Commentary

Predicting Drug Disposition via Application of BCS: Transport/Absorption/ Elimination Interplay and Development of a Biopharmaceutics Drug Disposition Classification System

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The Biopharmaceutics Classification System (BCS) was developed to allow prediction of *in vivo* pharmacokinetic performance of drug products from measurements of permeability (determined as the extent of oral absorption) and solubility. Here, we suggest that a modified version of such a classification system may be useful in predicting overall drug disposition, including routes of drug elimination and the effects of efflux and absorptive transporters on oral drug absorption; when transporter-enzyme interplay will yield clinically significant effects (e.g., low bioavailability and drug-drug interactions); the direction, mechanism, and importance of food effects; and transporter effects on postabsorption systemic drug concentrations following oral and intravenous dosing. These predictions are supported by a series of studies from our laboratory during the past few years investigating the effect of transporter inhibition and induction on drug metabolism. We conclude by suggesting that a Biopharmaceutics Drug Disposition Classification System (BDDCS) using elimination criteria may expand the number of Class 1 drugs eligible for a waiver of *in vivo* bioequivalence studies and provide predictability of drug disposition profiles for Classes 2, 3, and 4 compounds.

KEY WORDS: BCS; BDDCS; disposition; drug interactions; food effects; routes of elimination; transporter-enzyme interplay.

INTRODUCTION

Amidon and co-workers (1) recognized that the fundamental parameters controlling the rate and extent of oral drug absorption were the drug's aqueous solubility and gastrointestinal permeability. They devised a Biopharmaceutics Classification System (BCS) that categorized drugs into four classes according to their solubility and permeability (expressed as the extent of oral drug absorption) as depicted in Fig. 1. In 2000, the FDA used the BCS system as a science-based approach to allow waiver of *in vivo* bioavailability and bioequivalence testing of immediate-release solid dosage forms for Class 1 high-solubility, high-permeability drugs when such drug products also exhibit rapid dissolution (2).

At its core, the BCS is an experimental model, centrally embracing permeability and solubility, with qualifications related to pH and dissolution. The objective of the BCS is to predict *in vivo* pharmacokinetic performance of drug products from measurements of permeability and solubility. A drug substance is considered "highly soluble" when the highest dose strength is soluble in 250 ml or less of aqueous media over a pH range of 1–7.5 at 37°C. A drug substance is considered to be "highly permeable" when the extent of the absorption (parent drug plus metabolites) in humans is determined to be ≥90% of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose. In Table I, we have assembled a list of compounds in the four BCS classes, predominantly gathered from the literature (1,3–18) but judiciously edited. With respect to oral bioavailability, it is generally believed that the framework of the BCS could serve the needs of the earliest stages of discovery research. In this manuscript, we demonstrate that categorizing drugs into the four classes represented by BCS solubility and permeability criteria may provide significant new insights to the pharmaceutical scientific community. This classification system may be useful in predicting routes of elimination, effects of efflux and absorptive transporters on oral absorption, when transporter-enzyme interplay will yield clinically significant effects such as low bioavailability and drug-drug interactions, the direction and importance of food effects, and transporter effects on postabsorption systemic levels following oral and intravenous dosing. We propose that a modest revision of the BCS criteria may result in a classification system that yields predictability of *in vivo* disposition for all four classes, as well as increasing the number of Class 1 drugs eligible for bioequivalence study waivers.

As we were preparing this manuscript, the extensive evaluation of the WHO Essential Medicines List in terms of BCS classification based on measured solubility and permeability/absorption data was published (18). We have modified the manuscript to include many of the compounds evaluated

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Fig. 1. The Biopharmaceutics Classification System (BCS) as defined by the FDA (2) after Amidon *et al.* (1).

in that work. We agree with most of the classifications assigned, but not all, as our paper expands the utility of the classification to drug disposition. We have added comments about some of these differences throughout the manuscript.

