

Unit 5: Application of Pharmacokinetics

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5.1 Application to modified release drug products

Modified release products (sustained, controlled, extended release) are designed backwards from pharmacokinetics. The target is a plasma profile: a chosen concentration band held for a chosen time after a single dose, replacing several immediate release doses. The design calculation uses Unit 3 directly: the zero order input rate needed to hold a target concentration is $R = \text{target } C \times CL$ (the infusion equation of section 3.4 worn by a tablet), the immediate release loading portion is sized from the target concentration and V_d like a loading dose, and the total dose is the loading portion plus the rate multiplied by the intended duration. Pharmacokinetics also judges the result: the product shows a flattened curve (lower C_{max} , later T_{max} , smaller peak to trough fluctuation), its AUC must match the intended total exposure, and its in vitro release profile is tied to the plasma profile by the Level A IVIVC of section 2.9, which lets release specifications stand in for clinical performance. Two failure modes are pharmacokinetic: dose dumping, in which the entire dose releases at once (a particular danger with alcohol for some products), converting the regimen into an overdose bolus; and incomplete release, in which the tail of the dose is never released before the product leaves the gut's absorbing region.

5.2 Application to targeted drug delivery systems

Targeted delivery (MPH201T) is applied pharmacokinetics at the level of distribution. A carrier changes the drug's apparent volume of distribution and clearance routes: a liposome or nanoparticle too large for normal capillaries circulates with the plasma volume as its initial space, is cleared by the reticuloendothelial system rather than the kidney, and releases its drug on a schedule set by the carrier, so the plasma curve reflects the carrier's kinetics more than the molecule's. Evaluation therefore measures two concentrations, total drug and released (free) drug, because only the released drug acts and only it can be compared with the conventional product. A targeted product can show a much larger AUC of total drug yet deliver similar or smaller free drug exposure to most tissues, which is precisely its therapeutic point: exposure is redistributed, raised at the target (tumour, infection site) and lowered at the dose limiting organ (for liposomal doxorubicin, the heart).

5.3 Introduction to pharmacokinetics and pharmacodynamics (PK/PD)

Pharmacokinetics says what concentration the dose produces; pharmacodynamics says what effect that concentration produces; therapy needs the two joined. The link is the concentration effect relationship, typically a saturable curve described by the Emax model: $\text{Effect} = (E_{max} \times C) / (EC_{50} + C)$, where E_{max} is the maximum achievable effect and EC_{50} the concentration producing half of it. Joining the models explains everyday observations: effect lags plasma concentration when the drug must distribute to an effect site or act indirectly (the hysteresis loop when effect is plotted against concentration); effect persists after the drug leaves the plasma when binding is irreversible or the response long lived (aspirin on platelets, proton pump inhibitors); and tolerance is a time dependent change on the PD side. Antibiotic dosing is the most quantified PK/PD example: the indices predicting cure are C_{max}/MIC , AUC/MIC and the time above the MIC, each matched to a class of antibiotic.

5.4 Drug interactions as an applied problem

Unit 3 sections 3.9 to 3.12 gave the mechanisms. In practice, interactions are managed by prediction (knowing the isoforms and transporters a drug uses), by design (interaction studies are part of development, and the label states doses to use with strong inhibitors and inducers), and by monitoring (levels and endpoints after any change in a narrow index patient's medicines). Interactions are pharmacokinetics in reverse: the same equations predict how much an inhibitor raises a C_{ss} ($\text{new } C_{ss} = \text{old } C_{ss} \times (\text{old } CL / \text{new } CL)$) and how long induction takes to develop and wear off (enzyme turnover, days to weeks, not the inducer's half life).

5.5 Pharmacokinetics of biotechnology drugs: general principles

Biotechnology drugs (therapeutic proteins, monoclonal antibodies, oligonucleotides, and the products of sections 5.6 to 5.9) obey the same ADME words but by different machinery. **Absorption:** proteins are digested if swallowed, so they are injected; after subcutaneous injection, large molecules enter mainly through the lymphatics, slowly, so T_{max} is measured in days and bioavailability is incomplete and variable. **Distribution:** proteins are largely confined to plasma and extracellular fluid (small V_d) and cross membranes poorly. **Elimination:** there is no CYP metabolism; proteins are cleared by proteolysis throughout the body, by receptor mediated endocytosis after binding their target (target mediated drug disposition, saturable, making kinetics nonlinear at low doses), by the reticuloendothelial system for particles and complexes, and, for small proteins and peptides below the filtration size, by the kidney. **Immunogenicity** overlays everything: anti drug antibodies can accelerate clearance, neutralise activity, or both, and can appear or grow during treatment, so biotechnology kinetics is partly a moving target in a way small molecule kinetics is not.

