space the drug spreads into
Clearance	Cl	L/h	Volume of blood fully cleared of drug per hour
Bioavailability	F	fraction (0–1)	Fraction of the dose that reaches the blood (F = 1 for IV)
Loading dose	DL	mg	The big first dose
Maintenance dose	DM	mg	The regular repeated dose
Mean residence time	MRT	h	Average time one drug molecule spends in the body
Fraction remaining after one interval	e^(−k·τ)	fraction	How much of a dose is still left when the next dose is due

Explanation

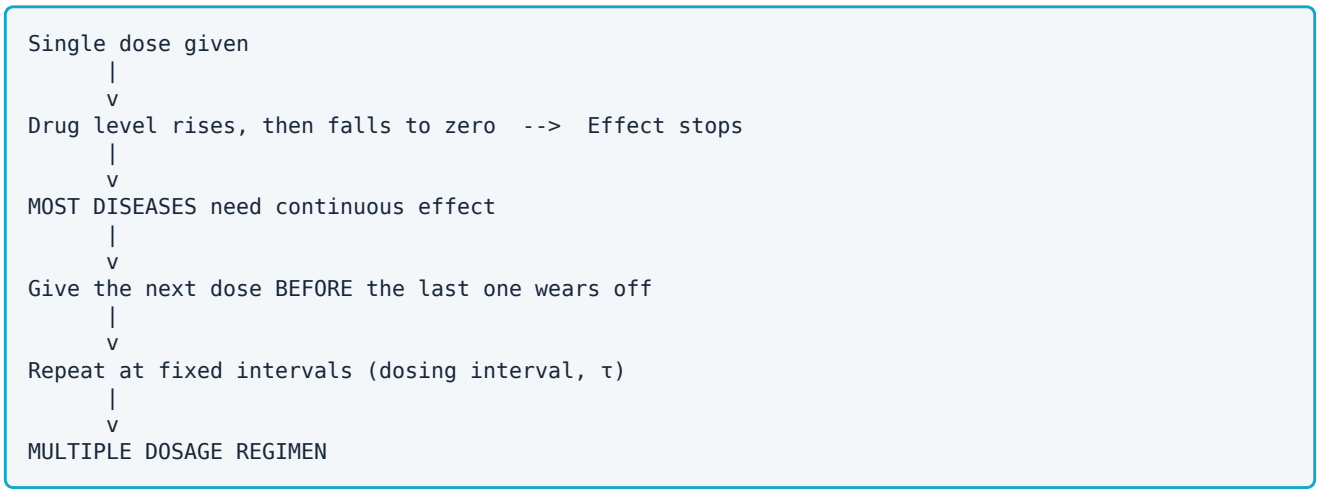
5.1 Why repeated dosing is needed: the multiple dosage regimen

Technical concept: A single dose gives a drug concentration that rises and then falls to zero. For most treatments — infections, blood pressure, epilepsy, diabetes — the effect must last days, weeks, or lifelong. One dose cannot do that.

Simple explanation: Think of keeping a room lit with candles. One candle burns out after a few hours, so you must light a new candle before the old one finishes. Medicines work the same way: one dose wears off, so you take another dose on schedule to keep the effect going.

Example: An antibiotic tablet given every 8 hours (τ = 8 h) for 5 days. Each tablet alone would fade away in a few hours, but repeated doses keep the germ-fighting level alive continuously.

Flowchart:



Key takeaway: Almost all drug therapy is a multiple dosage regimen — the same dose repeated at a fixed dosing interval τ.

5.2 Principle of superposition

Technical concept: In linear pharmacokinetics, the body's handling of a drug does not change with dose or with previous doses. Therefore the concentration after the second, third, or nth dose equals the sum of the concentration curves of all previous individual doses, each shifted in time.

Simple explanation: Imagine pouring one bucket of water into a bathtub every hour, while the bathtub has a small leak. The water level at any time is the leftover water from bucket 1 + leftover from bucket 2 + leftover from bucket 3, and so on. Each dose adds its share; the body subtracts by elimination. Nobody interacts with anybody — each dose behaves as if it were alone. That is superposition.

Example: Dose 1 alone gives 10 mg/L at time zero, falling to 5 mg/L after one interval. Dose 2 is given at that moment, adding 10 mg/L on top of the leftover 5 mg/L, so the level becomes 15 mg/L. Dose 3 adds 10 on top of what is left of doses 1 and 2, and so on. The total is always the sum of the leftovers.

Key takeaway: Superposition lets us predict multiple-dose levels by simply adding up single-dose curves — no new math is needed beyond addition of leftovers.

5.3 Drug accumulation

Technical concept: When the dosing interval τ is shorter than the time needed to fully eliminate a dose (in practice, always — since full elimination takes forever), some drug remains in the body when the next dose arrives. The new dose adds to the remainder, so levels rise with each dose. This rise is called accumulation. Accumulation stops when the amount eliminated during one interval equals the amount given in one dose — that balance point is steady state.

Simple explanation — the bathtub analogy: You pour one bucket of water into a leaky bathtub every hour. Early on, the water level rises because you pour in faster than it leaks out. After some time, the water gets deep enough that the leak (which is bigger when the tub is fuller) removes exactly one bucket per hour. From then on, the level goes up and down by only small amounts around a constant average. The rising part is accumulation; the flat-but-wavy part is steady state.

Example: A drug with half-life 6 hours given every 12 hours (τ = 12 h). After the first dose, by the time the second dose is due, one-quarter of the dose is still in the body (two half-lives have passed: 1/2 × 1/2 = 1/4). So the second dose piles onto that leftover quarter.

Mechanisms / Derivations

5.4 Derivation of the accumulation index R = 1 / (1 − e^(−k·τ))

Every step is shown. Read slowly — each line follows from the one before it.

What we want: A single number R that compares the peak concentration at steady state with the peak after the very first dose.

Symbols explained first:

- D = dose given (mg). F = fraction reaching blood. Vd = volume of distribution (L). So right after an IV bolus (or an instant-absorption dose), the concentration is $C_0 = F \cdot D / Vd$.
- k = elimination rate constant (h^{-1}). Between doses, concentration falls by first-order kinetics: $C(t) = C_0 \cdot e^{(-k \cdot t)}$.
- τ = dosing interval (h). The fraction of a dose remaining when the next dose is due is $f = e^{(-k \cdot \tau)}$.

Step 1 — After the first dose. Peak concentration after dose 1: $C_1 = F \cdot D / Vd$. Call this C_0 for short.

Step 2 — Just before dose 2 (trough after dose 1). The dose-1 level has decayed for one interval: $C = C_0 \cdot e^{(-k \cdot \tau)} = C_0 \cdot f$.

Step 3 — Peak after dose 2. Dose 2 adds a fresh C_0 on top of the leftover: $C_2(peak) = C_0 + C_0 \cdot f = C_0(1 + f)$.

