USE OF BIO-PREDICTIVE METHODS DURING EARLY FORMULATION SCREENING

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1X Dissolution / Simulations
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Topics

What is the intent of dissolution in the early space?

Physiochemical properties and prediction of bio performance

“Predictive” methodologies and case studies

Areas for improvement and discussion
What is the Intent of Dissolution in The “Early Development” Space?

Predict *in-vivo* performance of formulations (bio-predictive)

- In preclinical models
- In Phase I studies
- In Bio-comparison (BC) studies

Establish a dissolution model for predicting the performance of formulations *in-vivo* to guide market formulation and process development.

- Reduce number and complexity of animal studies.
- Take best formulations forward for human studies

Driving an understanding of what factors of the API/Formulation/Process are most important in developing bio-predictive methods

Assumption here is that dissolution is meaningful for PK performance…
When Bioavailability Depends on Dissolution...

Dissolution is the best surrogate for bio-performance if IVIVC can be established.

It enables selection/rank ordering of formulation candidates in early development without the need to perform actual in vivo (animal or human) studies significantly accelerating development.
When Bioavailability Depends on Dissolution...

Disintegration

tablet
K₁
granules

GI Tract

Solubilization

API crystalline
Particles (10-50 um)

K₂

Dissolved
Drug
molecules

K₃

lumen

Absorption of dissolved drug

flux drug removed = A(mem) [drug] in lumen X perm. rate const.

Dissolution ~ (Particle SA)(Diffusion Term)(C_{sol \ lim} – C(t)_{lum})

(Rate of API particle)

Sum of rates, K₁, K₂, K₃ is slower than rate of permeation

When Dissolution Rate Matters

If $1 > 2$, then dissolved drug concentration in the GI is “pegged” at the solubility limit – this is \textit{solubility/permeability limited} exposure. In this regime, different formulations of same API give similar AUC.

If $2 > 1$, then dissolved drug concentration in GI is \textit{below} the drug solubility limit, this is \textit{dissolution rate limited} (disso rate can’t keep up with permeability loses). In this regime AUC may be sensitive to formulation details...(API PSD, for example)

How to measure/compare “aggregate” API particle dissolution \textit{rates} – as they dissolve in aggregate (from different formulations) as this dissolution drives the [API] in GI fluids to the its solubility limit?

This scenario is called “Dissolution Rate Limited AUC”
How to Measure Aggregate Flux – Whole Dose Must Dissolve

In the case where C provides constant sink for dissolved drug to go, the rate “1” of transition from A to B matters, regardless of amount dosed, therefore the \textit{dissolution behavior of the entire dose matters}.

\textbf{How can this be measured?} Mimic the system! Put the dose inside a permeable membrane (only drug in solution gets through) and have large volume on other side of membrane to keep [drug] below its solubility limit or some sort of way to remove drug outside membrane (inside always driving to sol limit). Also, biphasic dissolution (aqueous/organic).

\textbf{Is there an even more simple way?} Simply put a \textit{portion} of dose into BR media AT the solubility limit, compare disso profile (rate) to get there!

\textbf{THIS IS 1X BIORELEVANT DISSOLUTION}
The Case for Conducting Bio-Predictive Dissolutions at the Solubility Limit of the Drug

Called “1X” dissolution: have your target concentration = solubility limit of the drug... then all drug particles must dissolve; formulation differences in rates of approach to solubility limit easier to see and whole “formulation response” is measured.

you need to see all the API dissolve to compare formulations, since our % dose absorbed (hopefully) approaches 100%..

Simply comparing the rate of reaching the solubility limit in FaSSIF for all formulations at 1X
Simulation of Dissolution

\[ \frac{dW}{dt} = \frac{DA(C_s - C)}{L} \]

This simulation is done at the solubility limit of the drug.
This Approach Allows Quantitative Comparisons Across Formulation Types

Calculated Dissolution at 1X - 5 ug/mL Drug Solubility, Varying PSD

Calculated Dissolution at Dose Relevant (40X) - 5 ug/mL Drug Solubility, Varying PSD
This Approach Allows Quantitative Comparisons Across Formulation Types

Understanding the dissolution rate of well dispersed API particles is the first step in evaluating dissolution performance – as a very well dispersed formulation with very fast granule dissolution will approach dispersed API dissolution rate.
Representative 1X Data Comparing Formulation Components

API calculated dispersed API
WG granule with surfactant
RC granule

“1x Formulation Yardstick”

% dissolved at 1x

0 10 20 30 40 50 60 70 80 90 100

0 10 20 30 40 50 60 70 minutes

Tablet

optimize
Practically, What Working at the Solubility Limit of the Drug Means

Using the 5 μg/mL solubility in FaSSIF example, and the 100 mg dose

To work at “1X” with a complete 100 mg tablet then would require a 20,000 mL volume

That’s a lot of FaSSIF!

