Title

BDDCS Predictions, Self-Correcting Aspects of BDDCS Assignments, BDDCS Assignment Corrections, and Classification for more than 175 Additional Drugs

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PREDICTING BDDCS CLASS USING IN SILICO METHODS

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ABSTRACT

Purpose: BDDCS predicts transporter effects, relying on clinical metabolism and *in vitro* solubility measurements to categorize drugs. *In silico* models would minimize laboratory requirements and help implement BDDCS in early-phase development. Here, we predict BDDCS class using GastroPlus™.

Methods: GastroPlus™ P_{eff} and D_o models were used to differentiate extensively from poorly metabolized drugs and highly from poorly soluble drugs, respectively. Area under the receiver operating characteristic (AUC) was used to assess differentiability.

Results: The GastroPlus™ P_{eff} model differentiates extent of metabolism (AUC = 0.80±0.04), while the GastroPlus™ D_o model differentiates solubility class (AUC = 0.87±0.03). Combining P_{eff} and D_o predictions, 69.7%, 70.5%, 50.8%, and 19.8% of drugs predicted as classes 1, 2, 3, or 4, respectively, were correctly predicted. Of drugs predicted as extensively metabolized, >85% are actually extensively metabolized. Of drugs predicted as class 3, 87% are highly soluble, while 36% are actually class 1 drugs.

Conclusions: *In silico* BDDCS predictions can inform pharmacokinetic predictions before dose selection. Drugs predicted as extensively metabolized may not require evaluation as substrates for gut absorptive transporters. Drugs predicted as class 3 may not require solubility characterization, though *in vitro* permeability should be assessed. Drugs predicted as class 4 require *in vitro* or *in vivo* investigation.

Keywords: Biopharmaceutics Drug Disposition Classification System, BDDCS, Drug Disposition, *In Silico* Prediction, Drug Development, Metabolism, Transporters

ABBREVIATIONS:

BDDCS: Biopharmaceutics Drug Disposition Classification System

GP: Gastro Plus™

P_{eff}: effective permeability

D_o: dose number

INTRODUCTION

The Biopharmaceutics Drug Disposition Classification System (BDDCS) predicts the clinical significance of drug transporters and metabolizing enzymes using clinical measures of the extent of metabolism and *in vitro* measures of solubility in relation to dose. Compounds are classified as extensively metabolized when their extent of metabolism ≥ 70% of the dose and poorly metabolized when ≤ 30% of the dose is metabolized. Solubility is defined by the dose number. Dose number (D_o) is the ratio of the compound's highest dose strength administered with 250 mL of water to a compound's minimum solubility in a pH range of 1-7.5. Thus, when the solubility is greater than or equal to the highest dose strength in 250 mL, $D_o \leq 1$. The entire dose will be able to go into solution with 250 mL of water and the drug is classified as highly soluble. Alternatively, when $D_o > 1$, the drug is classified as poorly soluble. Drugs can then be sorted into one of four categories: highly soluble, extensively metabolized class 1 compounds; poorly soluble, extensively metabolized class 2 compounds; highly soluble, poorly metabolized class 3 compounds; and poorly soluble, poorly metabolized class 4 compounds.

BDDCS was developed based on marketed compounds and has demonstrated substantial utility for understanding the effects of transporters and metabolizing enzymes for these compounds. Ideally, this system can be applied to drugs in development in order to predict which transporter and metabolizing enzyme effects will be relevant in the clinic. Specifically, metabolizing enzymes are expected to be clinically impactful for class 1 and 2, but not class 3 and 4 drugs. Drug transporters are not expected to be clinically relevant in the

pharmacokinetics of class 1 drugs, but are meaningful for classes 2, 3, and 4 drugs. Additionally, gut uptake transporters are unlikely to be clinically relevant for class 2 drugs. A more detailed overview of the predictions has been covered previously(1,2). These predictions may be useful in limiting unnecessary experiments, which may decrease development time and cost, benefitting both the consumer and the pharmaceutical company. However, the current classification system depends upon clinical metabolism data, which generally correlates with *in vitro* measures of permeability, as well as *in vitro* solubility measurements. Scientists must also know the highest dose strength to classify solubility, which is unknown until after clinical studies.

Wu and Benet observed that compounds that are extensively metabolized are also highly permeable in humans(3). We and others have shown that *in vitro* permeability rate predicts the extent of metabolism well(4,5). This can be a useful tool in predicting the extent of metabolism as a component of BDDCS class using *in vitro* or *in silico* methods.

