BCS Methodology: Solubility, Permeability & Dissolution

Donna A. Volpe, Ph.D.

Division of Applied Regulatory Science

Center for Drug Evaluation and Research | Food and Drug Administration

CDER Small Business & Industry Assistance (SBIA) Conference

Regulatory Best Practices for Global Access to Medicines, Including Anti-TB Medicines

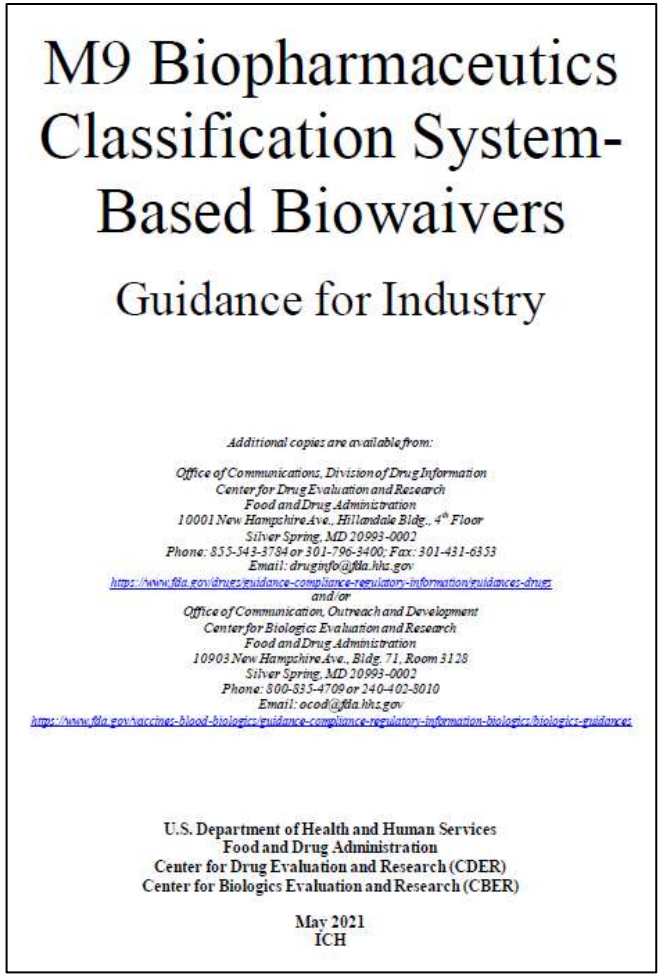
August 2022

Disclaimer

This presentation reflects the views of the presenter and should not be construed to represent the Food and Drug Administration's views or policies

Overview

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



M9 Biopharmaceutics Classification System-Based Biowaivers

Guidance for Industry

Additional copies are available from:

