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

Challenges for low solubility drug products

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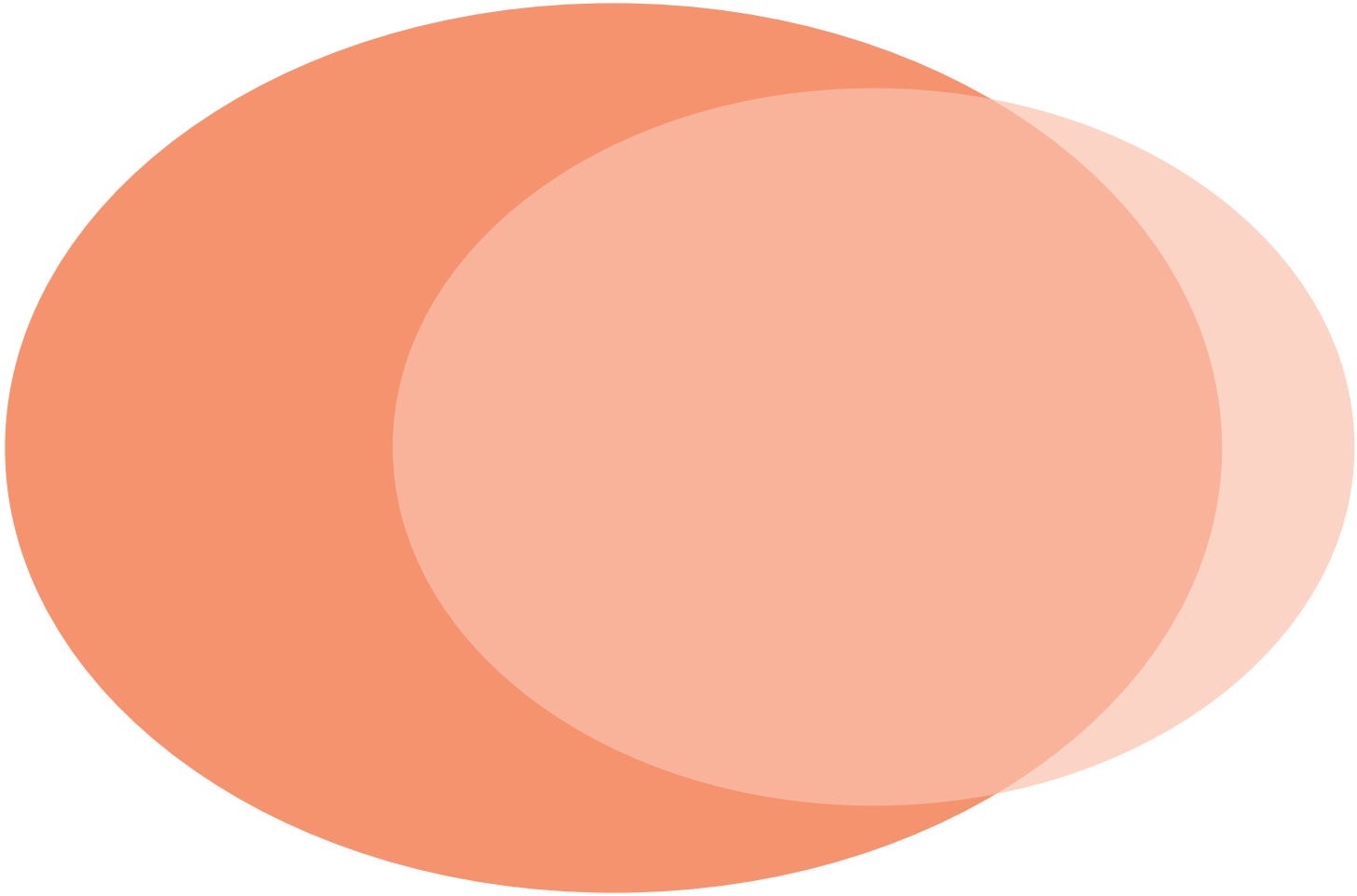
Outline

