



THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM (BCS): PRESENT STATUS AND FUTURE PROSPECTIVES

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Abstract

The Biopharmaceutical classification system (BCS) was introduced By Amidon *et al.*, (1995) as a method for classifying drug substances based on their dose/solubility ratio and intestinal permeability. It allows predicting the *in vivo* pharmacokinetic performance of drug products. The drug can be categorized into four classes of BCS, namely, High solubility high permeability, low solubility high permeability, High solubility low permeability and low solubility low permeability. An objective of BCS approach is to determine the equilibrium solubility of drug substances under physiological environment. The BCS helps in mathematically analyzing the kinetics and dynamics of drug in gastrointestinal tract (GIT) for New Drug Applications (NDA) and Abbreviated New Drug Applications (ANDA) filings and biowaivers. This step reduces time in the new drug development process. Further it helps to decide when the dissolution rate is likely to be the rate determining step. It also helps in the prediction of potential of inactive ingredients in the dosage form to alter the dissolution / absorption of the drug. The present review, apart from giving a brief overview of BCS classification system, highlights these and some of the more recent applications of BCS classification system.

KEYWORDS: in-vivo, new drug application, biowaivers

INTRODUCTION

BCS which was initially developed for primarily regulatory applications (INDAs and NDAs filing), has also got some other applications in both the pre clinical and clinical drug development processes¹. It is a valuable tool for formulation scientists and researchers, for the selection design and product development of any drug substance. It helps to improve the efficiency of drug development and review process by recommending a method for identifying expandable clinical bioequivalence test which could represent a class of immediate release solid oral dosage form for which *in vivo* parameters may be accessed based on *in vitro* dissolution tests. This can in turn save a lot of time and money. If an immediate release, orally administered drug product meets a specific criteria then FDA grants a waiver for expensive and time consuming studies^{3,4,5}. The principles of the BCS classification system can also be applied to scale-up and post approval changes in drug manufacturing.

Some Important Definitions:

1. **Absorption number (A_p):** The ratio of the mean residence time to mean absorption time.
2. **Dissolution number (D_p):** The ratio of mean residence time to mean dissolution time.
3. **Biowaiver:** A biowaiver is an exemption granted by the US FDA from conducting human bioequivalence studies when the active pharmaceutical ingredients meet certain solubility and permeability criteria *in vitro* and when the dissolution profile of the dosage form meets the requirements for the immediate release dosage forms¹³.
4. **High aqueous solubility:** The aqueous solubility of a drug substance is considered as high according to the US FDA BCS criteria when the ratio of the highest orally administered dose (in mg) to the solubility (mg/ml) is less than 250 ml. This criterion is met over the pH range 1-7.5 at 37°C. According to WHO guidelines when an active pharmaceutical ingredient shows a dose/solubility ratio of less than 250 ml at 37°C over a pH range of 1.2-6.8, it can be classified as “highly soluble”^{2, 34}.

5. Active Pharmaceutical Ingredient (API): Any substance or mixture of substances intended to be used in the manufacture of a pharmaceutical dosage form, and that, when so used, becomes an active ingredient of a pharmaceutical dosage form. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to affect the structure and function of the body¹⁵.

6. Generic Pharmaceutical Products: Pharmaceutical equivalent or pharmaceutically alternative product that may or may not be therapeutically equivalent. Multisource pharmaceutical products that are therapeutically equivalent are interchangeable²⁵.

7. Rapidly Dissolving Product: The product from which at least 85 % of the labeled amount of active ingredient is released within 30 minutes or less, from the test or the comparator product³⁴.

8. High Permeability: A drug is considered a highly permeable, when more than 90% of the orally administered dose is absorbed in the small intestine. According to WHO guidelines when an API is absorbed to an extent of 85% or more, it is considered to be “highly permeable”. The permeability criterion was relaxed from 90% in the FDA guidance’s to 85% in the WHO multisource document³⁵.