Step 4 — Peak after dose 3. Trough before dose 3 = $C_2(peak) \cdot f = C_0(1 + f) \cdot f = C_0(f + f^2)$. Add fresh C_0: $C_3(peak) = C_0 + C_0(f + f^2) = C_0(1 + f + f^2)$.

Step 5 — The pattern. After dose n, the peak is: $C_n(peak) = C_0(1 + f + f^2 + f^3 + \ldots + f^{(n-1)})$.

Step 6 — Add up the geometric series. The bracket is a geometric series with ratio f (and $f < 1$ because some drug is always eliminated, so f is a fraction). Its sum is: $1 + f + f^2 + \ldots + f^{(n-1)} = (1 - f^n) / (1 - f)$.

So $C_n(peak) = C_0 \cdot (1 - f^n) / (1 - f)$.

Step 7 — Let n become very large (steady state). As $n \to \infty$, $f^n \to 0$ (a fraction raised to a huge power vanishes). So: $C_ss(peak) = C_0 / (1 - f)$.

Step 8 — The accumulation index. R compares the steady-state peak with the first-dose peak: R = C_ss(peak) / C_0 = 1 / (1 − f) = 1 / (1 − e^(−k·τ)).

Done. Every symbol is now accounted for.

Factors affecting accumulation:

1. **Elimination rate constant k (or half-life):** A small k (long half-life) → f = e^(−k·τ) is close to 1 → denominator (1 − f) is tiny → R is large (heavy accumulation). A large k (short half-life) → f is near 0 → R ≈ 1 (almost no accumulation).
2. **Dosing interval τ:** A short τ (frequent dosing) → less time to eliminate → f close to 1 → large R. A long τ (infrequent dosing) → drug mostly gone → f near 0 → R ≈ 1.
3. **Dose size does NOT affect R** (in linear PK): doubling the dose doubles both C_0 and C_ss, so the ratio stays the same.

Simple version: Accumulation is big when the drug is eliminated slowly AND given often. It is small when the drug is eliminated quickly OR given rarely.

Flowchart:

```
f = e^(-k·τ)  =  fraction of dose left at next dose time
      |
      v
R = 1 / (1 - f)
      |
      +---> k small (long half-life)  --->  f near 1  --->  R LARGE
      +---> k large (short half-life) --->  f near 0  --->  R ~ 1
      +---> τ short (frequent doses)  --->  f near 1  --->  R LARGE
      +---> τ long (rare doses)       --->  f near 0  --->  R ~ 1
```

Key takeaway: R = 1/(1 − e^(−k·τ)). Slow elimination + frequent dosing = big accumulation; fast elimination or rare dosing = almost none.

5.5 Steady state

Technical concept: Steady state is reached when, over each dosing interval, the amount of drug eliminated equals the amount of drug administered. Peaks (Cmax,ss) and troughs (Cmin,ss) then repeat identically from dose to dose, and the average concentration (Cave,ss) is constant.

Simple explanation — back to the bathtub: Early on, you pour in more than leaks out, so the level rises (accumulation). As the water gets deeper, the leak gets faster. Eventually the leak removes exactly one bucket per hour — the same as you pour in. From that moment the average level stays the same forever, though it still rises a little with each pour and falls a little between pours. That is steady state: "in = out, on average."

Example: Theophylline tablets given every 8 hours. For the first 2 days the levels climb; after about 4–5 half-lives the morning and evening levels look the same every day — steady state is reached.

Time to reach steady state — the 4–5 half-lives rule: From Step 6 above, the fraction of steady state reached after n doses is $(1 - f^n)$, where $f = e^{(-k \cdot \tau)}$. If we dose once per half-life ($\tau = t_{1/2}$), then $f = 1/2$, and after n doses we reach $(1 - (1/2)^n)$ of steady state: after 1 dose 50%, 2 doses 75%, 3 doses 87.5%, 4 doses 93.75%, 5 doses 96.9%. So after about 4–5 half-lives, we are 94–97% of the way there — close enough to call it steady state. **Important:** this time depends ONLY on the half-life (k), NOT on the dose size or the dosing interval.

Steady-state equations:

First, the average concentration. At steady state, the amount in during one interval (F·D) equals the amount out during one interval ($Cl \cdot C_{ave,ss} \cdot \tau$). Rearranging:

$C_{ave,ss} = F \cdot Dose / (Cl \cdot \tau)$

Symbols: F = bioavailability, Dose = maintenance dose, Cl = clearance, τ = dosing interval.

The peak and trough at steady state follow from the accumulation derivation ($C_{ss(peak)} = C_0/(1 - f)$, and the trough is the peak decayed for one interval):

$C_{max,ss} = (F \cdot Dose / Vd) \cdot [1 / (1 - e^{(-k \cdot \tau)})]$ $C_{min,ss} = C_{max,ss} \cdot e^{(-k \cdot \tau)} = (F \cdot Dose / Vd) \cdot [e^{(-k \cdot \tau)} / (1 - e^{(-k \cdot \tau)})]$

Since $Cl = k \cdot Vd$, these are all consistent: $C_{ave,ss}$ is the average of the curve between $C_{max,ss}$ and $C_{min,ss}$.

Fluctuation and swing:

- **Fluctuation** = the absolute up-and-down: $C_{max,ss} - C_{min,ss}$. Big doses given rarely → big fluctuation. Small doses given often (or a slow-release product) → small fluctuation.
- **Swing** = the relative up-and-down: $(C_{max,ss} - C_{min,ss}) / C_{min,ss}$, sometimes expressed as the ratio $C_{max,ss} / C_{min,ss}$. Swing depends only on $k \cdot \tau$: $C_{max,ss} / C_{min,ss} = e^{(k \cdot \tau)}$.

Key takeaway: Steady state = in equals out per interval. It takes 4–5 half-lives to get there (depends only on half-life). $C_{ave,ss} = F \cdot Dose/(Cl \cdot \tau)$ is the single most-used equation in clinical pharmacokinetics.

5.6 Loading dose (DL) — full derivation

Purpose: For some drugs, waiting 4–5 half-lives for steady state is too slow (an emergency, or a drug with a very long half-life — e.g., a half-life of days means weeks of waiting). A loading dose is a large first dose that fills the body's "tank" to the target level immediately; maintenance doses then just top up what is lost.

Simple explanation: If you want a bathtub full of water quickly, you don't pour one bucket per hour and wait — you pour in many buckets at once to fill it, then switch to one bucket per hour to match the leak. The big first fill is the loading dose.

Derivation (every step shown):

Step 1 — Define the target. Let Css be the target concentration we want in the blood (often the desired average steady-state level).

Step 2 — How much drug must be in the body to give Css? By the definition of volume of distribution: Amount in body = Css × Vd. (Vd is the "size of the tank": concentration × volume = amount.)