Predicting Routes of Drug Elimination

Examining the drug substances listed in the four BCS classes in Table I, it becomes obvious that Class 1 and Class 2 compounds are eliminated primarily via metabolism, whereas Class 3 and Class 4 compounds are primarily eliminated unchanged into the urine and bile (Fig. 2). We are unaware that this simple categorization under BCS has previously recognized the correlation and fact that the high permeability of the Classes 1 and 2 compounds allows ready access to the metabolizing enzymes within hepatocytes, although Smith (19) has noted that more permeable lipophilic compounds make good substrates for cytochrome P450 (CYP) enzymes. Note that the differential permeability characteristics defined under BCS do not necessarily reflect differences in permeability into hepatocytes, as a number of Class 3 and Class 4 compounds are eliminated into the bile. Rather, the high vs. low permeability designation reflects differences in access to the metabolizing enzymes within the hepatocytes.

For the 130 drugs/compounds listed in Table I, only 13 of the substances do not have readily accessible, critically evaluated pharmacokinetic parameters (20,21). Upon reviewing the disposition characteristics of the Class 3 and Class 4 drugs listed in Table I, all but mebendazole are eliminated predominantly in the unchanged form by the renal or biliary route. We suspect that mebendazole is misclassified, as it is extensively metabolized [note that Lindenberg *et al.* (18) most recently listed mebendazole as either Class 2 or Class 4]. We propose that for the purposes of defining the BCS classification for predicting drug disposition, the extent of metabolism may be a better predictor than the 90% absorption characteristic.

One might suspect that the high-permeability compounds (Class 1 and Class 2) should have higher volumes of distribution than the low-permeability Class 3 and Class 4 compounds. When evaluating the published pharmacokinetic characteristics (20,21), we observed such a trend, but the con-

and major routes of elimination. Many highly protein bound acidic Class 1 and Class 2 compounds exhibit very low volumes of distribution (e.g., valproic acid, ibuprofen). It would be incorrect, however, to conclude that correction for protein binding would give a better prediction of the relative size of the volume of distribution in comparing Classes 1 and 2 compounds with Classes 3 and 4 drugs. In fact, our analysis demonstrates that the generally larger volumes of distribution for Class 1 and Class 2 compounds when compared to Class 3 and Class 4 compounds is independent of the degree of protein binding.

Most New Molecular Entities Are Class 2 Compounds

New molecular entities (NMEs) today are frequently large-molecular-weight, lipophilic, poorly water-soluble compounds that most often fall into BCS Class 2. Lipinski *et al.* (22) pointed out that leads obtained through high-throughput screening (HTS) tend to have higher molecular weights and greater lipophilicity than leads in the pre-HTS era. Lipinski's Rule of 5 was developed to set "drugability" guidelines for NMEs (23). In the drug discovery setting, the Rule of 5 predicts that poor absorption or permeation is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight is greater than 500, and the calculated Log P (CLog P) is greater than 5. However, Lipinski specifically states that the Rule of 5 only holds for compounds that are *not* substrates for active transporters (22,23). When the Rule of 5 was developed, information about drug transporters was very limited. We believe that almost all drugs are substrates for some transporter. Studies to date have not been able to show this because we are just beginning to gain the knowledge and tools that allow investigation of substrates for uptake transporters. In addition, unless a drug molecule can passively gain intracellular access, it is not possible to simply investigate whether the molecule is a substrate for efflux transporters.

Lipinski has noted that the Rule of 5 was intended as a very crude filter (24). Thus, it is not surprising that predictions based only on solubility and Log P or CLog P may frequently be in error, often because most drugs may be substrates for some transporter. We note that a recent evaluation of the provisional biopharmaceutical classification of WHO essential drugs (25) reported a generally good correlation between *in silico* parameters and BCS classification; however, some obvious misclassifications occurred. For example, acetaminophen (bioavailability = 88%), dapsone (93%), and theophylline (96%), all highly metabolized drugs, are listed as Class 4 compounds based only on physicochemical criteria (25), as opposed to their Classes 1 and 2 listings in Table I.