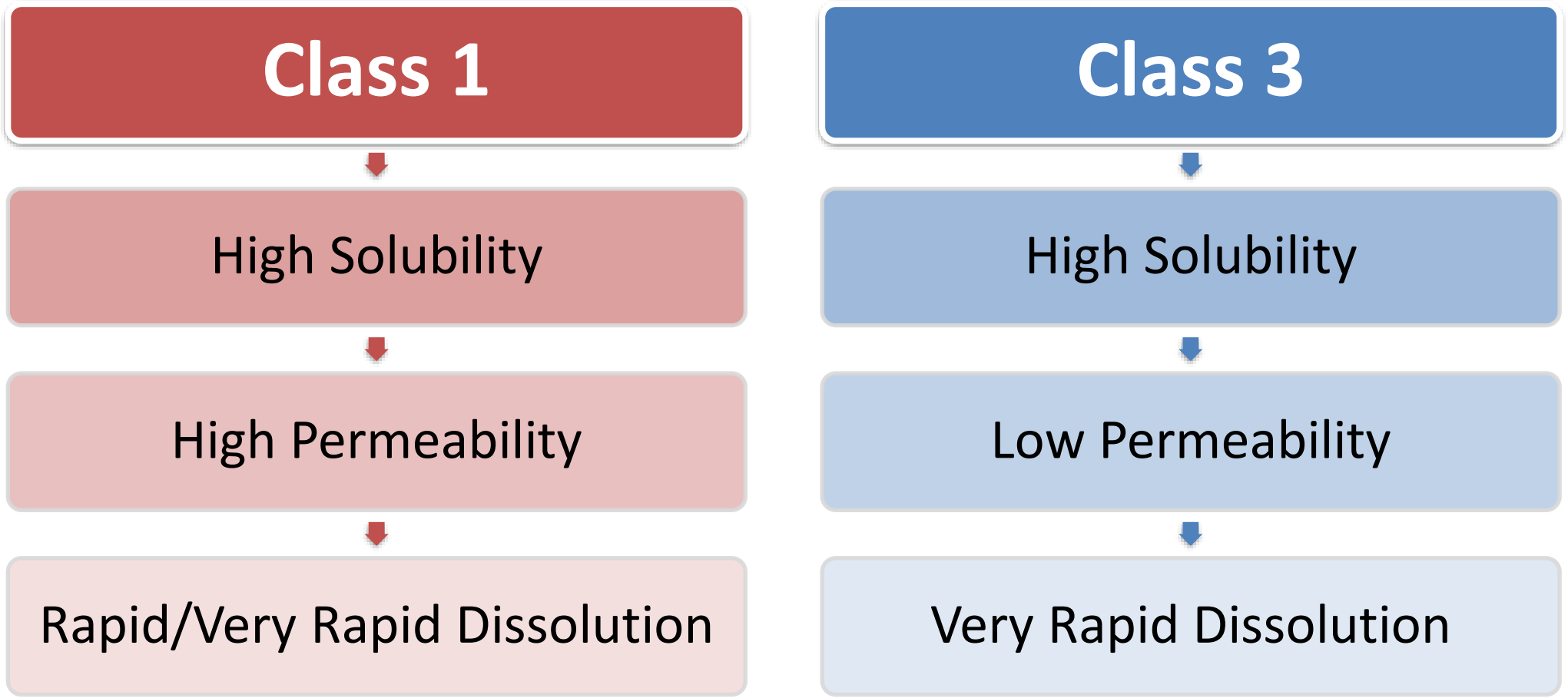
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/drugs/guidance-compliance-regulatory-information/guidances-drugs
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/vaccines-blood-biologics/guidance-compliance-regulatory-information-biologics/biologics-guidances

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

May 2021
ICH

https://www.fda.gov/media/148472/download

BCS Biowaivers



Classification of Drug Substance

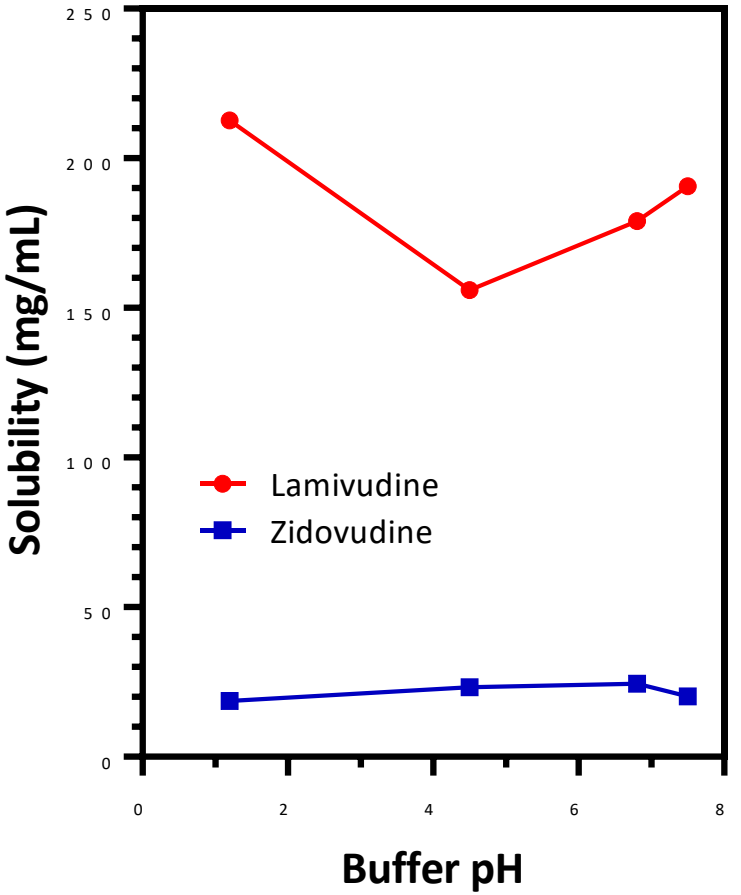
- **Solubility**
  - highly soluble (HS) if highest single therapeutic dose completely soluble in ≤250 mL aqueous media
- **Permeability**
  - highly permeable (HP) if absolute bioavailability is ≥85%, or
  - ≥85% of administered dose recovered in urine as parent drug, or as sum of parent drug and Phase 1/2 metabolites