- 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

Bio-relevant

- Typically used to inform early product development
  - Prediction of how the drug and dosage form behave *in-vivo*
  - Identification of factors limiting drug availability for absorption
  - May be used as input into PBPK, but more often, a standalone tool
  - **Complexity is often helpful!**

Bio-predictive (as input to PBPK)

- Likely to be finalised later in development
  - Built upon an understanding of what factors may limit drug absorption (including from biorelevant dissolution)
  - May be the QC/release method
  - Demonstrated as to be of use in predicting human *in-vivo* performance
  - **Simplicity is highly desirable!**

For more discussion on *in-vitro* test terminology, see: Grady, Haiyan, et al. "Industry's view on using quality control, biorelevant, and clinically relevant dissolution tests for pharmaceutical development, registration, and commercialization." *Journal of pharmaceutical sciences* 107.1 (2018): 34-41.

Emerging trends in *bio-relevant* dissolution

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

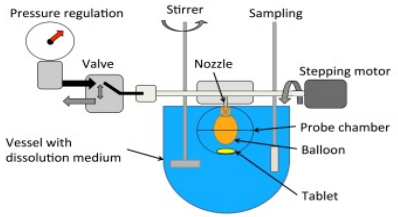
- Improved tests to predict low solubility drug behaviour in the GI tract which additionally account for factors such as:
  - Dynamic media change with GI transit
  - Supersaturation and precipitation
  - Motility/ hydrodynamics
  - Food and digestion
  - Buffer capacity
  - Permeation (to assess “free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

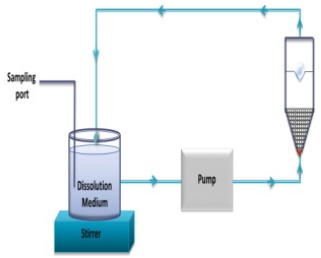
- The use of more holistic “GI tract in the lab” models
  - Aiming to account for more than one of the above factors

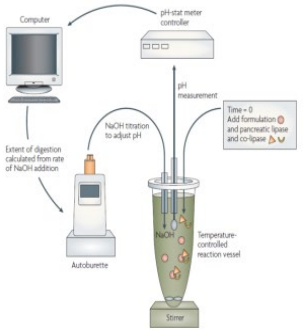
*Kostewicz, Edmund S., et al. "In vitro models for the prediction of in vivo performance of oral dosage forms." *European Journal of Pharmaceutical Sciences* 57 (2014): 342-366.

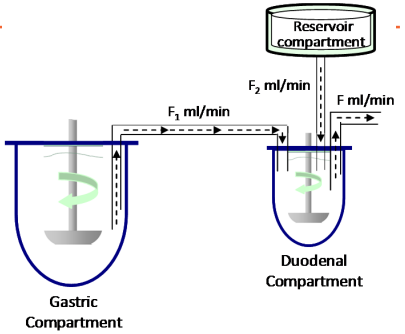
Butler, James, et al. "In vitro models for the prediction of in vivo performance of oral dosage forms: Recent progress from partnership through the IMI OrBiTo collaboration." *European Journal of Pharmaceutics and Biopharmaceutics* 136 (2019): 70-83.

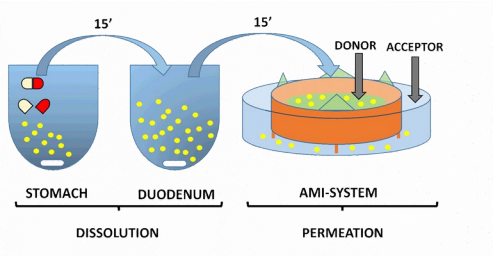
A few of the novel *in-vitro* set ups used in IMI OrBiTo…..

