BP602T · B.Pharm Semester VI · Theory Notes

Biopharmaceutics and Pharmacokinetics

Unit III — Pharmacokinetic Models

Unit III (10 hours)

Pills & Python Notes

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

Syllabus coverage: Unit III (10 hours).

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CHAPTER 1: Compartment Models and the One-Compartment Open Model — IV Bolus and IV Infusion

Learning Objectives

After studying this chapter, you should be able to:

1 Define a compartment model and explain what a "compartment" means in pharmacokinetics.

2 Classify pharmacokinetic models by number of compartments, open vs closed systems, and linear vs nonlinear kinetics.

3 Describe the properties (assumptions) of a compartment — well-stirred, uniform concentration, first-order transfer.

4 List the advantages and disadvantages of compartment modelling.

5 Explain the idea of curve fitting in simple words.

6 State the assumptions of the one-compartment open model.

7 Derive the IV bolus equation $C = C_0 \cdot e^{(-k \cdot t)}$ step by step, starting from the differential equation.

8 Define and calculate Kel (elimination rate constant), biological half-life ($t_{1/2}$), apparent volume of distribution (Vd), clearance (Cl), and AUC.

9 Derive the IV infusion equation $C(t) = (R_0/(k \cdot V)) \cdot (1 - e^{(-k \cdot t)})$ step by step.

10 Define steady-state concentration (Css) and calculate the time needed to reach steady state.

11 Write and apply the post-infusion (after the drip stops) equation.

12 Solve numerical problems on IV bolus and IV infusion confidently.

Definitions

Pharmacokinetics (PK): The study of *what the body does to the drug* — how the drug is absorbed, distributed, metabolised and excreted over time. (The famous ADME: Absorption, Distribution, Metabolism, Excretion.)

Biopharmaceutics: The study of *how the drug product and its formulation* (tablet, capsule, injection, syrup) affect the way the drug reaches the body and acts.

Compartment model: A mathematical way of describing the body. Instead of tracking the drug in every organ separately, we divide the body into a small number of imaginary boxes called "compartments." Each compartment is treated as if it were a single, well-mixed container of fluid,

and we write simple equations for how the drug moves between these containers. That is all a compartment model is — the body drawn as boxes, with arrows showing drug movement.

Compartment: One imaginary, well-stirred container in the model. It does NOT mean one real organ. One compartment can stand for the whole blood plus all tissues that fill and empty with drug at roughly the same speed.

Pharmacokinetic model: Any set of equations that predicts how the drug concentration in the body changes with time after a dose. The compartment model is the simplest and most widely used type.

Terminology (Glossary)

Term	Symbol	Simple meaning
Plasma concentration	C or Cp	Amount of drug in a given volume of blood plasma, at one moment of time.
Initial concentration	C_0 (C-zero)	The plasma concentration at time zero — immediately after an IV bolus, before any drug has been removed.
Elimination rate constant	k or Kel	The fraction of drug removed from the compartment per unit time. Unit: per hour (h^{-1}). It tells how *fast* the drug disappears.
Biological half-life	t½	The time needed for the plasma concentration to fall to HALF of its current value. If C is 100 and t½ is 2 hours, then after 2 h C = 50, after 4 h C = 25, and so on.
Apparent volume of distribution	Vd	An imaginary volume (in litres) that would be needed to hold all the drug in the body at the same concentration seen in plasma. It is "apparent" because it is a calculated number, not a real body part.
Clearance	Cl	The volume of plasma that is completely "cleaned" of drug per unit time (e.g., litres per hour). It measures the body's ability to remove the drug.
Area under the curve	AUC	The total area under the plasma concentration–time graph from time zero to infinity. It represents the *total exposure* of the body to the drug. Unit: concentration × time (e.g., mg·h/L).
Infusion rate	R_0 (R-zero)	The constant rate at which drug is dripped into the body during IV infusion, in amount per time (e.g., mg/h).
Steady-state concentration	Css	The constant plasma concentration reached during a continuous IV infusion, when the rate of drug going IN exactly equals the rate going OUT.

Term	Symbol	Simple meaning
First-order kinetics	—	When the rate of a process is *proportional to* the amount (or concentration) of drug present. Double the drug → double the rate.
Zero-order kinetics	—	When the rate of a process is *constant*, independent of how much drug is present (e.g., a drip pump running at fixed speed).
Curve fitting	—	Choosing the equation whose graph best matches the actual measured plasma concentration points.

Explanation: What Is a Compartment Model?

The problem

When a patient receives a drug, the drug travels through blood to the heart, liver, kidneys, muscles, fat, brain — everywhere. Measuring drug in every organ is impossible in a living patient. The only thing we can measure easily is the drug concentration in **blood plasma** (or serum) at different times after the dose.

The idea

Since we can only *see* plasma, we draw a simplified picture:

1. We imagine the body as one or more **boxes (compartments)**.
2. Each box behaves like a **bucket of water with a tap**: water (drug) enters, water leaves, and stirring keeps the water in the bucket uniform.
3. We write a simple **mathematical equation** for each box, describing "rate in minus rate out."
4. We match this equation to the measured plasma data (**curve fitting**). If the equation's curve passes through our measured points, the model is accepted as a useful description.

The bucket analogy (keep this in your mind for the whole chapter)

- **Bucket = compartment.** The body (or part of it) is a bucket.
- **Water = drug.** The amount of drug in the body.
- **Water level = concentration (C).** The height of water tells us how much drug is present.
- **Tap at the bottom = elimination.** Water flows out through the tap; the tap's opening size is the elimination rate constant **k**.
- **Pouring water in fast = IV bolus.** You dump a mug of water in instantly, then watch the level fall as the tap drains it.
- **Pouring water in slowly at a fixed rate = IV infusion.** You keep pouring steadily; the level rises until the water leaving through the tap equals the water being poured in — that stable level is **Css**.

Key takeaway: A compartment model is a simplified "boxes and arrows" picture of the body. It is not a photograph of the body; it is a *useful map* that lets us predict drug levels with simple maths.

Classification of Pharmacokinetic (Compartment) Models

Models are classified on three separate bases. A complete model name combines all three (for example: "one-compartment open linear model").

Basis 1: Number of compartments

Model	Simple meaning	Example behaviour
One-compartment	The whole body behaves as ONE well-mixed box. Drug distributes into tissues so fast that the entire body is at the same effective concentration at all times.	Plasma log-concentration vs time is a **single straight line** after IV bolus.
Two-compartment	The body behaves as TWO boxes: a **central compartment** (blood + organs with rich blood supply like heart, liver, kidney) and a **peripheral compartment** (muscles, fat — tissues the drug reaches slowly).	Plasma log-concentration vs time shows **two phases**: a fast distribution phase (drug moving into tissues) and a slow elimination phase.
Multicompartment	Three or more boxes. Used for drugs with very complex distribution (e.g., strong binding to deep tissues).	Used rarely; mostly in research and computer simulation.

Simple explanation: Ask: "Does the drug spread through the body in one smooth step, or in stages?" One stage = one compartment. Two stages (fast, then slow) = two compartments.

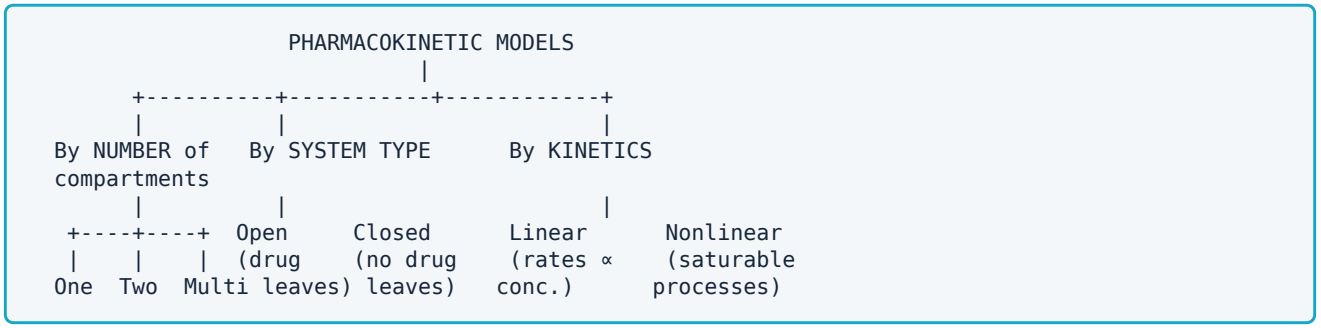
Basis 2: Open vs closed models

- **Open model:** Drug can *enter* the body (dose) and *leave* the body (elimination through urine, bile, etc.). The bucket has a tap — water leaves. **This is how real bodies work**, so almost all practical models are open.
- **Closed model:** Drug only moves *between* compartments but never leaves the system. No tap on the bucket. Used only for theoretical or in-vitro (test-tube) situations, such as drug moving between two chambers of a dialysis cell.

Basis 3: Linear vs nonlinear models

- **Linear model (first-order):** All rates are proportional to concentration. Doubling the dose doubles the plasma levels. The equations are simple, and parameters like k, Vd, Cl are *constant* — they do not change with dose.
- **Nonlinear model:** At least one process (usually metabolism by liver enzymes) becomes *saturated* at higher doses — the enzymes are "full" and cannot work faster. Then doubling the dose gives *more* than double the plasma level. The maths is harder and parameters change with dose.

Classification flowchart:



Properties (Assumptions) of a Compartment

For the maths to work, every compartment must behave like this:

1. **Well-stirred (well-mixed):** The drug mixes instantly and evenly throughout the compartment. Like sugar dissolved in a stirred cup of tea — the concentration is the same everywhere in the cup. So one concentration value C describes the whole compartment.
2. **Uniform concentration:** Follows from (1). We do not need to know the concentration in each corner; one number is enough.
3. **First-order transfer (for linear models):** Drug moves between compartments (and out of the body) at a rate *proportional to* how much drug is present. Rate = k × amount. No saturation.
4. **Instant distribution within the compartment:** Any drug entering the compartment spreads through it immediately, so there is no "filling up one side first."
5. **Measurable from plasma:** We assume the plasma (blood) we sample represents the central compartment, so measured C stands for the compartment's concentration.

Advantages of Compartment Modelling

1. **Simplicity:** The whole body's behaviour is reduced to one or two equations that a student can solve by hand.
2. **Prediction:** From a few blood samples we can *predict* drug levels at any future time — essential for deciding the next dose.
3. **Dosing design:** Lets us calculate the correct dose, dosing interval, and infusion rate for a patient (the core pharmacy relevance).
4. **Compares formulations:** Two tablet brands can be compared by their model parameters (bioequivalence studies).
5. **Explains half-life and clearance:** Gives physical meaning to t½, Vd, Cl — the numbers doctors and pharmacists actually use.

6 **Basis of software:** All pharmacokinetic software (used in hospitals and industry) is built on these same equations.

Disadvantages of Compartment Modelling

1 **Oversimplification:** The body is not really one or two buckets; real distribution is far more complex. The model is a map, not the territory.

2 **"Apparent" parameters:** Vd is not a real body volume; it is a calculated number that can confuse beginners.

3 **Assumes instant mixing:** In reality, distribution takes time; the one-compartment model ignores the distribution phase entirely.

4 **Fails for nonlinear drugs:** For drugs with saturable metabolism, the simple equations give wrong predictions at high doses.

5 **Needs good data:** Wrong or too few blood samples give wrong parameters ("garbage in, garbage out").

6 **Does not show where the drug goes:** It cannot tell us the concentration in the liver vs the brain — only the average behaviour.

Curve Fitting — A Brief Introduction

Simple explanation: After giving a drug, we measure plasma concentration at several times: 1 h, 2 h, 4 h, 8 h … We get a set of *points*. Curve fitting means **choosing the mathematical equation whose smooth curve passes closest to these points**.

- If the points fall on a **single straight line** (on a log-concentration plot), we fit the **one-compartment model**.
- If the points show a **bend (two slopes)**, we fit the **two-compartment model**.
- The "best fit" is found by adjusting the equation's parameters (k, Vd …) until the difference between the curve and the points is minimum. Computers do this; you do it by drawing the best straight line through the points on graph paper.

Example: You inject a drug IV and measure C = 100, 50, 25, 12.5 at 0, 1, 2, 3 hours. The points form a perfect straight line on a log plot → one-compartment model fits → you can now predict C at 5 hours (it will be 3.125). That is the power of curve fitting: a few points become a full prediction.

Key takeaway: The model is chosen by the *shape of the data*, not by guessing. The data decides how many compartments we need.

The One-Compartment Open Model

Simple explanation: We treat the *entire body as one single bucket*. The bucket is "open" because drug leaves it (elimination). This model is used when a drug distributes into all tissues so quickly that, for practical purposes, the whole body behaves as one well-mixed container.

Model assumptions

1. The body is a single, well-stirred compartment (uniform concentration everywhere).
2. **Distribution is instantaneous:** the drug spreads through the body immediately after entering blood, so there is no separate distribution phase. (This is the model's biggest simplification.)
3. **Elimination is first-order:** the rate of drug removal is proportional to the concentration — Rate = k × C.
4. Drug enters only by the defined route (IV bolus or IV infusion) and leaves only by elimination.
5. The measured plasma concentration C represents the concentration in the whole compartment.

When is it used? For drugs that distribute very fast and uniformly (many small water-soluble drugs), and as the first, simplest description of any drug before checking whether a two-compartment model fits better.

Before the Maths: Exponentials and Logarithms in Plain Words

You will see **e** and **ln** everywhere below. Here is all you need:

- **e (≈ 2.718)** is just a special number, like π (3.1416). It appears naturally whenever something grows or shrinks at a rate proportional to itself (population growth, radioactive decay, drug elimination).
- **e^(−k·t)** means "e raised to the power (−k·t)". Because the power is negative, this value *falls* as time passes: at t = 0 it equals 1; as t grows, it shrinks toward 0. It describes smooth, ever-slowing decline — exactly how drug washes out of the body.
- **ln (natural logarithm)** is the *reverse* of e. If e^x = y, then ln(y) = x. Just as subtraction undoes addition, ln undoes e.
- **Two facts we will use:**
- ln(a/b) = ln(a) − ln(b) — a ratio becomes a difference.
- ln(e^x) = x — ln "cancels" e.
- **ln vs $\log_{10}$:** Your calculator has both. ln is log to base e; log (written $\log_{10}$) is log to base 10. They are related: **$\ln(x) = 2.303 \times \log_{10}(x)$**. In pharmacokinetics we use **ln** because the equations come out simplest. A classic exam trap — see "Common Mistakes."

Key takeaway: e^(−k·t) = smooth decline. ln = the tool that straightens this decline into a line.

IV Bolus (Rapid Intravenous Injection)

Simple explanation: The full dose is injected directly into a vein *in seconds*. Think of dumping one mug of water into the bucket instantly at time zero, then doing nothing — just watching the tap drain the bucket. There is no absorption phase (the drug is already in blood), only elimination.

Symbols — know these before the equations

Symbol	Meaning	Unit
D (or Dose)	Amount of drug injected	mg (or µg)
C	Plasma concentration at time t	mg/L
C_0	Concentration at time zero (the instant after injection)	mg/L
V or Vd	Apparent volume of distribution	L
k (Kel)	Elimination rate constant — fraction of drug removed per unit time	h^{-1} (per hour)
t	Time after injection	h
X	Amount of drug in the body at time t	mg

Step-by-step derivation

Step 1 — Write the "rate in minus rate out" statement.

Amount of drug in the body at time t = X. After the bolus, no more drug enters, so:

Rate of change of amount = − (rate of elimination)

For first-order elimination, the elimination rate is proportional to the amount present:

$$(dX)/(dt) = -k \cdot X \quad (1)$$

Step 2 — Convert amount (X) to concentration (C).

Concentration = Amount ÷ Volume, so X = V·C. Since V is constant, dX/dt = V·(dC/dt). Substitute into (1):

$$V \cdot (dC)/(dt) = -k \cdot V \cdot C$$

Cancel V from both sides:

$$(dC)/(dt) = -k \cdot C \quad (2)$$

Read this in words: "The rate at which concentration falls equals k times the current concentration." When C is large, it falls fast; when C is small, it falls slowly — that is first-order behaviour.

Step 3 — Separate the variables (get all C's on one side, all t's on the other).

Divide both sides by C and multiply by dt:

$$\frac{dC}{C} = -k\,dt \quad (3)$$

Step 4 — Integrate both sides.

$$\int \frac{dC}{C} = -k \int dt$$

The integral of 1/C is ln(C) (this is a standard result — accept it as a fact):

$$\ln C = -k \cdot t + \text{constant} \quad (4)$$

Step 5 — Find the constant using the starting condition.

At time t = 0, the concentration is C_0 (the whole dose is present, nothing eliminated yet). Put t = 0 and C = C_0 into (4):

$$\ln C_0 = -k \cdot 0 + \text{constant} \Rightarrow \text{constant} = \ln C_0$$

Step 6 — Write the final integrated equation.

$$\ln C = -k \cdot t + \ln C_0$$

Rearrange (bring ln C_0 to the left):

$$\ln C - \ln C_0 = -k \cdot t$$

Use the log rule ln(a) − ln(b) = ln(a/b):

$$\ln\left(\frac{C}{C_0}\right) = -k \cdot t$$

Take e to the power of both sides (e undoes ln):

$$\frac{C}{C_0} = e^{(-k \cdot t)}$$

$$C = C_0 \cdot e^{(-k \cdot t)} \quad (5)$$

This is the IV bolus equation. It says: concentration starts at C_0 and declines exponentially with time, at a speed set by k.

Graphical meaning: If you plot **ln C against t**, equation (4) is a straight line: ln C = −k·t + ln C_0. The **slope = −k** and the **intercept = ln C_0**. So from real blood-sample data, draw the best

straight line through the ln C points → its slope gives k, and where it meets the t = 0 axis gives C_0.

Textual diagram — IV bolus model:

```
        Dose (IV bolus, instant)
                |
                v
        +-----------------+
        |  ONE COMPARTMENT |----k---->  ELIMINATED
        |   (whole body)   |  (urine, bile...)
        |   conc. = C      |
        +-----------------+
   C = C0 · e^(-k·t) : starts at C0, falls exponentially
```

Parameters from the IV bolus equation

1. Elimination rate constant, k (Kel)

k is the *fraction* of drug eliminated per unit time. k = 0.2 h^{-1} means 20% of the drug present is removed every hour (approximately — exactly, it is the constant in the exponential).

How to get k from data: Plot ln C vs t → straight line → **k = −(slope)**. From two points: $k = \ln(C_1/C_2) \div (t_2 - t_1)$.

2. C_0 = Dose / Vd

At time zero, the entire dose D is dissolved in the volume Vd, so:

$$C_0 = (\text{Dose})/(V_d) \quad (6)$$

3. Biological half-life, $t_{½}$ — derivation

Half-life is the time for C to fall from any value to half that value. Put $C = C_0/2$ at $t = t_{½}$ into equation (5):

$$(C_0)/(2) = C_0 \cdot e^{-k \cdot t_{(1/2)}}$$

Cancel C_0:

$$(1)/(2) = e^{-k \cdot t_{(1/2)}}$$

Take ln of both sides:

$$\ln((1)/(2)) = -k \cdot t_{(1/2)}$$

$\ln(1/2) = -\ln(2) = -0.693$:

$$-0.693 = -k \cdot t_{(1/2)}$$

$$t_{(1/2)} = (0.693)/(k) \quad (7)$$

Read in words: half-life and k are inversely related — a big k (fast elimination) means a short half-life.

4. Apparent volume of distribution, Vd

Rearrange equation (6):

$$V_d = (\text{Dose})/(C_0) \quad (8)$$

Simple explanation: Suppose you inject 500 mg and the first measured (back-extrapolated) concentration C_0 is 10 mg/L. Then Vd = 500/10 = 50 L — *as if* the drug dissolved in 50 litres at 10 mg/L. The number can be larger than the body's real fluid volume (~42 L for an adult) if the drug concentrates in tissues — that is why it is called "apparent."