Classification of Drug Product

- **Dissolution**
  - Both the test product and reference product exhibit:
    - very rapid (≥85% dissolved in ≤ 15 minutes), or
    - rapid (≥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±1°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

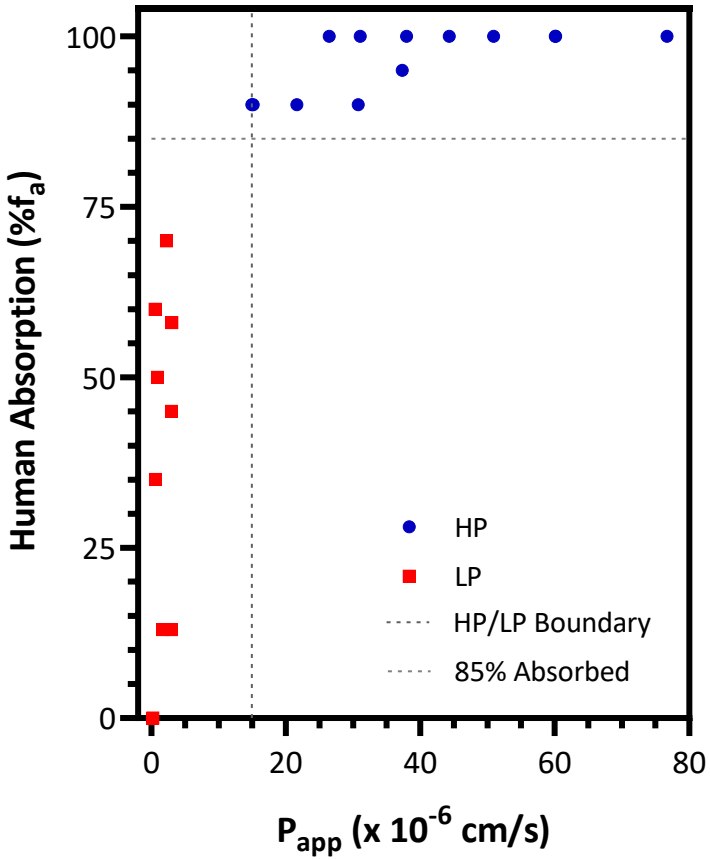
- Absolute bioavailability
- Mass balance