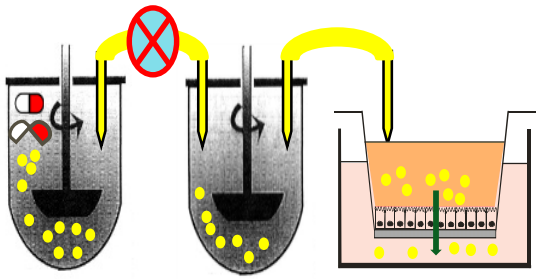


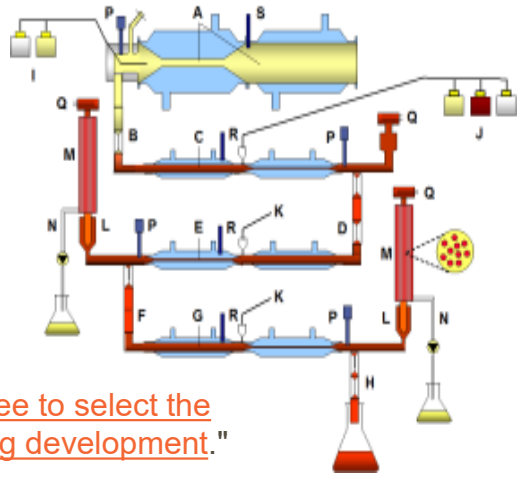


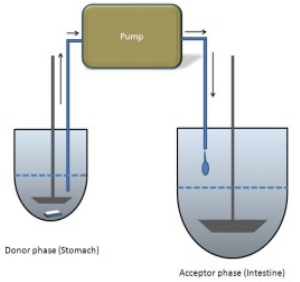










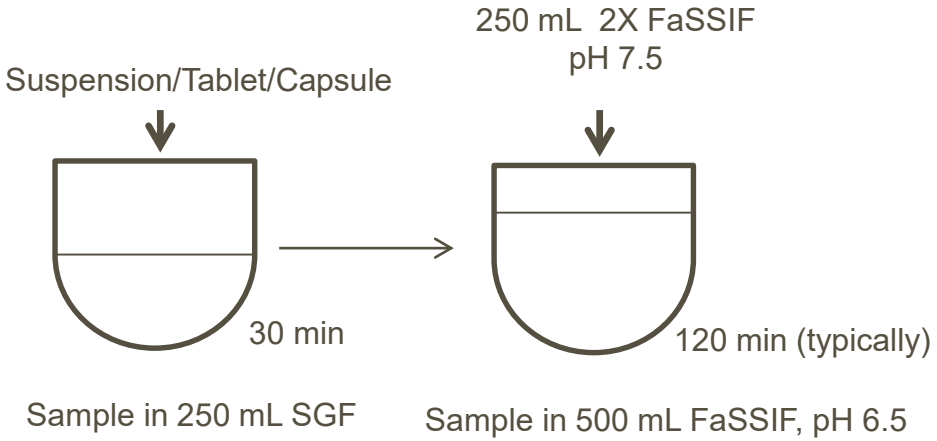


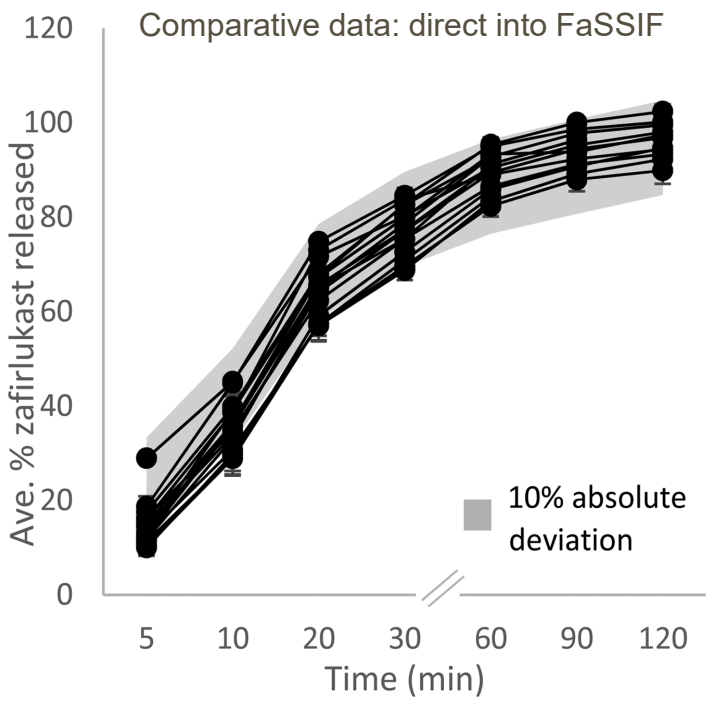
How to navigate through this maze of options?

