REVIEW ARTICLE

The Use of Biopharmaceutic Classification of Drugs in Drug Discovery and Development: Current Status and Future Extension of Biopharmaceutics Classification System II Focus

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ABSTRACT

Oral dosing is considered to be the most desired route for drug delivery. In general, the success of oral drug delivery is heavily dependent on a compound's ADME and physicochemical properties. Among the physicochemical properties, solubility and permeability are thought to be the most important factors. Biopharmaceutics Classification System (BCS) was proposed in the 1990s for classifying drugs based on their solubility and permeability. BCS was developed with the intention of facilitating biowaiver applications for BA/BE studies for compounds in development. In general, compounds with poor aqueous solubility or permeability are assumed to be at high risk of having low oral bioavailability. Due to its simplicity, this classification system was quickly adopted by the pharmaceutical industry to different drugs in development on the basis of their solubility and permeability. In the meantime, because of its popularity, the usage of the BCS has also been quickly expanded to the compounds that are in the pre-clinical stage of development. This expanded the usage of the system has led to the labeling of compounds in discovery stage as "BCS class X like." In particular, one of the most common pre-labels used is "BCS Class II-like compounds," and issues associated with such labels are discussed. This kind of labeling has been used by drug researchers to evaluate the risk associated with the development of a compound. In this commentary, we show that pre-labeling compound with BCS classification without sufficient information can lead to unnecessary confusion, added workload, and/or artificial concerns about the developability of drug candidates. To illustrate this point, an analysis of marketed BCS Class II drugs for fraction absorbed in human was coupled with theoretical considerations to show that most BCS-Class II like compounds can be easily developed with conventional formulation technologies.

Key words: BCS Classification, Drug discovery, Permeability, Solubility

INTRODUCTION

The Biopharmaceutics Classification System (BCS) was first introduced to the pharmaceutical industry in the mid-90s.[1] The BCS is based on simple, yet key parameters, such as drug dissolution/solubility and intestinal permeability, that control the fraction absorbed (Fa) of drugs.[1] Due to its simplicity and broad applicability, BCS has quickly gained popularity within both industry and regulatory environments. The US Food and Drug Administration (FDA) has published guidance for the pharmaceutical industry on the implementation of BCS.[2] According to the guidance published by the FDA, drug substances are classified into four categories: Class I - High permeability, high solubility, Class II - High permeability, low solubility, Class III - Low permeability, high solubility, and Class IV - Low permeability, low solubility. To define the usage of BCS, FDA has stated that the purpose of the guidance document is: (1) To recommends methods for classifying drugs based on dissolution/solubility and permeability and (2) to explain when a waiver for *in vivo* bioavailability and bioequivalence studies may be requested based on the approach of BCS.[2] This guidance has been widely used by the industry especially for the purpose of biowaiver for high soluble BCS Class I and III drugs.

Due to its popularity, the BCS classification has also quickly expanded to the preclinical stage and has been used to "describe" the drug candidates in development. The phrase such as "this drug candidate is BCS Class X-like compound" is nowadays commonly used in the pre-clinical stage by drug researchers to describe drug candidates and has been used as a tool to evaluate the development risks of drug candidate.[3-5] While this approach seems to be a very attractive way to understand developability of the drug candidate, it could nevertheless lead to wrong conclusions based on insufficient knowledge of the molecule. For example, usage of BCS was even found to be implemented at very early stages in the discovery where there is little to no information about the compounds that are required for such a classification (i.e., human dose range, PK, and PK/PD). The use of BCS at these early stages of discovery, unless done carefully, may lead to unnecessary confusion, added workload, and/or artificial concerns about the developability

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ISSN 2046 5114

of drug candidates or chemical series. For example, early classification as BCS Class II-like compound can be very misleading without the predicted human dose. Based on these considerations, it is clear that extreme caution should be exercised when applying BCS classification in these situations. Due to the prevalence of hydrophobic drugs in the pipeline of most pharmaceutical companies, there is widespread misuse of the terminology "BCS Class II-like" compounds during discovery stages. Hence, we would like to address this issue in detail in this article.