The Biopharmaceutical classification system (BCS) - a Brief Overview: The oral route of drug administration is the most preferable method for administering drugs for systemic effects. Whenever a new drug moiety is discovered, one of the first questions, a pharmaceutical company asks is whether or not the drug can be effectively administered by the oral route, for its intended effect. The development of dosage forms especially for the prolonged release purpose has been a challenge to formulators, because of many independent factors governing the absorption of the drug from the gastrointestinal tract, like dissolution rate, intrinsic solubility etc.⁶ and competitive objectives, that is, any action taken to improve one objective or set of objectives may cause another

objective or set of objectives to degrade⁷. For example, modifying the solubility of the drug substance to prolong its release in the gastrointestinal tract may cause a reduction in the overall bioavailability of formulation. A trial and error method of formulation does not allow the formulator to know how close a particular formulation is to the optimum solution. Hence a fast screen is needed, to enable them to formulate intelligently which would save time and money. For this purpose the drug substances are categorized into four classes based on their solubility parameter and permeability to bio-membranes. Such a classification system is called as a Biopharmaceutical Classification System (BCS)⁷ BCS takes into account the three *in-vitro* parameters namely, solubility, permeability and dissolution according to which the drugs can be categorized into the following four classes¹⁰⁻¹⁴

Class I : High Solubility - High Permeability, e.g., metoprolol, diltiazem, verapamil, propranolol

Class II : Low Solubility - High Permeability, e.g., gilbenclamide, phenytoin, mefenamic acid, ramipril, simvastatin

Class III : High Solubility - Low Permeability, e.g., acyclovir, neomycin, atenolol

Class IV : Low Solubility - Low Permeability, e.g., hydrochlorothiazide, furosemide

BCS is based on a scientific approach describing the three rate limiting steps in oral absorption, which are (1) drug liberation from dosage forms, (2) maintenance of its dissolved state throughout gastrointestinal (GI) tract, and (3) permeation of drug molecules through GI membrane in the blood. There is a fourth step, i.e., enterohepatic metabolism that influences the systemic availability as well as release of metabolites into the systemic circulation which influences the bioavailability. The Biopharmaceutical Drug Disposition Classification System (BDDCS) proposed by Wu and Benet⁹ takes into account the absorption process by including the fourth rate-limiting step of first pass effect.

Applications of Biopharmaceutical Classification System Regulatory Applications

Request for Biowaivers: The US Food and Drug Administration (US FDA) implemented in 2000 a guidance for industry on *in-vivo* bioequivalence and bioavailability study waivers (biowaivers) based on the Biopharmaceutical classification system (BCS). Now both US FDA and the European agency EMEA have issued guidelines under which pharmaceutical companies can request for a waiver from *in vitro* bioequivalence studies¹⁹. Considering the uncertainties associated with *in vitro* dissolution tests, the draft guidance recommends biowaivers only for rapidly dissolving products of highly soluble and highly permeable drugs (BCS class I drugs), that are not considered, by the FDA, to be "Narrow Therapeutic Index Drugs".

The following criteria are recommended for justifying the request for a waiver of *in vivo* bio-studies:

1. The drug substance should be highly soluble and highly permeable, defined as a Class I drug above.
2. An Immediate release drug product should be rapidly dissolving¹⁶.
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.

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.

BCS class I products possess high solubility and high permeability. For the immediate release products of these compounds intended for oral absorption permeation through the intestines generally exceeds the gastric emptying time. Therefore one can expect 100 % absorption if at least 85 % of the labeled amount is released within 30 minutes of the *in vitro* dissolution testing. For class III drugs permeability limits drug absorption while dissolution of drug occurs rapidly in GIT. Therefore waiver criteria may be appropriate for these products unless test and reference products do not contain products that would alter the drug permeability. The 2010 European Medicines Agency Bioequivalence Guideline²⁷ further extends its discussion of biowaivers to class III (low-permeability, high solubility drugs) as well. Therefore currently all class I and some class III compounds are eligible for biowaivers. Both Class II and class IV compounds are not suitable to meet the biowaivers criteria because they possess low solubility profile. Further acidic BCS II drugs have been suggested as possible candidates for biowaivers in scientific publications^{20, 21}.