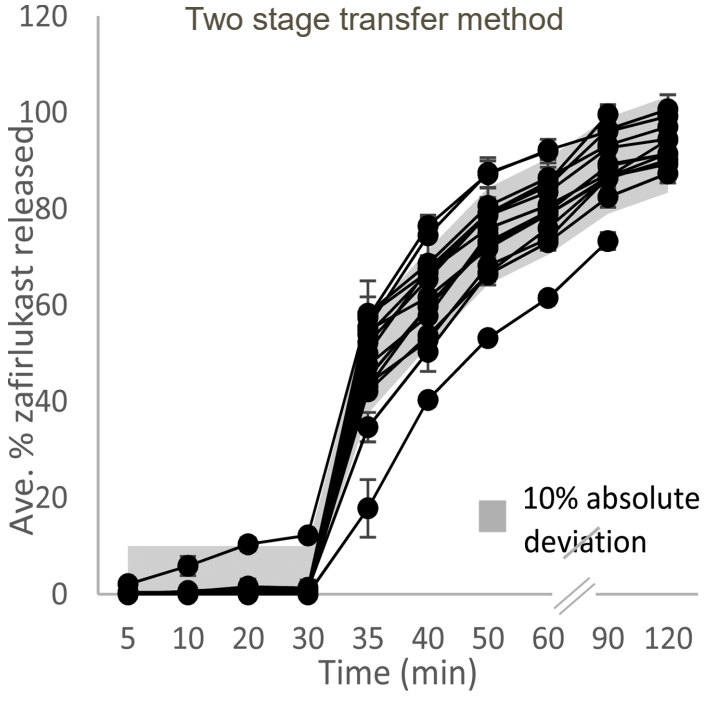
- A decision tree was devised: Andreas, C. J., et al. "Introduction to the OrBiTo decision tree to select the most appropriate *in vitro* methodology for release testing of solid oral dosage forms during development." *European Journal of Pharmaceutics and Biopharmaceutics* 130 (2018): 207-213.

Emerging biorelevant tools

Example 1: An IMI OrBiTo two stage transfer method:







Mann, James, et al. "Validation of dissolution testing with biorelevant media: an OrBiTo study." *Molecular pharmaceutics* 14.12 (2017): 4192-4201.