Some researchers have already made great strides in predicting BDDCS class prior to human studies. Varma *et al*.(5) have shown that BDDCS class can be predicted well using *in vitro* apparent permeability rate as measured in MDCK-LE cells at pH 6.5 for acids and pH 7.4 for bases and solubility measured at pH 1.2 in PBS for acidic compounds and in FassIF for all other compounds. They used an internally developed permeability rate cut-off of $5x10^{-6}$ cm/s, above which, compounds were predicted to be extensively metabolized, and below which, compounds were predicted as poorly metabolized. Dose strength is generally determined prior to and during phase I trials. This makes it difficult to accurately predict the dose number of a drug. This group proposed a solubility cut-off of 200 µg/mL, which corresponds to a 50 mg dose being entirely soluble in 250 mL of water. This approach correctly predicted 84% of the compounds in their dataset, specifically 83%, 83%, 88%, and 67% of class 1, 2, 3, and 4 drugs, respectively. Additionally, over 90% of the drugs predicted as class 1 or class 2 actually belonged to those classes and over 80% of the drugs predicted to be class 3 were actually class 3, while 40% of the drugs predicted to be class 4 actually were class 4. The small number of

drugs that actually are class 4 may have contributed to the poor predictions of class 4 molecules.

Pharmaceutical companies can universally apply this approach, yet slight modifications will be required. Since measured permeability rate is extremely variable between laboratories(6) and each laboratory may choose a different method of permeability rate evaluation, each laboratory will need to develop a permeability rate standard to predict the extent of metabolism. We have investigated compounds that perform well as standards depending on the method of investigation (i.e. labetalol for Caco-2, zidovudine for MDCK, or theophylline for PAMPA)(4). Additionally, each company will need to decide upon a predicted highest dose strength prior to assigning a solubility class. As mentioned above, Varma *et al*. decided to use 50 mg. Here we analyze different dose strengths as an initial predictor of dose in order to predict solubility.

To ease the time and cost of these predictions during development, an *in silico* approach is preferable. There have been at least two attempts to predict BDDCS class *in silico*. In 2007, Khandelwal *et al*.(7) developed models using machine learning methods including recursive partitioning, random forest, and support vector machines. They used molecular features to assign drugs to one of the four BDDCS classes, predicting 33.3% correct overall. In 2012, using the extended dataset published by Benet *et al*.(8), Broccatelli *et al*.(9) used a binary approach to predict the solubility and the extent of metabolism of the drugs before making a class prediction. Solubility was predicted using Naïve Bayes, k-nearest neighbor, and support vector machine models, where the solubility class was assigned using a consensus model, which predicted the class based on how it was predicted in a majority of the models. This model was 77% accurate. The extent of metabolism was predicted from a consensus model of a Naïve Bayes and two support vector machine models. This model was 79% accurate. When combining the solubility and extent of metabolism models to predict BDDCS class, however, this approach was 55% accurate.

We selected a similar approach as Broccatelli *et al*.(9), predicting extent of metabolism and solubility separately, but we decided to use validated commercially available models that predict *in vitro* permeability rate, which serves as a surrogate for the extent of metabolism, and that predict solubility and its derived parameter, dose number. We have shown that we can reliably predict the extent of metabolism using *in vitro* methods(4) and an *in vitro* provisional classification system has already been successfully developed by Varma *et al.*(5). We therefore set out to use a previously developed, commercially available *in silico* model to predict the extent of metabolism. Since we know that *in vitro* permeability rate methods can predict the extent of metabolism well, we expected that *in silico* permeability rate methods may also be able to predict the extent of metabolism. We therefore considered the GastroPlus™ effective permeability rate model (GP P_{eff}) as a predictor of the extent of metabolism (BDDCS classes 1 and 2 versus BDDCS classes 3 and 4). Additionally, we evaluated the GastroPlus™ dose number model (GP D_o) as a predictor of the solubility classification.

MATERIALS AND METHODS

Predicting Extent of Metabolism

We assigned extensively metabolized compounds a 1 as the positive class and poorly metabolized compounds a 0 as the negative class. We evaluated how well the GP P_{eff} predictions were segregated between extensively and poorly metabolized compounds, with the expectation that poorly metabolized compounds would have low predicted *in silico* permeability rates and that extensively metabolized compounds would have high predicted *in silico* permeability rates, using a receiver operating characteristic curve (ROC). When the area under the ROC curve (AUC) was greater than 0.8, the permeability rate model was considered capable of segregating extensively from poorly metabolized compounds.

The receiver operating characteristic curve is a method of determining how well a continuous feature predicts a binary classification outcome. In this case, the continuous feature is *in silico* permeability rate, while the binary classification outcome is extent of metabolism (extensive versus poor). The continuous feature is rank-ordered and the true positive rate (sensitivity) is plotted against the false positive rate, which is equal to 1-true negative rate (specificity) at each continuous value, resulting in high AUCs (> 0.8) when there is good segregation between the continuous values allotted to the classifications, or low AUCs (0.5-0.8) when the continuous values are not well segregated between the classifications. An AUC of 0.5 indicates complete integration of the continuous values between the segregated classes where essentially every other rank-ordered value belongs to one class. We further investigated specific performance measures at a threshold that would maximize the average between sensitivity and specificity.

- Sensitivity: the percent of highly metabolized compounds that were correctly assigned an extensive metabolism classification by high GP P_{eff}
- Specificity: the percent of poorly metabolized compounds that were correctly assigned a poor metabolism classification by low GP P_{eff}
- Positive Predictive Value: the percent of high GP P_{eff} compounds (thus predicted to be extensively metabolized) that are extensively metabolized
- Negative Predictive Value: the percent of low GP P_{eff} compounds (thus predicted to be poorly metabolized) that are poorly metabolized
- Accuracy: the percent of all compounds that were correctly assigned their metabolism class
- The average between sensitivity and specificity, and the average between positive and negative predictive value were also evaluated.