5. Clearance, Cl

Clearance = the volume of plasma completely cleared of drug per unit time. Derivation: elimination rate = k·X = k·Vd·C. But elimination rate is also defined as Cl·C (clearance × concentration). Equate:

$$Cl \cdot C = k \cdot V_d \cdot C$$

$$Cl = k \cdot V_d \quad (9)$$

Unit check: $(h^{-1})(L) = L/h$ ✓ — volume per time, as expected.

6. AUC (area under the curve) — derivation by integration

AUC = total area under the C–t curve from t = 0 to t = ∞:

$$AUC = \int_{0\to\infty} C\,dt = \int_{0\to\infty} C_0\, e^{(-k \cdot t)}\,dt$$

Take the constant C_0 out:

$$AUC = C_0 \int_{0\to\infty} e^{(-k \cdot t)}\,dt$$

The integral of $e^{(-k\cdot t)}$ is $-(1/k)\cdot e^{(-k\cdot t)}$. Evaluate from 0 to ∞:

$$AUC = C_0 \left[-(1)/(k)\, e^{(-k \cdot t)} \right]_0^{(\infty)} = C_0 \left(0 - (-(1)/(k)) \right) = (C_0)/(k)$$

Now substitute C_0 = Dose/Vd:

$$AUC = (\text{Dose})/(k \cdot V_d)$$

And since Cl = k·Vd:

$$AUC = (\text{Dose})/(Cl) \quad (10)$$

Read in words: Total drug exposure (AUC) = Dose ÷ Clearance. A patient with poor clearance (kidney failure) gets a *larger* AUC from the same dose — more exposure, more risk of toxicity. This single equation is why clearance matters clinically.

IV Infusion (Constant-Rate Intravenous Drip)

Simple explanation: Instead of dumping the whole dose at once, the drug is dripped into the vein at a *steady, constant rate* (like a saline drip). Back to the bucket: you keep pouring water in at a fixed rate while the tap drains it. The water level rises at first, then settles at a constant height where "in = out." That constant level is the **steady-state concentration, Css**.

This is used in hospitals for drugs that need a stable blood level — for example, during surgery or in intensive care — where ups and downs of bolus dosing would be unsafe.

Symbols — new ones for infusion

Symbol	Meaning	Unit
R_0	Infusion rate — constant amount of drug entering per unit time	mg/h
Css	Steady-state concentration (constant level reached during infusion)	mg/L
T	Duration of the infusion (when the drip is stopped)	h
C′ (C-prime)	Concentration at the moment the infusion stops	mg/L

k, V (Vd), Cl, t keep their earlier meanings.

Step-by-step derivation

Step 1 — "Rate in minus rate out" for the amount X.

Drug enters at constant rate R_0 (zero-order input) and leaves by first-order elimination k·X:

$$(dX)/(dt) = R_0 - k \cdot X \quad (11)$$

Step 2 — Convert to concentration. X = V·C, so dX/dt = V·(dC/dt):

$$V \cdot (dC)/(dt) = R_0 - k \cdot V \cdot C$$

Divide by V:

$$(dC)/(dt) = (R_0)/(V) - k \cdot C \quad (12)$$

Read in words: "Concentration rises because of the constant drip (R_0/V), and falls because of elimination (k·C)." Early on, C is small so elimination is weak → C rises fast. Later, C is large so elimination nearly balances the drip → C rises slowly and flattens.

Step 3 — Solve the differential equation.

This is a standard form. Trick: define a new variable that measures *how far C is from its final steady value*. Let the steady value be Cs (we will prove what it equals in Step 5). Define:

$$y = C - C_s \text{ where } C_s = (R_0)/(k \cdot V)$$

Then dC/dt = dy/dt (Cs is constant), and substituting into (12):

$$(dy)/(dt) = (R_0)/(V) - k(y + C_s) = (R_0)/(V) - k \cdot y - k \cdot C_s$$

But k·Cs = k·(R₀/(k·V)) = R₀/V, so the first and last terms cancel:

$$(dy)/(dt) = -k \cdot y$$

This is the same simple form as the IV bolus equation (2)! Its solution (same Steps 3–6 as before) is:

$$y = y_0 \cdot e^{(-k \cdot t)}$$

Step 4 — Apply the starting condition. At t = 0 (drip just started), C = 0, so $y_0 = 0 - Cs = -Cs$:

$$y = -C_s \cdot e^{(-k \cdot t)}$$

Convert back (C = y + Cs):

$$C = C_s - C_s \cdot e^{(-k \cdot t)} = C_s (1 - e^{(-k \cdot t)})$$

Replace Cs with R₀/(k·V):

$$C(t) = (R_0)/(k \cdot V) (1 - e^{(-k \cdot t)}) \quad (13)$$

This is the IV infusion equation. At t = 0: (1 − 1) = 0 → C = 0 ✓. As t → ∞: e^(−k·t) → 0 → C → R₀/(k·V) = constant ✓.

Step 5 — Steady-state concentration, Css.

At steady state, "in = out": R₀ = Cl·Css (elimination rate equals infusion rate). So:

$$C_{ss} = (R_0)/(Cl) = (R_0)/(k \cdot V) \quad (14)$$

Read in words: The final stable level = (how fast you pour in) ÷ (how fast the body clears). Double the drip rate → double the steady level. This is the single most-used infusion equation in clinical practice.

The infusion equation can therefore also be written in the neat form:

$$C(t) = C_{ss} (1 - e^{(-k \cdot t)}) \quad (15)$$

Textual diagram — IV infusion model:

```
  Constant drip R0 (mg/h)
         |
         v
+-----------------+----k---->  ELIMINATED
| ONE COMPARTMENT |
|   conc. = C(t)  |
+-----------------+
 C rises as Css·(1 - e^-kt), then flattens at Css = R0/Cl
```

Time to reach steady state

How long until the level is "practically" at Css? From (15), the fraction of steady state reached is:

$$\text{fracCC}_{ss} = 1 - e^{(-k \cdot t)}$$

Write time in units of half-lives: t = n·t½, and k·t½ = 0.693, so e^(−k·t) = e^(−0.693·n) = (1/2)^n. Hence:

$$\text{fracCC}_{ss} = 1 - ((1)/(2))^{n}$$

Half-lives elapsed (n)	% of Css reached	% still missing
1	50.0%	50.0%
2	75.0%	25.0%
3	87.5%	12.5%
4	93.75%	6.25%
5	96.9%	3.1%
6	98.4%	1.6%
7	99.2%	0.8%

Rule of thumb: Steady state is *practically* reached in **4–5 half-lives** (~94–97% of Css). Note: this depends ONLY on the half-life (k), NOT on the infusion rate. A faster drip gives a *higher* Css but does NOT reach it sooner.

Quick derivation for "time to reach 90% of Css" (a favourite exam question): Set C/Css = 0.90:

$$0.90 = 1 - e^{(-k \cdot t)} \Rightarrow e^{(-k \cdot t)} = 0.10$$

Take ln: −k·t = ln(0.10) = −2.303, so:

$$t_{(90\%)} = (2.303)/(k) \quad (16)$$

After the infusion stops (post-infusion decay)

Suppose the drip runs for T hours and is then stopped. At stop time, C = C′. After stopping, no drug enters — it is just like an IV bolus starting from C′:

$$C = C' \cdot e^{(-k \cdot (t - T))} \text{ for } t > T \quad (17)$$

where C' = $Css \cdot (1 - e^{(-k \cdot T)})$ from equation (15).

Read in words: The level at switch-off decays exponentially, with the same k as always. The clock for the decay starts at T.

Worked Numericals (Calculation Boxes)

Box 1 — Finding k and t½ from two plasma points (IV bolus)

Question: After an IV bolus, plasma concentrations are 16 mg/L at 1 h and 4 mg/L at 5 h. Calculate k and t½.

Step 1 — Formula: From $C = C_0 \cdot e^{(-k \cdot t)}$, for two points: $k = \ln(C_1/C_2) \div (t_2 - t_1)$.

Step 2 — Insert values: $k = \ln(16/4) \div (5 - 1) = \ln(4) \div 4$.

Step 3 — Calculate: $\ln(4) = 1.386$. $k = 1.386 \div 4 =$ **$0.3466\ h^{-1}$**.

Step 4 — Half-life: $t_{½} = 0.693/k = 0.693 \div 0.3466 =$ **2.0 h**.

Check (sanity): Concentration fell from 16 to 4 = two halvings in 4 hours → one halving every 2 h ✓.

Box 2 — Vd from IV bolus data

Question: A 500 mg IV bolus gives a back-extrapolated C_0 of 12.5 mg/L. Calculate Vd.

Step 1 — Formula: $Vd = Dose \div C_0$.

Step 2 — Insert values: Vd = 500 mg ÷ 12.5 mg/L.

Step 3 — Calculate: Vd = **40 L**.

Interpretation: The drug behaves as if dissolved in 40 L — close to total body water, suggesting wide distribution.

Box 3 — Clearance and AUC

Question: For the drug in Box 2, k = 0.2 h^{-1}. Calculate Cl and AUC.

Step 1 — Clearance: $Cl = k \times Vd = 0.2\ h^{-1} \times 40\ L =$ **8 L/h**.

Step 2 — AUC: AUC = Dose ÷ Cl = 500 mg ÷ 8 L/h = **62.5 mg·h/L**.

Alternative check: $AUC = C_0/k = 12.5 \div 0.2 = 62.5$ mg·h/L ✓ (both routes agree).

Box 4 — Infusion rate for a target Css

Question: A drug has Cl = 8 L/h. What constant IV infusion rate is needed to maintain Css = 10 mg/L?

Step 1 — Formula: Css = R_0/Cl → R_0 = Css × Cl.

Step 2 — Insert values: R_0 = 10 mg/L × 8 L/h = **80 mg/h**.

Unit check: (mg/L)(L/h) = mg/h ✓ — an amount per time, correct for a rate.

Box 5 — Time to reach 90% of steady state

Question: A drug has $t_{½}$ = 2 h. How long of infusion is needed to reach 90% of Css?

Step 1 — Find k: k = 0.693/$t_{½}$ = 0.693 ÷ 2 = 0.3466 h^{-1}.

Step 2 — Formula: $t_{90\%}$ = 2.303/k.

Step 3 — Calculate: t = 2.303 ÷ 0.3466 = **6.64 h**.

Sanity check: 90% is between 3 half-lives (87.5%) and 4 half-lives (93.75%) → between 6 and 8 h ✓.

Infographic Concept Box (for the designer)

Title: "One Bucket, Two Ways to Fill It"

Layout idea — two panels side by side:

- **LEFT panel — IV BOLUS:** A bucket with a tap. A hand dumps one mug of water in instantly (label: "Dose, all at once"). Below, a falling curve labelled C = C_0·e^(−k·t), starting high at C_0 and decaying. Three callouts: "k = tap size", "$t_{½}$ = 0.693/k", "Vd = Dose/C_0".
- **RIGHT panel — IV INFUSION:** The same bucket, but a pipe drips water in at a steady rate (label: "R_0, constant drip"). Below, a rising curve that flattens: C = Css·(1 − e^(−k·t)). Callouts: "Css = R_0/Cl", "Steady state in 4–5 half-lives", "After drip stops: decays like a bolus".
- **Bottom strip:** The golden triangle — Cl = k·Vd and AUC = Dose/Cl — with the caption "Three parameters, one family."

Examples (Quick Recap)

1 **IV bolus example:** 500 mg injected in 10 seconds → C_0 = 12.5 mg/L, k = 0.2 h^{-1} → at 5 h, C = 12.5·e^(−0.2×5) = 12.5·e^(−1) = 12.5 × 0.368 = 4.6 mg/L.

2 **Half-life reading:** $t_{½}$ = 2 h means every 2 hours the level halves — no calculation needed to estimate: 100 → 50 → 25 → 12.5.

3 **Infusion example:** R_0 = 80 mg/h, Cl = 8 L/h → Css = 10 mg/L, reached practically after ~4–5 half-lives.

Analogies

- **Bucket with a tap** (used throughout): compartment = bucket, drug = water, k = tap opening, bolus = dumped mug, infusion = steady pour, Css = level where in-flow equals out-flow.
- **Bathtub:** Same idea — pulling the plug while the shower runs; the water settles at a constant depth.
- **Leaking balloon:** A balloon with a tiny hole loses air faster when it is full (high pressure ≈ high concentration) — first-order behaviour you can feel.

Pharmacy Relevance

1 **Dose calculation:** Vd tells you the *loading dose* (Dose = C_target × Vd) and Cl tells you the *maintenance rate* (R_0 = Css × Cl) — the two most practical equations in clinical pharmacy.

2 **Dosing interval:** t½ decides how often to dose. A drug with t½ = 2 h needs frequent dosing or an infusion; t½ = 24 h suits once-daily tablets.

3 **Kidney/liver disease:** Organ failure lowers Cl → AUC rises → the same dose becomes toxic. The pharmacist reduces the dose or extends the interval using these equations.

4 **Therapeutic drug monitoring (TDM):** Measuring a patient's plasma level and comparing it with the model's prediction to adjust the dose individually.

5 **IV therapy in wards:** Nurses set drip rates; the pharmacist verifies that the prescribed R_0 will produce a safe Css.

India Context

- IV bolus and infusion calculations are routine in Indian hospital pharmacies for drugs given by drip — for example, fluids with electrolytes, and antibiotics administered intravenously in wards and ICUs. Always follow the hospital's own protocol and the prescriber's order; the equations in this chapter are learning tools, not prescriptions.
- Indian Pharmacopoeia monographs for injections specify the formulation; the *rate* of administration and monitoring are decided clinically using exactly the principles of this chapter (target level, clearance, half-life).
- In Indian B.Pharm and M.Pharm examinations, IV bolus/infusion numericals are among the most frequently asked calculation questions in biopharmaceutics papers — practise them until the steps are automatic.

Key Points (must remember)

1 A compartment = an imaginary, well-stirred box with uniform concentration.

2 Models are classified by: number of compartments, open/closed, linear/nonlinear.

3 One-compartment open model assumes instant distribution + first-order elimination.

4 IV bolus: C = C_0·e^(−k·t); ln C vs t is a straight line with slope −k.

5 $t_{½}$ = 0.693/k; Vd = Dose/C_0; Cl = k·Vd; AUC = Dose/Cl.

6 IV infusion: C(t) = Css·(1 − e^(−k·t)); Css = R_0/Cl.

7 Steady state is practically reached in 4–5 half-lives, independent of R_0.

8 After infusion stops: C = C′·e^(−k·(t−T)) — decay with the same k.

Common Confusions

Confusion	Clarification
k vs $t_{½}$	k is a *rate* (per hour); $t_{½}$ is a *time* (hours). They are inversely related: $t_{½}$ = 0.693/k. A large k means fast elimination and short half-life.
Vd is a real volume	No — it is "apparent." Vd = 40 L does not mean the body has a 40 L bag of fluid; it is the volume that *would* hold the dose at plasma concentration.
Cl is how fast drug leaves	Partly — Cl is a *volume per time* (L/h), not an amount per time. It is the volume of plasma "cleaned" per hour.
Css depends on Vd	No — Css = R_0/Cl. Vd affects *how fast* Css is reached (through k = Cl/Vd), not the final level.
k vs Kel	Same thing. Kel is just the written-out name of k ("elimination rate constant").
C_0 is the first measured sample	No — C_0 is found by *extending the straight line back* to t = 0, because some elimination already happened before the first sample.

Common Mistakes (read before every exam)

1 **ln vs $\log_{10}$:** Slope of the ln C vs t plot is −k. Slope of the $\log_{10}$ C vs t plot is −k/2.303. Mixing them gives a 2.303-fold error — the single most common numerical mistake.

2 **Unit errors:** Dose in mg with C in µg/mL, or time in minutes with k in h^{-1}. Convert everything to ONE consistent set (mg, L, h) before calculating. Remember 1 mg/L = 1 µg/mL.

3 **Forgetting that k needs consistent time units:** If t is in minutes, k comes out per minute; convert to per hour if the question asks in hours.

4 **Using C_0 = first measured concentration** instead of the back-extrapolated intercept — underestimates Vd.

5 **Thinking a bigger infusion rate reaches steady state faster** — it does not; only the half-life controls the time.

6 **Writing e^(+k·t)** (rising) for decay — the minus sign is everything.

7 **AUC units:** concentration × time (mg·h/L), not mg/h.

Mnemonics

- **"k is the Key that opens the tap"** — k controls how fast drug leaves.
- **"Half of 0.693"** — $t_{½}$ = 0.693/k; 0.693 is just ln(2), the log of a halving.
- **"Very Dumb = Dose over C-zero"** — Vd = Dose/C_0.
- **"CLearance Keeps Very Delightful"** — Cl = k·Vd.
- **"AUC = All Under Control = Dose/Cl"** — total exposure is dose divided by clearance.
- **"See-ess-ess = Rate-over-Clearance"** — Css = R_0/Cl.
- **"Four-to-five to stay alive"** — steady state in 4–5 half-lives (a reminder that stable levels take time).

Exam Summary

The one-compartment open model treats the body as a single well-stirred box with first-order elimination. **IV bolus** (instant dose) gives exponential decline: dC/dt = −k·C integrates to **C = C_0·e^(−k·t)**; from it come **$t_{½}$ = 0.693/k**, **Vd = Dose/C_0**, **Cl = k·Vd**, and **AUC = Dose/Cl** (by integration). **IV infusion** (constant drip R_0) gives dC/dt = R_0/V − k·C, solved to **C(t) = Css(1 − e^(−k·t))** with **Css = R_0/Cl**; practical steady state needs **4–5 half-lives**; after the drip stops, **C = C′·e^(−k(t−T))**. Curve fitting (matching the equation to measured points) decides whether one compartment is enough. Master the derivations, the parameter definitions, the ln-vs-$\log_{10}$ distinction, and unit consistency.

One-Minute Revision

- Compartment = imaginary well-stirred box; uniform concentration.
- Classify by: compartments (1/2/multi), open/closed, linear/nonlinear.
- Bolus: C = C_0e^(−kt). $t_{½}$ = 0.693/k. Vd = Dose/C_0. Cl = kVd. AUC = Dose/Cl.
- Infusion: C = Css(1 − e^(−kt)). Css = R_0/Cl. Steady state in 4–5 $t_{½}$.
- Drip stops → decays like bolus from C′.
- ln plot slope = −k; $\log_{10}$ plot slope = −k/2.303.
- Units: keep mg, L, h consistent!

Exam Questions

A. MCQs (with answer key)

1. In a one-compartment open model, the plot of ln C versus time after an IV bolus is: (a) a curve (b) a straight line with slope −k (c) a straight line with slope +k (d) a horizontal line

2. The biological half-life is related to the elimination rate constant by: (a) $t_{½} = k/0.693$ (b) $t_{½} = 0.693/k$ (c) $t_{½} = 2.303/k$ (d) $t_{½} = k \times 2.303$

3. Apparent volume of distribution is calculated as: (a) Dose × C_0 (b) C_0/Dose (c) Dose/C_0 (d) Cl/k

4. Clearance (Cl) is equal to: (a) k + Vd (b) k/Vd (c) k × Vd (d) Vd/k

5. AUC after an IV bolus equals: (a) Dose × Cl (b) Dose/Cl (c) Cl/Dose (d) k × Dose

6. During a constant IV infusion, steady state is practically reached after: (a) 1–2 half-lives (b) 2–3 half-lives (c) 4–5 half-lives (d) 10 half-lives

7. Steady-state concentration during IV infusion is: (a) R_0 × Cl (b) R_0/Cl (c) Cl/R_0 (d) R_0 × Vd

8. If the infusion rate is doubled, the time to reach steady state: (a) doubles (b) halves (c) remains the same (d) becomes zero

9. The slope of a $\log_{10}$ C versus time plot for first-order elimination is: (a) −k (b) −k/2.303 (c) −2.303k (d) +k/2.303

10. An "open" model means: (a) drug moves between compartments only (b) drug can enter and leave the system (c) the equations are unsolvable (d) distribution is instant

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

B. Viva Questions

1 What is a compartment in pharmacokinetics? Is it a real organ?

2 State the three bases of classifying pharmacokinetic models.

3 What does "well-stirred" mean, and why do we assume it?

4 Derive $C = C_0 \cdot e^{(-k \cdot t)}$ starting from $dC/dt = -k \cdot C$.

5 Why is Vd called "apparent"?

6 Derive $t_{½} = 0.693/k$.

7 What is clearance, in one sentence?

8 Derive AUC = Dose/Cl.

9 What is steady state, and why does it take 4–5 half-lives?

10 What happens to plasma concentration after an infusion is stopped? Write the equation.

C. Application-Based Questions

1 A patient with kidney failure has half the normal clearance of a drug. Using AUC = Dose/Cl, explain what happens to total drug exposure if the dose is unchanged, and what a pharmacist should recommend.