IMI OrBiTo two stage transfer method applications

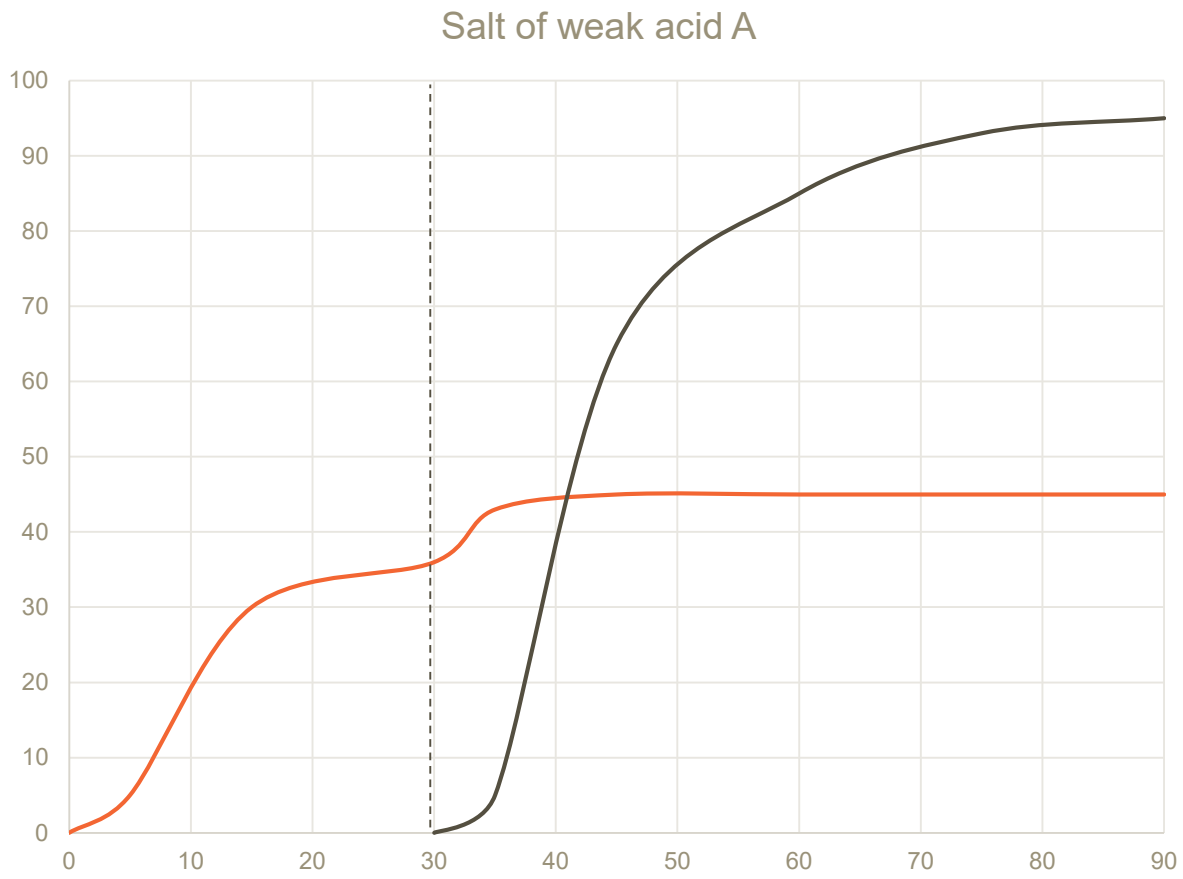
- When is this useful?
  - When exposure to the gastric environment substantially alters subsequent intestinal dissolution. This can occur for:
    - Slow to disintegrate/disperse formulations
    - Forms that undergo change in gastric conditions (e.g. some salts of low solubility drugs)
    - Drugs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

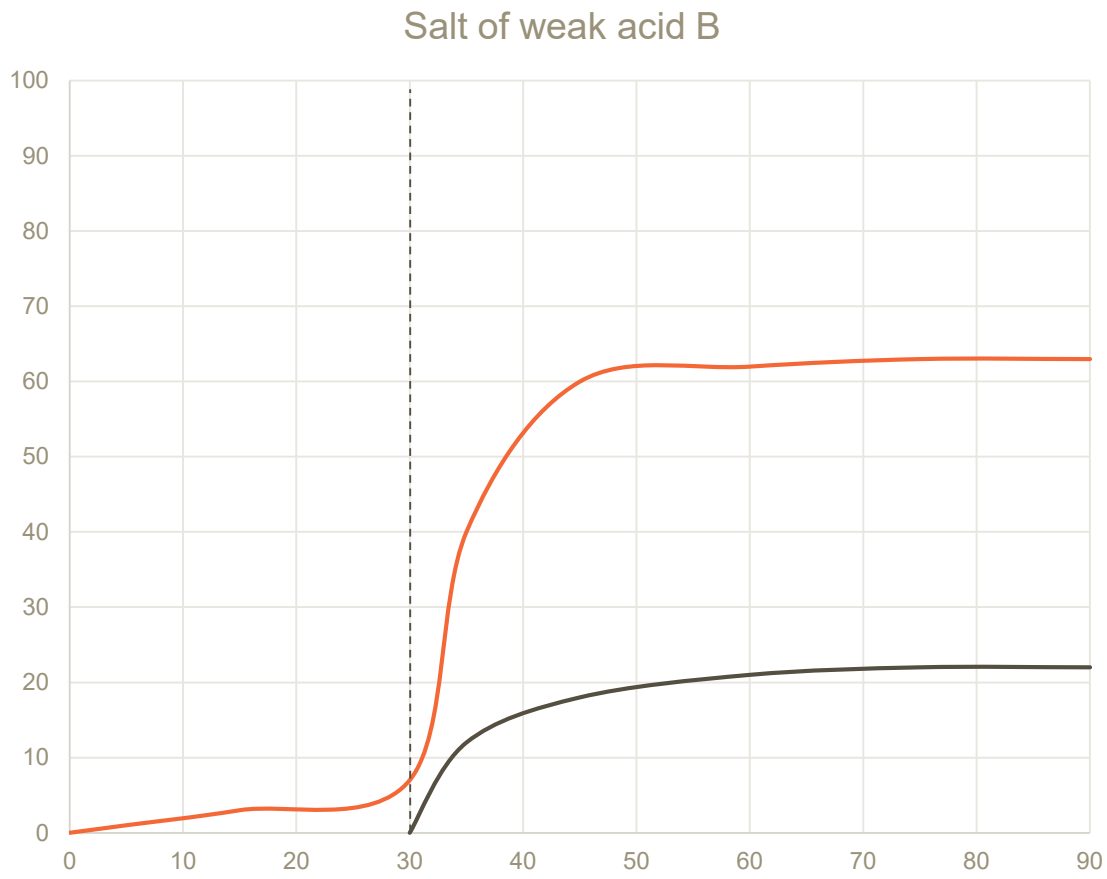
Mann, James, et al. "Validation of dissolution testing with biorelevant media: an OrBiTo study." *Molecular pharmaceutics* 14.12 (2017): 4192-4201.

