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## PREDICTING DRUG DISPOSITION, ABSORPTION / ELIMINATION / TRANSPORTER INTERPLAY AND THE ROLE OF FOOD ON DRUG ABSORPTION

Joseph M. Custodio<sup>1</sup>, Chi-Yuan Wu<sup>1,2</sup>, and Leslie Z. Benet<sup>1,3</sup>

<sup>1</sup> Department of Biopharmaceutical Sciences, University of California, San Francisco, San Francisco, California 94143, USA

### Abstract

The ability to predict drug disposition involves concurrent consideration of many chemical and physiological variables and the effect of food on the rate and extent of availability adds further complexity due to postprandial changes in the gastrointestinal (GI) tract. A system that allows for the assessment of the multivariate interplay occurring following administration of an oral dose, in the presence or absence of meal, would greatly benefit the early stages of drug development. This is particularly true in an era when the majority of new molecular entities are highly permeable, poorly soluble, extensively metabolized compounds (BDDCS Class 2), which present the most complicated relationship in defining the impact of transporters due to the marked effects of transporter-enzyme interplay. This review evaluates the GI luminal environment by taking into account the absorption / transport / elimination interplay and evaluates the physicochemical property issues by taking into account the importance of solubility, permeability and metabolism. We concentrate on the BDDCS and its utility in predicting drug disposition. Furthermore, we focus on the effect of food on the extent of drug availability (F), which appears to follow closely what might be expected if a significant effect of high fat meals is inhibition of transporters. That is, high fat meals and lipidic excipients would be expected to have little effect on F for Class 1 drugs; they would increase F of Class 2 drugs, while decreasing F for Class 3 drugs.

### Keywords

absorption; BCS; BDDCS; disposition; elimination; food effects; interplay; transporter

## 1. INTRODUCTION

Food-drug interactions have been widely associated with alterations of pharmacokinetic and pharmacodynamic parameters and proven to have significant clinical implications.<sup>1,2</sup> The influence of concomitant food intake prompted the Food and Drug Administration (FDA) to issue a guidance for industry entitled, “Food-Effect Bioavailability and Fed Bioequivalence Studies.”<sup>3</sup> As a result, it is common to find medication labeling containing language denoting

<sup>3</sup>To whom correspondence should be addressed. (University of California, San Francisco, 533 Parnassus Ave, Room U-68, San Francisco, CA 94143-0446; tel: 415.476.3853; fax: 415.476.8887; e-mail: leslie.benet@ucsf.edu).

<sup>2</sup>Current Address: Bristol-Myers Squibb, Pharmaceutical Research Institute, Princeton, New Jersey 08543, USA.

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that maximum effect is achieved if the drug is administered with a meal. Conversely, some drug products show a decrease in the extent of availability and decreased efficacy with meal coadministration. Of course there are very many drugs for which food-drug interactions are non-existent or negligible.

The effect of food on the extent of availability is a significant concern during drug development. Ideally, it is most advantageous if a recommendation of oral drug administration can be provided independent of meal considerations. A food-drug interaction model would be beneficial in the early stages of development when preclinical predictions could be of particular use and service to the industry. Although various *in vitro* and *in vivo* models can be found,<sup>4,5,6,7</sup> to date no standard system exists to predict drug absorption and the effect of food.

The role of food, and its subsequent digestion, in oral drug absorption may be attributed to a myriad of variables ranging from the chemical characteristics of the drug itself to the post-prandial changes in the gastrointestinal (GI) tract. Therefore, when attempting to predict variations in pharmacokinetics it is imperative to consider not only the physiochemical properties of the drug, but the GI luminal environment as well. In this review, we evaluate the GI luminal environment by taking into account the absorption / transport / elimination interplay and we evaluate the physiochemical property issues by taking into account the importance of solubility, permeability and metabolism. Here, we concentrate on combining these aspects into a comprehensive system to predict disposition and the role of food on drug absorption.

## 2. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM

### 2.1. The BCS and the FDA

The oral absorption of a drug is fundamentally dependent on that drug's aqueous solubility and gastrointestinal permeability. Extensive research into these fundamental parameters by Amidon *et al.*<sup>8</sup> led to the Biopharmaceutics Classification System (BCS) that categorizes drugs into four groups, Class 1 – Class 4 (Fig. 1). The BCS classifies compounds based on the critical components related to oral absorption. Centrally embracing permeability and solubility, the objective of the BCS is to allow prediction of *in vivo* pharmacokinetic performance of drug products from *in vitro* measurements of permeability and solubility.

In 2000, the FDA promulgated the BCS as a science based approach to allow waiver of *in vivo* bioavailability and bioequivalence testing for immediate release solid dosage forms for Class 1 compounds, highly soluble and highly permeable drugs, when such drug products also exhibit rapid dissolution.<sup>9</sup> In brief, bioequivalence is achieved if the generic product shows the same rate and extent of bioavailability with rate evaluated in terms of C<sub>max</sub> and extent measured in terms of AUC. The criteria include a 90% confidence interval around point estimates of the ratios of C<sub>max</sub> and AUC, test/reference, falling within 0.8–1.25 on a log normal distribution.

### 2.2. The Framework of the BCS

As depicted in Figure 1, the BCS sorts drugs on a scale in terms of solubility versus permeability. A drug substance is considered “highly soluble” when the highest marketed dose strength is soluble in 250 ml of aqueous media over a pH range of 1–7.5 at 37°C.<sup>9</sup> A drug substance is considered to be “highly permeable” when the extent of absorption in humans is determined to be greater or equal to 90% of an administered dose based on a mass balance determination or in comparison to an intravenous reference dose.<sup>9</sup> Accordingly, Class 1 compounds possess high properties of both solubility and permeability, while Class 4 compounds possess low properties; Class 2 are highly permeable and poorly soluble, while Class 3 possess the opposite characteristics of poor permeability and high solubility.

The classification framework of the BCS is believed to be useful in the earliest stages of drug discovery research. Its applications improve the prediction of oral absorption and disposition of new molecular entities. In addition, the BCS has proven to be an asset to the FDA by creating a framework for which to allow a waiver of *in vivo* bioequivalence studies for a suitable Class 1 compounds, albeit a limited number. In 2005, Wu and Benet<sup>10</sup> constructed a Table of 130 compounds in the four BCS classes (Table I). These compounds were predominantly gathered from available literature but judiciously edited.<sup>8,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26</sup> Extensive research into the assembled list of compounds in the four categories has demonstrated that the BCS provides further predictive utility. Here, we focus on its application with respect to the food-drug effect.

### 3. PREDICTING DRUG DISPOSITION

#### 3.1. Oral absorption and the gastrointestinal tract

A majority of drugs marketed worldwide are administered orally. The efficacy of these drugs is dependent on the oral bioavailability, which in turn, is dependent on extent of absorption. Oral absorption, in basic terms, is dependent on the intestinal drug solubilization and the intestinal drug permeability. The amount of drug that goes into solution is affected by factors such as volume, pH, temperature and the compound's octanol/water partition coefficient,  $\log P_{o/w}$ . Thermodynamically, the solubility of a drug is determined by the intermolecular forces in the solid state versus the intermolecular forces of the solute-solvent state.<sup>27</sup> The amount of drug that crosses the membrane is affected by factors such as concentration, temperature, time, surface area, viscosity, and affinity to a membrane transporter. Mechanistically, the permeability of a drug is additively determined by a number of parallel processes such as a passive component and one or more active components.<sup>28,29,30,31,32</sup>

