

Unit 1: Drug Absorption from the Gastrointestinal Tract

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Advanced Biopharmaceutics and Pharmacokinetics, subject code MPH202T, is a core Semester 2 subject of M.Pharm Pharmaceutics. It carries 4 credits and 60 hours of theory, taught at 4 hours per week, for 100 marks. Biopharmaceutics studies how the drug's physicochemical properties, its dosage form and the body's physiology together decide how much drug reaches the systemic circulation, and how fast. Pharmacokinetics describes, in numbers, what the body does to the drug (absorption, distribution, metabolism, excretion) and turns plasma data into parameters such as clearance, volume of distribution and half life used to calculate doses and regimens. The first unit follows a drug through the gastrointestinal tract: the mechanisms by which it crosses the gut wall, the pH-partition theory, dissolution and the Noyes-Whitney equation, and the modern transport model built on permeability, solubility and charge state. The second unit turns to drug product design and in vitro performance: the factors that make one formulation perform better than another, dissolution and drug release testing, and in vitro-in vivo correlation. The third unit is the mathematical core: compartment models for intravenous bolus, intravenous infusion and extravascular administration, the two compartment model, nonlinear pharmacokinetics with the Michaelis-Menten equation, and drug interaction mechanisms. The fourth unit measures drug product performance in vivo: bioavailability, bioequivalence and its crossover designs, the biopharmaceutics classification system, permeability methods and biosimilars. The last unit applies all of it to modified release products, targeted delivery and the biotechnology products (proteins, monoclonal antibodies, oligonucleotides, vaccines, gene therapies), whose behaviour follows the same principles with new complications. A student who completes this subject should be able to derive pharmacokinetic parameters from raw data, judge the quality of a dissolution or bioequivalence study, and use pharmacokinetic reasoning to design and evaluate a dosage regimen.

1.1 The gastrointestinal tract as the site of absorption

The oral route is the most used route because it is convenient, safe and cheap, and the gastrointestinal tract (GIT) is built for absorption: a long tube whose surface is enormously amplified. The small intestine is the principal site. Its wall is folded (folds of Kerckring), the folds carry villi, and each epithelial cell carries microvilli, the brush border. Together these multiply the small intestinal surface to roughly 200 square metres, against a plain tube area of less than one square metre.

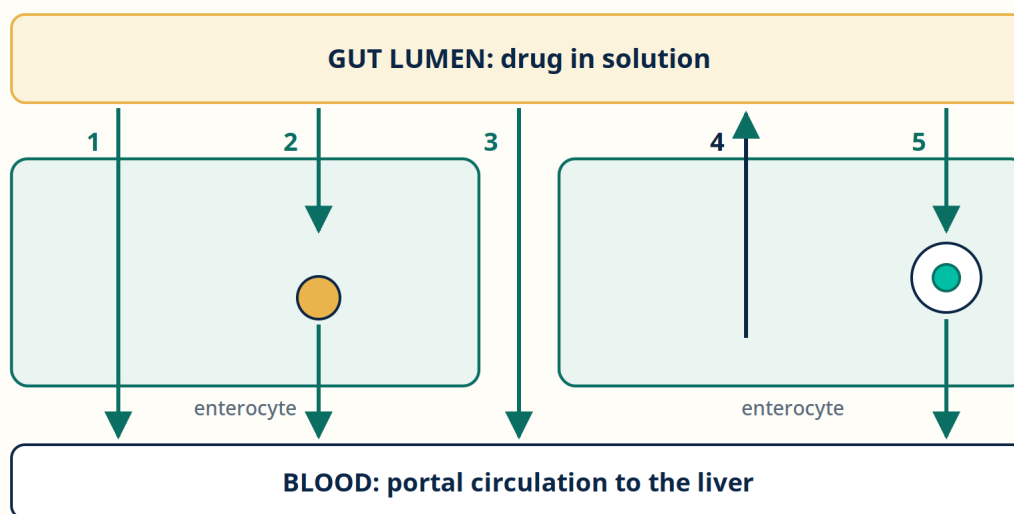
The regions differ in ways that matter. The stomach is mainly a mixing and holding organ with a thick mucus layer, a small surface and a strongly acidic lumen (pH about 1.2 to 2 fasting); most drugs are absorbed only weakly there despite the pH favourable to weak acids, because the surface is small. The small intestine (duodenum, jejunum, ileum) has a luminal pH rising from about 6 to about 7.4, the huge surface above, bile and pancreatic secretions, and a residence time of about 3 to 4 hours: it is where the great majority of oral absorption happens. The colon has a smaller surface, no villi, viscous contents and a large bacterial population; it matters for colonic delivery and for sustained release products whose remaining dose reaches it. Gastric emptying controls the rate at which drug is presented to the small intestine, so for most immediate release products gastric emptying, not the crossing of the gut wall, sets the pace of absorption: fatty food delays emptying, while liquids and small particles empty faster.

