

BCS Methodology: Solubility, Permeability & Dissolution

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Overview



- BCS Biowaivers and Classifications
- Solubility Methods
- Permeability Methods
- Dissolution Methods
- Gastrointestinal Stability Methods

M9 Biopharmaceutics Classification System- Based Biowaivers Guidance for Industry

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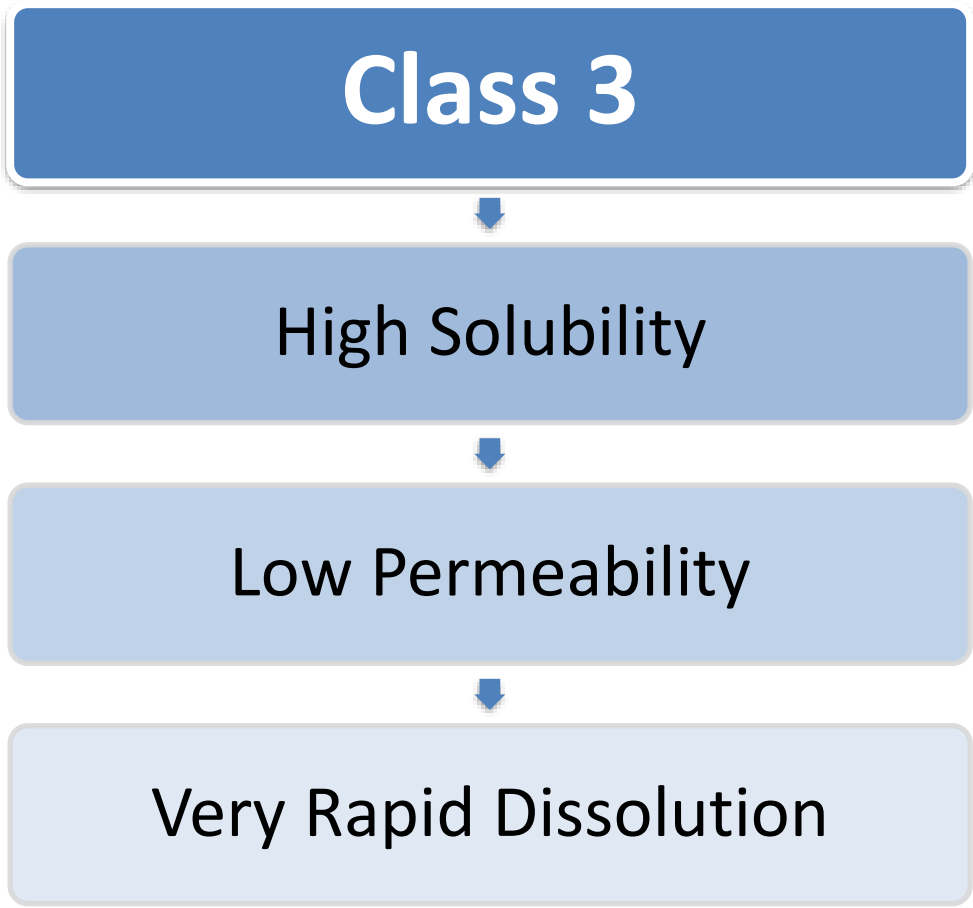
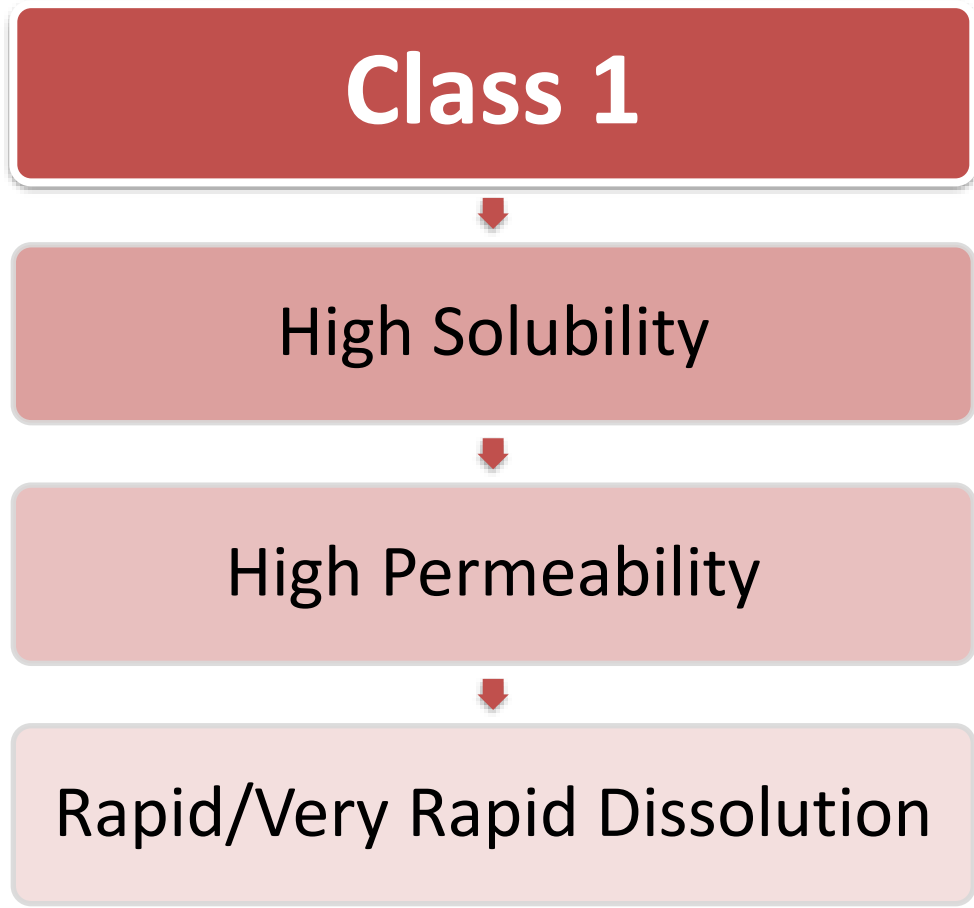
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BCS Biowaivers