Step 3 — Account for incomplete absorption. Only a fraction F of an oral dose reaches the blood. So the dose needed is: DL = (Css × Vd) / F.

Final formulas:

- **Oral (or any extravascular route): DL = Css·Vd / F**
- **IV bolus (F = 1): DL = Css·Vd**

That is the whole derivation: target level × tank size, corrected for the fraction lost before reaching blood.

When to use a loading dose:

1 **Emergencies** — when the therapeutic effect is needed immediately (e.g., a severe asthma attack, status epilepticus, dangerous arrhythmia). Textbook examples are discussed below.

2 **Drugs with a long half-life** — waiting 4–5 half-lives could take weeks (e.g., half-life of 2 days → 8–10 days to steady state). A loading dose skips the wait.

3 **Not needed** when the drug has a short half-life (steady state comes quickly anyway) or when immediate effect is not critical.

Caution: A loading dose gives high levels fast, so the risk of toxicity is higher — it must be calculated carefully and, for some drugs, given slowly (e.g., as a slow IV infusion rather than a rapid bolus).

5.7 Maintenance dose (DM) — derivation

Purpose: After the tank is filled (by the loading dose, or by accumulation over 4–5 half-lives), each interval loses some drug to elimination. The maintenance dose replaces exactly that loss, keeping the average level at target.

Simple explanation: Once the bathtub is full, you only need to pour in one bucket per hour to match the one bucket per hour leaking out. That hourly bucket is the maintenance dose.

Derivation (every step shown):

Step 1 — At steady state, in = out per interval. Amount in per interval = F·DM (only fraction F reaches blood). Amount out per interval = Cl·Cave,ss·τ (clearance × average concentration × time — the definition of how much drug the body removes).

Step 2 — Set them equal: F·DM = Cl·Cave,ss·τ.

Step 3 — Solve for DM, setting Cave,ss = Css (our target): DM = Cl·Css·τ / F.

Final formulas:

- **Oral: DM = Cl·Css·τ / F**
- **IV: DM = Cl·Css·τ** (F = 1)

Note this is just the Cave,ss equation rearranged — maintenance dose is whatever keeps the average level where you want it.

Clinical significance: The maintenance dose sets the AVERAGE level; the dosing interval sets the FLUCTUATION around it. To raise the average, increase the dose; to smooth the peaks and troughs without changing the average, shorten the interval and reduce each dose proportionally (since Cave,ss depends on Dose/τ — halving both keeps the average the same).

5.8 Textbook drug examples (illustrative, cautious wording)

These are classic textbook illustrations of loading/maintenance concepts, not prescribing instructions — actual doses are individualised by the physician.

- **Digoxin** (heart failure, arrhythmia): a classic example of a drug given with a loading ("digitalising") dose followed by smaller daily maintenance doses, because its effect is needed without waiting many half-lives.
- **Theophylline** (asthma/COPD): textbooks illustrate loading dose calculations for theophylline because in an acute severe attack the bronchodilator effect is needed immediately, not after 4–5 half-lives.
- **Phenytoin** (epilepsy, status epilepticus): a classic example where a loading dose is used to rapidly achieve therapeutic levels to stop seizures, followed by maintenance dosing.

Key takeaway: Loading dose fills the tank fast (DL = Css·Vd/F); maintenance dose replaces the leak (DM = Cl·Css·τ/F). Use a loading dose when you cannot afford to wait.

Classifications

Types of multiple dosage regimens

Type	Description	Example
Constant dose, constant interval	Same dose every τ	Most oral therapy (e.g., one tablet every 12 h)
Loading + maintenance	One large first dose, then smaller regular doses	Digoxin, theophylline, phenytoin (textbook examples)
Tapering regimen	Doses gradually reduced	Corticosteroids (to avoid withdrawal)
Titrated regimen	Dose adjusted based on response/levels	Warfarin, insulin (dose guided by monitoring)

Accumulation behaviour

Situation	f = e^(−k·τ)	R ≈	Meaning
τ much longer than t½	near 0	~1	No accumulation; each dose acts alone
τ = t½	0.5	2	Level doubles at steady state

Situation	f = e^(−k·τ)	R ≈	Meaning
τ much shorter than t½	near 1	large	Heavy accumulation; loading-dose-like build-up

Diagrams (Textual)

