

The Biopharmaceutics Classification System

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Biopharmaceutics Classification System

- ▶ The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability.
- ▶ When combined with the dissolution of the drug product, the BCS takes into account three major factors that govern the rate and extent of drug absorption from IR solid oral dosage forms. These factors are **dissolution, solubility, and intestinal permeability**.
- ▶ BCS categorized drugs according to two key physicochemical characteristics:
 - ❖ Solubility
 - ❖ Permeability

Biopharmaceutics Classification System

- ▶ The system is based on Fick's law as applicable to a biological membrane by the following expression:

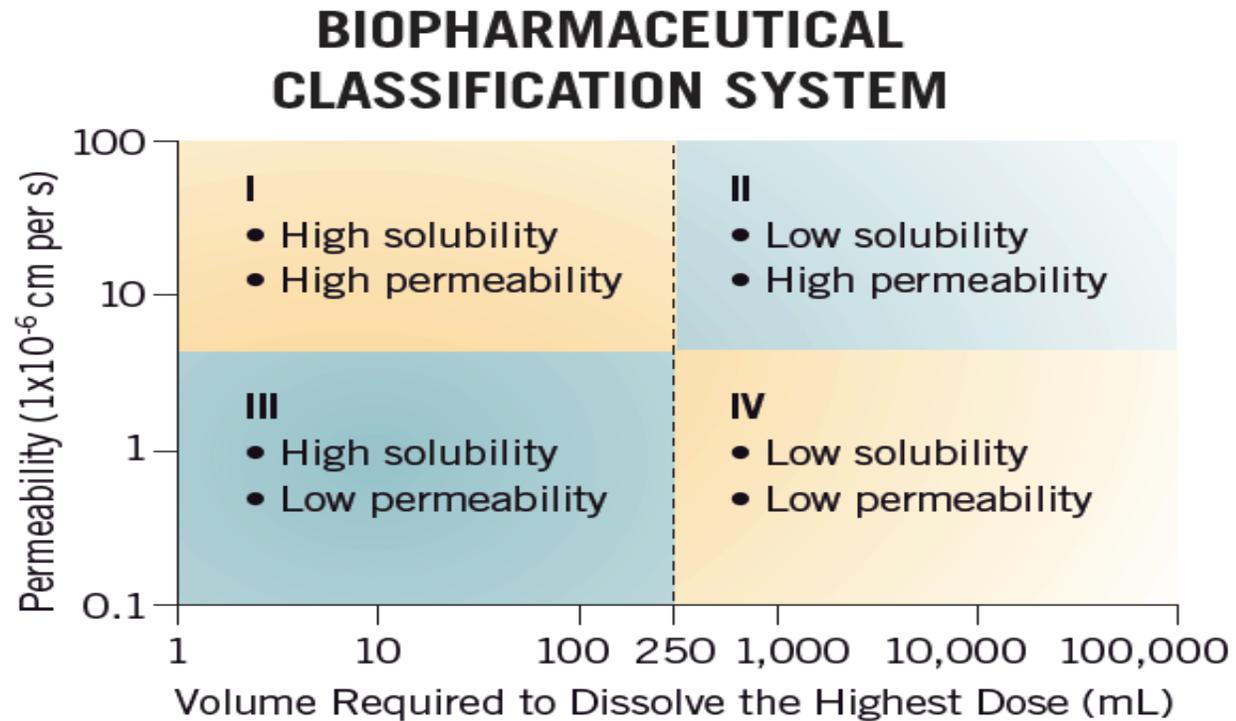
$$J_w = P_w C_w$$

J_w : the drug flux

P_w : permeability of the membrane

C_w : the drug concentration at the surface of the intestinal membrane

Biopharmaceutics Classification System



BCS class I

- ▶ BCS class I compounds are expected to dissolve quickly in the GI fluid and readily cross the intestinal wall through the passive diffusion process due to high solubility and permeability.
- ▶ Although class I compounds are expected to have excellent oral absorption, given their high solubility and high permeability, additional absorption barriers may exist beyond the scope of the BCS.
- ▶ For example, luminal complexation and degradation can significantly limit the amount of drug available for absorption. Even after the drug crosses the intestinal membrane, it may be metabolized within the enterocytes and/or pumped out of the cells due to efflux mechanisms.

BCS class II

- ▶ Drugs belonging to this class have low solubility and high permeability, hence, the dissolution rate becomes the governing parameter for bioavailability.
- ▶ These drugs exhibit variable bioavailability and need enhancement in the dissolution rate by different methods for improvement in bioavailability.