2 A doctor wants a stable plasma level of a short-half-life drug during surgery. Would you recommend repeated IV boluses or a constant IV infusion? Justify with the equations.

3 Two brands of an injectable give the same AUC but different C_0 values. What does this tell you about their Vd? (Hint: C_0 = Dose/Vd.)

4 Why can we not use the one-compartment model for a drug that shows two distinct phases on a log concentration–time plot?

D. Numerical Problems (with fully worked solutions)

Problem 1. After an IV bolus of 250 mg, plasma levels are 20 mg/L at 2 h and 5 mg/L at 6 h. Calculate (a) k, (b) t½, (c) Vd, (d) Cl, (e) AUC.

Solution: (a) $k = \ln(C_1/C_2)/(t_2 - t_1) = \ln(20/5)/(6 - 2) = \ln(4)/4 = 1.386/4 =$ **$0.3466\ h^{-1}$**. (b) $t_{½} = 0.693/k = 0.693/0.3466 =$ **2.0 h**. (c) First find C_0: from $C_1 = C_0 \cdot e^{(-k \cdot t_1)} \rightarrow C_0 = C_1 \cdot e^{(k \cdot t_1)} = 20 \cdot e^{(0.3466 \times 2)} = 20 \cdot e^{(0.6932)} = 20 \times 2.0 = 40$ mg/L. (Check: $e^{0.6932} \approx 2$, since ln 2 = 0.693.) Then $Vd = Dose/C_0 = 250/40 =$ **6.25 L**. (d) $Cl = k \cdot Vd = 0.3466 \times 6.25 =$ **2.17 L/h**. (e) $AUC = Dose/Cl = 250/2.17 =$ **115.2 mg·h/L**. (Check: $C_0/k = 40/0.3466 = 115.4$ ✓ — small rounding difference.)

Problem 2. A drug has Vd = 30 L and t½ = 3 h. (a) What IV bolus dose gives C_0 = 15 mg/L? (b) What will C be at 9 h? (c) What infusion rate maintains Css = 15 mg/L?

Solution: $k = 0.693/t_{½} = 0.693/3 = 0.231\ h^{-1}$. (a) $Dose = C_0 \times Vd = 15 \times 30 =$ **450 mg**. (b) $C = C_0 \cdot e^{(-k \cdot t)} = 15 \cdot e^{(-0.231 \times 9)} = 15 \cdot e^{(-2.079)} = 15 \times 0.125 =$ **1.875 mg/L**. (Sanity: 9 h = 3 half-lives → 15 → 7.5 → 3.75 → 1.875 ✓.) (c) $Cl = k \cdot Vd = 0.231 \times 30 = 6.93$ L/h. $R_0 = Css \times Cl = 15 \times 6.93 =$ **104 mg/h** (≈ 100 mg/h).

Problem 3. An IV infusion is run at 60 mg/h. The drug's Cl is 6 L/h and t½ is 4 h. (a) Calculate Css. (b) How long until 95% of Css is reached? (c) If the infusion is stopped at 12 h, what is C at 16 h?

Solution: (a) $Css = R_0/Cl = 60/6 =$ **10 mg/L**. (b) Set $C/Css = 0.95 \rightarrow e^{(-k \cdot t)} = 0.05 \rightarrow -k \cdot t = \ln(0.05) = -2.996 \rightarrow t = 2.996/k$. $k = 0.693/4 = 0.17325\ h^{-1}$. $t = 2.996/0.17325 =$ **17.3 h**. (Sanity: 95% is just past 4 half-lives = 16 h ✓.) (c) C' at 12 h: $C' = Css(1 - e^{(-k \cdot 12)}) = 10(1 - e^{(-0.17325 \times 12)}) = 10(1 - e^{(-2.079)}) = 10(1 - 0.125) = 8.75$ mg/L. After stopping, decay for $(16 - 12) = 4$ h: $C = 8.75 \cdot e^{(-0.17325 \times 4)} = 8.75 \cdot e^{(-0.693)} = 8.75 \times 0.5 =$ **4.375 mg/L**. (Sanity: 4 h = exactly one half-life → halves ✓.)

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CHAPTER 2: Extravascular Administration: Absorption Kinetics, Curve Fitting, Wagner–Nelson and Loo–Riegelman

BP602T — Biopharmaceutics and Pharmacokinetics · Semester VI · Unit III

1. Learning Objectives

After studying this chapter, you will be able to:

1 Draw the one-compartment open model for extravascular administration and write its differential equations.

2 Derive the Bateman equation **C(t) = ka·F·Dose / [Vd·(ka − k)] · (e^(−k·t) − e^(−ka·t))** step by step.

3 Derive **tmax = ln(ka/k) / (ka − k)** and calculate Cmax from it.

4 Explain lag time and flip-flop kinetics in simple words.

5 Apply the **method of residuals (feathering)** to estimate ka and k from oral plasma data.

6 State when the method of residuals fails.

7 Derive the **Wagner–Nelson** equation and calculate fraction of drug absorbed vs time.

8 Explain why Wagner–Nelson fails for two-compartment drugs and derive the **Loo–Riegelman** correction.

9 Solve numerical problems on all of the above.

2. Definitions

Term	Simple definition
Extravascular administration	Giving a drug by any route other than directly into a blood vessel — e.g., oral tablet, intramuscular injection, subcutaneous injection, transdermal patch. The drug must first be **absorbed** into the blood.
First-order absorption (ka)	Absorption in which the *rate* of absorption is proportional to the amount of drug still left at the absorption site. "First-order" = a fixed *fraction* (not a fixed amount) moves per unit time. ka is the first-order absorption rate constant (unit: h^{-1}).
First-order elimination (k)	Elimination in which the rate of drug leaving the body is proportional to the amount in the body. k is the first-order elimination rate constant (unit: h^{-1}).

Term	Simple definition
Bateman equation	The mathematical equation describing plasma concentration vs time after extravascular administration in a one-compartment model with first-order absorption and first-order elimination.
tmax	The time after dosing at which plasma concentration reaches its highest point (Cmax).
Cmax	The highest (peak) plasma drug concentration reached after a dose.
Lag time (tlag)	The delay between giving the dose and the first appearance of drug in plasma (time needed for disintegration, dissolution, gastric emptying).
Flip-flop kinetics	A situation where absorption is *slower* than elimination (ka << k). The terminal declining part of the plasma curve then shows the absorption rate, not the elimination rate — the two rate constants appear "flipped".
Method of residuals (feathering/stripping)	A curve-fitting technique that separates an oral plasma curve into two straight lines on a log plot to estimate ka and k.
Wagner–Nelson method	A calculation method that finds the *fraction of drug absorbed* at any time using only oral plasma concentration data (works for one-compartment drugs).
Loo–Riegelman method	An extension of Wagner–Nelson for drugs that follow a **two-compartment** model; it adds a correction term for drug sitting in peripheral tissues.
Deconvolution	Working *backwards* from the observed plasma curve to find the absorption (input) profile — Wagner–Nelson and Loo–Riegelman are deconvolution methods.

3. Terminology — Glossary Table

Symbol	Meaning	Unit	Explained simply
ka	First-order absorption rate constant	h^{-1} (per hour)	How fast drug moves from gut/muscle into blood. Bigger ka = faster absorption.
k (or kel)	First-order elimination rate constant	h^{-1}	How fast the body removes drug. Bigger k = faster removal.
k10	Elimination rate constant from the central compartment (two-compartment model)	h^{-1}	Same idea as k, but specifically from the blood/tissue-rich central compartment.
k12, k21	Distribution rate constants central→peripheral and peripheral→central	h^{-1}	How fast drug moves between blood and tissues, in each direction.
F	Bioavailability (fraction of dose reaching blood)	unitless (0–1)	If F = 0.8, then 80% of the swallowed dose actually enters the blood.

Symbol	Meaning	Unit	Explained simply
Dose	Amount of drug given	mg	What the patient swallows or is injected with.
Vd (or Vc)	Volume of distribution (or central volume)	L	A *proportionality* number linking amount in body to plasma concentration: Amount = Vd × C. Not a real physical volume.
C(t)	Plasma concentration at time t	mg/L (or µg/mL)	What we measure in blood samples.
AUC_0^t	Area under the C–t curve from 0 to t	mg·h/L	Total drug *exposure* up to time t.
AUC_0^∞	Total area under the curve from 0 to infinity	mg·h/L	Total drug exposure over all time.
A(t)	Cumulative amount of drug absorbed up to time t	mg	"How much has entered the body so far."
Fa(t)	Fraction of drug absorbed by time t	unitless (0–1)	A(t) divided by the total amount that will ever be absorbed.
Xp(t)	Amount of drug in the peripheral (tissue) compartment at time t	mg	Drug "hiding" in tissues, not visible in blood.
tlag	Lag time	h	Dead time before absorption starts.
e	Euler's number ≈ 2.718	—	The base of natural exponentials. e^(−k·t) describes smooth decay.
ln	Natural logarithm	—	ln(x) answers: "e raised to what power gives x?" Used to straighten exponential curves.

A 30-second refresher on exponentials and logarithms (absolute zero level):

- e^(−k·t) is a number that starts at 1 (when t = 0) and falls smoothly toward 0 as time passes. It is the mathematical shape of "a fixed fraction lost per hour".
- ln undoes the exponential: if y = e^(−k·t), then ln(y) = −k·t, which is a straight line. That is why we plot **ln(C) vs t** — a curving decay becomes a straight line whose slope is −k.
- If your calculator gives log base 10 ($\log_{10}$) instead of ln: ln(x) = 2.303 × $\log_{10}$(x). So a $\log_{10}$ plot has slope = −k/2.303.

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4. Explanation — The One-Compartment Model with First-Order Absorption

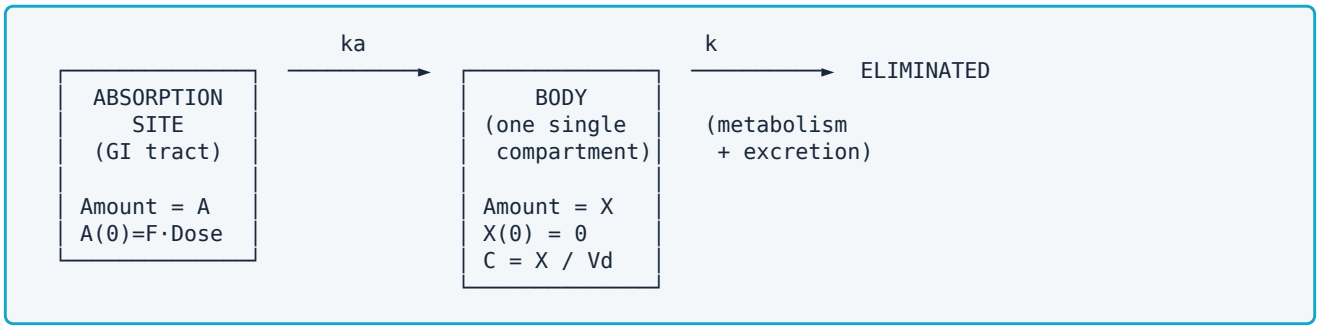
4.1 The picture (technical concept)

After an oral dose, drug sits at the **absorption site** (mainly the GI tract). From there it is absorbed into the single body compartment (blood + tissues behaving as one), and simultaneously the body

eliminates it (metabolism + excretion).

Simple explanation: Imagine a bucket (the body) being filled by a pipe (absorption from the gut) while it also leaks through a hole at the bottom (elimination). The water level (plasma concentration) first rises — because filling is faster at the start — then falls once the pipe runs dry and only the leak remains.

4.2 Diagram (textual)



- Only **F·Dose** (the bioavailable fraction) is available for absorption; the rest is lost (not absorbed / first-pass).
- Both arrows are **first-order**: rate ∝ amount present.

4.3 The differential equations

Amount at absorption site, A(t):

dA/dt = −ka · A, with **A(0) = F·Dose**

(Minus sign: the amount at the site only *decreases*.)

Amount in body, X(t):

dX/dt = ka·A − k·X, with **X(0) = 0**

(Rate in minus rate out. Plasma concentration **C = X / Vd**.)

4.4 Classification box — absorption input types

Type	Rate of absorption	Example	Equation shape
First-order absorption	Proportional to amount remaining at site (ka·A)	Most oral tablets/capsules, IM solutions	Bateman equation (this chapter)
Zero-order absorption	Constant rate (k_0), independent of amount	IV infusion, some controlled-release / transdermal systems	C rises linearly then falls
With lag time	No absorption until tlag, then first-order	Enteric-coated tablets (dissolve only in intestine)	Bateman shifted by tlag

Key takeaway: The extravascular one-compartment model = one input arrow (ka) + one output arrow (k) + the Bateman equation that results.

5. Mechanisms/Derivations — The Bateman Equation, Every Step Shown

Goal: Solve the two differential equations to get C as a function of t.

Step 1 — Solve for A(t) (amount at absorption site)

dA/dt = −ka·A. This is the classic "decay" equation. Its solution:

A(t) = F·Dose · e^(−ka·t)

Simple explanation: The absorbable amount starts at F·Dose and drains away exponentially with rate ka — exactly like a leaking tank.

Step 2 — Put A(t) into the body equation

dX/dt = ka·A − k·X becomes:

dX/dt + k·X = ka·F·Dose · e^(−ka·t)

Simple explanation: The body gains drug from the draining gut (right-hand side, which shrinks with time) and loses drug at rate k·X.

Step 3 — Multiply by the integrating factor e^(k·t)

This is a standard trick to solve "dX/dt + k·X = something" equations. Multiply every term by e^(k·t):

e^(k·t)·dX/dt + k·e^(k·t)·X = ka·F·Dose·e^(k·t)·e^(−ka·t)

The left side is exactly the derivative of a product (by the product rule):

d/dt [X·e^(k·t)] = ka·F·Dose · e^((k − ka)·t)

Simple explanation: We bundled the two left-side terms into one neat derivative — like packing two suitcases into one bag.

Step 4 — Integrate both sides from 0 to t

$\int_0^t$ d/dτ [X·e^(k·τ)] dτ = $\int_0^t$ ka·F·Dose·e^((k−ka)·τ) dτ

Left side: X(t)·e^(k·t) − X(0)·e^0 = X(t)·e^(k·t) − 0 (since X(0) = 0).

Right side: ka·F·Dose × [e^((k−ka)·τ) / (k − ka)]$_0^t$ = ka·F·Dose/(k − ka) · [e^((k−ka)·t) − 1].

So:

X(t)·e^(k·t) = ka·F·Dose/(k − ka) · (e^((k−ka)·t) − 1)

Step 5 — Divide by e^(k·t) and tidy up

X(t) = ka·F·Dose/(k − ka) · (e^(−ka·t) − e^(−k·t))

Multiply numerator and denominator by −1 to get the conventional form (positive denominator, since usually ka > k):

X(t) = ka·F·Dose/(ka − k) · (e^(−k·t) − e^(−ka·t))

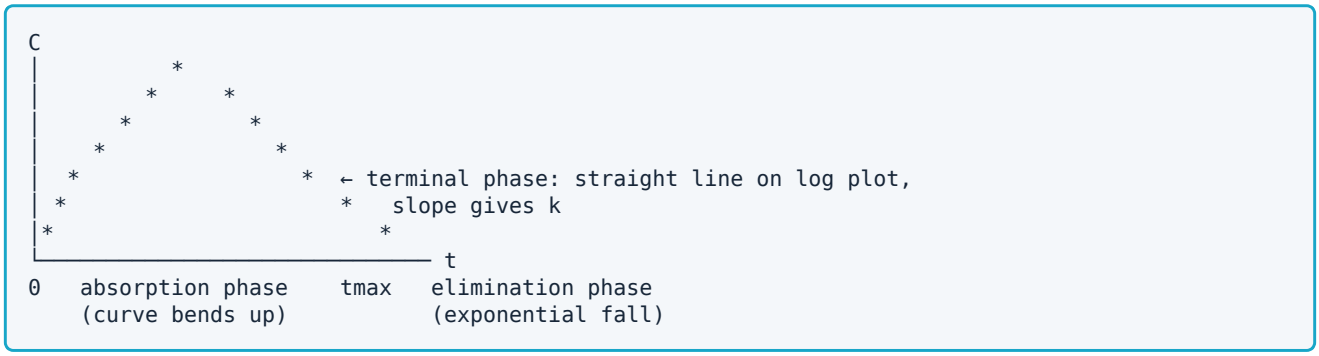
Step 6 — Convert amount to concentration: C = X / Vd

C(t) = ka·F·Dose / [Vd·(ka − k)] · (e^(−k·t) − e^(−ka·t)) ✓ — the Bateman equation

Reading the Bateman equation (from zero)

- **ka·F·Dose / [Vd·(ka − k)]** — a constant "height factor". Bigger dose or bioavailability → taller curve; bigger Vd → shorter curve.
- **(e^(−k·t) − e^(−ka·t))** — the shape. At t = 0 both exponentials equal 1, so C = 0 (nothing absorbed yet). Early on, e^(−ka·t) falls faster (ka > k), so the bracket grows → C rises. Late, e^(−ka·t) ≈ 0 and C falls as e^(−k·t) → the terminal phase shows elimination.
- The curve **rises, peaks, then falls** — the classic oral plasma profile.

5.1 Example curve shape (textual diagram)



Key takeaway: The Bateman equation is just "gut drains exponentially into body, body drains exponentially out" — solved with one clever multiplication (the integrating factor).

6. Lag Time (tlag)

Technical concept: Real tablets need time to disintegrate, dissolve, and travel to the absorbing region. No drug appears in plasma before tlag.

Simple explanation: It is like the few seconds between turning on a tap and water reaching the end of a long hose. Nothing comes out during that dead time.

How to handle it in equations: Nothing happens before tlag; after tlag the Bateman clock starts:

- C(t) = 0 for t < tlag
- For t ≥ tlag: replace every t in the Bateman equation by **(t − tlag)**:

C(t) = ka·F·Dose/[Vd·(ka − k)] · (e^(−k·(t−tlag)) − e^(−ka·(t−tlag))), t ≥ tlag

Consequences: tmax measured from the moment of dosing becomes **tlag + ln(ka/k)/(ka − k)**. On a log plot, the curve is simply shifted right by tlag.

Example: An enteric-coated tablet has tlag ≈ 1 h (no release in the stomach's acid). Its plasma curve looks identical to an immediate-release tablet's curve, just starting 1 hour later.

Key takeaway: Lag time shifts the whole Bateman curve to the right — subtract tlag before applying any Bateman formula.

---

7. tmax and Cmax — Full Derivation

7.1 Deriving tmax (technical concept → steps)

At the peak, the curve is flat: **dC/dt = 0**. Differentiate the Bateman equation. (The constant in front doesn't matter for finding where the slope is zero.)

C(t) = A·(e^(−k·t) − e^(−ka·t)), where A = ka·F·Dose/[Vd·(ka − k)].

Step 1 — Differentiate term by term. Rule: d/dt [e^(−k·t)] = −k·e^(−k·t).

dC/dt = A·(−k·e^(−k·t) − (−ka·e^(−ka·t))) = A·(−k·e^(−k·t) + ka·e^(−ka·t))

Step 2 — Set equal to zero and cancel A (A ≠ 0):

−k·e^(−k·tmax) + ka·e^(−ka·tmax) = 0

ka·e^(−ka·tmax) = k·e^(−k·tmax)

Simple explanation: At the peak, the absorption rate into blood exactly equals the elimination rate out of blood — inflow = outflow, so the level momentarily stops changing.

