The Biopharmaceutics Drug Disposition Classification System (BDDCS)

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FDA Approvals Over Past 50 Years
New Molecular Entities
Productivity of the pharma industry

Finding the true cost of a new drug is complex and controversial...

Akshat Rath | theconversation.com

* New drug cost and R&D spend could be 30% higher if non-PhRMA members are included

Data: USFDA, PhRMA

Dias 3
CDER New Molecular Entity (NME) and New Biologic License Application (BLA) Filings and Approvals
Rare or “orphan” diseases: affect 200,000 or fewer Americans. This is significant because patients with rare diseases often have few or no drugs available to treat their conditions.
ORKAMBI (Vertex)

a combination of lumacaftor and ivacaftor indicated for the treatment of cystic fibrosis (CF) in patients age 12 years and older who are homozygous for the F508del mutation in the CFTR gene.

(If the patients genotype is unknown, an FDA-cleared CF mutation test should be used to detect the presence of the F508del mutation on both alleles of the CFTR gene).
Rational Drug Design

Vertex was one of the first biotech firms to use an explicit strategy of rational drug design rather than combinatorial chemistry.
DRUGS USED TO BE DESIGNED WITH THE AVERAGE PATIENT IN MIND
NOW, THEY CAN BE TAILORED TO SPECIFIC PATIENTS' GENETICS, MICROBES, AND CHEMICAL COMPOSITION
The most sold drugs in 2014

1. Abilify Aripiprazole (Generic) - Psychosis; depression
2. Humira Adalimumab (AbbVie) - Crohn's disease; Rheumatoid arthritis
3. Nexium Esomeprazole (Generic) - Gastrointestinal Disorders
4. Crestor Rosuvastatin (AstraZeneca, Shionogi) - Cholesterol
5. Enbrel Etanercept (Amgen) - Rheumatoid
6. Advair Diskus, Seretide Fluticasone/salmeterol (GSK) - Asthma
8. Remicade Infliximab (Centocor Ortho Biotech, Inc., Mitsubishi, Tanabe Pharma) - Crohn's disease; rheumatoid arthritis
9. Lantus Solostar Insulin glargine (Sanofi-Aventis) - Diabetes mellitus type 1 and 2
10. Neulasta Filgrastim (Amgen) - Neutropenia
Simulating the Gastro-Intestinal Tract

- **mouth**
- **stomach**
- **duodenum**
- **jejunum**
- **ileum**
- **colon**

**Digestive Fluids and Enzymes**
- saliva
- amylase
- HCl
- pepsin
- Gastric lipase
- pancreatic enzymes

**Absorption**
- microbiota

**Hydrodynamics**
- Liquid volumes
- Transit times
The Stomach

Gastric secretions:
- Pepsin
- Gastric Lipase
- HCl
- Mucins

Gastric content
- Fasted state:
  - pH: 1.6 - 3
  - Vol: 25-75 ml
- Fed state:
  - pH: Food dependent
  - Vol: Food intake dependent

Leaky container – releasing digested food to the duodenum in a well controlled manner

Berthelsen et al, 2016
## Characterization of Human Fasted Gastric Fluids

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Volunteers Mean (± SD)</th>
<th>FaSSGF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>52.8 (±16.2)</td>
<td>-</td>
</tr>
<tr>
<td>pH</td>
<td>2.5 (±1.4)</td>
<td>1.6</td>
</tr>
<tr>
<td>Osmolality (mOsm/kg)</td>
<td>220 (±58)</td>
<td>120</td>
</tr>
<tr>
<td>Buffer capacity ((mmol/(L*ΔpH))</td>
<td>14.3 (±9.5)</td>
<td>-</td>
</tr>
<tr>
<td>Surface tension (mN/m)</td>
<td>34.8 (±5.2)</td>
<td>42.6</td>
</tr>
<tr>
<td>Bile salt (mM)</td>
<td>0.33 (±0.31)</td>
<td>0.08</td>
</tr>
<tr>
<td>Protein Content (g/L)</td>
<td>4.9 (±1.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>Gastric lipase (U/ml @pH2.8)</td>
<td>7.4 ± 4.0</td>
<td>-</td>
</tr>
</tbody>
</table>

