In Vitro Dissolution Absorption System (IDAS): Simultaneous Dissolution and Permeation Evaluation

Chris Bode, Ph.D.
VP Scientific & Corporate Communications
In Vitro Dissolution Absorption System

Biopharmaceutics Dissolution with Better *In Vivo* Correlation
A Closer Look at IDAS2

Dissolution Chamber
A Closer Look at IDAS2

Heating Jacket  Stirrer  Permeation Chambers
Why IDAS?

- Dissolution and permeability are routinely measured independently and under conditions that may have little physiological relevance
  - Poor discrimination, which impacts the link between *in vitro* drug product release characteristics and *in vivo* performance.
  - Limited utility in formulation development and optimization

- IDAS enables concomitant evaluation of bio-relevant processes
  - Improved IVIVC
Dissolution – Permeability Relationship: Class I

CLASS I

PROPRANOLOL

Dissolution

% DISSOLVED

TIME (MINUTES)

Permeability

% PERMEATED

TIME (MINUTES)
Dissolution – Permeability Relationship: Class II
Dissolution – Permeability Relationship: Class III

CLASS III
RANITIDINE

DISSOLUTION

PERMEABILITY

% DISSOLVED

TIME (MINUTES)

% PERMEATED

TIME (MINUTES)
Dissolution – Permeability Relationship: Class IV

CLASS IV
SAQUINAVIR

DISSOLUTION

PERMEABILITY

% DISSOLVED

TIME (MINUTES)

% PERMEATED

TIME (MINUTES)
Batch Release Data for Amlodipine - Q value was similar for different manufacturers

Data using IDAS shows marked differences in dissolution AUC and % permeated for different manufacturers

<table>
<thead>
<tr>
<th>Product</th>
<th>% Q (Average of 10 tablets)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLD</td>
<td>99.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Test 1</td>
<td>96.1</td>
<td>7</td>
</tr>
<tr>
<td>Test 2</td>
<td>97.5</td>
<td>3.2</td>
</tr>
<tr>
<td>Test 3</td>
<td>99.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Test 4</td>
<td>95.2</td>
<td>5.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Product</th>
<th>Dissolution AUC (0-2 hours)</th>
<th>% Permeation (0-2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLD</td>
<td>7304.8 ± 407.1</td>
<td>2.33 ± 0.52</td>
</tr>
<tr>
<td>Test 1</td>
<td>4001.3 ± 590.1*</td>
<td>0.25 ± 0.13*</td>
</tr>
<tr>
<td>Test 2</td>
<td>2166.1 ± 756.8*</td>
<td>0.51 ± 0.16*</td>
</tr>
<tr>
<td>Test 3</td>
<td>5043.8 ± 1157.7*</td>
<td>0.55 ± 0.35*</td>
</tr>
<tr>
<td>Test 4</td>
<td>6477.0 ± 1031.9</td>
<td>0.51 ± 0.16*</td>
</tr>
</tbody>
</table>

IDAS Achieves Relevant Discrimination
Application: Equivalence

Compound X Dissolution, Low Dose

Compound Y Dissolution, Low Dose
Compound X Permeation (Low Dose)

- RLD
- Test Formulation

Compound Y Permeation (Low Dose)

- RLD
- Test Formulation
IDAS Achieves Improved Dose Discrimination:
Dissolution vs. permeability in fasted state simulated intestinal fluid (FaSSIF) for a tablet with different strengths
Objective:

Evaluation of dissolution and permeation of the BCS Class 2 drug simvastatin from tablet formulation using FaSSIF (pH 6.5) and FeSSIF (pH 5.8, higher bile salt and phospholipid concentrations)

Faster and complete dissolution in FeSSIF, but permeation was not faster than in FaSSIF
Objective:
- To determine the effects of particle size of oral indomethacin formulation on drug dissolution and permeation using IDAS2

Methods
- Nano- and micro-sized indomethacin formulations were dosed at equal API level into the dissolution chamber.
- Indomethacin dissolution and permeation were measured by LC-MS/MS.
- The dissolution rate constant \( k_D \) and the permeation rate constant \( k_P \) were determined by simultaneously modeling the concentration vs. time profiles for both dissolution and permeation.
Application: Particle Size

Table 1. Comparison of in vitro IDAS results with in vivo human oral pharmacokinetics results

<table>
<thead>
<tr>
<th></th>
<th>Indomethacin</th>
<th>Submicron indomethacin</th>
<th>%Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IDAS parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$k_D$ ($\text{min}^{-1}$)</td>
<td>0.330</td>
<td>1.371</td>
<td>316</td>
</tr>
<tr>
<td>$k_P$ ($\text{min}^{-1} \cdot \text{cm}^{-2} \cdot 10^3$)</td>
<td>2.282</td>
<td>2.967</td>
<td>30.0</td>
</tr>
<tr>
<td>$D_{\text{max}}$ ($\text{ng/mL}$)</td>
<td>55325</td>
<td>64935</td>
<td>17.4</td>
</tr>
<tr>
<td><strong>Human oral PK parameters</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$ (ng$\cdot$mL$^{-1}$)$\cdot$mg$^{-1}$</td>
<td>47.39</td>
<td>59.22</td>
<td>25.0</td>
</tr>
<tr>
<td>AUC (ng$\cdot$h$\cdot$mL$^{-1}$)$\cdot$mg$^{-1}$)</td>
<td>155.2</td>
<td>152.8</td>
<td>-1.6</td>
</tr>
</tbody>
</table>

* Adapted from literature reference (2) and dose normalized.
Typical (single-stage) study design: 2 dose units (tablets, capsules) in 500 mL of FaSSIF with permeation chambers immersed in the dissolution vessel.

Gastric dissolution followed by emptying into the intestine modeled in vitro with a 2-stage study design: 2 dose units first exposed to SGF (pH 1.6) for 20 minutes before switching to FaSSIF (pH 6.5). The change is achieved by adding 5X FaSSIF, with only 25% dilution.

- BCS Class 2 weak bases: dipyridamole, ketoconazole, itraconazole
- Weak acid: warfarin
- Negative controls (BCS Class 1 weak bases): minoxidil, metoprolol
Application: Gastrointestinal Supersaturation

Dissolution

Dipyridamole

Ketoconazole

Itraconazole

Permeation

Warfarin

Minoxidil

Metoprolol

*pH shift (●) and pH 6.5 (■)*
More Information About IDAS

- https://www.absorption.com/kc/idas/
IDAS Resource Library

- **Publications**
  - **Supersaturation**: In Vitro and In Vivo Assessment of the Potential of Supersaturation to Enhance the Absorption of Poorly Soluble Basic Drugs (Li J, et al., J Pharm Innov., published online 7 Sep 2019; https://doi.org/10.1007/s12247-019-09404-5)
  - **Particle Size**: Simultaneous Analysis of Dissolution and Permeation Profiles of Nanosized and Microsized Formulations of Indomethacin Using the *In Vitro* Dissolution Absorption System 2 (Li J, et al., J Pharm Sci. 2019; 108: 2334-2340)