

### Unit 2: Biopharmaceutic Considerations in Drug Product Design and In Vitro Drug Product Performance

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#### 2.1 Introduction: drug product performance begins in vitro

A drug product performs in two arenas. In vitro performance is what the laboratory measures before any patient is involved: disintegration, dissolution and release, content uniformity, stability. In vivo performance, bioavailability and bioequivalence, is Unit 4. This unit covers the in vitro side and the design thinking connecting the two, because in vivo performance is largely decided by the in vitro properties built in.

#### 2.2 Biopharmaceutic factors affecting drug bioavailability and the rate limiting steps

Bioavailability, the rate and extent to which the active drug reaches the systemic circulation, is the product of surviving every step between the mouth and the blood. The biopharmaceutic factors can be read straight off the absorption chain of Unit 1:

- 1 **Release and dissolution from the dosage form.** If the drug does not leave the form and dissolve, nothing else matters (sections 1.5, 1.6 and formulation).
- 2 **Stability in the gastrointestinal fluids.** Acid labile drugs (penicillins, erythromycin, omeprazole) are destroyed in the stomach unless protected; lumen and gut wall enzymes digest peptides.
- 3 **Permeation of the gut wall.** Set by permeability and charge state (section 1.12) and by efflux transporters.
- 4 **First pass metabolism.** Drug absorbed from most of the gut passes through the liver via the portal vein before the systemic circulation; gut wall and liver enzymes (CYP3A4 above all) can remove a large fraction on this first pass, as with propranolol, verapamil and midazolam.

For any given product, one of these steps is the slowest, the **rate limiting step**, and only improvements to that step improve bioavailability. For a soluble, permeable drug, gastric emptying is often rate limiting; for a poorly soluble drug (the majority of new drug candidates), dissolution is rate limiting and particle size, solid form and formulation decide performance; for a soluble but poorly permeable drug, membrane permeation is rate limiting and no dissolution improvement helps; for a drug with extensive first pass metabolism, formulation can do little and dose or route must change. Identifying the rate limiting step correctly is the first act of rational drug product design, and it is the idea the biopharmaceutics classification system of Unit 4 formalises.

#### 2.3 Physicochemical nature of the drug

The properties of the drug substance that the designer must know, and can sometimes change, are:

- **Aqueous solubility and its pH profile.** Solubility sets  $C_s$  in the Noyes-Whitney equation and, with the dose, whether the dose can dissolve in the available gut fluid at all.
- **pKa and ionisation.** Sets charge state at every gut pH, hence the balance of solubility and permeability (section 1.12), and the feasibility of salt formation.
- **Partition coefficient (log P, and log D at a stated pH).** A measure of lipid solubility: too low and the membrane is a barrier, too high and the drug will not dissolve in water or leave the membrane. Most orally absorbed drugs sit in a moderate range.

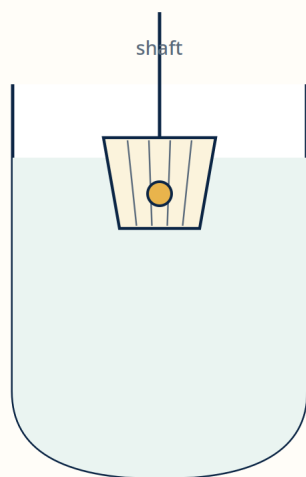
- **Particle size and surface area.** Direct control of dissolution rate (section 1.6).
- **Solid state form.** Polymorphs differ in solubility and stability; the stable form is the least soluble. The ritonavir episode, in which a new, less soluble polymorph appeared during production and forced the product off the market for reformulation, is the standing warning that solid form is a performance variable, not an academic detail.
- **Chemical stability.** Degradation in acid, solution, or by oxidation sets shelf life and may demand enteric protection.
- **Salt form.** The salt of an ionisable drug changes solubility, dissolution rate, stability, hygroscopicity and processability at once; salt selection is standard early development work.

## 2.4 Formulation factors affecting drug product performance

On the formulation side, performance is moved by the diluent (soluble lactose aids wetting and dissolution; insoluble diluents do not), the binder and granulation method (wet granulation gives dense granules that may dissolve more slowly than a direct compression blend), the disintegrant type, level and placement (inside the granules, outside them, or both), the lubricant (hydrophobic lubricants retard wetting, and over-mixing one into a blend is a classic cause of slow dissolution), surfactants and wetting agents (improving wetting, and solubilising drug in micelles), viscosity modifying agents, the coating, and the process itself: compression force, and for capsules the fill and shell condition.

