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Solubility-Permeability Interplay in Facilitating the Prediction of Drug Disposition Routes, Extent of Absorption, Food Effects, Brain Penetration and Drug Induced Liver Injury Potential

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Abstract

Here I detail the use of measures of permeability rate and solubility in predicting drug disposition characteristics through the utilization of the Biopharmaceutics Drug Disposition Classification System (BDDCS) and the Extended Clearance Classification System (ECCS) as well as the accuracy of the systems in predicting the major route of elimination and the extent of oral absorption of a new small molecule therapeutics. I compare the BDDCS and ECCS with the FDA Biopharmaceutics Classification System (BCS). I also detail the use of the BCS in predicting food effects and the BDDCS in predicting brain disposition of small molecule therapeutics and in validating DILI predictive metrics. This review provides an update of the current status of these classification systems and their uses in the drug development process.

Keywords

permeability rate; solubility; BDDCS; ECCS; BCS; food effects; brain penetration; DILI

Introduction

In 2005, Wu and Benet[1] first proposed that measures of the rate of membrane permeability could predict whether the major route of drug elimination in humans was via metabolism or via renal and/or biliary excretion of unchanged drug. This recognition was based on observations of drugs classified following the FDA biopharmaceutics classification system, BCS[2], where high permeability BCS Class 1 and 2 compounds were primarily eliminated by metabolism and low permeability BCS Class 3 and 4 compounds were primarily eliminated unchanged. However, the permeability criteria for the Wu and Benet[1] biopharmaceutics drug disposition classification system ,BDDCS, is rate of permeability, while the permeability criteria for BCS is extent of permeability[2]. Since 2005, our laboratory has classified 1475 drugs in terms of BDDCS criteria[3–5] as follows (with the most recent compilation[5] updating

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Declaration of Competing Interest

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some previous assignments): BDDCS Class 1: ≤ 30 % excreted unchanged, lowest drug water solubility over the pH range 1–6.8 > 0.44 mg/ml; BDDCS Class 2: ≤ 30 % excreted unchanged, lowest drug water solubility over the pH range 1–6.8 ≤ 0.44 mg/ml; BDDCS Class 3: > 30 % excreted unchanged, lowest drug water solubility over the pH range 1–6.8 > 0.44 mg/ml; BDDCS Class 4: > 30 % excreted unchanged, lowest drug water solubility over the pH range 1–6.8 ≤ 0.44 mg/ml.

BDDCS vs BCS

As mentioned above, Wu and Benet[1] developed BDDCS based initially on observed BCS characteristics. The BCS, as originally proposed by Amidon et al.[6], was developed in an attempt to reduce the regulatory burden of carrying out in vivo human studies to obtain regulatory approval and development of new formulations of immediate-release drug products. Drugs are classified in the BCS on the basis of the extent of intestinal permeability and the solubility of the amount of active drug present in the approved product[2]. However, the purpose of BDDCS was to aid in the prediction of drug disposition characteristics of a new molecular entity (NME) prior to dosing the drug to animals or humans. Therefore, there are important differences in the characteristics measured. The first, as initially recognized by Wu and Benet[1], was that the rate of intestinal permeability vs the extent of permeability should be the defining parameter for BDDCS to predict elimination characteristics, with rapid permeability rate favoring metabolism and poor permeability rate favoring excretion of unchanged drug.

One may ask, why should intestinal permeability rate predict the extent of metabolism. Importantly, we recognized that the permeability rate in any relevant membrane such as a Caco-2 cell line or even a nonbiologic PAMPA[7] would provide a reasonable estimate of the extent of metabolism. Certainly, all lipophilic drugs should partition to some extent into the kidney lumen or into the bile. But then high permeability rate compounds will be readily reabsorbed from the kidney lumen and from the bile facilitating multiple access to the metabolic enzymes. In essence the only way the body can eliminate these compounds is via metabolism. This explains why drugs with quite low hepatic clearance are still completely eliminated by metabolism. For example, diazepam with a drug clearance of 0.38 ml/min/kg and hepatic extraction ratio of 0.018, less than 1% of the dose is excreted unchanged in the urine[8]. Even with its high protein binding (1.3% unbound), some unchanged drug would be excreted in the kidney tubule, but as fluid is reabsorbed from the kidney tubule (glomerular filtration rate 120 ml/min but urine flow approximately 1 ml/min), a concentration gradient, tubular urine to plasma, is established and a high permeability compound is readily reabsorbed. For the drug to be excreted in the urine it must become more polar, less permeable and this is accomplished via metabolism. In contrast, for low permeability BDDCS Class 3 and 4 drugs, they are not reabsorbed significantly even with large tubular to plasma concentration ratios and are extensively eliminated unchanged.