Cautions

Prior to making further predictions related to transporter-enzyme interactions, food effects and drug-drug interactions, we wish to provide the following cautions.

a) There will always be exceptions to the broad general rules presented here (e.g., the Class 2 compound digoxin does not undergo extensive hepatic metabolism in humans, but it does in the rat). As research scientists, we find exceptions to predictability (and unexpected events) more intriguing and

Table I. Biopharmaceutics Classification System (BCS) Substrates[a]

High solubility		Low solubility	
Class 1		**Class 2**	
Abacavir	Ketorolac	Amiodarone[I]	Itraconazole[S,I]
Acetaminophen	Ketoprofen	Atorvastatin[S,I]	Ketoconazole[I]
Acyclovir[b]	Labetolol	Azithromycin[S,I]	Lansoprazole[I]
Amiloride[S,I]	Levodopa[S]	Carbamazepine[S,I]	Lovastatin[S,I]
Amitryptyline[S,I]	Levofloxacin[S]	Carvedilol	Mebendazole
Antipyrine	Lidocaine[I]	Chlorpromazine[I]	Naproxen
Atropine	Lomefloxacin	Cisapride[S]	Nelfinavir[S,I]
Buspirone[c]	Meperidine	Ciprofloxacin[S]	Ofloxacin
Caffeine	Metoprolol	Cyclosporine[S,I]	Oxaprozin
Captopril	Metronidazole	Danazol	Phenazopyridine
Chloroquine[S,I]	Midazolam[S,I]	Dapsone	Phenytoin[S]
Chlorpheniramine	Minocycline	Diclofenac	Piroxicam
Cyclophosphamide	Misoprostol	Diflunisal	Raloxifene[S]
Desipramine	Nifedipine[S]	Digoxin[S]	Ritonavir[S,I]
Diazepam	Phenobarbital	Erythromycin[S,I]	Saquinavir[S,I]
Diltiazem[S,I]	Phenylalanine	Flurbiprofen	Sirolimus[S]
Diphenhydramine	Prednisolone	Glipizide	Spironolactone[I]
Disopyramide	Primaquine[S]	Glyburide[S,I]	Tacrolimus[S,I]
Doxepin	Promazine	Griseofulvin	Talinolol[S]
Doxycycline	Propranolol[I]	Ibuprofen	Tamoxifen[I]
Enalapril	Quinidine[S,I]	Indinavir[S]	Terfenadine[I]
Ephedrine	Rosiglitazone	Indomethacin	Warfarin
Ergonovine	Salicylic acid		
Ethambutol	Theophylline		
Ethinyl estradiol	Valproic acid		
Fluoxetine[I]	Verapamil[I]		
Glucose	Zidovudine		
Imipramine[I]			
Class 3		**Class 4**	
Acyclovir	Fexofenadine[S]	Amphotericin B	
Amiloride[S,I]	Folinic acid	Chlorthalidone	
Amoxicillin[S,I]	Furosemide	Chlorothiazide	
Atenolol	Ganciclovir	Colistin	
Atropine	Hydrochlorothiazide	Ciprofloxacin[S]	
Bisphosphonates	Lisinopril	Furosemide	
Bidisomide	Metformin	Hydrochlorothiazide	
Captopril	Methotrexate	Mebendazole	
Cefazolin	Nadolol	Methotrexate	
Cetirizine	Pravastatin[S]	Neomycin	
Cimetidine[S]	Penicillins		
Ciprofloxacin[S]	Ranitidine[S]		
Cloxacillin	Tetracycline		
Dicloxacillin[S]	Trimethoprim[S]		
Erythromycin[S,I]	Valsartan		
Famotidine	Zalcitabine		