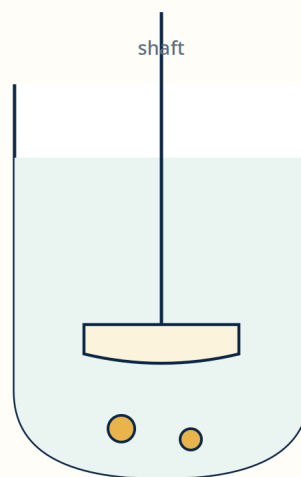
## 2.5 Dissolution and drug release testing: compendial methods

### Compendial Dissolution Apparatus (USP)



**Apparatus 1: BASKET**

tablet or capsule inside a rotating mesh basket



**Apparatus 2: PADDLE**

tablet sinks to the vessel bottom, paddle stirs above it

**Common conditions: about 900 mL medium, 37 plus or minus 0.5 C, defined rotation speed, sink conditions**

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*Figure: The two workhorse compendial apparatus. The basket holds the dosage form in a rotating wire mesh cage; the paddle stirs the vessel with the dosage form resting at the bottom. Every other variable, volume, temperature, speed, sampling, is fixed by the monograph.*

Dissolution testing is an official quality control test described in the pharmacopoeias (USP, IP, BP, EP) with standardised apparatus. Common conditions are a medium (usually 500 to 1000 mL of water, buffer or dilute acid, mimicking gut fluid and maintaining sink conditions) at 37 plus or minus 0.5 degrees Celsius, defined agitation, defined sampling times and a validated assay. The compendial apparatus are:

| Apparatus | Name                   | Typical use                                                                                              |
|-----------|------------------------|----------------------------------------------------------------------------------------------------------|
| USP 1     | Rotating basket        | Capsules, floating products, beads; typically 50 to 100 rpm                                              |
| USP 2     | Paddle                 | Tablets and capsules (with a sinker if the form floats); typically 50 to 75 rpm; the most used apparatus |
| USP 3     | Reciprocating cylinder | Products needing changing pH media, beads and modified release forms                                     |
| USP 4     | Flow-through cell      | Poorly soluble drugs, implants, powders; medium flows continuously so sink conditions are easy           |
| USP 5     | Paddle over disk       | Transdermal patches                                                                                      |
| USP 6     | Rotating cylinder      | Transdermal patches                                                                                      |
| USP 7     | Reciprocating holder   | Transdermal and other non-disintegrating products                                                        |

Drug release testing is the same idea applied to non-oral and modified release products, where the form is designed to release over hours and the test runs correspondingly longer with multiple sampling points. For modified release products the profile itself (amount released at several times, with limits at each) is the specification, not a single time point.

## 2.6 Alternative methods of dissolution testing

The compendial apparatus are compromises, and several alternative or supplementary methods exist for problems they handle badly. The **flow-through cell** suits poorly soluble drugs because fresh medium continuously restores sink conditions. **Biphasic dissolution** places an organic layer (for example octanol) over the aqueous medium so dissolved drug partitions continuously into it, mimicking absorption removing drug and maintaining sink. **Biorelevant media** (fasted and fed state simulated intestinal fluids, FaSSIF and FeSSIF, with bile salts and lecithin) imitate the gut rather than the buffer bottle, and serve development and IVIVC building rather than routine quality control. **Intrinsic dissolution** measures the rate from a compressed disk of pure drug of constant area, isolating the drug property from the formulation, a characterisation tool.

## 2.7 Meeting dissolution requirements

A monograph states the requirement as a **Q value**: the percentage of labelled amount that must dissolve at the stated time (for example, Q = 80 percent at 45 minutes). Because single units vary, compliance is judged in stages against the pharmacopoeial acceptance table:

- **Stage 1 (S1):** test 6 units. Each unit must dissolve not less than Q + 5 percent.
- **Stage 2 (S2):** if S1 fails, test 6 more. The average of all 12 units must be not less than Q, and no unit may be less than Q minus 15 percent.
- **Stage 3 (S3):** if S2 fails, test 12 more. The average of all 24 units must be not less than Q, not more than 2 units may be less than Q minus 15 percent, and no unit may be less than Q minus 25 percent.

