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Review Article

BIOPHARMACEUTICAL CLASSIFICATION SYSTEM AND BIOWAVER: AN OVERVIEW

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ABSTRACT
The biopharmaceutical classification system (BCS) has been developed to provide a scientific approach for classifying drug compounds based on solubility as related to dose and intestinal permeability in combination with the dissolution properties of the oral immediate release dosage form. BCS is to provide a regulatory tool for replacing certain bioequivalence (BE) studies by accurate in vitro dissolution tests. This review gives three dimensionless numbers which are used in BCS are absorption number, dissolution number, dose number.
Biowaver is an important tool for formulation development. Bioavailability (BA) and BE play a central role in pharmaceutical product development, and BE studies are presently being conducted for New Drug Applications (NDAs) of new compounds, in supplementary NDAs for new medical indications and product line extensions, in Abbreviated New Drug Applications (ANDAs) of generic products, and in applications for scale-up and post-approval changes. The principles of the BCS classification system can be applied to NDA and ANDA approvals as well as to scale-up and post approval changes in drug manufacturing. BCS classification can therefore save pharmaceutical companies a significant amount in development time and reduce costs. The aim of the present review is to present the status of BCS and discuss its future application in pharmaceutical product development.
KEYWORDS: Biopharmaceutical classification system, Biowaver, Solubility, Permeability.

INTRODUCTION

Since its inception in 1995, the biopharmaceutical classification system (BCS) has become an increasingly important tool for regulation of drug products world-wide.[1] The BCS is a scientific framework for classifying drug substances based upon their aqueous solubility and intestinal permeability. When combined with the dissolution of a drug product, the BCS takes into account 3 major factors which govern the rate and extent of drug absorption from immediate release (IR) solid oral dosage forms (tablets/capsules), viz: dissolution rate, solubility and permeability.[2] The introduction of the biopharmaceutics drug classification system (BCS) into the guidelines of the Food and Drug Administration (FDA) is a major step forward to classify the biopharmaceutical properties of drugs and drug products.[3] The Introduction of the Biopharmaceutics Classification System (BCS)[4], its validity and applicability have been the subject of extensive research and discussion[5]. These efforts have resulted in an improved SUPAC-IR guidance, a dissolution guidance[7], and a Food and Drug Administration (FDA) guidance on waiver of in vivo bioequivalence studies for BCS Class I drugs in rapid dissolution immediate-release (IR) solid oral-dosage forms[8-9].Until now, application of the BCS has been partially hindered by the lack of a freely available and accurate database summarizing solubility and permeability characteristics of drug substances. Based on mechanistic approaches to the drug absorption and dissolution processes, the BCS enables the regulatory bodies to simplify and improve the drug approval process.[1]The knowledge of the BCS characteristics of a drug in a formulation can also be utilized by the formulation scientist to develop a more optimized dosage form based on fundamental mechanistic, rather than empirical information.[3]

The tenets of biopharmaceutics, solubility and permeability, are of pivotal importance in new drug discovery and lead optimization due to the dependence of drug absorption and pharmacokinetics on these two properties. A classification system for drugs based on these two fundamental parameters, Biopharmaceutic Classification System (BCS), provides drug designer an opportunity to manipulate structure or physicochemical properties of lead candidates so as to achieve better "deliverability". Considering the facts for failure of NCEs, drug research, once concentrating on optimizing the efficacy and safety of the leads, dramatically transformed in the past two decades. With the enormous number of molecules being synthesized using

combinatorial and parallel synthesis, high throughput methodologies for screening solubility and permeability has gained significant interest in pharmaceutical industry. Ultimate aim of the drug discovery scientist in pharmacokinetic optimization is to tailor the molecules so that they show the features of BCS class I without compromising on pharmacodynamics. Thus, biopharmaceutical characterization during drug design and early development helps in early withdrawal of molecules with insurmountable developmental problems associated with pharmacokinetic optimization.[10]

BCS CLASSES

- Class I-high solubility/high permeability
- Class II-low solubility/high permeability
- Class III-high solubility/low permeability
- Class IV-low solubility/low permeability

In addition, immediate release (IR) dosage forms are categorized as having rapid or slow dissolution. According to the BCS, when certain criteria are met, the classification system can be used as a drug development tool to assess bioequivalence in vitro thus obviating the need to perform in vivo studies in human subjects. [7]

To-date, however, only drug products which fall in the Class I category, which contain highly soluble, highly permeable drug substances in IR solid oral dosage forms that exhibit rapid in vitro dissolution, may qualify for a waiver of in vivo bioequivalence studies.