***In Vitro* Methods**

- Validated and standardized Caco-2 cell assay

Caco-2 Cell Method Suitability

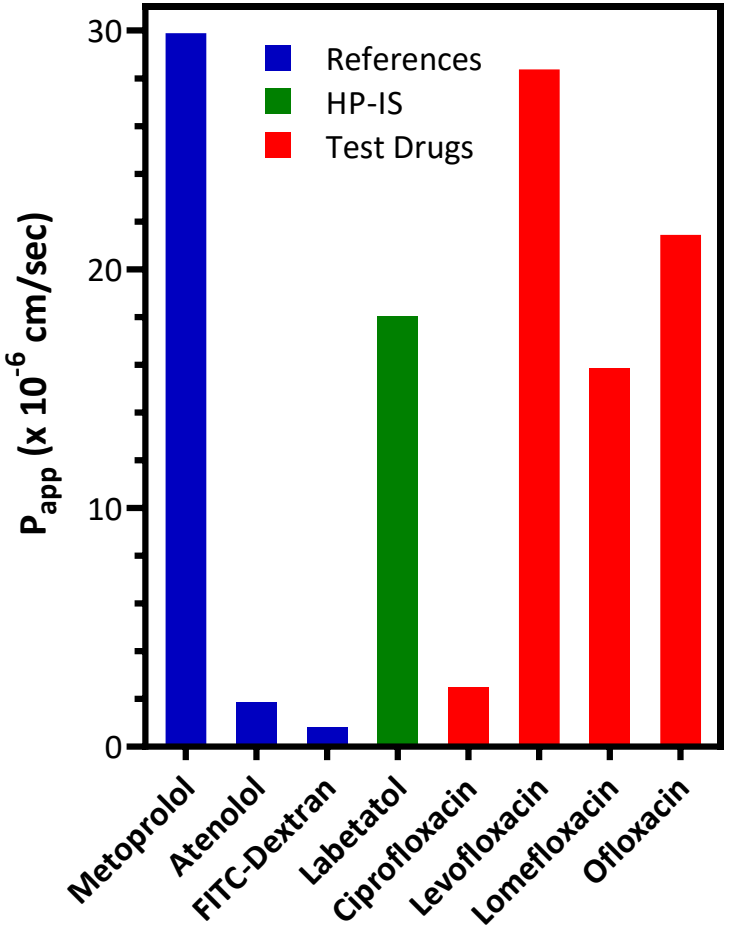
- Model drugs with known human intestinal absorption and passive absorption
- Establish method suitability with at least 5 model drugs per group of human fraction absorption (f_a) :
  - $f_a < 50\%$
  - $f_a = 50\text{-}84\%$
  - $f_a \geq 85\%$
- Internal standard at HP-LP boundary utilized for test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



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

Use of Permeability Method

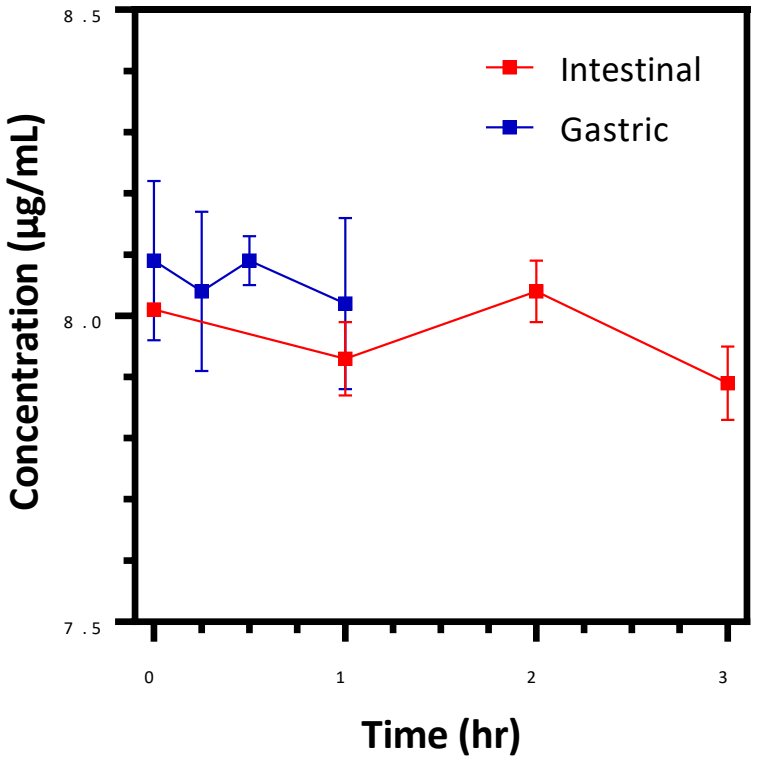
- Maintain same protocol for method suitability and classification experiments
- Demonstrate passive transport of test drug:
  - Evaluate test drug at several concentrations (*e.g.*, 0.01×, 0.1× and 1× the highest strength/250 mL), and
  - Bidirectional permeability of test drug
- Drug classified as 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 ≥85% of the dose is recovered as unchanged drug in urine
- Required if Caco-2 studies are used to support high permeability