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BCS class II

▶ Methods for enhancing the dissolution and absorption of class II drugs

❖ **Methods for enhancing solubility of drugs**

Buffering the pH of microenvironment

Use of salts of weak acids and weak bases

Use of solvates and hydrates

Use of selected polymorphic forms

Complexation

Use of surfactants

Prodrug approach

❖ **Methods enhancing the surface area of the drug**

Micronization

Use of surfactants (Enhancing effective surface area by facilitating proper wetting)

Solid dispersions (Dispersion of drugs in the solid matrix of water-soluble carriers)

BCS class III

- ▶ Permeation through the intestinal membrane forms the rate-determining step for these drugs.
- ▶ Since absorption is permeation rate limited, bioavailability is independent of drug release from the dosage form.
- ▶ For example, the various ranitidine products having different dissolution profiles produce superimposable plasma concentration versus time profile in-vivo.
- ▶ These drugs generally exhibit low bioavailability and permeability enhancement is generally required.

BCS class IV

- ▶ They exhibit both poor solubility and poor permeability, and they pose tremendous challenges to formulation development.
- ▶ As a result, a substantial investment in dosage form development with no guarantee of success should be expected. Drugs of this class exhibit poor and variable bioavailability.
- ▶ These drugs are generally not suitable for oral drug delivery or else some special drug delivery will be needed.
- ▶ **Some class IV compounds have surprisingly good oral bioavailability, how can you explain this?**

BCS-based biowaivers

- ▶ The first regulatory guidances encouraging the use of the BCS for biowaivers of Class I immediate-release (IR) solid oral dosage forms were issued by the US Food and Drug Administration (US-FDA) in 2000 and by the European Medicines Agency (EMA) in 2001.
- ▶ Later, the World Health Organization (WHO) and EMA published guidelines allowing the granting of BCS biowaivers for both Class I and Class III drugs.
- ▶ Initially, the WHO also considered granting biowaivers for some drugs of weak acids in Class II but presently grants biowaivers for only Class I and Class III drugs. In May 2015, the US-FDA revised its BCS Guidance to expand the biowaiver provision to Class III drugs.

BCS-based biowaivers

- ▶ The FDA may waive the requirement for performing an *in vivo* bioavailability or bioequivalence study for certain IR solid oral drug products that meet very specific criteria, namely, the
 - ▶ Permeability
 - ▶ Solubility
 - ▶ Dissolution of the drug.
- ▶ The pharmaceutical industry has taken advantage of this and BCS-based waivers are becoming more routine and result in significant savings.
- ▶ The principles may be used to establish bioequivalence in applications for **generic medicinal products, extensions of innovator products, variations that require bioequivalence testing, and between early clinical trial products and to-be-marketed products.**

BCS-based waivers

- ▶ For BCS class I drug products, the following should be demonstrated:
 - ❖ The drug substance is highly soluble
 - ❖ The drug substance is highly permeable
 - ❖ The drug product (test and reference) is rapidly dissolving
 - ❖ The product does not contain any excipients that will affect the rate or extent of absorption of the drug

BCS-based biowaivers

- ▶ For BCS class III drug products, the following should be demonstrated:
 - ❖ The drug substance is highly soluble
 - ❖ The drug product (test and reference) is very rapidly dissolving
 - ❖ The test product formulation is qualitatively the same and quantitatively very similar to the reference product.

BCS class III test drug product must contain the same excipients as the reference product. This is due to the concern that excipients can have a greater impact on absorption of low permeability drugs. The composition of the test product must be qualitatively the same (except for a different color, flavor, or preservative that could not affect the BA) and should be quantitatively very similar to the reference product.

BCS-based biowaivers

- ▶ BCS-based biowaivers are **not** applicable for the following:

1. Narrow Therapeutic Index Drugs

- ▶ Because of the critical relationship between the bioavailable dose and clinical performance.

2. Products Designed to be Absorbed in the Oral Cavity

- ▶ A request for a waiver of in vivo BA/BE studies based on the BCS is not appropriate for dosage forms intended for absorption in the oral cavity (e.g., sublingual or buccal tablets). Similarly, a biowaiver based on BCS for an orally disintegrating tablet can be considered only if the absorption from the oral cavity can be ruled out.

Solubility

- ▶ **Solubility:** A drug substance is considered highly soluble when the highest dose strength is soluble in 250 mL or less of aqueous medium over the pH range 1–6.8.
- ▶ The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (8 oz) of water.
- ▶ The solubility class is determined by calculating what volume of an aqueous medium is sufficient to dissolve the highest anticipated dose strength over a pH range of 1–6.8.
- ▶ Solubility can be determined using the shake-flask method (DESCRIBE IT!)

Permeability

- ▶ To be classified as highly permeable, a test drug should have an extent of absorption $>85\%$.

