Challenges and benefits of using PBPK to evaluate an IVIVC for drugs with non-ideal solubility and/or permeability

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Why IVIVC and what are the challenges to establishing an IVIV relationship?

**IVIVCs**

- Support bridging studies during clinical studies
- Support formulation and manufacturing changes after registration

**BUT,**

- So far, most IVIVCs have been for MR dosage forms
- Even for these, the in vitro results are usually generated with tests that resemble QC tests, so the IVIVC may not be very robust
- IVIV relationships for IR dosage forms have been difficult to attain with classical methods
Recommendation: pay attention to the *in vitro* test design!

Part I: biorelevant dissolution tests – what are these?
Hypothesis:
the closer the dissolution test conditions to the physiology, the better the chances of predicting product performance
Finding the right dissolution test…..

THREE important considerations:

WHERE in the GI tract is drug released from the dosage form?

HOW LONG does the dosage form have to release the drug?

COMPOSITION of the fluids into which the drug is released?
Finding the right dissolution test.....

**WHERE** in the GI tract is drug released from the dosage form? This will vary with the **drug product** e.g.

- Immediate release dosage forms
- Enteric coated dosage forms
- Extended release dosage forms
- Pulsatile delivery....

The site(s) of release and/or % released at each site of release are often also dependent on whether the dosage form is given before or after a meal, so the dissolution test should also reflect the **dosing conditions**
Finding the right dissolution test.....

**HOW LONG** does the dosage form have to release the drug?

- The drug must be released before or at its site(s) of absorption, otherwise release will not result in absorption. So it is important to understand the permeability of the drug at various points in the gut.

- The passage of the dosage form through the stomach depends on unit size and prandial state.
COMPOSITION of the fluids into which drug is released

The foods and drinks we consume, gastric juices, bile, pancreatic juices, bacterial fermentation as well as water re-uptake all combine to influence the composition of the GI fluids at various points in the gut.
GI-appropriate media composition and volume: “biorelevant” dissolution media

1. Fasted state

- Stomach:
  - **FaSSGF**: simulates reduced surface tension in the stomach

- Small intestine:
  - **FaSSIF**: to simulate basal bile secretion in upper SI

- Colon:
  - **FaSSCOF**: to simulate conditions in a fasted state PK study

2. Fed State

- **Stomach:**
  - **FeSSGF:** Milk/buffer pH 5 combination to simulate gastric conditions after a standard breakfast

- **Small intestine:**
  - **FeSSIF-V2** to simulate postprandial bile secretion, lipolysis products, increased buffer capacity and osmolality in upper SI after food intake

- **Colon:**
  - **FeSSCOF** to simulate the ascending colon in the fed state

Jantratid et al., Pharm. Res. 2008, Vertzoni et al., 2010
Biorelevant dissolution media

Using "instant" powders to make the biorelevant media:

„Study of a Standardized Taurocholate–Lecithin Powder for Preparing the Biorelevant Media FeSSIF and FaSSIF“

Dissolution Technologies

source: www.biorelevant.com
Case example 1: Relationship between dissolution and PK of Danazol (a poorly soluble but highly permeable drug)
Case example 1. danazol

Aqueous solubility: 1µg/ml  D:S 200 liters  H₂O
Dose: 200 mg  20 liters  FaSSIF
pKa: neutral  6 liters  FeSSIF
log P: 4.53
Danatrol dissolution profiles in various media at 100 rpm
Danazol’s food effect reflects its dissolution characteristics

Plasma profiles of danazol after administration in the fasted (●) and fed (○) state (from Charman et al.)
Part II: Combining biorelevant dissolution testing with PBPK modeling to achieve IVIV relationships for poorly soluble drugs
Biorelevant dissolution tests alone:

- Qualitative forecast of food effects and formulation trends possible

But, how can we arrive at a more *quantitative* prediction??