Solubility

The solubility class boundary is based on the highest dose strength of an IR product that is the subject of a biowaiver request. A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5. The volume estimate of 250 ml is derived from typical BE study protocols that prescribe administration of a drug product to fasting human volunteers with a glass (about 8 ounces) of water[8, 9, 10].

Permeability

The permeability class boundary is based indirectly on the extent of absorption (fraction of dose absorbed, not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across human intestinal membrane. Alternatively, nonhuman systems capable of predicting the extent of drug absorption in humans can be used (e.g., *in vitro* epithelial cell culture methods). In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the extent of absorption in humans is determined to be 90% or more of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose[19,20].

Dissolution

In this guidance, an IR drug product is considered rapidly dissolving when no less than 85% of the labeled amount of the drug substance dissolves within 30 minutes, using U.S. Pharmacopeia (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) 0.1 N HCl or Simulated Gastric Fluid USP without enzyme a pH 4.5 buffer; and (3) a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes [11,13-15]

SOLUBILITY DETERMINATION

- pH -solubility profile of test drug in aqueous media with a pH range of 1 to 7.5.
- Shake-flask or titration method.
- Analysis by a validated stability-indicating assay [8]

PERMEABILITY DETERMINATION

Extent of absorption in humans [21]

- Mass-balance pharmacokinetic studies.
- Absolute bioavailability studies.
- Intestinal permeability methods.
- *In vivo* intestinal perfusions studies in humans.
- *In vivo* or *in situ* intestinal perfusion studies in animals.
- *In vitro* permeation experiments with excised human or animal intestinal tissue.
- *In vitro* permeation experiments across epithelial cell monolayers. [8]

DISSOLUTION DETERMINATION

USP apparatus I (basket) at 100 rpm or USP apparatus II (paddle) at 50 rpm.

Dissolution media (900 ml): 0.1 N HCl or simulated gastric fluid, pH 4.5 buffer, and pH 6.8 buffer or simulated intestinal fluid.

Compare dissolution profiles of test and reference products using a similarity factor.

Drug dissolution and gastrointestinal permeability is the fundamental parameters controlling rate and extent of drug absorption. This classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers viz. [8,22,23]

Absorption number defined as the ratio of the mean residence time to mean absorption time[24,25].

Dissolution number defined as the ratio of mean residence time to mean dissolution time[26].

Dose number defined as the mass divided by the product of uptake volume (250 ml) and solubility of drug (4) Fundamental starting point for BCS is

$$J_w = P_w.C_w$$

Jw- Drug flux (mass/area / time) through the intestinal wall at any position

Pw- Permeability of this (complex) membrane

Cw- Drug concentration at membrane (intestinal) surface

$$\text{Absorption rate} = dm / dt = \iint_A P_w C_w da$$

Effective wall permeability is given by

$$Pe = Pa.\ Pw\ /\ (Pa + Pw)$$

Pa is apparent wall permeability to mass transport to intestinal membrane (aqueous mass transport coefficient)

Pw - Wall permeability

Pa - Estimated by equation

$$Pa\text{-}1\ (x) = 1.47(D/R)\ Gz\ 1/3\ (x/L)1/3$$

$$Do = (Mo/Vo) / Cs$$

$Dn - t_{res/}\ t_{diss}$

$A_n - t_{abs}^{-1}.\ t_{res}$

$t\ res = \pi R^2 L/Q$ mean recidence time

$t\ diss - r^2_0\ \zeta/3DCs$ Time Required for Particle of drug to dissolve.

$t\ abs^{-1} = kabs = (s/v)Peff = 2.Peff/R$ = The Effective Absorption Rate Constant[27]

ClassI - drugs exhibit a high absorption number and a high dissolution number. The rate limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate determining step. e.g. Metoprolol, Diltiazem, Verapamil, Propranolol[28, 29, 30].