*Berben, Philippe, et al. "Biorelevant dissolution testing of a weak base: Interlaboratory reproducibility and investigation of parameters controlling in vitro precipitation." *European journal of pharmaceutics and biopharmaceutics* 140 (2019): 141-148.

Example* profiles (form change in gastric media)

*Hypothetical, but loosely based upon real GSK examples



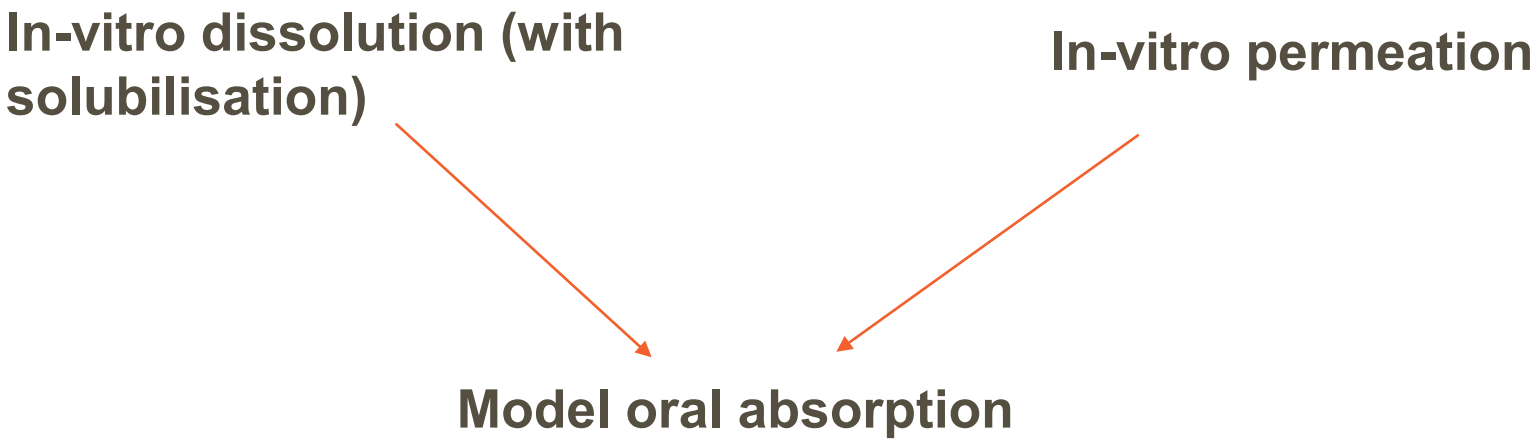


Single media (FaSSIF)