20 volunteers
Endoscopic examination
Fasted state

Non-Newtonian Sheer-thinning properties

Pedersen et al EJPB 2013
Recombinant Human Gastric Lipase (rHGL)

Titrated fatty acids (µmol)
Animal derived lipase
Bioneer HGL
Plant HGL
Ave HGJ

0
5
10
15

Olive Oil/Gum Arabic emul

Titrated fatty acids (µmol)
MC-SNEDDS

Animal derived lipase
Mammalian HGL
Plant HGL
Ave HGJ

Sn1 & 3 specific - like nHGL

Same TBU activity

Sassene et al (in prep)
Why gastric modelling so important…?

Storage and mixing of ingested material
Mechanical breakdown of solid matrices
Chemical breakdown of food constituents
Particulate separation
Controlled delivery to small intestine
For Pharmaceuticals?
  - Disintegration, dissolution, hydration, API solubilisation, Food effects
Gastric mixing and dilution mapping

Fundus mixing
- Low stirring
- Heterogeneous
- Strongly dependent on meal-type
- Potential for long residency

Marciani et al. Am. J. Physiology 280, G1227, 2001
Dynamic Gastric Model (DGM) Construction Overview

**Main Body:**
Gentle contraction
3-wave per min cycle
In-homogenously mixed environment

**Antrum:**
High shear at 10 min\(^{-1}\)
well mixed environment
Phase II contraction waves

**Emptying:**
Pulses
“House-keeper” wave
Phase III contraction
Fasted State – Gastric Emptying

Quantification of Gastrointestinal Liquid Volumes and Distribution Following a 240 mL Dose of Water in the Fasted State

Deanna M. Mudie, Kathryn Murray, Caroline L. Hoad, Susan E. Pritchard, Martin C. Garnett, Gordon L. Amidon, Penny A. Gowland, Robin C. Spiller, Gregory E. Amidon, and Luca Marciani
Fed State – Gastric Emptying

Intake of FDA breakfast

Intragastric Volume Changes after Intake of a High-Caloric, High-Fat Standard Breakfast in Healthy Human Subjects Investigated by MRI

Mirko Koziolek, Michael Grimm, Grzegorz Garbacz, Jens-Peter Kühn, and Werner Weitschies
Example: Capsule Behaviour in the Stomach

Capsule Endoscopy:
A minimally-invasive method directly visualizing capsule/tablet behavior in the human stomach (fasted).

- Human volunteers
- 240 ml of water co-dosed

Pedersen et al., Pharm Res, 2014
Digestion: Small Intestine

Duodenum

Food intake simulated secretion of Bile
- Bile salts (2-4mM Fasted to 8-20mM Fed)
- Phospholipids
- Cholesterol

Pancreatic enzymes
- Proteases (chymotrypsin, trypsin)
- Amylase
- Pancreatic triglyceride lipase
- Pancreatic lipase-related protein 2 (PLRP2)
- Carboxyl ester hydrolase (CEH)

Other changes: pH, viscosity, osm, surface tension, buffer capacity
Human Fasted Gastric and Intestinal Fluids

- pH
- Buffer capacity
- Osm
- Surface tension

Bergström et al, 2013
Bile salt and phospholipid in fasted GI fluids

Bergström et al, 2013
Digestion: Small Intestine

Bile & pancreatic duct

Pancreatic lipase
Colipase
Bile salt–phospholipid micelles

Absorption
Human intestinal fluids

Fed state: 60 min after intake of an emulsion
Large intestinal surface area

Drug absorption dependent on

- Solubility in intestinal fluids
- Permeability across
  - Mucus
  - epithelium

Mucus layer (produced by goblet cells)
- Penetration barrier
- Anchor....?
Absorption of drugs from tablets, granules, and small particles involves a sequence of disintegration and dissolution steps. The process begins with tablet disintegration, followed by granules and small particles, each leading to limited or best dissolution. The drug in solution facilitates absorption, indicating the final stage of drug absorption.
Dissolution rate (DR)

