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COMMENTARY

The BCS, BDDCS, and Regulatory Guidances

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INTRODUCTION

The BCS (Biopharmaceutics Classification System), based on aqueous solubility and intestinal permeability, has been widely used since 1995 to predict drug absorption during the course of pharmaceutical development (1). However, as will be discussed subsequently in more detail, when the BCS concepts were initiated, now more than 15 years ago, the term "intestinal permeability" was used interchangeably with both measures of rate and extent of absorption, believing from the data available at that time that permeability/absorption rate and extent are correlated. The BCS has also been utilized by regulatory authorities to determine whether *in vivo* bioequivalence studies may be waived for drug products in immediate release solid oral dosage forms (2,3). For example, the U.S. FDA currently grants waiver of *in vivo* bioequivalence studies for BCS Class 1 (highly soluble and highly permeable) drugs that are formulated in rapidly dissolving, immediate release products (2). In 2005, the BDDCS (Biopharmaceutical Drug Disposition Classification System), based on solubility and metabolism, was developed to predict drug disposition and potential drug-drug interactions in the intestine and/or liver (4). In view of the apparent correlation between drug metabolism and intestinal permeability rate, it was further suggested that extensive drug metabolism may provide an alternate (or additional) tool for characterizing high intestinal permeability under BCS (4,5). However, discrepancies between the two systems have been noted over the years. For instance, assignment of a drug class using BDDCS was not in accordance with that using BCS, and *vice versa* (4–6). In addition, it was found that some highly permeable drugs (as measured by the extent of absorption)

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under BCS may not exhibit extensive metabolism (7). Yet, the *in vitro* Caco-2 cell permeability recognized in the FDA's BCS Guidance may not always correctly predict the extent of drug absorption in humans (8). To address the underlying issues, this article aims to revisit the concept of both BCS and BDDCS and examine their applications in the waiver of *in vivo* bioequivalence testing for regulatory approval of drug applications.

THE BCS AND FDA GUIDANCE

The seminal development of BCS stems from the recognition that aqueous solubility and intestinal permeability are the two key factors governing drug absorption (1). As such, the BCS classifies all drugs into four classes: Class 1 (high solubility, high permeability), Class 2 (low solubility, high permeability), Class 3 (high solubility, low permeability), and Class 4 (low solubility, low permeability). Theoretically, as it is rationalized in the FDA Guidance, observed *in vivo* differences in the rate and extent of absorption from two pharmaceutically equivalent immediate release solid oral products may be due to differences in drug dissolution *in vivo*, particularly for Class 1 drugs (2). However, when the in vivo dissolution of such products is rapid in relation to gastric emptying and the drug has high permeability, the rate and extent of drug absorption are unlikely to be dependent on drug dissolution *in vivo* or gastrointestinal (GI) transit time (2). Accordingly, it is believed that demonstration of *in vivo* bioequivalence may not be necessary for a BCS Class 1 drug in immediate release solid oral dosage forms so long as the inactive ingredients in the dosage form do not significantly affect absorption of the active ingredient (2). To implement this approach for biowaivers, however, there is a need to set the boundaries for high solubility and high permeability. The FDA Guidance defines a drug substance as "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 at 37°C (2). However, there has been confusion regarding the terms *permeability* and *high permeability* when they apply to biowaivers in the regulation, as discussed below.