Predicting Solubility

We evaluated the dose number predictions in GastroPlus™ (GP D_o) for their ability to predict the actual dose number and solubility classification. We used known doses for the predictions, and when doses were unknown, we used 100 mg, which is the recommended dose prediction by the program, and is the dose that we selected for predictions based on dose analysis. The ability of GP D_o to predict solubility was evaluated with ROC curves. Because a low dose number (≤ 1) indicates a highly soluble compound, while a high dose number (> 1) indicates a poorly soluble compound, when we evaluated predicted dose number, we classified poorly soluble compounds as the positive class to generate the ROC plot, but calculated the performance parameters by assigning highly soluble compounds the positive class. We further investigated specific performance measures at a threshold that would maximize the average between sensitivity and specificity.

- Sensitivity: the percent of highly soluble compounds that were correctly assigned a high solubility classification
- Specificity: the percent of poorly soluble compounds that were correctly assigned a poor solubility classification
- Positive Predictive Value: the percent of compounds assigned a high solubility classification (by a low dose number) that are truly highly soluble
- Negative Predictive Value: the percent of compounds assigned a poor solubility classification (by a high dose number) that are truly poorly soluble
- Accuracy: the percent of all compounds that were correctly assigned their solubility class
- The average between sensitivity and specificity, and the average between positive and negative predictive value were also evaluated.

Evaluating Measured Solubility as an Indicator of FDA Solubility

Measured solubility as reported by Benet *et al.*(8) or Hosey *et al.*(1) was compared between BDDCS classes using Kruskal-Wallace one-way analysis of variance and comparing each class against one another with Dunn's multiple comparison test.

Evaluating Dose

We evaluated how simulated doses of 50, 75, 100, and 200 mg would affect the solubility classification of orally administered drugs. We first calculated what the dose number would be given a known experimentally measured solubility using the following equation:

$$Dose\ Number = \frac{Highest\ Dose\ Strength\ (mg)}{250\ mL\ x\ Minimum\ Solubility\ (\frac{mg}{mL})}$$

We then evaluated the performance of solubility assignment at various simulated doses compared to actual solubility assignment. When dose number ≤ 1, the drug is considered highly soluble, and when dose number > 1, the drug is considered poorly soluble. Performance of the simulated dose was evaluated with the following:

- Sensitivity: the percent of highly soluble compounds that were correctly assigned a high solubility classification at the simulated dose
- Specificity: the percent of poorly soluble compounds that were correctly assigned a poor solubility classification at the simulated dose
- Positive Predictive Value: the percent of compounds assigned a high solubility classification at the simulated dose that are truly highly soluble
- Negative Predictive Value: the percent of compounds assigned a poor solubility classification at the simulated dose that are truly poorly soluble
- Accuracy: the percent of all compounds that were correctly assigned their solubility class
- ROC AUC, the average between sensitivity and specificity, and the average between positive and negative predictive value were also evaluated. The

measured solubility at which the greatest average between sensitivity and specificity was obtained and associated with the dose that would determine the boundary between extensively and poorly metabolized compounds (Dose number = 1) using the dose number equation given above.

We additionally evaluated the accuracy of predicting each class and the predictive value of each class, assuming the extent of metabolism was already known.

Predicting BDDCS Class

The BDDCS Class was predicted using the P_{eff} model to predict the extent of metabolism with the D_o model from GastroPlus™ to predict the solubility class. The thresholds that delineate the classifications were selected using optimal thresholds based on maximum averages between sensitivity and specificity. Accuracy and predictive values of each class were calculated.

RESULTS

Evaluating Measured Solubility as an Indicator of FDA Solubility

Significant differences were found between the measured solubility of high FDA solubility (classes 1 and 3) and low FDA solubility (classes 2 and 4) drugs (Figure 1).