Although we examined the ability of in vitro permeability measures for 23 drugs from 4 different laboratories utilizing a Caco-2 membrane and 35 drugs using 4 different PAMPA measurements to successfully predict the extent of metabolism[7], we set no definitive measurement for a large number of compounds. This was accomplished in the following

year, when Pfizer scientists examined the ability of Madin-Darby canine kidney cells, selected for low endogenous efflux transport expression, to predict extensive versus poor metabolism using a cut-off of 5×10^{-6} cm/s for permeability classification[9], which they applied to 307 drugs.

A second distinguishing characteristic between BDDCS and BCS is the solubility determination. The BCS criteria is based on the solubility of the amount of drug in the highest approved regulatory dose, but BDDCS is attempting to make predictions before that dose is known and even before the drug is administered to animals and humans. Based on our earlier BDDCS classification[3] where solubility data were available for approximately 600 drugs, Dave and Morris[9] proposed that a solubility cut-off of 0.30 mg/ml over the pH range 1.0–6.8 would adequately predict high vs low solubility for the FDA criteria. With our more recent drug classification[5] where solubility data are available for 1156 drugs, we have slightly increased the cut-off to 0.44 mg/ml.

It is important to recognize that when trying to make drug disposition predictions for new molecular entities, one should use BDDCS criteria, not BCS classification. Bocci et al.[5] could identify 191 drugs for which published BDDCS and BCS classifications were available. The class correspondence was only 68%. The best correspondence was for Class 2, 81%, then Class 1, 69%, and Class 3, 64%, but for the 17 Class 4 drugs the correspondence was only 23%. Some of this discordance results from the difference in the permeability criteria, extent of permeability for BCS and rate of permeability for BDDCS. For example, high solubility pregabalin has a Caco-2 monolayer permeability rate[11] that is slightly less than mannitol, a compound used to test the leakiness of intact membranes, so it is a BDDCS Class 3 drug. Yet, it is essentially very slowly but completely (90%) absorbed making it a BCS Class 1 drug[12]. But an even more prevalent reason for the discordance is that BCS permeability is based on the extent of absorption following an oral dose, a much more difficult parameter to determine than the extent of metabolism, especially when intravenous dosing data in humans are not available, a condition found for the majority of orally dosed drugs.

Drug Disposition Predictions Based on BDDCS

As described above, based on the rate of permeability measurement of an NME, one can quite reasonably predict whether the major route of elimination will be metabolism versus renal and/or biliary elimination of unchanged drug. Wu and Benet[1] reported that the extent of metabolism (EoM) for the vast majority of approved drugs were either EoM ≥ 70 or ≤ 30%, quite easily separating BDDCS Classes 1 and 2 drugs from Classes 3 and 4 drugs. They also reasoned that poor passive permeability drugs (BDDCS Classes 3 and 4) would require transporters to achieve membrane permeability, but that transporters may not significantly affect drug disposition for high permeability rate compounds, especially for highly soluble BDDCS Class 1 drugs, where high concentrations of compounds would be available for passive diffusion, potentially swamping out the ability to demonstrate the presence of any active transporter processes. In contrast, although the high permeability rate BDDCS Class 2 drugs are primarily eliminated by metabolism, transporter processes may or may not be clinically relevant in drug disposition, since the lower available concentration of

the BDDCS Class 2 drugs resulting from their lower solubility characteristics would not lead to passive permeability swamping out the active transport processes.

