BP602T · B.Pharm Semester VI · Theory Notes

Biopharmaceutics and Pharmacokinetics

Unit V — Nonlinear Pharmacokinetics and PK Software

Unit V (6 hours)

Pills & Python Notes

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

Syllabus coverage: Unit V (6 hours).

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CHAPTER 6: Nonlinear Pharmacokinetics and PK Software (In-Silico Methods)

BP602T — Biopharmaceutics and Pharmacokinetics, B.Pharm Semester VI, Unit V

6.1 Learning Objectives

After studying this chapter, the student will be able to:

1 Explain, in simple words, what **linear** pharmacokinetics means and how it differs from **nonlinear** pharmacokinetics.

2 Detect non-linearity from dose–concentration data (non-proportional AUC or Css with dose).

3 List and explain the **seven reasons** for non-linear pharmacokinetics, each with a drug example.

4 Describe why drugs like **phenytoin, salicylates and ethanol** show dangerous non-linear behaviour, and explain the clinical meaning: a small dose increase can cause a large jump in drug concentration.

5 Derive the **Michaelis–Menten equation** ($-dC/dt = Vmax \cdot C/(Km + C)$) from basic enzyme kinetics.

6 Explain the meaning of **Vmax** and **Km**, and distinguish the linear case ($C << Km$) from the saturated case ($C >> Km$).

7 Estimate **Km and Vmax** from two steady-state dose–concentration pairs (two-point method) and from the Lineweaver–Burk style linearisation.

8 Predict a new steady-state concentration after a dose change using $R = Vmax \cdot Css/(Km + Css)$.

9 Solve numerical problems on non-linear PK with all steps shown.

10 Describe what **PK software** does — curve fitting, non-compartmental analysis, simulation — and name the functional categories of tools used (compartmental modelling, NCA, population PK, physiologically-based PK, scientific computing), with their typical uses in drug development and teaching.

6.2 Definitions

Linear pharmacokinetics. The body's handling of a drug is called *linear* when the concentration (AUC, or steady-state concentration Css) rises in direct proportion to the dose. Double the dose → double the AUC and double the Css. *Simple meaning:* the body's elimination machinery never gets "full"; every extra milligram is handled the same way as the previous one.

Nonlinear pharmacokinetics. The body's handling of a drug is called *nonlinear* (or dose-dependent, or capacity-limited) when AUC or Css does **not** rise in proportion to the dose.

Simple meaning: some step in absorption, distribution, or elimination gets *saturated* — like a gate that can only let a fixed number of people through. Extra drug piles up and the concentration jumps more than expected.

Saturation. A state in which the proteins that handle a drug (enzymes, carriers, binding proteins) are all occupied and cannot work any faster. Once saturated, giving more drug does not increase the elimination rate — it only increases the drug left in the body.

Therapeutic window. The range of drug concentration that is safe and effective — high enough to work, low enough to avoid toxicity. For nonlinear drugs like phenytoin, this window is narrow, and crossing it is easy.

In-silico method. "In silico" means "in the computer" (as opposed to in the lab or in the body). PK software uses mathematics on a computer to fit curves, calculate PK parameters, and simulate what would happen at different doses — without doing another experiment on a patient or animal.

6.3 Terminology (Glossary)

Term	Simple meaning
Linear PK	AUC or Css rises in direct proportion to dose.
Nonlinear PK	AUC or Css rises out of proportion to dose; also called dose-dependent or capacity-limited kinetics.
Dose proportionality	The test for linearity: doubling the dose doubles AUC/Css.
AUC	Area under the concentration–time curve; total drug exposure of the body.
Css (steady-state concentration)	The average concentration reached when dosing continues and the amount going in equals the amount going out.
R (dosing rate)	Amount of drug given per unit time at steady state (e.g., mg/day). At steady state, input rate = elimination rate.
Km (Michaelis constant)	The drug concentration at which the elimination rate is exactly half of Vmax. Shows how tightly the enzyme holds the drug.
Vmax	The maximum elimination rate the enzyme system can achieve when every enzyme molecule is busy.
Zero-order elimination	Constant amount eliminated per unit time (e.g., 50 mg/day), independent of concentration. Seen at saturation.
First-order elimination	Constant *fraction* eliminated per unit time (e.g., 10% per hour), proportional to concentration. Seen when C << Km.
Capacity-limited	The body has a fixed maximum capacity to handle the drug; above that, kinetics become non-linear.
TDM (Therapeutic Drug Monitoring)	Measuring drug concentration in the patient's blood and adjusting the dose — essential for nonlinear drugs.
NCA (Non-Compartmental Analysis)	Calculating PK parameters (AUC, half-life, clearance) directly from data without assuming a compartment model.
Curve fitting	Using software to find the best equation line that passes through measured concentration–time points.

Term	Simple meaning
Population PK	Studying how PK parameters vary across a group of patients (age, weight, disease) rather than one person.
PBPK (Physiologically-Based PK)	A model built from real body organs and blood flows, used to predict drug behaviour in different people or situations.

6.4 Explanation

6.4.1 What linearity means — first, the normal case

Before learning non-linearity, understand the *normal*, well-behaved case: **linear pharmacokinetics**.

Imagine you give a patient 100 mg of a drug and the total drug exposure (AUC) is 10 units. Now you give 200 mg. If the AUC becomes 20 units, and 300 mg gives 30 units, the drug is linear. The rule is simple:

> **Double the dose → double the AUC. Double the dose → double the steady-state concentration.**

The body's machinery — the enzymes that destroy the drug, the kidneys that excrete it — handles every extra milligram exactly like the last one. Nothing gets "full". Most drugs behave this way at normal doses.

6.4.2 What non-linearity means — when the machinery gets full

Now imagine the same experiment with **phenytoin** (an epilepsy medicine):

- 300 mg/day → Css = 10 mg/L
- 400 mg/day → Css = 20 mg/L (dose ↑ 33%, concentration ↑ 100%!)
- 500 mg/day → Css = 50 mg/L (dose ↑ 25%, concentration ↑ 150%!)

The concentration does NOT rise in proportion to the dose. It explodes upward. This is **nonlinear pharmacokinetics**.

Simple explanation: The liver's enzymes that destroy phenytoin have a fixed maximum speed — like a toll booth that can only let 10 cars per minute pass. At low doses, cars arrive slowly and pass smoothly (linear). But once traffic exceeds the booth's capacity, cars pile up in a jam. The jam grows much faster than the number of arriving cars. That jam is the drug concentration shooting up in the blood.

6.4.3 How to detect non-linearity

Non-linearity is detected with a simple test:

> **Give two or more different dose levels. Measure AUC (after a single dose) or Css (at steady state). Check whether they rise in proportion to dose.**

- AUC doubles when dose doubles → linear. ✓

- AUC rises **more** than the dose (or Css jumps disproportionately) → non-linear, usually saturation of elimination (metabolism, protein binding, secretion).
- AUC rises **less** than the dose → also non-linear, usually saturation of *absorption* (the gut carriers are full, so extra drug is not absorbed) or induction of enzymes over time.

So the diagnostic rule in one line: **"If it is not proportional, it is non-linear."**

6.5 Reasons for Non-Linearity

There are seven important reasons. Each is explained from zero, with a drug example. The memory hook is **PAMES-EH** (see the Mnemonics section): **P**rotein binding, **A**bsorption, **M**etabolism, **E**nterohepatic recycling, **S**ecretion (tubular), **E**nzyme induction, **H**epatic blood flow.

6.5.1 Capacity-limited (saturable) metabolism — the most famous reason

From zero: The liver destroys many drugs using enzymes. Each enzyme molecule can process only a limited number of drug molecules per minute. The total number of enzyme molecules is fixed. So the liver has a **maximum destruction speed** — the Vmax you will meet in the Michaelis–Menten section.

At low drug concentrations, most enzyme molecules are idle, waiting. Any extra drug molecule finds a free enzyme immediately, so elimination keeps pace with dose — this looks linear. At high concentrations, **all** enzyme molecules are busy. Extra drug molecules must wait in a queue. The elimination rate cannot increase further — it becomes constant (zero-order). Extra drug therefore accumulates, and the blood concentration shoots up out of proportion.