[a] The listed compounds are predominantly gathered from the literature (1,3–18).
[b] The compounds listed in *italic* are those falling in more than one category by different authors, which could be a result of the definition of the experimental conditions (i.e., acyclovir, amiloride, atropine, and captopril are listed in Classes 1 and 3 but all are highly soluble). Furosemide, hydrochlorothiazide, and methotrexate are listed in Classes 3 and 4, but they are all poorly permeable. Mebendazole is listed as Classes 2 and 4, but the compound is poorly soluble. Interesting examples are ciprofloxacin and erythromycin, which are listed in Classes 2 and 3; it could just be that the properties of the compounds are intermediate between Classes 2 and 3. Ciprofloxacin has also been listed as Class 4.
[c] The compounds listed in bold are primarily CYP3A substrates where metabolism accounts for more than 70% of the elimination; superscript I and/or S indicate P-gp inhibitors and/or substrate, respectively.

science as a whole, exceptions are clues to new discoveries and new hypotheses.

b) The BCS classification criteria for bioequivalence evaluation will not necessarily be appropriate for predicting

sential Medicines List (18), and as will be discussed subsequently.

c) High-permeability drugs are defined as compounds that exhibit 90% absorption in humans following oral dosing

High Solubility	Low Solubility
Class 1 Metabolism	**Class 2** Metabolism
Class 3 Renal and/or Biliary Elimination of Unchanged Drug	**Class 4** Renal and/or Biliary Elimination of Unchanged Drug

(High Permeability for Class 1 and Class 2; Low Permeability for Class 3 and Class 4)

Fig. 2. Predominant routes of drug elimination for drug substances by BCS class.

High Solubility	Low Solubility
Class 1 Transporter effects minimal	**Class 2** Efflux transporter effects predominate
Class 3 Absorptive transporter effects predominate	**Class 4** Absorptive and efflux transporter effects could be important

(High Permeability for Class 1 and Class 2; Low Permeability for Class 3 and Class 4)

Fig. 3. Transporter effects on drug disposition by BCS class.

these criteria because of the activity *in vivo* of uptake transporters in the intestine, rather than just due to high lipid passive diffusion permeability as reflected in Log P. Thus, some BCS drugs listed in Class 2 (and possibly some Class 1 drugs) may show marked changes in bioavailability when intestinal uptake transporters are inhibited.

d) It is probable that some compounds that should be considered Class 1 in terms of drug absorption and disposition are listed as Class 2 according to the FDA BCS criteria due to the requirement of good solubility and rapid dissolution at low pH values, which is not limiting for drug disposition. This was recently discussed in terms of acidic drugs (26).

We believe that a different set of criteria, particularly those relating to permeability but also to solubility, must be developed when using BCS in predicting drug disposition. We welcome the opportunity to work with the FDA and pharmaceutical manufacturers in setting simple *in vitro* surrogate permeability standards, as we discuss further in the section entitled "Biopharmaceutics Drug Disposition Classification System."

PREDICTING THE EFFECTS OF TRANSPORTERS

Oral Dosing and the Predictability of Transporter Effects

Recent work from our laboratory, initially based on cellular system studies evaluating transporter-enzyme interplay (27–29) have led us to the generalizations regarding transporter effects following oral dosing depicted in Fig. 3. The boldface italic items that follow represent the major predictive generalizations of this section of the current paper.

Transporter effects will be minimal for Class 1 compounds. The high permeability/high solubility of such compounds allows high concentrations in the gut to saturate any transporter, both efflux and absorptive. That is, Class 1 compounds may be substrates for both uptake and efflux transporters *in vitro* in cellular systems under the right conditions [e.g., midazolam (30) and nifedipine (31) are substrates for P-glycoprotein], but transporter effects will not be important clinically. As stated above in Caution d, it is probable that some compounds that should be considered Class 1 in terms

to the requirement of good solubility and rapid dissolution at low pH values. Such pH effects would not be limiting *in vivo* where absorption takes place from the intestine. Examples of this from Table I may include the NSAIDs diclofenac, diflunisal, flurbiprofen, indomethacin, naproxen, and piroxicam, as discussed by Yazdanian *et al.* (26), and warfarin, which is almost completely bioavailable (20,21). In contrast, ofloxacin is listed as Class 2 because of its low solubility at pH 7.5.

