Bio-predictive dissolution methods with a view to integration in PBPK/ PBBM:

Challenges for low solubility drug products

James Butler
GSK Senior Fellow
GlaxoSmithKline R&D
Ware, UK
Outline

• Terminology: *bio-predictive* versus *bio-relevant*
• Emerging trends in bio-relevant dissolution
• Bio-predictive methods for low solubility drugs: is single media dissolution enough?:
  ◦ *When to use 2+ media/compartments in parallel to simulate transit*
• Bio-predictive methods for low solubility drugs: More than dissolution?
  ◦ *Accounting for other factors, such as supersaturation/precipitation, degradation, digestion, interplay with permeation etc.*
• “GI tract in the lab” systems
• The test complexity dilemma for PBPK input
  ◦ *Would categorisation of the required in-vitro test method complexity be useful?*
Test terminology: **bio-predictive** versus **bio-relevant**

- **Bio-predictive**: proven usefulness in predicting *in-vivo* outcomes
- **Bio-relevant**: simulates the *in-vivo* environment in some aspect beyond that typical in a QC/batch release method
## Bio-predictive versus bio-relevant

<table>
<thead>
<tr>
<th>Bio-relevant</th>
<th>Bio-predictive (as input to PBPK)</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Typically used to inform early product development</td>
<td>- Likely to be finalised later in development</td>
</tr>
<tr>
<td>- Prediction of how the drug and dosage form behave <em>in-vivo</em></td>
<td>- Built upon an understanding of what factors may limit drug absorption</td>
</tr>
<tr>
<td>- Identification of factors limiting drug availability for absorption</td>
<td>- (including from biorelevant dissolution)</td>
</tr>
<tr>
<td>- May be used as input into PBPK, but more often, a standalone tool</td>
<td>- May be the QC/release method</td>
</tr>
<tr>
<td>- Complexity is often helpful!</td>
<td>- Demonstrated as to be of use in predicting human <em>in-vivo</em> performance</td>
</tr>
</tbody>
</table>

Emerging trends in *bio-relevant* dissolution

Informed by *in-vitro* tools optimised in the IMI OrBiTo collaboration*

- Improved tests to predict low solubility drug behaviour in the GI tract which additionally account for factors such as:
  - Dynamic media change with GI transit
  - Supersaturation and precipitation
  - Motility/ hydrodynamics
  - Food and digestion
  - Buffer capacity
  - Permeation (to assess “free drug” availability)

- The use of more holistic “GI tract in the lab” models
  - Aiming to account for more than one of the above factors


A few of the novel *in-vitro* set ups used in IMI OrBiTo.....

How to navigate through this maze of options?

- A decision tree was devised: Andreas, C. J., et al. "Introduction to the OrBiTo decision tree to select the most appropriate *in vitro* methodology for release testing of solid oral dosage forms during development." *European Journal of Pharmaceutics and Biopharmaceutics* 130 (2018): 207-213.
Emerging biorelevant tools

Example 1: An IMI OrBiTo two stage transfer method:

Suspension/Tablet/Capsule

Sample in 250 mL SGF

30 min

250 mL 2X FaSSIF

pH 7.5

120 min (typically)

Sample in 500 mL FaSSIF, pH 6.5

Comparative data: direct into FaSSIF

When is this useful?

- When exposure to the gastric environment substantially alters subsequent intestinal dissolution. This can occur for:
  - Slow to disintegrate/disperse formulations
  - Forms that undergo change in gastric conditions (e.g. some salts of low solubility drugs)
  - Drugs that significantly degrade in gastric conditions
  - Drugs/formulations that supersaturate (and may precipitate) in the stomach
  - *Weak bases which subsequently precipitate*


Example* profiles (form change in gastric media)

*Hypothetical, but loosely based upon real GSK examples

Salt of weak acid A

Salt of weak acid B

- Single media (FaSSIF)
- Dual media: FaSSGF 30mins, then FaSSIF
Emerging biorelevant tools

Example 2: Accounting for permeation in a drug release test

In-vitro dissolution (with solubilisation) → In-vitro permeation → Model oral absorption

But what if solubilisation and permeation are inter-dependent?
METHODOLOGY – *in vivo*

Fenofibrate example– slides provided by Patrick Augustijns

METHODOLOGY – *in vitro*

## RESULTS – *in vivo* & *in vitro*

### In vivo

<table>
<thead>
<tr>
<th></th>
<th>Micro fasted</th>
<th>Micro fed</th>
<th>Nano fasted</th>
<th>Nano fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duodenal AUC(_{0-230\text{min}}) (µM.h)</td>
<td>4.11 ±0.91</td>
<td>41.1 ± 21.2</td>
<td>14.7 ± 5.10</td>
<td>103 ± 37.2</td>
</tr>
<tr>
<td>Plasma AUC(_{0-8\text{h}}) (µM.h)</td>
<td>35.8 ± 12</td>
<td>47.8 ± 13.4</td>
<td>121 ± 12.5</td>
<td>75.7 ± 16.3</td>
</tr>
</tbody>
</table>