Drug examples: **Phenytoin** (antiepileptic — the textbook example), **salicylates/aspirin** (at high doses the metabolic pathways saturate and the half-life lengthens), **ethanol/alcohol** (the liver destroys alcohol at a nearly fixed rate of about one standard drink per hour — that is why drinking twice as much does not clear twice as fast; the enzyme is saturated).

Clinical meaning: For phenytoin, a small dose increase — even 10% — can more than double the blood concentration (worked out in Calculation Box 6.3). This can push the patient from "no seizures" into **toxicity** (drowsiness, slurred speech, unsteady walking, double vision). That is why phenytoin doses are adjusted in very small steps and blood levels are monitored (TDM).

6.5.2 Saturable plasma protein binding

From zero: Most drugs in blood stick ("bind") to plasma proteins like albumin. Only the **free** (unbound) drug can leave the blood, reach its target, be destroyed by the liver, or cause side effects. Normally, there is plenty of protein, so the *fraction* that is free stays constant — linear behaviour.

But proteins have a fixed number of binding seats. At high drug concentrations, all seats fill up. Extra drug molecules have nowhere to sit, so they remain **free**. The free fraction rises. Since only free drug is cleared, clearance suddenly increases, and total drug concentration rises *less* than proportionally — while the **free (active) concentration can rise dangerously**.

Drug examples: **Phenytoin** (highly protein-bound; at high doses binding saturates), **salicylates** (aspirin displaces other drugs and its own binding saturates at high doses).

Clinical meaning: Measuring only the *total* drug level can mislead — the free, active drug may be much higher than expected. This is why, in some patients (low albumin, kidney disease), pharmacists interpret phenytoin levels with special corrected formulas.

6.5.3 Saturable active tubular secretion (and reabsorption)

From zero: The kidney removes drugs in two main ways: passive filtration (through the glomerulus, like water through a sieve — this is linear) and **active secretion** (pumps in the tubule wall grab drug molecules from blood and throw them into the urine — these pumps are limited in number, so they can saturate).

When the secretion pumps are saturated, the kidney cannot excrete extra drug any faster. Renal clearance falls, and the drug concentration in blood rises more than proportionally to the dose.

Drug example: **Penicillin** and related antibiotics are actively secreted by the renal tubules; at high doses the secretion pathway saturates. (The reverse also happens with **probenecid**, which blocks these pumps and raises penicillin levels — the same pumps, deliberately saturated by a second drug.)

Clinical meaning: At high doses, the drug stays in the body longer than a linear model would predict — dosing intervals designed from low-dose data may overdose the patient.

6.5.4 Saturable GI absorption

From zero: Some drugs are absorbed from the gut not by simple diffusion but by **carrier proteins** — molecular "ferries" that carry drug molecules across the intestinal wall. There are only so many ferries. At high doses, all ferries are busy, and the extra drug simply passes out unabsorbed.

Here the non-linearity goes the *other* way: AUC rises **less** than proportionally with dose, because the body cannot absorb the extra drug.

Drug examples: **Amoxicillin** and **riboflavin (vitamin B2)** use carrier-mediated absorption; very large doses are absorbed poorly, so "more dose" gives diminishing returns.

Clinical meaning: Simply increasing the dose may not increase the effect — the pharmacist should know that poor response at high dose may be an absorption ceiling, not a need for still more drug.

6.5.5 Enzyme induction / autoinduction

From zero: Some drugs **instruct the liver to make more enzyme** — this is called *induction*. More enzyme means faster destruction of the drug. If the drug induces the enzymes that destroy *itself*, it is called **autoinduction**: the drug speeds up its own elimination over days to weeks.

Here the non-linearity shows as a **time-dependent** change: the same dose gives a high concentration on day 1 but a much lower concentration on day 14, because the liver has built more enzyme machinery in between. AUC falls over time instead of staying constant.

Drug example: **Carbamazepine** (antiepileptic) famously induces its own metabolism — patients often need a dose increase after 2–3 weeks because the drug "eats itself" faster.

Clinical meaning: A dose that worked in week 1 may fail in week 3. Seizures may return — not because the disease worsened, but because the drug induced its own destruction. The pharmacist must counsel the patient not to panic and not to change the dose themselves.

6.5.6 Enterohepatic recycling

From zero: Some drugs, after being processed by the liver, are dumped into the bile, enter the intestine, get **reabsorbed** back into the blood, and visit the liver again — a loop called *enterohepatic recycling*. Each loop gives the drug another chance to be destroyed, but the loop itself is capacity-limited (bile transporters can saturate).

This produces a second peak in the concentration–time curve and prolongs the drug's stay in the body in a non-proportional way: small changes in dose or in gut/bile function change how many loops the drug completes.

Drug examples: drugs with significant biliary excretion and reabsorption show secondary peaks; the loop also explains why some drugs have unexpectedly long half-lives.

Clinical meaning: Anything that interrupts the loop (e.g., bile-binding resins) can shorten the drug's action; anything that slows the gut can lengthen it — effects a linear model would not predict.

6.5.7 Changes in hepatic blood flow

From zero: For drugs that the liver extracts very efficiently (**high-extraction drugs**), the limiting step is not the enzyme but **how fast blood delivers the drug to the liver**. Clearance then depends on liver blood flow. Anything that changes blood flow — food, exercise, posture, other drugs, heart failure — changes clearance, and the change is not proportional to dose.

Drug example: high-extraction drugs such as **propranolol** show this behaviour: their clearance follows blood flow, not enzyme capacity.

Clinical meaning: Two patients on the same dose can have very different concentrations if their liver blood flow differs (e.g., an elderly patient with a weak heart vs a young athlete). Dose must be individualised.

Summary table of reasons

#	Reason	Direction of non-proportionality	Classic example
1	Saturable metabolism	AUC/Css rise **more** than dose	Phenytoin, salicylates, ethanol
2	Saturable protein binding	Total level rises **less**; free level rises **more**	Phenytoin, salicylates
3	Saturable tubular secretion	Renal clearance falls; levels rise **more**	Penicillin
4	Saturable GI absorption	AUC rises **less** than dose	Amoxicillin, riboflavin
5	Enzyme induction/autoinduction	AUC **falls over time** at same dose	Carbamazepine
6	Enterohepatic recycling	Secondary peaks; prolonged, unpredictable levels	Biliary-excreted drugs
7	Changed hepatic blood flow	Clearance follows blood flow, not dose	Propranolol (high-extraction)

Key takeaway: Saturation is the common thread. Whenever a limited number of "workers" (enzymes, carriers, binding seats, pumps, ferries) must handle the drug, high doses fill all the workers, and the body's handling stops being proportional to dose.

6.6 The Michaelis–Menten Method

This is the mathematical heart of nonlinear pharmacokinetics. It is named after Leonor Michaelis and Maud Menten, who described how enzymes work. We will build it from absolute zero — no prior enzyme knowledge assumed.

6.6.1 From zero: how an enzyme destroys a drug

An enzyme is a protein "machine" in the liver. Think of it as a worker with two hands. The process has three steps:

1. **Binding:** The free enzyme (E) grabs a drug molecule, the *substrate* (S). They form a combined unit, the **enzyme–substrate complex (ES)**. Rate constant: **k1** (how fast they join).
2. **Unbinding:** Sometimes the complex falls apart again without doing anything — the drug escapes unchanged. Rate constant: **k2**.
3. **Conversion:** The enzyme converts the drug into a metabolite (P, the product) and becomes free again, ready for the next drug molecule. Rate constant: **k3**.

In symbols:

E + S ⇌ ES → E + P (k1 forward, k2 backward, k3 to product)

The crucial fact: **the enzyme is not used up**. One enzyme molecule destroys thousands of drug molecules, one after another — but only one at a time. That "one at a time" limit is what creates saturation.

6.6.2 The derivation, step by step

We want the **rate of drug destruction**, v. That rate equals the rate at which the complex ES turns into product:

v = k3 × [ES] …(A)

where [ES] is the concentration of the enzyme–substrate complex.