Classification of Drug Substance



- **Solubility**

- highly soluble (HS) if highest single therapeutic dose completely soluble in ≤ 250 mL aqueous media

- **Permeability**

- highly permeable (HP) if absolute bioavailability is $\geq 85\%$, or
- $\geq 85\%$ of administered dose recovered in urine as parent drug, or as sum of parent drug and Phase 1/2 metabolites

Classification of Drug Product



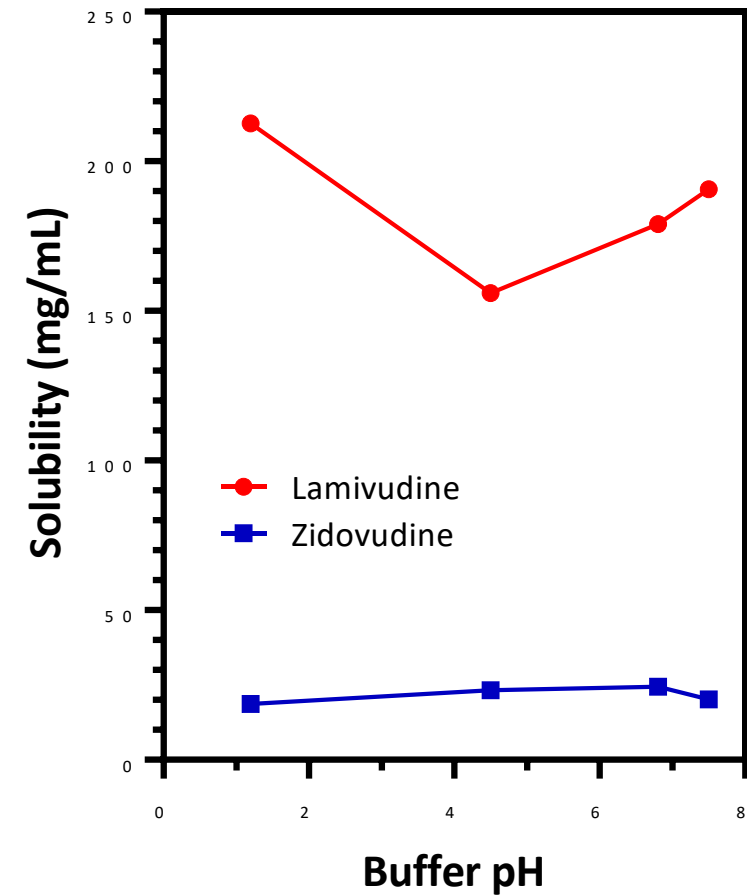
- **Dissolution**

- Both the test product and reference product exhibit:
 - very rapid ($\geq 85\%$ dissolved in ≤ 15 minutes), or
 - rapid ($\geq 85\%$ dissolved in ≤ 30 minutes) dissolution