As depicted in Fig. 1, as summarized by Shugarts and Benet[13], most BDDCS Class 1 drugs do not exhibit clinically significant transporter effects in the liver and kidney due to the significant passive permeability masking any potential active processes as explained above. In contrast, BDDCS Classes 3 and 4 drugs are likely to show clinically significant transported effects in the liver and intestine due to their poor membrane permeability. BDDCS Class 2 drugs, although predominantly eliminated by metabolism, can potentially show both uptake and efflux transporter effects in the liver, but only efflux transporter effects in the intestine.

ECCS vs BDDCS

Varma and Pfizer coworkers[9] expanded the BDDCS findings to address liver and kidney clearance predictions only through their Extended Clearance Classification System (ECCS), which incorporated differentiation based on the molecular weight and charge status of the substrate and redefined the 4 classes. High and low permeability acids plus zwitterions were designated Classes 1 and 3, respectively, and these classes were subdivided as A for acids and zwitterions with molecular weights < 400 Da and B for acids and zwitterions with molecular weights ≥ 400 Da. Classes 2 and 4 comprised both high and low permeability, respectively, basic plus neutral compounds. The major predictions of ECCS are a) clearance of high molecular (≥ 400 Da) acids and zwitterions (ECCS Classes 1B and 3B) will be rate limited by hepatic organic ion transporter polypeptide (OATP) uptake. Although hepatic uptake will be the rate limiting step for clearance of these acids and zwitterions, high versus low permeability will dictate the major route of elimination (i.e., metabolism for ECCS Class 1B and renal elimination for ECCS Class 3B); b) high permeability acids and zwitterions (ECCS Classes 1A and 1B) will not be appreciably metabolized by CYP3A, therefore F_G (the fraction of the absorbed oral drug not metabolized in the intestinal membranes) will be close to 1.0; c) basic and neutral BDDCS Classes 1 and 2 compounds (ECCS Class 2 drugs) will be metabolized in rank order by CYP3A4 > UGTs > CYP2D6 > esterases and CYP2C enzymes; d) low permeability, low molecular weight (< 400 Da) acids and zwitterions (ECCS Class 3A) will be eliminated renally; e) low permeability bases and neutral compounds (ECCS Class 4) will be eliminated renally. More recently, Pfizer scientists[14] have proposed that clearance of ECCS Class 1A may be rate limited by organic anion transporter 2 (OAT 2) uptake, although the clinical relevance of this finding is not confirmed.

The Potential Accuracy of the ECCS and BDDCS Predictions and Application to BCS

One would not expect relatively simple four category systems such as ECCS and BDDCS to provide 100% accurate predictions, but the quality of the predictions is quite remarkable. An evaluation is possible by examining the 363 compounds that Pfizer scientists investigated in presenting the ECCS[15]. In their initial 2015 paper[9], Pfizer scientists reported “the proposed scheme correctly predicted the rate-determining clearance mechanism to be either

metabolism, hepatic uptake or renal for ~92% of total compounds", but I present here our analysis in Table 1 of the more detailed data presented the subsequent year[15].

Permeability Rate Predictability of Metabolism versus Excretion of Unchanged Drug

As can be seen in Table 1, measure of the permeability rate accurately predicts elimination by metabolism versus elimination of unchanged drug being the major route with 90% accuracy for the 363 drugs tabulated by El Kattan et al.[15] Predictability is best for neutral and basic metabolized drugs (ECCS Class 2; 95%) and low molecular weight acids excreted unchanged (ECCS Class 3A; 96%), while predictability is poorest for high molecular weight acids (ECCS Class 1B; 62%). An important advance of ECCS[9, 14] was the identification of rate limiting hepatic uptake of high molecular weight acids that are substrates for OATPs, but this was only observed for 63% of the high permeability acids (ECCS Class 1B) and was also seen for 28% of the low permeability acids (ECCS Class 3B), presumably via rate limiting biliary excretion, but without supporting documentation. As the ratios of the total number of Class 3 and 4 drugs to the total number investigated in the ECCS[15] and the BDDCS[5] are almost exactly the same (approx. 29%), we would expect about 90% predictability for both systems in estimating metabolism or excretion of unchanged drug being the major route of elimination. Thus, permeability rate is probably one of the best in vitro predictors of in vivo drug disposition available to the scientific community.

