Biopharmaceutics Drug Disposition Classification System (BDDCS) --- Its Impact and Application

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Wu and Benet recognized that for drugs exhibiting high intestinal permeability rates the major route of elimination in humans was via metabolism, while drugs exhibiting poor intestinal permeability rates were primarily eliminated in humans as unchanged drug in the urine and bile.

Therefore they suggested that at least for drugs on the market, where extent of metabolism is always known, but extent of absorption may not have been quantitated, that metabolism may serve as a surrogate for permeability rate.
Major Routes of Drug Elimination

- **High Solubility**
  - **Class 1**: Metabolism
  - **Class 3**: Renal & Biliary Elimination of Unchanged Drug

- **Low Solubility**
  - **Class 2**: Metabolism
  - **Class 4**: Renal & Biliary Elimination of Unchanged Drug
Biopharmaceutics Drug Disposition Classification System

BDDCS

- **Class 1**: High Solubility, Extensive Metabolism
- **Class 2**: Low Solubility, Extensive Metabolism (Rapid Dissolution and ≥70% Metabolism for Biowaiver)
- **Class 3**: High Solubility, Poor Metabolism
- **Class 4**: Low Solubility, Poor Metabolism

Wu and Benet, Pharm. Res. 22: 11-23 (2005)
Major Differences Between BDDCS and BCS

**Purpose:** BCS – Facilitate biowaivers of in vivo bioequivalence studies. BDDCS – Prediction of drug disposition and potential DDIs in the intestine & liver.

**Criterion:** BDDCS – Predictions based on intestinal permeability rate BCS – Biowaivers are based on extent of intestinal absorption (permeability), which in a number of cases does not correlate with jejunal permeability rates
What are the Implications for New Molecular Entities and DDIs?

• For an NME, measuring a surrogate of human intestinal absorption, such as Caco-2 permeability or even PAMPA, allows prediction of the major route of elimination in humans prior to dosing either to animals or man.

• Furthermore, one knows whether DDIs relating to metabolism will be a major factor or not.
The recognition of the correlation between intestinal permeability rate and extent of metabolism allows prediction of BDDCS class for an NME to be based on passive membrane permeability. Our recent work suggests that even measurements in nonviable membranes like PAMPA will give the correct prediction.

The Role of BCS (Biopharmaceutics Classification System) and BDDCS (Biopharmaceutics Drug Disposition Classification System) in Drug Development. L. Z. Benet. *J. Pharm. Sci.* 102, 34-42 (2013)
The recognition of the correlation between intestinal permeability rate and extent of metabolism and our finding that a nonviable membrane can serve as surrogate marker preceded an explanation for these findings.

We suspect that high permeability rate compounds are readily reabsorbed from the kidney lumen and from the bile facilitating multiple access to the metabolic enzymes. This would be particularly important for metabolically eliminated drugs with low hepatic clearance (e.g., diazepam).
The Use of BDDCS for Drugs on the Market

- Predict potential drug-drug interactions not tested in the drug approval process
- Predict the potential relevance of transporter-enzyme interplay
- Assist the prediction of when and when not transporter and/or enzyme pharmacogenetic variants may be clinically relevant
- Predict when transporter inhibition of uremic toxins may change hepatic elimination
- Predict the brain disposition
- Increase the eligibility of drugs for BCS Class 1 biowaivers using measures of metabolism
Oral Dosing Transporter Effects

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<tr>
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Oral Dosing Transporter Effects

High Solubility

Class 1
Transporter effects minimal in gut and liver

Class 2
Efflux transporter effects predominate in gut, but both uptake & efflux transporters can affect liver

Low Solubility

Class 3
Absorptive transporter effects predominate (but can be modulated by efflux transporters)

Class 4
Absorptive and efflux transporter effects could be important
Class 1 highly soluble, high permeability, extensively metabolized drugs

- Transporter effects will be minimal in the intestine and the liver
- Even compounds like verapamil that can be shown in certain cellular systems (MDR1-MDCK) to be a substrate of P-gp will exhibit no clinically significant P-gp substrate effects in the gut and liver
Class 1 Drugs

A major proposition of BDDCS is that Class 1 drugs are not substrates of clinical relevance for transporters in the intestine and liver.