Step 3 — Collect the exponentials on one side. Divide both sides by k·e^(−ka·tmax):

ka/k = e^(−k·tmax) / e^(−ka·tmax) = e^(−k·tmax + ka·tmax) = e^((ka − k)·tmax)

Step 4 — Take the natural log of both sides:

ln(ka/k) = (ka − k)·tmax

tmax = ln(ka/k) / (ka − k) ✓

Alternative form: tmax = [ln(ka) − ln(k)] / (ka − k). (Same thing, since ln(a/b) = ln a − ln b.)

7.2 Computing Cmax

Put tmax back into the Bateman equation:

Cmax = ka·F·Dose/[Vd·(ka − k)] · (e^(−k·tmax) − e^(−ka·tmax))

Handy shortcut: From Step 2 above, ka·e^(−ka·tmax) = k·e^(−k·tmax), so e^(−ka·tmax) = (k/ka)·e^(−k·tmax). Substituting:

Cmax = ka·F·Dose/[Vd·(ka − k)] · e^(−k·tmax) · (1 − k/ka)

This needs only one exponential — fewer calculator steps, fewer mistakes.

7.3 Special case: what if ka = k?

The formula gives 0/0 (ln(1) = 0 on top, ka − k = 0 below). Taking the mathematical limit:

tmax = 1/k (when ka = k), and C(t) = (F·Dose/Vd)·k·t·e^(−k·t)

Key takeaway: tmax depends *only* on the two rate constants — not on dose, not on Vd. Double the dose and the peak gets twice as tall but arrives at the same time.

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8. Flip-Flop Kinetics — Explained From Zero

8.1 The normal situation (ka > k)

For a normal immediate-release tablet, absorption is fast and elimination is slow (ka > k). The terminal (late) part of the curve is e^(−k·t) — it shows **elimination**. The method of residuals (Section 9) then gives ka from the early "residual" line.

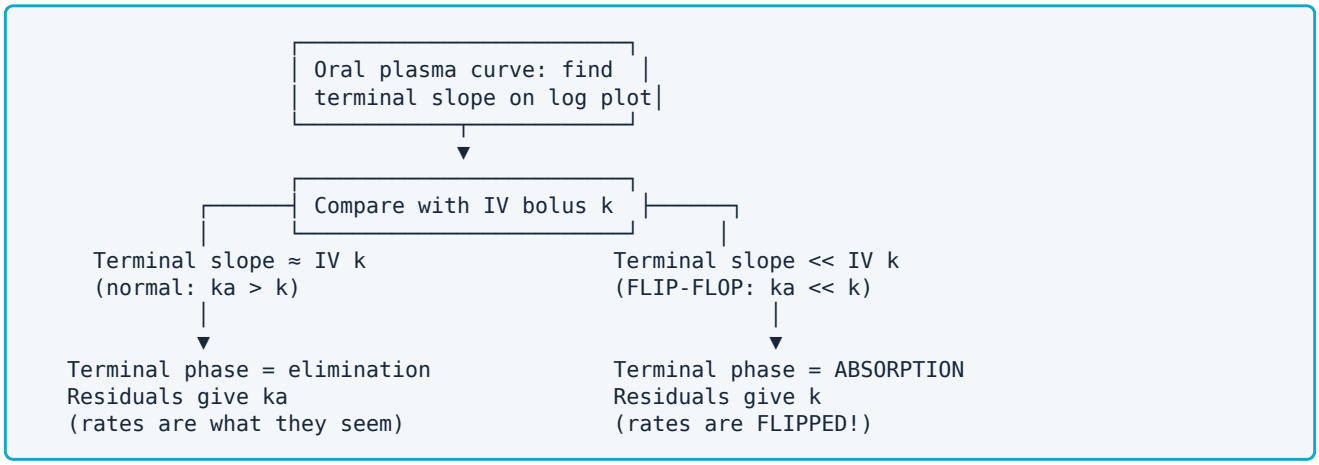
8.2 The flipped situation (ka << k)

Now imagine an **extended-release tablet** or a **depot intramuscular injection** (e.g., a long-acting contraceptive or antipsychotic injection): the drug trickles in very slowly, but once in blood it is eliminated quickly. Here **ka << k** — absorption is the slow, rate-limiting step.

Look at the Bateman bracket: (e^(−k·t) − e^(−ka·t)). If ka << k, then e^(−k·t) dies out *first*, and at late times only e^(−ka·t) survives. So the terminal phase now has slope **−ka**, not −k!

Simple explanation: Picture the bucket again. Normally the pipe fills fast and the leak is slow — the late water level falls at the leak's pace (k). In flip-flop, the pipe drips very slowly while the leak is wide — the water level now falls at the *drip's* pace (ka). The slow step always controls what you see late in the curve.

Flowchart — which rate constant does the terminal phase show?



8.3 Why it matters (pharmacy relevance)

- If you naively read the terminal half-life of a sustained-release product as the "elimination half-life", you will be wrong — you are actually measuring how slowly the formulation releases drug.
- Flip-flop is *expected and intended* in modified-release and depot products: the formulation, not the body's enzymes, controls how long drug stays in blood.

8.4 Example

An IV bolus of a drug shows elimination half-life 2 h (k = 0.347 h^{-1}). The same drug as an extended-release capsule shows a terminal half-life of 10 h. Since 10 h >> 2 h, this is flip-flop: the 10 h half-life is the *absorption* half-life (ka = 0.693/10 = 0.069 h^{-1}). The formulation releases drug slowly — exactly as designed.

Key takeaway: The terminal slope always shows the *slower* of the two processes. If absorption is slower, the rate constants flip: terminal = ka, residuals = k.

CALCULATION BOX 1 — Bateman tmax and Cmax

Problem: A 500 mg tablet is given orally. F = 0.8, Vd = 50 L, ka = 1.0 h^{-1}, k = 0.2 h^{-1}. No lag time. Find tmax and Cmax.

Step 1 — Write down what is known: Dose = 500 mg; F = 0.8; Vd = 50 L; ka = 1.0 h^{-1}; k = 0.2 h^{-1}.

Step 2 — tmax = ln(ka/k) / (ka − k): ka/k = 1.0 / 0.2 = 5. ln(5) = 1.609. ka − k = 1.0 − 0.2 = 0.8 h^{-1}. tmax = 1.609 / 0.8 = **2.01 h**.

Step 3 — Height factor A = ka·F·Dose / [Vd·(ka − k)]: Numerator: 1.0 × 0.8 × 500 = 400. Denominator: 50 × 0.8 = 40. A = 400 / 40 = 10 mg/L.

Step 4 — Cmax using the shortcut Cmax = A · e^(−k·tmax) · (1 − k/ka): e^(−k·tmax) = e^(−0.2 × 2.01) = e^(−0.402) = 0.669. (1 − k/ka) = 1 − 0.2/1.0 = 0.8. Cmax = 10 × 0.669 × 0.8 = **5.35 mg/L**.

Check by full Bateman: C(2.01) = 10 × (e^(−0.402) − e^(−2.01)) = 10 × (0.669 − 0.134) = 10 × 0.535 = 5.35 mg/L ✓

Answer: tmax ≈ 2.0 h, Cmax ≈ 5.35 mg/L.

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9. Curve Fitting — Method of Residuals (Feathering/Stripping)

9.1 Purpose (technical concept)

We have real blood-sample data (C at several times) after an oral dose. We want to work *backwards* to find ka and k — the two rate constants that produced the curve. The Bateman equation has both exponentials mixed together, so we "peel" them apart.

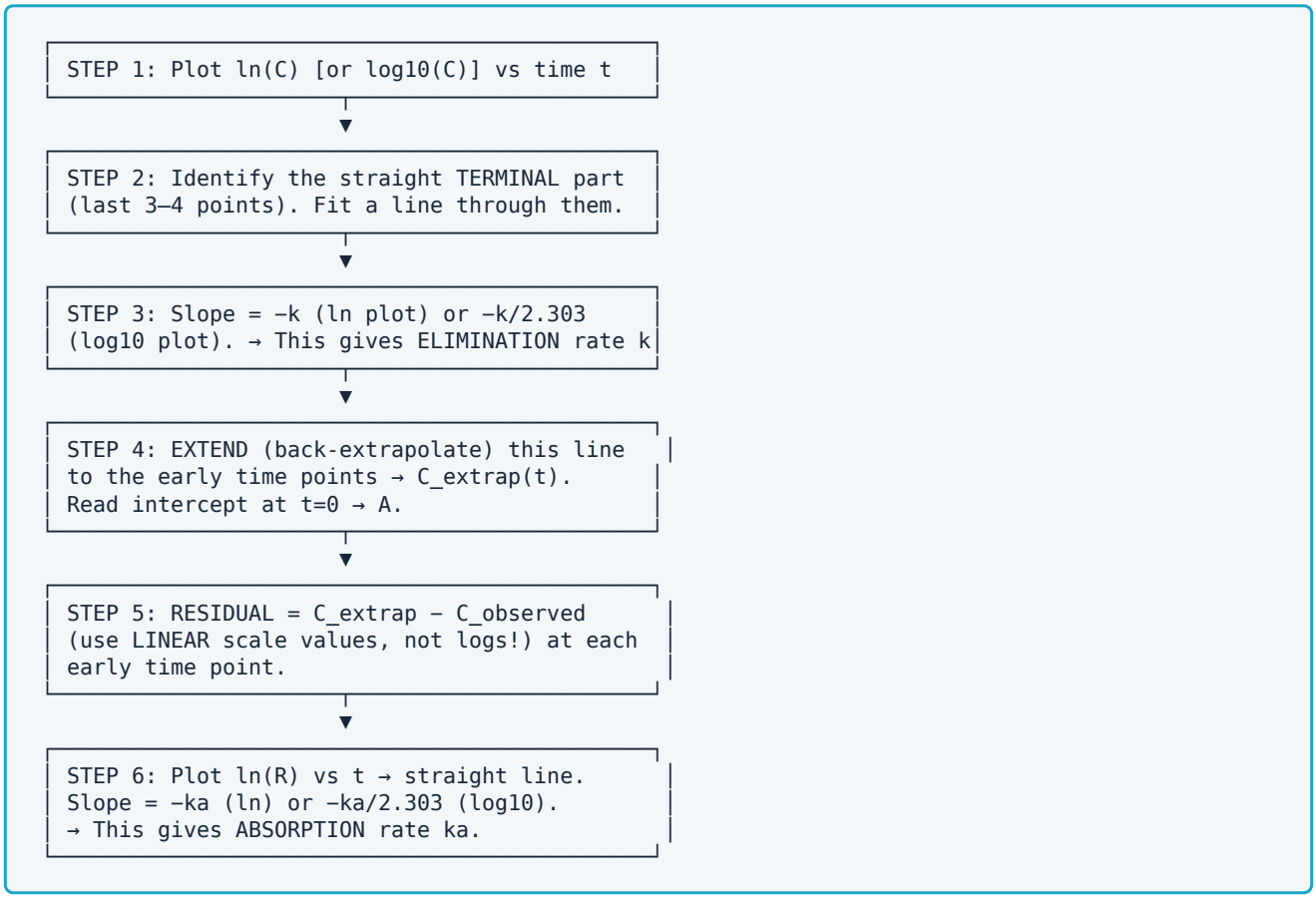
Simple explanation: The oral curve is two exponentials glued together. At late times, the fast one (absorption, ka) has finished, so the tail is a pure single exponential (elimination, k). We measure the tail, extend it backwards, and subtract it from the early data — the *leftover* ("residual") is the pure absorption exponential. Like hearing two singers, waiting till one stops, recording the other alone, then subtracting to isolate the first voice.

9.2 Why the math works

C(t) = A·e^(−k·t) − A·e^(−ka·t), where A = ka·F·Dose/[Vd·(ka−k)].

- **Late times:** e^(−ka·t) ≈ 0 (absorption over), so C ≈ A·e^(−k·t). On a log plot this is a straight line → slope gives **k**, and extrapolating back to t = 0 gives intercept **A**.
- **Residual:** R(t) = (extrapolated late line) − (observed C) = A·e^(−k·t) − [A·e^(−k·t) − A·e^(−ka·t)] = **A·e^(−ka·t)**. On a log plot, residuals form a straight line → slope gives **ka**.

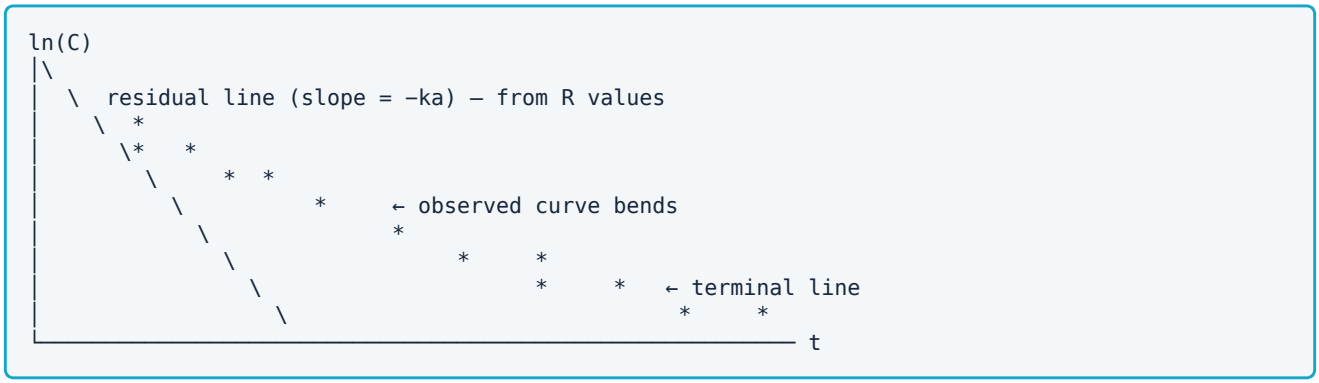
9.3 Flowchart — step-by-step procedure



Golden rules:

- Use **at least 3 points** for each line.
- Residuals must be calculated from **linear-scale** concentrations (never subtract logs!).
- Only the **early** points (before the peak region ends) give valid residuals; late residuals are tiny and noisy — ignore them.

9.4 Diagram — what the feathering plot looks like (textual)



The terminal line is extended back (dashed); the vertical gap between it and the observed points = residuals, which themselves form the steeper residual line.

CALCULATION BOX 2 — ka by Method of Residuals (worked example)

Problem: A 500 mg oral dose gives the following plasma concentrations. Estimate k and ka by the method of residuals.

t (h)	1	2	4	6	8	10	12
C (µg/mL)	6.72	7.80	6.49	4.87	3.61	2.68	1.98

Step 1 — Terminal line (use t = 6, 8, 10, 12 h): ln(C): ln(4.87) = 1.583; ln(3.61) = 1.284; ln(2.68) = 0.986; ln(1.98) = 0.683. Slope between t=6 and t=12: (0.683 − 1.583)/(12 − 6) = −0.900/6 = −0.15 h^{-1}. So **k = 0.15 h^{-1}**. (Terminal half-life = 0.693/0.15 = 4.6 h.)

Step 2 — Extrapolate the terminal line back. The line is ln(C) = ln(A) − 0.15·t. Using t=12: 0.683 = ln(A) − 1.8 → ln(A) = 2.483 → **A = 12.0 µg/mL** (intercept). Extrapolated values C_extrap = 12.0·e^(−0.15·t):

- t=1: 12.0 × e^(−0.15) = 12.0 × 0.8607 = 10.33
- t=2: 12.0 × e^(−0.30) = 12.0 × 0.7408 = 8.89
- t=4: 12.0 × e^(−0.60) = 12.0 × 0.5488 = 6.59

Step 3 — Residuals R = C_extrap − C_observed (linear scale!):

- t=1: 10.33 − 6.72 = 3.61
- t=2: 8.89 − 7.80 = 1.09
- t=4: 6.59 − 6.49 = 0.10

Step 4 — Plot ln(R) vs t: ln(3.61) = 1.284; ln(1.09) = 0.086; ln(0.10) = −2.30. Slope between t=1 and t=2: (0.086 − 1.284)/(2 − 1) = −1.198 ≈ **−1.2 h^{-1}**. So **ka = 1.2 h^{-1}**. (Absorption half-life = 0.693/1.2 = 0.58 h — absorption much faster than elimination, as expected.)

Verification: With ka = 1.2, k = 0.15, A = 12: tmax = ln(1.2/0.15)/1.05 = ln(8)/1.05 = 2.079/1.05 = 1.98 h — matches the observed peak near t = 2 h ✓

Answer: k = 0.15 h^{-1}, ka = 1.2 h^{-1}.

9.5 When the method of residuals FAILS

Situation	What goes wrong	Why (simple words)
ka ≈ k	The two exponentials are nearly identical; residuals are tiny and the residual line is too short/noisy to measure	You are trying to separate two voices singing almost the same note — subtraction leaves nearly nothing
ka < k (flip-flop)	The method still "works" but the labels swap: terminal slope = ka, residual slope = k	The slow singer (absorption) is the one still singing at the end
Too few early points	Residual line has only 1–2 points — unreliable slope	Can't draw a trustworthy line through one dot

Situation	What goes wrong	Why (simple words)
Lag time ignored	Early residuals distorted; ka underestimated	The clock started late but you measured from time zero
Multi-compartment drug	Terminal phase is a mix of distribution + elimination; neither line is pure	The song has three singers, not two — need Loo–Riegelman thinking

Key takeaway: Feathering peels the curve into "late = slow process, residuals = fast process". It needs the two rates to be clearly different (ka at least ~2–3× k) and plenty of early data points.

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10. Wagner–Nelson Method — Fraction Absorbed vs Time

10.1 Purpose (technical concept)

After an oral dose we can *see* drug in blood, but we want to know the **absorption profile**: what fraction of the dose has been absorbed at each time point? This is the *input* function — crucial for comparing formulations (e.g., is the generic absorbed at the same speed as the brand?) and for building in-vitro/in-vivo correlations (IVIVC).

Simple explanation: Blood concentration is the *result* of absorption minus elimination. Wagner–Nelson does clever bookkeeping: "drug absorbed so far = drug still in the body now + drug the body has already eliminated." Both terms on the right can be calculated from the plasma curve — so we recover the absorption story from blood data alone. No IV data needed.

10.2 Full derivation — every step shown

Setup: One-compartment body. Let **A(t)** = cumulative amount of drug absorbed into the body up to time t (this is what we want). Let X(t) = amount in the body now, eliminated with rate constant k.

Step 1 — Write the mass balance rate equation. Rate of change of body amount = (rate absorbed in) − (rate eliminated out):

$$\frac{dX}{dt} = \frac{dA}{dt} - k \cdot X$$

Step 2 — Rearrange to isolate the absorption rate:

$$\frac{dA}{dt} = \frac{dX}{dt} + k \cdot X$$

Simple explanation: What entered = what stayed + what left. Obvious once said aloud!

Step 3 — Integrate both sides from 0 to t.

Left: $\int_0^t \left(\frac{dA}{d\tau}\right)d\tau = A(t) - A(0) = A(t) - 0 = A(t)$. (Nothing absorbed at time zero.)

Right, first term: $\int_0^t \left(\frac{dX}{d\tau}\right)d\tau = X(t) - X(0) = X(t) - 0 = X(t)$.

Right, second term: $k \cdot \int_0^t X(\tau)d\tau = k \times$ (area under the *amount*-vs-time curve from 0 to t).

So: **$A(t) = X(t) + k \cdot (\text{AUC of } X)_0^t$**

Step 4 — Divide everything by Vd (since X = Vd·C, and AUC of X = Vd × AUC of C):

$A(t)/Vd = C(t) + k \cdot AUC_0^t$ ✓ — the Wagner–Nelson equation

Reading it: (absorbed so far, as a concentration) = (in blood now) + k × (exposure so far, which measures what was eliminated).