As an oral dose transits through the gastrointestinal (GI) tract, not only can it decompose but it may also undergo gut wall metabolism.<sup>33,34</sup> Moreover, the drug is exposed to intestinal transporters, both efflux and absorptive (Fig. 2).<sup>35,36,37,38</sup> The environment of the GI tract varies markedly following meal ingestion.<sup>39,40</sup> Effects on absorption have been characterized as reduced, delayed, increased and accelerated, and those causing no change in absorption.<sup>41</sup> The volume of intestinal fluids may increase 2–3 fold following a meal and the levels of phospholipids and bile salts in the gut also may increase 4–5 fold.<sup>42,43</sup>

It is well documented that food can influence the pharmacokinetics of a drug by affecting one or more of the factors (e.g. bile flow, splanchnic blood flow, GI pH, gastric emptying, physical/chemical interactions with the drug) listed by the FDA.<sup>2,3</sup> Chelation of a drug to certain food components can result in decreased bioavailability.<sup>44</sup> Decreased solubility at higher gastrointestinal pH can occur for poorly soluble weak bases leading to a decrease in bioavailability.<sup>45</sup> More rapid splanchnic blood flow is believed to improve the bioavailability of drugs that experience a significant first pass effect.<sup>46</sup> Enhanced solubility in the postprandial intestine can markedly improve the bioavailability of a poorly soluble drug.<sup>47</sup> Prolonged stomach exposure due to delayed emptying can reduce bioavailability due to drug interaction with the gastric acid secretions or by simply causing increased degradation of an unstable compound.<sup>8,48</sup>

While evidence as described above, of drug, meal, and formulation interactions, as well as their influences on intestinal absorption and elimination within the GI environment can be readily found in the current literature, much less is known about such influences and their clinical significance with respect to intestinal transporters. This work discusses the latter, the less extensively characterized effects on transporters, while focusing on the ever important absorption/elimination/transport interplay. Understanding the absorption/elimination/transport interplay is integral in predicting the role of food on drug disposition.

### 3.2. Predicting routes of elimination

Critical evaluation of drug substances listed in the four BCS classes on Table I allows for prominent trends to become apparent specifically with respect to major routes of elimination. 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 the bile (Fig. 3). This is consistent with the generally held belief that more permeable lipophilic compounds make good substrates for Cytochrome P450 (CYP) enzymes.<sup>49</sup> While the theory that metabolism increases as lipid solubility (log P) increases was noted, it had not been previously been recognized in terms of the Biopharmaceutics Classification System.<sup>10</sup> It is important to note that the differential permeability characteristics defined in the BCS do not necessarily reflect differences in permeability into hepatocytes. This is evident by the fact that a high number of Class 3 and Class 4 compounds are eliminated into the bile. The differential permeability characteristics denoted by the high versus low designation reflects the differential access of the compound to the metabolizing enzymes within the hepatocytes.

Recognition of the elimination pathway differences for Class 1 and Class 2 drugs versus Class 3 and Class 4 drugs, combined with the inherent difficulty in quantifying the percent of drug absorbed in humans at a level of 90%, prompted Wu and Benet<sup>10</sup> to suggest a revised category scheme entitled the Biopharmaceutics Drug Disposition Classification System (BDDCS)(Fig. 4).

### 3.3 Framework of the BDDCS

The BDDCS replaces the permeability criteria with the major route of elimination because of the belief that it is easier and less ambiguous to determine the assignment of BDDCS for marketed drugs based on the extent of metabolism than using permeability (i.e. extent of absorption) in BCS assignments thereby eliminating many instances of uncertainty in human permeability leading to differences in class designation by different authors.

When initially proposed, “extensive metabolism” was defined as  $\geq 50\%$  metabolism of an oral dose *in vivo* in humans. Further consideration of this parameter designation led to the realization that there are very few drugs/compounds that are intermediately metabolized. It is now proposed that the definition of “extensive metabolism” be pushed to  $\geq 70\%$  metabolism of an oral dose *in vivo* in humans while the “poor metabolism” be defined as  $\geq 50\%$  of the dose be excreted unchanged. Use of the more stringent BDDCS metabolism criteria versus the BCS permeability characterization resulted in only 10 compounds requiring reclassification and allowed for the inclusion of an additional 38 drugs/compounds. An updated list modified from the BDDCS Table first published by Wu and Benet<sup>10</sup> is provided in Table II.

### 3.4 Predicting the effects of transporters

The investigation of the effects of drug transporters on drug disposition has been ongoing for many years.<sup>50</sup> The well characterized Madin Darby Canine Kidney (MDCK) cell line has been widely utilized throughout industry and academia with the most frequent application being the MDCK-MDR1 cell line incorporating the stable expression of the MDR1 gene encoding for the P-glycoprotein (P-gp) efflux transporter.<sup>51,52,53</sup> Compared to various alternative cell monolayers, the MDCK-MDR1 cell system possesses very tight junctions as reflected by their high transepithelial electrical resistance (TEER) values. TEER values are measured by the Millicell electrical resistance system utilizing “chopstick” electrodes (Millipore Corporation, Bedford, MA) and are expressed in units of resistance and surface area. Our laboratory, similar to other research groups, employs semi-porous membranes with a pore size of 0.4 $\mu\text{m}$  and surface area of 4.2  $\text{cm}^2$  upon which a cell monolayer is grown and, therefore, the ohm ( $\Omega$ ) resistance measured is then multiplied by 4.2  $\text{cm}^2$ . The MDCK-MDR1 cells, mentioned above as having very high TEER, possess values of approximately 5000–6000  $\Omega \cdot \text{cm}^2$ . The

untransfected parental MDCK cell system possesses TEER values of approximately 200–300  $\Omega\cdot\text{cm}^2$ . The commonly used human colonic adenocarcinoma cell system (Caco-2) possesses TEER values of approximately 800–1000  $\Omega\cdot\text{cm}^2$ . It should be noted that reported TEER values for the same cell line can vary significantly from laboratory to laboratory. This may be attributed to variables such as the growth media and the frequency of media replacement as well as the passage of the cells at the time of experimentation. For example, Lu *et al.*<sup>54</sup> reported Caco-2 cells, passage 44, to have TEER values of  $664 \pm 42 \Omega\cdot\text{cm}^2$  while the same cells, but of passage 98, possessed TEER values of  $1423 \pm 12 \Omega\cdot\text{cm}^2$ .

Measurement of the bidirectional transport, apical to basolateral (A→B) and basolateral to apical (B→A), across the MDCK-MDR1 monolayer allows for the calculation of apparent permeability ( $P_{\text{app}}$ ) values as well as net flux ratios (B→A/A→B). Transport studies by Polli and coworkers<sup>52</sup> with various drugs in the MDCKII-MDR1 cell system demonstrate that P-gp substrates display a net flux ratio of 2 or higher. It has also been shown using studies in Caco-2 cells that drugs with  $P_{\text{app}}$  values less than  $1 \times 10^{-6}$  cm/sec are poorly (0–20%) absorbed; drugs with  $P_{\text{app}}$  values between  $1\text{--}10 \times 10^{-6}$  cm/sec are moderately (20–70%) absorbed; and drugs with  $P_{\text{app}}$  values greater than  $10 \times 10^{-6}$  cm/sec are well (70–100%) absorbed.<sup>55</sup>

Recent advances in the pharmaceutical sciences have provided new and improved tools for discovering and investigating transporter substrates. Although numerous substrates of the P-gp efflux transporter have been identified, this has not been the case for intestinal uptake transporters. Until now studies have not been able to show which drugs and compounds gain access into the cell by means of carrier mediated uptake transporters. Various studies have documented the utility of Caco-2 cells and that these cells do endogenously express a multitude of uptake transporters.<sup>56,57,58,59,60</sup> Unfortunately, the sensitivity of assays run in Caco-2 cells have proved unsuccessful in consistently identifying uptake transporter substrates. However, isolation and stable transfection of uptake transporter proteins has lead to new lines that allow investigation of substrates for uptake transporters.<sup>61,62</sup> The MDCK-PepT1 cell system has been used to for permeability screening of classic peptide substrates.<sup>63</sup> The HEK/OATP2B1 cells have been used to demonstrate the effects of fruit juices on glyburide uptake.<sup>64</sup>