Step 1 — Steady-state assumption. During the reaction, ES is formed and broken down continuously. We assume its concentration stays roughly constant (formation = breakdown). This is the *steady-state assumption*:

$$d[ES]/dt = 0$$

Formation of ES happens at rate k1[E][S]. Breakdown of ES happens two ways: unbinding (k2[ES]) and conversion (k3[ES]). So:

k1[E][S] − k2[ES] − k3[ES] = 0 **k1[E][S] = (k2 + k3)[ES]** ...(1)

Step 2 — Enzyme conservation. The total enzyme [E]t is fixed (the body does not create or destroy enzyme during the reaction). Enzyme is either free or bound:

[E]t = [E] + [ES], so **[E] = [E]t − [ES]** ...(2)

Step 3 — Substitute (2) into (1):

k1([E]t − [ES])[S] = (k2 + k3)[ES] k1[E]t[S] − k1[ES][S] = (k2 + k3)[ES] k1[E]t[S] = [ES](k2 + k3 + k1[S]) **[ES] = k1[E]t[S] / (k2 + k3 + k1[S])** ...(3)

Step 4 — Simplify. Divide the top and bottom of (3) by k1:

[ES] = [E]t[S] / ((k2 + k3)/k1 + [S])

Step 5 — Define the two famous constants:

- **Km = (k2 + k3)/k1** — the *Michaelis constant*.
- **Vmax = k3[E]t** — the *maximum rate*, achieved when every enzyme molecule is occupied ([ES] = [E]t).

Then [ES] = [E]t[S]/(Km + [S]), and from (A), v = k3[ES]:

v = Vmax × [S] / (Km + [S]) — the Michaelis–Menten equation ✓

Step 6 — Translate to pharmacokinetics. In PK, the "substrate" is the drug in the body at concentration **C**, and v is the **rate of drug elimination** (−dC/dt, the fall of concentration with time):

−dC/dt = Vmax × C / (Km + C)

That is the complete derivation. Memorise the shape: *rate = (maximum × concentration) ÷ (constant + concentration).*

6.6.3 What Vmax and Km really mean

Vmax — the ceiling speed. Imagine a kitchen with 10 cooks, each making one dosa per minute. The kitchen can never exceed 10 dosas per minute — that is Vmax. It depends on **how much enzyme exists** ([E]t). More enzyme (e.g., after induction) → higher Vmax. Units: amount per time (e.g., mg/day).

Km — the concentration at half speed. Set C = Km in the equation: rate = Vmax·Km/(Km + Km) = Vmax/2. So **Km is the drug concentration at which the elimination rate is exactly half of Vmax**. It measures how tightly the enzyme grips the drug:

- **Small Km** = the enzyme grabs the drug eagerly → saturation happens at *low* concentrations (dangerous — e.g., phenytoin has a small Km, so it saturates at normal therapeutic levels).
- **Large Km** = the enzyme is lazy about binding → saturation needs very high concentrations (safer).

6.6.4 The two extreme cases — linear vs saturated

Case 1: C is much smaller than Km (C << Km). The drug concentration is tiny compared to Km. Then Km + C ≈ Km (adding a drop to a bucket changes nothing):

$$-dC/dt \approx Vmax \times C / Km = (Vmax/Km) \times C$$

The rate is proportional to concentration — this is **first-order (linear) kinetics**, with rate constant k = Vmax/Km. *Simple meaning:* nearly all enzyme molecules are free; every extra drug molecule finds a worker instantly.

Case 2: C is much larger than Km (C >> Km). The concentration swamps Km. Then Km + C ≈ C:

$$-dC/dt \approx Vmax \times C / C = Vmax$$

The rate is constant — this is **zero-order kinetics**. *Simple meaning:* every enzyme molecule is busy; extra drug just joins the queue. The toll-booth traffic jam.

Between the two extremes lies the curved transition — the full Michaelis–Menten hyperbola.

6.6.5 Estimating Km and Vmax

Method A — Two-point method (uses steady-state data at two dose levels).

At steady state, the dosing rate **R** (drug in per day) equals the elimination rate (drug destroyed per day):

$$\mathbf{R = Vmax \times Css / (Km + Css)} \quad \ldots(\star)$$

With two dose levels we have two equations, two unknowns (Km, Vmax) — solvable:

$$R1 = Vmax \cdot Css1/(Km + Css1); \quad R2 = Vmax \cdot Css2/(Km + Css2)$$

Solving (worked in Calculation Box 6.1) gives:

$$\mathbf{Km = Css1 \cdot Css2 \cdot (R2 - R1) / (R1 \cdot Css2 - R2 \cdot Css1) \quad Vmax = R1 \cdot (Km + Css1) / Css1}$$

Conditions for validity: the patient must truly be at steady state at both dose levels; one saturable pathway must dominate elimination; and protein binding should not be changing wildly between the two levels.

Method B — Lineweaver–Burk style linearisation (the concept).

Take reciprocals of both sides of the Michaelis–Menten equation. From v = Vmax·C/(Km + C):

1/v = (Km/Vmax)·(1/C) + 1/Vmax

This is the equation of a straight line (y = mx + c) if we plot **1/v on the y-axis** against **1/C on the x-axis**:

- Slope = Km/Vmax
- y-intercept = 1/Vmax → gives Vmax directly
- x-intercept = −1/Km → gives Km

In PK terms: at steady state, v is replaced by the dosing rate R and C by Css: **1/R = (Km/Vmax)·(1/Css) + 1/Vmax**. Plot 1/R vs 1/Css for several dose levels, draw the best straight line, read off slope and intercepts → Km and Vmax. *Exam note:* you usually only need the concept and the axis labels, not a full graph.

6.6.6 Predicting steady-state concentration after a dose change

Rearrange equation (★) to solve for Css. Starting from R = Vmax·Css/(Km + Css):

R(Km + Css) = Vmax·Css R·Km + R·Css = Vmax·Css R·Km = Css(Vmax − R) **Css = R·Km / (Vmax − R)**

Reading this formula: as the dosing rate R approaches Vmax, the denominator (Vmax − R) shrinks toward zero, and Css explodes toward infinity. That is the mathematical picture of the phenytoin cliff: **as the dose nears the liver's maximum capacity, concentration shoots up without limit.** Also note: if R ≥ Vmax, no steady state is possible at all — the drug accumulates forever. A very useful safety check.

6.7 Calculation Boxes (Worked Numericals)

Calculation Box 6.1 — Estimating Km and Vmax by the two-point method

Problem: A patient on phenytoin reaches steady state at two dose levels: Dose 300 mg/day → Css = 10 mg/L; Dose 400 mg/day → Css = 20 mg/L. Estimate Km and Vmax.

Step 1 — List the data. R1 = 300 mg/day, Css1 = 10 mg/L; R2 = 400 mg/day, Css2 = 20 mg/L.

Step 2 — Write the Km formula. Km = Css1·Css2·(R2 − R1) / (R1·Css2 − R2·Css1)

Step 3 — Numerator: 10 × 20 × (400 − 300) = 200 × 100 = **20,000**

Step 4 — Denominator: (300 × 20) − (400 × 10) = 6,000 − 4,000 = **2,000**

Step 5 — Km = 20,000 / 2,000 = ***10 mg/L***

Step 6 — Vmax = R1·(Km + Css1)/Css1 = 300 × (10 + 10)/10 = 300 × 20/10 = ***600 mg/day***

Step 7 — Check with the second dose level: Predicted R2 = Vmax·Css2/(Km + Css2) = 600 × 20/(10 + 20) = 12,000/30 = **400 mg/day** ✓ matches the given dose.

Answer: Km = 10 mg/L, Vmax = 600 mg/day. *Interpretation:* this patient's liver can destroy at most 600 mg of phenytoin per day, and the enzyme is half-saturated at 10 mg/L — which is inside the therapeutic range, so saturation at normal doses is expected.

Calculation Box 6.2 — Predicting the new Css after a dose increase

Problem: Using Km = 10 mg/L and Vmax = 600 mg/day from Box 6.1, predict the steady-state concentration if the dose is raised to **500 mg/day**.

Step 1 — Write the Css formula: Css = R·Km/(Vmax − R)

Step 2 — Insert values: R = 500, Km = 10, Vmax = 600 Css = 500 × 10 / (600 − 500) = 5,000 / 100 = **50 mg/L**

Step 3 — Compare with the old level: Old: 300 mg/day → 10 mg/L. New: 500 mg/day → 50 mg/L. Dose increased by only **67%** (300 → 500), but concentration increased **5 times** (10 → 50).