Diagram 1 — Drug level vs time: single dose vs multiple doses

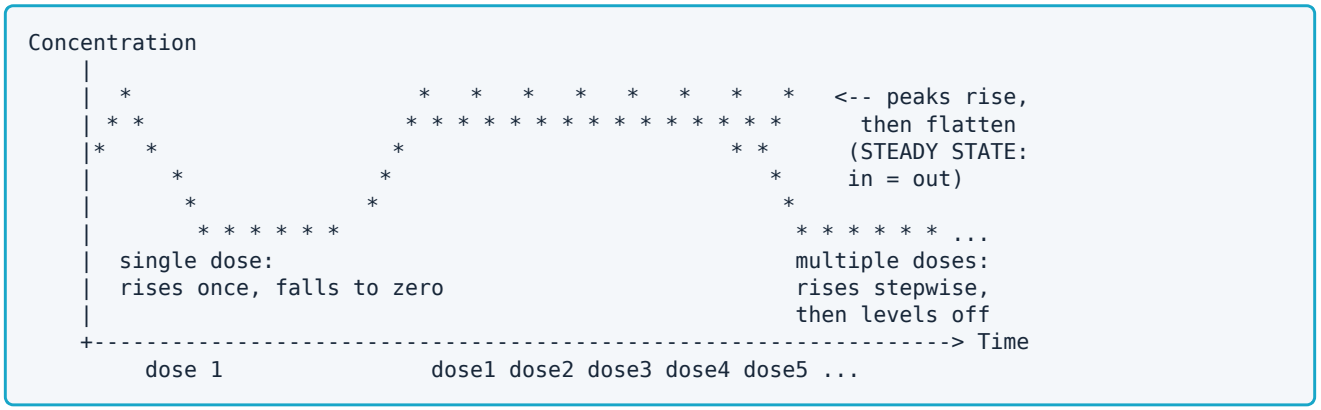


Diagram 2 — The bathtub analogy for accumulation and steady state

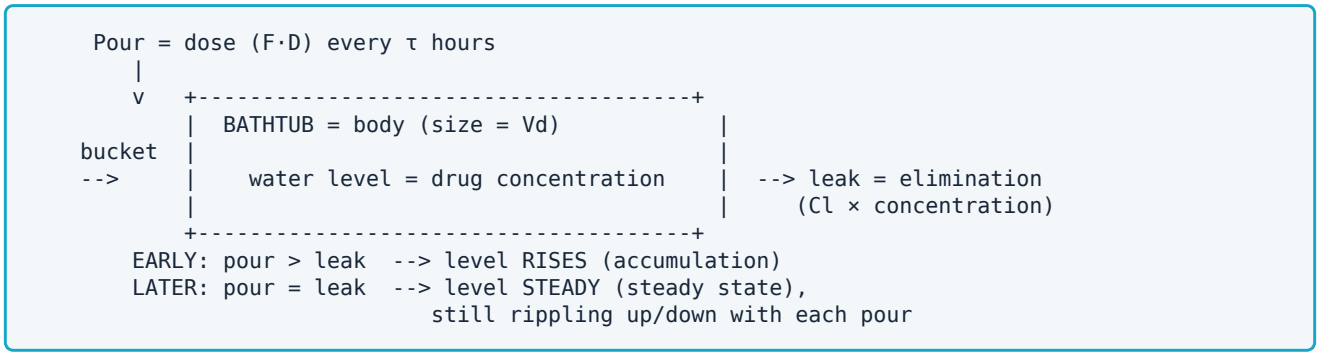


Diagram 3 — Steady-state peaks, troughs and average

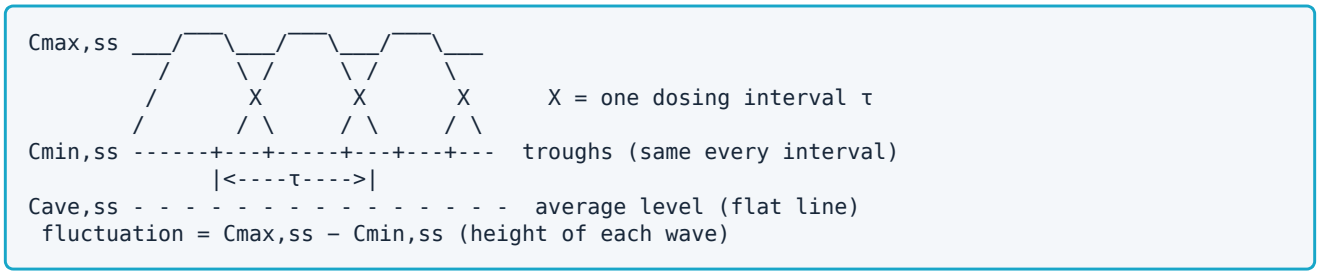
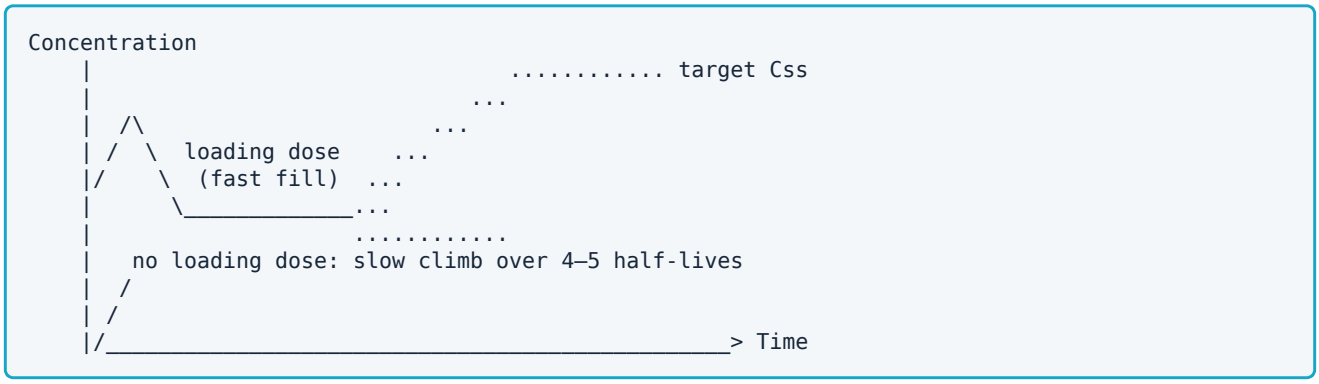
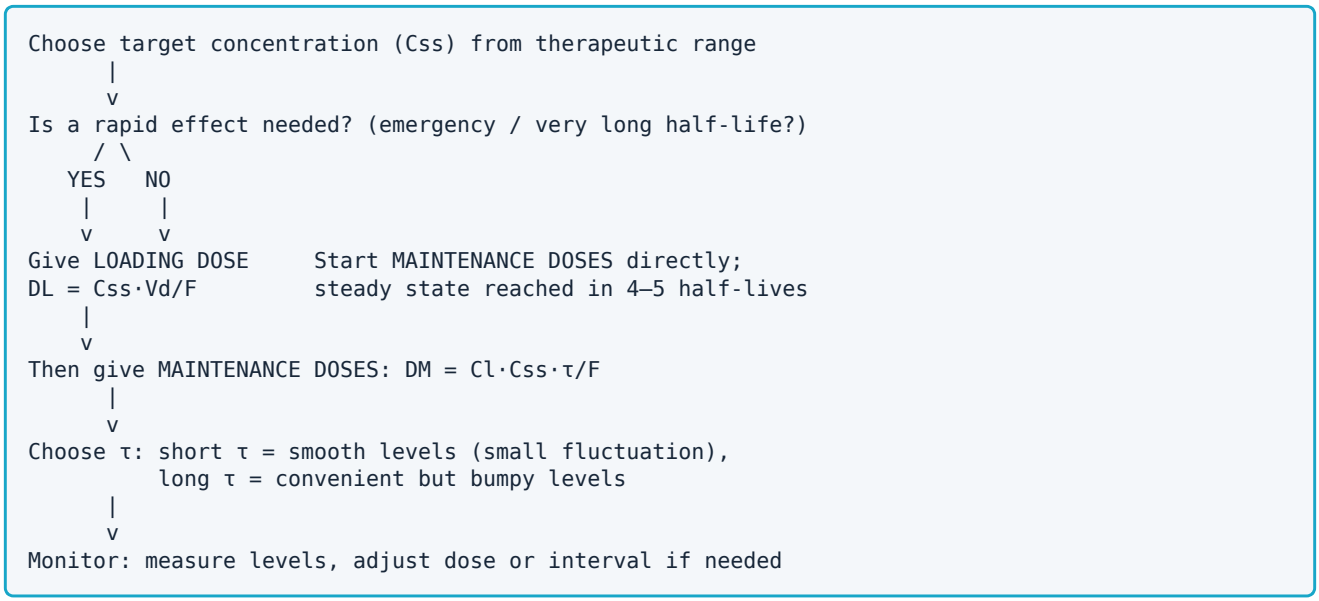