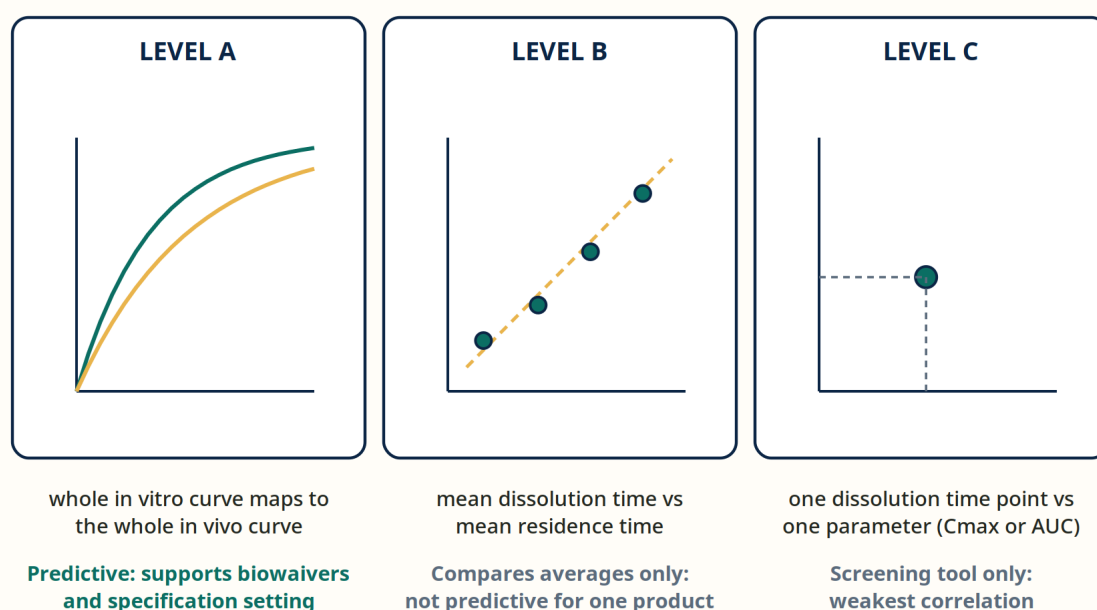
The staged design balances two risks: rejecting a good batch because of one odd unit, and accepting a genuinely poor batch. Meeting the requirement is a property of the whole distribution of units, not of the average alone, so formulation work aims at a mean comfortably above Q with a small spread, not at a mean exactly at Q.

## 2.8 Problems of variable control in dissolution testing

Dissolution is a sensitive test, and much laboratory discipline is controlling variables that have nothing to do with the product: **mechanical variables** (shaft wobble, vessel centring, paddle or basket height, vibration, worn baskets with clogged or distorted mesh), **medium variables** (dissolved air forming bubbles on tablets and baskets, so media are deaerated where the monograph requires; pH drift; temperature gradients between vessels), **dosage form behaviour** (a tablet that floats, sticks to the vessel wall, or cones, accumulating as a mound under the paddle where agitation is weakest), **sampling variables** (probe position, filter adsorption of drug, and sample volumes changing later concentrations if not corrected), and **analytical variables** (assay drift, standard preparation). The mirror lesson for design: robust formulations tolerate small changes in these variables; knife edge formulations do not.

## 2.9 In vitro-in vivo correlation (IVIVC)

### In Vitro In Vivo Correlation: the Three Levels



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Figure: The IVIVC levels ranked by what they relate and by predictive strength. Only Level A, a point to point relation across the whole profile, can substitute for in vivo studies across the life of a product.

An IVIVC is a mathematical relationship between an in vitro property of the dosage form, usually its dissolution profile, and the in vivo response, usually the plasma profile or the fraction absorbed. Four levels are recognised, in decreasing strength:

- **Level A:** a point to point relationship between the in vitro dissolution curve and the in vivo input (fraction absorbed) curve, usually obtained by deconvolution of the plasma data. The whole in vitro curve maps to the whole in vivo curve, so any dissolution profile can be converted into a predicted plasma profile. This is the only level accepted as a full surrogate for bioequivalence in changes to modified release products.
- **Level B:** relates mean in vitro dissolution time to a mean in vivo quantity (mean residence time or mean absorption time). It uses all the data but collapses each curve to one number, so different profiles with the same mean look identical; it cannot alone justify major changes.
- **Level C:** relates one dissolution time point (for example percent dissolved at 2 hours) to one parameter (for example C<sub>max</sub> or AUC). Useful in early development for screening; too weak for regulatory substitution.