We have also shown that this excellent permeability predictability of the major route of elimination holds equally well for both drugable and non-drugable compounds[16]. BDDCS builds upon the Rule of 5 and can quite successfully predict drug disposition characteristics for drugs both meeting and not meeting Rule of 5 criteria[16].

Absorption Extent Predictability

Of the drugs evaluated by El-Kattan et al.[15], information was available concerning the extent of absorption for 201 compounds. Of these, 138 were high permeability rate compounds and 97.1% exhibited $F_{abs} \geq 70\%$. Of course, this is the basis for BCS, that is, high permeability rate compounds will exhibit high permeability extent. But what about the inverse, does low permeability rate predict low extent of absorption? Not very well, for the 63 low permeability rate compounds, 52.4% exhibit $F_{abs} \geq 70\%$. This reflects the discontinuity between BDDCS and BCS discussed previously. BDDCS and ECCS classification must be used to predict drug disposition characteristics, not BCS classification. However, the data above provide justification for a potential expansion of BCS to include Class 2 drugs, since good absorption is expected as long as the drug is solubilized.

Solubility Class Prediction for BDDCS and BCS

BDDCS requires one to be able to predict FDA solubility (based on the lowest solubility of the highest regulatory approved dose in 250 ml of water over the pH range 1–6.8) prior to knowing the dose. As noted above, Dave and Morris[10] estimated that solubility could be predicted using a cut-off 0.30 mg/ml based on the approximately 600 drugs for which solubility was known as published by Benet et al.[3] With the expansion of the BDDCS data base to 1475 compounds, Bocci et al.[5] found that 0.44 mg/ml provided a slightly better cutoff. Table 2, taken from that work, summarizes the number of correctly and incorrectly

classified drugs using the 0.44 mg/ml cutoff prior to knowing the highest approved dose. Overall, the prediction accuracy using the 0.44 mg/ml cutoff is 89%. This is only slightly higher than the overall predictability (87%) using the previously proposed 0.30 mg/ml cutoff. Bocci et al.[5] note that all 37 of the classes 2 and 4 incorrectly predicted drugs in Table 2 are dosed in high quantities (≥ 150 mg), while 64 of 88 incorrectly predicted class 1 and 3 drugs are dosed at low quantities (≤ 10 mg). Since BDDCS and BCS use the same solubility differentiator, the 0.44 mg/ml cutoff can also be used as an early predictor for BCS solubility with about 89% accuracy.

Overall BDDCS, ECCS and BCS Predictability

Thus, using an in vitro measure of membrane permeability rate to differentiate BDDCS Classes 1 and 2 from 3 and 4, and using the 0.44 mg/ml solubility cutoff to differentiate BDDCS Classes 1 and 3 from 2 and 4, it is possible to assign a BDDCS classification to an NME before ever dosing the drug to animals and humans with about 85% accuracy for small molecules. This is slightly lower than the 90% predictability of ECCS to predict elimination characteristics as noted in Table 1. However, as noted subsequently, BDDCS provides a number of other predictions beyond elimination characteristics. In contrast, using membrane permeability rate and a 0.44 mg/ml solubility cutoff to predict BCS class is only accurate to about 68% and should not be used, since there are regulatory implications to BCS class assignment.

BBDCS Predictions Beyond Elimination Characteristics

We have demonstrated that permeability rate-solubility interplay may provide a number of useful predictions beyond drug elimination characteristics that can be made using BDDCS criteria prior to dosing a drug to animals and humans as summarized here.