Absorption is a chain of steps: the dosage form must disintegrate, the drug must dissolve and survive acid and enzymes in the lumen and gut wall, and it must cross the epithelial cell layer. The slowest step is the

rate limiting step, an idea that returns in Unit 2.

1.2 Mechanisms of drug absorption

Mechanisms of Drug Absorption Across the Gut Wall



- 1 Passive transcellular diffusion: unionised, lipophilic drug crosses the cell
- 2 Carrier mediated uptake: transporters carry drug into and through the cell
- 3 Paracellular: small hydrophilic molecules pass the tight junction
- 4 Efflux: P-glycoprotein pumps drug back into the lumen
- 5 Endocytosis: vesicles carry particles and macromolecules across

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Figure: The routes by which a drug molecule can cross the intestinal epithelium. Passive transcellular diffusion carries most marketed drugs; the other routes matter for specific drug classes and are targets of modern formulation design.

A drug can cross the intestinal epithelium by several mechanisms, and a real drug often uses more than one.

- **Passive diffusion (transcellular).** The drug partitions from the aqueous lumen into the lipid cell membrane, diffuses across the cell and partitions out into the blood. No energy or carrier is involved, the rate is proportional to the concentration gradient and to lipid solubility, and the process is not saturable. This is the route of most small, moderately lipophilic drugs, and the route the pH-partition theory (section 1.3) describes.
- **Paracellular transport.** The drug passes between the cells, through the tight junctions that seal the epithelial sheet. The aqueous pores are narrow (a few angstroms), so this route is restricted to small hydrophilic molecules and contributes little for most drugs, but it is the only passive route available to very polar compounds. Section 1.13 returns to the tight junction complex.
- **Carrier mediated transport.** Membrane proteins carry specific substrates: facilitated diffusion moves the drug down its concentration gradient without energy; active transport moves it against the gradient at the cost of ATP or an ion gradient. Uptake transporters carry some drugs and drug-like nutrients: PEPT1 carries beta-lactam antibiotics and valaciclovir, and amino acid and glucose transporters carry look-alikes (L-DOPA, gabapentin). Carrier mediated absorption is saturable, so the fraction absorbed can fall as dose rises, and it is subject to competition and inhibition, a source of drug interactions (Unit 3).
- **Efflux transport.** Other membrane proteins pump drug back into the lumen. P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) and related efflux transporters sit on the luminal (apical)

membrane of the enterocyte and eject absorbed molecules, working with the metabolising enzyme CYP3A4 inside the cell as a first pass barrier in the gut wall. Efflux limits the bioavailability of drugs such as digoxin, ciclosporin and many anticancer agents, and inhibiting it raises their blood levels.

- **Endocytosis and transcytosis.** Cells take up particles and macromolecules in vesicles (pinocytosis for fluid, phagocytosis for particles, receptor mediated endocytosis for ligands) and, in some cells, carry them across. Quantitatively minor for conventional drugs, but the entry route exploited in research for oral delivery of peptides, nanoparticles and vaccines.
- **Ion pair transport and pore transport.** A highly ionised drug can cross as a neutral ion pair with an oppositely charged ion; very small molecules (below about 150 to 200 in molecular weight, such as urea) can pass through water filled membrane pores. Both are minor routes listed for completeness.

