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Review Article

BIOPHARMACEUTICS CLASSIFICATION SYSTEM: A STRATEGIC TOOL FOR CLASSIFYING DRUG SUBSTANCES

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ABSTRACT
The biopharmaceutical classification system (BCS) is a scientific approach for classifying drug substances based on their dose/solubility ratio and intestinal permeability. The BCS has been developed to allow prediction of in vivo pharmacokinetic performance of drug products from measurements of permeability and solubility. Moreover, the drugs can be categorized into four classes of BCS on the basis of permeability and solubility namely; high permeability high solubility, high permeability low solubility, low permeability high solubility and low permeability low solubility. The present review summarizes the principles, objectives, benefits, classification and applications of BCS.
KEY WORDS: BCS, Permeability, Solubility.

INTRODUCTION

The BCS serves as a guiding tool for formulation scientists for recommending a strategy to improve the efficiency of drug development by proper selection of dosage form and bioequivalence tests, to recommend a class of dosage forms[1,2,3]. The fundamental basis for the BCS was established by Dr. Gordon Amidon who was presented with a Distinguished Science Award at the August 2006 International Pharmaceutical Federation (FIP) Congress in Salvador, Brazil.

The BCS is a scientific framework for classifying a drug substance based on its aqueous solubility and intestinal permeability[4,5,6]. The BCS, when combined with the in vitro dissolution characteristics of the drug product, 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[5,6,7]. The BCS classification system is based on the scientific rationale that, if the highest dose of a drug candidate is readily soluble in the average volume of fluid present in the stomach (250 ml) and the drug is more than >90% absorbed, then the in vitro drug product dissolution profiles should allow assessment of the equivalence of different drug formulations. Solubility and dissolution can be easily measured in vitro[6,7]. The importance of drug dissolution in the gastrointestinal tract and permeability across the gut wall barrier in the oral absorption process has been well known since the 1960s, but the research carried out to constitute the BCS has provided new quantitative data of great importance for modern drug development especially within the area of drug permeability[1]. The concept of BCS provides a better understanding of the relationship between drug release from the product and the absorption process[5-8]. The bioavailability will be affected only by the in vivo performance of the dosage form, if dissolution/drug release is rate limiting for the dosage form. In contrast, as long as the permeation through bio-membranes is a rate-limiting process, bioavailability and bioequivalence are not so dependent upon the drug release behavior of the dosage form[8]. Each class of the BCS is having its designated rate-limiting step and the possible tactics for its modification that enable the formulator to select and optimize a dosage form for the drug substance belonging to a particular class of BCS[8,9]. An Industrial Implementation Strategy for the Biopharmaceutics Classification System is shown in figure 1.

Principle of BCS

The principle of the BCS is that if two drug products yield the same concentration profile along the gastrointestinal (GI) tract, they will result in the same plasma profile after oral administration. This concept can be summarized by the equation, $\mathbf{J = P_w C_w}$, where **J** is the flux across the gut wall, $\mathbf{P_w}$ is the permeability of the gut wall to the drug and $\mathbf{C_w}$ is the concentration profile at the gut wall[12]. In terms of bioequivalence (BE), it is assumed that highly permeable, highly soluble drugs housed in rapidly dissolving drug products will be bioequivalent

and unless major changes are made to the formulation, dissolution data can be used as a surrogate for pharmacokinetic data to demonstrate BE of two drug products. The BCS thus enables manufacturers to reduce the cost of approving scale-up and post approval changes to certain oral drug products without compromising public safety interests.

Objectives of BCS

BCS is a valuable tool for the formulation scientists, for the selection and design of the formulation of any drug substance[13]. The main objectives of BCS are to improve the efficiency of 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 form for which BE may be accessed based on in vitro dissolution tests; and to recommend methods for classification according to dosage form dissolution along with the solubility and permeability characteristics of drug products.