Diagram 4 — Loading dose vs no loading dose

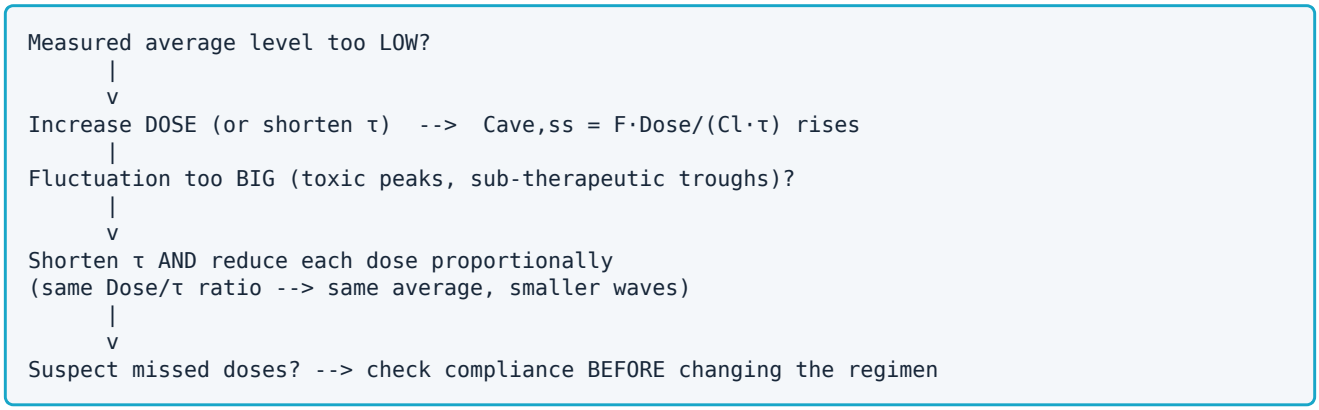


Flowcharts

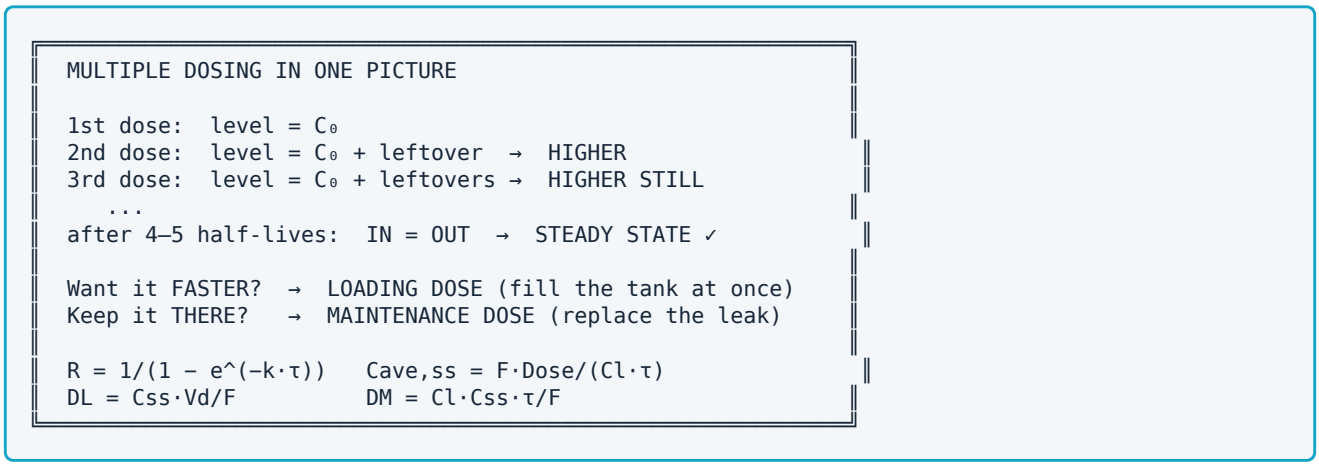
Flowchart 1 — Designing a multiple dosage regimen



Flowchart 2 — Adjusting a regimen that is off-target



Infographic Concept Box



Tables

Table 1 — Multiple dosage regimen PK parameters: summary

Parameter	Formula	What it tells you
Fraction remaining after τ	f = e^(−k·τ)	How much of each dose survives to the next dose time
Accumulation index	R = 1/(1 − e^(−k·τ))	Steady-state peak ÷ first-dose peak
Time to steady state	~4–5 × t½	How long until levels stabilise (depends only on t½)
Average steady-state conc.	Cave,ss = F·Dose/(Cl·τ)	The target level your regimen produces
Peak steady-state conc.	Cmax,ss = (F·Dose/Vd)·[1/(1 − e^(−k·τ))]	Highest level each interval
Trough steady-state conc.	Cmin,ss = Cmax,ss·e^(−k·τ)	Lowest level each interval
Fluctuation	Cmax,ss − Cmin,ss	Size of the ups and downs
Swing (ratio)	Cmax,ss/Cmin,ss = e^(k·τ)	Relative size of the ups and downs
Loading dose	DL = Css·Vd/F (IV: Css·Vd)	Big first dose to reach target fast
Maintenance dose	DM = Cl·Css·τ/F (IV: Cl·Css·τ)	Regular dose to hold the target

Table 2 — Adjusting regimens: changing dose vs changing interval

Change	Effect on Cave,ss	Effect on fluctuation	When to use
Increase dose (same τ)	Increases proportionally	Increases (bigger waves)	Level too low overall
Decrease dose (same τ)	Decreases proportionally	Decreases	Level too high overall
Shorten τ (reduce dose to keep Dose/τ same)	Unchanged	Decreases (smoother)	Peaks toxic / troughs ineffective
Lengthen τ (increase dose to keep Dose/τ same)	Unchanged	Increases (bumpier)	Convenience, if still safe

Table 3 — Missed or late dose: what happens

Situation	What happens to levels	Practical point
One missed dose (short t½ drug)	Level falls steeply; effect may be lost	Take as soon as remembered, unless almost time for the next dose — never double up without advice
One missed dose (long t½ drug)	Level dips only slightly; little harm	Steady state is forgiving; resume normal schedule
Repeated missed doses	Falls back toward zero; steady state lost	Re-accumulation takes another 4–5 half-lives (or a loading dose, on medical advice)
Late dose	Trough dips lower, then next peak overshoots slightly	Resume; the regimen self-corrects within a few intervals

Examples (Worked Into the Text)

1 **Antibiotic every 8 hours:** τ = 8 h keeps the level above the minimum effective concentration all day — a classic constant-interval regimen.

2 **Once-daily tablet for blood pressure:** τ = 24 h works only if the half-life is long enough that the trough is still effective the next morning.

3 **Emergency asthma (theophylline-type scenario, textbook illustration):** waiting 4–5 half-lives is unacceptable, so a loading dose is used to reach the target level within minutes to hours, then maintenance doses hold it.

4 **Missed dose of a long-half-life drug:** missing one daily dose of a drug with a 3-day half-life barely moves the level — accumulation makes the regimen forgiving.

Analogies

1 **Bathtub with a leak (accumulation & steady state):** pouring buckets in = dosing; the leak = elimination; rising water = accumulation; constant average level = steady state. Used throughout this chapter.