Noyes-Whitney equation:

\[
DR = \frac{dX}{dt} = \frac{AD}{h}(C_s - C_b)
\]

Solid drug particle

stagnant layer (h = thickness) with concentration = \( C_s \)

Bulk solvent

bulk solution with concentration = \( C_b \)
Massbalance in a gut segment

\[ \frac{dM}{dt} = AJ = AP_{\text{eff}} CS \]

\[ \frac{dM_{\text{in}}}{dt} \quad \rightarrow \quad \frac{dM_{\text{out}}}{dt} \]
Transit time in the small intestine ?

Pharmacokinetics and Transit Parameters
Danazol BA in healthy volunteers

<table>
<thead>
<tr>
<th></th>
<th>Standard</th>
<th>Standard + 800 ml water</th>
<th>Standard + lipid-rich meal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (ng/ml)</td>
<td>25±17</td>
<td>23±15</td>
<td>60±24&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>3.1 (2.3-4.0)</td>
<td>3.8 (2.5-5.2)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.0 (2.9-5.7)&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Absolute bioavailability (%)</td>
<td>11±5.2</td>
<td>17±3.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>44±12&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gastric residence time, $T_{\text{lag}}$ (min.)</td>
<td>14±11</td>
<td>25±13</td>
<td>44±20&lt;sup&gt;ab&lt;/sup&gt;</td>
</tr>
<tr>
<td>Gastric emptying rate, $T_{50%}$ (min.)</td>
<td>13±9.0</td>
<td>30±28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49±25&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Small intestinal transit time (min.)</td>
<td>241±58</td>
<td>269±38</td>
<td>268±106</td>
</tr>
</tbody>
</table>

*Standard*: Administration of danazol in the fasted state with 200 ml water.

<sup>a</sup> Significantly different from *Standard* ($p<0.05$).

<sup>b</sup> Significantly different from *Standard + 800 ml water* ($p<0.05$).

Sunesen et al., 2005
Evaluation of drug substances

Evaluation of "drugability" – "druglikeness"

• Lipinskis Rule of Five
• The Biopharmaceutical Classification system
• Etc...
Lipinski's Rule of Five

In general, an orally active drug has:

1. Not more than 5 hydrogen bond donors (OH and NH groups)

2. Not more than 10 hydrogen bond acceptors (notably N and O)

3. A molecular weight under 500 g/mol

4. A partition coefficient log $P$ less than 5
The Biofarmaceutics Classification System (BCS)

Based on fundamental variables:
- Permeability and solubility

Identify controlling variables

Simplify registration procedures
- Eg. FDA’s SUPAC (Scale-Up and Post-Approval Changes for manufacturing of drugs).
Biopharmaceuticals Classification System

High Solubility

1. Acetaminophen
   Propranolol
   Metoprolol
   Valproic acid

High Permeability

2. Carbamazepine
   Cyclosporine
   Digoxin
   Ketoconazole
   Tacrolimus

Low Solubility

3. Cimetidine
   Ranitidine
   Peptides

Low Permeability

4. Chlorothiazide
   Furosemide
   Methotrexate

Amidon et al., Pharm Res 12: 413-420, 1995
Marketed vs NME in development

Distribution of 698 oral immediate release drugs on the market and NME percentages from a data set of 28,912 medicinal chemistry compounds

Benet LZ, J Pharm Sci, 2013
BCS - Definition:
High solubility

A drug compound that, in the highest human dose, is soluble in 240 ml aqueous media over the entire physiological pH range (pH 1-7.5).

$$D_0 = \frac{M_0}{250} \frac{1}{C_s} \leq 1$$
BCS - Definition:
High permeability

A drug compound, for which the absorbed fraction in humans is 90% or more of the administered dose.
Three important dimensionless parameters in oral drug delivery:

**Dose number:**

\[ D_0 = \frac{M_0}{V_0} \frac{1}{C_s} \]

\[ V_0 = 240 \text{ ml} \]

**Dissolution number:**

\[ D_n = \frac{t_{\text{res}}}{t_{\text{diss}}} \]

\[ t_{\text{diss}} = r_0^2 \rho / 3DC_s \]

**Absorptions number:**

\[ A_n = \frac{t_{\text{res}}}{t_{\text{abs}}} \]

\[ t_{\text{abs}} = \frac{V}{S} P_{\text{eff}} \]
Fraction absorbed vs. Human jejunal permeability

Lennernäs et al.
Intestinal permeability and plasma pharmacokinetic assessment simultaneously

Loc-I-Gut

Hans Lennernäs
# Dose and dissolution numbers

<table>
<thead>
<tr>
<th>Drug substance</th>
<th>Dose (mg)</th>
<th>$C_S$ (mg/ml)</th>
<th>$V_{sol}$ (ml)</th>
<th>$D_0$</th>
<th>$D_n$</th>
</tr>
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<tbody>
<tr>
<td>Piroxicam</td>
<td>20</td>
<td>0,007</td>
<td>2857</td>
<td>11,4</td>
<td>0,15</td>
</tr>
<tr>
<td>Cimetidin</td>
<td>800</td>
<td>6,00</td>
<td>133</td>
<td>0,53</td>
<td>129</td>
</tr>
<tr>
<td>Chlorthiazid</td>
<td>500</td>
<td>0,786</td>
<td>636</td>
<td>2,54</td>
<td>17,0</td>
</tr>
<tr>
<td>Digoxin</td>
<td>0,5</td>
<td>0,024</td>
<td>20,8</td>
<td>0,08</td>
<td>0,52</td>
</tr>
<tr>
<td>Griseofulvin</td>
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<td>33333</td>
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<td>0,32</td>
</tr>
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<td>Carbamazepin</td>
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<td>0,26</td>
<td>769</td>
<td>3,08</td>
<td>5,61</td>
</tr>
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## Dose number:

$$D_0 = \frac{M_0}{V_0} \cdot \frac{1}{C_S}$$

## Dissolution number:

$$D_n = \frac{t_{res}}{t_{diss}}$$

Amidon et al., 1995
Absorption parameters for some drugs

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$$D_0 = \frac{M_0}{V_0} \frac{1}{C_S}$$

**Dissolution number:**

$$D_n = \frac{t_{res}}{t_{diss}}$$

Amidon et al., 1995
Three important dimensionless parameters in oral drug delivery:

**Dose number:**

\[ D_0 = \frac{M_0}{V_0} \frac{1}{C_s} \]

\[ V_0 = 250 \text{ ml} \]

**Dissolution number:**

\[ D_n = \frac{t_{res}}{t_{diss}} \]

\[ t_{diss} = r_0^2 \rho / 3DC_s \]

**Absorptions number:**

\[ A_n = \frac{t_{res}}{t_{abs}} \]

\[ t_{abs} = \frac{V}{S P_{\text{eff}}} \]
Wu C.Y. and Benet L.Z.

Predicting drug disposition via application of BCS: transport/absorption/elimination interplay and development of a biopharmaceutics drug disposition classification system

Pharmaceutical Research, 22, 11-23, 2005
The fate of a drug in the body

- Formulation
- Administration route
- Absorption
- Distribution
- Metabolism
- Excretion
Routes of intestinal absorption

paracellular  
transcellular  

efflux  
endocytosis  

passive  
carrier mediated  
specialized
Interplay between P-gp and CYP3A4 in the enterocytes
First pass metabolism