It is important to note that 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. To alleviate this complexity many researchers have employed a double transfection approach. A fine example is represented by recent work by Matsushima *et al.*<sup>65</sup> with the MDCKII line; one line containing both the OATP1B1 and MDR1 genes and another line containing both OATP1B1 and BCRP. With such tools, it is now feasible to evaluate vectorial transport of drugs and compounds that are substrates for both uptake and efflux transporters.<sup>66,67,68</sup>

It has been the belief of our laboratory that almost all drugs are substrates for some transporter. However, this is not to say that transporter effects will always be clinically relevant. One of the reasons researchers employ the MDCK-MDR1 cell line is because of its superior TEER values. This exceedingly tight cell system allows for increased sensitivity in identifying P-gp substrates. However, a transporter effect observed in the MDCK-MDR1 cell system may not necessarily be observed in the Caco-2 cell system. The lower TEER values of the Caco-2 cells makes for a leakier system that we believe is far more representative of the human intestine. Consequently, for certain drugs considered to be “model” P-gp substrates it may be difficult to predict their transporter interactions in the gut. In fact, Sahin *et al.* (2007 AAPS Annual Meeting, Abstract #1733) have shown that verapamil, which is designated as a model P-gp substrate by the FDA,<sup>9</sup> has a net flux ratio close to one in the Caco-2 cell system. Furthermore, Sahin *et al.* (2007 AAPS Annual Meeting, Abstract #1733) demonstrated that this ratio remained unchanged in the presence of a P-gp inhibitor suggesting that verapamil absorption

is controlled by its passive diffusion and not P-gp. Work such as this has been ongoing in our laboratory for several years and has led us to a number of generalizations regarding transporter effects following oral dosing (Fig. 5).

**3.4.1. Class 1 compounds**—The gut lumen of the gastrointestinal tract is sufficiently leaky so that small molecular weight, soluble, non-polar compounds (i.e. Class 1 compounds) readily pass through the membrane. Alternatively, the high permeability/high solubility of Class 1 drugs 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 (for example, midazolam<sup>69</sup> and verapamil<sup>9</sup> are substrates for P-glycoprotein), but transporter effects will not be important clinically.

**3.4.2. Class 2 compounds**—Similarly, for Class 2 drugs, the high permeability will allow ready access into the gut membranes making intestinal uptake transporters generally unimportant due to the rapid permeation of the drug molecule into the enterocytes. That is, absorption of Class 2 compounds is primarily passive and a function of lipophilicity. However, the low solubility of these compounds 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 and the rate of absorption of Class 2 drugs. Moreover, there will be little opportunity to saturate intestinal enzymes such as CYP3A4 and UDP-glucuronosyltransferases (UGTs) due to the low solubility. 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 enzymes. Many Class 2 compounds are primarily substrates for CYP3A as well as substrates or inhibitors of the efflux transporter P-glycoprotein. Work in our laboratory has characterized this interplay in the absorption process for the investigational cysteine protease inhibitor K77<sup>70,71</sup> and the immunosuppressive sirolimus,<sup>72</sup> substrates for CYP3A and P-glycoprotein and for raloxifene,<sup>73</sup> a substrate for UGTs and P-glycoprotein. However, as noted in Figure 5, Class 2 compounds may be affected by both uptake and efflux transporters in the liver.<sup>74</sup>

**3.4.3. Class 3 and Class 4 compounds**—For Class 3 compounds, sufficient drug 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. That is, since influx of Class 3 compounds will generally be rate limited by an absorptive transporter, the counter effects of efflux transporters will not be saturated and can also be important. In general, these principles also hold for Class 4 compounds, although Class 4 drugs may achieve sufficient solubility in the natural surfactant containing gut contents so that they act like Class 3 compounds.

## 4. PREDICTING THE EFFECTS OF FOOD ON ABSORPTION

### 4.1. Fleisher et al. and the trends in the BCS

Fleisher and coworkers<sup>14</sup> documented several cases of food effects while taking into account the drug and its formulation classifications as established by the Biopharmaceutics Classification System (BCS).<sup>9</sup> The review of Fleisher<sup>14</sup> showed that in general high fat meals have no effect on the extent of oral drug availability for BCS Class 1 compounds, generally showed increased availability for Class 2 compounds, and generally showed decreased availability for Class 3 compounds. For example, *in vivo* studies such as that reported by Gupta *et al.*<sup>75</sup> for cyclosporine, a Class 2 drug, demonstrated that when given with a high fat meal

to healthy volunteers, bioavailability markedly increased as compared to individuals receiving the drug with a low fat meal. More recently, Ratain *et al.*<sup>47</sup> showed that the bioavailability of the new anti-cancer agent, lapatinib, increased 325% when coadministered with a high fat meal when compared with fasting conditions. Lapatinib is a Class 2 drug. In contrast, the angiotensin converting enzyme (ACE) inhibitor captopril, a BCS Class 3 compound, shows a significant decrease in serum drug levels when administered with a meal.<sup>76</sup> These observations are consistent with what might be predicted, in terms of our group's Biopharmaceutics Drug Disposition Classification System (BDDCS), if high fat meal ingestion results in an inhibitory effect on intestinal transporter function.

In the BDDCS, we predict that high fat meals will have no significant effect on Class 1 drugs, despite the fact that many Class 1 drugs are transporter substrates, because the high gut permeability and intestinal fluid high solubility possessed by this class of drugs dictate that transporter effects will be minimal. For Class 2 compounds, which are highly metabolized and therefore are often dual substrates of enzymes and transporters, we predict an increase in bioavailability due in part to transporter inhibition resulting in decreased extraction of the drug. For Class 3 compounds, which are poorly metabolized and poorly permeable and therefore are often reliant on uptake transporters, we predict a decrease in bioavailability due in part to transporter inhibition resulting in the reduction of AUC.

#### 4.2. FDA's Guidance to the Industry

It is well known that food can influence drug bioavailability, both increasing and decreasing the extent of availability and the rate of availability. In December 2002, the FDA issued a guidance entitled, "Food-Effect Bioavailability and Fed Bioequivalence Studies."<sup>3</sup> High fat meals are recommended by the FDA for food-effect studies, as such meal conditions (800–1000 calories; 50–65% from fat, 25–30% from carbohydrates, and 15–20% protein) are expected to provide the greatest effects on gastrointestinal physiology so that systemic drug availability is maximally affected. An example of a test meal that would be suitable for a food effect bioavailability and fed bioequivalence study would include the following: two eggs fried in butter, two strips of bacon, two slices of toast with butter, four ounces of hash browns potatoes and eight ounces of whole milk.<sup>3,77</sup>

It is generally believed that food effects result from changes in drug solubility and other factors as listed by the FDA,<sup>3</sup> 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." However, it is also necessary to consider the fluidic environment and the resulting components present in the GI tract following a meal high in fat.

#### 4.3. The postprandial intestine

A myriad of variables are introduced into the gastrointestinal tract upon ingestion and subsequent digestion of a meal. In addition to the actual constituents of meal, the resulting changes in the volume of intestinal fluids and the fluidic environment is significant. While the total volume may vary by individual, estimated volumes have been reported as follows: 300–500 ml for the fasted state stomach; 800–900 ml for the fed state stomach; 500 ml for the fasted state small intestine; 900–1000 ml for the fed state small intestine.<sup>1,41</sup> The basal level gastric secretions are estimated to be about 300 ml and may increase up to five times following a meal. The increased gastric secretions introduce bile and alter intestinal pH, which may influence the bioavailability of a given compound.<sup>78</sup> The larger volume GI environment may influence dissolution by simply presenting more liquid to the drug as well as creating a solvent drag effect. For poorly soluble compounds, the higher levels of bile may allow for enhanced wetting

of the drug as well as increased micellar solubilization, both of which can increase the dissolution rate.<sup>79</sup>

Food constituents have been widely studied with the caloric make-up of various meals being evaluated in humans to determine the pharmacokinetic variations in response to ingestion of meals high in fiber, high in protein, high in carbohydrates, and high in fat. (e.g., studies with indinavir following high calorie protein, fat and carbohydrate meals.<sup>45</sup>) These examples, save for the high fat meal, are outside the scope of this review. Our predictions focus on the influences of high fat meals because, as recommended by the FDA in food-effect studies,<sup>3</sup> such meals are believed to produce maximum effect if any is to be observed.