Step 4 — Safety check: Is R < Vmax? 500 < 600 ✓, so a steady state exists — but only just. The denominator (600 − 500 = 100) is small, which is why Css is so large.

Answer: Css ≈ 50 mg/L. *Clinical warning:* this level is far above the usual therapeutic range — the patient would likely show toxicity. In real practice the dose would never be jumped like this without blood-level monitoring.

Calculation Box 6.3 — Why a 10% dose increase can double the concentration

Problem: The same patient (Km = 10 mg/L, Vmax = 600 mg/day) is stable at 500 mg/day with Css = 50 mg/L (from Box 6.2). The dose is increased by just **10%** to 550 mg/day. What is the new Css?

Step 1 — New dosing rate: R = 500 × 1.10 = **550 mg/day**

Step 2 — Css = R·Km/(Vmax R) = 550 × 10/(600 550) = 5,500/50 = ***110 mg/L***

Step 3 — Compare: Dose: 500 → 550 mg/day (**+10%**). Concentration: 50 → 110 mg/L (**+120% — more than doubled**).

Step 4 — Why? Look at the denominator: Vmax − R shrank from 100 to 50. The dose is now very close to the liver's maximum capacity (600 mg/day). The enzymes are almost fully saturated, so nearly all of the extra drug piles up in the blood instead of being destroyed.

Answer: Css ≈ 110 mg/L — more than double, from a mere 10% dose rise. *This is the single most exam-worthy and clinic-worthy fact of nonlinear PK: near saturation, tiny dose changes cause huge concentration swings. Always adjust phenytoin-type drugs in small steps with blood-level monitoring.*

6.8 Application of PK Software: In-Silico Methods

6.8.1 Introduction — what "in-silico" means

From zero: Experiments can be done *in the body* (in vivo), *in glassware* (in vitro), or *in the computer* (**in silico** — from "silicon", the material of computer chips). PK software performs in-silico pharmacokinetics: it takes measured drug concentrations, fits mathematical equations to them, calculates PK parameters, and **simulates** what would happen under different doses, in different patients, or with different formulations — all on a screen, before (or instead of) another human or animal experiment.

Why it matters: real clinical trials are slow, expensive, and expose people to risk. A good simulation can answer "what if we double the dose?" or "what if the patient has kidney failure?" in minutes, guiding safer and cheaper decisions.

6.8.2 What PK software does — the three core jobs

1. **Curve fitting.** You feed in measured concentration–time points (from blood samples). The software finds the equation (one-compartment, two-compartment, Michaelis–Menten, etc.) whose curve passes closest to your points, and reports the best parameter values (clearance, volume, rate constants, Km, Vmax). Doing this by hand with graph paper is possible for simple cases but impractical for real data.
2. **Non-compartmental analysis (NCA).** The software calculates AUC (by the trapezoidal rule), half-life, clearance, and mean residence time directly from the data, without assuming any compartment model. This is the workhorse of bioequivalence studies.

3 **Simulation.** Once a model is fitted, the software predicts concentrations for doses, schedules, or patient types you have *not* tested — "what-if" scenarios. Example: simulate 10 different doses of a nonlinear drug and find the one that keeps Css inside the therapeutic window, before trying it in a patient.

6.8.3 Categories of tools (by function, with widely known examples)

Note: tool names below are widely known examples mentioned only to orient the student; this is not an endorsement, and no versions, prices, or performance claims are made — such details change and must be checked from official sources.

Functional category	What it does	Widely known example(s)	Typical uses
Compartmental modelling software	Fits 1-, 2-, or 3-compartment (and nonlinear) models to concentration–time data; estimates rate constants, V, Cl, Km, Vmax	Tools in the style of classic PK modelling programs	Research, teaching curve fitting, analysing nonlinear data
Non-compartmental analysis (NCA) tools	Computes AUC, Cmax, tmax, half-life, clearance by numerical methods without a model	Spreadsheet add-ins and dedicated NCA modules	Bioequivalence studies, first-pass analysis of trial data
Population PK tools	Analyses data from many patients together; separates typical values from patient-to-patient variability; finds covariates (weight, age, kidney function)	NONMEM-style programs	Dose individualisation, regulatory submissions, sparse-sample studies
Physiologically-based PK (PBPK) tools	Builds a virtual body from real organs, blood flows, and enzyme amounts; predicts absorption and drug–drug interactions mechanistically	GastroPlus-style platforms	Predicting food effects, drug interactions, paediatric or pregnancy dosing, formulation design
General scientific computing	Flexible programming environments for custom models, statistics, and graphics	MATLAB-style and R-style environments	Teaching, research prototyping, custom simulations

6.8.4 Simulation for dose optimisation and "what-if" scenarios

Simulation is where in-silico methods earn their keep. Typical what-if questions a pharmacist or formulator can explore:

- **Dose optimisation:** For a nonlinear drug, simulate Css at 300, 350, 400, 450, 500 mg/day and pick the dose that lands inside the therapeutic window — instead of experimenting on the patient (recall Calculation Box 6.3: near saturation, guessing is dangerous).
- **Missed or extra dose:** Simulate what happens to concentrations if a patient misses two doses, or accidentally doubles one.
- **Special populations:** Simulate exposure in a patient with kidney failure, liver disease, or an elderly patient, by adjusting clearance and volume in the model.
- **Drug interactions:** If a second drug inhibits the metabolising enzyme (lowering Vmax), simulate how much the first drug's Css will rise.

- **Formulation changes:** For a modified-release tablet, simulate whether the new release rate keeps concentrations in range.

Simple analogy: Simulation is a **flight simulator for dosing** — the pilot (pharmacist/doctor) practices crashes on the computer, not with real passengers.

6.8.5 Role in drug development and in teaching

- **Drug development:** In-silico PK supports decisions at every stage — predicting human doses from animal data, designing clinical trials (how many blood samples, at what times), justifying doses to regulators, and exploring drug–drug interactions without testing every combination in people. It reduces the number of animal and human experiments needed.
- **Teaching:** For a B.Pharm student, PK software turns abstract equations into visible curves. Change Km with a slider and watch the concentration–time curve bend from linear to saturated; simulate phenytoin dosing and *see* the cliff from Calculation Box 6.3. Concepts that take pages of algebra become obvious in one picture. Many colleges use such tools in biopharmaceutics practicals and demonstrations.

Cautious note for exams and practice: software output is only as good as the model and the data behind it — "garbage in, garbage out". A simulation never replaces clinical judgement or therapeutic drug monitoring; it guides them.

6.9 Comparison Tables

Table 6A — Linear vs Nonlinear Pharmacokinetics

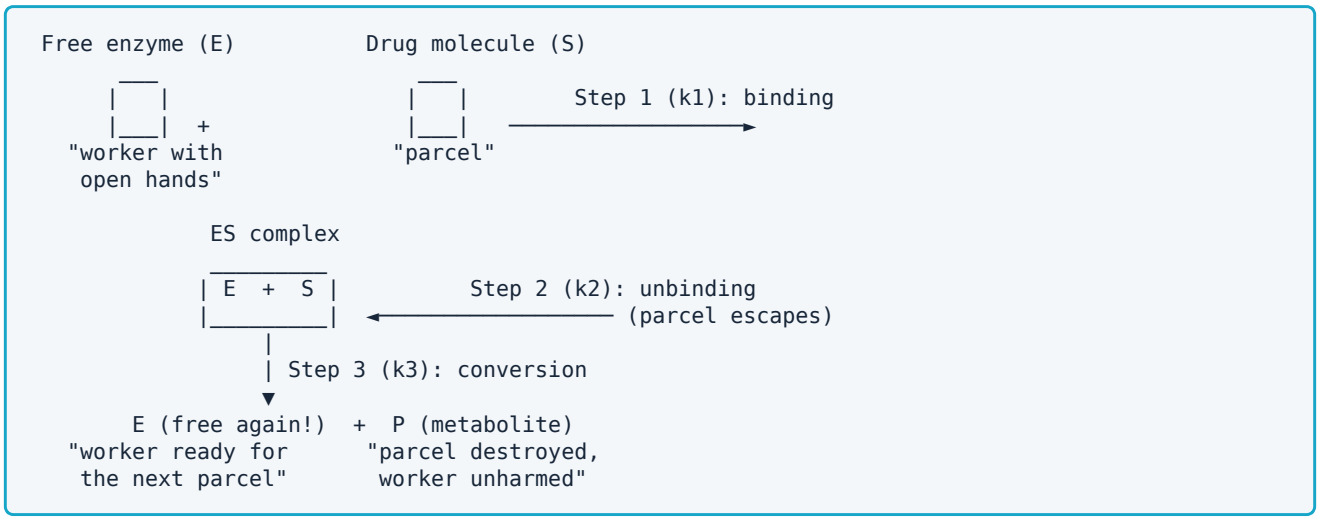
Feature	Linear PK	Nonlinear PK
AUC vs dose	Proportional (double dose → double AUC)	Not proportional (more or less than expected)
Css vs dose	Proportional	Disproportionate — often explodes upward near saturation
Clearance	Constant, independent of dose/concentration	Changes with dose/concentration
Half-life	Constant	Changes with dose (lengthens when metabolism saturates)
Underlying cause	Enzymes/carriers never saturated at used doses	Some step saturates: metabolism, binding, secretion, absorption
Rate equation	First-order: rate = k·C	Michaelis–Menten: rate = Vmax·C/(Km + C)
Dose adjustment	Simple proportional scaling works	Needs TDM; small steps; model-based prediction
Examples	Most drugs at normal doses	Phenytoin, salicylates (high dose), ethanol, carbamazepine (autoinduction)
Clinical risk	Predictable	Small dose change → large concentration swing → toxicity risk