Solubility Methods



- Evaluate solubility of drug substance over a pH range of 1.2 to 6.8 at $37 \pm 1^\circ\text{C}$
- At least three pH conditions within this range
- Buffers at pH 1.2, 4.5 and 6.8 should be evaluated



Dezani *et al.* Braz J Pharm Sci. 2013

Solubility Experiments



- Equilibrium solubility experiments with a shake-flask technique
- Alternative method may be employed if justified
- Measure the pH after the addition of drug and adjust pH of test solution if necessary
- Measure the pH of solution at the end of experiment
- Conduct experiment over a suitable timeframe to reach equilibrium



Solubility Experiments



- Drug substance classified by its lowest measured solubility
- Minimum of three replicate determinations in compendial media
- Measure drug substance by a suitably validated method
- Demonstrate stability of the drug substance in the solubility media (*e.g.*, < 10% degradation)

Permeability Methods



Human Pharmacokinetic Studies

- Absolute bioavailability
- Mass balance

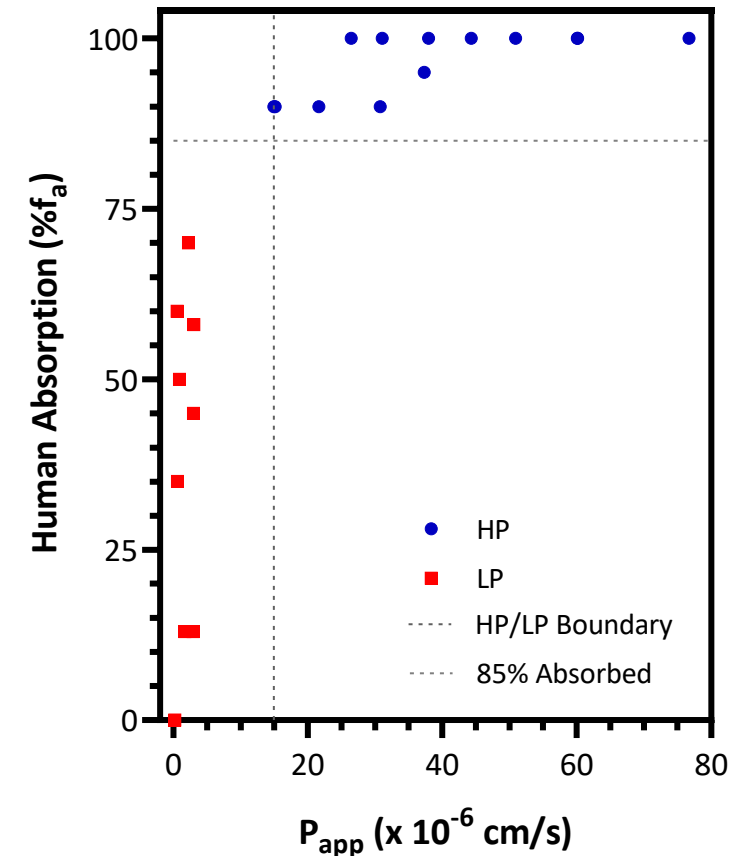
In Vitro Methods

- Validated and standardized Caco-2 cell assay

Caco-2 Cell Method Suitability



- Model drugs with known human intestinal absorption and passive absorption
- Establish method suitability with at least 5 model drugs per group of human fraction absorption (f_a) :
 - $f_a < 50\%$
 - $f_a = 50-84\%$
 - $f_a \geq 85\%$
- Internal standard at HP-LP boundary utilized for test drug classification