Triglycerides are predominant in our fatty foods, and their digestion and absorption have been widely examined.<sup>80</sup> When fats reach the small intestines, fluid secretion increases with peak bile flow occurring about 30 minutes post meal. The fed state bile concentrations may increase to 10–20 mM from levels of the fasted state of 4–6 mM. Bile acids, their salts and lipases break down fats into monoglycerides and fatty acids that are capable of traversing the intestinal mucosal cell membrane. In addition, bile salts undergo aggregation into polymolecular micelles that, when emulsified with the breakdown products of lipid hydrolysis, increase in size, which results in improved solubilization capacity. Both bile salts and lipids have been reported to reduce the function of transporters.<sup>81,82,83</sup> Konishi and coworkers<sup>81,82</sup> have documented the increased cellular accumulation of P-gp substrates in the presence of various monoglycerides. Moreover, studies have reported the inhibitory effect of taurocholate on additional transporters.<sup>84</sup>

The fact that monoglycerides are a product of dietary triglyceride hydrolysis in the digestive tract, combined with the upregulation of bile salts during fatty meal digestion, suggests a trend in the observed variations in drug disposition. Examining the directional changes for the extent of availability in light of the predictions concerning the effects of transporters on drug bioavailability presented in the BDDCS, we hypothesize that drug-transporter interactions could be an important mechanism for the food effect in addition to the other mechanisms listed above in the FDA guidance.

#### 4.4. Predicting effects by BDDCS Class

The predicted effects of food on absorption by BDDCS class is summarized in Figure 6.

**4.4.1. Class 1 compounds**—High fat meals will have no significant effect on the extent of bioavailability for Class 1 compounds. Complete absorption would be expected for high solubility/high permeability compounds. Because the absorption process would be dominated by passive diffusion for Class 1 compounds, no significant transporter drug interactions would be expected. However, high fat meals may delay stomach emptying and therefore cause an increase in peak time.

**4.4.2. Class 2 compounds**—High fat meals will increase the extent of bioavailability for Class 2 compounds. This increased bioavailability with a concomitant high fat meal could be due to inhibition of efflux transporters, such as P-gp, in the intestine. Benet *et al.*<sup>85,86</sup> have reported that a dynamic interplay exists between P-gp and CYP3A4 demonstrating that P-gp efflux transport prolongs the exposure of drug to CYP3A4 by “cycling” the drug in and out of the cell. Therefore, inhibition of P-gp limits the “cycling,” reducing access of drug to the metabolizing enzyme. This mechanism is specifically relevant to compounds that are dual substrates of both enzyme and transporters, as is the case for Class 2 drugs. Hence, blocking the transporter decreases the amount of drug metabolized thereby increasing the bioavailability. Another mechanism that could be acting in concert with the transporter inhibition is increased solubilization of drug in the intestinal lumen (e.g. micelle formation). In addition to change in



exposure, 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.

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<sup>®</sup>) eliminates the food effects associated with the older olive oil formulation (Sandimmune<sup>®</sup>). In practice, drug formulators attempt to enable a Class 2 compound to function in the body as a Class 1 compound, thereby eliminating food effects on the extent of availability and other transporter-drug interactions.

**4.4.3. Class 3 and Class 4 compounds**—High fat meals will decrease the extent of availability for Class 3 compounds. Class 3 compounds could show lower extent of availability with high fat meals due to inhibition of uptake transporters in the intestine. Recent evidence suggests that intestinal drug uptake can be decreased by inhibiting organic anion transporting polypeptides (OATPs), as shown by the effect of fruit juices on fexofenadine<sup>87</sup> and glyburide.<sup>64</sup> As noted in Figure 5, Class 3 compounds will also be substrates for intestinal efflux transporters. Depending upon whether the meal effects are more pronounced on efflux or influx transporters for a Class 3 drug that is a substrate for both, an unexpected increase in the extent of bioavailability or no meal effect can be observed. Wu and Benet<sup>10</sup> hypothesized that this may be the explanation for the lack of a high fat meal effect on acyclovir and the slight increase observed with ganciclovir.<sup>88</sup> For Class 3 drugs, peak time would be expected to be increased by a high fat meal due to the combination of delayed stomach emptying and slower absorption.

For Class 4 compounds, it is difficult to predict what will occur, as all of the interacting effects mentioned for Class 2 and Class 3 compounds can be seen here. However, although not shown in Figure 6, if high fat meal effects are to occur, an increase of the extent of bioavailability is more likely, resulting from the combination of increased solubilization of drug in the intestine and inhibition of efflux transporters.

#### 4.5. Predicting effects by statistical modeling regression analysis

In addition to the Fleisher *et al.*<sup>14</sup> examination of food-drug effects based on the BCS and the Wu and Benet<sup>10</sup> examination based on the BDDCS, other groups have utilized a statistical modeling approach to predict the effect of food on drug absorption. Singh<sup>89</sup> applied Pearson's correlation test on a diverse set of drugs and concluded that partition coefficient, solubility and dose/solubility ratio are the most useful parameters in determining the dependence and correlation of the effect of food on absorption. Gu *et al.*<sup>90</sup> employed a logistic regression model to evaluate the relationship between the physiochemical properties of a given drug and the effect of food on AUC of that drug. Focusing on the physiochemical parameters of solubility and log D at pH 7, the polar and total surface areas, number of hydrogen bond donors and acceptors, and the clinical dose used in the published food effect study, the authors categorized 92 marketed drugs based on dose number and maximum allowable dose (MAD). These 92 drugs sufficiently cover all response groups (positive effect, negative effect and no effect) and were selected because of their previously assigned BCS Class and their known and documented response to high fat meals during clinical studies. Further subcategorizing the drugs into either  $MAD < \text{clinical dose}$  or  $MAD \geq \text{clinical dose}$ , Gu *et al.*<sup>90</sup> were able to apply their logistic regression model and concluded that the critical parameters for food effect prediction are solubility, permeability and dose, reinforcing the aforementioned beliefs of those such as Fleisher *et al.*<sup>14</sup> and Wu and Benet.<sup>10</sup> However, Gu *et al.*<sup>90</sup> also concluded that their statistical method provided a better food-effect prediction than that the BCS classification (80% vs. 67%). The authors successfully predicted 74 out of 92 drugs into the correct response category with

97% accuracy for positive effect, 79% accuracy for negative effect and 68% accuracy for no effect.

As is the case with any modeling, limitations exist. Lipinski's Rule of 5 was developed to set "drugability" guidelines for NMEs.<sup>91,92</sup> In the drug discovery setting, the Rule of 5 predicts that poor absorption or permeation is most 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<sup>91,92</sup> specifically states that the Rule of 5 only holds for compounds that are not substrates for active transporters. Likewise, in reference to their statistical approach, Gu *et al.*<sup>90</sup> state, "The current model also cannot predict food effect on the activity of a specific transporter responsible for the absorption of a particular compound as the current understanding of food effect on transporter is limited."