How is this made practical?

We work with granules (example here, 1/40th weight of a tablet in 500 mL FaSSIF) or portions of tablets – or pre-disintegrated in SGF
This Approach Allows Quantitative Comparisons Across Formulation Types

<table>
<thead>
<tr>
<th>Formulation Attribute</th>
<th>1x Dissolution Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formulation processes strive to disperse the API particles to their primary size from a tablet</td>
<td>Formulations that do this better will have faster rates of dissolution than those that do this poorly</td>
</tr>
<tr>
<td>Granulation of API</td>
<td>Granulation can help with dispersion of particles in dissolution – also over granulation can add additional dissolution rate slowing (increase in r term (particle density))</td>
</tr>
<tr>
<td>Addition of Surfactants</td>
<td>Helping wet the particles may improve dissolution rate</td>
</tr>
</tbody>
</table>

Understanding the dissolution rate of well dispersed API particles is the first step in evaluating dissolution performance – as a very well dispersed formulation with very fast granule dissolution will approach dispersed API dissolution rate.
## 1X Dissolution – Case Study

### Amorphous by Spray drying (FFP Formulation)

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Quantity</th>
</tr>
</thead>
<tbody>
<tr>
<td>30% Drug A API</td>
<td></td>
</tr>
<tr>
<td>65% Copovidone</td>
<td></td>
</tr>
<tr>
<td>5% SLS Surfactant</td>
<td></td>
</tr>
</tbody>
</table>

### Formulation

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug in SDI</th>
<th>SLS in SDI</th>
<th>PVPVA in SDI</th>
<th>SLS in tablet</th>
<th>Test Hypothesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>FM 1 Tablet</td>
<td>30%</td>
<td>5%</td>
<td>65%</td>
<td>0%</td>
<td>High Probably of Success based upon prior knowledge</td>
</tr>
<tr>
<td>FM 2 Tablet</td>
<td>33%</td>
<td>0%</td>
<td>67%</td>
<td>5%</td>
<td>Test necessity of SLS in SDI</td>
</tr>
<tr>
<td>FM 3 Tablet</td>
<td>99.5%</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>Test whether supersaturation is enough to get adequate PK</td>
</tr>
<tr>
<td>FM 2 Capsule</td>
<td>99.5%</td>
<td>0%</td>
<td>0%</td>
<td>5%</td>
<td>Test whether supersaturation is enough to get adequate PK</td>
</tr>
</tbody>
</table>

### Graph (PEG400 solution - PG treated (n=6), Solid Dispersion DFC (VA64) - PG treated (n=6), Conventional DFC (TPGS) - PG treated (n=5))

- **PEG400 solution - PG treated (n=6)**
- **Solid Dispersion DFC (VA64) - PG treated (n=6)**
- **Conventional DFC (TPGS) - PG treated (n=5)**

<table>
<thead>
<tr>
<th>Conc (uM)</th>
<th>0.0</th>
<th>4.0</th>
<th>8.0</th>
<th>12.0</th>
<th>16.0</th>
<th>20.0</th>
<th>24.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hr)</td>
<td>0.0</td>
<td>4.0</td>
<td>8.0</td>
<td>12.0</td>
<td>16.0</td>
<td>20.0</td>
<td>24.0</td>
</tr>
</tbody>
</table>
Drug A – 1X Dissolution

Drug A - 1x Sink Biorelevant Dissolution - First BC Study, Clinical Tablets and Capsules - SGF/FaSSIF 100 RPM USP II

Dissolution rate is an indicator of pK performance

[Drug A] = 100 ug/mL
[Drug A] = 50 ug/mL

FM 1 Tablet
FM 2 Tablet
FM 3 Tablet

Dissolution rate is an indicator of pK performance
Exploratory BC PK Data

**FM 1 Tablet**
Based upon SDI – 30% DL, 65% Copovidone, 5% SLS

**FM 2 Tablet**
Based upon SDI – 33% DL, 67% Copovidone
SLS added external to SDI

**FM 3 Capsule**
Based upon SDI - neat amorphous drug
SLS added external to SDI

**FM 3 Tablet**

Dissolution rate is an indicator of pK performance
Two-Stage Dissolution

During the typical two-stage dissolution, 1X addition of FaSSIF creates sudden pH change for the 2nd stage. This may be especially problematic for weak bases, which may undergo precipitation in the 2nd stage.