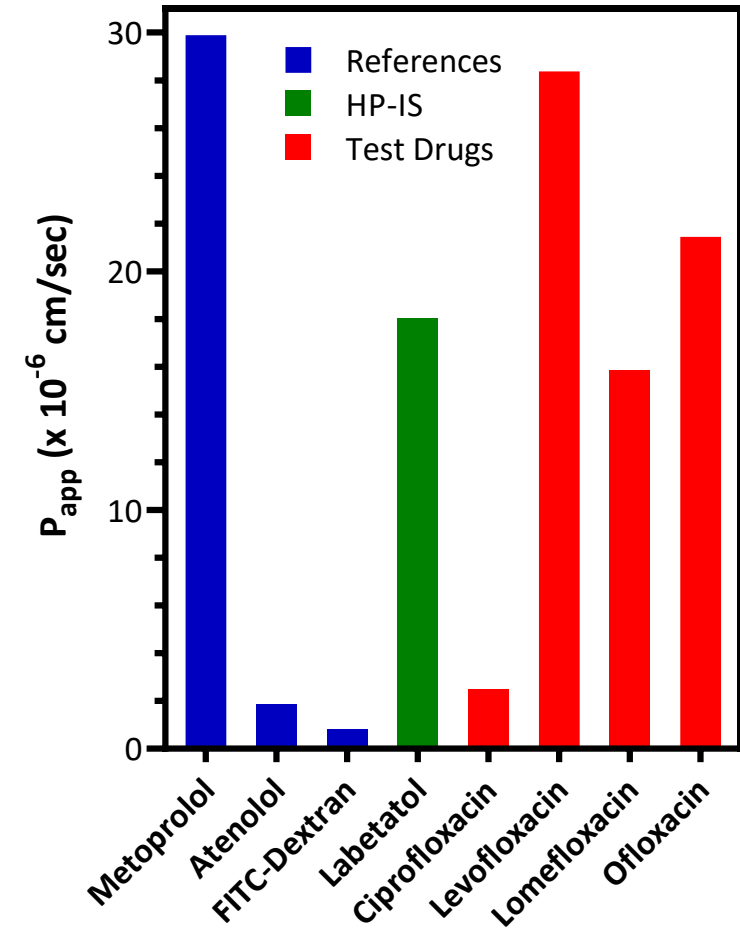


Volpe *et al.* Clin Res Reg Affairs. 2007

Use of Permeability Method



- Maintain same protocol for method suitability and classification experiments
- Demonstrate passive transport of test drug:
 - Evaluate test drug at several concentrations (*e.g.*, 0.01×, 0.1× and 1× the highest strength/250 mL), and
 - Bidirectional permeability of test drug
- Drug classified as highly permeable when its P_{app} is equal to or greater than of HP internal standard

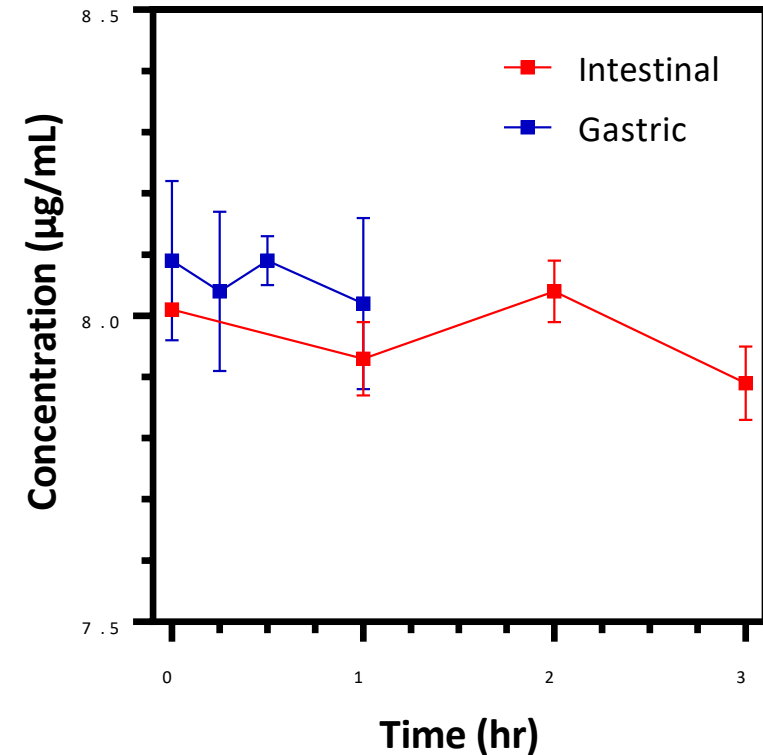


Volpe. AAPS PharmSci. 2004

Gastrointestinal Stability Methods



- Provide if mass balance studies are used to demonstrate high permeability
 - unless $\geq 85\%$ of the dose is recovered as unchanged drug in urine
- Required if Caco-2 studies are used to support high permeability