Table 6B — Software-Assisted vs Manual Calculation

Feature	Manual calculation	Software-assisted (in-silico)
Curve fitting	Graph paper / linear plots; only simple models	Fits complex and nonlinear models to data in seconds
NCA parameters	Hand trapezoidal rule; slow, error-prone	Instant AUC, half-life, clearance from raw data
Nonlinear (Km, Vmax) estimation	Two-point or Lineweaver–Burk by hand; needs ideal data	Robust fitting even with messy, sparse real-world data
Simulation / what-if	Practically impossible by hand	Simulate untested doses, populations, interactions
Population analysis	Not feasible manually	NONMEM-style tools handle hundreds of patients
Teaching value	Builds fundamental understanding	Visual, interactive; shows the "cliff" instantly
Limitations	Time-consuming; simple models only	"Garbage in, garbage out"; needs valid model and good data
Best use	Learning concepts; quick bedside checks	Research, development, regulatory work, complex dosing

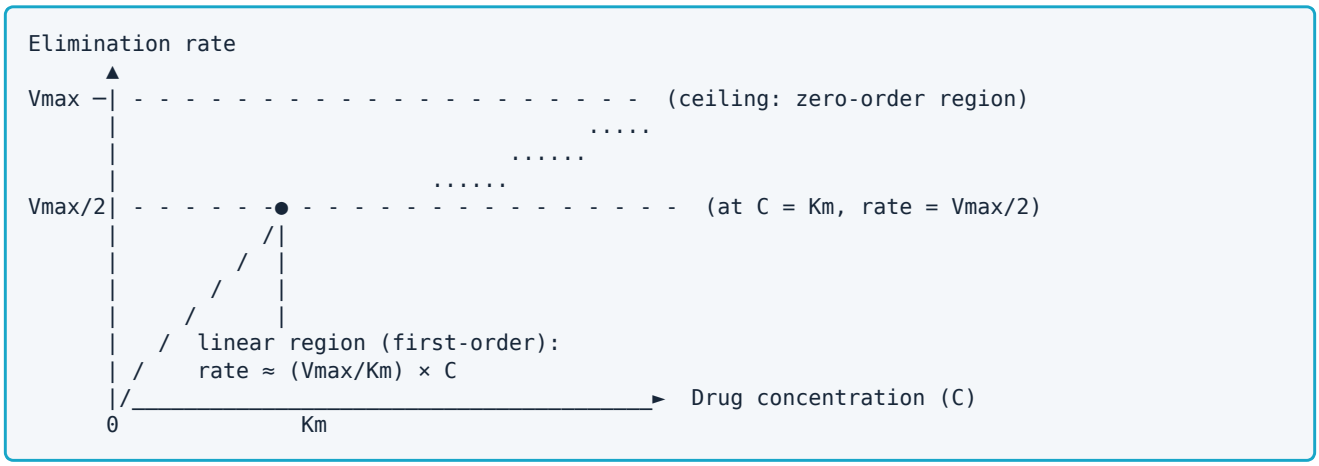
6.10 Diagrams (Textual)

Diagram 6.1 — The enzyme at work (E + S ⇌ ES → E + P)



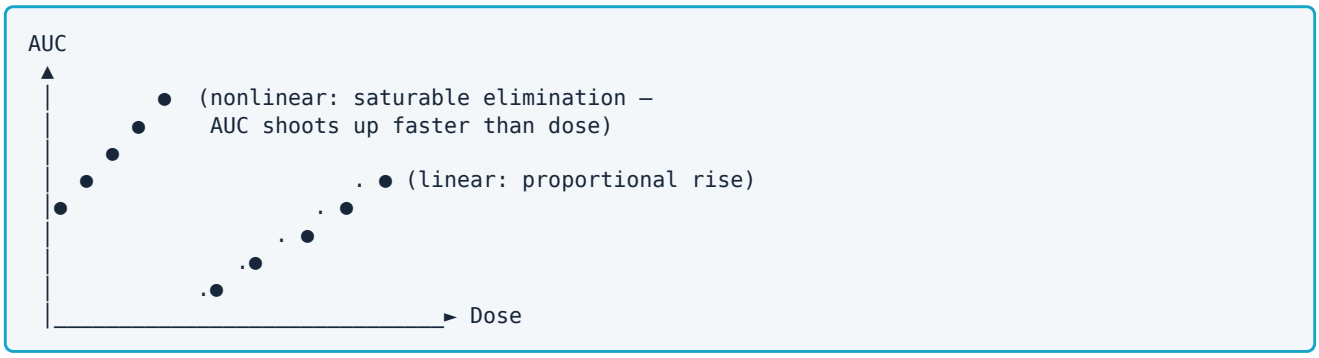
Reading the diagram: the worker (enzyme) is never consumed — it handles one parcel at a time, then is free again. When parcels arrive faster than workers can process them, a queue forms: **saturation**.

Diagram 6.2 — Michaelis–Menten curve: elimination rate vs concentration



Reading the curve: at low C the curve is a straight line (linear PK); it bends as enzymes fill up; it flattens at Vmax (saturated, zero-order). Km marks the concentration where the rate is half-maximal.