5.6 Proteins and peptides

Therapeutic proteins and peptides divide by size and origin: replacement proteins (insulin, growth hormone, erythropoietin, clotting factors), enzymes, cytokines and peptide hormones. Their behaviour follows section 5.5 with peptide specific features: small peptides are filtered by the kidney and attacked by peptidases, so natural peptides often have half lives of minutes, and medicinal chemistry buys time: sequence changes resisting peptidases, and above all PEGylation (covalent attachment of polyethylene glycol), which enlarges the molecule beyond the filtration size, shields it from proteases and antibodies, and can stretch a half life from hours to days, as in pegfilgrastim and peginterferon. Insulin is the model system: its formulations (rapid, short, intermediate and long acting) engineer the absorption rate from the injection site to sculpt the plasma profile, the extravascular mathematics of section 3.5 in therapeutic use.

5.7 Monoclonal antibodies

Monoclonal antibodies (immunoglobulin G molecules engineered against a single target: trastuzumab against HER2, rituximab against CD20, adalimumab against TNF) are the largest class of biotechnology drugs. Their pharmacokinetics is distinctive: given intravenously or subcutaneously (bioavailability typically 50 to 80 percent subcutaneously, absorbed through the lymph over several days); distributed in a volume close to plasma plus accessible interstitial fluid; eliminated by proteolysis after cellular uptake, with target mediated clearance adding a saturable component, large when target is abundant and dose small, so clearance falls as dose rises until that pathway saturates; and recycled by FcRn, giving half lives of typically 2 to 4 weeks. Elimination is neither renal nor CYP based, so organ impairment and classic CYP interactions matter far less than for small molecules. Anti drug antibodies, when they form, can clear the antibody rapidly and destroy the response.

5.8 Oligonucleotides

Oligonucleotide drugs (antisense oligonucleotides and small interfering RNAs, and related aptamers of MPH201T) are short synthetic nucleic acid chains that bind a target RNA and change the protein made from it. Their pharmacokinetics is a chemistry story: unmodified oligonucleotides are destroyed by nucleases in minutes, so marketed molecules carry stabilising chemistry (phosphorothioate backbones, 2 prime sugar modifications) that also makes them bind plasma proteins, keeping them in circulation and delivering them to tissues, above all liver and kidney. Plasma half life is short (hours) because tissue distribution is fast, but tissue half life is long (weeks), the molecule being stable inside cells and its effect lasting until the target RNA and protein turn over: dosing intervals of weeks to months follow from the tissue, not the plasma, kinetics. Delivery is the limiting problem: most tissues take up oligonucleotides poorly, solved for the liver by conjugating the molecule to a GalNAc ligand for a liver cell receptor, the strategy behind several approved siRNA drugs. Elimination is by nuclease metabolism to shorter fragments excreted in urine; CYP enzymes are not involved.

5.9 Vaccines (immunotherapy) and gene therapies

Vaccines and gene therapies stretch the pharmacokinetic framework to its limit. A **vaccine** is not meant to maintain a plasma concentration: its product is an immune response, so its evaluation is pharmacodynamic almost by definition: antigen dose, the adjuvant, the kinetics of antigen presentation and antibody production, and the persistence of immune memory, the therapeutic quantity, measured in years. (The PCI text lists vaccines under the heading immunotherapy.) **Gene therapies** deliver a nucleic acid that makes the patient's own cells produce a protein, by viral vectors (adeno associated virus above all) or by lipid nanoparticles carrying mRNA. Their disposition studies measure biodistribution and persistence of the vector and duration of expression rather than a plasma curve: a one time treatment whose expression may last years, with vector clearance, shedding in body fluids, and immune responses to the vector as the studied quantities. The conventional parameters of Unit 3 apply to the carrier and the early phase, after which pharmacology is governed by expression and cell turnover.

The subject in one chain
Dissolution (Unit 1) decides whether the drug is available to absorb
Permeation and first pass decide the fraction that survives (Units 1, 4)
Compartment kinetics turn the curve into parameters (Unit 3)
Bioequivalence proves a new product matches the old (Unit 4)
PK/PD and biotechnology apply the same thinking to harder drugs (Unit 5)

Frequently Asked Questions

Q: What is the difference between biopharmaceutics and pharmacokinetics? Biopharmaceutics studies how the drug's properties, the dosage form and the body's physiology together decide how much drug becomes available and how fast. Pharmacokinetics measures and models what then happens in the body over time, expressing absorption, distribution, metabolism and excretion as parameters such as clearance, volume of distribution, half life and AUC.