The request for biowaivers in accordance to 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. This has resulted in the following outcomes:

1. **INDs and NDAs:** BCS based biowaivers are applicable to the formulations intended to be marketed where changes in composition, components of the formulation, or method of preparation occurs to the clinical trial formulation, as long as the formulation has a rapid and similar *in vitro* dissolution profile. This approach is useful if the drug is highly soluble and highly permeable (BCS class I drugs) and both the pre and post change formulations are pharmaceutically equivalent²²⁻²⁶.
2. **ANDA:** For a highly soluble highly permeable drug substance formulated whose dissolution is rapid as defined in section III, US FDA guidelines, an *in- vivo* bioequivalence study can be waived, provided that the reference listed drug product is also highly soluble and both the test product and the reference product have similar dissolution profile, i.e., this approach is suitable only when the test and the reference products are pharmaceutically equivalent. Where feasible the choice of dissolution apparatus (USP I or II) is should be limited to that established for the reference product.
3. **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 immediate release product intended for oral use. Further the drug substance should be highly soluble and highly permeable provided that the dissolution remains rapid for pre and post change product and both pre and post change products exhibit similar dissolution profile.

4. Approval of Generics: Because generics were required to meet essential safety, efficacy, and BE criteria, few were approved under these regulations till 1984. In 1984, the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Act)²⁹ was passed, and established the abbreviated new drug application procedure (ANDA), permitted the FDA to approve generic products for drugs that had already been found safe and effective, and formalized the criteria for pharmaceutical equivalence and Bioequivalence. Further in 1995 the introduction of biopharmaceutical classification system (BCS) by Amidon *et al.* made the approval of generics further easier. Provisions for post approval changes for BCS Class I rapid release oral dosage form has made it possible for generic pharmaceutical companies to obtain approval without necessarily conducting their bioequivalent studies.

5. Cost Savings: After the introduction of the biopharmaceutical classification system in 1995 a considerable increase in NDA and ANDA filing of drugs has been noticed. The total number of NDAs filed in 2010 was 86. According to the FDA, about 80% of all filed applications will eventually be approved¹⁷. Recently, DiMasi noted an approval rate of approximately 90% for NDAs (18). It was estimated that about 25% of the total products approved were classified as highly soluble and highly permeable which could request for a biowaiver for the bioequivalence studies. Using the 25% estimated above, there is the potential to save one quarter the annual expenditures on bioequivalence studies estimated as \$22 to \$38 million dollars/year. Additional indirect savings can occur if bioequivalence studies are rate limiting to drug development. For example, let us suppose the results of a bioequivalence study are needed before proceeding with development of a compound with eventual peak sales of one billion dollars/year. It can be easily assumed that results of *in vitro* dissolution can be obtained 6 weeks earlier than results from an *in vivo* bioequivalence trial which translates into a potential additional \$110 million dollars in sales from a 6 week earlier approval. Further, by not having to run a human bioequivalence trial, clinical resources are freed to be applied elsewhere which is an asset to the industry³⁰.

Drug Development: The classification of drugs into four classes according to the biopharmaceutical classification system (BCS) can help the formulators to know many *in vivo* parameters which can be of great help in formulation of dosage form.

Class I drugs exhibit a high absorption number and a high dissolution number. If dissolution is very rapid, then gastric emptying rate becomes the rate determining step, *e.g.*, Metoprolol, Diltiazem, Verapamil, Propranolol. The metabolism of these drugs is not rate limited either by dissolution or permeability. Intake of meals along with these drugs also does not have any significant effects in their dissolution and permeability *e.g.* Metoprolol, Diltiazem, Verapamil, Propranolol. *In vitro* – *In vitro* correlation (IVIVC) is usually expected for class I drugs. These drugs are the least problematic when one intends to prepare their

dosage form. The major challenge in development of drug delivery system for class I drugs is to achieve a target release profile associated with a particular pharmacokinetic and/or pharmacodynamic profile. Formulation approaches include both control of release rate and certain physicochemical properties of drugs like pH-solubility profile of drug.