The balance of uptake and efflux transporters, with passive permeability, decides the permeability term of the transport model in section 1.12.

1.3 The pH-partition theory of drug absorption

pH-Partition Theory: Ionisation of a Weak Acid

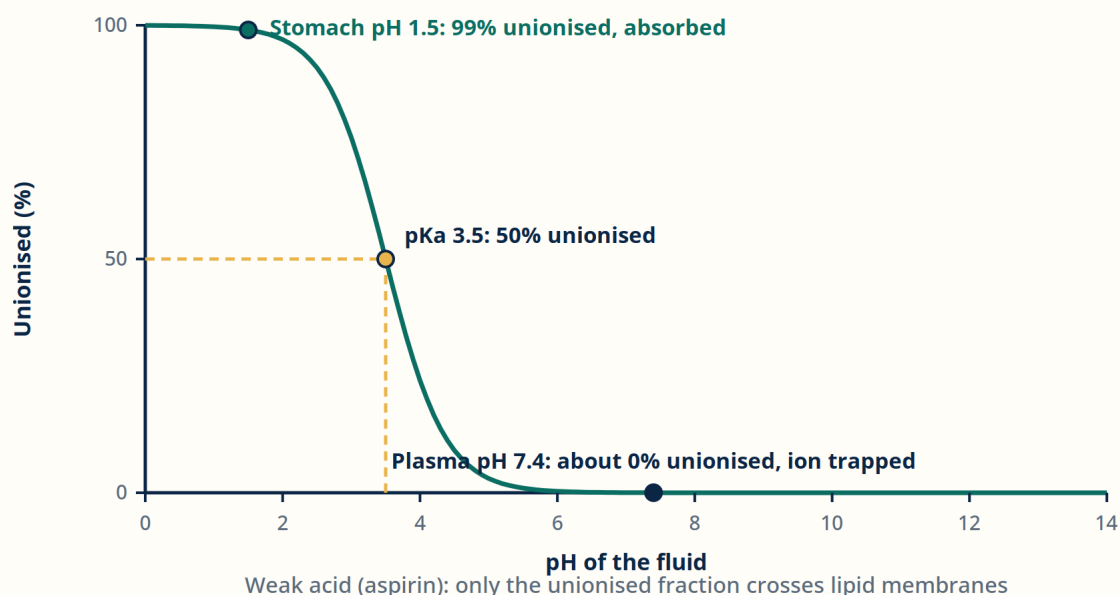


Figure: The pH-partition idea in one picture: membranes pass the unionised species, so the ionisation set by local pH decides how much drug is available to cross, and ionisation on the far side traps it there.

Most drugs are weak acids or weak bases, existing in solution as a mixture of ionised and unionised molecules whose proportions are set by the fluid pH and the drug's pKa. The pH-partition theory states that the lipid membrane is permeable essentially only to the unionised species, so absorption is fastest where pH makes the drug mostly unionised: a weak acid in acid, a weak base in alkali. The Henderson-Hasselbalch equations give the proportions:

- For a weak acid: $\text{pH} = \text{pKa} + \log\left(\frac{[\text{ionised}]}{[\text{unionised}]}\right)$
- For a weak base: $\text{pH} = \text{pKa} + \log\left(\frac{[\text{unionised}]}{[\text{ionised}]}\right)$

Worked example. Aspirin is a weak acid with pKa 3.5. In fasting gastric fluid at pH 1.5, the ratio ionised to unionised is 10 raised to (1.5 - 3.5), that is 0.01: about 99 percent of the aspirin is unionised and available to cross membranes. In plasma at pH 7.4 the ratio is 10 raised to (7.4 - 3.5), about 7900: aspirin reaching

the blood is almost completely ionised, and because the ionised form crosses back only very slowly, it is effectively trapped in the plasma.