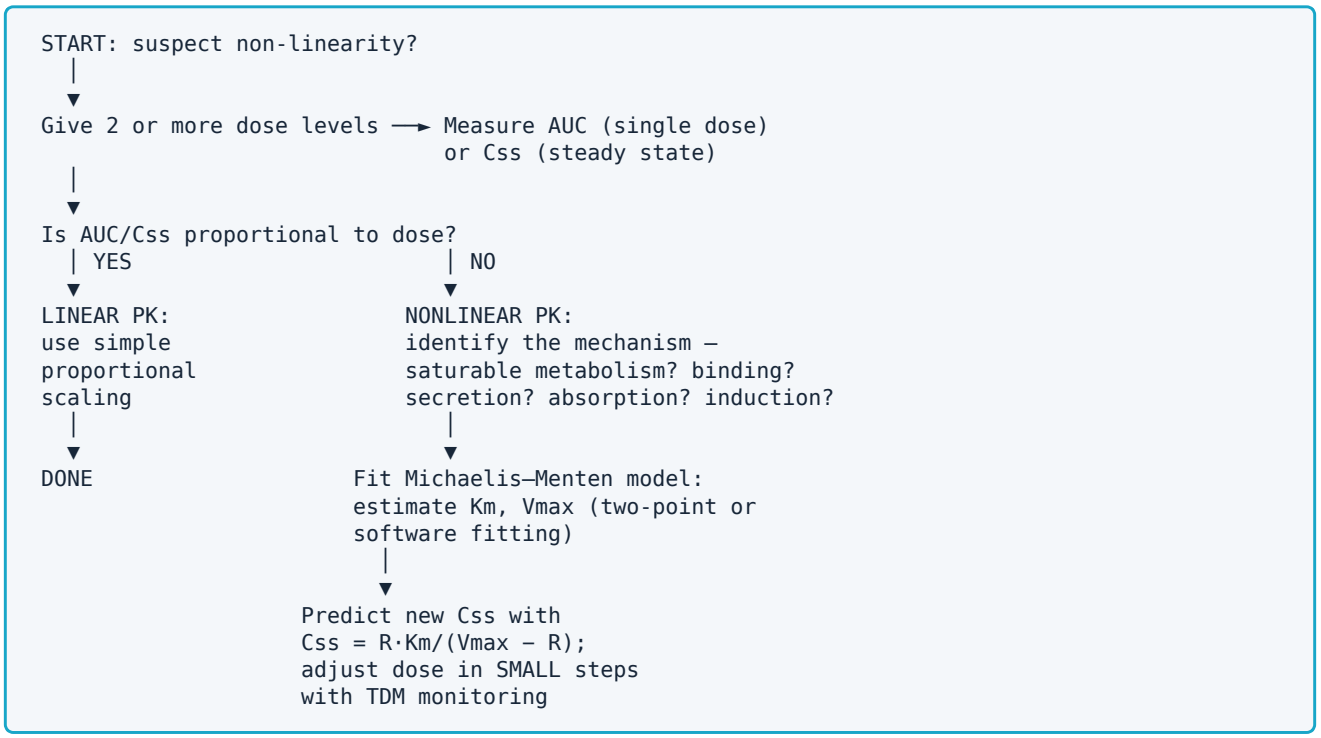
Diagram 6.3 — Detecting non-linearity: AUC vs dose



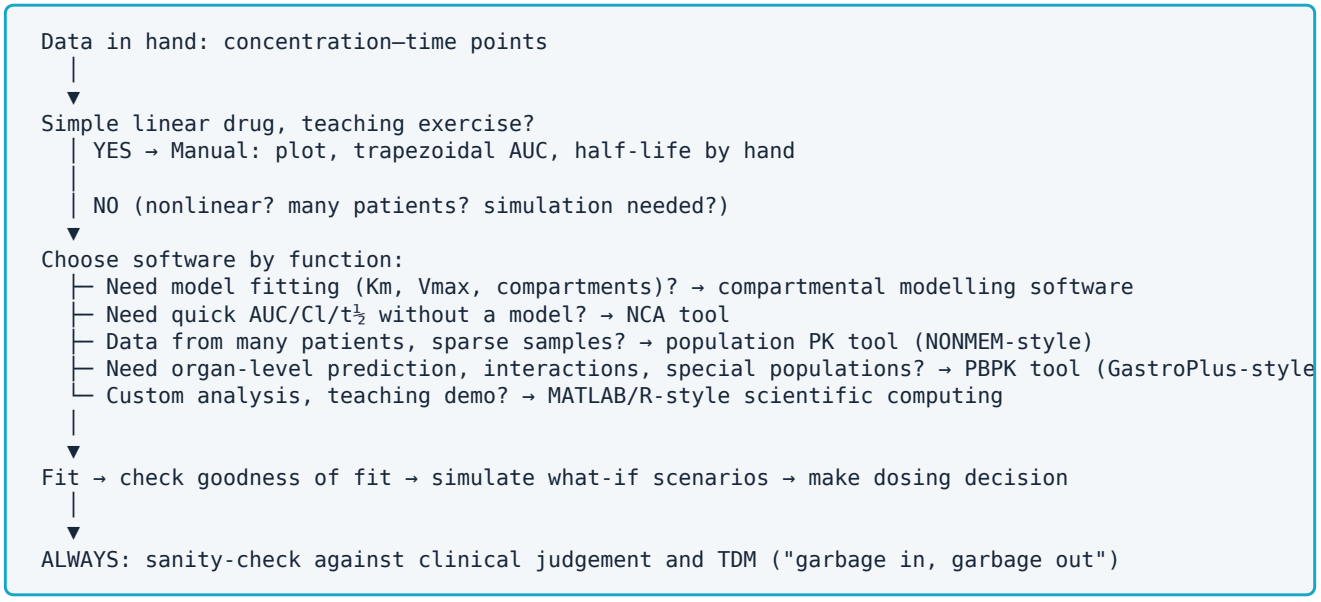
Reading the plot: the dotted straight line is linear behaviour. Points curving **above** the line = saturable elimination (phenytoin pattern). Points curving **below** the line = saturable absorption or induction.

6.11 Flowcharts (Textual)

Flowchart 6.1 — How to detect and handle non-linearity



Flowchart 6.2 — Choosing the analysis path: manual vs software



6.12 Infographic Concept Box

INFOGRAPHIC CONCEPT: "The Phenytoin Cliff"

Visual idea for a poster or slide: A mountain-climbing trail graph.

- **X-axis (trail distance):** daily dose — 300 → 400 → 500 → 550 mg/day (evenly spaced markers).
- **Y-axis (altitude):** steady-state concentration — 10 → 20 → 50 → 110 mg/L.
- **The trail:** starts as a gentle slope (300→400 mg), then steepens sharply (400→500 mg), then becomes a near-vertical **cliff face** (500→550 mg).
- **A red dashed horizontal line** marks the top of the therapeutic window ("toxicity above this line").
- **A cartoon liver with tiny worker-enzymes** at the base: at 300 mg most workers idle (green); at 550 mg every worker is red-faced and sweating, with a long queue of drug molecules waiting.
- **Caption:** *"Near saturation, the dose–concentration trail turns into a cliff. A 10% step in dose a 120% leap in concentration. Tread in small steps. Monitor blood levels."*

One-line message: Saturation turns gentle dose slopes into cliffs — that is why nonlinear drugs are dosed in baby steps.

6.13 Examples (Drug Stories)

1 **Phenytoin and the 10% trap.** A stable epilepsy patient on 500 mg/day (Css 50 mg/L in our worked example) gets a "small" 10% increase to 550 mg/day. The new Css is 110 mg/L — toxicity (ataxia, nystagmus, drowsiness) follows. Lesson: near Vmax, dose and concentration are no longer friends.

2 **Aspirin at two doses.** Low-dose aspirin (antiplatelet) is handled linearly, but high anti-inflammatory doses saturate the metabolic pathways — the half-life stretches from hours to much longer, and salicylate accumulates. Same drug, two behaviours, depending on dose.

3 **Alcohol's fixed speed.** The liver clears ethanol at an almost constant rate (zero-order) because the enzyme is saturated at the concentrations reached after even moderate drinking. Drinking twice as much does not double the clearance rate — it doubles the *time* needed to sober up. A everyday-life example of Michaelis–Menten saturation.

4 **Carbamazepine's disappearing act.** Started at a dose that controls seizures, carbamazepine induces its own metabolism over 2–3 weeks; blood levels fall and seizures may return. The pharmacist explains autoinduction and the doctor raises the dose — the opposite direction from the phenytoin story, but equally non-linear.

6.14 Analogies (Making It Stick)

1. **The toll booth (saturation).** Cars = drug molecules; the toll booth = the enzyme. At 3 a.m., cars pass straight through (linear). At rush hour, the booth processes a fixed 10 cars/minute no matter how many arrive — the queue (blood concentration) grows out of proportion. That queue is non-linear PK.
2. **The kitchen with 10 cooks (Vmax).** Ten cooks, one dosa each per minute → Vmax = 10 dosas/minute, fixed forever. Km is the crowd size at which the kitchen runs at half speed (5 dosas/minute). A small café (small Km) gets overwhelmed by a modest crowd — like phenytoin saturating at therapeutic levels.
3. **Musical chairs (protein binding).** Drug molecules circle chairs (albumin binding seats) while the music plays. While chairs are free, the same fraction always sits. When all chairs are taken, every newcomer must keep standing (free drug) — the free fraction suddenly jumps.
4. **The ferry across the river (GI absorption).** Ferries (carrier proteins) carry passengers (drug) across. A few passengers → everyone crosses (linear). A festival crowd → ferries run full continuously (saturated); extra people simply cannot cross — absorption hits a ceiling.
5. **The flight simulator (PK software).** A pilot trains crashes in a simulator, not with real passengers. A pharmacist simulates a risky dose change on the computer, not on the patient.

