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Biopharmaceutics classification system- basis for waiver of *in-vivo* bioavailability and bioequivalence studies

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ABSTRACT

The Biopharmaceutical classification system (BCS) was introduced by Amidon et al in 1995 to reduce the need for in vivo bioequivalence (BE) studies, utilization of in vitro dissolution tests as a surrogate for in vivo bioequivalence studies. This step certainly reduces timelines in the drug development process, both directly and indirectly, and reduces unnecessary drug exposure in healthy volunteers, which is the normal study population in BE studies. The principles of the BCS classification system can be applied to NDA (New Drug Application) and ANDA (Abbreviated New Drug Application) approvals as well as to scale-up and post approval changes in drug manufacturing.

Key words: Biopharmaceutics Classification System; solubility; permeability; dissolution; bioequivalence; immediate-release products.

INTRODUCTION

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability [1]. When combined with the in vitro dissolution characteristics of the drug product, the BCS takes into account three major factors: solubility, intestinal permeability, and dissolution rate, all of which govern the rate and extent of oral drug absorption from IR solid oral-dosage forms [2, 3].

The objectives of the BCS are (4):

- To improve the efficiency of the drug development and review process by recommending a strategy for identifying expendable clinical bioequivalence test.
- To recommend a class of immediate-release (IR) solid oral dosage forms for which bioequivalence may be assessed based on in vitro dissolution tests.
- To recommend methods for classification according to dosage form dissolution along with the solubility–permeability characteristics of the drug product.

The BCS, which is based on scientific principles, presents a new paradigm in bioequivalence. According to the tenets of the BCS, certain drug products can be considered for biowaivers (i.e., product approval based on in vitro dissolution tests rather than bioequivalence studies in human subjects). At first, biowaivers were only applied to scale-up and post approval changes (SUPAC) (5), but later the biowaiver principle was extended to the approval of new generic drug products. As a result, unnecessary human experiments can be avoided, and the cost of developing generic products can be significantly lowered (6).

BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS)

The BCS classification is based on aqueous solubility and intestinal permeability of a drug substance. It allows for the prediction of in vivo pharmacokinetics of oral immediate-release (IR) drug products by classifying drug compounds into four classes (Table 1) based on their solubility related to dose and intestinal permeability in combination with the dissolution properties of the dosage form (8, 9).

The solubility classification of a drug in the BCS is based on the highest dose strength in an IR product. A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media over the pH range of 1.0–7.5; otherwise, the drug substance is considered poorly soluble. The volume estimate of 250 mL is derived from typical bioequivalence study protocols that prescribe the administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water (2, 3).

The permeability classification is based directly on the extent of intestinal absorption of a drug substance in humans or indirectly on the measurements of the rate of mass transfer across the human intestinal membrane (5). A drug substance is considered highly permeable when the extent of intestinal absorption is determined to be 90% or higher. Otherwise, the drug substance is considered to be poorly permeable (2, 3).

Table 1. The Biopharmaceutics Classification System

Class	Solubility	Permeability
I	High	High
II	Low	High
III	High	Low
IV	Low	Low

FDA GUIDANCE ON BIOWAIVERS (10)

FDA Bio waiver guidance provides recommendations for sponsors of investigational new drug applications (INDs), and applicants that submit new drug applications (NDAs), abbreviated new drug applications (ANDAs), and supplements to these applications for immediate-release (IR) solid oral dosage forms, and who wish to request a waiver of in vivo bioavailability (BA) and/or bioequivalence (BE) studies.

An IR drug product is considered rapidly dissolving when 85 percent or more of the labeled amount of the drug substance dissolves within 30 minutes, using United States Pharmacopeia (USP) Apparatus I at 100 rpm (or Apparatus II at 50 rpm or at 75 rpm when appropriately justified (see section III.C.)) in a volume of 500 mL or less in each of the following media: (1) 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.
An IR product is considered very rapidly dissolving when 85 percent or more of the labeled amount of the drug substance dissolves within 15 minutes using the above mentioned conditions.

BIOWAIVERS BASED ON BCS (10)

Recently FDA has issued draft guidance in May 2015 'Waiver of In-Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System'; following are the highlights of guidance:

This guidance is applicable for BA/BE waivers (bio waivers) based on BCS, for BCS class 1 and class 3 immediate-release solid oral dosage forms.