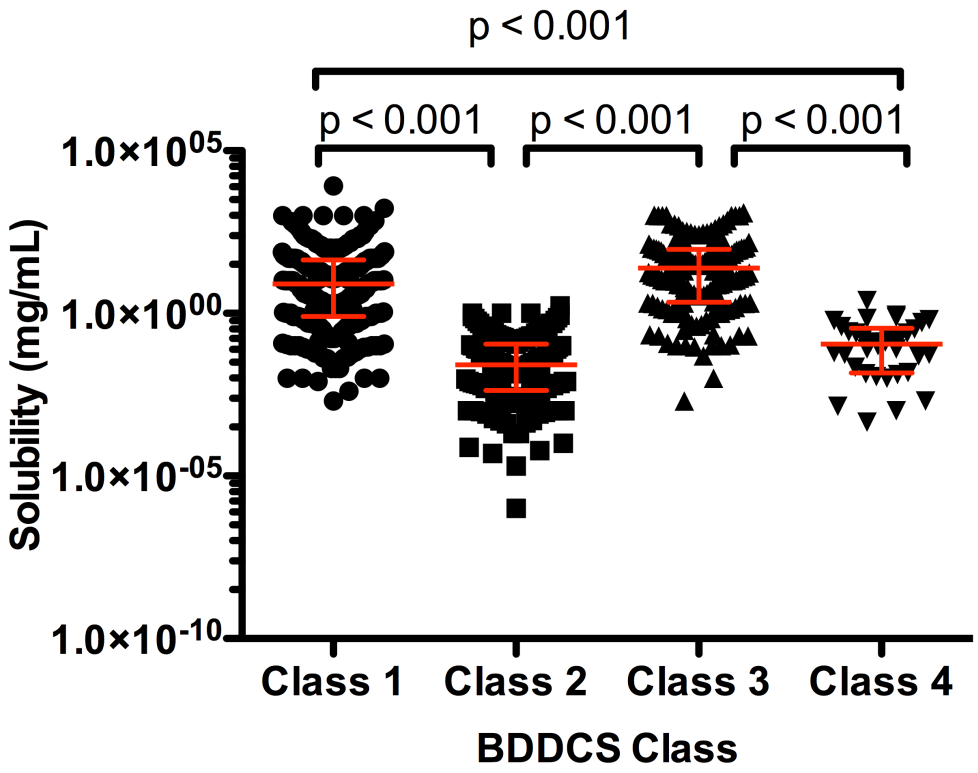

Figure 1.

Additionally, a significant difference was observed between classes 1 and 3 ($p < 0.05$). The ROC AUC between class 1 and 3 is 0.61. The solubility boundary conditions of classes 1 and 3 versus 2 and 4 are detailed in Table I. This indicates what dose would be required under certain conditions to change the FDA solubility classification of a drug.

Table I. Boundary Conditions of Currently Classified Drugs

BDDCS	Boundary Solubility	Dosing Condition
Class 2 or 4	2.5 mg/mL maximum	If solubility is > 2.5 mg/mL, the drug will only be poorly soluble if requiring a dose > 625 mg
Class 1 or 3	0.002 mg/mL minimum	If solubility is < 0.002 mg/mL, the dose must be < 0.5 mg to be a high solubility drug

Evaluating Dose

Class 4 drugs had significantly higher doses than each of the other classes for orally administered drugs as seen in Figure 2. The dose of class 4 drugs was also significantly higher than class 1 and 2 drug for intravenously administered drugs, and had a higher mean and median dose value than class 3 drugs, although the difference was insignificant. Alternatively, class 1 drugs had the lowest doses for orally administered and intravenously administered drugs, although there was no significant difference in the doses of class 1 and 2 intravenously administered drugs.

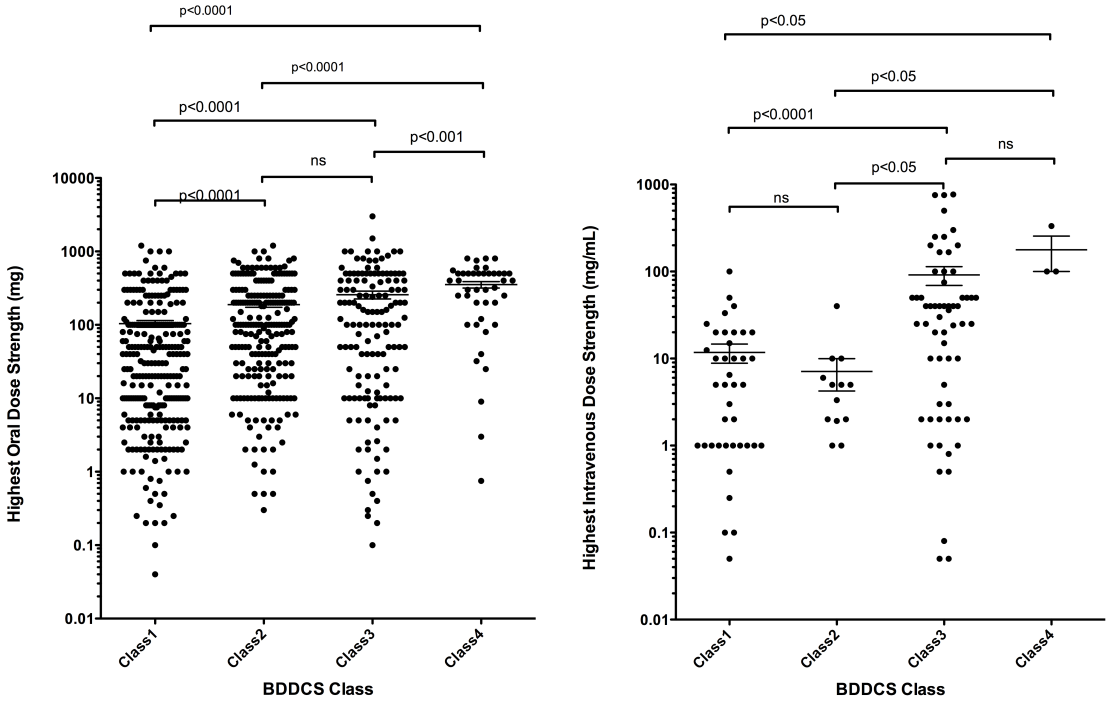

Figure 2.