BCS-BASED PERMEABILITY

Retrospectively, the theoretical analysis of BCS for estimating the extent of absorption has been developed on the basis of a mass balance approach that incorporates effective permeability, free drug concentration and available surface area in the intestine (1). The term *permeability* originated from Fick's first law that relates the diffusive flux to the concentration gradient. The flux goes from regions of high concentration to regions of low concentration, and permeability represents an experimentally determined transport coefficient of the compound under study (9). In this context, intestinal permeability is a constitutive property that may depend on the method used and location of the intestine where it is measured. Since absorption may occur in some regions/segments of the intestine or throughout the GI tract, permeability can be expressed as "local permeability" or "average permeability" along the GI tract. As indicated in the FDA Guidance, the permeability class boundary can be determined directly by measuring the rate of mass transfer across human intestinal membrane (2). It can also be determined indirectly based on the extent of absorption (specifically, fraction of dose absorbed) of a drug substance in humans (2). This recommendation came from the results of *in vivo* studies on 34 drugs and endogenous substances, wherein a good correlation was established between jejunal permeability obtained from human intestinal perfusion studies and the fraction of oral dose absorbed using pharmacokinetic studies in humans (10). Although jejunal permeability may not represent the 'average' permeability along the GI tract, it is determined in the region with the largest surface area and the highest expression of transporter proteins in the intestine, thus is useful to approximate the fraction of the oral dose absorbed. The FDA Guidance denotes that a drug substance is considered to be highly permeable when the extent of absorption in humans is 90% or more of an administered dose, which appears to reflect more on the notion of average permeability than local permeability in the intestine (2). It should be noted that the use of *local permeability* may misclassify the permeability class of some drugs, as demonstrated by a recent investigation utilizing rat intestine where sotalol permeability is low at pH 6.5 and 7.0 in comparison with metoprolol (a reference standard), but exceeds the threshold at pH 7.4 (11).

Apart from human intestinal perfusion and pharmacokinetic studies, the FDA BCS Guidance also indicates other methods for determining drug permeability in the GI tract, including *in vitro* permeation studies across a monolayer of cultured epithelial cells (*e.g.*, Caco-2 cells) (2). Although Caco-2 monolayers can be used to predict drug transport by different pathways across the intestinal epithelium, the best correlation with the fraction absorbed *in vivo* is obtained for passively transported drugs (12). In addition, Caco-2 cells are known to have varying expressions of enzymes and transporters. Hence, the FDA Guidance further recommends limiting the use of nonhuman permeability test methods for drug substances that are absorbed by passive mechanisms (2). In this context, if a drug is found highly permeable using Caco-2 cells, it is absorbed extensively and thus can be classified as highly permeable under BCS. On the other hand, however, low permeability as determined by Caco-2 cells does not necessarily dictate

low permeability under BCS. This was demonstrated by another study on sotalol where the drug was found to exhibit low permeability using Caco-2 cells, yet clinical studies showed that it has linear pharmacokinetics and an absolute bioavailability of 98% (8). Two possible reasons for this disparity between Caco-2 cells and clinical studies are (a) the lower surface area in the cell model and/or (b) fewer openings (pores) in the tight junction of the Caco-2 monolayers compared with those in the human intestine (8). Accordingly, when the results of *in vitro* studies are in conflict with those obtained from pharmacokinetic studies in humans, the permeability class determination based on a pharmacokinetic approach is preferred for justifying biowaivers in drug applications.

THE BDDCS AND DRUG METABOLISM

The concept of BDDCS was initially derived from the observations that the great majority of BCS Class 1 and 2 compounds (high permeability) are primarily eliminated by metabolism, whereas the great majority of BCS Class 3 and 4 compounds (low permeability) are primarily eliminated unchanged into the urine and/or bile (4). In conjunction with the findings of transporter-enzyme interplay from several cellular and animal studies, the BDDCS classifies drug substances into four classes based on aqueous solubility and extent of metabolism: Class 1 (high solubility, extensive metabolism), Class 2 (low solubility, extensive metabolism), Class 3 (high solubility, poor metabolism), and Class 4 (low solubility, poor metabolism).