ClassII- Drugs have a high absorption number but a low dissolution number. In vivo drug dissolution is then a rate limiting step for absorption except at a very high dose number. The absorption for class II drugs is usually slower than class II and occurs over a longer period of time. In vitro- In vivo correlation (IVIVC) is usually accepted for class I and class II drugs. e.g. Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedinpine. [31, 33, 34]

For ClassIII drugs, permeability is rate limiting step for drug absorption. These drugs exhibit a high variation in the rate and extent of drug absorption. Since the dissolution is rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. e.g. Cimetidine, Acyclovir, Neomycin B, Captopril. [32]

Class IV drugs exhibit a lot of problems for effective oral administration. Fortunately, extreme examples of class IV compounds are the exception rather than the rule and are rarely developed and reach the market. Nevertheless a number of class IV drugs do exist. e.g. Taxol. [35]

BIOWAIVER EXTENSION POTENTIAL

Potential of Redefining BCS Solubility Class Boundary

The solubility class boundary requires that the highest strength of a drug substance is soluble in 250 ml or less of aqueous media over the pH range of 1.0–7.5. The pH range of 1.0–7.5 for solubility studies is a stringent requirement and may not be necessary. Under fasting conditions, the pH range in the GI tract vary from 1.4 to 2.1 in the stomach, 4.9 to 6.4 in the duodenum, 4.4 to 6.6 in the jejunum, and 6.5 to 7.4 in the ileum. Furthermore, it generally takes approximately 85 min for a drug to reach the ileum. By the time the drug reaches the ileum, the dissolution of the drug product is likely complete if it meets the rapid dissolution criterion, i.e., no less than 85% dissolved within 30 min. Therefore, it would appear reasonable to redefine the pH range for BCS solubility class boundary from 1.0–7.5 to 1.0–6.8 in alignment with dissolution pH ranges, which are pH 1.0, 4.5, and 6.8 buffers. The dose volume of 250 ml seems a conservative estimate of what actually is available *in vivo* for solubilization and dissolution. The physiological volume of the small intestine varies from 50 to 1100 ml with an average of 500 ml under the fasted conditions. If the drug is not in solution in the stomach, gastric emptying would then expose it to the small intestine, and the solid drug would dissolve under the effect of additional small intestinal fluid. However, because of the large variability of the small intestinal volume, an appropriate definition of the volume for solubility class boundary would be difficult to set. Another factor influencing *in vivo* solubility is bile salt/ micelle solubilization[39]. Intestinal solubility is perhaps the most important solubility because this is the absorbing region for most drugs. Many acidic drugs whose solubility is low at low pH are well absorbed. For example, most nonsteroidal anti-inflammatory drugs, such as flurbiprofen, ketoprofen, naproxen, and oxaprozin, are poorly soluble in the stomach but are highly soluble in the distal intestine and their absolute human bioavailability are 90% or higher, thus exhibiting behavior similar to those of BCS Class I drugs[40]. The solubility classification is based on the ability of a drug to dissolve in plain aqueous buffers. However, bile salts are present in the small intestine, even in the fasted state. The average bile salt concentration in the small intestine is estimated to be approximately 5 mM[36]. Based on physiological factors, Dressman designed two kinds of media, one to simulate the fasted-state conditions in the small intestine and the other to simulate the fed-state conditions in the small intestine[36]. These two media may be used in drug discovery and development processes to assess *in vivo* solubility and dissolution and have the potential to be used in drug regulation, i.e., dissolution methodology for bioequivalence demonstration using more physiologically relevant media, although more extensive research is needed. Other criteria, such as intrinsic dissolution rate, may be useful in the classification of the biopharmaceutic properties of drugs. The intrinsic dissolution method has been widely used in pharmaceutical industries to characterize drug

substances. A good correlation between the intrinsic dissolution rate and BCS solubility classification was found for 17 BCS model drugs[43]. Thus, the intrinsic dissolution rate may be used when the solubility of a drug cannot be accurately determined, although more validation research needs to be conducted.[10,36,37,38]

Potential of Redefining BCS Permeability Class Boundary

The permeability class boundary is based on the extent of intestinal absorption (fraction of dose absorbed) of a drug substance in humans or on measurements of the rate of mass transfer across intestinal membranes. Under the current BCS classification, a drug is considered to be highly permeable when the fraction of dose absorbed is equal to or greater than 90%. The criterion of 90% for the fraction of dose absorbed can be considered conservative because the experimentally determined fraction of dose absorbed is seen to be less than 90% for many drugs that are generally considered completely or well-absorbed. This suggests that a class boundary of 85% might be appropriate in defining high permeability, although it remains to be justified and debated.[9]

BCS and Dissolution Method Development

BCS 1

•gastric emptying is rate-limiting step
•simple method (pH 1.2, 15 mins) can be used to demonstrate bioavailability
•IVIVC unlikely to be possible
•Biowaiver readily gained