The inability of a logistic regression analysis to accurately predict a negative food effect for fexofenadine (model predicted no food effect)<sup>90</sup> is an example of the limitations inherent in statistical modeling. As suggested, the misprediction could be attributed to the high log D value of fexofenadine that is listed as 2.68 and is calculated using ACD/PhysChem Batch software. (It should be noted that a search through the literature reveals different calculated values reported by different investigators for log D and log P for the same compound.) However, as acknowledged above, transporter effects are not accounted for in such models and may be a cause for the erroneous prediction of fexofenadine, which is a known uptake transporter substrate. Fexofenadine is a BDDCS Class 3 drug, a class of compounds for which we believe transporters will play a significant role in oral drug absorption. Furthermore, for Class 3 drugs we predict a decrease in bioavailability due in part to transporter inhibition by high fat meals, which fits with the effect observed for fexofenadine *in vivo*.

Much work has been done to develop models to closely represent the upper GI tract that would mimic physiological media conditions of a fasted and a fed state as well as various other gastric and intestinal fluids.<sup>42</sup> These studies have been primarily applied to evaluating food effects on dissolution properties of various classes of drugs as well as various dosage forms (e.g. soft-gels versus hard gelatin capsules) and have demonstrated that simulated physiological fluids mimicking the fed state can increase the solubility of certain compounds.<sup>42,93,94</sup> Such studies have led to the potential explanation that changes in bioavailability are attributed to increased solubility.<sup>90</sup> While this finding may provide a reasonable explanation for the increase in bioavailability for many poorly soluble drugs, it does not explain the decrease in bioavailability frequently observed in BCS and BDDCS Class 3 drugs or the variability in bioavailability in food-effects for Class 4 drugs. Therefore, it is an inadequate and inappropriate generalization for the effect of food on absorption. It has also been postulated that components of high fat meals cause changes in bioavailability by impeding the access of drug to the epithelium surface of the intestinal enterocytes.<sup>1,90</sup> While this finding may provide a reasonable explanation for the decrease in bioavailability for Class 3 drugs, it does not explain the increase observed in Class 2 or the variability observed in Class 4 drugs. Taking efflux and influx transporters into account, however, may help elucidate the behavioral trends currently observed in the literature.

## 5. JUICE/FOOD/HERBAL EXTRACT EFFECTS

Considerable effort has been put into elucidating the effects of food on drug absorption and disposition. With very few exceptions, the mechanistic research representative of this effort has been retrospective in that first, an *in vivo* food effect is observed in a patient, followed by *in vitro* studies to determine the cause of that effect. Such is the scenario that led to the discovery of grapefruit juice's potent inhibition of metabolic function in the intestine.<sup>95</sup>

Regarding intestinal metabolism, metabolic food-drug interactions have been widely reported with Cytochrome P450 3A4 (CYP3A4) receiving considerable attention. This is not surprising

as numerous drug marketed worldwide are metabolized by CYP3A4. Documented examples include, but are not limited to, modulations in metabolism of drugs such as cyclosporine, felodipine, and indinavir affected by interactions with garlic, grapefruit juice, St John's wort, and red wine.<sup>2</sup> Except for the inducing effect of St. John's wort, these food constituents act as direct inhibitors or inactivators of CYP3A4.

The breadth of reports on food-enzyme interactions is in stark contrast to the more limited literature on food-transporter interactions. As mentioned earlier, however, new and improved tools are becoming available for discovering and investigating transporter substrates, which has facilitated the identification of transporter inhibitors and inducers. Thus, the publication rate on food-transporter interactions is increasing as a result.

### 5.1. Studies with fexofenadine

Fexofenadine, a Class 3 drug, has been shown to be a substrate for OATPs and P-glycoprotein. Dresser *et al.*<sup>87</sup> first described a decrease in the oral bioavailability of fexofenadine due to the inhibition of OATPs by fruit (orange, grapefruit and apple) juices. This research group noted the counterposing effects for Class 3 compounds such as fexofenadine.<sup>96,97</sup> That is, fexofenadine is a substrate for a gut uptake transporter, OATP, and a gut efflux transporter, P-glycoprotein,<sup>98</sup> but the fruit juice effects on uptake were more pronounced than they were on efflux,<sup>96,97</sup> therefore oral bioavailability is decreased. Kamath *et al.*<sup>99</sup> reported the counteractive effects of fruit juices on uptake and efflux with respect to the oral bioavailability of fexofenadine in rats.

### 5.2. Grapefruit juice effects

It is well known that grapefruit juice inhibits intestinal CYP3A4 and increases the bioavailability of many Class 1 and Class 2 compounds. However, with the recognition that grapefruit juice can also inhibit OATPs and P-glycoprotein, a number of studies have been carried out to investigate this potential interaction. No effect on the bioavailability of digoxin, a Class 4 BDDCS drug that is not a substrate for CYP3A4 in humans, was observed with concomitant grapefruit juice.<sup>100</sup> In contrast, grapefruit juice ingestion significantly reduced the bioavailability of talinolol, another Class 4 BDDCS drug, where the authors concluded that the effect of grapefruit juice on inhibition of uptake was more significant than for efflux.<sup>101</sup>

### 5.3. The effects of herbal extracts

More recently, attention has focused on the potential effects of constituents of herbal extracts in terms of transporter inhibition that could potentially affect bioavailability. A number of diverse substances including curcumin,<sup>102</sup> flavonoids,<sup>103</sup> extracts from bitter melon,<sup>81,82</sup> tea catechins,<sup>104</sup> cnicinidin<sup>105</sup> and alkyl gallates<sup>106</sup> have all been shown to be effective inhibitors of P-glycoprotein and thus could lead to increased bioavailability.

Most recently, Fuchikami *et al.*<sup>107</sup> demonstrated that many herbal extracts can inhibit human OATP2B1. They suggested that these inhibitory effects may be primarily attributable to flavonoids. Less work has been carried out with other transporters, but Tseng *et al.*<sup>108</sup> have shown that mustard oils can inhibit MRP1 mediated transport, while Wu and coworkers<sup>109</sup> have shown that plant phenols can inhibit MRPs 1, 4 and 5.

Thus, as seen above, it may be expected that food and herbal extracts can inhibit both uptake and efflux transporters in the intestine and the final result on drug bioavailability will be dependent on which is the more important component of absorption.

## 6. EFFECT OF LIPIDS

### 6.1. Influence of lipids

High fat meals, as recommended by the FDA in Food-Effect Bioavailability and Fed Bioequivalence Studies,<sup>3</sup> result in significantly higher levels of lipids than compared to a fasting state.<sup>110,111</sup> Persson *et al.*<sup>112</sup> employed the *in vivo* single-pass perfusion model in the proximal human jejunum to evaluate the GI response to meal and showed that the tri-, di-, monoglyceride and free fatty acid levels rapidly and markedly increased to 9.5 mM in response to food. Considerable attention has been focused not only on lipids resulting from food ingestion but also on lipids introduced to the GI tract from lipidic excipients, since enhanced bioavailability has been demonstrated for poorly water-soluble drugs when coadministered with a high fat meal or a lipid-based formulation to deliver the drug.<sup>113</sup> Increased lipid levels has also been shown to influence the pharmacokinetics of lipid soluble compounds that bind extensively to triglyceride-rich lipoproteins with effects being greater for more lipophilic compounds.<sup>114,115</sup>