The Effect of Dose Changes on Dose Number

Table II shows how changing a dose (from 50, 75, 100, or 200 mg) affects how well the solubility class (1 and 3 versus 2 and 4) was predicted using the measured solubility and with a theoretical dissolution volume of 250 mL.

Table II. The Effect of Dose Changes on Dose Number

Performance Measure	Dose (mg)			
	50	75	100	200
% of Highly Soluble Compounds Correct (Sensitivity)	0.87	0.84	0.82	0.77
% of Poorly Soluble Compounds Correct (Specificity)	0.78	0.84	0.89	0.97
% of Those Predicted to Be Highly Soluble Correct (PPV)	0.88	0.90	0.93	0.98
% of Those Predicted to Be Poorly Soluble Correct (NPV)	0.77	0.75	0.74	0.70
Average between Sensitivity and Specificity	0.83	0.84	0.86	0.87
Average between PPV and NPV	0.82	0.82	0.83	0.84
Accuracy	0.84	0.84	0.85	0.84
ROC AUC	0.82	0.84	0.85	0.87

Table III shows how changing the dose will affect the accuracy of the solubility class predictions for classes 1-4 and the predictive value assuming the extent of metabolism is known. For example, the predictive value of drugs predicted to be class 1 when the dose is 50 mg is the percentage of class 1 and 2 drugs having dose number ≤ 1 that belong to class 1.

Table III. Performance Measures When Various Doses are Estimated for Each BDDCS Class

	Class 1		Class 2		Class 3		Class 4	
Dose (mg)	Accuracy*	Predictive Value**	Accuracy	Predictive Value	Accuracy	Predictive Value	Accuracy	Predictive Value
50	0.84	0.87	0.82	0.78	0.92	0.89	0.64	0.72
75	0.82	0.90	0.86	0.77	0.87	0.91	0.73	0.65
100	0.80	0.93	0.91	0.76	0.86	0.93	0.79	0.65
200	0.74	0.98	0.97	0.72	0.81	0.98	0.94	0.62

* Accuracy represents the percent of the compounds in the class that were correctly assigned solubility class for each dose

** Predictive value represents the percent of predictions that are correct when the extent of metabolism is known

The ROC AUC of solubility as a predictor of solubility class when dose was not estimated was 0.93. The optimal average between sensitivity and specificity was found at 0.4 mg/mL, which corresponds to a 100 mg dose to achieve a dose number = 1.

Using In Silico Models to Predict the Extent of Metabolism and Solubility Class

Figure 3 shows the ROC plots and performance measures for the GP P_{eff} model as a predictor of the extent of metabolism and the GP D_o as a predictor for solubility class. Since AUC values were ≥ 0.80, each of these models significantly discriminated their predicted classes. A threshold of 1.72×10^4 cm/s resulted in the highest average between sensitivity and specificity for the GP P_{eff} model, while a threshold of 1.11 resulted in the highest average between sensitivity and specificity for the GP D_o model. The performance measures are listed at these thresholds on Figure 3.