(This lack of any transporter influence on BDDCS Class 1 drugs is probably the reason biowaivers are always successful for such drugs.)
Intestinal: Transporter Effects

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<td>efflux transporters)</td>
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Efflux transporter effects will predominate for Class 2 compounds. The high permeability of these compounds will allow ready access into the gut membranes, but the low solubility will limit the concentrations coming into the enterocytes, thereby preventing saturation of the efflux transporters.
Transporter-enzyme interplay will be primarily important for Class 2 compounds that are substrates for CYP 3A and Phase 2 gut enzymes (e.g. glucuronosyltransferases) where efflux transporter effects can control the access of the drug to the gut enzymes. DDIs in the intestine can lead to changes in metabolism that result from efflux transporter inhibition.
Recent Transporter Interplay
Reviews from the Benet Lab


- The Role of BCS (Biopharmaceutics Classification System) and BDDCS (Biopharmaceutics Drug Disposition Classification System) in Drug Development. L.Z. Benet. J. Pharm. Sci. 102, 34-42 (2013).
Oral Dosing Transporter Effects

- **High Solubility**
  - **Class 1**: Transporter effects minimal in gut and liver
  - **Class 3**: Absorptive transporter effects predominate (but can be modulated by efflux transporters)

- **Low Solubility**
  - **Class 2**: Efflux transporter effects predominate in gut, but both uptake & efflux transporters can affect liver
  - **Class 4**: Absorptive and efflux transporter effects could be important
Class 2 poorly soluble, highly permeable, extensively metabolized drugs

- Efflux transporter effects will be important in the intestine and the liver
- In the intestine efflux transporter–enzyme (CYP 3A4 and UGTs) interplay can markedly affect oral bioavailability
- In the liver the efflux transporter-enzyme interplay will yield counteractive effects to that seen in the intestine.
- Uptake transporters can be important for the liver but not the intestine.
Class 2 poorly soluble, highly permeable, extensively metabolized drugs --- DDIs are seen as changes in metabolism

- Efflux transporter effects will be important in the intestine and the liver — **Metabolism changes due to transporter DDIs**
  - In the intestine efflux transporter–enzyme (CYP 3A4 and UGTs) interplay can markedly affect oral bioavailability — *The overlap of inhibitors for gut enzymes and gut efflux transporters can cause multiple DDI causation.*
  - In the liver the efflux transporter-enzyme interplay will yield counteractive effects to that seen in the intestine --- **Inhibition of efflux transporters causes decreased metabolism in the intestine and increased metabolism in the liver.**

- Uptake transporters can be important for the liver but not the intestine --- **Inhibition of uptake transporters causes decreased metabolism in the liver**
Elucidating Rifampin’s Inducing and Inhibiting Effects on Glyburide Pharmacokinetics and Blood Glucose in Healthy Volunteers: Unmasking the Differential Effect of Enzyme Induction and Transporter Inhibition for a Drug and Its Primary Metabolite

HongXia Zheng, Yong Huang, Lynda Frassetto, and Leslie Z. Benet

Clinical Pharmacology & Therapeutics

85:78-85 (2009)
Study Design

Effects of Single IV Rifampin (RIF) on Glyburide

Ten Healthy Volunteers

Visit 1
Day 1
Glyburide 1.25mg P.O.
(PK Study)

Visit 2
Day 8
Rifampin 600mg I.V.
Glyburide 1.25mg P.O.
(PK Study)
Study Design (Continued)
Inhibition and Induction Effects of RIF on Glyburide

ALL Healthy Volunteers

\[ \text{Rifampin 600mg P.O. for 6 days}\]

\[ \text{Rifampin 600mg I.V.} \]
\[ \text{Glyburide 1.25mg P.O. (PK study)} \]

Visit 3
Day 15

Visit 4
Day 17

\[ \text{Glyburide 1.25mg P.O. (PK study)} \]
Inhibition of Glyburide Uptake by IV RIF

- **C<sub>max</sub>**: 81% ↑*
- **T<sub>1/2</sub>**: 31% ↓*
- **AUC<sub>0-inf</sub>**: 125% ↑*
- **CL/F**: 53% ↓*
- **V<sub>ss/F</sub>**: 60% ↓*