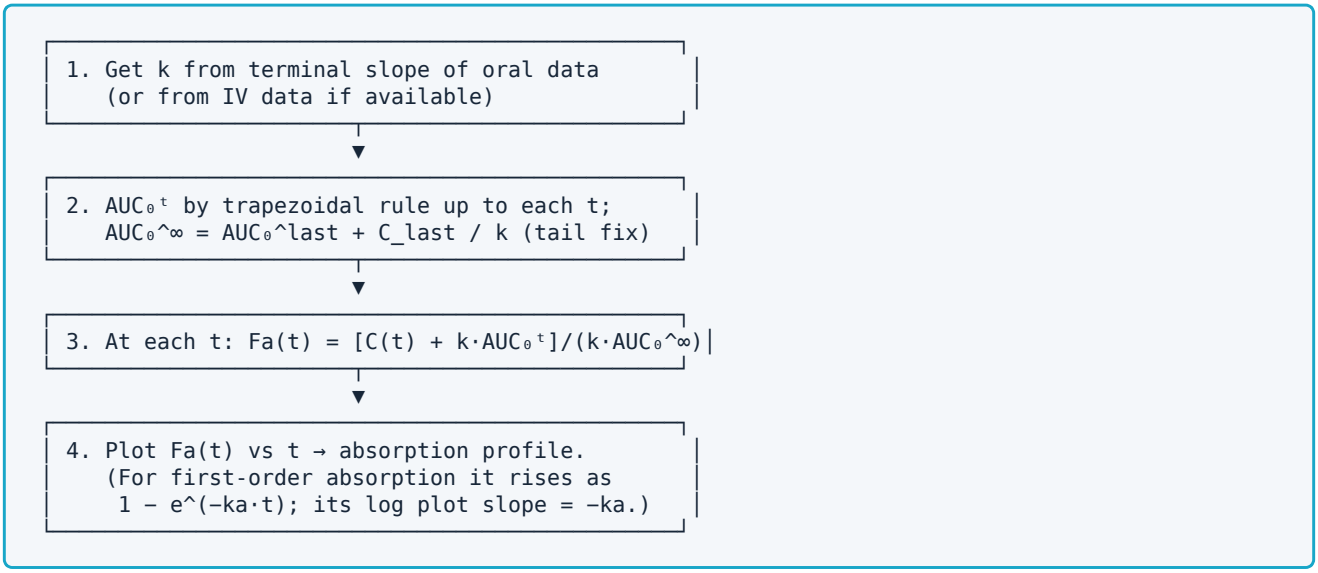
Step 5 — Total absorbed at infinite time. As t → ∞, all drug is eliminated: X(∞) = 0, i.e., C(∞) = 0. So:

$A(\infty)/Vd = k \cdot AUC_0^{\infty}$

Step 6 — Fraction absorbed:

$Fa(t) = A(t)/A(\infty) = [\ C(t) + k \cdot AUC_0^t\ ] / [\ k \cdot AUC_0^{\infty}\ ]$ ✓

10.3 How to use it — flowchart



Assumptions (must hold): one-compartment behaviour; k is constant (linear pharmacokinetics); F and Vd don't change during absorption.

CALCULATION BOX 3 — Wagner–Nelson Fraction Absorbed

Problem: Using the data from Calculation Box 2 (k = 0.15 h^{-1}), find the fraction of drug absorbed at t = 2 h.

t (h)	0	1	2	4	6	8	10	12
C (µg/mL)	0	6.72	7.80	6.49	4.87	3.61	2.68	1.98

Step 1 — AUC_0^2 by trapezoidal rule:

- 0→1 h: (0 + 6.72)/2 × 1 = 3.36

- 1→2 h: (6.72 + 7.80)/2 × 1 = 7.26
- **AUC_0^2 = 3.36 + 7.26 = 10.62 µg·h/mL**

Step 2 — AUC_0^∞ (need the full curve first):

- 2→4: (7.80+6.49)/2 × 2 = 14.29; 4→6: (6.49+4.87)/2 × 2 = 11.36
- 6→8: (4.87+3.61)/2 × 2 = 8.48; 8→10: (3.61+2.68)/2 × 2 = 6.29
- 10→12: (2.68+1.98)/2 × 2 = 4.66
- AUC_0^{12} = 10.62 + 14.29 + 11.36 + 8.48 + 6.29 + 4.66 = 55.70
- Tail: AUC_{12}^∞ = C_last/k = 1.98/0.15 = 13.20
- **AUC_0^∞ = 55.70 + 13.20 = 68.90 µg·h/mL**

Step 3 — Wagner–Nelson at t = 2 h: Fa(2) = [C(2) + k·AUC_0^2] / [k·AUC_0^∞] = [7.80 + 0.15 × 10.62] / [0.15 × 68.90] = [7.80 + 1.59] / 10.335 = 9.39 / 10.335 = **0.909 → 90.9%**

Sanity check: True absorption was first-order with ka = 1.2 h^{-1}, so true Fa(2) = 1 − e^(−1.2×2) = 1 − 0.0907 = 0.909 ✓ — the method recovers the truth!

(For reference: Fa(1 h) = 69.9%, Fa(4 h) = 99.0% — absorption essentially complete by 4 h.)

Answer: ≈ 91% of the absorbable dose is absorbed by 2 h.

> **Key takeaway:** Wagner–Nelson = "absorbed = present + eliminated". It needs only oral data + k, and it reconstructs the hidden absorption profile.

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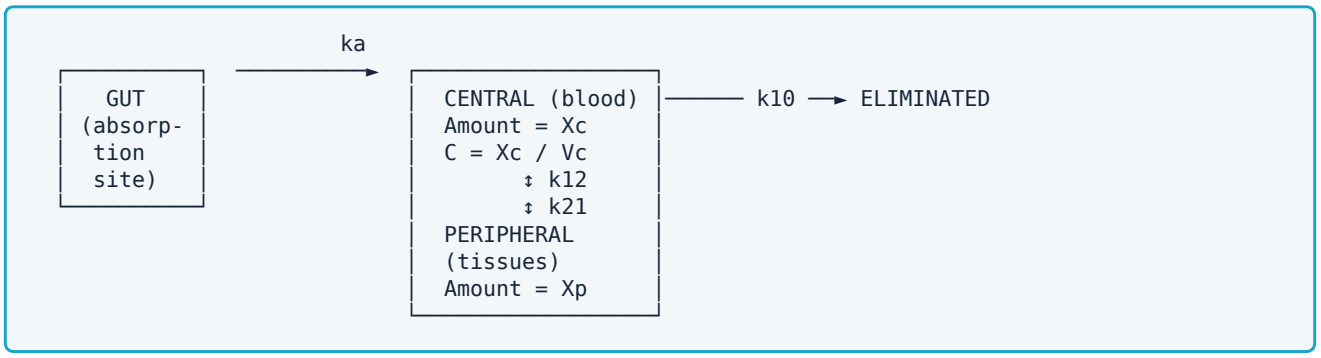
11. Loo–Riegelman Method — For Two-Compartment Drugs

11.1 Why Wagner–Nelson is not enough (technical concept)

Wagner–Nelson assumes the body is **one** compartment: drug is either in blood or eliminated. But many drugs distribute into a **peripheral compartment** (muscles, fat, other tissues). Mid-way through the profile, a large chunk of absorbed drug is *sitting in tissues* — neither in blood nor eliminated. W–N ignores it and therefore **underestimates** how much has been absorbed.

Simple explanation: Counting money: W–N counts "cash in wallet + cash already spent" and calls it total income. But if you also lent cash to a friend (tissues), W–N misses it and your income looks smaller than it really is. Loo–Riegelman adds "cash lent to friend" — the **Xp(t)/Vc** correction term.

11.2 The two-compartment picture (diagram, textual)



- k12: central → peripheral; k21: peripheral → central; k10: elimination from central.
- These three constants come from an **IV bolus study** of the same drug (biexponential fit): if IV data fit C = A·e^(−α·t) + B·e^(−β·t), then k21 = (A·β + B·α)/(A + B), k10 = α·β/k21, k12 = α + β − k21 − k10.

11.3 Full derivation — every step shown

Step 1 — Mass balance: account for every molecule. Cumulative absorbed A(t) must equal drug in central + drug in peripheral + drug eliminated so far:

$$A(t) = Xc(t) + Xp(t) + k10 \cdot \int_0^t Xc(\tau)d\tau$$

Simple explanation: Income = wallet + lent to friend + spent. Nothing else exists.

Step 2 — Divide by Vc (central volume; Xc = Vc·C):

$$\mathbf{A(t)/Vc = C(t) + k10 \cdot AUC_0^t + Xp(t)/Vc} \checkmark$$ — the Loo–Riegelman equation

Compare with W–N: identical, **plus the tissue correction term Xp(t)/Vc**.

Step 3 — Find Xp(t) from the blood data. The peripheral compartment obeys:

$$dXp/dt = k12 \cdot Xc - k21 \cdot Xp$$

Simple explanation: Tissues gain drug from blood (k12·Xc) and return it (k21·Xp). Solving gives a "memory" formula — tissue amount now depends on the whole past blood history:

$$Xp(t) = k12 \cdot \int_0^t Xc(\tau) \cdot e^{(-k21 \cdot (t-\tau))}\, d\tau$$

Simple explanation of the integral: Each past moment τ contributed drug k12·Xc(τ), but only the fraction e^(−k21·(t−τ)) of it is still there now (the rest returned to blood). Add up all past contributions.

Step 4 — Practical step-by-step computation (interval by interval, Δt apart):

$$Xp_{new} = Xp_{old} \cdot e^{(-k21 \cdot \Delta t)} + [k12 \cdot \bar{X}c/k21] \cdot (1 - e^{(-k21 \cdot \Delta t)})$$

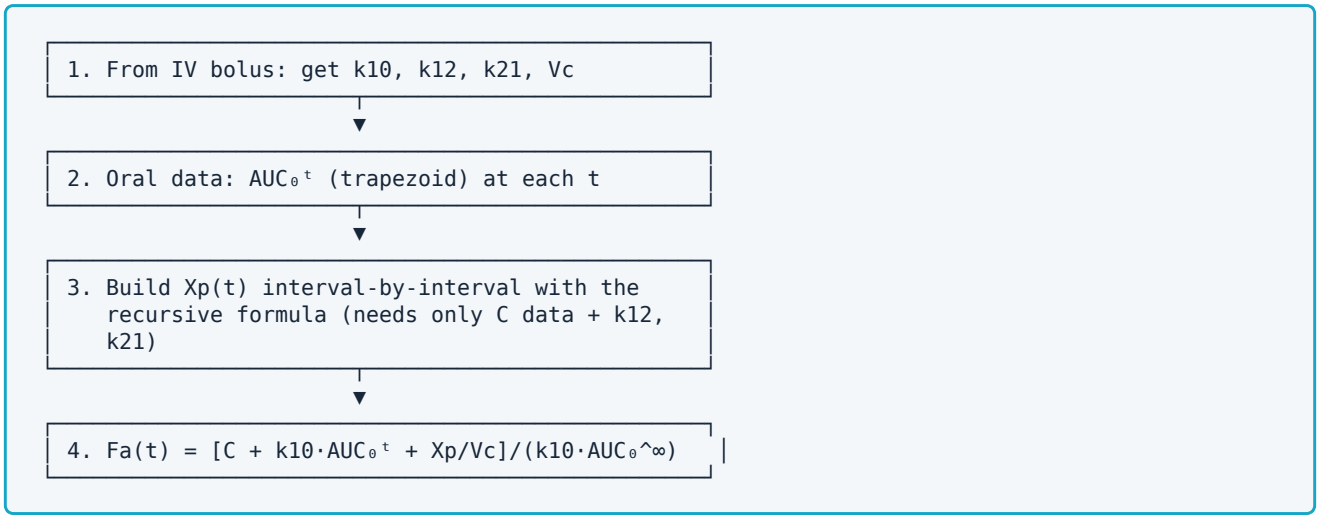
where $\bar{X}c$ = average central amount (Vc × average C) in that interval. *Simple explanation:* Old tissue drug partly returns (first term); new drug arrives based on average blood level (second term).

Step 5 — Total absorbed: At t → ∞, Xc = Xp = 0, so $A(\infty)/Vc = k10 \cdot AUC_0^{\infty}$. Hence:

Fa(t) = [C(t) + k10·AUC₀ᵗ + Xp(t)/Vc] / [k10·AUC₀^∞] ✓

Requirements: IV bolus data to get k10, k12, k21 (W–N needed only oral data — this is the price of the correction).

11.4 Flowchart — Loo–Riegelman procedure



CALCULATION BOX 4 — Loo–Riegelman Corrected Absorption

Problem: A drug follows two-compartment kinetics. From IV bolus: k10 = 0.30 h^{-1}, k12 = 0.40 h^{-1}, k21 = 0.50 h^{-1}, Vc = 20 L. A 400 mg oral dose (F = 1) gives:

t (h)	0	1	2	3
C (mg/L)	0	8.1	8.2	7.1

Find the fraction absorbed at t = 3 h by Loo–Riegelman, and compare with naive Wagner–Nelson.

Step 1 — AUC_0^3 (trapezoid): (0+8.1)/2 × 1 + (8.1+8.2)/2 × 1 + (8.2+7.1)/2 × 1 = 4.05 + 8.15 + 7.65 = **19.85 mg·h/L**

Step 2 — Build Xp(t). Useful numbers: e^(−k21·Δt) = e^(−0.5×1) = 0.6065; (1 − 0.6065) = 0.3935. Central amounts Xc = C × Vc: Xc(0)=0, Xc(1)=162, Xc(2)=164, Xc(3)=142 mg.

- Interval 0→1: $\bar{X}c$ = (0+162)/2 = 81.

Xp(1) = 0 + (0.40 × 81 / 0.50) × 0.3935 = 64.8 × 0.3935 = **25.5 mg**

- Interval 1→2: $\bar{X}c$ = (162+164)/2 = 163.

Xp(2) = 25.5 × 0.6065 + (0.40 × 163 / 0.50) × 0.3935 = 15.47 + 130.4 × 0.3935 = 15.47 + 51.31 = **66.8 mg**

- Interval 2→3: $\bar{X}c$ = (164+142)/2 = 153.

Xp(3) = 66.8 × 0.6065 + (0.40 × 153 / 0.50) × 0.3935 = 40.51 + 122.4 × 0.3935 = 40.51 + 48.16 = **88.7 mg**

Step 3 — Loo-Riegelman at t = 3 h: A(3)/Vc = C(3) + k10·AUC_0^3 + Xp(3)/Vc = 7.1 + 0.30 × 19.85 + 88.7/20 = 7.1 + 5.96 + 4.44 = **17.50 mg/L** Total absorbable/Vc = F·Dose/Vc = 400/20 = 20 mg/L. **Fa(3) = 17.50/20 = 0.875 → 87.5%** ✓

Step 4 — Compare with naive Wagner–Nelson (using terminal slope β ≈ 0.142 h^{-1} as "k"): A(3)/Vc = 7.1 + 0.142 × 19.85 = 7.1 + 2.82 = 9.92 mg/L → Fa ≈ **49.6%** ✗ — a gross underestimate!

Answer: Loo–Riegelman gives ≈ 88% absorbed at 3 h; Wagner–Nelson wrongly gives ≈ 50% because it ignores the 4.44 mg/L sitting in tissues.

> **Key takeaway:** For two-compartment drugs, always add the tissue term Xp/Vc — otherwise you "lose" the drug hiding in peripheral tissues.

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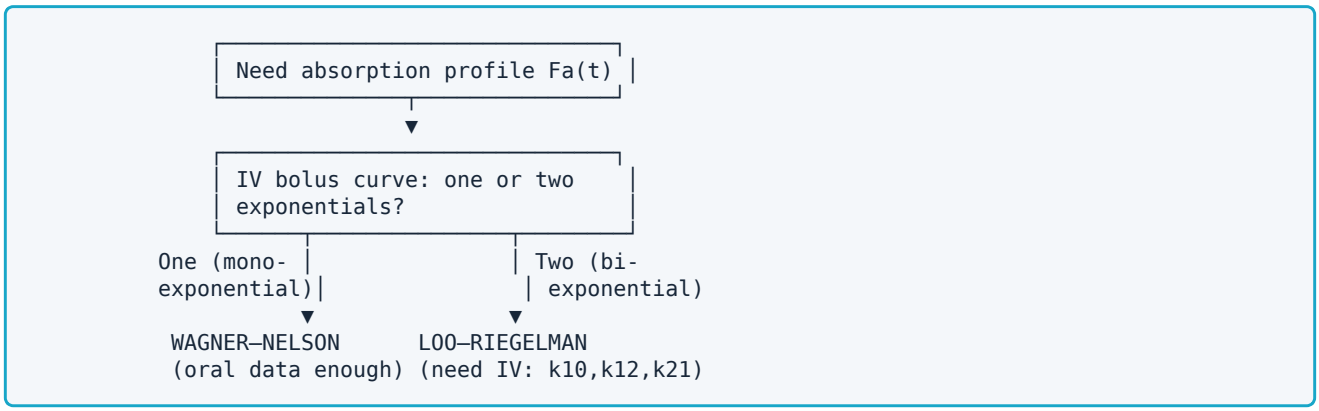
12. Classification — Choosing the Right Method (comparison table)

Feature	Wagner–Nelson	Loo-Riegelman
Body model	**One-compartment**	**Two-compartment**
Data needed	Oral plasma data only (+ k)	Oral data **+ IV bolus data** (for k10, k12, k21)
Key equation	A(t)/Vd = C(t) + k·AUC_0^t	A(t)/Vc = C(t) + k10·AUC_0^t + **Xp(t)/Vc**
Tissue drug	Ignored (assumed zero)	Corrected via Xp(t)
When to use	Drug shows one-compartment behaviour	Drug shows distribution phase (biexponential IV curve)
Error if misapplied	Fine for 1-cpt drugs	W–N on 2-cpt drug → **underestimates** Fa mid-profile

Decision flowchart:



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13. Analogy Box — The Whole Chapter in One Story

The wedding feast analogy. The kitchen (gut) sends out dishes (drug) to the dining hall (blood) at some serving speed (ka). Guests eat dishes (elimination, k). A photographer counting *dishes on tables right now* (C) cannot directly see the serving speed — but if she also counts *empty plates cleared* (k·AUC), she reconstructs servings: **served = on tables + cleared (Wagner–Nelson)**. But if some dishes were carried to a *second hall* (tissues, Xp) that she never checks, her count is short — she must add **dishes in the second hall (Loo–Riegelman)**. And if the kitchen serves slower than guests eat (flip-flop), the tables empty at the *serving* pace, not the eating pace.

14. Pharmacy Relevance

1. **Formulation comparison:** Fa(t) profiles let formulators compare how fast different tablet formulations release drug — the backbone of **bioequivalence** decisions for generics.
2. **IVIVC (in-vitro/in-vivo correlation):** The W–N absorption profile is plotted against % drug dissolved in the lab dissolution test. A good correlation means the dissolution test can *predict* blood levels — saving expensive human trials for minor formulation changes.
3. **Modified-release design:** Flip-flop analysis tells whether a sustained-release product is truly release-rate-controlled (desired) or just slowly eliminated.
4. **Dose timing:** tmax tells clinicians when to expect peak effect (and peak side effects) after an oral dose.
5. **Method of residuals in practice:** Still the quickest way to get ka from a pilot oral study before full compartmental modelling software is used.

15. India Context

- India is among the world's largest manufacturers of **generic medicines**; every generic oral product must show bioequivalence with the innovator, and absorption-rate analysis (ka, Fa(t) profiles, deconvolution) is part of the pharmacokinetic evaluation reported to regulators such as the **CDSCO**.
- Indian contract research organisations (CROs) conducting BA/BE studies routinely use Wagner–Nelson-type deconvolution when developing **IVIVC for modified-release formulations** (e.g., extended-release antidiabetics and cardiovascular drugs widely made in India) — a faster in-vitro dissolution test that predicts in-vivo absorption saves repeat human studies.
- For B.Pharm students: these methods appear in university exams under "methods to determine absorption kinetics" and in interviews for formulation R&D and clinical pharmacology roles in Indian pharma companies. (No specific company or product claims are made here.)