The primary purpose of BDDCS was to predict drug disposition of new molecular entities and the importance of transporters in drug absorption and elimination. However, since there appeared to be a very good correlation between high metabolism and high permeability (hence extensive absorption), it has been recommended that the extent of drug metabolism (*i.e.*, ≥ 90% metabolized) be added as an alternative method for the extent of drug absorption (*i.e.*, ≥ 90% absorbed) in defining BCS Class 1 drugs for biowaivers (5). This may be rationalized by the lipophilic nature of a number of drugs, which is not only important in facilitating the permeation of these compounds into the intestinal membrane, but also critical in allowing their access to the metabolizing enzymes. Indeed, many drugs with a fair degree of lipophilicity have been found to be highly permeable and also extensively metabolized in the intestine and/or liver (4–7). It is noteworthy that the matrix of drug metabolism in BDDCS is limited to the metabolic processes involving CYP450 and Phase 2 enzymes (such as glucuronidation and sulfation) that occur after drug absorption. There may be other enzymes that are not localized in the liver or intestinal mucosa, *e.g.*, hydrolytic enzymes, such as esterases, and gut bacteria that are responsible for reduction of some compounds.

INTESTINAL PERMEABILITY IN BCS *VS.* DRUG METABOLISM IN BDDCS

A question that has been raised is whether the classification of intestinal permeability under BCS refers to the rate or extent of transport across the intestinal mucosa. The theoretical basis of BCS may indicate that permeability is a measure of rate as denoted in Fick's first law, but it is also a measure of extent as implied by the mass balance equation (1,9). In the earlier studies, the BCS-based permeability values were determined using human jejunal permeability by the single-pass perfusion technique at steady-state, and the measured permeability was found to be correlated with the fraction of oral dose absorbed for 34 compounds with different structural diversity (9,10). Hence, BCS-based permeability has been used by the FDA as a surrogate for extent of absorption, and a drug substance is considered to be highly permeable when the extent of absorption is ≥90% (2). However, based on the perfusion or possibly permeation approaches, it is likely that the permeability classification under BCS reflects both rate and extent of drug absorption.

A major difference between the predictions of BCS and BDDCS lies in the concept of whether permeability is viewed as the rate or extent of drug transport across the cell membranes. While BCS biowaivers are primarily based on the extent of absorption in the GI tract, BDDCS predictions are focused on metabolism, which relates to the rate of permeation in the intestine and/or liver. Therefore, a high degree of metabolism (≥90% of the dose) will dictate high extent of absorption (≥90%), but not *vice versa*. The high permeability classification in BCS reflects high extent of absorption (≥90%) as defined by the FDA Guidance. However, when the drug is extensively absorbed and classified as highly permeable under BCS, it may not have high metabolism. This is in agreement with the finding that drug metabolism in BDDCS is better correlated with permeability in BCS for lipophilic drugs that are absorbed by transcellular transport, as opposed to hydrophilic drugs that are absorbed through carrier-mediated or paracellular transport (7).

With the emphasis on the rate of permeation across intestinal mucosa, BDDCS further predicts that high permeation for Class 1 compounds will produce high concentrations in the gut, leading to the saturation of any transporters, and thus transporter effect will be minimal. In contrast, for BDDCS Class 2 compounds, intestinal uptake (or absorptive) transporters will be unimportant due to the rapid permeation of the molecules. In view of the high

permeation rate, Class 2 compounds will have high lipophilicity and are primarily absorbed through passive mechanism. Meanwhile, however, because of their low aqueous solubility, there is little opportunity for Class 2 compounds to saturate transporters. Hence, efflux transporters may be operative for drug absorption, and transporter-enzyme interplay will be important in the intestine. BDDCS Class 3 compounds may need an uptake/absorptive transporter to facilitate absorption due to the low permeation rate in the intestine. On the other hand, for Class 4 compounds, oral bioavailability is low and highly variable, and thus transporter effects will be relevant. Based on the similar concepts, BDDCS has been used to predict food-drug effects, drug-drug interactions, and transporter effects on post-absorption systemic levels and after intravenous dosing (4). Computational models have been proposed to assign BDDCS class from molecular structure (13). In addition, the use of BDDCS in the area of systems chemical biology has been outlined previously (14,15).