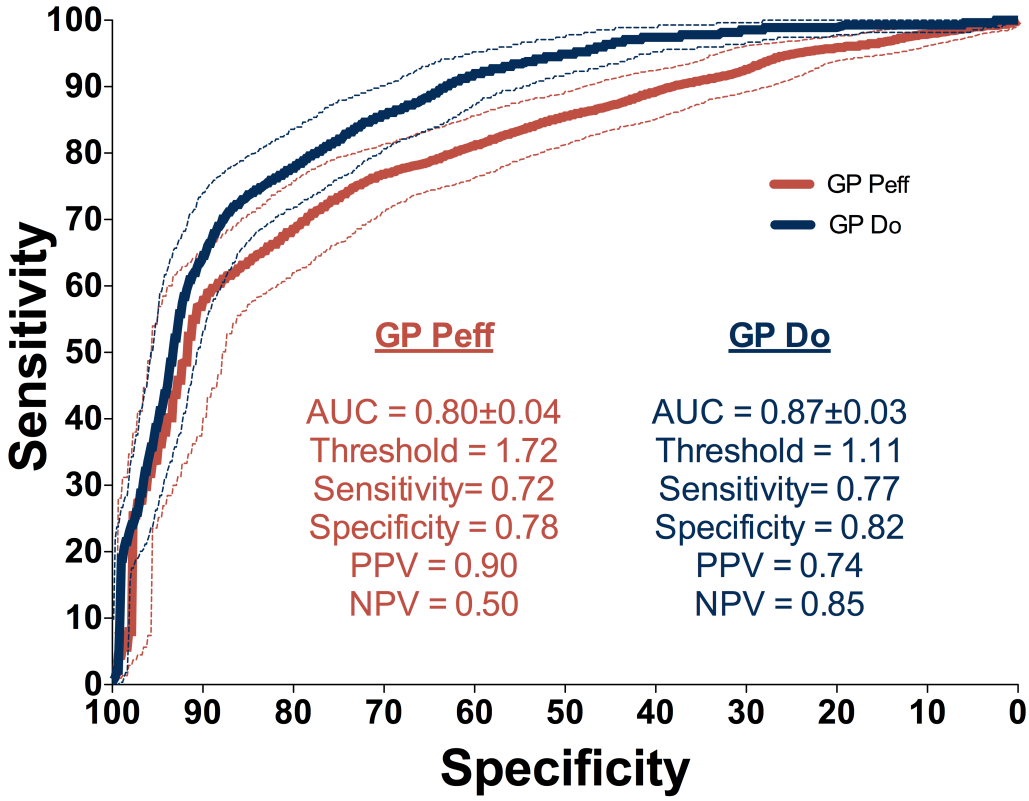

Figure 3.

Predicting BDDCS Class

Figure 4 depicts the predicted P_{eff} versus the predicted dose number, as calculated in GastroPlus™ for the drugs in our dataset. The results of these predictions are outlined in Table IV. Table V shows how drugs were predicted compared to their actual class.

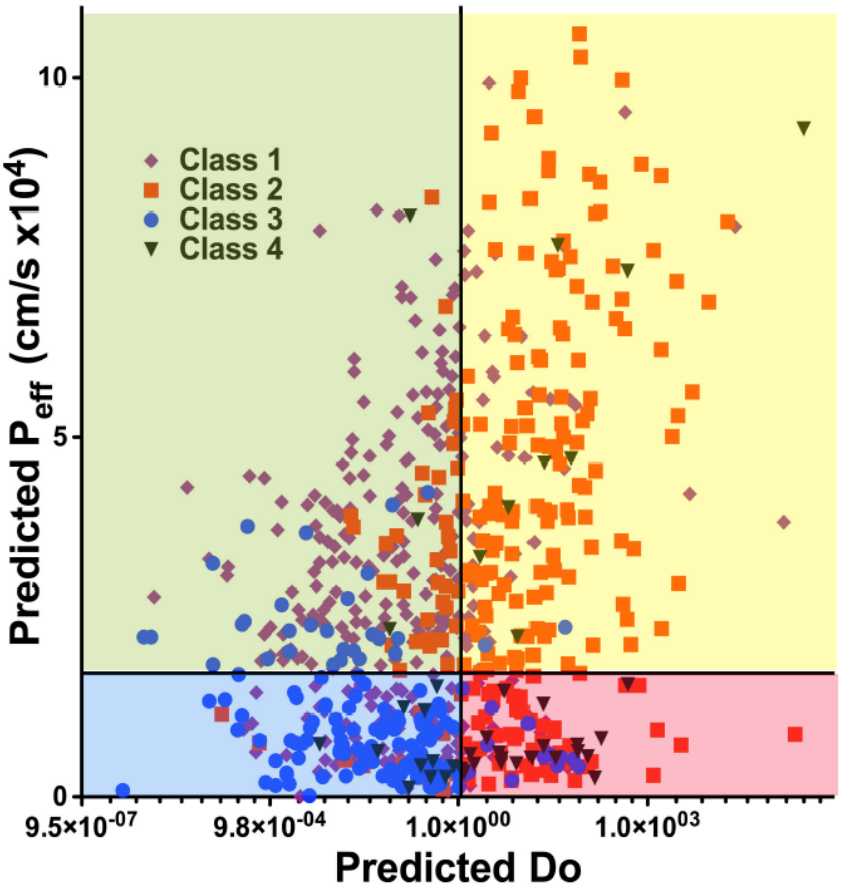

Figure 4.

Table IV. Performance of BDDCS *In Silico* Predictions

BDDCS Class	Predictive Value	Accuracy
1	69.7	54.1
2	70.5	57.8
3	50.8	69.3
4	19.8	45.2

Table V. Confusion Matrix of BDDCS Predictions

Actual	Predicted			
	1	**2**	**3**	**4**
1	152	46	69	14
2	36	134	13	49
3	27	2	97	14
4	3	8	12	19

DISCUSSION

BDDCS is a powerful system that predicts when transporters are clinically irrelevant. We expect that almost all drugs are substrates for some transporters, and that *in vitro* experiments will often predict that a drug is a substrate for a transporter. However, we are unaware of any examples of highly soluble, extensively metabolized class 1 drugs that exhibit clinically relevant transporter effects. That is, the disposition of the drug is independent of the function of transporters. This is extremely powerful in predicting potential drug-drug interactions and understanding barriers to organ access. For instance, Broccatelli *et al.*(10) have shown that while efflux transporters can effectively decrease the central nervous system concentrations of class 2 drugs and uptake transporters and efflux transporters affect central nervous system access for class 3 and 4 drugs, class 1 drugs have no barriers to central nervous system access. Since transporters can be so important in mediating systemic and organ drug exposure, they must be evaluated during development. However, successful BDDCS class prediction, particularly of class 1 drugs, could be used to reduce the time and cost of development by eliminating unnecessary transporter studies. Alternatively, it can be used to inform which transporter studies may be necessary for class 2, 3, and 4 drugs and alert the developer to possible transporter interactions.