2 **Candles in a room (why repeat dosing):** one candle burns out; light the next before the room goes dark.

3 **Filling a bucket with a hole (loading vs maintenance):** pour a jugful at once to fill it fast (loading dose); then drip steadily to match the leak (maintenance dose).

4 **Staircase vs escalator (accumulation):** each dose is a step up; elimination slides you partway down between steps; eventually the steps and slides balance and you hover at the same height, stepping up and sliding down in place.

Calculation Boxes (Dedicated, Every Step Shown)

BOX 1 — Accumulation index from k and τ. A drug has k = 0.1 h^{-1} and is given every 8 hours (τ = 8 h). Find R.

Step 1: Compute k·τ = 0.1 × 8 = 0.8. Step 2: Compute e^(−k·τ) = e^(−0.8) = 0.449 (use a calculator: e^(−0.8) ≈ 0.4493). Step 3: R = 1 / (1 − 0.449) = 1 / 0.551 = 1.81. **Answer: R ≈ 1.8.** The steady-state peak is about 1.8 times the first-dose peak — moderate accumulation.

BOX 2 — Cmax,ss, Cmin,ss and Cave,ss. A drug is given orally: Dose = 500 mg, F = 0.8, Vd = 50 L, Cl = 5 L/h, τ = 12 h, k = 0.1 h^{-1}. Find Cave,ss, Cmax,ss, Cmin,ss.

Step 1: Cave,ss = F·Dose/(Cl·τ) = (0.8 × 500)/(5 × 12) = 400/60 = **6.67 mg/L**. Step 2: First-dose peak C_0 = F·Dose/Vd = (0.8 × 500)/50 = 400/50 = 8 mg/L. Step 3: k·τ = 0.1 × 12 = 1.2; e^(−1.2) = 0.301. R = 1/(1 − 0.301) = 1/0.699 = 1.43. Step 4: Cmax,ss = C_0 × R = 8 × 1.43 = **11.44 mg/L**. Step 5: Cmin,ss = Cmax,ss × e^(−k·τ) = 11.44 × 0.301 = **3.44 mg/L**. Check: average of the wave ≈ (11.44 + 3.44)/2 ≈ 7.4, close to Cave,ss = 6.67 (exact average of an exponential decay is slightly below the midpoint — consistent ✓). **Answers: Cave,ss = 6.67 mg/L; Cmax,ss = 11.44 mg/L; Cmin,ss = 3.44 mg/L.**

BOX 3 — Loading dose and maintenance dose (textbook-style illustration). Target Css = 10 mg/L. Drug: Vd = 40 L, Cl = 4 L/h, F = 1 (IV), τ = 12 h. Find DL and DM.

Step 1: DL = Css·Vd/F = (10 × 40)/1 = **400 mg** (IV loading dose). Step 2: DM = Cl·Css·τ/F = (4 × 10 × 12)/1 = **480 mg** every 12 hours. Step 3 (sanity check): Cave,ss = F·DM/(Cl·τ) = 480/(4 × 12) = 480/48 = 10 mg/L = target ✓. **Answers: DL = 400 mg IV; DM = 480 mg IV every 12 h.** (Illustrative textbook-style calculation, not a prescribing recommendation.)

BOX 4 — Time to steady state for a long-half-life drug. A drug has t½ = 36 hours and is given once daily without a loading dose. How long until steady state?

Step 1: Steady state takes ~4–5 half-lives (depends only on half-life, not on dose or interval). Step 2: 4 × 36 = 144 h; 5 × 36 = 180 h. Step 3: 144 h = 6 days; 180 h = 7.5 days. **Answer: about 6–7.5 days.** This long wait is exactly why drugs with long half-lives are classic candidates for a loading dose.

Pharmacy Relevance

- **Designing dosage regimens** is the core clinical job of pharmacokinetics: choosing dose + interval to keep levels inside the therapeutic window (above minimum effective, below toxic).
- **Therapeutic drug monitoring (TDM):** for narrow-therapeutic-index drugs (digoxin, theophylline, phenytoin — the textbook examples in this chapter), blood levels are measured at steady state (trough, just before a dose) and the regimen is adjusted using Cave,ss = F·Dose/(Cl·τ).
- **Patient counselling:** explaining *why* the patient must not skip doses (accumulation lost, 4–5 half-lives to rebuild) and *why* they must not double up after a miss (peaks can overshoot into toxicity) comes straight from this chapter's equations.

- **Formulation choice:** when fluctuation is a problem, the pharmacist can suggest a modified release product or a shorter interval — the same average level with smoother waves.

India Context

- In India, most chronic therapy (hypertension, diabetes, epilepsy, tuberculosis) is given as multiple dosage regimens, often once- or twice-daily for convenience and adherence.
- Fixed-dose combinations (very common in the Indian market) are designed so that each component's τ suits the combination — a practical application of interval selection.
- Patient adherence is a major challenge: missed doses are common, so pharmacists counselling Indian patients should explain the missed-dose rules from Table 3 in simple language ("if you miss one tablet, take it when you remember unless the next one is near — never take two together").
- Modified release once-daily products are widely used in India to improve adherence where thrice-daily dosing fails.

Introduction to Pharmacokinetic Considerations of Modified Release Products

5.9 Why the PK of modified release products differs

Technical concept: In an immediate-release tablet, the drug dissolves and is absorbed quickly, so absorption is much faster than elimination (ka >> k). The decline of blood levels then reflects elimination. In a modified release (extended/sustained-release) product, the formulation releases drug slowly, so absorption becomes the slowest step — it becomes **rate-limiting**.

Simple explanation: Normally the body's "leak" (elimination) decides how fast levels fall. With a slow-release tablet, the tablet is like a tap dripping drug in slowly — now the *tap*, not the leak, decides the shape of the level-time curve. The drug appears to stay in the body longer, not because elimination slowed down, but because new drug keeps arriving.

Flip-flop kinetics: When absorption is slower than elimination (ka < k), the terminal (late) part of the concentration-time curve reflects the *absorption* rate, not the elimination rate. The two rate constants have "flipped" roles — hence "flip-flop". A common student trap: calculating a "half-life" from the tail of a slow-release product's curve actually measures absorption, not elimination.

Extended MRT: Mean residence time (MRT) is the average time a drug molecule spends in the body. Because a modified release product feeds drug in over many hours, the average molecule's stay is stretched — MRT is extended compared with an immediate-release product. For an IV bolus, MRT = 1/k; for oral products, MRT also includes the absorption time, which modified release products deliberately lengthen.

Depot / infusion-like kinetics: Some modified release products (e.g., monthly depot injections, implants) release drug at an almost constant rate — mathematically like a slow IV infusion. Their steady-state level follows the infusion equation Css = Rate/Cl, with very small fluctuation.