Efflux transporter effects will predominate for Class 2 compounds. The high permeability of these compounds will allow ready access into the gut membranes and uptake transporters will have no effect on absorption, but the low solubility will limit the concentrations coming into the enterocytes, thereby preventing saturation of the efflux transporters. Consequently, efflux transporters will affect the extent of oral bioavailability (F_{extent}) and the rate of absorption of Class 2 compounds.

Transporter-enzyme interplay in the intestines will be important primarily for Class 2 compounds that are substrates for CYP3A and Phase 2 conjugation enzymes. For such compounds, intestinal uptake transporters will generally be unimportant due to the rapid permeation of the drug molecule into the enterocytes as a function of their high lipid solubility. That is, absorption of Class 2 compounds is primarily passive and a function of lipophilicity. However, due to the low solubility of these compounds, there will be little opportunity to saturate apical efflux transporters and intestinal enzymes such as CYP 3A4 and UDP-glucuronosyltransferases (UGTs). Thus, changes in transporter expression, and inhibition or induction of efflux transporters will cause changes in intestinal metabolism of drugs that are substrates for the intestinal metabolic enzymes. Note the large number of Class 2 compounds in Table I that are primarily substrates for CYP3A (compounds listed in bold) as well as substrates or inhibitors of the efflux transporter P-glycoprotein (indicated by superscripts S and I, respectively). Work in our laboratory has characterized this interplay in the absorptive process for the investigational cysteine protease inhibitor K77 (28,32) and sirolimus (29), substrates for CYP3A and P-glycoprotein, and more recently for raloxifene (33), a substrate for UGTs and P-glycoprotein.

Absorptive transporter effects will predominate for

will be available in the gut lumen due to good solubility, but an absorptive transporter will be necessary to overcome the poor permeability characteristics of these compounds. However, intestinal apical efflux transporters may also be important for the absorption of such compounds when sufficient enterocyte penetration is achieved via an uptake transporter.

It has been suggested (Refs. 5, 15, and others in meeting presentations) that products containing Class 3 drug substances should qualify for a waiver of *in vivo* bioequivalence studies on the basis of dissolution studies alone, as for drug products containing Class 1 drugs. This is inappropriate, as it is now obvious that components of a Class 3 drug formulation can affect uptake transporters and modify bioavailability. Until more is known about the importance of intestinal transporters and validated methodology to predict the effects of formulation components on these transporters has been developed, any expansion of *in vivo* bioequivalence study waivers beyond Class 1 compounds is unwise policy. However, our proposal, presented below, could increase the number of drugs that qualify for Class 1 bioequivalence study waivers.

It would be expected that Class 4 compounds could be substrates for both absorptive and efflux transporters. On first principles, we might expect that no Class 4 compounds would become effective drugs due to their solubility and permeability deficiencies. However, it is probable that a number of Class 4 compounds are misclassified in terms of *in vivo* characteristics, as solubility in aqueous solutions may not reflect solubility in gut contents. For example, the FDA generated publication (15) and others have suggested that solubility measurements in surfactant containing solution may be a more appropriate basis for the solubility criteria. For true Class 4 compounds, oral bioavailability is minimal and transporter effects could be relevant, for example, where a change from 2% to 3% bioavailability could make a significant difference.