While BDDCS classes have been successfully predicted *in vitro*, there are currently no *in silico* predictive methods that are sensitive enough to apply during drug development. Therefore, we examined the potential to predict BDDCS class using commercially available *in silico* methodology. We used predicted dose number from GastroPlus™ to predict solubility and predicted P_{eff} as a surrogate predictor of the extent of metabolism.

During early development, it is advantageous to predict transporter effects, yet dose is frequently unknown until clinical studies. Varma *et al*.(5) have suggested utilizing a 50 mg dose (equivalent to a solubility of 200 µg/mL at a dose number = 1) as an initial prediction to predict BDDCS class. We analyzed 4 doses to determine their effect on predicting BDDCS class when solubility is known. The performance is relatively stable across the dosages. This is likely

because there is a significant difference in measured solubility independent of dose (Figure 1) and thus only large changes in dose will have an effect on the dose number of many drugs. Currently, transporter studies are carried out for all drugs. Because BDDCS predictions could potentially be used to eliminate transporter studies, which are unnecessary for class 1 drugs, but are important to ensure the safety and efficacy of other drugs, we wished to be conservative with the false prediction rate of class 1 drugs. At 100 mg, only 7% of the compounds that are predicted to be class 1 when the extent of metabolism is known to be extensive are false positives, while 80% of the class 1 compounds were still correctly predicted when 100 mg was used as the dose (Table III). When we evaluated how measured solubility is segregated between classes 1 and 3 versus classes 2 and 4 using ROC analysis, we found that a dose of 100 mg maximized the average between sensitivity (the percent of class 1 and 3 drugs correctly predicted by measured solubility alone) and specificity (the percent of class 2 and 4 drugs correctly predicted by measured solubility alone). Thus, we selected 100 mg as an estimated dose when dose is unknown.

Predicting BDDCS Class

While GP D_o predicts solubility class well and GP P_{eff} predicts the extent of metabolism well (Figure 2), combining these to predict BDDCS class results in poor predictability and accuracy for each class (Table IV). However, by analyzing where the errors occurred, these predictions may still be useful.

Of class 1, 2, 3, or 4 drugs, 95%, 94%, 99%, and 93% are correctly predicted by at least one property, respectively. Additionally, 90% of the drugs that are predicted as extensively metabolized class 1 or 2 drugs by a high *in silico* P_{eff} actually are extensively metabolized (Table V). Since class 1 and 2 drugs do not require gut uptake transporters for absorption and are not clinically relevant substrates of them, it is unlikely that drugs predicted to be class 1 or 2 will need to be evaluated for gut uptake. Of the drugs predicted to be class 3, 87% are highly

soluble (actually class 1 or class 3), but 36% of the drugs predicted to be class 3 are extensively metabolized. Since such a large proportion of these drugs are actually extensively metabolized, it may be advantageous to carry out *in vitro* permeability rate studies to predict the extent of metabolism and potentially eliminate unnecessary transporter studies, if the drug is indeed a class 1 drug. Solubility characterization, however, is likely unnecessary at this stage. Finally, since only 20% of the drugs predicted to be class 4 *in silico* are actually class 4 drugs, and only 40% predicted to be class 4 by *in vitro* measures are actually class 4, a BDDCS classification may only be assigned to these drugs after clinical studies and dose selection.

While using *in silico* methods to predict BDDCS class may not predict the exact BDDCS class well, we have analyzed the data with respect to how predictions may influence generalized transporter studies. More than 70% of drugs predicted as class 2, 3, or 4 actually belong to one of those classes. While class 2 drugs do not require gut uptake studies, but class 3 and 4 do, gut efflux studies, as well as hepatic and brain transporter studies are necessary for all class 2, 3, and 4 drugs. Therefore, by carrying out transporter studies for drugs predicted to be in classes 2, 3, or 4 by the *in silico* methodology outlined here, only 30% of the transporter studies are ultimately unnecessary and “wasteful”. This is still better than needlessly testing all class 1 drugs. Unfortunately, improving *in silico* predictability of class 1 drugs is necessary to eliminate transporter studies for even drugs predicted to be class 1 since 30% of the drugs predicted to be class 1 are actually class 2, 3, or 4 drugs. This is problematic since, if transporters were not evaluated, 30% of the drugs may have transporter effects that need to be evaluated prior to human dosing.

In Figure 5, we show a chart that can be used to interpret which studies need to be carried out when *in silico* predictions of certain classes are made. Additionally, uptake transport studies should be conducted for drugs that are predicted to be class 3 after considering permeability rate.