*P<0.05
CYP450 Induction Effect on Glyburide When No RIF Present in the Plasma

C<sub>max</sub> 48% ↓ *

AUC<sub>0-inf</sub> 63% ↓ *

CL/F 197% ↑ *

V<sub>ss</sub>/F 32% ↑ ns
Uptake Inhibition and CYP450 Induction Effects on Glyburide When RIF Present in the Plasma

- **C<sub>max</sub>**: 9%
- **AUC<sub>0-inf</sub>**: 22%
- **CL/F**: 37%
- **V<sub>ss/F</sub>**: 43%
High Solubility

Class 1
Transporter effects minimal in gut and liver

Class 2
Efflux transporter effects predominate in gut, but both uptake & efflux transporters can affect liver

Low Solubility

Class 3
Absorptive transporter effects predominate (but can be modulated by efflux transporters)

Class 4
Absorptive and efflux transporter effects could be important
Class 3

highly soluble, low permeability, poorly metabolized drugs

- Uptake transporters will be important for intestinal absorption and liver entry for these poor permeability drugs
- However, once these poorly permeable drugs get into the enterocyte or the hepatocyte efflux transporter effects can occur.
Class 3
highly soluble, low permeability, poorly metabolized drugs

• Uptake transporters will be important for intestinal absorption and liver entry for these poor permeability drugs

• However, once these poorly permeable drugs get into the enterocyte or the hepatocyte efflux transporter effects can occur.

• DDIs will be transporter mediated and cause changes in biliary and renal excretion for Class 3 and 4 drugs
The Use of BDDCS for Drugs on the Market

- Predict potential drug-drug interactions not tested in the drug approval process
- Predict the potential relevance of transporter-enzyme interplay
- Assist the prediction of when and when not transporter and/or enzyme pharmacogenetic variants may be clinically relevant
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- Predict the brain disposition
- Increase the eligibility of drugs for BCS Class 1 biowaivers using measures of metabolism
Recently the FDA has recommended that studies in renal failure patients be carried out even for drugs where renal elimination of unchanged drug is minimal.

This recommendation comes about in part based on a finding that was related to the development and characterization of BDDCS.
Studies of Drugs Primarily Eliminated by Metabolism in Renal Failure Patients

Potential inhibition or downregulation of metabolic enzymes by uremic toxins could be tested *in vitro*.

We began to recognize that previously unexplained effects of renal disease on hepatic metabolism can result from accumulation of substances (toxins) in renal failure that modify hepatic uptake and efflux transporters.


Hepatic Clearance, but Not Gut Availability of Erythromycin Is Altered in Patients with End-Stage Renal Disease

Hong Sun, Lynda A. Frassetto, Yong Huang and Leslie Z. Benet

Clinical Pharmacology & Therapeutics

Erythromycin is a Class 3 drug that is primarily eliminated unchanged in the bile. It is a substrate for hepatic uptake transporters that we have shown can be inhibited by uremic toxins in end-stage renal disease patients.
Erythromycin PK Parameters (mean ± SD) in 12 ESRD patients and 12 controls after 125 mg iv and 250 mg oral doses

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Controls</th>
<th>ESRD Patients</th>
<th>% Change (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL_H$ (L/h/kg)</td>
<td>0.51 ± 0.13</td>
<td>0.35 ± 0.14</td>
<td>31% ↓ (p = 0.01)</td>
</tr>
<tr>
<td>$F$ %</td>
<td>15 ± 6</td>
<td>21 ± 7</td>
<td>36% ↑ (NS, p = 0.36)</td>
</tr>
<tr>
<td>$F_H$ %</td>
<td>50 ± 10</td>
<td>64 ± 15</td>
<td>28% ↑ (p = 0.015)</td>
</tr>
<tr>
<td>$F_{abs} \cdot F_G$ %</td>
<td>33 ± 30</td>
<td>35 ± 28</td>
<td>← →</td>
</tr>
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</table>
Potential DDIs Predicted by BDDCS

• Class 1: Only metabolic in the intestine and liver
• Class 2: Metabolic, efflux transporter and efflux transporter-enzyme interplay in the intestine. Metabolic, uptake transporter, efflux transporter and transporter-enzyme interplay in the liver.
• Class 3 and 4: Uptake transporter, efflux transporter and uptake-efflux transporter interplay
Caution