16. Infographic Concept Box — "The Absorption Detective Kit"

Four tools, one mystery: HOW FAST did the drug get in?

Tool	Question it answers	Needs
Bateman equation	What does the curve *look like*?	ka, k, F, Dose, Vd
✂ **Method of residuals**	What are ka and k *from data*?	Oral C–t data (ka ≠ k)
+ **Wagner–Nelson**	*How much* absorbed *by each time*? (1-cpt)	Oral data + k
Loo–Riegelman	Same, but *tissues included* (2-cpt)	Oral data + IV data

Memory hook: *"Bateman draws it, Residuals peel it, Wagner counts it, Loo corrects it."*

17. Key Points (chapter at a glance)

1 Extravascular one-compartment model: dA/dt = −ka·A; dX/dt = ka·A − k·X; C = X/Vd.

2 **Bateman:** C(t) = ka·F·Dose/[Vd·(ka−k)] · (e^(−k·t) − e^(−ka·t)). Rises, peaks, falls.

3 **tmax = ln(ka/k)/(ka − k)** — depends only on ka and k, not on dose or Vd.

4 **Cmax** = Bateman at tmax; shortcut: A·e^(−k·tmax)·(1 − k/ka).

5 **Lag time:** shift the clock — use (t − tlag); tmax(from dosing) = tlag + ln(ka/k)/(ka−k).

6 **Flip-flop (ka << k):** terminal phase shows *absorption*; residual line gives k. Compare with IV data to detect.

7 **Method of residuals:** terminal line → k; extrapolate back; residuals → ka. Fails when ka ≈ k.

8 **Wagner–Nelson:** A(t)/Vd = C(t) + k·AUC_0^t; Fa(t) = [C(t) + k·AUC_0^t]/[k·AUC_0^∞]. One-compartment only.

9 **Loo–Riegelman:** A(t)/Vc = C(t) + k10·AUC_0^t + Xp(t)/Vc. Adds the tissue term; needs IV data (k10, k12, k21).

10 W–N on a two-compartment drug **underestimates** fraction absorbed — that's exactly when L–R is needed.

18. Common Confusions (cleared)

Confusion	Truth
ka vs k	ka = IN (absorption, gut→blood); k = OUT (elimination, body→urine/metabolism). Different arrows, different numbers.
"Terminal half-life is always elimination half-life"	Only if ka > k. In flip-flop (ka << k) the terminal half-life is the *absorption* half-life.
Fraction absorbed (Fa) vs bioavailability (F)	Fa(t) = how much of the *absorbable* dose is in by time t (goes 0→1). F = what fraction of the *given* dose ever becomes absorbable (a single number, ≤ 1).

Confusion	Truth
Wagner–Nelson vs Loo–Riegelman	W–N: one-compartment, oral data enough. L–R: two-compartment, needs IV data, adds Xp/Vc tissue term.
tmax vs half-life	tmax = time of the *peak* (depends on both ka and k). Half-life = time to fall by half in the terminal phase (depends on one rate).
Residuals: which line is which?	Terminal line (late data) = the SLOW process; residual line (early leftovers) = the FAST process. Normally slow = k, fast = ka; flipped in flip-flop.

19. Common Mistakes (and how to avoid them)

1 ✗ Subtracting log values to get residuals → ✓ Always subtract **linear-scale** concentrations (C_extrap − C_observed), then take logs.

2 ✗ Using $\log_{10}$ slope directly as k → ✓ k = 2.303 × |slope of $\log_{10}$ plot|; k = |slope of ln plot|.

3 ✗ Forgetting the tail correction AUC_last^∞ = C_last/k → ✓ Without it, AUC_0^{∞} (and every Fa) is underestimated.

4 ✗ Applying Wagner–Nelson to a two-compartment drug → ✓ Check IV data first; if biexponential, use Loo–Riegelman.

5 ✗ Sign/denominator error in Bateman → ✓ Denominator is (ka − k) paired with (e^(−k·t) − e^(−ka·t)); both forms are consistent — verify C(0) = 0 as a quick check.

6 ✗ Ignoring lag time for enteric-coated/delayed products → ✓ Shift time by tlag before feathering or fitting.

7 ✗ Reading ka from the terminal phase in flip-flop and calling it "elimination" → ✓ Always compare oral terminal slope with IV elimination data.

20. Mnemonics

- **Bateman's B-A-T:** "**B**oth **A**bsorption and **T**ermination — **E**xponentially **M**inus **A**bsorption **N**et": C ∝ (e^(−k·t) − e^(−ka·t)) — elimination term first, absorption term subtracted.
- **tmax recipe:** "**T**op = **L**n of ratio, **B**ottom = **D**ifference" → tmax = **L**n(ka/k) / (ka−k).
- **Wagner–Nelson in one line:** "**W**hat went in = **W**hat's there + **W**hat went out" → A/Vd = C + k·AUC.
- **Loo–Riegelman:** "**L**oo **L**ooks for **L**urking tissue drug" → add Xp/Vc.
- **Flip-flop:** "**F**ormulation **F**eeds **F**aintly" — when the formulation feeds drug faintly/slowly, the tail follows the feed (ka), not the exit (k).
- **Residuals order:** "**T**ail first, **T**hen **T**race back, **T**ake residuals" — terminal → extrapolate → residuals.

21. Exam Summary (one page)

- **Model:** Gut (A) —ka→ Body (X) —k→ out. dA/dt = −kaA; dX/dt = kaA − kX.

- **Bateman:** C(t) = ka·F·Dose/[Vd(ka−k)]·(e^(−kt) − e^(−kat)). Derived via integrating factor e^(kt).
- **tmax** = ln(ka/k)/(ka−k) (from dC/dt = 0); **Cmax** = Bateman at tmax.
- **Lag time:** use (t − tlag).
- **Flip-flop (ka<<k):** terminal slope = ka; seen in SR tablets, depot injections.
- **Residuals:** log C vs t → terminal line (k) → extrapolate → R = C_extrap − C_obs → log R vs t (ka). Needs ka ≠ k, ka > k normally.
- **Wagner–Nelson:** A(t)/Vd = Ct + k·AUC_0^t; Fa(t) = (Ct + k·AUC_0^t)/(k·AUC_0^∞). One-compartment; oral data enough.
- **Loo–Riegelman:** A(t)/Vc = Ct + k10·AUC_0^t + Xp(t)/Vc; needs IV data (k10, k12, k21); Xp built recursively.

22. One-Minute Revision

Oral one-compartment: Bateman C(t) = ka·F·Dose/[Vd(ka−k)]·(e^(−kt) − e^(−kat)). Peak at tmax = ln(ka/k)/(ka−k). Lag time shifts everything right. If absorption is slower than elimination → flip-flop: terminal phase shows ka. Feathering: terminal line gives k, residuals give ka. Wagner–Nelson: absorbed = in blood + eliminated → Fa = (C + k·AUC_0^t)/(k·AUC_0^∞). Two compartments? Add tissue term Xp/Vc → Loo–Riegelman (needs IV data).

23. Exam Questions

A. MCQs (with answer key)

Q1. In the one-compartment extravascular model with first-order absorption, the Bateman equation is: a) C(t) = (F·Dose/Vd)·e^(−k·t) b) C(t) = ka·F·Dose/[Vd·(ka−k)]·(e^(−k·t) − e^(−ka·t)) c) C(t) = ka·F·Dose/[Vd·(ka+k)]·(e^(−k·t) + e^(−ka·t)) d) C(t) = (F·Dose/Vd)·(1 − e^(−ka·t))

Q2. tmax after oral administration is given by: a) ln(ka·k)/(ka+k) b) ln(ka/k)/(ka−k) c) (ka−k)/ln(ka/k) d) 0.693/k

Q3. Which statement about tmax is TRUE? a) It increases when the dose is doubled b) It depends only on ka and k c) It depends on Vd d) It is always equal to the elimination half-life

Q4. Flip-flop kinetics occurs when: a) ka >> k b) ka << k c) ka = k d) F = 1

Q5. In flip-flop kinetics, the terminal phase of the log plasma curve gives: a) The elimination rate constant k b) The absorption rate constant ka c) The distribution rate constant d) Bioavailability F

Q6. In the method of residuals, the residual at each early time point is calculated as: a) log(C_extrap) − log(C_observed) b) C_extrap − C_observed (linear scale) c) C_observed − C_extrap (linear scale) d) AUC_extrap − AUC_observed

Q7. The method of residuals FAILS when: a) ka is much larger than k b) ka ≈ k c) There are many early data points d) F = 1

Q8. The Wagner–Nelson equation is: a) $A(t)/Vd = C(t) + k \cdot AUC_0^t$ b) $A(t)/Vd = C(t) - k \cdot AUC_0^t$ c) $A(t)/Vc = C(t) + k10 \cdot AUC_0^t + Xp(t)/Vc$ d) $Fa(t) = C(t)/Cmax$

Q9. The Loo–Riegelman method differs from Wagner–Nelson by: a) Not needing the elimination rate constant b) Adding a peripheral-compartment correction term Xp(t)/Vc c) Using only IV data d) Assuming zero-order absorption

Q10. If Wagner–Nelson is applied to a drug that actually follows two-compartment kinetics, the fraction absorbed will be: a) Overestimated b) Underestimated c) Exactly correct d) Equal to bioavailability F

Answer key: Q1–b, Q2–b, Q3–b, Q4–b, Q5–b, Q6–b, Q7–b, Q8–a, Q9–b, Q10–b.

B. Viva Questions

1 What is the Bateman equation, and what does each symbol in it mean?

2 Derive tmax starting from dC/dt = 0. (Expect: ka·e^(−ka·tmax) = k·e^(−ka…tmax) → tmax = ln(ka/k)/(ka−k).)

3 Why does the plasma curve after an oral dose first rise and then fall?

4 What is lag time? How do you adjust the Bateman equation for it?

5 Explain flip-flop kinetics with one real formulation example (e.g., extended-release tablet, depot injection).

6 In the method of residuals, why must residuals be calculated on the linear scale and not from log values?

7 When does the method of residuals fail? What would you do instead?

8 State the Wagner–Nelson equation and its two key assumptions.

9 Why does Wagner–Nelson underestimate absorption for two-compartment drugs?

10 What extra data does Loo–Riegelman need, and why?

C. Application-Based Questions

1 **Formulation troubleshooting:** Two brands of the same drug show identical AUC but Brand B has a later tmax and lower Cmax. Using the Bateman equation, explain which parameter most likely differs between the brands and why AUC is unchanged. *(Hint: ka differs; AUC = F·Dose/(Vd·k) is independent of ka.)*

2 **IVIVC project:** You must show that a new dissolution test predicts in-vivo absorption of a modified-release tablet. Outline how you would use the Wagner–Nelson method and the dissolution data to build the correlation, and state when you would switch to Loo–Riegelman.

3 **Depot injection:** A monthly depot antipsychotic injection shows a terminal half-life of 25 days, but the IV drug's half-life is 20 hours. Is this flip-flop? What does the 25-day half-life actually measure, and why is this desirable for the product?

D. Numerical Problems (with fully worked solutions)

N1. tmax/Cmax with lag time. A 250 mg enteric-coated tablet: F = 0.9, Vd = 40 L, ka = 0.8 h^{-1}, k = 0.25 h^{-1}, tlag = 0.5 h. Find tmax (from dosing) and Cmax.

Solution:

- tmax = tlag + ln(ka/k)/(ka − k) = 0.5 + ln(0.8/0.25)/(0.8 − 0.25) = 0.5 + ln(3.2)/0.55 = 0.5 + 1.1632/0.55 = 0.5 + 2.115 = **2.62 h**.
- Height factor A = ka·F·Dose/[Vd·(ka−k)] = (0.8 × 0.9 × 250)/(40 × 0.55) = 180/22 = 8.182 mg/L.
- Effective time for Cmax = tmax − tlag = 2.115 h.
- Cmax = 8.182 × (e^(−0.25×2.115) − e^(−0.8×2.115)) = 8.182 × (e^(−0.5288) − e^(−1.692)) = 8.182 × (0.5892 − 0.1842) = 8.182 × 0.4050 = **3.31 mg/L**.
- **Answer: tmax ≈ 2.6 h from dosing; Cmax ≈ 3.3 mg/L.**

N2. Detecting flip-flop. IV bolus of Drug X: elimination half-life = 2 h. Extended-release capsule of X: terminal half-life = 10 h. (a) Is this flip-flop? (b) Calculate ka and k.

Solution:

- k (true elimination) = 0.693/2 = **0.347 h^{-1}**.
- Terminal slope of oral curve (0.693/10 = 0.0693 h^{-1}) is much smaller than IV k → **yes, flip-flop**: absorption is rate-limiting.
- ka = 0.693/10 = **0.069 h^{-1}** (the terminal phase measures absorption here).
- **Answer: Flip-flop confirmed; k = 0.35 h^{-1}, ka = 0.069 h^{-1}. The 10 h "half-life" is the absorption half-life — the formulation controls duration, as intended.**

N3. Wagner–Nelson from scratch. A 200 mg oral dose (k = 0.10 h^{-1}) gives: t = 1, 2, 4, 8, 12 h with C = 3.0, 4.2, 4.8, 3.6, 2.4 µg/mL. Calculate the fraction absorbed at t = 4 h.

Solution:

- AUC_0^4 = (0+3.0)/2×1 + (3.0+4.2)/2×1 + (4.2+4.8)/2×2 = 1.50 + 3.60 + 9.00 = **14.10 µg·h/mL**.
- AUC_4^12 = (4.8+3.6)/2×4 + (3.6+2.4)/2×4 = 16.80 + 12.00 = 28.80.
- AUC_0^12 = 14.10 + 28.80 = 42.90. Tail = C_last/k = 2.4/0.10 = 24.00.
- AUC_0^∞ = 42.90 + 24.00 = **66.90 µg·h/mL**.
- Fa(4) = [C(4) + k·AUC_0^4]/[k·AUC_0^∞] = [4.8 + 0.10×14.10]/[0.10×66.90] = [4.8 + 1.41]/6.69 = 6.21/6.69 = **0.928 → 92.8%**.
- **Answer: ≈ 93% absorbed by 4 h.**

24. References

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CHAPTER 3: Non-Compartmental Analysis — AUC, AUMC, MRT and Statistical Moment Theory

BP602T Biopharmaceutics and Pharmacokinetics · Unit III

1. Learning Objectives

After studying this chapter, you will be able to:

1 Explain what a **non-compartmental model** is and why it is called "model-independent".

2 Define **AUC**, **AUMC**, and **MRT** in simple words.

3 Calculate **AUC** from plasma concentration–time data using the **trapezoidal rule** and extrapolate it to infinity.

4 Apply the **log-trapezoidal rule** and explain when it is used.

5 Calculate **AUMC** from the same data using the trapezoidal rule.

6 Calculate **MRT** as AUMC/AUC and explain its physical meaning.

7 Derive the relationships **AUC = Dose/Cl**, **MRT = 1/k** (one-compartment IV bolus), **Vss = Cl × MRT**, and **t½ = 0.693 × MRT**.

8 Calculate **MAT** (mean absorption time) from oral and IV MRT values.

9 Explain **statistical moment theory** — zeroth, first, and second moments.

10 Compare **non-compartmental vs compartmental analysis** and list advantages and limitations of NCA.

2. Definitions

- **Non-compartmental analysis (NCA):** A method of calculating pharmacokinetic parameters (AUC, AUMC, MRT, clearance, Vss) directly from the plasma concentration–time curve **without**

assuming any compartment structure (no "one-compartment" or "two-compartment" boxes). It uses the *moments* (area-type measures) of the curve.

- **AUC (Area Under the Curve):** The total area under the plasma concentration–time curve from time zero to infinity. It represents the **total exposure** of the body to the drug.
- **AUMC (Area Under the first Moment Curve):** The area under the curve of **(concentration × time) plotted against time**. It is the "first moment" of the concentration–time curve.
- **MRT (Mean Residence Time):** The **average time a drug molecule spends in the body** after administration. Calculated as MRT = AUMC / AUC.
- **Statistical moment:** A mathematical way of summarising the shape of a curve — the zeroth moment is the area (AUC), the first moment is AUMC, the second moment measures the spread of residence times.
- **MAT (Mean Absorption Time):** The average time taken for drug molecules to be absorbed. Calculated as MRT(oral) − MRT(IV).
- **Vss (Steady-state volume of distribution):** The volume of distribution at steady state, calculated as Cl × MRT.

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3. Terminology (Glossary Table)

Term	Short form	Meaning	Units
Area under the curve	AUC	Total area under C–t curve, 0 → ∞	(concentration × time), e.g., µg·h/mL
Area under the first moment curve	AUMC	Area under (C × t) vs t curve, 0 → ∞	(concentration × time²), e.g., µg·h²/mL
Mean residence time	MRT	Average time a drug molecule stays in the body	h (hours)
Mean absorption time	MAT	Average time for absorption of drug	h
Clearance	Cl	Volume of blood cleared of drug per unit time	L/h or mL/min
Steady-state volume of distribution	Vss	Apparent volume when drug is fully distributed	L or mL
Elimination rate constant	k (or kel)	First-order rate at which drug is eliminated	h^{-1} (per hour)
Half-life	t½	Time for concentration to fall by half	h
Trapezoidal rule	—	Method of calculating area by dividing the curve into trapezoids (shapes)	—
Zeroth moment	M0	AUC — total area	µg·h/mL
First moment	M1	AUMC — area of (C×t) vs t	µg·h²/mL
Extrapolation	—	Extending the measured area beyond the last data point up to infinity	—

Term	Short form	Meaning	Units
Linear-up / log-down	—	Use linear trapezoid when C is rising, log trapezoid when C is falling	—

⚠ **Units alert (common exam trap):** AUC units are **concentration × time** (µg·h/mL). AUMC units are **concentration × time × time = µg·h²/mL** — time is *squared*. Writing AUMC units as µg·h/mL is one of the most common mistakes.

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4. Explanation — Non-Compartmental Models from Absolute Zero

4.1 What is a "compartment"?

Simple explanation: In compartmental modelling (one-compartment, two-compartment), we *assume* the body is made of imaginary "boxes". For example, the one-compartment model assumes the drug spreads instantly and evenly throughout the body — the whole body is treated as one box.

Simple example: Think of the body as a bathtub of water. In a one-compartment model, we assume that when you pour ink (the drug) into the bathtub, it mixes instantly and evenly — the whole bathtub has the same colour at any moment.

4.2 The big idea of non-compartmental analysis

Technical concept: Non-compartmental analysis (NCA) does **not** assume any boxes or compartments. It does not assume one-compartment, two-compartment, or any model at all.

Simple explanation: Instead of guessing how the body is built, NCA just **looks at the actual data** — the measured plasma concentration–time curve — and calculates parameters straight from the *shape* of the curve. The shape is described by its **moments** (areas).

Analogy: A compartmental modeller is like a person who assumes every room in a house has furniture arranged the same way, then guesses details. The NCA analyst is like a person who simply **measures what actually happened** — how long the guest stayed (MRT), how much food they ate in total (AUC) — without guessing the room layout.

Key takeaway: NCA = no assumed compartment structure; parameters are calculated directly from the **moments** (AUC, AUMC) of the observed concentration–time curve. That is why it is also called **"model-independent" analysis**.

4.3 Principles of NCA

The entire method rests on **three principles**:

1 **All parameters come from the curve's moments.** AUC (zeroth moment) and AUMC (first moment) are calculated by the trapezoidal rule — nothing else is needed.

2 **Elimination must be first-order.** NCA assumes the drug is eliminated by a first-order process (a constant *fraction* removed per unit time), so that Cl = Dose/AUC holds.

3 **The terminal phase must be truly "terminal".** Extrapolation to infinity uses the terminal elimination rate constant (k), which must describe elimination (for IV) — not absorption or distribution.

4.4 When is NCA preferred vs compartmental modelling?

Use NCA when:

- You want a **quick, standard, model-free** summary of a pharmacokinetic study (e.g., bioavailability/bioequivalence studies — the standard regulatory approach).
- You want **clearance (Cl)** and **Vss** without committing to a compartment model.
- The data do not clearly fit one-, two-, or three-compartment models.
- You are comparing formulations (NCA parameters like AUC and Cmax are the comparison tools).