Lipid based delivery systems<sup>116</sup> are an ever-growing segment of pharmaceuticals that primarily involves BDDCS Class 2 compounds, as the benefits provided by lipid formulations for BDDCS Class 4 drug are insufficient to overcome their poor permeability characteristics. With the goal of the lipid systems being to improve drug solubilization behavior, the formulation utilized depends on the aqueous solubility of the drug as well as the drug's solubility in lipids. This also holds true when high fat meals are coadministered with the goal of solubility enhancement, as exemplified in a study in which Mueller *et al.*<sup>117,118</sup> demonstrated that fat-rich meal effects are drug formulation dependent. Moreover, Kaukonen *et al.*<sup>119</sup> demonstrated that triglyceride (TG) lipid suspension formulations differentially affected various model, poorly soluble compounds, including griseofulvin, danazol and halofantrine, which had previously been shown to exhibit a significant high fat meal effect. The authors examined the effects of various TG formulations on griseofulvin, danazol, halofantrine and diazepam and cinnarizine observing that simple TG solutions offer better solubilization for the more lipophilic compounds while the TG suspensions better enhance the solubility of the less lipid-soluble drugs by increasing the solubilization capacity of the colloidal phase.<sup>118</sup> The colloidal phase is one example of the various phases that occur in the gastrointestinal tract resulting from the digestion of lipids that are ingested in formulations or food.<sup>79,120</sup> Accordingly, the role of these intermediate digestion phases, including the lamellar ( $L_{\alpha}$ ) liquid crystalline phase and the viscous cubic (C) phase in addition to the aqueous colloidal liquid ( $L_1$ ) phases, must also be taken into account.<sup>121,122</sup> Besides the influences on solubilization capacity and intermediate digestion phases, lipids have also been widely reported to influence lymphatic transport of drugs.<sup>116</sup> Again, however, these influences are only mentioned and cannot be adequately covered in this review, as our emphasis is lipidic effects on transporters, both efflux and influx, and predicting when such effects may play a significant role in altering drug availability.

### 6.2. Lipid effects on transporters

The fact that triglycerides are predominant in high fat meals is of particular relevance when considering the effect of lipids on the intestinal transporter function. As discussed in Section 4.3., triglycerides are hydrolyzed in the gut into monoglycerides and fatty acids that are capable of traversing the intestinal mucosa cell membrane. Konishi *et al.*<sup>81,82</sup> previously documented the inhibitory effect of monoglycerides on P-gp activity. The authors employed Caco-2 cells and the known P-gp substrates, rhodamine-123 and daunomycin and demonstrated that various monoglycerides and fatty acids were capable of inhibiting P-gp mediated efflux, thereby increasing the cellular accumulation of rhodamine-123 and daunomycin.<sup>81,82</sup>

The inhibitory effect of monoglycerides reported by Konishi *et al.*<sup>81,82</sup> is highlighted here since monoglycerides are found in lipid excipients. For example, Peceol<sup>®</sup>, an excipient used to enhance absorption of poorly water soluble compounds, is in fact, 2,3-dihydroxypropyl (Z)-octadec-9-enoate, also known as monoolein. Subramanian and Wasan<sup>123</sup> have suggested that Peceol<sup>®</sup> possesses inhibitory properties of P-gp. Following one week treatment of Caco-2 cells with Peceol<sup>®</sup> (0.25% v/v), the authors reported decreased MDR1 mRNA levels and decreased P-gp protein expression levels.<sup>124,125</sup>

An increased level of monoglycerides following high fat meal ingestion coincides with the upregulation of bile secretions from the gallbladder. As a result, increased levels of bile salts accompany high monoglycerides levels. In addition to the inhibitory effect of bile salt on uptake transport mentioned earlier, studies have shown effects on efflux transport as well. Ingels and coworkers<sup>83,126</sup> employed the bile salt, sodium taurocholate, and the known P-gp substrate, cyclosporine. The authors studied the changes in the apical to basolateral (A→B) flux and the basolateral to apical (B→A) flux across Caco-2 cell monolayers demonstrating that an increase in bile salts results in a decreased B→A flux and an increased A→B flux, amounting to a decrease in net flux ratio of ~16 (control buffer) to ~1 (control buffer plus 3 mM sodium taurocholate). A reduction of the net flux ratio to a level where A→B and B→A fluxes are nearly equivalent (i.e. ratio = 1) is consistent with inhibition of an efflux transporter such as a P-gp.

To further assess the effects of lipids on transporter function, we evaluated the bidirectional transport of vinblastine, a Class 2 drug, in MDCKI-MDR1 and control MDCKI cells grown on permeable filter supports evaluating basolateral to apical (B→A) and apical to basolateral (A→B) transport. Figure 7A depicts the bidirectional flux in MDCKI cells transfected with human MDR1. The B→A transport of vinblastine in this transfected cell is 26-fold higher than the A→B transport. When 300 μM monoolein was added to the transport buffer, B→A transport decreased and A→B transport increased so that the ratio in the presence of monoolein was only 2; a 92% decrease. In control MDCKI cells it can be seen that monoolein has no effect on the B→A and A→B transport fluxes (Fig. 7B). These results suggest a potentially important inhibitory effect of monoglycerides on drug bioavailability. This can be interpreted as suggesting that the monoglycerides, which appear as breakdown products from a high fat meal, may be responsible for the increased bioavailability of Class 2 compounds.

## 7. SUMMARY AND FUTURE PROSPECTS

The BCS, as developed by Amidon *et al.*,<sup>8</sup> has proven to be an asset to the FDA by creating a framework by which waivers of *in vivo* bioequivalence studies for suitable Class 1 compounds can be approved. However, the full predictive utility of a classification system may be realized and facilitated by the BDDCS, as developed by Wu and Benet,<sup>10</sup> as this system allows for concurrent consideration of the absorption / transport / elimination interplay thereby extending predictive application to food effects, specifically high fat meals. The majority of new molecular entities are highly permeable, poorly soluble, extensively metabolized compounds (BDDCS Class 2), and are vulnerable to food effects, as are the poorly permeable, poorly metabolized Class 3 and 4 compounds. Isolation and stable transfection of uptake transporter proteins has led to new tools that allow investigation of substrates for uptake transporters. This will allow for improved predictions of drug disposition as the various intestinal transporters responsible for the uptake of Class 3 and 4 drugs are identified and characterized. Advances in statistical regression modeling have reinforced the critical importance of solubility and permeability in predicting food effects. Yet we believe food effects cannot be predicated based on solubility and permeability alone. Knowledge and inclusion of a wider database of compounds into the BDDCS will assist in confirming current trends as well as identifying new trends. Benet and Oprea will soon publish such a compilation for more than 500 drugs.

Incorporating the vast information on the structural similarities of the drugs within a given class will also improve predictability. In combination with the knowledge of when transporters may play a significant role, we may be progressing towards an accepted system to predict drug absorption and the effect of food.