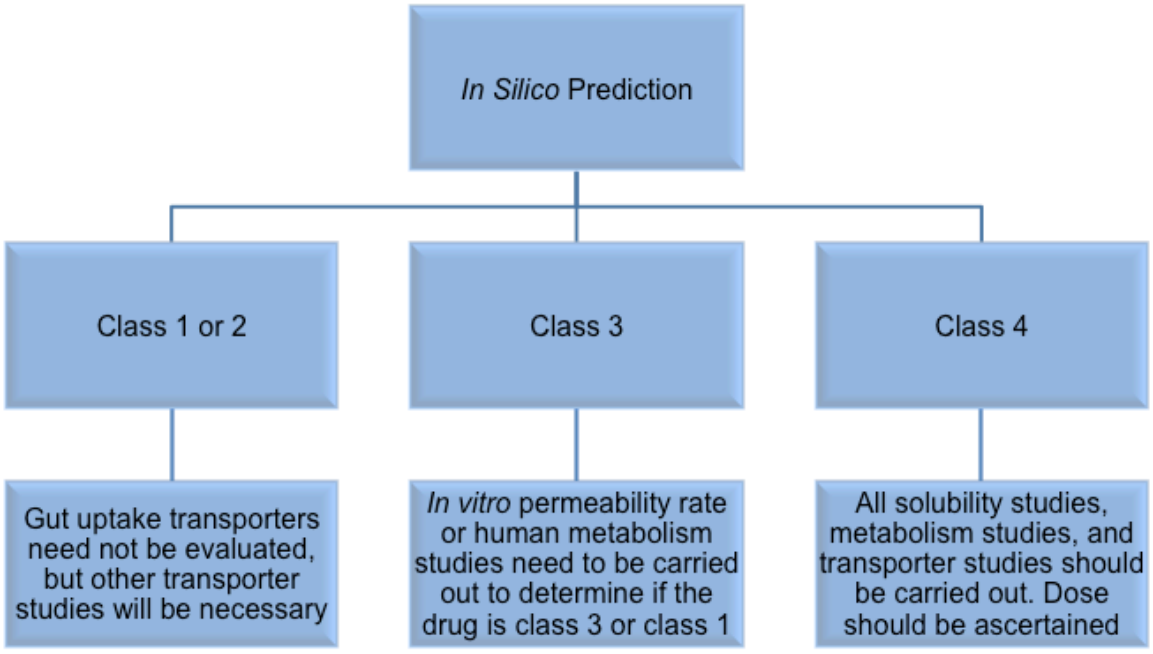

Figure 5.

Alternative Methods

We have envisioned several other methods of predicting BDDCS class *in silico*. Data-mining approaches that predict each of the four classes individually (a quartenary classification approach) such as support vector machines may be useful. However, our preliminary attempts at this classification have been less successful than using the binary approach outlined here. Alternatively, we could develop models that predict the [binary] extent of metabolism and the continuous solubility, continuous dose number, or binary solubility. However, several attempts have been made at predicting continuous solubility finding that continuous solubility is not useful in predicting BDDCS class without knowing the dose. Therefore, predicting dose number or a binary solubility classification would likely be the most effective remaining approaches.

Benet *et al*.(8) showed that *in silico* predictions of the minimum solubility of drugs over the pH range 3-7.5 are well segregated between class 2 and 3 drugs, but are unexpectedly similar when comparing class 1 and 4 drugs. Similarly, CLogP, serving as a permeability rate surrogate, is able to differentiate between classes 2 and 3, but confounds classes 1 and 4. These relatively simple *in silico* parameters are therefore able to predict when a drug is likely to be class 2 or 3, but a drug having a more moderate LogP ($0 < \text{LogP} < 2$) or predicted minimum solubility is unable to be accurately classified. Additionally, we have shown that there is no significant difference in the measured or calculated LogP of extensively metabolized class 1 and 2 compounds and class 3 and 4 compounds primarily eliminated as unchanged drug in the bile, although both are significantly higher than the LogP of renally eliminated compounds(4). Therefore, LogP is an unreliable indicator of BDDCS class. While we continue to investigate these confounding factors, currently the best prediction approach remains *in vitro*. These *in vitro* measures can reasonably predict BDDCS class prior to *in vivo* studies.

CONCLUSIONS

BDDCS has been successfully applied to understand and predict the disposition of currently marketed drugs. It could be applied with extensive utility prior to carrying out clinical studies during development, but would require non-clinical information. *In vitro* approaches have been successfully developed to predict the BDDCS class of new molecular entities. While *in silico* approaches thus far have limited predictive utility, some information may be garnered to direct transporter studies prior to dose selection.

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Legends to Figures:

Figure 1. Distribution of measured solubility between BDDCS classes 1-4.

Figure 2. Highest dosage strength of orally and non-orally administered compounds by BDDCS class.

Figure 3. Receiver operating characteristic curves of GastroPlus™ predicted dose number and effective permeability.

Figure 4. Predicted BDDCS class. Drugs with properties falling within each box are classified according to their predicted permeability rate and predicted dose number. Compounds in the green box are predicted as class 1, yellow as class 2, blue as class 3, and red as class 4. The legend shows the actual class of each drug.

Figure 5. Interpreting necessary further studies given an *in silico* BDDCS prediction.