6.15 Pharmacy Relevance (Why a Pharmacist Must Know This)

1. **Dose adjustment of narrow-window drugs.** Phenytoin, carbamazepine, and high-dose salicylates demand small dose steps and blood-level monitoring. The pharmacist is often the one who spots a dangerous "small" dose increase on a prescription.
2. **Therapeutic drug monitoring (TDM).** Interpreting a phenytoin level requires knowing it is nonlinear: a level slightly above range after a small dose hike is expected and urgent, not a lab error.
3. **Patient counselling.** Epilepsy patients must understand: never double a missed phenytoin dose yourself, never stop abruptly, and report drowsiness, double vision, or unsteady walking immediately — these are saturation-toxicity signals.
4. **Detecting interactions.** A second drug that inhibits the metabolising enzyme lowers Vmax — the phenytoin cliff moves closer. The pharmacist anticipates the interaction before toxicity appears.
5. **In-silico support in practice.** Hospital and industry pharmacists increasingly meet model-based dosing (population PK, PBPK predictions). Understanding what the software does — and its "garbage in, garbage out" limit — keeps the pharmacist in charge of the decision, not the computer.

6.16 India Context

- **Epilepsy care and phenytoin:** Phenytoin remains a widely used, affordable antiepileptic in India. Because it is nonlinear with a narrow therapeutic window, Indian hospital pharmacists and physicians rely on **therapeutic drug monitoring (TDM)** — available at major government medical colleges, tertiary hospitals, and reference laboratories — to guide its dosing. The pharmacist's role in counselling patients never to self-adjust the dose is especially important where follow-up visits may be infrequent.
- **Salicylates:** Aspirin is commonly available and sometimes taken in high doses for pain or fever without prescription. Pharmacists counsel that high doses saturate metabolism, prolong the drug's stay, and raise the risk of toxicity (ringing in the ears, rapid breathing) — a direct, everyday consequence of nonlinear PK.
- **Teaching with software:** Many Indian pharmacy colleges now demonstrate PK concepts with computer-based curve fitting and simulation in biopharmaceutics practicals, since in-silico tools make the abstract "saturation cliff" visible to students without costly experiments.
- **Regulatory note (cautious):** model-based and simulation-supported evidence is increasingly part of drug development dossiers worldwide, including those reviewed for the Indian market; the trend favours pharmacists who can read and question a simulation, not just operate software.

6.17 Key Points (Chapter at a Glance)

1 Linear PK: double the dose → double the AUC/Css. Nonlinear PK: not proportional.

2 Detect non-linearity by comparing AUC or Css across two or more dose levels.

3 Seven reasons (PAMES-EH): saturable **P**rotein binding, **A**bsorption, **M**etabolism, **E**nterohepatic recycling, tubular **S**ecretion, **E**nzyme induction, **H**epatic blood flow.

4 Phenytoin is the classic saturable-metabolism drug: small dose rise → huge concentration jump → toxicity.

5 Michaelis–Menten: $-dC/dt = Vmax \cdot C/(Km + C)$, derived from $E + S \rightleftharpoons ES \rightarrow E + P$ with the steady-state assumption.

6 Vmax = maximum elimination rate (depends on enzyme amount); Km = concentration at half Vmax (measures binding tightness).

7 $C << Km$ → first-order (linear), rate ≈ $(Vmax/Km) \cdot C$; $C >> Km$ → zero-order (saturated), rate ≈ Vmax.

8 At steady state: $R = Vmax \cdot Css/(Km + Css)$; rearranged: $Css = R \cdot Km/(Vmax - R)$. If R approaches Vmax, Css explodes — no steady state exists if $R \geq Vmax$.

9 Two-point method estimates Km and Vmax from two steady-state dose–concentration pairs; Lineweaver–Burk plots 1/R vs 1/Css as a straight line (slope Km/Vmax, intercept 1/Vmax).

10 PK software does curve fitting, NCA, and simulation; functional families include compartmental modelling, NCA tools, population PK (NONMEM-style), PBPK (GastroPlus-style), and MATLAB/R-style scientific computing — aids, not replacements, for clinical judgement and TDM.

6.18 Common Confusions (Cleared)

1 **"Nonlinear means the drug doesn't work."** No — it only means concentration doesn't rise proportionally with dose. The drug works; it is just harder to dose predictably.

2 **"Zero-order means nothing is eliminated."** No — zero-order means a *constant amount* is eliminated per unit time (e.g., 600 mg/day), regardless of concentration. Elimination continues; it just can't speed up.

3 **"Km is a rate."** No — Km is a *concentration* (mg/L). Vmax is the rate (mg/day). Mixing them up is the most common derivation error.

4 **"A small Km means weak binding."** Opposite — small Km means the enzyme binds the drug *tightly* and saturates at *low* concentrations (more dangerous).

5 **"If AUC rises less than dose, the drug is linear."** No — that is also non-linear (saturable absorption or induction). Any non-proportionality = non-linear.

6 **"Software replaces TDM and clinical judgement."** No — software *guides* dosing; blood-level monitoring and the pharmacist's judgement remain essential, especially near saturation.

7 **"Lineweaver–Burk is the most accurate estimation method."** It is mainly a teaching/visualisation tool; reciprocal plots magnify errors at low concentrations. Modern practice fits the nonlinear equation directly with software.

6.19 Common Mistakes (Exam Hall Warnings)

1 Writing the Michaelis–Menten equation upside down — it is Vmax·C/(Km + C), not Km·C/(Vmax + C).

2 Forgetting the steady-state condition (R = elimination rate) before applying R = Vmax·Css/(Km + Css) — the formula is invalid for single-dose data.

3 Using total instead of free concentration arguments loosely — for highly protein-bound drugs, saturation of binding changes the picture.

4 Predicting Css with the linear rule ("dose up 10%, level up 10%") for a nonlinear drug — the central clinical blunder this chapter warns against.

5 In the two-point method, mixing up which is R1/Css1 vs R2/Css2, or getting a negative Km — a negative Km signals arithmetic error or data that don't fit one saturable pathway.

6 Stating software names with invented version numbers, prices, or "best/fastest" claims — describe function only; never fabricate details.

7 In derivations, skipping the enzyme-conservation step ([E]t = [E] + [ES]) — examiners look for it.

6.20 Mnemonics

- **Reasons for non-linearity — "PAMES-EH":** *Phenytoin And Metabolising Enzymes Saturate — EnteroHepatic too!*

Protein binding · **A**bsorption (GI) · **M**etabolism · **E**nterohepatic recycling · **S**ecretion (tubular) · **E**nzyme induction · **H**epatic blood flow.

- **Km vs Vmax — "Konc, Velo":** **K**m is a **Konc**entration (mg/L); **V**max is a **Velo**city/rate (mg/day).
- **Saturation direction — "MAMA":** **M**etabolism saturates → levels rise **M**ore than dose; **A**bsorption saturates → levels rise less (**A** little).
- **The cliff formula — "Rush-hour rule":** *Css = R·Km/(Vmax R)* — "as R **rushes** toward Vmax, Css shoots through the roof."
- **Software jobs — "FNS":** **F**itting, **N**CA, **S**imulation — "the software **F**its, **N**umbers, **S**imulates."

6.21 Exam Summary (One Page)

Nonlinear PK = AUC/Css not proportional to dose, because a limited-capacity step (enzyme, carrier, binding protein, pump) saturates. Detect by dose-proportionality testing. Seven reasons: PAMES-EH. Star drugs: phenytoin, salicylates, ethanol (saturable metabolism); carbamazepine (autoinduction); penicillin (tubular secretion); amoxicillin/riboflavin (absorption); propranolol (blood-flow-limited). Michaelis–Menten from E + S ⇌ ES → E + P via steady-state: −dC/dt = Vmax·C/(Km + C). Km = conc. at half Vmax = (k2+k3)/k1; Vmax = k3[E]t = ceiling rate. C<<Km → first-order (k = Vmax/Km); C>>Km → zero-order (= Vmax). Steady state: R = Vmax·Css/(Km+Css) → Css = R·Km/(Vmax−R); R→Vmax ⇒ Css explodes. Two-point method and Lineweaver–Burk (1/R vs 1/Css) estimate Km, Vmax. Clinical core: near saturation, tiny dose changes → huge level swings → dose in small steps with TDM. In-silico PK software: curve fitting, NCA, simulation; families — compartmental modelling, NCA tools, population PK (NONMEM-style), PBPK (GastroPlus-style), MATLAB/R-style computing; used for dose optimisation, what-if scenarios, drug development, and teaching. Software aids judgement; it never replaces TDM.

