Volume to dissolve applied dose (VDAD) and apparent dissolution rate (ADR) – tools to predict *in vivo* bioavailability from orally applied drug suspensions
Overview

- Introduction
- Methods and Materials
- Results
- Summary
Gi tract environment

**Stomach**

pH: fasted, 1-3; fed, up to 7
(Dressman JB et al., Adv Drug Del Rev 59; 2007)

Half-life gastric emptying: ~ 20-40 min. (water)
(Lin HC et al. Digestive Diseases and Sciences 6; 2005)

Liquid Volume: fasted, 25ml, secretion 1-2ml/min; fed, secretion 10-50ml/min
(Kong F et al., JFS 73; 2008)

**Small Intestine**

pH: fasted, 6 - 7.5, fed, 5 - 7.5
(Dressman JB et al., Adv Drug Del Rev 59; 2007)

Transit Time: ~ 2 - 4 hours
(Maurer AH et al. Seminars in Nuclear Medicine 4; 1995)

Liquid Volume: fasted, ~ 90 - 165 ml
Fed, up to ~ 400 ml
(Sutton SC, AAPS 11; 2009, Marciani L et al., Gastroenterology 138; 2010)

→ Orally applied compounds have to face varying conditions
GI tract environment

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GI tract environment

Various scenarios possible

→ Compound not dissolving throughout entire GI tract

→ Compound dissolves in stomach, precipitates in intestine (crystalline?amorphous?), e.g. bases

→ Compound not dissolving in stomach, but dissolves in intestine; e.g. acids

→ Compound soluble throughout entire GI tract

→ Varying conditions may influence dissolution, thus bioavailability
PhysChem selection pressure

Pfizer compound file (Gribbon P et al., DDT 10; 2005)

% of low solubility compounds (<5mg/L)

marketed compounds (clogP)

(Vieth M et al., J Med Chem 47; 2004)

→ PhysChem selection pressure increased with time
Confirmed HTS hits at BSP show lower solubility, higher clogP, and higher clogD<sub>7.5</sub> when compared to oral market drugs (< Dec. 2004)

_datasets described in M. Lobell et al., ChemMedChem 2006, 1, 1229-1236_
Increasing number of low solubility compounds

Reasons

HTS Assays performed from DMSO stock solutions
→ concentration in assay is reflected by kinetic solubility

Broadening of chemical space
→ supported by launch of combinatorial chemistry
→ increased ligand-receptor affinity often achieved by addition of lipophilic residues
→ occasionally IP status

Indication (e.g. Cancer)

→ Various matters of modern drug discovery contribute to an increase of low-solubility compounds
Increasing number of low solubility compounds

Problems

Difficulties in reaching sufficient multiples of exposure during animal toxicology testing

Poor absorption in humans

→ lack of efficacy
→ increased risk of absorption variability (often supported by increased food effect)
→ increased risk of side effects with compounds of low safety window
→ increased cost for development of drug product (e.g. solubilization technologies)
→ increased cost due to respective clinical trials

→ Solubility related absorption limitation may lead to an unacceptable risk for the patient
→ Attrition risk increased due to increased cost and decreased probability of success
Typical project team conversation

PK scientist: The oral bioavailability of solid compound in rat is really low…

Chemist: Oh no, that sucks!

PK scientist: Indeed, maybe formulation development can save the compound?

Chemist: Yeah, that sounds like a really great idea!

Form.Scient.: No way, make the compound more soluble!

Chemist (a bit displeased since he already spent 3 years on lead optimization):

´So then, how soluble do you want it´?

→ How soluble must a compound be at a given dose to ensure complete in vivo dissolution?
Correlation of *thermodynamic solubility or dissolution* with oral *relative bioavailability (BA suspension vs. BA solution)* reveals thermodynamic solubility and *in vitro* dissolution data that indicate sufficient in vivo dissolution.
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Compound Inclusion Criteria

- 37 structurally diverse compounds
- molecular weight: 289 to 676 g/mol
- clogP values (BioByte™): -0.49 to 6.93
- topological polar surface areas (TPSA): 49.3 to 162 Å²
- calculated pKa values for strongest acid: -2.23 to no deprotonation
- calculated pKa values for strongest base: 12.4 to no protonation

Structurally diverse compound set was used for studies
### Caco-2 transport assay

Validated using 20 market compounds (fraction dose absorbed in humans ($F_{\text{abs}}$) known)

<table>
<thead>
<tr>
<th>Permeability BCS classification</th>
<th>Fraction dose absorbed human [%]</th>
<th>Papp values in Caco-2 assay [nm/s]</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>≥ 90</td>
<td>≥ 70</td>
</tr>
<tr>
<td>Moderate</td>
<td>50-90</td>
<td>10-70</td>
</tr>
<tr>
<td>Low</td>
<td>&lt; 50</td>
<td>&lt; 10</td>
</tr>
</tbody>
</table>

\[
P_{\text{app}} = \frac{V \text{ (receiver)} \times \text{conc. (receiver @ 2h)}}{\text{conc. (donor @ 0h)} \times \text{surface area} \times \text{time}}
\]

**Efflux Ratio:** $P_{\text{app bas}} / P_{\text{app ap}}$

→ Compounds exhibit $P_{\text{app}}$ values > 10nm/s, indicating moderate to high permeability
→ Compounds exhibit absolute bioavailabilities (solution, p.o. rat) of > 20%
Compound Inclusion Criteria

Micronization (Air Jet Mill)