http://www.doctorfungus.org/thedrugs/images/antifung1.jpg
<table>
<thead>
<tr>
<th>High Solubility</th>
<th>Low Solubility</th>
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<tbody>
<tr>
<td><strong>Class 1</strong></td>
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<tr>
<td>Abacavir</td>
<td>Itraconazole</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>S,I</td>
</tr>
<tr>
<td>Acyclovir b</td>
<td>Ketoconazole</td>
</tr>
<tr>
<td>Amiloride S,I</td>
<td>I</td>
</tr>
<tr>
<td>Amitriptyline S,I</td>
<td>Lansoprazole</td>
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<tr>
<td>Antipyrine</td>
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<td>Atropine</td>
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<tr>
<td>Buspirone c</td>
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<td>Caffeine</td>
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<td>Captopril</td>
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<td>Cyclophosphamide</td>
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<td>Desipramine</td>
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<td>Doxepin</td>
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<td>Imipramine I</td>
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<td>Prednisolone</td>
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<td>Danazol</td>
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<td>Griseofulvin</td>
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<td>Ibuprofen</td>
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<td>Indinavir S</td>
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<td>Indomethacin</td>
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<td>Itraconazole S,I</td>
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<td>Ketoconazole I</td>
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<td>Lansoprazole I</td>
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<td>Lovastatin S,I</td>
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</tr>
<tr>
<td>Mebendazole</td>
<td></td>
</tr>
<tr>
<td>Naproxen</td>
<td></td>
</tr>
<tr>
<td>Nelfinavir S,I</td>
<td></td>
</tr>
<tr>
<td>Nifedipine S</td>
<td></td>
</tr>
<tr>
<td>Ofloxacin</td>
<td></td>
</tr>
<tr>
<td>Oxaprozin</td>
<td></td>
</tr>
<tr>
<td>Phenazopyridine</td>
<td></td>
</tr>
<tr>
<td>Phenytoin S</td>
<td></td>
</tr>
<tr>
<td>Piroxicam</td>
<td></td>
</tr>
<tr>
<td>Raloxifene S</td>
<td></td>
</tr>
<tr>
<td>Ritonavir S,I</td>
<td></td>
</tr>
<tr>
<td>Saquinavir S,I</td>
<td></td>
</tr>
<tr>
<td>Sirolimus S</td>
<td></td>
</tr>
<tr>
<td>Spironolactone I</td>
<td></td>
</tr>
<tr>
<td>Tacrolimus S,I</td>
<td></td>
</tr>
<tr>
<td>Talinolol S</td>
<td></td>
</tr>
<tr>
<td>Tamoxifen I</td>
<td></td>
</tr>
<tr>
<td>Terfenadine I</td>
<td></td>
</tr>
<tr>
<td>Warfarin</td>
<td></td>
</tr>
</tbody>
</table>

**BOLD:** CYP3A substrates (21/44)
**ITALICS:** Not decided (3/44)
<table>
<thead>
<tr>
<th>Low Permeability</th>
<th>High Solubility</th>
<th>Low Solubility</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class 3</strong></td>
<td></td>
<td><strong>Class 4</strong></td>
</tr>
<tr>
<td>Acyclovir</td>
<td>Fexofenadine&lt;sup&gt;S&lt;/sup&gt;</td>
<td>Amphotericin B</td>
</tr>
<tr>
<td>Amiloride&lt;sup&gt;S,I&lt;/sup&gt;</td>
<td>Folinic acid</td>
<td>Chlorthalidone</td>
</tr>
<tr>
<td>Amoxicillin&lt;sup&gt;S,I&lt;/sup&gt;</td>
<td><em>Furosemide</em></td>
<td>Chlorothiazide</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Ganciclovir</td>
<td>Colistin</td>
</tr>
<tr>
<td>Atropine</td>
<td><em>Hydrochlorothiazide</em></td>
<td>Ciprofl oxacin&lt;sup&gt;S&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Lisinopril</td>
<td>Furosemide</td>
</tr>
<tr>
<td>Bidisomide</td>
<td>Metformin</td>
<td><em>Hydrochlorothiazide</em></td>
</tr>
<tr>
<td>Captopril</td>
<td><em>Methotrexate</em></td>
<td>Mebendazole</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Nadolol</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>Cetirizine</td>
<td>Pravastatin&lt;sup&gt;S&lt;/sup&gt;</td>
<td>Neomycin</td>
</tr>
<tr>
<td>Cimetidine&lt;sup&gt;S&lt;/sup&gt;</td>
<td>Penicillins</td>
<td></td>
</tr>
<tr>
<td>Ciprofl oxacin&lt;sup&gt;S&lt;/sup&gt;</td>
<td>Ranitidine&lt;sup&gt;S&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Cloxacillin</td>
<td>Tetracycline</td>
<td></td>
</tr>
<tr>
<td>Dicloxacillin&lt;sup&gt;S&lt;/sup&gt;</td>
<td>Trimethoprim&lt;sup&gt;S&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Erythromycin&lt;sup&gt;S,I&lt;/sup&gt;</td>
<td>Valsartan</td>
<td></td>
</tr>
<tr>
<td>Famotidine</td>
<td>Zalcitabine</td>
<td></td>
</tr>
</tbody>
</table>