1. Pharmacokinetic studies in human

- ❖ Mass balance studies (stability considerations should be noted)
- ❖ Absolute bioavailability studies

2. Intestinal permeability methods

- ❖ In vivo intestinal perfusion studies in humans
- ❖ In vivo or in situ intestinal perfusion studies using suitable animal models
- ❖ In vitro permeation studies using excised human or animal intestinaltissues
- ❖ In vitro permeation studies across a monolayer of cultured epithelial cells

Permeability

- ▶ When using these methods, the experimental permeability data should correlate with the known extent-of-absorption data in humans.
- ▶ After oral drug administration, in vivo permeability can be affected by the effects of efflux and absorptive transporters in the gastrointestinal tract, by food, and possibly by the various excipients present in the formulation.

Dissolution

- ▶ The dissolution class is based on the in vitro dissolution rate of an IR drug product under specified test conditions and is intended to indicate rapid in vivo dissolution in relation to the average rate of gastric emptying in humans under fasting conditions.
- ▶ An IR A drug product is considered rapidly dissolving when not less than **85%** of the label amount of drug substance dissolves within **30** minutes using USP Apparatus I at 100 rpm or Apparatus II at 50 rpm in a volume of 900 mL or less in each of the following media: (1) acidic media such as 0.1 N HCl or simulated gastric fluid USP without enzymes, (2) a pH 4.5 buffer, and (3) a pH 6.8 buffer or simulated intestinal fluid USP without enzymes.

Dissolution

- ▶ An IR product is considered very rapidly dissolving when a mean of 85 percent or more of the labelled amount of the drug substance dissolves within 15 minutes, using the previously mentioned conditions.
- ▶ A minimum of 12 dosage units of the test and reference drug product for each strength should be evaluated to support a biowaiver request.
- ▶ Samples should be collected at a sufficient number of intervals to characterize the entire dissolution profile of the drug product (e.g., 5, 10, 15, 20, and 30 minutes).

Example of BCS-based biowaivers

- ▶ One example is pregabalin, developed by Pfizer (Kalamazoo, Michigan, U.S.A.).
- ▶ Pregabalin is a highly soluble compound with a minimum solubility of 33 mg/mL over the pH range of 1 to 7.5 at 37°C.
- ▶ In addition, pregabalin demonstrates high permeability with an extent of absorption of more than 90% .
- ▶ The in vitro dissolution rates of all capsule formulations met the rapidly dissolving criteria, that is, more than 85% within 30 minutes.
- ▶ FDA approved the biowaiver for pregabalin capsules in phase 3 development, which certainly shortened the submission timeline and eliminated the costs associated with in vivo BE studies.

Example of BCS-based biowaivers

- ▶ In Europe, the German regulatory authority (BfArM, Bonn) has granted approval of sotalol hydrochloride generic product based on the BCS class I approach.
- ▶ The highest dose strength of sotalol (160 mg) is soluble in 250 mL of aqueous buffers at pH 1, 4.5, 6.8, and 7.5.
- ▶ Further, Caco-2 permeability studies and absolute human BA of 90% suggest that sotalol falls in the high-permeability class. Additionally, the generic drug products demonstrated 85% drug release within 15 minutes.

Example of BCS-based biowaivers

- ▶ The Swedish regulatory agency, Medical Products Agency (MPA), has approved Tranexamic acid based on BCS
- ▶ Tranexamic acid is a BCS class III class drug
- ▶ Its maximum dose 1.5 g is freely soluble in 250 ml buffer within pH 1 to 6.8. It has linear pharmacokinetics with a 55% of fraction absorbed
- ▶ Because the generic products demonstrate similar dissolution profiles with the innovator product, with more than 85% drug release in five minutes within pH 1.2 to 6.8, MPA approved the biowaiver for the 500 mg dose strength.

BCS-based biowaivers

- ▶ Similarities and Differences in Criteria for an Acceptable BCS-Based Biowaiver for the US-FDA, EMA, and WHO.
- ▶ <https://link.springer.com/article/10.1208/s12248-016-9877-2/tables/1>
 - ▶ Davit, Barbara M., et al. "BCS biowaivers: similarities and differences among EMA, FDA, and WHO requirements." *The AAPS journal* 18.3 (2016): 612-618.

Biopharmaceutics Drug Disposition Classification System

		High Solubility	Low Solubility
Permeability	High	Class 1 Transporter effects minimal	Class 2 Efflux transporter effects predominate
	Low	Class 3 Absorptive transporter effects predominate	Class 4 Absorptive and efflux transporter effects could be important
		High Solubility	Low Solubility
Permeability	High	Class 1 Metabolism	Class 2 Metabolism
	Low	Class 3 Renal and/or biliary elimination of unchanged drug	Class 4 Renal and/or biliary elimination of unchanged drug

FIGURE 12-21 Classification of Drugs Based on Biopharmaceutics Drug Disposition Classification System (BDDCS). Data from Wu and Benet (2009).