REGULATORY APPLICATIONS OF BCS AND BDDCS

In the U.S., the waiver of *in vivo* bioequivalence studies is granted for BCS Class 1 (high solubility and high permeability) drugs that are formulated in rapidly dissolving, immediate release solid oral dosage forms (2). This has been based on the three-tier rationale where (i) high solubility ensures that drug solubility does not limit dissolution, and hence absorption, (ii) high permeability ensures that drug is completely absorbed during the limited transit time through the small intestine, and (iii) rapid dissolution ensures that the gastric emptying process is the rate-limiting step for absorption of highly soluble and highly permeable drugs. To support the claim of high permeability, drug sponsors are allowed to use mass balance, absolute bioavailability, or human intestinal perfusion studies (2). Additionally, recommended methods not involving human subjects include *in vivo* or *in situ* intestinal perfusion in a suitable animal model (*e.g.*, rats), and/or *in vitro* permeability methods using exercised intestinal tissues or monolayers of suitable epithelial cells (2). The FDA Guidance indicates that when a single method fails to conclusively demonstrate a permeability classification, two different methods may be advisable (2). In view of the possible laboratory-to-laboratory variability in determining the permeability class under BCS, drug sponsors are required to demonstrate suitability of their permeability methods intended for biowaivers (2).

Since the publication of the FDA BCS Guidance in 2000, possible new class boundaries have been proposed for additional biowaiver based on the underlying physiology of the GI tract (16–19). These may include narrowing the required pH range for solubility measurement and reducing the high permeability requirement. New criteria were also proposed for extending biowaiver to BCS Class II and III drugs, such as creating a new intermediate solubility (and/or permeability) class boundary, increasing the dose volume for solubility classification, utilizing intrinsic dissolution method for solubility classification, as well as including bile salts for solubility measurement and surfactants in dissolution testing. However, it has been pointed out that further research is necessary for adoption of these new criteria and possible extension of biowaivers (16,18).

In lieu of high permeability, the European Medicines Agency (EMA) has recently revised its bioequivalence guideline, indicating that demonstration of complete absorption in humans is preferred for biowaiver of BCS Class 1 drug applications (3). Complete absorption is considered to be established where measured extent of absorption is ≥85% (3,16). The EMA Guideline acknowledges that complete absorption is generally related to high permeability. However, it states that complete drug absorption should be justified based on reliable investigations in humans, and data from absolute bioavailability or mass-balance studies could be used to support this claim (3). It appears that the matrix of drug metabolism in BDDCS can also be used to justify the notion of complete absorption inasmuch as greater than or equal to 85% of the oral dose is metabolized by CYP450 and/or Phase 2 enzymes. In addition to BCS Class 1 drugs, the EMA will grant biowaivers for BCS Class 3 drugs with limited absorption (3). The EMA Guideline has recognized the higher risks in making an inappropriate biowaiver decision for BCS Class 3 than Class 1 drugs, including the possibility of site-specific absorption, transporter interactions at the absorption site, excipient interaction with the active ingredient, and therapeutic risks (3). In the U.S., research is currently ongoing to examine these relevant scientific issues so that extension of biowaivers can be considered for other drug products in immediate release solid oral dosage forms (18).

CONCLUSIONS

1. Both BCS-based permeability and BDDCS-based metabolism can be used as a surrogate for extent of drug absorption and support for a waiver of *in vivo* bioequivalence studies. Specifically, if a drug is classified as high permeability under BCS or has high metabolism (≥90%) under BDDCS, the extent of drug absorption is ≥90%.

2. High metabolism in BDDCS may be supported by mass balance studies in humans, which includes measures of metabolites from CYP450 and/or Phase 2 enzymes in the intestinal mucosa and/or liver.
3. Approaches to demonstrating high permeability in BCS may include (a) absolute bioavailability or mass balance studies in humans, (b) urinary recovery of unchanged drug in humans, (c) *in vivo* intestinal perfusion studies in humans, (d) *in vitro* permeation studies across a monolayer of cultured epithelial cells (*e.g.*, Caco-2 cells), and/or (e) high metabolism as defined under BDDCS.

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