6.22 One-Minute Revision

Linear = proportional; nonlinear = saturated somewhere. Test: two doses, compare AUC/Css. Reasons: PAMES-EH. Equation: −dC/dt = Vmax·C/(Km+C). Km = half-speed concentration; Vmax = ceiling rate. Low C → first-order; high C → zero-order. Steady state: Css = R·Km/(Vmax−R) — near Vmax, levels explode (phenytoin!). Estimate Km, Vmax by two-point method or Lineweaver–Burk. Software: fitting, NCA, simulation — guides dosing, never replaces monitoring.

6.23 Exam Questions

A. MCQs (with answer key)

Q1. Linear pharmacokinetics means: a) The drug is eliminated only by the kidney b) AUC and Css rise in direct proportion to dose c) The half-life changes with dose d) The drug follows zero-order kinetics **Answer: b**

Q2. Non-linearity is detected by: a) Measuring the drug's colour b) Checking whether AUC or Css rise in proportion to dose across two or more dose levels c) Counting the number of metabolites d) Measuring protein binding once **Answer: b**

Q3. In the Michaelis–Menten equation $-dC/dt = Vmax \cdot C/(Km + C)$, Km represents: a) The maximum elimination rate b) The drug concentration at which the elimination rate is half of Vmax c) The first-order rate constant d) The volume of distribution **Answer: b**

Q4. When C >> Km, the elimination follows: a) First-order kinetics b) Second-order kinetics c) Zero-order kinetics (rate ≈ Vmax) d) No elimination **Answer: c**

Q5. When C << Km, the apparent first-order rate constant equals: a) Vmax b) Km c) Vmax/Km d) Km/Vmax **Answer: c**

Q6. The classic example of saturable metabolism with a narrow therapeutic window is: a) Paracetamol at low dose b) Phenytoin c) Amoxicillin d) Propranolol **Answer: b**

Q7. Carbamazepine shows non-linearity because of: a) Saturable GI absorption b) Autoinduction of its own metabolism c) Saturable protein binding d) Enterohepatic recycling **Answer: b**

Q8. In a Lineweaver–Burk style plot for steady-state PK data, the axes are: a) R vs Css b) 1/R vs 1/Css c) log R vs log Css d) R vs 1/Css **Answer: b**

Q9. Which functional category of PK software analyses data from many patients together to find patient-to-patient variability? a) NCA tools b) Population PK tools (NONMEM-style) c) Spreadsheet add-ins d) Curve-fitting only tools **Answer: b**

Q10. The greatest clinical danger of nonlinear drugs like phenytoin is that: a) They stop working suddenly b) A small dose increase near saturation can cause a disproportionately large rise in concentration and toxicity c) They cannot be given orally d) They always need intravenous dosing **Answer: b**

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

B. Viva Questions

1 Define linear pharmacokinetics in one sentence. *(AUC/Css proportional to dose.)*

2 How do you detect non-linearity experimentally? *(Two or more dose levels; check proportionality of AUC/Css.)*

3 State the Michaelis–Menten equation in PK form and name each symbol. *(dC/dt = Vmax·C/(Km + C); Vmax = max elimination rate, Km = half-saturation concentration, C = drug concentration.)*

4 What is the physical meaning of Km? *(Concentration at which elimination rate is half of Vmax; measures enzyme–drug binding tightness.)*

5 What happens to the rate equation when C << Km and when C >> Km? *(First-order with k = Vmax/Km; zero-order at Vmax.)*

6 Name three drugs showing saturable metabolism. *(Phenytoin, salicylates/aspirin at high dose, ethanol.)*

7 Why must phenytoin doses be changed in small steps? *(Near saturation, a small dose rise causes a huge concentration jump — toxicity risk.)*

8 What are the three core jobs of PK software? *(Curve fitting, non-compartmental analysis, simulation.)*

C. Application-Based Questions

1 A patient's phenytoin level is 18 mg/L on 400 mg/day. The doctor proposes raising the dose to 500 mg/day "since levels rise proportionally." As the pharmacist, what do you advise, and which formula supports your caution? *(Advise against proportional thinking; near saturation Css = R·Km/(VmaxR) predicts a disproportionate jump — recommend a smaller step with repeat TDM.)*

2 Two patients take the same dose of a high-extraction drug; one has heart failure. Why might their concentrations differ greatly, and which reason for non-linearity is involved? *(Hepatic blood-flow dependence — clearance follows blood flow, which is reduced in heart failure.)*

3 A carbamazepine patient is seizure-free in week 1 but seizures return in week 3 on the same dose. Explain and suggest the pharmacist's counselling points. *(Autoinduction lowered levels; counsel adherence, no self dose changes, report recurrence, expect a medically supervised dose increase.)*

4 You must choose a software approach to predict drug exposure in children from adult data without a new trial. Which functional category fits, and what is its key limitation? *(PBPK (GastroPlus-style) — mechanistic organ-based prediction; limitation: only as good as the model assumptions and input data — "garbage in, garbage out.")*

D. Numerical Problems (with fully worked solutions)

Problem 1. A patient at steady state shows: 200 mg/day → Css = 8 mg/L; 300 mg/day → Css = 16 mg/L. Estimate Km and Vmax by the two-point method, and verify with the second dose level.

Solution: Step 1 — R1 = 200, Css1 = 8; R2 = 300, Css2 = 16. Step 2 — Km = Css1·Css2·(R2 − R1)/(R1·Css2 − R2·Css1) = 8 × 16 × (300 − 200) / (200 × 16 − 300 × 8) = 128 × 100 / (3,200 − 2,400) = 12,800/800 = **16 mg/L**. Step 3 — Vmax = R1·(Km + Css1)/Css1 = 200 × (16 + 8)/8 = 200 × 24/8 = **600 mg/day**. Step 4 — Verify: predicted R2 = 600 × 16/(16 + 16) = 9,600/32 = **300 mg/day** ✓. **Answer: Km = 16 mg/L, Vmax = 600 mg/day.**

Problem 2. For the patient in Problem 1 (Km = 16 mg/L, Vmax = 600 mg/day), predict Css if the dose is increased to 400 mg/day. Compare the percentage rise in dose vs the percentage rise in concentration.

Solution: Step 1 — Css = R·Km/(Vmax − R) = 400 × 16/(600 − 400) = 6,400/200 = **32 mg/L**. Step 2 — Old: 300 mg/day → 16 mg/L. New: 400 mg/day → 32 mg/L. Step 3 — Dose rise = (400 − 300)/300 = **33%**; concentration rise = (32 − 16)/16 = **100%** (doubled). **Answer: Css ≈ 32 mg/L — a 33% dose increase doubles the concentration.**

Problem 3. A drug has Vmax = 500 mg/h and Km = 20 mg/L. Calculate the elimination rate (a) at C = 2 mg/L and (b) at C = 200 mg/L. Show that case (a) is approximately first-order and case (b) approximately zero-order.

Solution: Step 1 — General: rate = Vmax·C/(Km + C). Step 2 — (a) C = 2: rate = 500 × 2/(20 + 2) = 1,000/22 = **45.5 mg/h**. First-order prediction: (Vmax/Km)·C = (500/20) × 2 = 25 × 2 = 50 mg/h. 45.5 ≈ 50 ✓ (approximately first-order, since 2 << 20). Step 3 — (b) C = 200: rate = 500 × 200/(20 + 200) = 100,000/220 = **454.5 mg/h**. Zero-order prediction: Vmax = 500 mg/h. 454.5 ≈ 500 ✓ (approximately zero-order, since 200 >> 20 — a 100-fold rise in C from case (a) raised the rate only ~10-fold, and it is approaching the ceiling). **Answer: (a) ≈ 45.5 mg/h (first-order-like); (b) ≈ 454.5 mg/h (zero-order-like, near Vmax).**

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