- **Multiple Level C:** relates one pharmacokinetic parameter to the amount dissolved at several time points; stronger than C, still short of A.

A correlation can only exist when dissolution is rate limiting in vivo; for rapidly dissolving immediate release products absorbed under permeation or gastric emptying control, Level A correlation is generally not achievable (section 2.2).

## 2.10 Dissolution profile comparisons

When a formulation changes (a scale up, a site transfer, a modified release redesign), the first question is whether its dissolution profile still matches the reference profile. The standard model independent comparison uses two numbers calculated from the mean profiles at matched time points:

- **Difference factor f1** = [ sum of  $|R_t - T_t|$  over all time points / sum of  $R_t$  ] x 100, where  $R_t$  and  $T_t$  are the percentages dissolved of reference and test at time t. Profiles are similar when f1 is 0 to 15.
- **Similarity factor f2** =  $50 \times \log_{10} \{ [1 + (1/n) \times \text{sum of } (R_t - T_t) \text{ squared}] \text{ raised to minus } 0.5 \times 100 \}$ , where n is the number of time points. Profiles are similar when f2 is between 50 and 100.

**Worked example.** Reference profile at 10, 20, 30 and 45 minutes: 30, 50, 70, 85 percent. Test profile: 32, 52, 68, 83 percent. The differences are 2, 2, 2 and 2 percent, so the sum of absolute differences is 8 and the sum of  $R_t$  is 235, giving  $f1 = 8/235 \times 100 = 3.4$ . For f2, each squared difference is 4, the mean over 4 points is 4, so  $f2 = 50 \times \log_{10}(100 / \text{square root of } 5) = 50 \times \log_{10}(44.72) = 50 \times 1.65 = 82.5$ . Since f1 (3.4) is below 15 and f2 (82.5) is above 50, the profiles are declared similar. The rules of use matter as much as the formulas: use mean profiles from 12 units, matched time points, only one time point after both profiles pass 85 percent dissolved, and respect variability limits, because f2 from noisy or mismatched points is meaningless. Very rapidly dissolving products (both profiles at or above 85 percent in 15 minutes) are accepted as similar without calculation.

## 2.11 Drug product stability

A drug product must perform not only on the day it is made but on the last day of its shelf life, so stability is a design property, not an afterthought. The designer considers chemical stability (hydrolysis, oxidation, photolysis, interactions with excipients, for example the reaction of amine drugs with reducing sugars), physical stability (polymorph conversion, capsule shell cross linking that slows dissolution, suspension crystal growth, emulsion creaming), and microbiological stability for liquid and semi solid products. Packaging is part of the formulation for stability purposes: moisture barrier blisters, desiccants, amber containers, nitrogen filling. Stability is proven by long term and accelerated storage studies testing assay, degradation products and, importantly here, dissolution: a product whose assay is unchanged but whose dissolution has slowed on storage has lost performance an assay alone would not reveal.

## 2.12 Considerations in the design of a drug product

The design logic of the unit, in order: define the target profile (route, onset, duration, dose frequency); characterise the drug (section 2.3); identify the rate limiting step (section 2.2); choose the dosage form and formulation strategy attacking that step (salt, particle size, solubilisation, protection from acid or enzymes); develop an in vitro test measuring the controlling property and, where possible, a correlation linking it to in vivo behaviour (sections 2.5 to 2.10); and set specifications and a stability programme (sections 2.7, 2.11) holding the product at its designed performance for its whole life at production scale.

Design logic of Unit 2, in one view

Target profile (onset, duration, dose)

|

v

Drug properties: solubility, pKa, permeability, stability, dose

|

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Rate limiting step identified (dissolution? permeation? first pass?)

|

v

Formulation strategy attacks that step

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In vitro test measures the controlling property (dissolution, release)

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v

IVIVC or profile comparison links in vitro to in vivo

|

v

Specifications and stability programme hold the performance

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