Coupling with PBPK models (IV-IS-IV-R):

- Quantitative forecast of food effects and formulation trends possible, since contributions of all steps affecting bioavailability can be addressed
**Initial Assumptions in the model**
- Negligible absorption from the stomach
- Simultaneous solid and liquid emptying from the stomach (disintegrating dosage form)
- No intestinal permeability restrictions (for high permeable drugs)
IV-IS-IV Strategy to predict oral absorption

Set up in vitro dissolution testing
Biorelevant media: fasted/fed, gastric/intestinal
Test parameters: apparatus, volume, hydrodynamics

Understand in vivo performance
Further investigation to understand absorption mechanism and identify key factor which affect on the in vivo performance

- Development of a desired formulation
  (no food effect, less variability, high BA)
- Control strategy with a key attribute
  (design space, quality by design)

Predict in vivo drug release
Qualitative prediction based on the extent in dissolution, comparing with the in vivo data (AUC, ranking order)

Predict PK profile with in silico PBPK modeling
Quantitative prediction based on the extent in dissolution, comparing with the in vivo data (AUC, $C_{\text{max}}$, $T_{\text{max}}$)

Linkage

- Development of a desired formulation
- Control strategy with a key attribute

Graphs:
- Dissolved % vs. Time
- Concentration (ng/mL) vs. Time
Case example 2: Coupling biorelevant dissolution with PBPK to understand the effect of particle size on PK of aprepitant (poorly soluble, highly permeable)
**Case example: Aprepitant**

**BCS Class 2 (low solubility and high permeability)**

- **pK$_a$**: 9.7 (basic)
- **Cs**: 0.02 mg/mL in SGF$_{sp}$ (pH 1.2), 0.0007 mg/mL in SIF$_{sp}$ (pH 6.8)
- **Log $P$**: 4.8
- **$P_{app}$**: $7.8 \times 10^{-6}$ cm/sec (Caco-2)

Micronized, nanosized formulations

Indication: Emesis
Dissolution of aprepitant 125mg in biorelevant media

Micronized

Nanoformulation
Simulated profiles of aprepitant in the fasted and fed state

Micronized

Nanoformulation

Y. Shono et al. EJPB 76:95-104 (2010)
Value added: prediction of z value (=> particle size) at which food effect is eliminated
1. Effects of dissolution rate (z) on PK profile

Fasted: highly dependent on dissolution rate in addition to solubility
Fed: no significant effect of dissolution rate \( \implies \) depends on gastric emptying
2. Effects of gastric emptying rate on PK profile in the fed state
Case example 3: prediction of PK of a Merck & Co. development compound, which is neither highly soluble nor highly permeable and, being a weak base, might precipitate upon entry into the small intestine
Case example: Compound A

BCS Class 4 (neither solubility or permeability is high)

\[ pK_a : 4.2, 7.6, 9.1 \text{ (basic)} \]
\[ Cs : 0.02 \text{ mg/mL in } SGF_{sp} \text{ (pH1.2), } 0.0007 \text{ mg/mL in } SIF_{sp} \text{ (pH 6.8)} \]
\[ \text{Log } D : 1.4 \text{ @ pH 1.5, } 3.5 \text{ @ pH 7.4} \]
\[ P_{app} : 0.8 \times 10^{-6} \text{ cm/sec (Caco-2)} \]
A precipitation step for the fasted state and a limitation to permeability were introduced into the Stella Model.
Compound A transfer model data

Transfer model data revealed transfer rate dependent precipitation in the fasted state, but no precipitation in the fed state.
Only when biorelevant media are used and precipitation in the fasted state as well as a permeability restriction is invoked, is it possible to simulate the in vivo profiles accurately.
Case example 4: prediction of nifedipine (poorly soluble, highly permeable, first pass substrate) PK after administration of the Adalat osmotic pump formulation
Step 1: in silico description of nifedipine PK to account for first pass (using PK-SIM)

Dressman
nifedipine release and dissolution in vitro

- Step 2: release and dissolution in the Type 3 tester (BioDis) using a biorelevant media profile
Nifedipine PK

- Step 3: prediction of PK profile based on PK-SIM model for first pass AND biorelevant dissolution testing

**Conclusion:** drug dissolution after release from the MR dosage form is rate-limiting to absorption
Strategy to understand and forecast oral drug absorption
Combine results from biorelevant dissolution tests with physiologically based pharmacokinetic modeling to create "in vitro – in silico – in vivo" relationships
IVIVC Challenges ahead

- Integration of appropriately biorelevant dissolution data (i.e. use the right level of biorelevant media)

- Appropriate integration of dissolution data into the commercial PBPK models (especially for MR dosage forms that do not have robust, zero-order release kinetics)

- Appropriate integration of precipitation data into commercial PBPK models
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