Benefits of Knowing BCS Category of A Compound

It can save both time and money-if the immediate - release, orally administered drug meets specific criteria then FDA will grant a waiver for expensive and time-consuming bio-equivalence studies[3,4,14]. The aim of the BCS is to provide a regulatory tool for the replacement of certain BE studies by conducting accurate in vitro dissolution tests[1,15]. This step will certainly reduce time in the drug development process, both directly and indirectly[1-5]. It has also been reported that the application of a BCS strategy in drug development will lead to significant direct and indirect savings for pharmaceutical companies. BCS has been developed primarily for regulatory applications, but it has also several other applications in both the pre-clinical and clinical drug development processes and has gained wide recognition within the research-based industry[5]. Combined with the dissolution, the BCS takes into account the three major factors governing bioavailability viz. dissolution, solubility and permeability[3,15]. This classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers[5,6].

Concept of BCS

The in-vivo performance of orally administered drugs depends upon their solubility and tissue permeability characteristics. If the absorption of the drug is permeation rate limited then the in-vitro dissolution study can be used to demonstrate the bioavailability (BA) or BE of the drug product through in vitro - in vivo correlation (IVIVC)[7,8,9]. On the other hand if absorption of the drug is dissolution rate limited then specifically designed in-vivo study will be required to access the absorption rate and to demonstrate the bioequivalence ultimately[1,8]. Such a drug substance is a good candidate for controlled delivery provided they qualify in terms of their pharmacokinetics and pharmacodynamics for controlled release development. If a drug itself is having low solubility and a slow dissolution rate, the release rate will automatically get slower and the absorption will be governed by the gastric emptying rate[1,5,6]. Therefore, the dosage form must be able to restrain within the absorption window for a sufficient time so that absorption can take place. Hence the BCS can work as a guiding tool for the development of various oral drug delivery technologies (Figure 2). 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[15,16].

Classification System of BCS

According to the Biopharmaceutics Classification System (BCS) drug substances are classified as follows[4,10,17-23] (Figure3):

Class I - High Permeability, High Solubility: Example: Metoprolol, Diltiazem, Verapamil, Propranolol. These compounds are well absorbed and their absorption rate is usually higher than excretion.

Class II - High Permeability, Low Solubility: Example: Glibenclamide, Phenytoin, Danazol, Ketoconazole, Mefenamic acid. The BA of these products is limited by their solvation rate. A correlation between the in-vivo bioavailability and the in vitro solvation can be found.

Class III - Low Permeability, High Solubility: Example: Cimetidine, Acyclovir, Neomycin B, Captopril. The absorption is limited by the permeation rate but the drug is solvated very fast. If the formulation does not change the permeability or gastro-intestinal duration time, then class I criteria can be applied.

Class IV - Low Permeability, Low Solubility: Example: Hydrochlorothiazide, Taxol. These compounds have a poor bioavailability. Usually they are not well absorbed over the intestinal mucosa and a high variability is expected.

This classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers[3,8,15], viz., Absorption number, defined as the ratio of the mean residence time to mean absorption time; Dissolution number, defined as the ratio of mean residence time to mean dissolution time; and Dose number, defined as the mass divided by the product of uptake volume (250 ml) and solubility of drug[16,24].

Extension to BCS

Bergstrom et al. (2003) devised a modified BCS, in which they categorized the drugs into six classes based on the solubility and permeability[3]. The solubility was classified as "high" or "low" and the permeability was allotted as "low", "intermediate," or "high"[3]. This new classification was developed based on the calculated surface area descriptors on the one hand and solubility and permeability on the other. The results showed that multivariate data analysis of easily comprehended molecular surface descriptors provides computational tools for prediction of both aqueous drug solubility and drug permeability. Surface areas related to the nonpolar part of the molecule resulted in good predictions of solubility, whereas surface areas describing the polar parts of the molecule resulted in good predictions of permeability[1]. The established correlations were used to perform a theoretical biopharmaceutical classification of WHO listed drugs into six classes, resulting in a correct prediction for 87% of the essential drugs. Of the 23 compounds, 20 (87%) were sorted correctly into their respective Classes I-VI. The three compounds that were wrongly classified were amitryptiline, acyclovir and doxycycline. To overcome this type of false predictions it was suggested that larger data sets covering larger parts of structural space would be needed in development models[15].