The theory is a useful first approximation, not the whole truth, and its limitations are standard examination material:

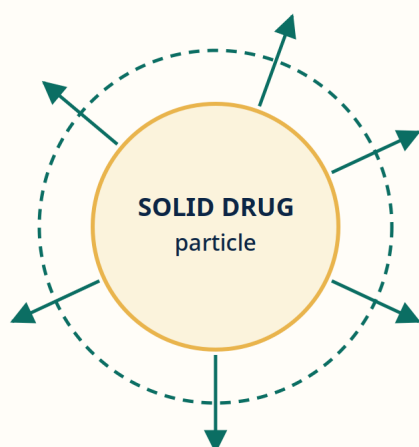
- It predicts that weak acids should be absorbed mainly from the stomach, yet in practice most are absorbed mainly from the small intestine, whose surface area and blood flow outweigh the less favourable pH. pH sets the fraction available to cross; area and time decide how much actually crosses.
- The ionised species is not completely impermeable; it crosses slowly by the paracellular route and through pores, so even highly ionised drugs show some absorption.
- The pH at the membrane surface is not the bulk luminal pH: an acidic microclimate exists at the intestinal surface (section 1.13).
- The theory ignores transporters and dissolution. A drug that is unionised but undissolved is not absorbed at all.

1.4 Factors affecting drug absorption

The factors fall in three groups. **Physiological factors** include gastric emptying rate (usually the pacing step for immediate release forms), intestinal motility and transit time, gastrointestinal pH and its change with food, disease and age, blood flow to the gut, food (which can delay, reduce or occasionally increase absorption, for example by stimulating bile), gut wall and hepatic first pass metabolism, and the bacterial flora metabolising some drugs in the colon. **Physicochemical factors** include aqueous solubility, dissolution rate, pKa and the resulting ionisation at gut pH, lipid solubility (partition coefficient), particle size and surface area, the solid state form, and chemical stability in gut fluids. **Formulation factors** cover the dosage form type (sections 1.7 to 1.10), the excipients, and manufacturing variables such as compression force and coating. A useful rule: absorption fails if any one of dissolution, stability or permeation fails, and improving the factor that is not rate limiting changes nothing.

1.5 Dissolution and the Noyes-Whitney equation

Drug Dissolution: the Noyes-Whitney Picture



$$dM/dt = (D \times A / h) \times (C_s - C)$$

Each term is a formulation lever:

D: diffusion coefficient of the drug
A: surface area, rises as particles get smaller
C_s: saturation solubility in the medium
C: concentration already dissolved in bulk
h: layer thickness, thinned by agitation

Stagnant diffusion layer (thickness h): concentration = C_s at the surface

Bulk medium beyond the layer: concentration C, kept low (sink conditions)

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Figure: Dissolution as Noyes and Whitney pictured it: a thin stagnant layer saturated at C_s surrounds the particle, and diffusion across that layer is the slow step that the equation describes.

A solid drug cannot cross the gut wall; it must first dissolve. Dissolution is the process by which drug molecules leave the solid surface and enter solution, and for poorly soluble drugs it is the rate limiting step of the whole absorption chain. It has two steps: molecules detach from the crystal surface into a thin, stagnant saturated layer around the particle (the diffusion layer, of thickness h), then diffuse from this layer into the bulk fluid, where the concentration is lower. Diffusion across the stagnant layer is the slow step, which is why the Noyes-Whitney equation is a form of Fick's law:

$$dM/dt = (D \times A / h) \times (C_s - C)$$

where dM/dt is the rate of dissolution (amount per unit time), D the diffusion coefficient in the medium, A the surface area of solid exposed, h the diffusion layer thickness, C_s the saturation solubility (the concentration in the stagnant layer) and C the bulk concentration at time t. Dividing by the medium volume V gives dC/dt = (D x A / (V x h)) x (C_s - C).

Two ideas follow directly. First, under **sink conditions**, when the bulk concentration stays low (conventionally below about 10 to 20 percent of C_s) because dissolved drug is removed, by absorption in the body or by a large medium volume in vitro, the term (C_s - C) stays nearly equal to C_s and the dissolution rate is nearly constant. Second, every factor in the equation is a lever for the formulator: the rate rises in proportion as the factors change. Section 1.6 takes the factors one by one.