For BCS class 1 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, and
• The product does not contain any excipients that will affect the rate or extent of absorption of the drug

For BCS class 3 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, e.g., falls within scale-up and post-approval changes (SUPAC) IR level 1 and 2 changes, in composition to the reference

DIFFERENT DISSOLUTION MEDIA FOR VARIOUS CLASSES OF BCS

Class I drug substances

Substances that belong to class I possess good aqueous solubility and are transported through the GI mucosa. Their bioavailability after oral administration is usually close to 100 %, provided they are not decomposed in GIT and do not undergo extensive first pass metabolism [11]. After administration, the dosage form quickly passes into stomach and, usually disintegrates there, so it is logical to use a dissolution medium that reflects the gastric conditions. Simulated gastrointestinal fluid (SGF) without enzymes is suitable for many immediate release dosage forms of this class. For some capsules, an enzyme (pepsin) may have to be added to the medium to ensure the timely dissolution of the shell [12]. In case of weak acidic drugs simulated intestinal fluid without enzyme may be used due to hampered dissolution of this drug by the SGF medium. Water is less suitable medium than the aforementioned buffers, because it has a nominal buffer capacity zero; therefore, the pH may vary during the test [13]. Ensure and Milk as dissolution media can improve the drug solubility includes the solubilization of drugs in the fatty part of the fluid. Of these media contains similar ratio of protein/ fat/carbohydrate. Use of ensure and milk have been vigorously suggested as a media suitable for simulating fed state in the stomach [14, 15].

Class II drug substances

Substances that belong to class II possess poor aqueous solubility but are easily transported across the GI mucosa. Suitable bio-relevant media for class II drugs are: (a) SGFsp plus surfactant (e.g., Triton X- 100), to simulate the fasted state in the stomach. This medium is specifically useful for weak basic drugs, because these are most soluble under acidic condition. Presence of surfactant in the gastric may play a role in the wetting and solubilization of poorly soluble acids in the stomach [16]. (b) Ensure and Milk as dissolution media can improve the drug solubility include the solubilization of drugs in the fatty part of the fluid. Both of these media contains similar ratio of protein/ fat/ carbohydrate [14, 15]. (c) FaSSIF (Fasted state simulated intestinal fluid) and FeSSIF (Fed state simulated intestinal fluid) are the recently developed to simulate the intestinal condition. The two media are particularly useful for forecasting the in-vivo dissolution of the poorly soluble drugs from different formulations and for assessing potential for foods effects on the in-vivo dissolution. The dissolution rate of the poorly soluble drug is often better in FaSSIF and FeSSIF than in the simple aqueous buffers because of the increased wetting of the drug surface and micellar solubilization of the drug by the bile components of these media [13, 17]. (d) Hydro-alcoholic mixtures as dissolution media were popular for the dissolution of poorly soluble drugs. Particular significance of these media over the surfactant containing media is that they do not tend to foam, which makes deaeration and volume adjustment somewhat less frustrating [11, 13].

Class III drug substances

Despite their good aqueous solubility, class III substances fail to achieve complete bioavailability after oral dosing because of their poor membrane permeability. A simple aqueous media can be used [13, 18].

Class IV drug substances

Class IV drugs combine poor solubility with poor permeability. Therefore, similar to class III drugs, they usually do not approach complete bioavailability. Two compendial media i.e. SGFsp & SIFsp with addition of a surfactant to ensure the complete release of drug from formulation can be used [11, 13, 18].

DISSOLUTION TIME FOR BCS CLASSES

The duration of dissolution test must be tailored to not only the site of absorption for the drug but also timing of administration. If this is best absorbed from the upper small intestine and is to be administered in the fasted state, dissolution test in a medium simulating fasted gastric conditions with duration of 15 to 30 minutes are appropriate. On the other hand, if a drug is administered with food and well absorbed through the small intestine and proximal large intestine, duration of as long as 10 hours (with appropriate changes to the composition dissolution medium) could be envisaged [18]. Class I drugs show the high solubility that's why, U.S. FDA recommended one point test for IR dosage form in a simple medium and 85 % or more of the drug to be released within 30 minutes. Similar conditions applied for class III drugs due to having high solubility as similar to that of class I drugs. In case of class II and IV drugs having low solubility (if these drugs designed as extended release formulations) demand at least three specification points, the first after 1-2 hours (about 20-30 % drug release) provide assurance against premature

drug release. The second specification point has to be close to 50 % drug release (definition of the dissolution pattern). At last point, the dissolution limit should be at least 80 % to ensure almost quantitative release [19].

CONCLUSION

The Biopharmaceutics Classification System provides a regulatory tool for replacing certain bioequivalence studies with accurate in vitro dissolution tests during the process of generic drug development. BCS applications for Class 2 and 3 are challenging, but at the same time provide opportunities for lowering regulatory burden with scientific rational. BCS also provides an avenue to predict drug disposition, transport, absorption, elimination. The in- vivo performance of the drug depends upon its solubility and permeability. The biopharmaceutical classification system is the guiding tool for the prediction of in vivo performance of the drug substance and development of drug delivery system to suit that performance.

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