# PharmacoLearn

**MPH203T Computer Aided Drug Delivery System, M.Pharm Semester 2**

## Unit 4: Computer Aided Biopharmaceutical Characterization, PK/PD Simulation and Clinical Development

*Free notes at pharmacolearn.fyi*

### 4.1 Gastrointestinal absorption simulation: introduction and theoretical background

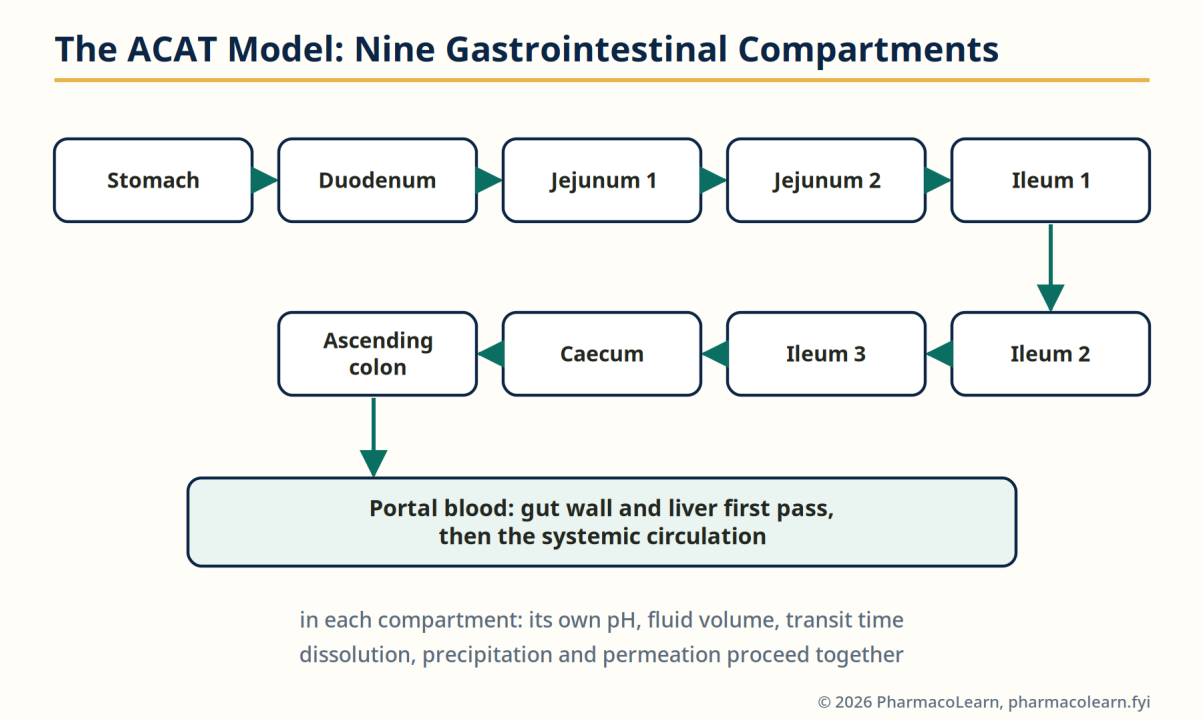


*Figure: The ACAT model of gastrointestinal absorption simulation. The dose transits nine compartments, each with its own pH, fluid volume and transit time, dissolving and permeating as it goes.*

Gastrointestinal absorption simulation predicts the plasma profile of an oral dose before the dose is ever given to a human, by simulating the journey MPH202T described: disintegration, dissolution, transit through changing gut conditions, permeation, gut wall and liver first pass, and entry into a pharmacokinetic model of the body. The theoretical core is the compartmental absorption and transit (CAT) model and its advanced form, the ACAT model, which divides the gastrointestinal tract into nine compartments: stomach, duodenum, two jejunal and three ileal segments, caecum and ascending colon. Each compartment carries its own pH, fluid volume, surface area and transit time, and the dose moves through them in sequence, dissolving, possibly precipitating, permeating and being degraded at compartment specific rates, while absorbed drug passes the gut wall (with its transporters and enzymes, Unit 2) and the liver before reaching the systemic model. The governing mathematics is a chain of mass balance differential equations, one set per compartment, integrated numerically. The commercial platforms built on this theory, GastroPlus being the widely used example, and the PBPK platforms such as the Simcyp simulator for the systemic side, are the working instruments of the sections that follow. The value of the exercise is foresight: formulation variants, doses, food effects and special populations can be compared in silico, and the expensive experiments reserved for the questions the model cannot settle.