Predicting Food Effects

All approved drug products are required to be studied to determine the effects of high-fat meals on the bioavailability of the dosage form, with this information included in the drug label[17]. Fleisher et al.[18], in 1999, summarized published studies examining the effects of high-fat meals as summarized in Fig. 2 adapted from Custodio et al.[19] Meals usually slow down stomach emptying resulting in the peak time (T_{peak}) increasing with highly soluble class 1 and 3 drugs and for most of class 2 drugs. Due to the small number of class 4 drugs, no conclusion can be reached. Clear differentiation is seen in the extent of bioavailability (F_{extent}) for BCS Classes 1, 2 and 3 drugs. As shown in Fig. 2, in general high-fat meals have little effect of F_{extent} for BCS Class 1 drugs; high-fat meals increase F_{extent} for BCS Class 2 drugs and decrease F_{extent} for BCS Class 3 drugs; again, there is not enough data to make a conclusion for BCS Class 4 drugs. It is difficult to explain the basis for these findings as food effects and drug absorption are complicated processes. One could suggest that this is a solubilization outcome and that high-fat meals increase the solubility of poorly soluble drugs (Class 2), and that the fat addition decreases the solubility of highly soluble drugs (Class 3), but then why is there no effect on the highly soluble Class 1 drugs? Custodio et al.[19] speculated that the effects were consistent with high-fat meals inhibiting intestinal efflux transporters consistent with the relevance of these transporters as

given in Fig. 1. But we conclude that the outcome only appears to be predictive for about 70% of food effect studies[3]. However, as reviewed by Bocci et al.[5], a number of recently published unsuccessful attempts to predict food effects by FDA scientists including the use of physiologic based pharmacokinetic (PBPK) models[20, 21] were carried out for drugs where, in contrast, the general predictions of Fig. 2 were consistent with the clinical results.

Since the food effect outcome is an extent measure, we believe now that it may be more appropriate to utilize BCS class, rather than BDDCS class, in making the prediction. In addition, food effect studies will not be relevant until the effective human dose is known, so the BCS class may be determined. The difficulty relates to the quandary that unless an iv human dose is given it can be difficult to know the extent of absorption. Can the food effect be reasonably predicted? Not with any certainly, which could eliminate the need for human studies as per the FDA Guidance[17]. The field is a long way from predicting food effects quantitatively, and PKPD approaches appear even poorer than just using the Fig. 2 summary, and we recommend that regulatory agencies continue to require such studies. However, animal studies of food effects are just a waste of time and money, providing no better predictions than BCS based on Table 2.

Predicting Brain Disposition

Broccatelli et al.[22] investigated 153 drugs that met three criteria: a) the presence or absence of central human pharmacodynamic effects was known; b) the drug's permeability rate/metabolism and BDDCS class had been determined; and c) experimental in vitro results were available as to whether the drug was or was not a substrate for P-glycoprotein (P-pg, ABCB1), since it is recognized that P-gp is an effective efflux transporter in the brain preventing brain accumulation and central effects of such substrates[23]. The authors reported that 17 of the 153 drugs were high permeability rate-high solubility BDDCS Class 1 compounds that exhibited P-gp efflux in vitro. However, all 17 of these P-gp substrates, including sertraline, verapamil and zolmitriptan, exhibit central pharmacodynamic effects. This supports the conclusion for BDDCS Class 1 shown in Fig. 1 that transporters are clinically insignificant for such drugs, and that this also holds for other membranes than the liver and intestine, including the brain. The important implication of these results in drug development is that BDDCS Class 1 compounds are likely to be brain permeable and achieve pharmacodynamically relevant concentrations, whether this is desired or not. Generally, one might think that from a physical chemical perspective, drug sponsors would prefer Class 1 compounds, however, this is not true if central drug effects are not desired. Our lab has shown that almost all antidepressants[24] and antihypertensives[25] are BDDCS Class 1 drugs.

Using BDDCS to Validate DILI Predictive Metrics

Drug induced liver injury (DILI) is the leading cause of drug failure in clinical trials and a major reason for drug withdrawals from the market. Idiosyncratic DILI is very complex; several mechanisms appear to induce autoimmune response, reactive metabolites are believed to be involved in most idiosyncratic DILI, and DILI is dependent on both dose and extent of metabolism. A multitude of toxicology efforts attempt to develop methodologies to predict DILI for an NME that are complex and very time-consuming.

However, we found that in general these methodologies often do no better than just avoiding BDDCS class 2 compounds[26, 27]. As seen in Fig. 3, more and more drugs fall within BDDCS Class 2 with increasingly severe hepatic liability. In our analysis, none of the DILI predictive metrics, except keeping daily dose < 50 mg, provides any better prediction of DILI than just avoiding BDDCS Class 2 drugs.