5.10 Wagner–Nelson and Loo–Riegelman: relevance

Simple explanation: These are classic mathematical methods that work *backwards*: from the blood-level curve, they calculate how much drug has been absorbed up to each time point. That is exactly what you need when testing a modified release product — you want to prove it releases drug slowly and completely.

- **Wagner–Nelson method:** used when the drug follows a one-compartment model. From blood levels and the elimination rate constant, it computes the fraction of drug absorbed over time.
- **Loo–Riegelman method:** the extension for drugs that follow a two-compartment model (drug distributes into tissues as well).
- **Relevance to modified release:** both methods let formulators check that the slow in-vivo absorption matches the design, and they are the mathematical backbone for building an IVIVC.

5.11 In-vitro–in-vivo correlation (IVIVC) — basic concept

Technical concept: An IVIVC is a validated mathematical relationship between an in-vitro property of the dosage form (usually the dissolution/release profile measured in the laboratory) and an in-vivo response (usually the absorption profile or blood levels in the body). If a good correlation exists, the laboratory dissolution test can predict how the product will behave in patients — and can be used for quality control and for approving small formulation changes without repeating human studies.

Simple explanation: Dissolve the slow-release tablet in a beaker and measure how fast drug comes out (in-vitro). Give it to volunteers and measure blood levels (in-vivo). If "50% released in the beaker at 4 hours" always matches "50% absorbed in the body at 4 hours", you have a correlation — the beaker test becomes a reliable stand-in for the human test.

Key takeaway: IVIVC connects the lab bench to the patient: good correlation means the dissolution test predicts real absorption.

5.12 Steady-state design for once-daily products

Technical concept: A once-daily (τ = 24 h) modified release product is designed so that the slow input rate keeps $C_{min,ss}$ above the minimum effective concentration for the full 24 hours while $C_{max,ss}$ stays below the toxic level. Because input is spread out, fluctuation is small even with a long interval — achieving with one tablet what would otherwise need 3–4 immediate-release doses.

Simple explanation: Instead of three bumpy immediate-release doses a day, one slow-release tablet drips drug in all day: the peaks are lower, the troughs are higher, and the patient takes just one tablet — better levels and better adherence.

Key takeaway: Modified release trades a fast, bumpy input for a slow, smooth one: same average level (Cave,ss = F·Dose/(Cl·τ) still rules), much smaller fluctuation.

Key Points

1 A multiple dosage regimen repeats the same dose every τ hours to maintain continuous effect.

2 Superposition: total concentration = sum of leftover contributions of all previous doses.

3 Accumulation happens because the next dose arrives before the last is fully eliminated; it stops at steady state (in = out per interval).

4 R = 1/(1 − e^(−k·τ)); big R when elimination is slow and dosing is frequent; dose size does not change R.

5 Steady state takes ~4–5 half-lives — depends only on half-life.

6 Cave,ss = F·Dose/(Cl·τ) — the most important clinical PK equation.

7 Cmax,ss and Cmin,ss repeat identically each interval; fluctuation = Cmax,ss − Cmin,ss.

8 Loading dose DL = Css·Vd/F fills the tank fast — use in emergencies and for long-half-life drugs.

9 Maintenance dose DM = Cl·Css·τ/F replaces what is eliminated each interval.

10 To change the average level, change the dose; to smooth fluctuation without changing the average, shorten τ and reduce each dose proportionally.

11 A missed dose of a long-half-life drug matters little; repeated misses lose steady state (4–5 half-lives to rebuild).

12 Modified release products make absorption rate-limiting (flip-flop), extend MRT, and give smooth once-daily levels; Wagner–Nelson/Loo–Riegelman extract absorption profiles and IVIVC links lab dissolution to body absorption.

Common Confusions

1 **"Steady state means constant concentration."** No — the level still rises and falls between doses; only the *pattern* repeats and the *average* is constant.

2 **"A bigger dose reaches steady state faster."** No — time to steady state depends only on half-life (4–5 t½), never on dose size.

3 **"Accumulation means toxicity."** Not necessarily — accumulation is normal and expected; it becomes toxicity only if the steady-state level exceeds the toxic threshold.

4 **"The loading dose replaces maintenance doses."** No — the loading dose only fills the tank; maintenance doses must follow to replace ongoing elimination, or levels will fall again.

5 **"The half-life measured from a slow-release product's curve is the elimination half-life."** Often wrong — with flip-flop kinetics the tail reflects slow *absorption*, not elimination.

6 **"Cave,ss depends on Vd."** No — Cave,ss = F·Dose/(Cl·τ) has no Vd in it. Vd affects the peaks and troughs (Cmax,ss, Cmin,ss), not the average.

Common Mistakes

1 Forgetting F in oral loading/maintenance dose formulas (using DL = Css·Vd for an oral drug overestimates nothing — actually it *underestimates* the needed dose; divide by F).

2 Mixing up k and t½ in the accumulation index — convert first: k = 0.693/t½.

3 Using e^(−k·τ) with τ in hours but k in min^{-1} (units must match).

4 Computing "steady state" after a fixed number of *doses* instead of 4–5 *half-lives* (5 daily doses of a 36-hour-half-life drug is nowhere near steady state).

5 Doubling the dose after a missed dose ("catching up") — this overshoots the peak; the correct action is usually to skip and resume, or take the single missed dose if remembered soon.

6 Reading flip-flop: reporting the slow-release product's terminal slope as the elimination rate constant.

Mnemonics

- **"4–5 halves to heaven (steady state)"** — steady state arrives after 4–5 half-lives.
- **"LOAD the truck, MAINTAIN the road"** — Loading dose = fill it up fast; Maintenance dose = keep it going.
- **"DL needs Vd; DM needs Cl"** — DL = Css·**V**d/F (fill the **V**olume); DM = **Cl**·Css·τ/F (replace what **Cl**earance removes).
- **"In = Out, that's what steady state's about"** — the balance definition.
- **"FLIP-FLOP: slow sip, long trip"** — when absorption sips slowly, the drug's trip in the body looks long.

Exam Summary

Multiple dosing is needed because single doses wear off. By superposition, each new dose adds to the leftovers of earlier ones, so levels accumulate until elimination per interval equals the dose per interval — steady state. Accumulation index R = 1/(1 − e^(−k·τ)) grows with slow elimination and frequent dosing. Steady state needs 4–5 half-lives (half-life only). Key equations: Cave,ss = F·Dose/(Cl·τ); Cmax,ss = (F·Dose/Vd)/(1 − e^(−k·τ)); Cmin,ss = Cmax,ss·e^(−k·τ). Loading dose DL = Css·Vd/F gives instant target levels (emergencies, long half-life drugs — textbook examples

digoxin, theophylline, phenytoin); maintenance dose DM = Cl·Css·τ/F holds the level. Missed doses dip levels; doubling up overshoots. Modified release products make absorption rate-limiting (flip-flop), extend MRT, smooth fluctuation for once-daily dosing; Wagner–Nelson (one-compartment) and Loo–Riegelman (two-compartment) recover absorption profiles, and IVIVC links laboratory dissolution to in-vivo absorption.