Q: Why does the Noyes-Whitney equation matter to a formulator? Because it names every lever controlling dissolution rate in one expression: $dM/dt = (D \times A / h) \times (C_s - C)$. Increasing surface area A by micronisation, raising C_s by salt or solid form selection, and reducing diffusion layer thickness h by agitation each raise the rate proportionally. For a poorly soluble, dissolution limited drug, these are the main tools for improving bioavailability.

Q: What is the pH-partition theory, and what is its main limitation? The theory states that membranes are crossed mainly by the unionised fraction, so a weak acid is best absorbed where it is unionised (acidic

fluid) and a weak base where it is unionised (alkaline fluid), the proportions coming from the Henderson-Hasselbalch equation. Its main limitation is that it ignores surface area and blood flow: weak acids are in practice absorbed mainly from the small intestine, not the stomach, because the intestine offers an enormous surface.

Q: How are K, half life, Vd, clearance and AUC obtained from an IV bolus study? Plot log plasma concentration against time; the straight line's slope gives K (slope = minus K / 2.303) and its intercept gives C₀. Then $t_{1/2} = 0.693 / K$, $V_d = \text{Dose} / C_0$, $AUC = C_0 / K$, and $CL = K \times V_d$, which must agree with Dose / AUC .

Q: Why does steady state take 4 to 5 half lives, and what decides the steady state level? During constant infusion or repeated dosing, drug accumulates because each interval adds drug while elimination removes a fraction of what is present; concentration approaches its plateau exponentially with the elimination rate constant, reaching about 90 percent in 3.32 half lives and practical steady state in 4 to 5 half lives, whatever the dose. The level itself is set by input and clearance alone: $C_{ss} = \text{infusion rate} / CL$ (or $F \times \text{Dose} / (CL \times \text{interval})$ orally). Changing the dose changes the level, not the time to reach it.

Q: What is the flip-flop phenomenon? After extravascular dosing, the terminal slope of the log concentration curve reflects the slower of absorption (k_a) and elimination (K). Normally k_a is larger and the slope gives K; if absorption is slower than elimination, as with many sustained release products, the slope gives k_a instead. Reading it as K misreports the absorption half life as the elimination half life: this reversal is flip-flop kinetics, suspected whenever a modified release product appears to have a much longer half life than the same drug given intravenously.

Q: Why is phenytoin the classic example of nonlinear pharmacokinetics? Phenytoin is eliminated by a saturable (Michaelis-Menten) pathway, and therapeutic concentrations sit near K_m , in the mixed order region. Its steady state concentration is $C_{ss} = K_m \times R / (V_{max} - R)$, so as the dosing rate R approaches V_{max} , C_{ss} rises disproportionately: with V_{max} 500 mg/day and K_m 4 mg/L, raising the dose from 300 to 400 mg/day raises C_{ss} from 6 to 16 mg/L, and 450 mg/day gives a toxic 36 mg/L. Small dose increments and level monitoring are therefore mandatory.

Q: What are the acceptance limits for bioequivalence, and why 80 to 125 percent? The 90 percent confidence interval for the ratio of geometric means (test over reference) of log transformed AUC and C_{max} must lie entirely within 0.80 to 1.25. The limits are symmetric on the log scale ($\log 0.80 = \text{minus } \log 1.25$), which is why the upper limit is 125 and not 120. It is the whole interval, not the mean ratio, that must fit, so an imprecise study can fail even with a mean ratio near 1.00.

Q: What is the biopharmaceutics classification system and what is a biowaiver? The BCS classifies drugs by solubility and permeability into four classes: I high/high, II low/high, III high/low, IV low/low, and so predicts which step limits absorption (dissolution for class II, permeation for class III). A biowaiver waives the in vivo bioequivalence study for an immediate release class I product (and defined class III cases) dissolving very rapidly, accepting dissolution data instead, because absorption of such a drug is controlled by gastric emptying and cannot plausibly differ between fast dissolving products.

Q: Why can a biosimilar not be approved by an ordinary bioequivalence study? A biosimilar is a protein made by a different living cell process, so it is highly similar to the reference biologic but never structurally identical. Plasma curves cannot prove two such molecules share structure, potency and immunogenicity, so approval rests on a stepwise comparability exercise: analytical and functional comparison, comparative pharmacokinetic and pharmacodynamic data where a marker exists, clinical comparison in a sensitive population, and immunogenicity testing, judged as a totality of evidence.

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