Our papers[26, 27] explicitly state that BDDCS classification should not be used as a DILI predictive metric. However, we emphasize that if a new DILI predictive metric cannot be differentiated from avoiding BDDCS Class 2 drugs, there can be no confidence in the metric and the toxicity hypotheses implied. Since toxicologists are not familiar with BDDCS or BCS, they generally ignore our recommendations, spending considerable resources developing metrics that most often cannot be differentiated from this simple avoidance of BDDCS Class 2 compounds. However, recently Brecklinghaus et al.[28], summarizing collaborative efforts of several academic and industry European and Mid-East toxicology groups, recognized these observations and wrote “In future, it will be important to study if readouts from in vitro tests e.g., cytotoxicity, carrier inhibition, gene expression alterations, reactive metabolite formation etc. will improve DILI prediction independent from BDDCS class. For this purpose, large sets of compounds (> 100) with sufficient substances from all four BDDCS will be required.”

Conclusions

Here I detail the use of measures of permeability rate and solubility in predicting drug disposition characteristics through the utilization of the Biopharmaceutics Drug Disposition Classification and Extended Clearance Classification Systems and the accuracy of the systems in predicting the major route of elimination and the extent of oral absorption of a new small molecule therapeutic. I compared the BDDCS and ECCS with the FDA Biopharmaceutics Classification System. I also detailed the use of the BCS in predicting food effects and the BDDCS in predicting brain disposition of small molecule therapeutics and in validating DILI predictive metrics. This review provides an update of the current status of these classification systems and their uses in the drug development process. One may ask in this era of big data and artificial intelligence (AI) whether there will be continued interest in classification systems such as BDDCS and ECCS? However, since the classification systems are so easy to use, with documented positive outcomes for the predictions as presented here, until documentation shows that big data and AI usefulness is more precise, I anticipate that these classification systems will not disappear.

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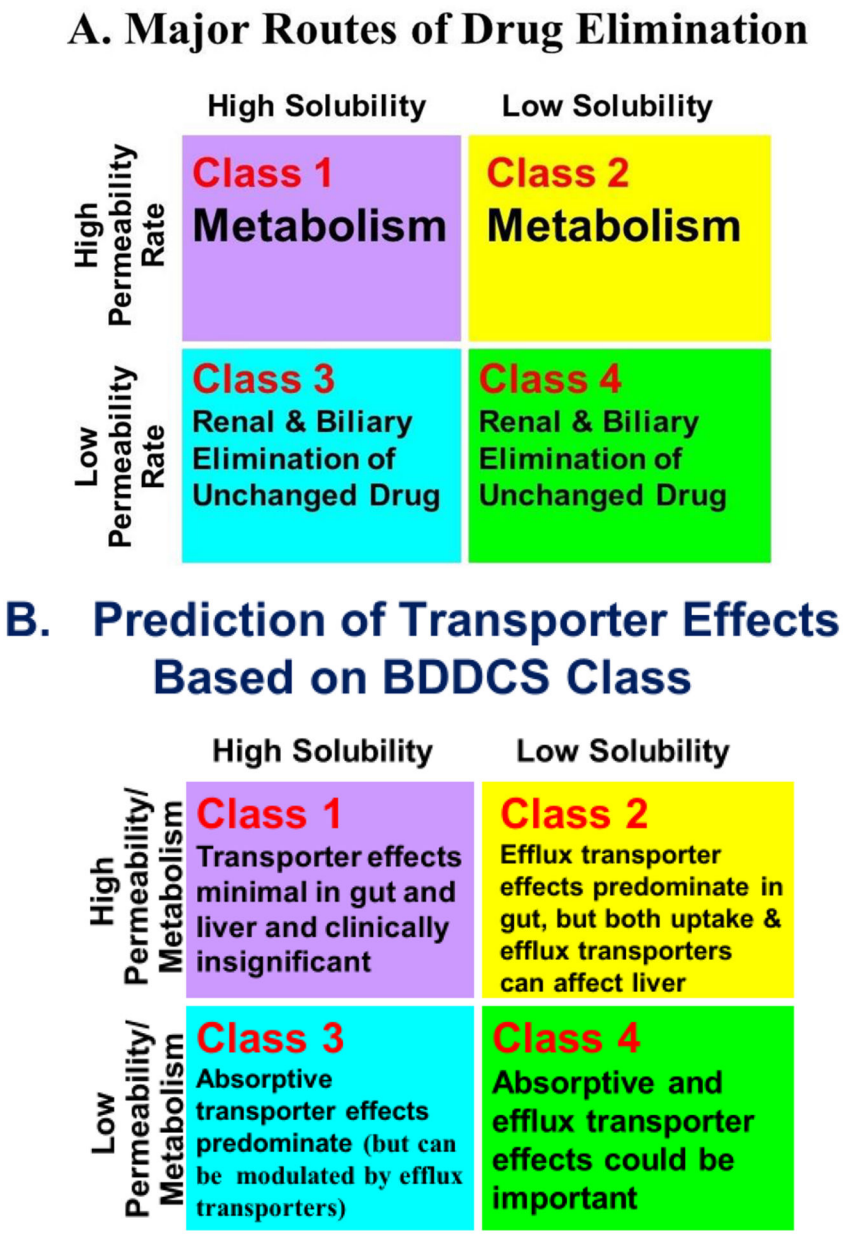