*BOLD*: CYP3A substrates  
*ITALICS*: Not decided
Major Routes of Drug Elimination

- **High Solubility**
  - Class 1: Metabolism

- **Low Solubility**
  - Class 2: Metabolism

- **High Permeability**
  - Class 3: Renal & Biliary Elimination of Unchanged Drug

- **Low Permeability**
  - Class 4: Renal & Biliary Elimination of Unchanged Drug
Implications of a Correlation between Permeability and Metabolism?

If the intestinal absorption (or Caco-2 permeability) of a compound is known:

→ the major route of elimination (metabolism or excretion) can be predicted.

Note:
The permeability parameter does not predict the ability for the compound to enter the liver / hepatocytes, but rather the access to the metabolic enzymes within the hepatocytes. (Some non-metabolized Classes 3 & 4 compounds will be excreted in the bile)
BDDCS

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

BDDCs predicts:

- The major **route of elimination** of an NME in humans (metabolism vs excretion of unchanged drug in the urine and bile)
- The relevance of **transporters** and transporter-enzyme interplay in drug disposition as detailed in Fig. 2 and Table 1
- Central or lack of central effects
- The effects of **high fat meals** on the bioavailability
Biopharmaceutics Drug Disposition Classification System (BDDCS)

- **Class 1 (High Solubility, Extensive Metabolism)**
  - High Solubility
  - Extensive Metabolism
  - (Rapid Dissolution and ≥70% Metabolism for Biowaiver)

- **Class 2 (Low Solubility, Extensive Metabolism)**
  - Low Solubility
  - Extensive Metabolism

- **Class 3 (High Solubility, Poor Metabolism)**
  - High Solubility
  - Poor Metabolism

- **Class 4 (Low Solubility, Poor Metabolism)**
  - Low Solubility
  - Poor Metabolism
What about active transport / transporter effects?
Class 1
Highly soluble, High permeability, Extensively metabolized drugs

Transporter effects - minimal in the intestine and the liver

Even compounds like verapamil that can be shown in certain cell models (MDCK-MDR1) to be a substrate of P-gp - will exhibit no clinically significant P-gp effects in the gut and liver

(but the BBB and the kidney are not the gut and liver)
Class 2
Poorly soluble, Highly permeable, Extensively metabolized drugs

Uptake transporters can be important for the liver but not the intestine.

Efflux transporter effects will be important in the intestine and the liver.

Efflux transporter–enzyme (CYP 3A4 and UGTs) interplay in the intestine can markedly affect oral bioavailability.

Efflux transporter-enzyme interplay in the liver will yield counter-active effects to that seen in the intestine.
Class 1: High Solubility
Transporter effects minimal in gut and liver

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

Class 3: High Permeability/High Metabolism
Absorptive transporter effects predominate (but can be modulated by efflux transporters)

Class 4: Low Permeability/Low Metabolism
Absorptive and efflux transporter effects could be important
Advantage of BDDCS:

Drugs can generally be correctly classified without running expensive and time consuming permeability studies in humans.