Formulation sample → 250 mL double concentration (2X) (FaSSIF, pH 6.9) → Sample in 250 mL SGF → 30 min → Sample in 250 mL SGF → 120 min → Sample in 500 mL FaSSIF → Sudden increase in pH (1.8 to 6.5)

Two-stage dissolution
Multi-compartment Transfer Model to Predict Dissolution/Precipitation of Weakly Basic Drug

Flow rate 5 mL/min

Gastric compartment (SGF, 250 mL, 100 rpm)

Intestinal compartment (FaSSIF, 250 mL, 50 rpm)

Sink/supersaturation (FaSSIF, pH 7.0)

Reservoir compartment (FaSSIF, pH 7.0)
Case Study: Ketoconazole

Ketoconazole: Weak dibasic antifungal agent

pKa: 2.94, 6.51

BCS II

Permeability:
Caco-2 Peff=53x10^{-6} cm/sec

Solubility:
- Virtually insoluble at pH 5 or higher
- Detailed solubility profile (right)

Administration:
- Exposure was well known as being affected by elevated stomach pH
- Recommended to codose w/acidic cola drink

<table>
<thead>
<tr>
<th>pH</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 (FaSSGF)</td>
<td>9</td>
</tr>
<tr>
<td>3 (buffer)</td>
<td>1.8</td>
</tr>
<tr>
<td>3.5 (buffer)</td>
<td>0.7</td>
</tr>
<tr>
<td>4.5 (buffer)</td>
<td>0.25</td>
</tr>
<tr>
<td>5 (buffer)</td>
<td>0.1</td>
</tr>
<tr>
<td>6.5 (buffer)</td>
<td>0.007</td>
</tr>
<tr>
<td>SGF</td>
<td>6</td>
</tr>
<tr>
<td>FaSSIF</td>
<td>0.02537</td>
</tr>
</tbody>
</table>
Ketoconazole Tablets: Transfer vs Two-Stage

Some precipitation observed in the transfer model; significant precipitation in two-stage dissolution

A small amount of precipitation was observed in fasted adult study

Transfer Model Summary

A multicompartment transfer system was established to investigate the in vivo behavior of weak basic compounds.

Preliminary data showed promising results to support transfer model as an alternative way to estimate in vivo precipitation in intestinal compartment for weak basic compounds.

Opportunities:

- In silico model – Develop full mathematical model to describe simultaneous transfer/precipitation process
- Nanoparticle formers/enabling formulation
ASD Motivation

• A tool for drug product development, including early phase formulation screening
• Help predict the in vivo impact of
  – salts,
  – solid forms,
  – formulation composition,
  – particle size,
  – process

using an in vitro system that mimics the dynamic conditions of the human gastrointestinal tract.
ASD Concept

- Capture *supersaturation, precipitation* and *dissolution* phenomena as they occur in vivo.

- Dynamic dissolution system designed to simulate the stomach and duodenum environment:

  - fluid compositions
  - mixing (not peristalsis)
  - transit times
  - fluid flows
  - pH
  - fluid volume
Physical Model

-UV-vis fiber optic probes and pH probes in both chambers for data acquisition.
Physiological Modeling

Stomach Secretion Rate = 2 mL/min

Resting Volume = 50 mL
Dosing Volume = 200 mL

Stomach Emptying:
First order decay (w.r.t. Volume)
Emptying Half-life = 15 min

Duodenum:
Constant volume = 30 mL

Fluids:
Stomach – 0.01 N HCl or higher pH buffer
Duodenum – Phosphate buffer, pH 6.8 or FaSSIF w/o lecithin
Typical Results

Gastric Emptying + Intestinal Fluid + Gastric Fluid

Dissolution + Gastric Emptying + Intestinal Fluid + Gastric Fluid

Stomach is diluted by gastric fluid.

Drug dissolution evident in the stomach.

Concentration vs. Time (min)

-20 0 20 40 60 80 100 120 140 160 180 200

Concentration vs. Time (min)

-20 0 20 40 60 80 100 120 140 160 180 200

Stomach
Duodenum
Drug-Concentration Profiles

- Expected duodenum concentrations can be calculated from experimental stomach data.
Dissolution and Precipitation

- Deviations from the expected duodenum profiles indicate either additional dissolution or precipitation.
ASD/Human Comparison

- In vitro data: Human ASD
- In vivo data: 12 Human volunteers.