Use compartmental modelling when:

- You need to **predict** concentrations at times or doses you did not measure (simulation).
- You need parameters like **distribution rate constants (k12, k21)** or **micro-constants** for IV infusion design.
- You want to understand *where* the drug goes (tissue distribution), not just how long it stays.

Key takeaway: NCA is the first choice for **bioavailability/bioequivalence** and routine parameter estimation. Compartmental models are the first choice when you must **predict and simulate**.

5. Classifications

5.1 Types of moments used in NCA

Moment	Name	What it is	Formula
Zeroth moment	AUC	Area under C–t curve	$\int_0^\infty C \cdot dt$
First moment	AUMC	Area under (C×t)–t curve	$\int_0^\infty C \cdot t \cdot dt$
Second moment	—	Measures spread of residence times	$\int_0^\infty C \cdot t^2 \cdot dt$

What is an integral (∫)? — explained from zero: The symbol ∫ simply means **"area under the curve"**. $\int_0^{\infty} C \cdot dt$ means: *add up all the little slices of area under the concentration–time curve, starting at time zero and going on to infinity.* You never actually measure to infinity — you measure up to your last blood sample and then **extrapolate** (estimate) the remaining tail.

5.2 Types of trapezoidal calculations

Type	When to use	Segment formula (from t_1 to t_2)
Linear trapezoidal	C is **rising** (absorption phase)	$(C_1 + C_2)/2 \times (t_2 - t_1)$
Linear trapezoidal	Default for whole curve	$(C_1 + C_2)/2 \times (t_2 - t_1)$
Log trapezoidal ("log-down")	C is **falling** (elimination phase)	$(C_1 - C_2)/\ln(C_1/C_2) \times (t_2 - t_1)$

5.3 Route-dependent MRT

Route	MRT formula
IV bolus	MRT_iv = AUMC/AUC = 1/k (one-compartment)
IV infusion (duration T)	MRT = MRT_iv + T/2
Oral	MRT_po = MRT_iv + MAT

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6. Mechanisms / Derivations

6.1 The trapezoidal rule — full derivation in words

Technical concept: To find the area under the curve between two measured points (t_1, C_1) and (t_2, C_2), we draw a straight line between them. The shape under that line is a **trapezoid** (a four-sided shape with one pair of parallel sides).

Simple explanation: Imagine a field with a curved boundary. You cannot measure the curved area exactly, so you cut it into strips. Each strip is approximately a trapezoid — and the area of a trapezoid is easy: **average of the two heights × width**.

Derivation:

- Height at $t_1 = C_1$, height at $t_2 = C_2$.
- Width = $(t_2 - t_1)$.
- Average height = $(C_1 + C_2)/2$.
- Area of one strip = $\mathbf{(C_1 + C_2)/2 \times (t_2 - t_1)}$.
- Total AUC = sum of all strips: $AUC_{0 \to t_last} = \Sigma\, (C_i + C_{i+1})/2 \times (t_{i+1} - t_i)$.

Analogy: Think of steps of a staircase. If you want the area under the staircase, you measure each step's left and right heights, average them, and multiply by the step width. Add all steps — that is your AUC.

Key takeaway: Trapezoidal rule = average of the two concentrations × time between them, added strip by strip.

6.2 Log-trapezoidal variant

Simple explanation: During the falling (elimination) phase, the concentration drops in a *curve*, not a straight line. A straight-line cut *overestimates* the area a little. The **log-trapezoidal** formula corrects for the curve shape.

For a falling segment ($C_1 > C_2$):

$AUC(t_1 \to t_2) = (C_1 - C_2) / \ln(C_1/C_2) \times (t_2 - t_1)$

where ln is the natural logarithm.

When to use it: Standard practice is **"linear-up, log-down"** — use the linear rule while the curve is rising (absorption phase) and the log rule while it is falling (elimination phase). If in doubt in an exam, the linear trapezoidal rule alone is acceptable unless the question asks for the log-down variant.

6.3 Extrapolation of the residual area to infinity

Technical concept: Blood samples stop at the last measurable time point (t_last), but drug is still leaving the body. The remaining tail area must be **extrapolated** (estimated) to infinity.

Simple explanation: After your last measurement, the drug keeps falling at the terminal elimination rate k. For a first-order decline, the area under the tail is simply:

AUC(t_last → ∞) = C_last / k

where C_last is the last measured concentration and k is the terminal elimination rate constant (slope of ln C vs t, found from the last few points).

Derivation (in words): The tail is C(t) = C_last·e^(−k·(t−t_last)). The area under an exponential tail is (height at start)/rate = C_last/k.

Common mistake: Forgetting this step. $AUC_{0 \to t_last}$ alone is **not** AUC — the exam expects you to add the tail. If the tail is more than ~20% of the total AUC, your sampling was too short and the estimate is unreliable.

Total AUC: $AUC_{0 \to \infty}$ = $AUC_{0 \to t_last}$ (trapezoids) + C_last/k (tail).

6.4 AUC units

AUC = concentration × time. Common units: **µg·h/mL** (or mg·h/L — these are the same thing, since 1 mg/L = 1 µg/mL).

6.5 The relation AUC = Dose / Cl (IV)

Technical concept: For an IV dose (100% of the dose reaches the blood), total drug cleared from the body = Cl × AUC. Since all the dose is eventually eliminated, **Dose = Cl × AUC**, so:

Cl = Dose / AUC (IV bolus)

Simple explanation: Think of clearance as a drain pipe and AUC as the total drug exposure. A **bigger drain (higher Cl)** empties the drug faster, so the total exposure (AUC) is **smaller**. They are inversely related — double the clearance, halve the AUC.

Key takeaway: Cl = Dose/AUC needs **no compartment assumption** — it is the crown jewel of NCA.

6.6 AUMC — definition and trapezoidal calculation

Technical concept: AUMC is the area under the **first moment curve**: plot **(C × t)** on the y-axis against **t** on the x-axis, and find the area. Each point's height is concentration multiplied by its own time.

Simple explanation: AUMC is like AUC, but each concentration is **weighted by how late it occurs**. A concentration of 5 µg/mL at 10 hours contributes more to AUMC than the same 5 µg/mL at 1 hour, because those drug molecules stayed longer. AUMC measures not just *how much* drug, but *how much* × *how long*.

Trapezoidal calculation: Replace C with (C×t) in the trapezoid formula:

$AUMC(t_1 \to t_2) = (C_1 \cdot t_1 + C_2 \cdot t_2)/2 \times (t_2 - t_1)$

Extrapolation of the AUMC tail: AUMC(t_last → ∞) = **C_last·t_last/k + C_last/k²**.

(Reason: ∫ from t_last to ∞ of C·t·dt for an exponential tail splits into the two terms — a full derivation is in the reference books; for exams, use the formula.)

Total AUMC: $AUMC_{0 \to \infty}$ = $AUMC_{0 \to t_last}$ (trapezoids) + tail.

6.7 MRT — the statistical moment

Definition: MRT = AUMC / AUC = (first moment)/(zeroth moment).

Simple explanation — "average waiting time" analogy: Imagine a hospital waiting room. Patients arrive and leave at different times. If you want the **average waiting time**, you would (roughly) weight each patient's waiting time and average over all patients. **MRT is exactly that — the average time a drug molecule "waits" in the body before leaving.** The AUMC is the total of (amount × time), and dividing by the total amount (AUC) gives the average time.

Physical meaning: MRT is the average time a drug molecule spends in the body after an IV bolus dose — from entry to exit.

6.8 Why MRT_iv = 1/k for a one-compartment IV bolus

Show-why derivation (simple steps):

For a one-compartment IV bolus: $C(t) = C_0 \cdot e^{(-kt)}$, where C_0 = Dose/V.

- AUC = $\int_0^{\infty} C_0 \cdot e^{(-kt)} \cdot dt$ = **C_0/k**.
- AUMC = $\int_0^{\infty} C_0 \cdot t \cdot e^{(-kt)} \cdot dt$ = **C_0/k^2**.
- MRT = AUMC/AUC = $(C_0/k^2) \div (C_0/k)$ = **1/k**. ✓

Simple meaning: A drug eliminated faster (bigger k) stays a shorter average time. If k = 0.2 h^{-1}, the average molecule stays 1/0.2 = 5 hours.

6.9 MRT for infusion and oral routes

- **IV infusion** (given steadily over duration T): molecules enter at different times, so the average molecule spends its body-residence time *plus* the average waiting time inside the infusion. MRT_infusion = MRT_iv + **T/2**.
- **Oral dose:** the molecule must first be **absorbed** before it can be eliminated. MRT_po = MRT_iv + **MAT**, where MAT = mean absorption time.

6.10 Vss = Cl × MRT

Technical concept: Vss is the volume of distribution at steady state.

Derivation in words: Clearance (volume/time) × mean residence time (time) = volume. Dimensionally: (L/h) × (h) = L. So:

Vss = Cl × MRT

It estimates how widely the drug distributes, **without assuming compartments** — one of NCA's greatest strengths.

6.11 Half-life from MRT

For a one-compartment drug: $t_{½} = 0.693/k$, and since MRT = 1/k:

$t_{½}$ = 0.693 × MRT (one-compartment only)

⚠ **Common confusion:** This relation is valid **only** for a one-compartment drug. For multi-compartment drugs, $t_{½}$ (terminal) ≠ 0.693 × MRT.

6.12 MAT = MRT_oral − MRT_iv

Technical concept: If elimination is the same after IV and oral dosing (formulation-independent elimination — same drug, same body), then the *extra* time the oral dose spends in the body must be the **absorption time**.

MAT = MRT_po − MRT_iv

What MAT tells you: It measures how **slow or fast absorption** is. A long MAT means slow, prolonged absorption (e.g., a sustained-release tablet); a short MAT means rapid absorption (e.g.,

an oral solution). Comparing MAT across formulations tells the formulator which formulation releases drug more slowly.

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7. Diagrams (Textual)

Diagram 1 — AUC as area under the curve

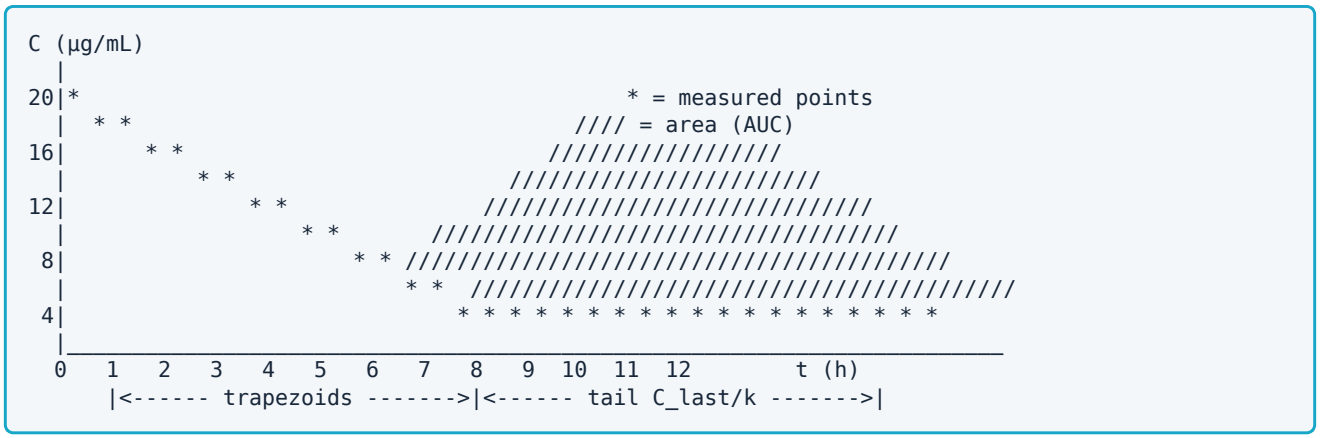

Diagram 2 — One trapezoid strip

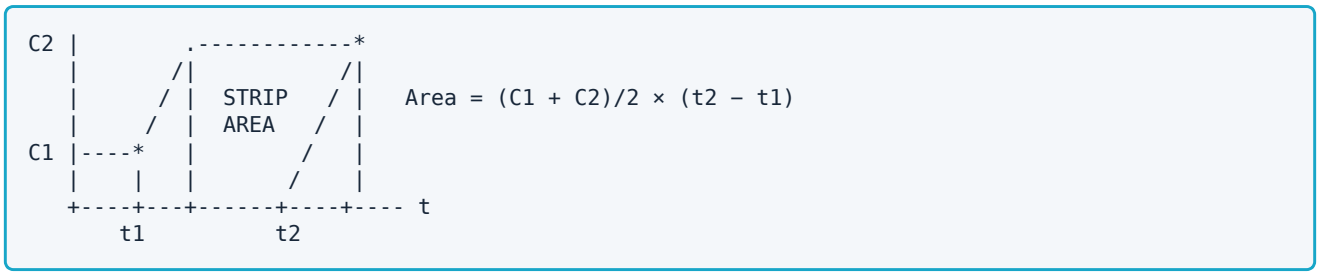

Diagram 3 — AUMC: weight by time

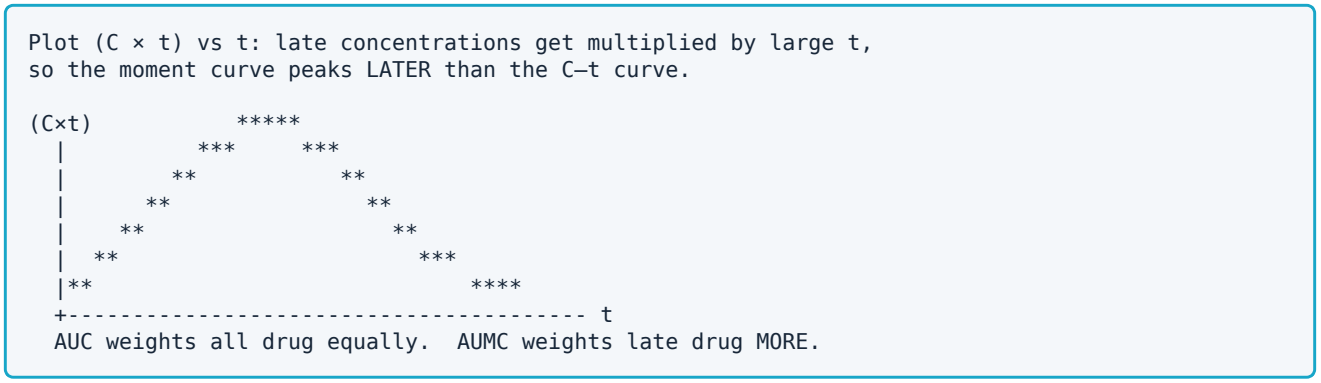

Diagram 4 — MRT as average residence time

```
Drug molecules entering the body:

  molecule A:  |====|                    leaves at 2 h
  molecule B:  |==========|              leaves at 5 h
  molecule C:  |================|        leaves at 8 h

  Average = (2 + 5 + 8)/3 = 5 h  →  this is MRT.

  MRT = AUMC/AUC  =  "total molecule-hours ÷ total molecules"
```

8. Flowchart — NCA Calculation Workflow

```
START: plasma concentration–time data (t, C)
        |
        v
Step 1: Calculate AUC(0 → t_last)
        by trapezoidal rule: Σ (Ci + Ci+1)/2 × Δt
        (linear-up / log-down)
        |
        v
Step 2: Find terminal k
        slope of ln C vs t using last 3–4 points
        |
        v
Step 3: Extrapolate tail: C_last / k
        AUC(0 → ∞) = trapezoids + tail
        |
        v
Step 4: Calculate AUMC(0 → t_last)
        by trapezoidal rule on (C × t): Σ (Ci·ti + Ci+1·ti+1)/2 × Δt
        |
        v
Step 5: Extrapolate AUMC tail: C_last·t_last/k + C_last/k²
        AUMC(0 → ∞) = trapezoids + tail
        |
        v
Step 6: MRT = AUMC / AUC
        |
        v
Step 7: Cl = Dose / AUC        (IV)
        Vss = Cl × MRT
        |
        v
Step 8 (if oral data also available):
        MAT = MRT_po − MRT_iv
        |
        v
END: report AUC, AUMC, MRT, Cl, Vss, (MAT)
```

9. Infographic Concept Box

```
╔═══════════════════════════════════════════════════════╗
║       NCA IN ONE GLANCE — "The Moment Family"         ║
╠═══════════════════════════════════════════════════════╣
║                                                       ║
║   MOMENT 0 → AUC  = total exposure    (µg·h/mL)       ║
║   MOMENT 1 → AUMC = exposure × time   (µg·h²/mL)      ║
║                                                       ║
║        MRT = AUMC ÷ AUC   =  average stay (h)         ║
║                                                       ║
║   From these two moments alone:                       ║
║     Cl  = Dose ÷ AUC        (how fast it leaves)      ║
║     Vss = Cl × MRT          (how widely it spreads)   ║
║     MAT = MRT_po − MRT_iv   (how slowly it absorbs)   ║
║                                                       ║
║   NO compartments assumed. NO model fitted.           ║
║   Just the curve, its area, and its weighted area.    ║
╚═══════════════════════════════════════════════════════╝
```

10. Tables

Table 1 — NCA parameters at a glance

Parameter	Formula	What it tells you	Route needed
$AUC_{0\to\infty}$	Trapezoids + C_last/k	Total drug exposure	Any
$AUMC_{0\to\infty}$	Trapezoids on (C·t) + tail	Exposure weighted by time	Any
MRT	AUMC/AUC	Average time drug stays in body	Any
Cl	Dose/AUC	How fast body removes drug	IV
Vss	Cl × MRT	Extent of distribution at steady state	IV
MAT	MRT_po − MRT_iv	How slow absorption is	Oral + IV
$t_{½}$ (1-compartment)	0.693 × MRT	Half-life from MRT	IV

Table 2 — NCA vs compartmental analysis

Feature	Non-compartmental (NCA)	Compartmental
Assumes compartments?	**No** — model-independent	Yes (1, 2 or 3 compartments)
Basis	Moments of the curve (AUC, AUMC)	Fitted exponential equations
Main parameters	AUC, AUMC, MRT, Cl, Vss	k, k12, k21, V1, V2, micro-constants
Prediction/simulation	Not possible	Possible
Best use	Bioavailability, bioequivalence, routine PK	Study design, dose prediction, IV infusion design
Needs rich data?	Needs good terminal-phase sampling	Can work with sparser data if model is known
Limitation	Sensitive to sampling schedule and k estimate	Wrong model choice gives wrong answers

11. Examples

Example 1 — AUC as total exposure: Two tablets give the same AUC (100 µg·h/mL) but one peaks early and the other peaks late. NCA says their **total exposure is identical** — a key idea in bioequivalence: same AUC ≈ same total drug delivered.

Example 2 — MRT in everyday terms: A cinema show lasts 3 hours on average per viewer. If viewers trickle out at different times, the *mean residence time* of a viewer is 3 hours. Similarly, MRT = 5 h means the average drug molecule spends 5 hours in the body.

Example 3 — MAT and formulation: An immediate-release paracetamol tablet has MAT ≈ 0.5 h; a sustained-release tablet of the same drug has MAT ≈ 4 h. The extra MRT of the SR tablet is (almost) entirely absorption time — MAT reveals the formulation's release behaviour.

Example 4 — Vss without compartments: A drug's Vss = 50 L in a 70 kg adult. Since blood volume is only ~5 L, NCA tells us (with no model at all) that the drug distributes extensively into tissues.