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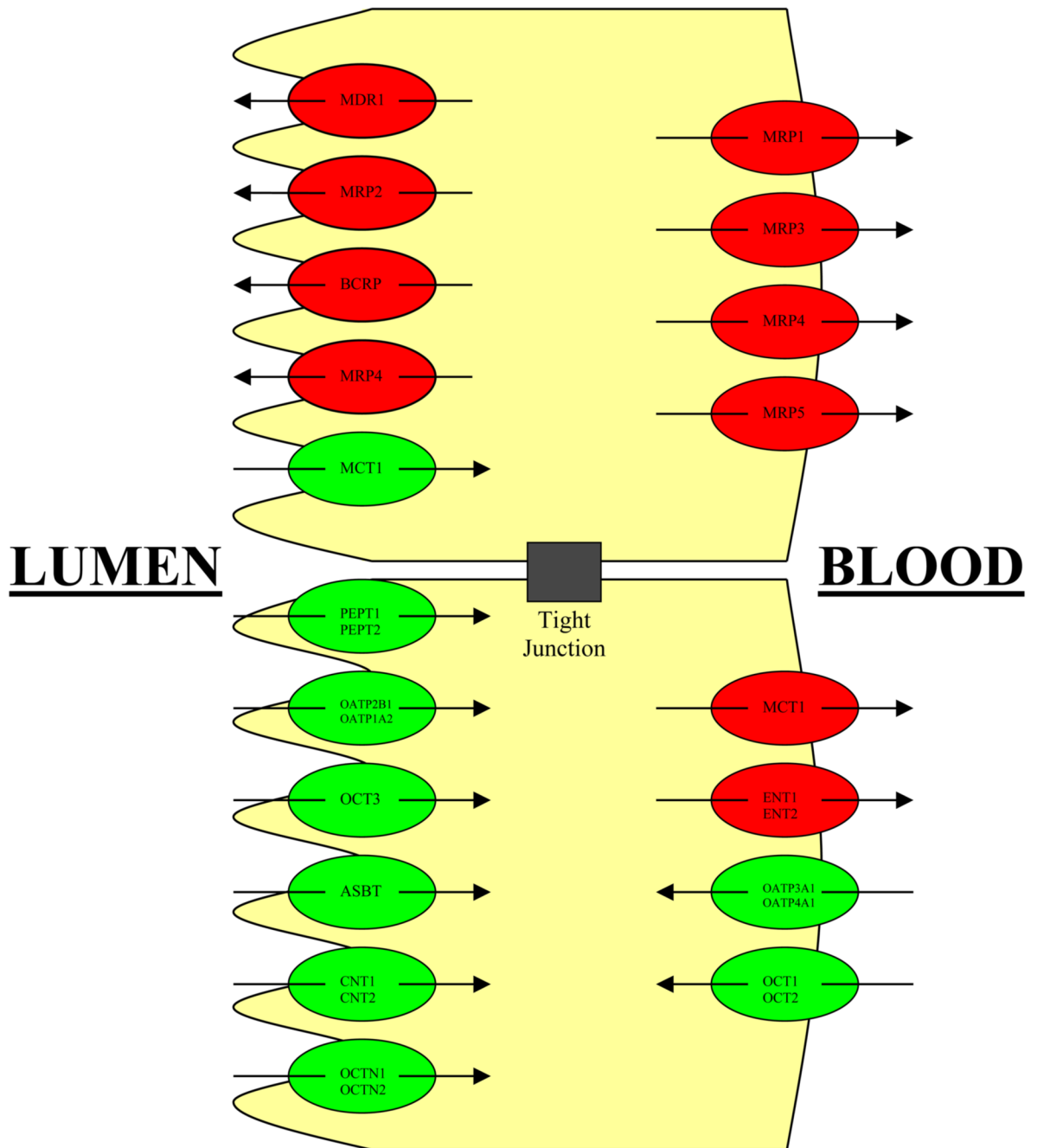
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	High Solubility	Low Solubility
High Permeability	<p><b><u>Class 1</u></b></p> <p>High Solubility High Permeability Rapid Dissolution</p>	<p><b><u>Class 2</u></b></p> <p>Low Solubility High Permeability</p>
Low Permeability	<p><b><u>Class 3</u></b></p> <p>High Solubility Low Permeability</p>	<p><b><u>Class 4</u></b></p> <p>Low Solubility Low Permeability</p>

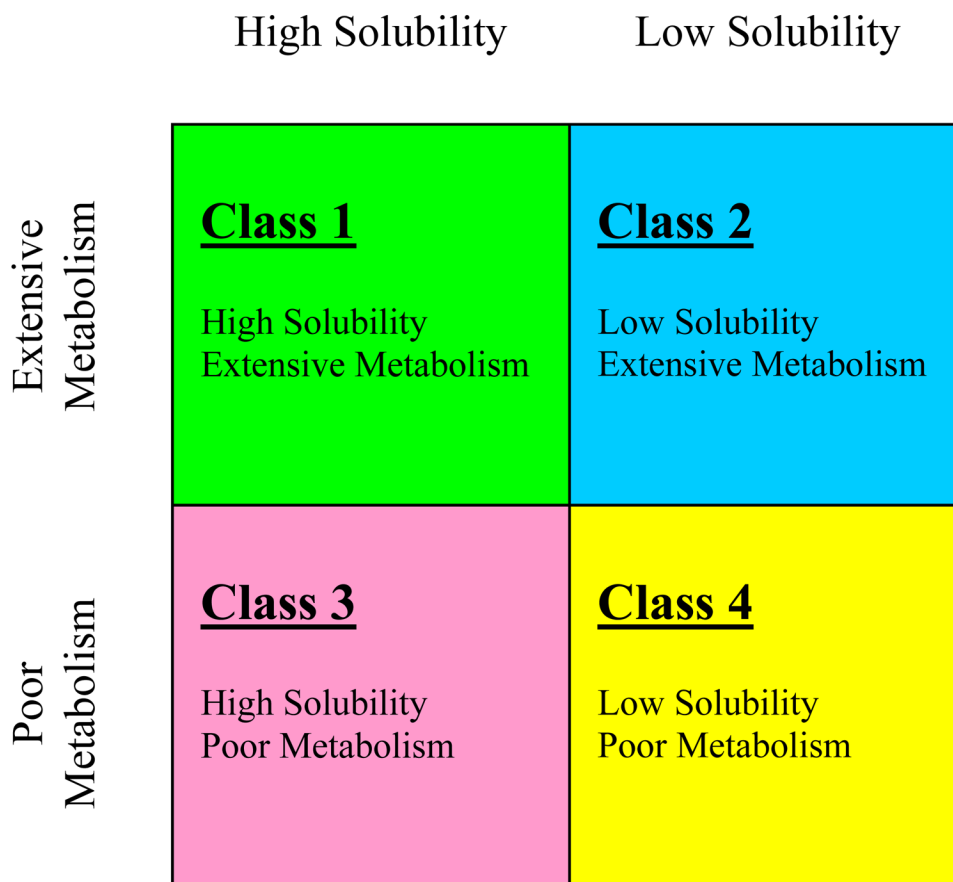
**Figure 1.**  
The Biopharmaceutics Classification System (BCS) as defined by the FDA<sup>9</sup> after Amidon *et al.*<sup>8</sup>



**Figure 2.** Various transporters, both efflux and absorptive, that are expressed in the gastrointestinal tract.

	High Solubility	Low Solubility
High Permeability	<b><u>Class 1</u></b> Metabolism	<b><u>Class 2</u></b> Metabolism
Low Permeability	<b><u>Class 3</u></b> Renal and/or Biliary Elimination of Unchanged Drug	<b><u>Class 4</u></b> Renal and/or Biliary Elimination of Unchanged Drug