Class II 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 I and occurs over a longer period of time. For class II drugs also *In vitro*- *In vivo* correlation (IVIVC) is usually expected for class I drugs. High fat diet generally increases their absorption into the blood stream due to inhibition of efflux transporters in the intestine and a solubilizing effect of drug into intestinal lumen. With these drugs efforts to increase the dissolution rate would enhance their bioavailability. Therefore these drug candidates are preferred for dissolution enhancement in industries. The systems that are developed for class II drugs are based on micronisation, lyophilization, addition of surfactants, formulation as emulsions and microemulsions systems, use of complexing agents like cyclodextrins, *etc.*, *e.g.*, Phenytoin, Danazol, Ketoconazole, Mefenamic acid, Nifedipine.

For Class III 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. High fat meals would decrease the absorption of these drugs due to inhibition of uptake transporters. Peptides and proteins constitute the part of class III and the technologies handling the local and systemic delivery of proteins and peptides are on rise now a day, *e.g.*, Cimetidine, Acyclovir, Neomycin B, Captopril.

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. The route of choice for administering such drugs is parenteral with the formulation containing solubility enhancers, *e.g.* Taxol.

It has been found out that highly permeable class I and class II compounds have easy and a greater access to the metabolizing enzymes within hepatocytes. Smith³¹ has noted that more permeable lipophilic compounds are good substrates for cytochrome P450 enzymes. Therefore according to BCS classification it becomes obvious that class I and class II compounds are eliminated via metabolism while class III and class IV compounds are eliminated unchanged into urine and bile. Upon reviewing the elimination characteristics of some of the drugs it was observed that most of the drugs follow this correlation except a few like Mebendazole which is predominantly eliminated in the unchanged form in the urine and bile. Lindenberg *et al*³¹ listed Mebendazole as either class II or class IV so it is suspected that the drug is misclassified, *e.g.*, Valporic acid, Ibuprofen^{32, 33}.

One also might suspect that the high permeability compounds (class I and class II) might have higher volumes of distribution than the low permeability drugs (class III and class IV). Such a trend is observed in many cases but for those class I and class II drugs which have high plasma protein binding V_d is quite low. This proves that the extent of plasma protein binding of drugs influences their V_d to a

greater extent than their rate of absorption through the GI tract.

With this knowledge BCS classification system can be used in categorizing routes of elimination, predicting the effects of efflux and absorptive transporters on drug absorption, predicting the effect of food in drug absorption and determination of some post absorption *in-vivo* parameters. Finally great use of the BCS is emphasized as a simple tool in early drug development to determine the rate-limiting step in the oral absorption process, which has facilitated the information involved in the overall drug development process

CONCLUSION

The Biopharmaceutical Classification System (BCS) is not only a useful tool for obtaining waivers for *in-vivo* bioequivalence studies but also for decision making in the discovery and early development of new drugs and formulations thereof. The data obtained through measurement of solubility and permeability in the discovery/development can be utilized for the preliminary BCS classification of pipeline compounds. As our knowledge of GI compounds becomes more sophisticated, we will be able to design the *in-vitro* tests that would better simulate the *in vivo* conditions in the GI tract. This in turn would result in more powerful predictions of *in vivo* parameters of drugs and ultimately to a significant reduction in human and animal studies required to optimize the formulations.

Although BCS has brought a revolution in drug approval and developmental process, there is always a scope for amendments in its principles. Efforts should be constantly done to utilize the concepts of BCS beyond the immediate release solid oral dosage form.

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