12. Analogies

1. **AUC = total rainfall.** Imagine rain falling into a bucket over a day. The *rate* of rain at each hour is like concentration; the *total water collected* is like AUC — total exposure, whatever the pattern.
2. **AUMC = rainfall weighted by lateness.** If late-evening rain counts double, you would multiply each hour's rain by the hour number. AUMC does exactly this with drug concentrations.
3. **MRT = average waiting time.** In a railway waiting room, some passengers wait 10 minutes, some 2 hours. The average waiting time = MRT. The drug's "waiting room" is the body.
4. **Trapezoids = staircase area.** Measuring the area under a staircase step by step (average of left and right heights × step width) is exactly the trapezoidal rule.
5. **MAT = queue at the gate.** IV drug walks straight into the waiting room; oral drug queues at the entry gate (absorption). The difference in their average total times = the queue time = MAT.

13. Calculation Boxes (Worked Numericals)

Standard dataset used in Boxes 1–3: A 500 mg IV bolus dose. Plasma concentrations measured:

t (h)	0	1	2	4	6	9	12
C (µg/mL)	20.0	16.4	13.4	9.0	6.0	3.3	1.8

Terminal k from the last points: k = 0.2 h^{-1} (from ln C vs t slope).

Calculation Box 1 — AUC by trapezoidal rule, with extrapolation to infinity

Question: Calculate $AUC_{0\to\infty}$ for the data above.

Step 1 — Trapezoids (linear), segment by segment:

Segment (h)	Calculation	Area (µg·h/mL)
0 → 1	(20.0 + 16.4)/2 × 1	18.20
1 → 2	(16.4 + 13.4)/2 × 1	14.90
2 → 4	(13.4 + 9.0)/2 × 2	22.40
4 → 6	(9.0 + 6.0)/2 × 2	15.00
6 → 9	(6.0 + 3.3)/2 × 3	13.95
9 → 12	(3.3 + 1.8)/2 × 3	7.65

Step 2 — Add them: $AUC_{0\to12}$ = 18.20 + 14.90 + 22.40 + 15.00 + 13.95 + 7.65 = **92.10 µg·h/mL**.

Step 3 — Extrapolate the tail: C_last/k = 1.8 / 0.2 = **9.00 µg·h/mL**.

Step 4 — Total: $AUC_{0\to\infty}$ = 92.10 + 9.00 = **101.10 µg·h/mL**.

Step 5 — Clearance: Cl = Dose/AUC. Dose = 500 mg = 500,000 µg. Cl = 500,000 / 101.10 = 4945.6 mL/h ≈ **4.95 L/h**.

✓ Answer: $AUC_{0\to\infty}$ = **101.1 µg·h/mL**; Cl = **4.95 L/h**.

Calculation Box 2 — AUMC by trapezoidal rule, with extrapolation

Question: Calculate $AUMC_{0\to\infty}$ for the same data.

Step 1 — Compute (C × t) at each point:

t (h)	0	1	2	4	6	9	12
C·t (µg·h/mL)	0	16.4	26.8	36.0	36.0	29.7	21.6

Step 2 — Trapezoids on (C·t):

Segment (h)	Calculation	Area (µg·h^2/mL)
0 → 1	(0 + 16.4)/2 × 1	8.20
1 → 2	(16.4 + 26.8)/2 × 1	21.60

Segment (h)	Calculation	Area (µg·h²/mL)
2 → 4	(26.8 + 36.0)/2 × 2	62.80
4 → 6	(36.0 + 36.0)/2 × 2	72.00
6 → 9	(36.0 + 29.7)/2 × 3	98.55
9 → 12	(29.7 + 21.6)/2 × 3	76.95

Step 3 — Add them: $AUMC_{0\to12}$ = 8.20 + 21.60 + 62.80 + 72.00 + 98.55 + 76.95 = **340.10 µg·h²/mL**.

Step 4 — Extrapolate the tail: $C_{last}\cdot t_{last}/k + C_{last}/k^2$ = (1.8 × 12/0.2) + (1.8/0.04) = 108 + 45 = **153.00 µg·h²/mL**.

Step 5 — Total: $AUMC_{0\to\infty}$ = 340.10 + 153.00 = **493.10 µg·h²/mL**.

✓ Answer: $AUMC_{0\to\infty}$ = **493.1 µg·h²/mL**. (Note the units — h²!)

Calculation Box 3 — MRT, Vss and t½

Question: Using the AUC and AUMC from Boxes 1–2, find MRT, Vss and t½.

Step 1 — MRT = AUMC/AUC = 493.10 / 101.10 = **4.88 h**.

Check: For a one-compartment IV bolus, MRT should equal 1/k = 1/0.2 = 5.0 h. Our 4.88 h ≈ 5.0 h ✓ (small difference is normal — the trapezoidal rule is an approximation).

Step 2 — Vss = Cl × MRT = 4.95 L/h × 4.88 h = **24.2 L**.

Check: V = Dose/C_0 = 500,000 µg / 20 µg/mL = 25,000 mL = 25 L. Our 24.2 L ≈ 25 L ✓.

Step 3 — t½ = 0.693 × MRT = 0.693 × 4.88 = **3.38 h** (one-compartment relation).

✓ Answer: MRT = **4.88 h**, Vss = **24.2 L**, t½ ≈ **3.4 h**.

Calculation Box 4 — MAT from oral vs IV MRT

Question: The same drug given as an oral tablet gives MRT_po = 7.5 h. The IV MRT from Box 3 is 4.88 h. Calculate MAT and interpret it.

Step 1 — MAT = MRT_po − MRT_iv = 7.5 − 4.88 = **2.62 h**.

Step 2 — Interpret: On average, a drug molecule spends 2.62 h being absorbed before it even begins its "IV-like" residence. If a sustained-release version showed MAT = 6 h, the formulator would know absorption/release is much slower.

✓ Answer: MAT = **2.62 h** — absorption is moderately fast (immediate-release type).

Calculation Box 5 — Log-trapezoidal vs linear (one segment)

Question: For the falling segment t = 6 → 9 h (C: 6.0 → 3.3 µg/mL), compare the linear and log-trapezoidal areas.

Linear: (6.0 + 3.3)/2 × 3 = **13.95 µg·h/mL**.

Log-trapezoidal: (6.0 − 3.3)/ln(6.0/3.3) × 3 = 2.7/ln(1.818) × 3 = 2.7/0.5978 × 3 = **13.55 µg·h/mL**.

Interpretation: The log-down value (13.55) is slightly smaller — the linear rule *overestimates* the falling curve. Over a full profile this correction improves accuracy, which is why "linear-up/log-down" is standard practice.

✓ Answer: Linear = 13.95, log-down = 13.55 µg·h/mL — log-down avoids overestimation on the declining phase.

14. Pharmacy Relevance

1. **Bioavailability & bioequivalence:** Regulatory bioequivalence decisions are built on NCA parameters — AUC (extent) and Cmax (rate). This chapter is the mathematical foundation of generic drug approval.
2. **Dose calculation:** Cl = Dose/AUC lets pharmacists compute the dose needed for a target exposure: Dose = Cl × target AUC (used in drugs like carboplatin, dosed by target AUC).
3. **Formulation development:** MAT compares how fast different formulations (tablet vs capsule vs SR tablet) release drug — a direct tool for the formulation scientist.
4. **Therapeutic drug monitoring:** MRT and t½ guide dosing-interval decisions — a drug with long MRT needs less frequent dosing.
5. **No model, no bias:** In early drug development, when the compartment structure is unknown, NCA gives trustworthy Cl and Vss values for first-in-human dose decisions.

15. India Context

- Indian generic companies (among the world's largest suppliers of generic medicines) run **bioequivalence studies** for every generic product — and every one of those studies is analysed by **non-compartmental methods** to compute AUC and Cmax for comparison with the innovator product.
- The Central Drugs Standard Control Organisation (CDSCO) guidance on bioavailability/bioequivalence studies follows the same NCA-based approach ($AUC_{0\to t}$, $AUC_{0\to\infty}$, Cmax) used by regulators worldwide — so this chapter's methods are exactly what an Indian BA/BE scientist applies daily.
- For B.Pharm students: university exams in biopharmaceutics routinely ask trapezoidal-rule AUC numericals — practising Boxes 1–5 above is direct exam preparation.

16. Key Points

1. NCA assumes **no compartments** — parameters come straight from the curve's moments.
2. **AUC** = total area under C–t curve (zeroth moment); units µg·h/mL.
3. **Trapezoidal rule:** $(C_1 + C_2)/2 \times \Delta t$, summed strip by strip; use **log-down** on the falling phase.
4. **Always extrapolate to infinity:** add C_last/k for AUC; add C_last·t_last/k + C_last/k² for AUMC.
5. **AUMC** = area under (C×t) vs t (first moment); units µg·h²/mL — time squared.
6. **MRT = AUMC/AUC** = average time a drug molecule spends in the body.
7. One-compartment IV bolus: **MRT = 1/k** and **t½ = 0.693 × MRT**.
8. **Cl = Dose/AUC** (IV) and **Vss = Cl × MRT** — no model assumed.
9. **MAT = MRT_oral − MRT_iv** measures absorption speed.
10. NCA is preferred for bioequivalence and routine PK; compartmental models are preferred for prediction and simulation.

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17. Common Confusions

Confusion	Clarification
"AUC and AUMC are the same thing"	No. AUC weights every concentration equally; AUMC weights late concentrations more (multiplied by time). MRT needs both.
"MRT is the same as half-life"	No. MRT is the *average* stay time; t½ is the time for concentration to halve. Related (t½ = 0.693·MRT) only for one-compartment drugs.
"NCA needs a compartment model"	Exactly the opposite — NCA is *model-independent*; that is its whole point.
"$AUC_{0\to t_last}$ is enough"	No — you must extrapolate to infinity (add the tail), otherwise you underestimate exposure.
"MAT = MRT_iv − MRT_po"	Wrong order. MAT = MRT_po − MRT_iv (oral stays longer because of absorption).
"Vss and Vd are identical"	Vss is the volume at *steady state* (from NCA); Vd (or V_1, Vβ) comes from compartmental models. Related but not identical concepts.

18. Common Mistakes (Exam Hall Warnings)

1. **Wrong AUMC units** — writing µg·h/mL instead of **µg·h²/mL**. Time is squared in AUMC. (Most common mistake in this chapter.)
2. **Forgetting the extrapolation** — reporting $AUC_{0\to t_last}$ as the final AUC. Always add C_last/k.
3. **Using the wrong tail formula for AUMC** — the AUMC tail is C_last·t_last/k + C_last/k², *not* C_last/k.
4. **Mixing up MAT subtraction order** — MAT = MRT_po − MRT_iv, never the reverse.

5 **Applying t½ = 0.693 × MRT to multi-compartment drugs** — valid only for one-compartment.

6 **Dose unit mismatch in Cl = Dose/AUC** — if AUC is in µg·h/mL, convert dose to µg before dividing, or your clearance will be off by 1000×.

7 **Using linear trapezoids on a steeply falling phase** without considering log-down — overestimates AUC.

8 **Estimating k from too few or non-terminal points** — k must come from the true terminal log-linear phase (last 3–4 points).

---

19. Mnemonics

- **"AM-V" chain: A**UC → **M**RT → **V**ss. From the curve you get **A**UC, divide moments to get **M**RT, multiply by Cl to get **V**ss. *"Ask Me the Volume."*
- **"Moment over Area":** MRT = **M**oment (AUMC) over **A**rea (AUC) — the name tells the formula.
- **"PO stays longer":** MAT = MRT_**po** − MRT_iv — **P**ills **O**rally stay longer, so oral MRT comes first in the subtraction.
- **"Tail rules":** AUC tail = **C/k** (one term); AUMC tail = **two terms** (C·t/k + C/k²) — *"AUMC is fancier, so its tail has two parts."*
- **"h-squared":** AUMC units have **h²** — *"AUMC: the Area Under the Moment Curve is doubly timed."*

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20. Exam Summary

Non-compartmental analysis (NCA), also called model-independent analysis, calculates pharmacokinetic parameters directly from the **moments of the plasma concentration–time curve** without assuming any compartment structure. The **zeroth moment** is **AUC** (total area, µg·h/mL), calculated by the **trapezoidal rule** — $(C_1+C_2)/2 \times \Delta t$ per segment — with the **log-trapezoidal** variant on the declining phase, plus **extrapolation to infinity** (C_{last}/k). The **first moment** is **AUMC** (area under C×t vs t, µg·h²/mL), with tail $C_{last} \cdot t_{last}/k + C_{last}/k^2$. **MRT = AUMC/AUC** is the average time a drug molecule spends in the body; for a one-compartment IV bolus, MRT = 1/k and t½ = 0.693·MRT. Two powerful model-free relations follow: **Cl = Dose/AUC** (IV) and **Vss = Cl × MRT**. **MAT = MRT_oral − MRT_iv** quantifies absorption speed. NCA is the standard method for **bioavailability/bioequivalence** studies; its limitations are sensitivity to sampling design and inability to simulate or predict. Second-moment analysis gives the **variance of residence times**.

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21. One-Minute Revision

No compartments — just the curve. AUC = total area (trapezoids + C_last/k tail). AUMC = time-weighted area (trapezoids on C×t + two-term tail), units h^2. MRT = AUMC ÷ AUC = average stay time. IV bolus one-compartment: MRT = 1/k. Cl = Dose ÷ AUC. Vss = Cl × MRT. MAT = oral MRT − IV MRT = absorption time. $t_{½}$ = 0.693 × MRT (one-compartment only). NCA = model-independent; best for bioequivalence.

22. Exam Questions

A. MCQs (with answer key)

Q1. Non-compartmental analysis is also called: a) Model-dependent analysis b) Model-independent analysis c) Two-compartment analysis d) Michaelis–Menten analysis

Q2. The zeroth statistical moment of the plasma concentration–time curve is: a) AUMC b) MRT c) AUC d) Cmax

Q3. The correct units of AUMC are: a) µg/mL b) µg·h/mL c) µg·h^2/mL d) µg/mL·h^{-1}

Q4. The extrapolated tail area from t_last to infinity for AUC is: a) C_last × k b) C_last/k c) k/C_last d) C_last × t_last

Q5. MRT is calculated as: a) AUC/AUMC b) AUMC/AUC c) Dose/Cl d) Cl × Vss

Q6. For a one-compartment IV bolus, MRT equals: a) k b) 1/k c) 0.693/k^2 d) k/0.693

Q7. Vss is given by: a) Dose/AUC b) Cl × MRT c) MRT/Cl d) AUC × k

Q8. MAT is calculated as: a) MRT_iv − MRT_po b) MRT_po − MRT_iv c) MRT_po + MRT_iv d) MRT_po × MRT_iv

Q9. The log-trapezoidal rule is preferred when the concentration is: a) Rising b) Falling c) Constant d) Zero

Q10. Which parameter CANNOT be obtained by NCA? a) Clearance b) Vss c) Distribution micro-constants (k12, k21) d) MRT

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

B. Viva Questions

1 What is meant by "model-independent" analysis?

2 Define AUC and AUMC in one sentence each.

3 Why do we extrapolate AUC to infinity? What is the formula for the tail?

4 Explain MRT as "average waiting time" with a daily-life example.

5 Derive MRT = 1/k for a one-compartment IV bolus.

6 Why does AUMC have time-squared units?

7 What does a large MAT tell you about a formulation?

8 When would you choose compartmental modelling over NCA?

9 What is the second moment used for?

10 Why must elimination be first-order for Cl = Dose/AUC to hold?

C. Application-Based Questions

1 Two brands of the same drug show identical AUC but different Cmax. Using NCA concepts, explain what is the same and what differs between the brands, and what this means for a patient.

2 A sustained-release tablet shows MRT_po = 9 h while the IV MRT is 4 h. Calculate MAT and explain to a formulator what it reveals about the product.

3 In a bioequivalence study, the extrapolated AUC tail exceeds 25% of total AUC. What went wrong with the study design, and what should be done?

4 A new drug's Vss by NCA is 400 L in an adult. Without any compartment model, what can you conclude about its distribution? What dosing caution follows?

5 Explain why NCA — and not a compartmental model — is the regulatory standard for comparing a generic product with an innovator product.

D. Numerical Problems (with fully worked solutions)

Problem 1. Plasma data after a 250 mg IV bolus: t (h) = 0, 2, 4, 8, 12; C (µg/mL) = 12.5, 8.2, 5.4, 2.3, 1.0. Terminal k = 0.21 h^{-1}. Calculate $AUC_{0\to\infty}$ and Cl.

Solution:

- Trapezoids: (12.5+8.2)/2×2 = 20.7; (8.2+5.4)/2×2 = 13.6; (5.4+2.3)/2×4 = 15.4; (2.3+1.0)/2×4 = 6.6. Sum = **56.3 µg·h/mL**.
- Tail: C_last/k = 1.0/0.21 = **4.76 µg·h/mL**.
- $AUC_{0\to\infty}$ = 56.3 + 4.76 = **61.06 µg·h/mL**.
- Cl = Dose/AUC = 250,000 µg / 61.06 = 4094 mL/h ≈ **4.09 L/h**. ✓

Problem 2. For the data in Problem 1, the $AUMC_{0\to t_last}$ by trapezoids on (C×t) is 330 µg·h^2/mL. Calculate $AUMC_{0\to\infty}$ and MRT.

Solution:

- Tail: C_last·t_last/k + C_last/k^2 = (1.0×12/0.21) + (1.0/0.0441) = 57.14 + 22.68 = **79.82 µg·h^2/mL**.
- $AUMC_{0\to\infty}$ = 330 + 79.82 = **409.82 µg·h^2/mL**.
- MRT = 409.82/61.06 = **6.71 h**. ✓
- Check: 1/k = 1/0.21 = 4.76 h… the MRT here (6.71 h) exceeds 1/k, suggesting the data are not perfectly one-compartment — a realistic reminder that MRT = AUMC/AUC is model-free, while 1/k assumes one compartment.

Problem 3. An oral capsule of a drug gives MRT_po = 8.2 h. IV data for the same drug give MRT_iv = 5.0 h and Cl = 6.0 L/h. Calculate (a) MAT, (b) Vss, (c) t½ (assume one-compartment).

Solution:

- (a) MAT = 8.2 − 5.0 = **3.2 h**.
- (b) Vss = Cl × MRT_iv = 6.0 × 5.0 = **30 L**.
- (c) $t_{½}$ = 0.693 × MRT_iv = 0.693 × 5.0 = **3.47 h**. ✓

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23. Statistical Moment Theory — Summary

Technical concept: Statistical moment theory treats the concentration–time curve the way statistics treats a distribution of data. Just as a dataset has a mean and variance, the curve has moments:

- **Zeroth moment (M_0)** = $\int C \cdot dt$ = **AUC** — the total "mass" of the curve.
- **First moment (M_1)** = $\int C \cdot t \cdot dt$ = **AUMC** — the mass weighted by time.
- **Second moment (M_2)** = $\int C \cdot t^2 \cdot dt$ — used to find the **variance of residence times** (how spread out the individual molecule stay-times are): Variance = $M_2/M_0 - MRT^2$.

Simple explanation: If AUC answers "how much drug in total?", the first moment answers "how much, and for how long?", and the second moment answers "did all molecules stay about the same time, or did some leave early and some very late?"

How Cl, Vss, MRT derive from moments (no compartments):

1. MRT = M_1/M_0 = AUMC/AUC — the *mean* of the residence-time distribution.
2. Cl = Dose/AUC — from mass balance (all IV dose is eventually eliminated), independent of any model.
3. Vss = Cl × MRT — combines the two moments into a distribution volume.

Advantages of NCA:

- No model assumption — no risk of choosing the wrong compartment model.
- Simple, standardised, and regulator-accepted (bioequivalence).
- Gives robust Cl and Vss with minimal mathematics.

Limitations of NCA:

- **Cannot predict or simulate** concentrations at unmeasured times or new doses.
- Sensitive to the **sampling schedule** — sparse or short sampling corrupts AUC, k, and the tails.
- Assumes **first-order (linear)** elimination; fails for saturable (Michaelis–Menten) kinetics.
- Gives no information about *where* the drug distributes (no tissue-level insight).
- MRT and Vss are meaningful mainly when disposition is linear.

Key takeaway: Moments turn a wiggly curve into trustworthy numbers — AUC, AUMC, MRT, Cl, Vss — with zero assumptions about the body's hidden boxes. The price of that honesty: NCA describes, but never predicts.

24. References

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