**Figure 3.**  
Predominant routes of elimination by BCS class.



**Figure 4.**  
The Biopharmaceutics Drug Disposition Classification System (BDDCS) after Wu and Benet.  
10

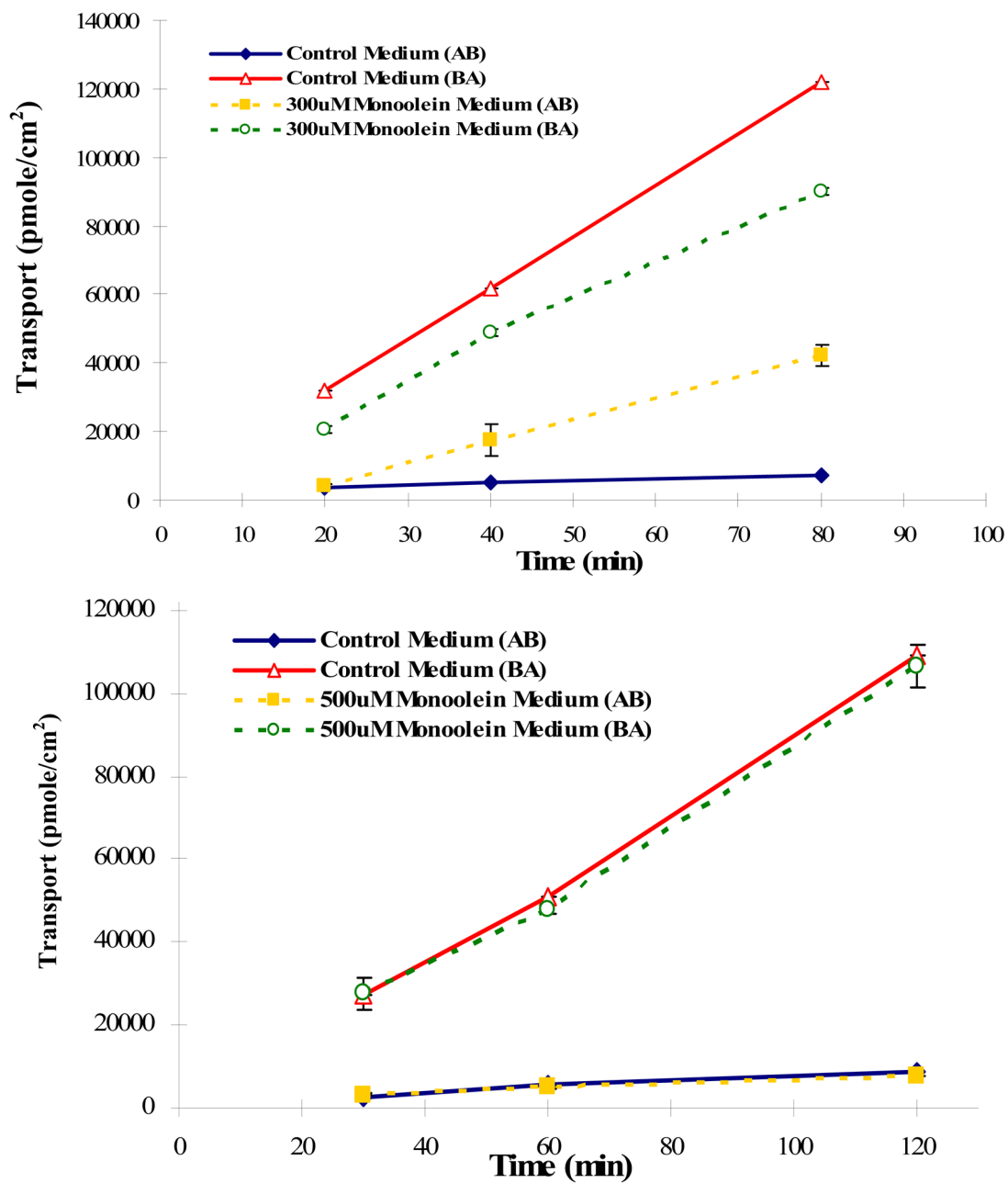


		High Solubility	Low Solubility
Metabolism	Extensive	<p><b><u>Class 1</u></b></p> <p>Transporter effects minimal</p>	<p><b><u>Class 2</u></b></p> <p>Efflux transporter effects predominate in the gut, while absorptive and efflux transporter effects occur in the liver</p>
	Poor	<p><b><u>Class 3</u></b></p> <p>Absorptive transporters effects predominate (but may be modulated by efflux transporters)</p>	<p><b><u>Class 4</u></b></p> <p>Absorptive and efflux transporters effects could be important</p>

**Figure 5.**  
Transporter effects, following oral dosing, by BDDCS class.

		High Solubility	Low Solubility
Extensive Metabolism	<b><u>Class 1</u></b>	$F_{\text{extent}} \leftrightarrow$ $T_{\text{max}} \uparrow$	<b><u>Class 2</u></b> $F_{\text{extent}} \uparrow$ $T_{\text{max}} \uparrow \downarrow \leftrightarrow$
	Poor Metabolism	<b><u>Class 3</u></b> $F_{\text{extent}} \downarrow$ $T_{\text{max}} \uparrow$	<b><u>Class 4</u></b> $F_{\text{extent}} \uparrow \downarrow \leftrightarrow$ $T_{\text{max}} \uparrow \downarrow \leftrightarrow$

**Figure 6.**  
Predicted high fat meal effects by BDDCS class.



**Figure 7.** Bidirectional transport of vinblastine in (A) MDCKI-MDR1 cells and (B) MDCKI cells in the presence and absence of 300 and 500  $\mu\text{M}$  monoolein added to both apical and basolateral compartments.

**Table I**

130 compounds categorized by BCS Class.

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

**Table II**

168 compounds categorized by BDDCS Class.

	<b>High Solubility</b>		<b>Low Solubility</b>		
<b>Extensive Metabolism</b>	<b>Class 1</b>		<b>Class 2</b>		
	Abacavir	Ketoprofen	Albendazole	Ketoconazole	
	Acetaminophen	Ketorolac	Amiodarone	Lansoprazole	
	Albuterol	Labetolol	Atorvastatin	Lopinavir	
	Allopurinol	Levamisole	Azathioprine	Lovastatin	
	Amitypyline	Levodopa	Azithromycin	Mebendazole	
	Antipyrine	Lidocaine	Carbamazepine	Mefloquin	
	Buspirone	Meperidine	Carvedilol	Nalidixic acid	
	Caffeine	Metoprolol	Chlorpromazine	Naproxen	
	Chloramphenicol	Metronidazole	Cisapride	Nelfinavir	
	Chlorpheniramine	Midazolam	Clofazamine	Nevirapine	
	Codeine	Minocycline	Cyclosporine	Nifedipine	
	Colchicine	Misoprostol	Danazol	Oxaprozin	
	Cyclophosphamide	Morphine	Dapsone	Phenytoin	
	Desipramine	Phenobarbital	Diclofenac	Piroxicam	
	Dexamethasone	Phenylalanine	Diflunisal	Praziquantel	
	Diazepam	Prednisolone	Efavirenz	Raloxifene	
	Diltiazem	Primaquine	Flurbiprofen	Rifampin	
	Diphenhydramine	Promazine	Glipizide	Ritonavir	
	Disopyramide	Promethazine	Glyburide	Saquinavir	
	Doxepin	Propranolol	Griseofulvin	Sirolimus	
	Enalapril	Pyranzinamide	Haloperidol	Spirolactone	
	Ergonovine	Quinidine	Ibuprofen	Sulfamethoxazole	
	Ergotamine	Quinine	Indinavir	Tacrolimus	
	Ethinyl estradiol	Rosiglitazone	Indomethacin	Tamoxifen	
	Fluoxetine	Salicylic acid	Itraconazole	Terfenadine	
	Glucose	Theophylline	Ivermectin	Warfarin	
	Hydralazine	Valproic acid			
	Imipramine	Verapamil			
	Isoniazid	Zidovudine			
	Isosorbid dinitrate				
	<b>Poor Metabolism</b>	<b>Class 3</b>		<b>Class 4</b>	
		Acyclovir	Ganciclovir	Acetazolamide	
Amiloride		Hydrochlorothiazide	Aluminum hydroxide		
Amoxicillin		Lamivudine	Amphotericin		
Atenolol		Levofloxacin	Chlorothiazide		
Atropine		Lisinopril	Chlorthalidone		
Bidisomide		Lithium	Ciprofloxacin		
Bisphosphonates		Lomefloxacin	Colistin		
Captopril		Metformin	Digoxin		
Cefazolin		Methotrexate	Furosemide		
Cetirizine		Metoclopramide	Neomycin		
Chloroquine		Nadolol	Nystatin		
Cimetidine		Neostigmine	Ofloxacin		
Cloxacillin		Penicillins	Phenazopyridine		
Dicloxacillin		Pravastatin	Talinolol		
Doxycycline		Pyridostigmine			
Ephedrine		Ranitidine			
Erythromycin		Riboflavin			
Ethambutol		Tetracycline			
Famotidine		Trimethoprim			
Fexofenadine		Valsartan			
Fluconazole		Zalcitabine			
Folinic acid					