Ketoconazole dosed as 240 mL of a solution acidified to pH 2.7

L. Burns, K. Kovach

FaSSIF Solubility: 0.007 mg/mL
Case Study– Free base conversion

♦ Solid forms: free base & a salt
♦ Properties: Low solubility, $pK_a \sim 7$
Case Study - Salt supersaturation and precipitation

Stomach concentrations

Low dose

High dose

Duodenum concentrations

D₀=0.03

D₀=0.1

D₀=120

D₀=450

Some precipitation
Decision Tree Guides Experiments

- **Run ASD experiments.**
  - **Conventional Formulation?**
    - **Yes**
      - **BCS Class?**
        - **I or III**
          - ASD Not Needed, use USP disso
        - **II or IV**
          - No
    - **No**
      - **Run ASD: high dose, low gastric pH**
        - **Precip?**
          - **Yes**
            - Use ASD to determine rank order exposure differences
          - **No**
            - **Use USP Disso (SGF) to rank order**

- **Disso rate in SIF rapid?**
  - **Yes**
    - Use USP disso (SIF) to rank order
  - **No**
    - **Use ASD to rank order**
ASD Areas for Improvement

- Field of study would benefit from some standardization
  - Fluid compositions
  - Solids transport
  - Agitation
  - Fed vs. fasted simulations

- Enhancements to physical system
  - More compartments → transit time
  - Automated low-volume sampling
  - Methods to simulate removal of aqueous drug from system (absorption)
Acknowledgements

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- Paul Harmon
- Wei Xu
- Adam Socia
- Mike Socki
- Justin Pennington

Transfer Model
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- Wei Zhu
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- David Sperry
- Lee Burns
- Karl Kovach
- Shobha Bhattachar

M-CERSI Organizing committee and you!
Physiochemical Properties and the Prediction of Performance

Rate of dissolution is described by the Noyes-Whitney equation:

\[
\frac{dW}{dt} = \frac{DA(C_s - C)}{L}
\]

- \(A\) is the surface area of the solid.
- \(C\) is the concentration of the solid in the bulk dissolution medium.
- \(C_s\) is the concentration of the solid in the diffusion layer surrounding the solid.
- \(D\) is the diffusion coefficient.
- \(L\) is the diffusion layer thickness.

The Noyes-Whitney equation represents the influence of key physiochemical properties on the dissolution rate.
Influence of Physiochemical Properties on the Dissolution Rate

\[
\frac{dW}{dt} = \frac{DA(C_s - C)}{L}
\]

**A** is the surface area of the solid
- Surface area is directly related to particle shape and size
- Particle size naturally occurs as a distribution

**C** is the concentration of the solid in the bulk dissolution medium.
- At \( t=0 \), this is 0

**\( C_s \)** is the concentration of the solid in the diffusion layer surrounding the solid.
- This is the solubility limit of the drug.
- At \( t=0 \), the difference \( (C_s - C) \) represents the total capability of the particle to dissolve

**D** is the diffusion coefficient.

**L** is the diffusion layer thickness.

Commercial software packages can accurately simulate dissolution curves using these data.
- FaSSIF/250 mL/50 rpm/pH 6.5FaSSIF/pH 7.0
- Sink/supersaturation compartment

Pump (5 mL/min)

SGF/250 mL/100 rpm
Case Study: Dipyridamole

Characteristics

- Inhibits thrombus formation (antiplatelet)
- Free base with pKa of 6.4
- BCS Class II
- Permeability: Estimated human Peff 1.5 (cm/sec x 10⁻⁴)

Dose Information

- Tablets: 25 mg, 50 mg, 75 mg
- Recommended dose: 75-100 mg 4 times daily
- Significantly decreased exposure with famotidine-treated healthy elderly patients
- The absolute bioavailability is 27 +/- 5.5% (range 11% – 44%)

<table>
<thead>
<tr>
<th>pH</th>
<th>Solubility (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.5</td>
<td>2.2</td>
</tr>
<tr>
<td>4.2</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>0.0054</td>
</tr>
<tr>
<td>6</td>
<td>0.0010</td>
</tr>
<tr>
<td>7</td>
<td>0.0005</td>
</tr>
<tr>
<td>7.8</td>
<td>0.0006</td>
</tr>
<tr>
<td>SGF</td>
<td>8</td>
</tr>
<tr>
<td>FaSSIF</td>
<td>0.01148</td>
</tr>
</tbody>
</table>

Molecular Weight: 504.6, pKa = 6.4

Dipyridamole Tablets: Transfer vs Two-Stage

Both models indicate dipyridamole does not undergo rapid precipitation.

Absorption modeling studies also indicate a prolonged in vivo precipitation.

Dipyridamole precipitation is concentration dependent (Box K, et al. Approaches for measuring intestinal precipitation rates of oral drugs [abstract]).
ASD/Human Comparison of Duodenal Concentration Profile

- **In vitro data**: ASD
- Dipyridamole dosed as 240 mL of a solution acidified to pH 2.7

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