BDDCS limits:

At this time - not sufficient for the regulatory agencies

BUT
It gives scientists a roadmap for predicting drug disposition and drug-drug interaction characteristics very early and with little additional expense.
### Biopharmaceutic Drug Disposition Classification System (BDDCS)

<table>
<thead>
<tr>
<th>Class 1</th>
<th>Class 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>High solubility</td>
<td>Low solubility</td>
</tr>
<tr>
<td>Rapid dissolution</td>
<td>High permeability</td>
</tr>
<tr>
<td>High permeability</td>
<td>Ext. Metabolism</td>
</tr>
<tr>
<td>Ext. Metabolism</td>
<td>Efflux in gut</td>
</tr>
<tr>
<td>Minimal transporter</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Class 3</th>
<th>Class 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>High solubility</td>
<td>Low solubility</td>
</tr>
<tr>
<td>Low permeability</td>
<td>Low permeability</td>
</tr>
<tr>
<td>Poor metabolism</td>
<td>Poor metabolism</td>
</tr>
<tr>
<td>Transporters+efflux</td>
<td>+Transporters &amp; efflux</td>
</tr>
</tbody>
</table>

**Jejunal Permeability**

\[ P_{eff} \times 10^{-4} \text{ cm/sec} \]

**Solubility**: Volume (ml) of water required to dissolve the highest dose at the lowest solubility in the pH 1-7.5 range.
Bioequivalence

• Determination of relative bioavailability

• Test of a product compared to another product:
  • a batch from a clinical trial
  • from a new factory, upscaling
  • generic drugs

• 90% confidence interval within 0.80-1.25 (AUC-ratio)
• 90% confidence interval within 0.80-1.25 (Cmax-ratio), but 0.75-1.33 allowed
Clinical bioequivalence studies can be avoided and replaced by dissolution

Biowaivers

Generally the case for BCS **Class I** compounds (FDA, EMA)

Case to case evaluation

- Narrow therapeutic index
- Pharmaco-kinetics
- Excipients
85% release within 15 min (30 min)

Rapid releasing tablets and capsules: the drug substance dissolves in the gastric fluid.

Absorption rate primarily controlled by gastric emptying time:

- Dissolution controlled by disintegration (tablet, capsule) therefore, disintegration test may substitute dissolution in the quality control (ICH guideline)

- Bioequivalence studies may be based on dissolution tests (FDA guide, EU guide)

- EU guide 15 min, FDA guide 2000, 30 min
85% release within 15 min (30 min)

SUPAC guidelines
- change of excipient supplier
- change of excipient
- change of manufacturing method

Bioequivalence can be demonstrated by the use of dissolution testing

-----

This demonstrates that the introduction of BCS means deregulation of drug manufacturers
In Vivo In Vitro Correlations

- The possibility of defining predicative in vitro methods
**BSM Class and In Vivo In Vitro Correlation (IVIVC)**

<table>
<thead>
<tr>
<th>Jejunal Permeability Peff (x10^-4) cm/sec</th>
<th>Rapid Dissolution</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Likely</td>
</tr>
<tr>
<td>10</td>
<td>I</td>
</tr>
<tr>
<td>Dissolution rate &gt; gastric emptying</td>
<td>Dissolution likely to be “rate determining” IVIVC possible (would need to be demonstrate)</td>
</tr>
<tr>
<td>- dissolution not likely to be rate determining</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>III</td>
</tr>
<tr>
<td>As Class I – But permeability issues need to be examined</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td>IV</td>
</tr>
<tr>
<td>Generally “problem” drugs</td>
<td>IV</td>
</tr>
<tr>
<td>IVIVC not expected, but may be possible</td>
<td></td>
</tr>
<tr>
<td>0.01</td>
<td></td>
</tr>
</tbody>
</table>

“Solubility”: Volume (ml) of water required to dissolve the highest dose at the lowest solubility in the pH 1-7.5 range
Developability Classification systems