### 4.2 Model construction

Building an absorption simulation follows a fixed discipline. **First, assemble the compound inputs:** molecular weight, pKa values, log P and its pH dependence, solubility as a function of pH (section 2.4), permeability (section 2.5), plasma protein binding, blood to plasma ratio, and clearance mechanisms, each flagged by source, measured, predicted in silico or taken from the literature, because the output can be no better than the weakest input. **Second, add the formulation inputs:** dose, dosage form type, particle size distribution, and the measured dissolution profile, which the model converts into in vivo release. **Third, choose the physiology:** the standard fasted or fed gut model, or a population variant for age, disease or species. **Fourth, run and compare:** simulated against any observed data that exist, from animal studies or earlier clinical work, with the model accepted for prediction only where it reproduces what is known, the verification step that separates simulation from speculation. **Fifth, document the assumptions:** software models used for decisions, and especially for regulatory submissions, carry a record of inputs, versions and checks.

## 4.3 Parameter sensitivity analysis in absorption simulation

Unit 1 defined sensitivity analysis generally; in absorption simulation it has a specific job, because the input list of section 4.2 mixes well measured numbers with rough predictions, and the user must know which uncertainty matters. The platform varies one input at a time (solubility across its plausible range, permeability likewise, particle size, gastric emptying time) and reports the effect on the outputs that drive decisions: fraction absorbed, Cmax and AUC. The standard lessons recur. For a BCS class II drug the output is exquisitely sensitive to solubility and particle size and almost indifferent to permeability, so the formulation budget goes to dissolution. For a class III drug the pattern reverses. A prediction robust across the plausible range of every uncertain input can be carried forward with confidence; a prediction that flips when one poorly known input moves is a finding in itself, it identifies the single experiment most worth doing. Parameter sensitivity analysis is thus the bridge between the virtual work of this unit and the bench work it directs.

## 4.4 The virtual trial

A virtual trial runs the simulation not for one standard subject but for a population of virtual subjects, each assembled by sampling physiology and drug parameters from their distributions: gastric pH and emptying, transit times, enzyme and transporter abundance, body size, plasma binding, and the variability of the compound inputs themselves. The machinery is Monte Carlo simulation, hundreds or thousands of runs whose results are summarised as a distribution of outcomes, a mean profile with its spread, the fraction of subjects outside a target window, the predicted variability a real trial should expect. Virtual trials answer questions no single run can: whether a formulation robust in the average subject stays robust in slow emptiers; what sample size a bioequivalence study needs given predicted variability; how a dose performs across renal function or age bands before those patients are exposed. They are the population modeling of section 1.9 turned forward, from analysing data to generating it, and they inherit its ethics (section 3.9): a virtual trial that replaces an uninformative real trial is a gain, while one that overstates its certainty to skip a necessary trial is a hazard.

## 4.5 Fed versus fasted state simulation

Food changes oral absorption through several mechanisms at once: gastric pH rises, emptying slows, bile salt and lipid concentrations in the intestine climb (raising the solubility of lipophilic drugs), splanchnic blood flow increases, and the dosage form itself may behave differently, including the risk of dose dumping from some modified release products. Clinical food effect studies are therefore standard, and predicting them is a prized simulation task. The fed state model adjusts the physiology compartment by compartment: longer gastric residence, higher intestinal solubilisation capacity through bile micelles, altered fluid volumes and

transit, and the compound's measured solubility in fed state simulated media feeds the dissolution side. A model that reproduces the observed fasted profile and then, with only the physiology switched, predicts the fed profile and its direction, exposure up, down or unchanged, has demonstrated the mechanistic credibility of section 1.3. Such predictions guide whether the product is labelled with or without food, whether a food effect study can be argued unnecessary, and which formulation changes would blunt an unwanted food effect.

## 4.6 In vitro dissolution and in vitro in vivo correlation in simulation

Within a simulation platform, a validated Level A relationship turns formulation questions into computations: change the coating, predict the new dissolution, and read off the predicted plasma consequence, which is the computational heart of biopharmaceutical characterization and the technical basis of the biowaiver argument next.

| IVIVC level | What is correlated | Predictive power |
|---|---|---|
| Level A | Whole dissolution curve against whole in vivo absorption curve, point to point | Predicts the plasma profile; dissolution can serve as a surrogate |
| Level B | Mean in vitro dissolution time against mean in vivo residence or absorption time | Summary only; several profiles share one mean, so profiles cannot be predicted |
| Level C | One dissolution measurement against one PK parameter (Cmax or AUC) | Screening and quality use; no profile prediction |

## 4.7 Biowaiver considerations

A biowaiver is a regulatory decision to approve a product, or a change to one, without a new in vivo bioequivalence study, on the strength of in vitro and in silico evidence. The established BCS based biowaiver (MPH202T, section 4.8) waives the study for rapidly dissolving immediate release products of high solubility drugs under defined conditions, because gastric emptying, not formulation, controls their absorption. Simulation extends the reasoning: a verified absorption model, exercised across the plausible range of product and patient variation (the virtual trial of section 4.4), can argue that two formulations cannot differ in vivo by more than a stated amount, or that a manufacturing change or site transfer leaves exposure unchanged. The regulatory posture is deliberately cautious, and the considerations that decide acceptance are consistent: the model must be verified against observed data for the same or closely related products; its sensitive parameters (section 4.3) must be measured, not guessed; the claim must stay inside the conditions the evidence covers; and the consequence of error must be proportionate, a biowaiver argument for a narrow therapeutic index drug faces a far higher bar. Simulation supports biowaivers; it does not yet replace the judgement that grants them.