BCS 2

•Dissolution may be rate-limiting
•Dissolution profile in multiple media should be assessed
•IVIVC may be possible
•Biowaiver may be possible

BCS 3

•Permeability is the rate-limiting step
•Limited IVIVC may be possible
•Biowaiver unlikely

BCS 4

•Both dissolution and permeability may be rate- limiting
•Dissolution profile in multiple media should be assessed
•IVIVC difficult to achieve
•Biowaiver unlikely[41]

BIOWAIVER

The term biowaiver is applied to a regulatory drug approval process when the dossier (application) is approved based on evidence other than in vivo bioequivalence test. For solid oral dosage forms, biowaiver(s) generally rely on a dissolution test.[8]

It was then recognized that dissolution rate has a negligible impact on bioavailability of highly soluble and highly permeable (BCS Class I) drugs when their formulation's dissolution is sufficiently rapid[42]. As a result, various regulatory agencies including the United States Food and Drug Administration (FDA) now allow bioequivalence of formulations of BCS Class I drugs to be demonstrated by in vitro dissolution (often called a biowaiver)[8,44,12]. The WHO has recently recommended biowaivers for Class III and some Class II drugs and AAPS-FDA scientific conferences have recommended biowaivers for Class III compounds as well.[45] The "Waiver of In-vivo Bioavailability and Bioequivalence Studies for Immediate Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System" is an FDA guidance document, which allows pharmaceutical companies to forego clinical bioequivalence studies, if their drug product meets the specification detailed in the guidance. The principles of the BCS classification system can be applied to NDA and ANDA approvals as well as to scale-up and post approval changes in drug manufacturing. BCS classification can therefore save pharmaceutical companies a significant amount in development time and reduce costs.[43]

Biowaivers Based on BCS

Considering the uncertainties associated with in vitro dissolution tests, the proposed draft guidance recommends biowaivers only for rapidly dissolving products of highly soluble and highly permeable drugs, that are not considered, by the FDA, to be "Narrow Therapeutic Index Drugs." The criteria for defining the therapeutic index of a drug is currently under consideration at the FDA. It is proposed that BCS based biowaivers apply for situations during both pre (IND/NDA and ANDA) and post approval phases. In the current proposal the following criteria are recommended for justifying the request for a waiver of in vivo biostudies

1. The drug substance should be highly soluble and highly permeable, defined as a class I drug.
2. An IR drug product should be rapidly dissolving, as defined above.
3. For waivers of an in vivo relative bioavailability study, dissolution should be greater than 85% in 30 minutes in the three recommended dissolution media (acidic media, such as 0.1 N HCl or Simulated Gastric Fluid USP without enzymes, a pH 4.5 buffer; and a pH 6.8 buffer or Simulated Intestinal Fluid USP without enzymes). For waivers of in vivo bioequivalence, test and reference products should exhibit similar dissolution profiles under the dissolution test conditions defined for rapidly dissolving products.

Two dissolution profiles may be considered similar when compared using the f2 metric (f2 > 50) as

described in the guidance for industry on dissolution testing[7]. When both the test and the reference products dissolve 85% or more of the label amount in < 15 minutes, in all three dissolution media recommended above, a profile comparison is unnecessary.

4. The drug should not be a narrow therapeutic index drug. This limitation is expected to be applied primarily to NDA and ANDA bioequivalence studies after approval, as well as bioequivalence studies submitted in an ANDA, recognizing that during the IND period an investigational drug may not be clearly identified as a narrow therapeutic index drug.

5. Excipients used in the dosage form should have been used previously in FDA approved IR solid dosage forms. The quantity of excipients in the IR product should be consistent with their intended function. Large quantities of certain excipients, such as surfactants (e.g., sodium lauryl sulfate) or osmotic ingredients (e.g., sorbitol) may be problematic.

6. All other application commitments should be met.

CONCLUSION: BCS is to provide a regulatory tool for replacing certain bioequivalence (BE) studies by accurate in vitro dissolution tests. Biowaver an imperative tool for formulation development which uses methods other than *In vivo*.BCS classification can therefore save pharmaceutical companies a significant amount in development time and reduce costs. The aim of the present review is to present the status of BCS and discuss its future application in pharmaceutical product development

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Major Routes of Drug Elimination

	High solubility	Low solubility
High permeability	**Class 1** Metabolism	**Class 3** Metabolism
Low permeability	**Class 2** Renal & Biliary Elimination of Unchanged Drug	**Class 4** Renal & Biliary Elimination of Unchanged Drug