1.6 Factors affecting the dissolution rate

- **Surface area and particle size.** Rate is proportional to A, so reducing particle size (micronisation, and in modern practice nanosizing) is the oldest and most reliable way to speed dissolution of a poorly soluble drug; griseofulvin is the classic example whose bioavailability roughly doubled on micronisation. Very fine powders can aggregate and float, so wetting agents may be needed to realise the area.

- **Solubility (Cs).** Rate is proportional to Cs. A salt of a weak acid or base usually dissolves faster than the free form because it creates a surface pH favourable to its own dissolution; a metastable polymorph or the amorphous form has a higher apparent solubility than the stable crystal, at the price of a risk of converting back.
- **Diffusion layer thickness (h).** Agitation thins the layer: faster stirring or faster gut motility increases the rate, which is why dissolution results depend on stirring speed and why the method must control it (Unit 2).
- **Diffusion coefficient (D).** D falls as medium viscosity rises, so viscous vehicles and gel forming excipients slow dissolution; D falls with molecular size.
- **Temperature and medium.** Solubility and D rise with temperature; medium pH changes Cs directly for ionisable drugs, so dissolution media mimic gastric or intestinal pH.
- **Wetting.** A hydrophobic powder surface traps air and reduces the effective area; surfactants and hydrophilic excipients improve wetting and raise the rate.

1.7 Role of the dosage form: solutions

A solution (including elixirs, hydroalcoholic solutions, and syrups, concentrated sugar solutions) contains the drug already dissolved, so the dissolution step is absent and the drug is available for absorption as soon as it reaches the intestine. Solutions therefore usually give the fastest onset and highest bioavailability of the oral forms, and are the reference against which other forms are judged. Their disadvantages are practical: chemical stability is poorer (hydrolysis is fastest in solution), taste masking is difficult, doses are bulky and less precisely measured, and precipitation can occur if the drug is near its solubility limit when diluted or when its pH changes in the gut. For a solution, absorption is governed by gastric emptying and membrane permeation alone, so the ranking of oral forms by absorption speed usually begins: solution, then suspension, then capsule, then tablet, with coated and sustained release forms slowest of all.

1.8 Role of the dosage form: suspensions

A suspension is a dispersion of fine solid drug particles in a liquid vehicle. Dissolution is present, but because the drug is already divided into small particles with a large surface area, it is usually fast, and suspensions are absorbed nearly as quickly as solutions and clearly faster than tablets of the same drug. Their biopharmaceutic risks are particle growth on storage (crystal growth and caking change A and therefore the dissolution rate), poor redispersion if the bottle is not shaken, and dose non-uniformity. The particle size distribution of a suspension is a critical quality attribute for exactly the reason the Noyes-Whitney equation gives: it sets A.

1.9 Role of the dosage form: capsules

A capsule is a dose of drug (powder, granules or pellets) in a gelatin shell. On contact with gut fluid the shell hydrates, softens and ruptures within minutes, releasing contents that behave much like a powder or suspension. Capsules therefore absorb at rates between suspensions and tablets. The variables that matter are the filling (loose powder disaggregates freely; a plug formed under pressure behaves more like a tablet), the excipients (a hydrophilic diluent such as lactose aids wetting; a little disintegrant helps the plug break up), and the shell, which must be stored so it does not cross link and dissolve slowly, a known cause of failed dissolution in aged capsules. Soft gelatin capsules carry the drug dissolved or dispersed in a liquid fill, which for poorly soluble lipophilic drugs can approach the performance of a solution.