Food Effects (High-Fat Meals)

It is well-known that food can influence drug bioavailability, both increasing and decreasing the extent of availability (F_{extent}) and the rate of availability. In December 2002, the FDA issued a guidance entitled "Food-Effect Bioavailability and Fed Bioequivalence Studies" (34). Fleisher *et al.* (6) noted that food effects on the extent of bioavailability could generally be predicted based on BCS class, as depicted in Fig. 4. We have added the time to peak exposure (T_{max}) designations to the figure. High-fat meal studies are recommended by the FDA, as such meal conditions are expected to provide the greatest effects on gastrointestinal physiology so that systemic drug availability is maximally affected (34). It is generally believed that food effects result from changes in drug solubility and other factors as listed by the FDA (34), such as food may: "delay gastric emptying; stimulate bile flow; change gastrointestinal pH; increase splanchnic blood flow; change luminal metabolism of a drug substance; and physically or chemically interact with a dosage form or a drug substance." We hypothesize that although these other factors may be important, drug-transporter interactions could often be the primary mechanism for the food effect. We suspect that high-fat meals may inhibit drug transporters, both influx and efflux, and we have carried out preliminary studies that suggest that a high fat meal will inhibit P-glycoprotein (J. M. Custodio and
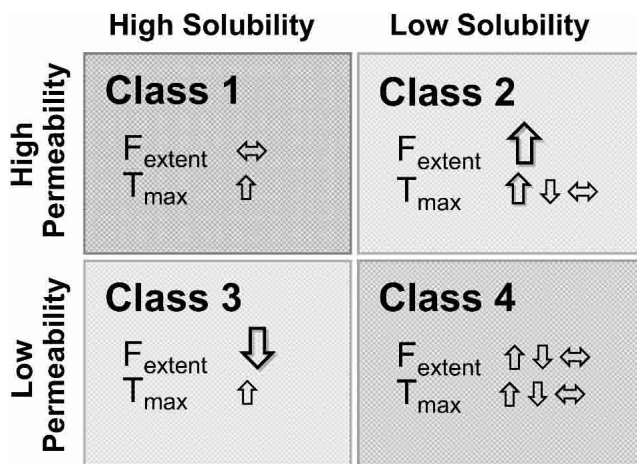

Fig. 4. Predictability of high-fat meal effects by BCS class after Fleischer *et al.* (6).

High-fat meals will have no significant effect on F_{extent} for Class 1 compounds because complete absorption may be expected for high solubility/high permeability compounds, and as noted previously, no transporter drug interactions would be expected for Class 1 compounds.

However, high-fat meals may delay stomach emptying and therefore cause an increase in peak time.

High-fat meals will increase F_{extent} for Class 2 compounds due to inhibition of efflux transporters in the intestine and additional solubilization of drug in the intestinal lumen (e.g., micelle formation). Peak time could decrease due to inhibition of efflux cycling or increase due to slowing of stomach emptying; a combination of the two will usually be dominated by the delayed emptying. This will be true in cases where membrane permeation is passive, such as for the immunosuppressants cyclosporine, tacrolimus, and sirolimus. However, if high permeability for a Class 2 compound results from uptake transporters, rather than ready partition into the intestinal membranes (see Caution c above), high-fat meals could inhibit both uptake and efflux transporters. Then, depending upon the relative magnitude of inhibition of uptake and efflux transporters, meal effects may be confounding, more likely having little effect on F_{extent}, but still increasing peak time due to delayed gastric emptying.

Formulation changes that markedly increase the solubility of Class 2 compounds will decrease or eliminate the high-fat meal effects for these drugs. We believe that this is the reason that the newer cyclosporine microemulsion formulation (Neoral) eliminates the food effects associated with the older olive oil formulation (Sandimmune). In practice, drug formulators attempt to enable a Class 2 compound to function as a Class 1 compound, thereby eliminating food effects on F_{extent} and other transporter-drug interactions, as explained earlier for Class 1 drugs.

High-fat meals will decrease F_{extent} for Class 3 compounds due to inhibition of uptake transporters in the intestine. Recent evidence suggests that intestinal drug uptake can be decreased by inhibiting organic anion transporting polypetides, as shown by the effect of fruit juices on fexofenadine (35). As noted above, some Class 3 compounds can be substrates for intestinal efflux transporters. Depending upon

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