BCS Class Boundaries

The drugs are classified in BCS on the basis of solubility, permeability and dissolution parameters[18,21,22]. The class boundaries for these parameters include, solubility class boundaries which are based on the highest dose strength of an immediate release product. A drug is to be considered highly soluble when the highest dose strength is soluble in 250ml or less of aqueous media over the pH range of 1 to 7.5. The volume estimate of 250ml is derived from typical bioequivalence study protocols that prescribe administration of a drug product to fasting human volunteers with a glass of water. Permeability class boundaries which are based indirectly on the extent of absorption of a drug substance in humans and directly on the measurement of rates of mass transfer across human intestinal membrane. Non-human systems capable of prediction the drug absorption in humans can be used (such as in-vitro culture methods). A drug substance is to be considered highly permeable when the extent of absorption in humans is determined to be 90 % or more of the administered dose based on a mass-balance determination or in comparison to intravenous dose (Figure 4). Dissolution class boundaries which include an immediate release products is to be considered rapidly dissolving when not less than 85% of the labeled amount of the drug substance dissolve within 30 minutes using USP Dissolution Apparatus 1 at 100 RPM or Apparatus 2 at 50 RPM in a volume of 900ml or less in 0.1 N HCl or simulated gastric fluid or pH 4.5 buffer and pH 6.8 buffer or simulated intestinal fluid[22].

Determination of Solubility

The solubility of a substance is the amount of substance that has passed into solution when equilibrium is attained between the solution and undissolved substance at a given temperature and pressure[19]. 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 of 1-7.5. The volume estimate of 250 ml is derived form the typical volume of water consumed during the oral administration of dosage form which is about a glassful or 8 ounces of water. The pH solubility profile of the drug substance is to be determined at 37 ± 1°C in aqueous medium with pH in the range of 1-7.5[12,19-22]. A sufficient number of pH conditions should have been evaluated to accurately define the pH-solubility profile. The number of pH conditions for a solubility determination depends upon ionization characteristics of the test drug substance. A minimum of three replicate determinations of solubility in each pH condition should be carried out. Standard buffer solutions described in pharmacopoeias are considered appropriate for use in solubility studies. If these are not suitable for physical or chemical reasons other buffer solutions can also be used provided the pH of these solutions is verified[20,21]. Methods other than shake flask method are also used with justification to support the ability of such methods to predict equilibrium solubility of test drug substance, for example; acid or base titration methods. The concentration of drug substance in selected buffers or pH conditions should have been determined using a validated solubility-indicating assay that can be distinguished between the drug substances from its degradation products[16].

Determination of Permeability

These methods range from simple oil/water (o/w) partition coefficient to absolute bioavailability studies. The methods that are routinely used for determination of permeability are human studies including mass balance studies[25], absolute bioavailability studies[26], intestinal perfusion methods[27]; in vivo or in situ intestinal perfusion in a suitable animal model[28]; in vitro permeability methods using excised intestinal tissues[29] and monolayer of suitable epithelial cells e.g. Caco-2 cells or TC-7 cells[29]. In mass balance studies, unlabelled stable isotopes or radiolabelled drug substances are used to determine the extent of drug absorption. In absolute bioavailability studies, oral bioavailability is determined

and compared against the intra venous bioavailability as reference. Intestinal perfusion models and in vitro methods are to be recommended for passively transported drugs. The observed low permeability of some drug substances in human could be attributed to the efflux of drug by various membrane transporters like p-glycoprotein. This leads to misinterpretation of the permeability of drug substance[30,42]. An interesting alternative to intestinal tissue models is the use of well-established in vitro systems based on the human adenocarcinoma cell line Caco-2. These cells serve as a model of small intestinal tissue. The differentiated cells exhibit the microvilli typical of the small intestinal mucosa and the integral membrane proteins of the brush-border enzymes. In addition, they also form the fluid-filled domes typical of a permeable epithelium. Recent investigations of Caco-2 cell lines have indicated their ability to transport ions, sugars and peptides. The directed transport of bile acids and vitamin B12 across Caco-2 cell lines has also been observed. These properties have established the Caco-2 cell line as a reliable in vitro model of the small intestine[16,42].

Regulatory Applications of BCS

INDs/NDAs

A specific objective is to establish in vivo performance of the dosage form used in the clinical studies that provided primary evidence of efficacy and safety. The sponsor may wish to determine the relative BA of an IR solid oral dosage form by comparison with an oral solution, suspension, or intravenous injection[2,31,32]. The BA of the clinical trial dosage form should be optimized during the IND period (Figure 5).