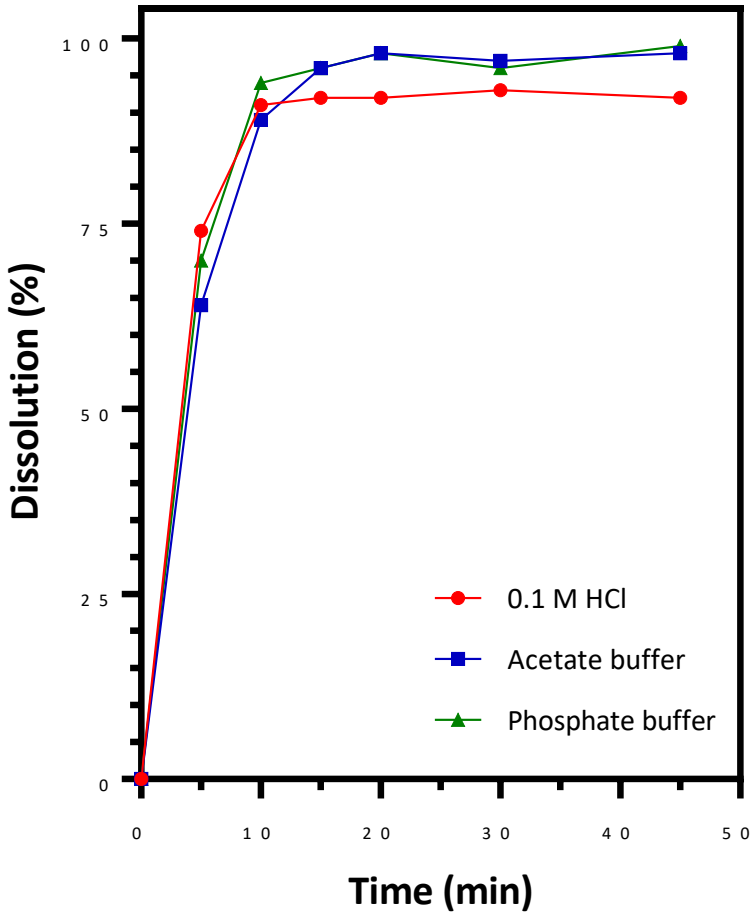
Asafu-Adjaye *et al*. J Pharm Biomed Anal. 2007

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

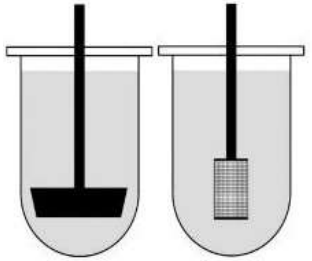
- Similar *in vitro* dissolution characteristics (*i.e.*, based on f2 comparison) under all the defined conditions
- Test product from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater



Kus-Slowinska *et al*. Pharmaceutics. 2020

Dissolution Conditions

- Apparatus: paddle or basket
- Volume of dissolution medium: ≤ 900 mL
- Temperature of the dissolution medium: 37±1°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]
- Volpe *et al*. Classification of drug permeability with a Caco-2 cell monolayer assay. Clin Res Reg Affairs. 2007; 24:39-47.
- Volpe. Permeability classification of representative fluoroquinolones by a cell culture method. AAPS PharmSci. 2004; 6:1-6.
- 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.


FDA
U.S. FOOD & DRUG
ADMINISTRATION