Figure 1.

Based on BDDCS: A. Prediction of major route of drug elimination; B. Prediction of transporter effects as adapted from Shugarts and Benet[12]

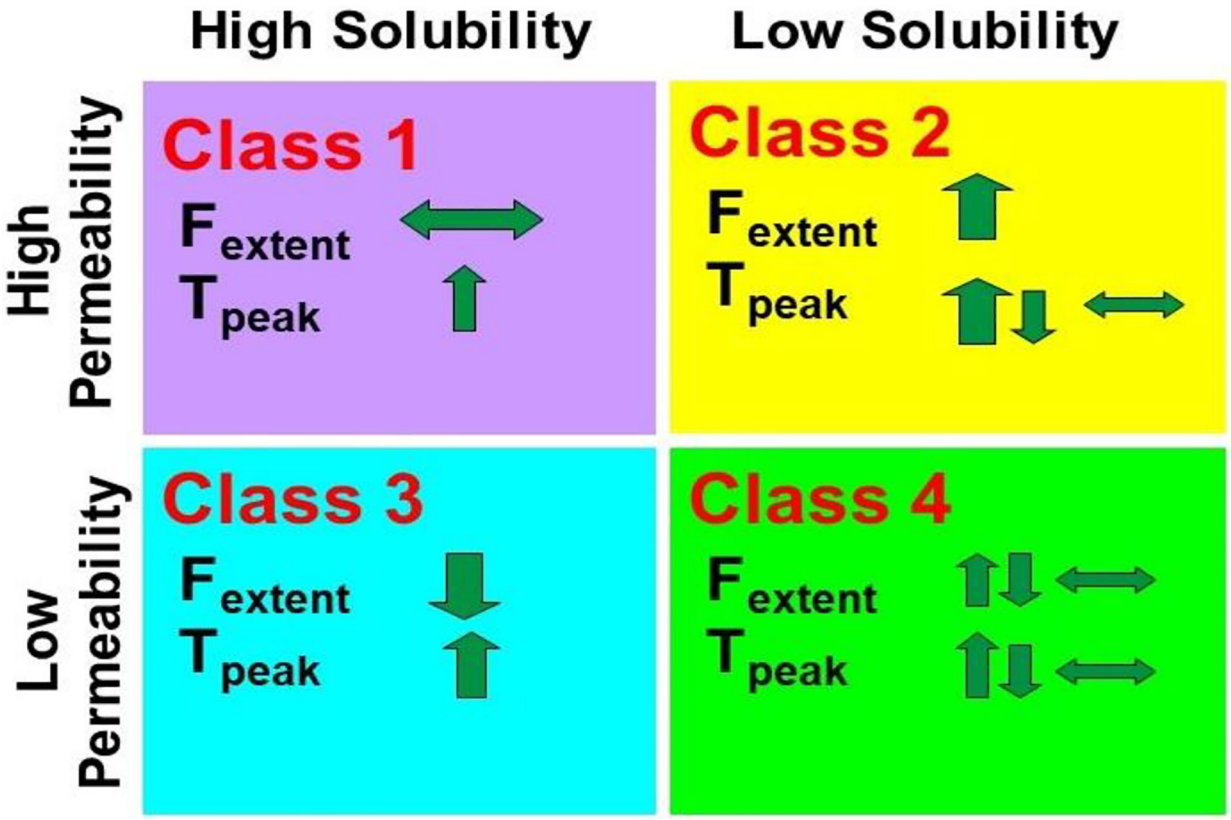

Figure 2.
Summary of the effects of high-fat meals on the extent of bioavailability (F_{extent}) and peak time (T_{peak}) for BCS drugs as presented by Fleischer et al.[17] as adapted from Custodio et al.[18]

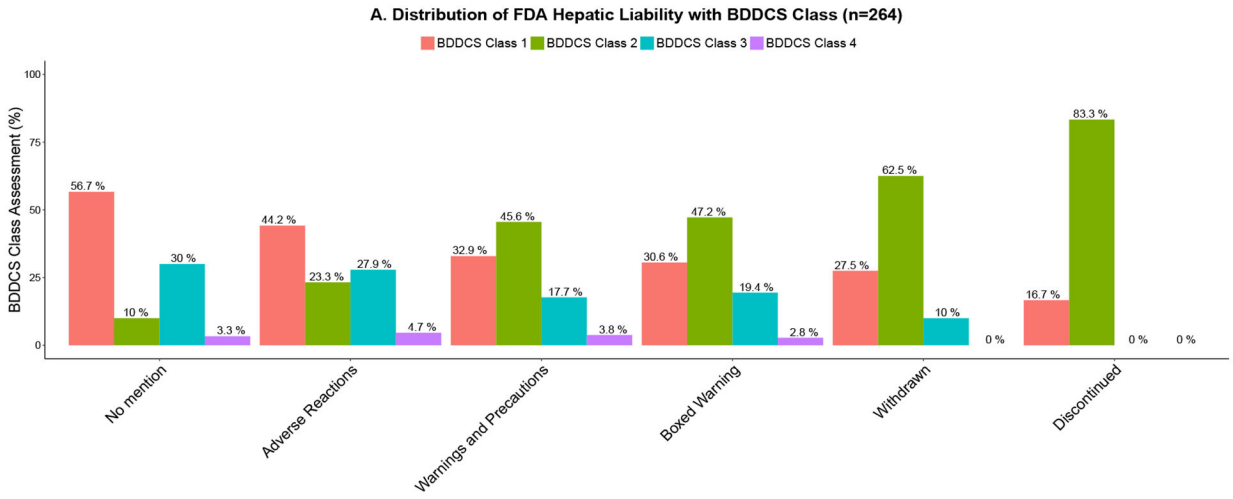

Figure 3.

Distribution of BDDCS class of hepatic liability for FDA listing of 264 drugs as reported by Chan and Benet[25].

Table 1.

Evaluation of the Accuracy of ECCS Assignment

ECCS Class	No. Drugs	No. Correct Metab. or Renal Predict.	No. Metab. but Low Perm.	No. Renal but High Perm.	% Error	No./% Hep. Uptake Rate Lim.
1A	36	30	3	3	16.7%	1/2.8%
1B	19	12	5	2	37.8%	12/63.2%
2	203	193	6	4	4.9%	
3A	27	27	1		3.7%	
3B	39	35	4		10.3%	11/28.2%
4	39	30	8	1	23.1%	
Totals	363	327			9.9%	

Abbreviations: No. – number; Metab. – metabolism; Predict. – prediction; Perm. – permeability rate; Hep. – hepatic; Lim. - limited

Table 2.

Predictability of 0.44 mg/ml as the BDDCS Solubility Assignment Cutoff as Reported by Bocci et al.[5]

	Solubility > 0.44 mg/ml	**Solubility ≤ 0.44 mg/ml**
BDDCS Classes 1 and 3	TRUE soluble (637; 87.9%)	FALSE soluble (88; 12.1%)
BDDCS Classes 2 and 4	False insoluble (37; 8.6%)	TRUE insoluble (394; 91.4%)