BCS-based biowaivers are applicable to the to-be-marketed formulation when changes in components, composition, and/or method of manufacture occur to the clinical trial formulation, as long as the dosage forms have rapid and similar in vitro dissolution profiles. This approach is useful only BCS Class 1 drug and the formulations pre- and post change are pharmaceutical equivalents. BCS-based biowaivers are intended only for BE studies[33-36].

ANDAs

BCS-based biowaivers can be requested for rapidly dissolving IR test products containing highly soluble and highly permeable drug substances provided that the reference listed drug product is also rapidly dissolving and the test product exhibits similar dissolution profiles to the reference listed drug product. This approach is useful when the test and reference dosage forms are pharmaceutical equivalents. The choice of dissolution apparatus (USP Apparatus I or II) should be the same as that established for the reference listed drug product[33-40].

Post Approval Changes

BCS-based biowaivers can be requested for significant post approval changes (e.g., Level 3 changes in components and composition) to a rapidly dissolving IR product containing a highly soluble highly permeable drug substance provided that dissolution remains rapid for the post change product and both pre- and post change products exhibit similar dissolution profiles. This approach is useful only when the drug products pre- and post change are pharmaceutical equivalents[35,42].

The use of the BCS to obtain waivers of bioequivalence studies for immediate-release solid oral dosage forms has made it possible for generic pharmaceutical companies to obtain FDA approval of some generic products without having to conduct a bioequivalence study comparing the generic and brand products. The advent of the BCS has thus made it possible for generic companies to perform drug development on certain products in a more time and cost-effective manner. In addition, use of the BCS can eliminate the need to expose human subjects to the test and reference products[38-41].

CONCLUSION

The poor solubility and permeability account for many pharmacokinetic failures and a high percentage of drug molecules get rejected due to it. The cost of formulating a poorly absorbable molecule to the product stage becomes very high if poor pharmaceutical properties are not discovered in its development. Thus, fast and reliable in vitro prediction strategies are needed to expel out the problematic molecules at the initial stages of discovery. FDA's BCS is an effort to trim down the critical components related to oral absorption. BCS has been employed to waive in vivo bioequivalence testing for new and generic drugs. Moreover, the BCS eliminates unnecessary drug exposures to healthy subjects and provides economic relief and maintains high public health standard for therapeutic equivalence, based upon biowaivers. Hence, the drugs can be categorized based on number of doses and their intestinal permeability values. Additionally, the BCS classification permits the observation of defined characteristics for intestinal absorption of all four classes using suitable cutoff points for both dose number and effective intestinal permeability values. This system provides for selection of a suitable technology for new drug discovery and development.

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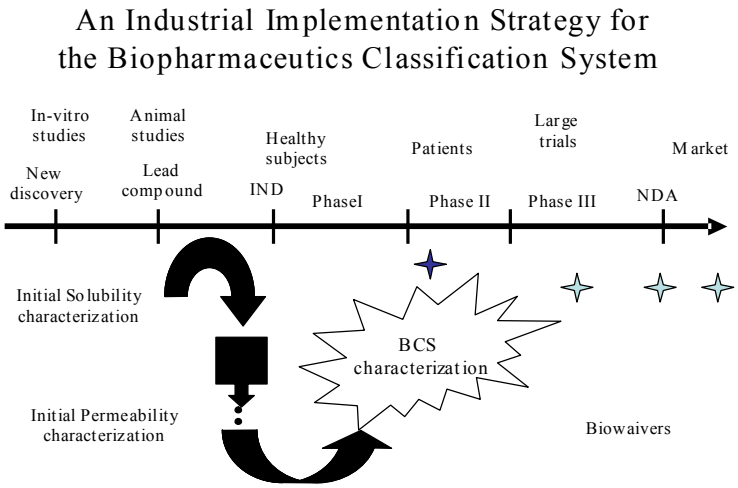

Figure 1. An Industrial Implementation Strategy for the Biopharmaceutics Classification System