## 4.8 Computer simulations in pharmacokinetics and pharmacodynamics: the whole organism

At the whole organism level, PK simulation means the compartmental and PBPK models of Unit 2 run forward in time: dose in, predicted concentration time curve out, for any regimen, route or population the model is built to represent. Its routine uses are regimen design (loading and maintenance doses from clearance and volume), prediction of accumulation and time to steady state (MPH202T, Unit 3), interaction prediction (an inhibitor's effect entered as a change in the relevant clearance and the new steady state computed), and trial design, where simulations fix sampling schedules (with optimal design, section 1.8) and expected variability before patients are recruited. Pharmacodynamic simulation joins an effect model, most often the saturable Emax relationship of MPH202T section 5.3, possibly with delays for distribution to

the effect site or indirect mechanisms such as cell turnover, so that the output is effect against time: onset, peak, duration, and the consequence of missed or doubled doses. Population platforms combine both with the variability machinery of section 1.9, so a development team can ask, and answer numerically, what fraction of the target population a proposed dose puts inside the therapeutic window.

## 4.9 Simulation at the levels of tissues, organs, cells, proteins and genes

The syllabus descends the biological scale, and each level has its simulation style. **Isolated tissues and organs:** perfused organ and tissue bath preparations are modeled as small systems in their own right, concentration in the bath, uptake into the tissue, response as a function of exposure, and such models both interpret preclinical experiments and feed parameters upward into PBPK tissue compartments. **Cells:** cell level models describe transport across the cell membrane, intracellular binding and metabolism, and the signalling cascades by which a receptor event becomes a cellular response, systems of differential equations for pathway components, the quantitative core of systems pharmacology. **Proteins:** at the molecular level, docking predicts how a ligand sits in a binding site, and molecular dynamics simulates the protein and ligand moving in solvent over time, estimating binding stability and the conformational changes behind agonism and resistance mutations. **Genes:** gene level work is computational genomics and network modeling, expression data analysed for pathway activity, genetic variants in enzymes and transporters (Unit 2) entered as parameter changes in the higher level models, so that a polymorphism in a clearance enzyme becomes, computationally, a different virtual patient.

## 4.10 Computers in clinical development: clinical data collection and management

Clinical trials are the most expensive data pharmaceutical science collects, and computers run their collection. The paper case report form has given way to **electronic data capture (EDC)**: investigators enter data on electronic case report forms with built in range and consistency checks at the point of entry, patients increasingly report outcomes directly through electronic patient reported outcome devices and diaries, and laboratory and imaging data flow in electronically from central facilities. Behind the forms sits the clinical data management system and its discipline: a data management plan, edit checks programmed against the protocol, queries raised and resolved with sites, coding of adverse events and medications against standard dictionaries (MedDRA for events, the WHO drug dictionary for medicines), reconciliation against safety databases, and finally database lock, the frozen, auditable state from which statisticians analyse. International data standards (the CDISC family, including the SDTM structure for tabulated study data) make trial datasets machine readable and submittable in a form regulators can analyse directly.

## 4.11 Regulation of computer systems

Because regulated decisions rest on electronic records, the systems holding them are themselves regulated. The landmark instrument is the US FDA's **21 CFR Part 11** (1997), which sets the conditions under which electronic records and electronic signatures are considered trustworthy equivalents of paper and ink: system validation, secure audit trails that record who created, changed or deleted a record and when, authority checks limiting users to their roles, record retention and accurate copies for inspection. The European counterpart is Annex 11 to the EU GMP guide, and the industry's working framework for achieving compliance is the GAMP guide (Good Automated Manufacturing Practice, published by ISPE), which classifies software by category and scales the validation effort to risk. Underneath the rules sits one principle, data integrity, summarised in the ALCOA expectations: records must be attributable, legible, contemporaneous, original and accurate. Validation is the documented demonstration that a system does what it is intended to do, from specification through testing to controlled change, and it applies to the instruments of this whole subject, the LIMS, the EDC platform, the manufacturing automation and the modelling software used in submissions, where the credibility of a simulation is partly the credibility of the

validated system that produced it.

```
The gastrointestinal absorption simulation workflow
Compound inputs: solubility, pKa, log P, permeability
   |
   v
Formulation inputs: dose, particle size, dissolution profile
   |
   v
ACAT model: nine gut compartments, transit and pH
   |
   v
Gut wall and liver first pass (transporters, Unit 2)
   |
   v
Systemic PK model: plasma profile out
   |
   v
Verify against observed data, then predict:
fed state, new formulations, virtual populations
```

---

*More free M.Pharm notes and unit wise PDFs at pharmacolearn.fyi*
*Free video lectures on the PharmacoLearn YouTube channel*