A simple 4 category system won’t predict every interaction. BDDCS doesn’t propose that every drug in the class will be substrates or not substrates for uptake and efflux transporters. Rather, BDDCS enumerates what interactions should and should not be investigated.
The Use of BDDCS for Drugs on the Market

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**Increase the eligibility of drugs for BCS Class 1 biowaivers using measures of metabolism**
Since extent of metabolism correctly predicts high vs low intestinal permeability for at least 33 of 35 “drugs”, where human permeability measurements exist, Benet and co-workers\(^a\) propose the following:

“We recommend that regulatory agencies add the extent of drug metabolism (i.e., ≥90% metabolized) as an alternate method for the extent of drug absorption (i.e., ≥90% absorbed) in defining Class 1 drugs suitable for a waiver of in vivo studies of bioequivalence.”

A major advantage of BDDCS is that for drugs on the market, we know the extent of metabolism and they can generally be correctly classified without expensive and time consuming human permeability studies.

I am very pleased that the January 2010 EMA “Guideline on the Investigation of Bioequivalence” includes metabolism as a criteria for permeability and that EMA only accepts extent of absorption as a criteria for Class 1 biowaivers. Also, the FDA has said informally that they would accept metabolism information as a basis for biowaivers.
Additional Uses of BDDCS for New Molecular Entities and Its Role in Drug Development

- Predict the major route of elimination for an NME in humans (metabolisms vs excretion of unchanged drug in the urine and bile)
- Predict the relevance of transporters and transporter-enzyme interplay in drug disposition as described earlier for drugs on the market
- Predict central or lack of central effects
- Predict the effects of high fat meals on the extent of bioavailability
How can the concepts presented be used in predicting DMPK of an NME?

- In silico methodology, at present, is not sufficient (except possibly for $V_{ss}$). We cannot predict clearance & bioavailability.

- Permeability measures in Caco-2, MDCK or PAMPA vs metoprolol or labetalol will predict Class 1 & 2 vs. 3 & 4 and thus major route of elimination in humans.

- Is solubility over the pH range 1-7.5 more than 0.2 mg/ml (i.e., 50 mg highest dose strength) as proposed by Pfizer scientists, defining Class 1 & 3 vs. 2 & 4?
Can *in silico* models predict BDDCS class?

BDDCS Applied to Over 900 Drugs

Leslie Z. Benet, Fabio Broccatelli, and Tudor I. Oprea

Additional Uses of BDDCS for New Molecular Entities and Its Role in Drug Development

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The Use of BDDCS in Predicting the Brain Disposition of Orally Administered Drugs

Fabio Broccatelli, Caroline A. Larregieu, Gabriele Cruciani, Tudor I. Oprea and Leslie Z. Benet

Advanced Drug Delivery Reviews 64, 95-109 (2012)
From the literature we were able to identify 153 drugs that met three criteria:

a) central or lack of central pharmacodynamic effects were known (BBB+ or BBB-)

b) the BDDCS class was identified

c) information was available as to whether the drug was or was not a substrate for P-glycoprotein
In the analysis we found 18 of the 153 drugs were high permeability BDDCS Class 1 compounds that were also substrates of P-glycoprotein.

But of those 18 BDDCS Class 1 drugs, 17 (94.4%) exhibited central pharmacodynamic effects in humans.
Class 1 Drugs

A major proposition of BDDCS is that Class 1, P450/UGT metabolized drugs are not substrates of clinical relevance for transporters in the intestine, liver, kidney and brain.
Another Implication

Class 1 compounds will achieve brain concentrations whether this is desired or not for an NME, which could be the rationale for not always wanting Class 1 NMEs.
DDI Food Effects (High Fat Meals)
Fleisher et al., Clin Pharmacokinet. 36(3):233-254, 1999
The observed effects of high fat meals on the extent of bioavailability, $F_{extent}$, is consistent with high fat meals inhibiting transporters in the BDDCS predictions. Even if this is not found to be true, the supposition allows predictions of food effects on drug bioavailability. However, many factors are related to food effects, and the predictions here on $F$ are only correct @ 70% of the time.
The Use of BDDCS for Drugs on the Market

enguin potential drug-drug interactions not tested in the drug approval process

Predict the potential relevance of transporter-enzyme interplay

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- Sarah Shugarts, PhD
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- Chi-Yuan Wu, PhD
- HongXia Zheng, MD, PhD

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