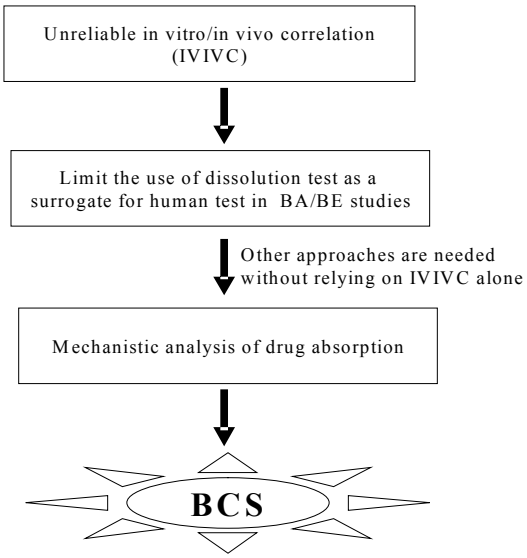

Figure 2. Concept of Biopharmaceutics Classification System

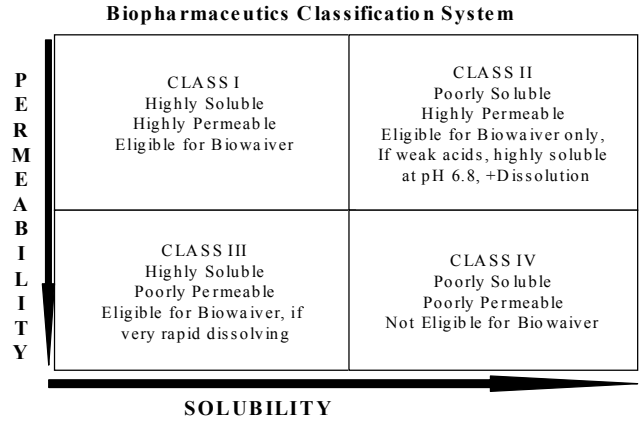

Figure 3. Classes under Biopharmaceutics Classification System

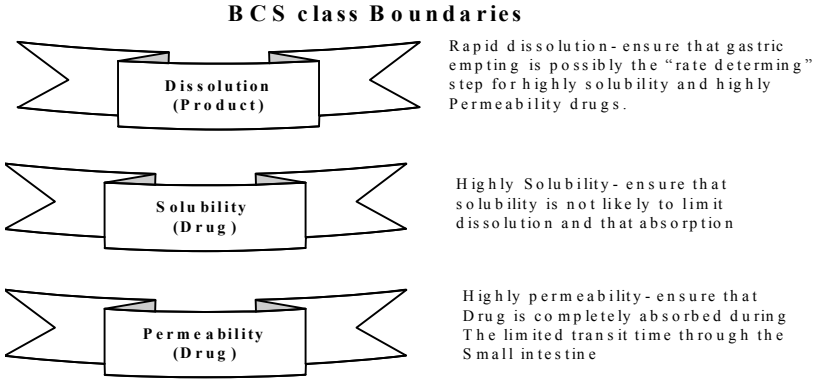

Figure 4. Biopharmaceutics Classification System Class Boundaries

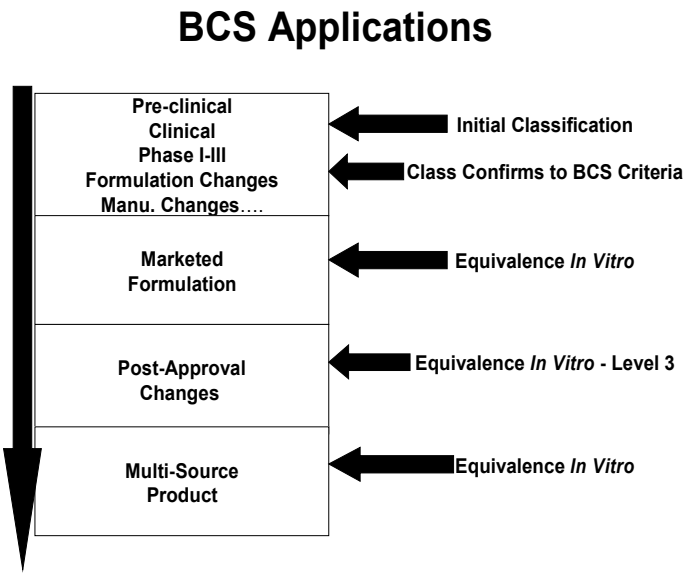

Figure 5. Regulatory Applications of Biopharmaceutics Classification System