- Particle Size
  - Ø x10, 0.7 µm
  - Ø x50, 2.1 µm; Ø x90, 5.2 µm

- XRPD
- FT-Raman Spec.
- DSC

→ Particle size in the single digit micrometer range
→ Micronization had no significant influence on solid state characteristics
**Experimental Procedures**

### Apparent Dissolution Rate

- 1 mg micronized API per cell
- Flow Rate 2 ml / min
- pH 1, 4.5, 6.8
- 2 minute fractions collected over 14 minutes
- HPLC Analytics

→ Apparent dissolution rate was determined using the Mini-Flow-Thru Cell
→ Thermodynamic Solubility was determined using the Shake Flask Method
**Experimental Procedures**

**Relative Bioavailability**

**Micronized API suspension**

**API solution (e.g. PEG/EtOH/H2O)**

**Immediate release tablet (micronized API)**

**API solution (e.g. PEG 400)**

\[
\frac{AUC_{\text{norm}}(\text{suspension/tablet})}{AUC_{\text{norm}}(\text{solution})} = \text{relative bioavailability}
\]

→ Relative bioavailability is postulated to represent *in vivo* dissolution
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Relative bioavailability rat vs. human (p.o.)

~ 50% relative bioavailability in rat is considered uncritical with respect to in vivo dissolution in human.
Relative bioavailability (rat p.o.) increases with increasing in vitro dissolution.
Relative bioavailability (rat p.o.) > 50% is reached with ~ 150 – 200 µg API dissolved.

Rel. BA > 50% considered uncritical
Log Volume to dissolve applied dose vs. rel. BA (rat p.o.)

Rel. BA > 50% considered uncritical

Log (Volume to dissolve applied dose [L/kg]) @ 25°C

→ Relative bioavailability (rat p.o.) > 50% is reached with ´volumes to dissolve the applied dose´ of < 100 ml/kg (pH 4.5) and < 500 ml/kg (pH 7)

→ Correlation @ pH 1 is of limited predictive value: gastric pH in rat is 3.8 - 5

Example: dose 10mg/kg; solubility @ pH 7: 40 mg/L

\[ \text{Lg VDAD} = \text{Lg} \left( \frac{\text{dose}}{\text{solubility}} \right) = \text{Lg} \left( \frac{10 \text{ mg/kg}}{40 \text{ mg/L}} \right) = \text{Lg} 0.25 \text{ L/kg} = -0.60 = \sim 60\% \text{ rel. BA} \]
When the dose/solubility ratio is >1000 ml, even in the presence of favorable physiological factors (pH, bile salts), the solubility is likely to cause problems with bioavailability. 

(Dressman JB et al., Clin Pharmacokinet 47; 2008)

Compounds with aqueous solubilities of < 100 mg/L often present dissolution limitations to absorption.

(Hörter D et al., Adv Drug Del Rev 46; 2001)

A solubility of 10 - 100 mg/L received a medium risk (‘0’, on a ‘+, 0, -’ scale) in the Aventis PhysChem Score card

(Balbach S et al., Journal of Pharmaceutics 275; 2004)

Example: dose 10 mg/kg; solubility @ pH 7: 40 mg/L

Dose/solubility ratio: 17.5L

Solubility of 40 mg/L

+ (low risk)

→ Current estimates of critical solubility values that would dictate absorption limitation appear to be rather conservative
### Biopharmaceutics Classification System (BCS):

A drug substance is considered highly soluble when the highest dose strength is soluble in 250 ml or less of aqueous media over the pH range of 1-7.5

- **Class 1:** High Solubility – High Permeability
- **Class 2:** Low Solubility – High Permeability
- **Class 3:** High Solubility – Low Permeability
- **Class 4:** Low Solubility – Low Permeability

### Thermodynamic Solubility

<table>
<thead>
<tr>
<th>Compound</th>
<th>pH 1</th>
<th>pH 4.5</th>
<th>pH 7</th>
<th>Daily dose [mg]</th>
<th>Volume to dissolve daily dose at worst case pH [L]</th>
<th>Prelim. BCS classification</th>
<th>Rel. BA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td></td>
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<tr>
<td>1</td>
<td>&gt;10000</td>
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<td>22</td>
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<td>3.18</td>
<td>55</td>
<td>4</td>
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<tr>
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<td>19.1</td>
<td>429</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>&gt; 10000</td>
<td>215</td>
<td>&lt; 1</td>
<td>70</td>
<td>&gt; 70</td>
<td>42</td>
<td>4</td>
</tr>
</tbody>
</table>

→ Complete in vivo dissolution despite ´class 2/4´ according to BCS classification
→ BSC classification might be too strict
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Summary

- In vivo dissolution was described by means of relative bioavailability (solution vs. suspension, p.o.)

- A diverse set of 37 compounds with Papp > 10 nm/s and > 20% F (rat) was used to perform in vitro/in vivo correlation of dissolution

- A relative bioavailability in rat (p.o.) of 50% was assumed to be rather uncritical with respect to in vivo dissolution in humans

- Apparent dissolution rates of ~ 150-200 µg/14 minutes (under respective assay conditions) result in relative bioavailability > 50% (rat p.o.)

- Volumes to dissolve applied dose of ~100 ml/kg (pH 4.5) – 500 ml/kg (pH 7) result in relative bioavailability > 50% (rat p.o.)

- Data provide guidance for medicinal chemists during the lead optimization phase
Thanks to all my dear colleagues!

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Volume to dissolve applied dose (VDAD) and apparent dissolution rate (ADR) – tools to predict in vivo bioavailability from orally applied drug suspensions

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