### In vitro

![Graph A](image1.png)

![Graph B](image2.png)

**Conclusion:** Micellar/food entrapment plays an important role in understanding the behaviour of fenofibrate.
Emerging biorelevant tools

Some examples of “GI tract in the lab” systems

**Advantages of these complex set ups:**

- Realistic secretions (including bile and enzymes), volumes, GI dynamics, motility, etc in a single test.
- Especially useful for complex scenarios such as predicting the impact of food
- Reliable (>80%) predictors for inequivalence

**Disadvantages:**

- Slow throughput: one dosage form at a time
- Not readily incorporated into PBPK?
**Prediction of food effects using TIM systems** (data collated by Ronald Schilderink, Treskelion)

<table>
<thead>
<tr>
<th>API</th>
<th>Formulation</th>
<th>Meal type</th>
<th><strong>In vivo fed/fasted ratio</strong></th>
<th><strong>TIM in vitro fed/fasted ratio</strong></th>
<th>Publication TIM data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Danirixin</td>
<td>DNX HBr</td>
<td>High fat meal</td>
<td>0.64 (AUC0-inf)</td>
<td>0.9 (TIM-1)</td>
<td>Bloomer et al. 2017</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Cataflam IR</td>
<td>Ensure Plus</td>
<td>1.0 (AUC0-8h)</td>
<td>1.0 (TIM-1)</td>
<td>Van den Abeele et al 2017</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ciproxin ER</td>
<td>High fat meal</td>
<td>1.0 (AUC)</td>
<td>1.2 (TIM-1) 1.0 (tiny-TIM)</td>
<td>Verwei et al. 2016</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Paracetamol IR</td>
<td>High caloric meal</td>
<td>0.94 (AUC0-inf)</td>
<td>1 (TIM-1)</td>
<td>Souliman et al. 2006</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>Sinaspril *crushed</td>
<td>Infant formula</td>
<td>No food effect</td>
<td>No food effect (tiny-TIM\textsubscript{pediatrics})</td>
<td>Havenaar et al. 2013</td>
</tr>
<tr>
<td>Fosamprenavir</td>
<td>Telzir IR</td>
<td>Scandi-shake Mix</td>
<td>No food effect AUC</td>
<td>No food effect bioacc. Effect on disintegration (TIM-1)</td>
<td>Brouwers et al. 2011</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>Celebrex</td>
<td>High fat meal</td>
<td>1.6 (AUC0-inf)</td>
<td>2.0 (TIM-1)</td>
<td>Lyng et al. 2016</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Noxfal Suspension</td>
<td>Coca-cola</td>
<td>1.7 (AUC)</td>
<td>1.5 (TIM-1 &amp; tiny-TIM)</td>
<td>Verwei et al. 2016</td>
</tr>
<tr>
<td>Nifedipine</td>
<td>Adalat XL MR</td>
<td>High fat meal</td>
<td>1.7 (AUC0-8h)</td>
<td>3.5 (TIM-1) 3.6 (tiny-TIM)</td>
<td>Verwei et al. 2016</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>Noxfal Suspension</td>
<td>High fat meal</td>
<td>4 (AUC0-72h)</td>
<td>13.8 (TIM-1) 12.9 (tiny-TIM)</td>
<td>Verwei et al. 2016</td>
</tr>
</tbody>
</table>
Future role of “GI tract in the lab” systems to aid PBPK

• External validation of model predictions
  • Potential to reduce the need for human data to validate PBPK models?

• Potentially, provide improved inputs for PBPK modelling when complexity is needed

• “Model the in-vitro model”
  • Model the formulation and drug behaviour in the complex in-vitro model as a step to human prediction
  • Analogous to building a PBPK model for an animal species, then translating to human
For integration into PBPK, is it useful to categorise the bio-predictive method complexity needed?

- Building on the concept for selecting the most appropriate test media

A possible “test method complexity” cascade

An adequately bio-predictive test as input into PBPK:

**Level 0:** One “single stage” test/media (and/or solubility data) is adequate. May be the QC/ release method

**Level I:** Multiple tests in a suite of “single stage” media

**Level II:** Multiple media/compartment sequential testing to mimic GI transit if drug/ formulation properties demand it (e.g. form change in gastric media)

**Level III:** Dissolution alone is not enough……. i.e. when availability of drug for absorption depends upon additional factors (motility, precipitation, digestion, degradation, micellar entrapment, etc)
A rational, science-led approach to incorporating **bio-predictive** dissolution into PBPK will be key as industry seeks to link modelling and dissolution specification setting.

For some low solubility drugs and their (complex) formulations, the integration of data from emerging **bio-relevant** tools and PBPK will be essential.
Break-out questions

- What tools and strategies could be applied to adequately account for low solubility drugs where form change in-vivo, (e.g. in the stomach) after oral administration is likely?

- How can we ensure that “beyond dissolution” additional factors are appropriately considered when determining the input parameters for modelling the behavior of low solubility drug products in the GI tract? Is there a systematic approach that can be devised to optimally achieve this?
Acknowledgements

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Questions?