DEFINITIONS OF SOLUBILITY AND PERMEABILITY AS PER FDA GUIDANCE[2]

To aid further discussion, the exact definitions of solubility and permeability of the compound as per FDA guidance document is reproduced here:[2]

1. "Solubility: A drug substance is considered highly soluble when the highest strength is soluble in 250 mL or less of aqueous media within the pH range of 1–6.8 at 37 ± 1°C."
2. Permeability: "The permeability class of a drug substance is based indirectly on the extent of absorption (fraction of dose absorbed and not systemic BA) of a drug substance in humans and directly on measurements of the rate of mass transfer across the human intestinal membrane. Alternatively, other systems that are capable of predicting the extent of drug absorption in humans can be used (e.g., *in situ* animal and *in vitro* epithelial cell culture methods). A drug substance is considered to be highly permeable when the systemic BA or the extent of absorption in humans is determined to be 85% or more of an administered dose based on a mass balance determination (along with evidence showing stability of the drug in the GI tract) or in comparison to an intravenous reference dose."

Based on the above definitions, it is clear that the purpose of BCS is to mainly to support biowaiver applications. In this system, drug permeability and solubility are simply defined in a two-band classification as either "high" or "low" with no gray areas in between. As mentioned in the previous sections, this approach is unlikely to be suitable for the compounds in the discovery phase where sufficient data are often lacking.

COMMENTARY ON PERMEABILITY AND SOLUBILITY OF COMPOUNDS LABELED "BCS CLASS II-LIKE"

If a BCS-type approach is to be used to classify compounds in the discovery stage, then the determination and subsequent impact of permeability and solubility of the compound on developability needs to be further understood.

Permeability Classification

Direct measurement of human intestinal permeability is seldom implemented for drugs candidate due to the complexity of the procedure. Fortunately, *in vitro* systems such as Caco2 and MDCK have been discovered to be a good surrogate model to estimate the human intestinal permeability.[5-11] Therefore, in theory, permeability classification of compounds based on *in vitro* measurements can be done in a straightforward manner. However, it is important to note that a number of compounds fall into the gray zone of having moderate *in vitro* permeability, which makes practicing "permeability classification" less straightforward. Oftentimes, these compounds are labeled as "between classes" (i.e., straddling different BCS classes assuming that solubility is known). Despite this issue, it is less ambiguous to define a compound as having "high permeability" (permeability classification for BCS I and II compounds) as the cutoff for this category is robustly defined.[12-16]

Solubility Classification

Classifying compounds as "high or low solubility," however, are not easy. Based on the BCS, a high solubility compound is one where the full dose needs to be solubilized in 250 mL of aqueous medium in the pH range of 1–6.8. The volume limit of 250 mL of water is based on what patients take with the drug in the clinic. However, this volume does not account for additional factors such as (a) the existing fluid present in the GI tract during dose administration, (b) the amount of fluid that will be secreted during the absorption window (usually 3–5 h), and (c) increased compound solubility in the GI fluid due to the presence of bile (typical for more lipophilic drugs). Therefore, the definition of having the highest dose to be fully dissolved in the 250 mL of water is an "exceptionally tight requirement." Again the intention of this definition is purely based on applications for biowaivers, where the goal is to match the target drug product (i.e., tablet or capsule) to that of an equivalent "aqueous solution formulation." This then ensures that no PK changes will occur due to compound solubility/dissolution thereby obviating the need for a human BA or BE study. Thus, this definition of high solubility as per BCS should not be confused with the drug absorption potential under the normal GI transit conditions.