Asafu-Adjaye *et al.* J Pharm Biomed Anal. 2007

Gastrointestinal Stability Experiments

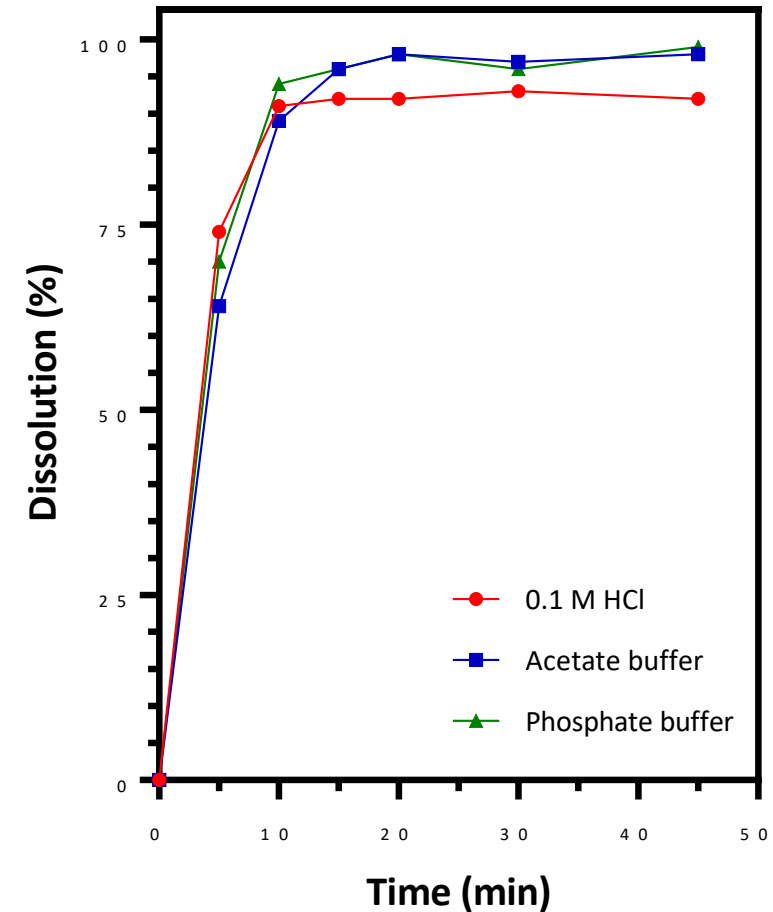
- Stability documented using compendial or simulated gastric and intestinal fluids
- Drug solutions incubated at 37°C for 1 hour (gastric fluid) or 3 hours (intestinal fluid)
- Drug concentrations measured using a suitably validated method
- Significant degradation (>10%) of a drug precludes BCS high permeability classification



Dissolution Methods



- Similar *in vitro* dissolution characteristics (*i.e.*, based on f2 comparison) under all the defined conditions
- Test product from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater

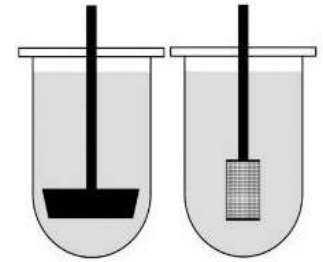


Kus-Slowinska *et al.* Pharmaceuticals. 2020

Dissolution Conditions



- Apparatus: paddle or basket
- Volume of dissolution medium: ≤ 900 mL
- Temperature of the dissolution medium: $37 \pm 1^\circ\text{C}$
- Agitation: paddle (50 rpm) or basket (100 rpm)
- At least 12 units each of reference and test product
- Pharmacopoeial buffers: pH 1.2, pH 4.5, and pH 6.8



Dissolution Conditions



- No organic solvents or surfactants in dissolution medium
- For gelatin capsules or tablets with gelatin coatings the use of enzymes may be acceptable, if justified
- Filter samples during collection
- Minimum of three time points (zero excluded)
- Same time points for test and reference products

Summary



- FDA's M9 BCS-based biowaiver guidance provides:
 - definition of BCS classes
 - biowaiver requirements
 - methodology for classifications
 - discussion of excipients
 - detailed information on permeability, solubility, dissolution and stability methods

References



- Food and Drug Administration. Guidance for Industry: M9 Biopharmaceutics Classification System-Based Biowaivers. March 2021. [<https://www.fda.gov/media/148472/download>]
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- Asafu-Adjaye *et al.* Validation and application of a stability-indicating HPLC method for the *in vitro* determination of gastric and intestinal stability of venlafaxine. J Pharm Biomed Anal. 2007; 43:1854-1859.
- Dezani *et al.* Equilibrium solubility *versus* intrinsic dissolution: characterization of lamivudine, stavudine and zidovudine for BCS classification. Braz J Pharm Sci. 2013; 49:853-863.
- Kus-Slowinska *et al.* Solubility, permeability, and dissolution rate of naftidrofuryl oxalate based on BCS criteria. Pharmaceutics. 2020; 12:1238.