One-Minute Revision

- τ = time between doses. Superposition = add up leftovers.
- Accumulation: levels rise till in = out → steady state.
- R = 1/(1 − e^(−k·τ)). Slow k + short τ = big R.
- Steady state in 4–5 half-lives (only half-life matters).
- Cave,ss = F·Dose/(Cl·τ). Fluctuation = Cmax,ss − Cmin,ss.
- DL = Css·Vd/F (fill fast). DM = Cl·Css·τ/F (replace leak).
- Loading dose: emergencies + long half-life drugs.
- Missed dose: don't double up.
- Modified release: absorption becomes rate-limiting → flip-flop → smooth once-daily levels. IVIVC = lab dissolution predicts body absorption.

Exam Questions

MCQs (with Answer Key)

1 The accumulation index R is given by:

a) 1/(1 + e^(−k·τ)) b) 1/(1 − e^(−k·τ)) c) e^(−k·τ) d) k·τ

1 Time required to reach steady state depends on:

a) Dose size b) Dosing interval c) Half-life of the drug d) Bioavailability

1 The average steady-state concentration is:

a) F·Dose·Cl/τ b) F·Dose/(Cl·τ) c) Dose·Vd/F d) Cl·τ/(F·Dose)

1 A loading dose is indicated when:

a) The drug has a very short half-life b) Immediate therapeutic effect is needed c) The drug is given orally d) The patient missed a dose

1 The maintenance dose formula for IV administration is:

a) Css·Vd b) Css·Vd/F c) Cl·Css·τ d) F·Dose/(Cl·τ)

1 Flip-flop kinetics occurs when:

a) Elimination is faster than absorption b) Absorption is slower than elimination c) ka = k d) The drug is given IV

1 If the dosing interval equals the half-life, the accumulation index R is approximately:

a) 1 b) 1.5 c) 2 d) 4

1 Which method is used to calculate the fraction absorbed for a one-compartment drug?

a) Loo–Riegelman b) Wagner–Nelson c) Trapezoidal rule d) IVIVC

1 After a missed dose, the correct general advice is:

a) Always double the next dose b) Skip it and never resume c) Take it when remembered unless the next dose is near; do not double up d) Stop therapy

1 In the equation DL = Css·Vd/F, Vd represents:

a) Rate of elimination b) The apparent volume the drug distributes into c) Fraction absorbed d) Dosing interval

Answer Key: 1-b, 2-c, 3-b, 4-b, 5-c, 6-b, 7-c, 8-b, 9-c, 10-b

Viva Questions

1 Define steady state in one sentence.

2 State the principle of superposition.

3 Write the formula for the accumulation index and name each symbol.

4 Why does dose size not affect the accumulation index?

5 How many half-lives are needed to reach steady state, and why?

6 Derive the loading dose formula in three steps.

7 When is a loading dose clinically justified? Name two textbook example drugs.

8 How would you reduce fluctuation without changing the average steady-state level?

9 What is flip-flop kinetics, and why does it matter for modified release products?

10 What is IVIVC in simple words?

Application-Based Questions

1 A patient on a twice-daily drug with a 6-hour half-life misses two consecutive doses. Using the concepts of this chapter, explain what happens to their drug levels and how long it will take to return to steady state after resuming. Should they double the next dose? Justify.

2 A physician wants smoother blood levels for a patient whose peaks cause side effects but whose average level is correct. Using $C_{ave,ss} = F \cdot Dose/(Cl \cdot \tau)$, propose a regimen change that keeps the average the same but reduces fluctuation. Alternatively, suggest a formulation-based solution.

3 A once-daily modified release tablet shows a terminal half-life of 20 hours on its concentration-time curve, while the immediate-release version of the same drug has a half-life of 6 hours. Explain this observation using flip-flop kinetics and state which value represents true elimination.

4 In an emergency, a drug with a half-life of 48 hours must reach its target concentration today. Explain why starting maintenance doses alone is unacceptable and calculate-style reasoning for why a loading dose solves the problem (no numbers needed — use the 4–5 half-lives rule).

Numerical Problems (Fully Worked Solutions)

Problem 1. A drug has an elimination rate constant k = 0.15 h^{-1} and is administered every 6 hours. Calculate the accumulation index R. What does the value mean?

Solution: Step 1: k·τ = 0.15 × 6 = 0.9. Step 2: e^(−0.9) = 0.4066. Step 3: R = 1/(1 − 0.4066) = 1/0.5934 = 1.685. **Answer: R ≈ 1.69.** The steady-state peak will be about 1.7 times the peak after the first dose — moderate accumulation because the 6-hour interval is shorter than the half-life ($t_{½}$ = 0.693/0.15 = 4.62 h), so a good fraction of each dose survives to the next dose.

Problem 2. An oral drug: Dose = 250 mg, F = 0.9, Vd = 30 L, Cl = 3 L/h, τ = 8 h. The elimination rate constant k = Cl/Vd = 0.1 h^{-1}. Calculate Cave,ss, Cmax,ss and Cmin,ss.

Solution: Step 1: Cave,ss = F·Dose/(Cl·τ) = (0.9 × 250)/(3 × 8) = 225/24 = **9.375 mg/L**. Step 2: C_0 = F·Dose/Vd = (0.9 × 250)/30 = 225/30 = 7.5 mg/L. Step 3: k·τ = 0.1 × 8 = 0.8; e^(−0.8) = 0.4493; R = 1/(1 − 0.4493) = 1.816. Step 4: Cmax,ss = 7.5 × 1.816 = **13.62 mg/L**. Step 5: Cmin,ss = 13.62 × 0.4493 = **6.12 mg/L**. **Answers: Cave,ss = 9.38 mg/L, Cmax,ss = 13.62 mg/L, Cmin,ss = 6.12 mg/L.** Fluctuation = 13.62 − 6.12 = 7.5 mg/L.

Problem 3. (Textbook-style illustration.) Target steady-state concentration Css = 15 mg/L. Drug parameters: Vd = 50 L, Cl = 6 L/h, F = 0.75 (oral), τ = 12 h. Calculate the oral loading dose and the oral maintenance dose. Verify the maintenance dose reproduces the target.

Solution: Step 1: DL = Css·Vd/F = (15 × 50)/0.75 = 750/0.75 = **1000 mg**. Step 2: DM = Cl·Css·τ/F = (6 × 15 × 12)/0.75 = 1080/0.75 = **1440 mg every 12 h**. Step 3 (verification): Cave,ss = F·DM/(Cl·τ) = (0.75 × 1440)/(6 × 12) = 1080/72 = 15 mg/L = target ✓. **Answers: DL = 1000 mg; DM = 1440 mg every 12 h.** (Illustrative calculation only — not a prescribing recommendation.)

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