To further exemplify this point, a Fa analysis of a large number (n > 80) of marketed BCS Class II drugs was performed.[12-17] Based on the Fa analysis, the compounds were categorized into three different buckets (Fa >80%, between 60 and 80%, and 40 and 80%) and the result is shown in Figure 1. Based on the analysis, it is clear that

the majority of the BCS II show good Fa in human and only a very small percentage of drugs have Fa in human <50%. This result is not a surprise since absorption of drugs in this class can be considered to be happening under the sink or near sink conditions. Hence, for low dose compounds (i.e., <50 mg), ensuring good dissolution of the drugs through particle size reduction will be sufficient to allow for good Fa to be achieved. This can be further rationalized through the use of Noyes-Whitney Equation which describes the dissolution rate of the drug.

$$\frac{dM}{dt} = \frac{DA(C_s - C_t)}{h}$$

Where dM/dt is the dissolution rate, D is the diffusion coefficient, A is the surface area of the drug, h is the diffusion layer thickness, C_s is the aqueous solubility, and C_t is the *in situ* drug concentration. When the dose is reasonably low, the absorption of a BSC II drug can be considered to be under the sink or near sink condition (drug dissolved = drug absorbed). Under these conditions, C_t can be assumed to be zero. Now as an example, consider a typical "BCS Class II-like" drug with a molecular weight of 500 Daltons, a low solubility (C_s) of 1 µg/mL, and a small particle radius (*r*) of 2 µm. For a single particle, the diffusion layer thickness (h) can be assumed to be equal to the particle radius (*r*). From the Noyes-Whitney equation, it is estimated that it will take about 40 min to dissolve one particle. For this calculation, the diffusion coefficient (D) and surface area (A) are estimated using.

$$D = 9.9\times10^{-5}\times MW - 0.453$$

$$A = 4\pi r^2$$

Compared with the normal GI transit time in humans, 40 min of dissolution time may not be a problem. This is supported by the evidence that majority of the marketed BCS II drugs can be formulated using conventional techniques with a certain level of particle size control without the need of resorting to enabling formulations (i.e., solid dispersion, liquid filled capsules, and so forth). Therefore, drug researchers should not be overly skeptical of developing compounds that are pre-labeled as BCS II-like.

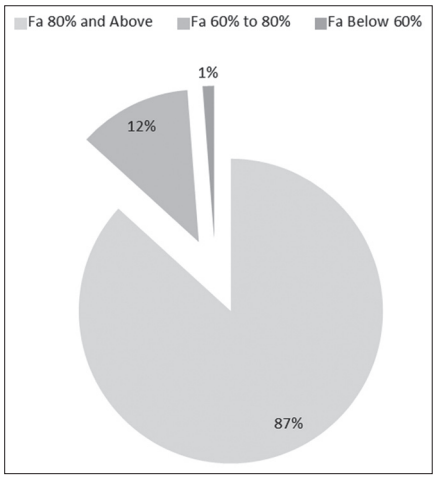

Figure 1: Fa analysis of Biopharmaceutics Classification System II drugs (*n* > 80)

CONCLUSION

The BCS classification system and its intended usage as defined by regulatory agencies have been briefly described. Furthermore, the suitability of applying this classification system to compounds in the pre-clinical phase was discussed. Despite the fact that BCS is not intended to be used during early development, inevitably drug researchers still adopt it to pre-label discovery compounds to assign the risk of developability. In this article, we focused on the common issue of pre-labeling discovery compounds as "BCS II-like compounds" and corresponding ramifications of such a classification on further development of the compounds.

It was shown that the absorption potential for "BCS II-like compounds" under the normal GI transit condition is considered reasonable and this is further supported by the fact that a number of marketed BCS II drugs show good human Fa data. Based on the analysis of commercial drugs and theoretical treatment based on the Noyes-Whitney equation it was shown that even for drugs that are considered to be poorly soluble (i.e., BCS II-like) at low doses, it is entirely possible to obtain good Fa in human with convention formulation technologies using just particle size reduction.

The appropriate usage of the BCS classification in the drug discovery phase requires both in-depth knowledge of the molecule's solubility and permeability and full understanding of the boundaries. Drug researchers should be cautious about using this system during the early phases of drug development as it could artificially inflate the risk associated with the development of "BCS Class II-like" molecules. Therefore, drug researchers should not be overly skeptical of developing compounds that are BCS II-like.

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