1.10 Role of the dosage form: tablets

The tablet is the most used and most engineered oral form, with the longest chain of steps before absorption: it must disintegrate into granules, the granules must deaggregate into primary particles, and only then can the drug dissolve. Each step adds time and variability, so tablets usually show the slowest and most variable absorption of the immediate release forms, and tablet formulation is largely the art of keeping those steps fast: disintegrants (starch, croscarmellose, sodium starch glycolate), a soluble diluent, lubricant kept at the minimum level (excess hydrophobic lubricant such as magnesium stearate coats particles and slows wetting and dissolution), and compression force high enough for strength but not so high that disintegration slows. Coatings add their own delay: film coats rupture quickly, enteric coats deliberately prevent release until the tablet leaves the stomach, sugar coats add bulk and time.

1.11 Dissolution methods and the correlation of in vitro with in vivo data

Because dissolution is the gatekeeper step for solid forms, in vitro dissolution testing is the standard laboratory method for predicting and controlling it: the form sits in a measured volume of medium at 37 degrees Celsius under defined agitation, and samples over time build a profile. The apparatus and discipline of the test are Unit 2 material; the point here is what the test is for. It should rank formulations in the same order as the body does. The **correlation of in vivo data with in vitro dissolution data** rests on the idea that, when dissolution is rate limiting in vivo, the fraction dissolved in vitro should track the fraction absorbed in vivo, formalised as IVIVC in Unit 2 (section 2.9).

1.12 Transport model: permeability, solubility and charge state

The pH-partition theory is an older idea built on one property, lipid solubility. The modern transport model, developed largely by Avdeef and reflected in the reference list of this subject, describes intestinal absorption through three properties of the molecule, measured together:

- **Permeability:** the rate at which the molecule crosses a membrane model, measured in artificial membrane systems (PAMPA) or cell monolayers (Caco-2, section 4.9), combining passive transcellular, paracellular and transporter contributions.
- **Solubility:** the amount that can dissolve, measured as a function of pH across the gastrointestinal range, since an ionisable drug's solubility differs at every pH.
- **Charge state:** the distribution of ionisation states at each pH, worked out from the pKa values. Charge state links the other two: it sets solubility at each pH (ionised species are more soluble) and permeability at each pH (the unionised species permeates best), so the two pH profiles slope in opposite directions and the pH of best absorption is a compromise.

The pH partition hypothesis survives inside this model: the intrinsic permeability of the unionised species is the ceiling value, from which effective permeability at any pH follows by weighting by the fraction unionised.

1.13 Properties of the GIT that shape the transport model

Three properties of the tract itself complete the picture. **First, the pH gradient:** luminal pH rises from about 1.2 to 2 in the fasting stomach, through about 6 in the duodenum, to about 7.4 in the ileum and falls slightly in the colon, so a travelling molecule meets changing charge state and solubility, and weak bases dissolving in the stomach may precipitate in the intestine. **Second, the pH microclimate:** the mucosal surface carries an unstirred water layer and a microclimate whose pH (about 5.3 to 6.1 in the jejunum) is more acidic than the bulk luminal pH. A drug is absorbed from this microclimate, so its ionisation at the membrane is set by the microclimate pH: one reason weak acids are absorbed from the intestine better than bulk pH predicts. The **intracellular pH environment** (about 7.0 to 7.2 inside the enterocyte) then sets the ionisation of whatever has crossed the apical membrane, contributing to ion trapping and to the behaviour of intracellular enzymes and efflux transporters. **Third, the tight junction complex:** tight

junctions, protein complexes (claudins, occludin, junctional adhesion molecules) joining the cells near their apical surface, seal the paracellular space, fence off the apical from the basolateral membrane, and are dynamically regulated. They restrict the paracellular route of section 1.2 to very small hydrophilic molecules, and safely modulating them is an active strategy for delivering peptides.

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The absorption chain, and where this unit's ideas act
Tablet or capsule
  | disintegration and deaggregation (dosage form, Unit 1 sections 1.7 to 1.10)
  v
Solid drug particles
  | dissolution: Noyes-Whitney, proportional to A and (Cs - C) (sections 1.5, 1.6)
  v
Drug in solution in gut fluid
  | permeation: pH-partition, transporters, tight junctions (sections 1.2, 1.3, 1.12, 1.13)
  v
Portal blood, then liver (first pass metabolism), then systemic circulation
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