Butler & Dressman, 2010, JPS
Developability Classification systems
Oral Drug Development – use of Dissolution

- Phys-chem characterization
- IDR
- Simulated GI fluids
- Permeability

API

Formulation development
- Release / Dissolution tests
- Physiologically relevant

Quality Target Product Profile

Quality Control
Dissolution

Final Dosage Form
WP 1: Physico-chemical tools – Understanding the API
UCPH, UU, U-Strath, Sirius, U-Goethe, EFPIA contributors

Supersaturation and precipitation
uDiss Profiler

Palmelund et al, submitted
Supersaturation & Precipitation Studies in fasted state intestinal media

Department of Pharmacy

Palmelund et al, submitted
Supersaturation & Precipitation
Induction time vs. Degree of Supersaturation (DS)

Supersaturation propensity is drug dependent

Department of Pharmacy

Palmelund et al, submitted
Supersaturation & Precipitation
Precipitation inhibitor effect

Effect of precipitation inhibitors can be assessed
Facilitating drug development

Department of Pharmacy

Palmelund et al, submitted
Mucus-secreting cells

Caco-2 cells
**Solid state form**

**Crystalline form of a drug**
Solids with orientational and positional long-range order in three dimensions.

**Amorphous form of drug**
Solids with no orientational or positional long-range order.

**Amorphous forms**
- Higher solubility
- Enhanced dissolution rate
- Physically and chemically unstable

(Perrie and Rades 2012)

(Nielsen et al 2013, EJPB)
Solubility and intrinsic dissolution rate of furosemide

Apparent solubility in intestinal medium pH 6.5

Intrinsic dissolution rate in intestinal medium pH 6.5

(Nielsen et al 2013, EJPB)
Dissolution profiles by µ-Diss profiler

- Amorphous salt
- Amorphous acid
- Crystalline acid
Bioavailability in rats

<table>
<thead>
<tr>
<th></th>
<th>Amorphous salt</th>
<th>Amorphous acid</th>
<th>Crystalline acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T_{\text{max}}$ (min)</td>
<td>23.3±5.2</td>
<td>41.3±7.5</td>
<td>38.8±12.5</td>
</tr>
<tr>
<td>$C_{\text{max}}$ (µg/mL)</td>
<td>4.7±2.0</td>
<td>3.6±1.2</td>
<td>3.2±1.1</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-60\ \text{min})}$ (µg·min/mL)</td>
<td>193.9±72.0</td>
<td>138.4±38.7</td>
<td>110.0±24.9</td>
</tr>
<tr>
<td>$\text{AUC}_{(0-1440\ \text{min})}$ (µg·min/mL)</td>
<td>1564.0±487.9</td>
<td>1684.9±610.7</td>
<td>1611.0±361.0</td>
</tr>
<tr>
<td>Absolute BA (%)</td>
<td>25.1±7.2</td>
<td>28.3±10.7</td>
<td>26.8±6.7</td>
</tr>
</tbody>
</table>
Method

UV Imager - Setup

Flow through dissolution coupled with Raman spectroscopy
Dissolution Visualisation by UV imaging

- Analysed at 365 nm wavelength filter.
- The experiments were carried out at 23-25°C
  - In a simulated intestinal medium at pH 6.5
  - Constant flow rate of 1 mL/min.

(A) amorphous furosemide salt  
(B) crystalline salt  
(C) amorphous acid form  
(D) crystalline acid
Amorphous salt during dissolution

Flow through dissolution coupled with Raman Spectroscopy

PCA plot of the conversion of amorphous salt during dissolution
Rapid trihydrate formation during dissolution – probably responsible for disappointing *in vivo* performance.
Take Home message

Increasing cost of drug development
Increasing number of drugs
Lots of biologics – but still not majority

Classifications of drugs
Lipinski’s rule of 5
Biopharmaceutics Classification system
Biopharmaceutics Drug Disposition Classification system

Solubility, Permeability, absorption mechanism, metabolism