Dual media: FaSSGF 30mins, then FaSSIF

Emerging biorelevant tools

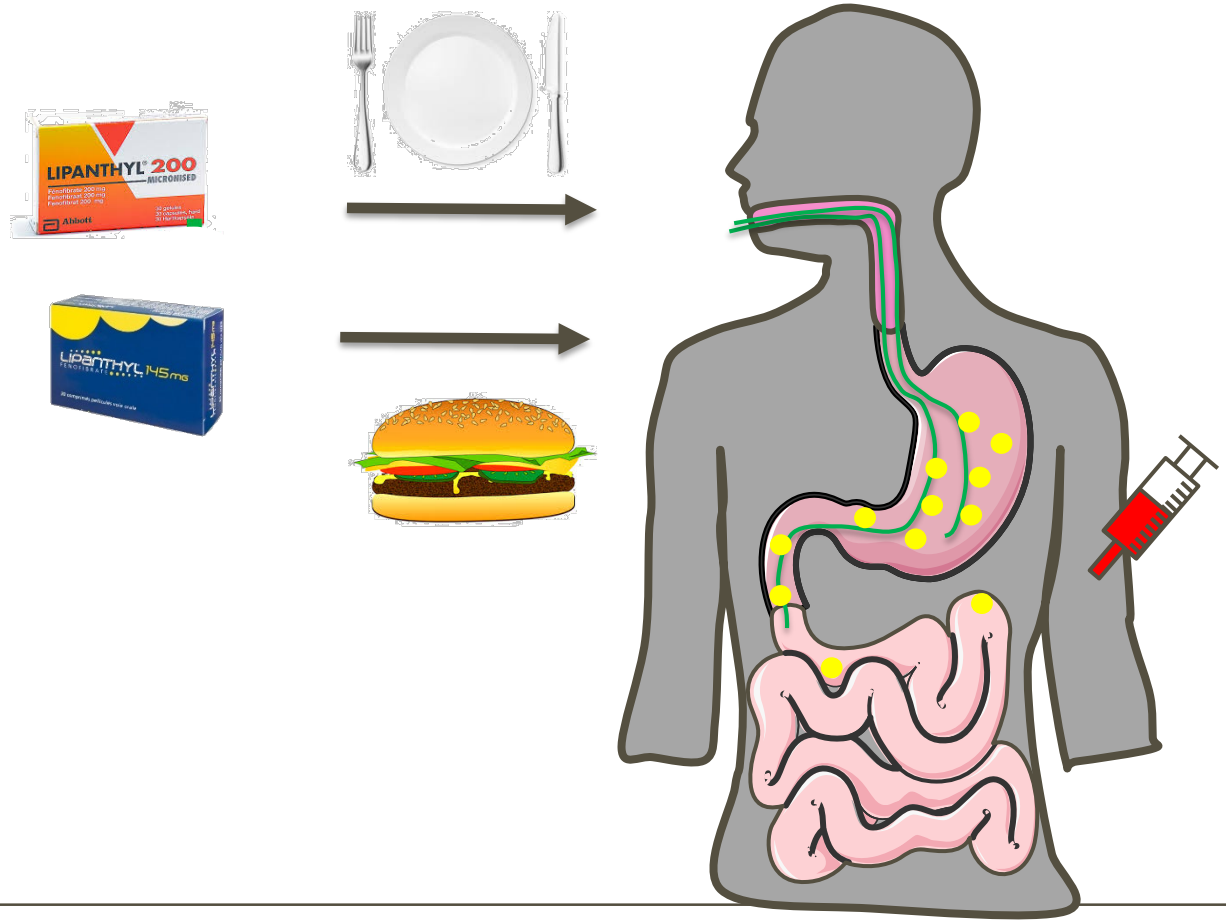
Example 2: Accounting for permeation in a drug release test

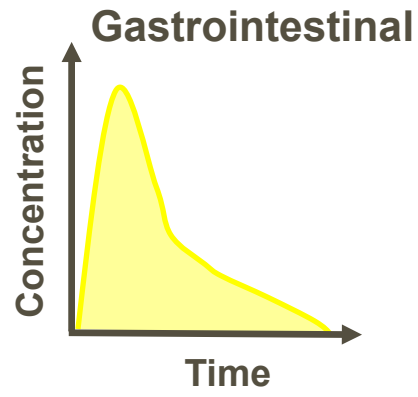


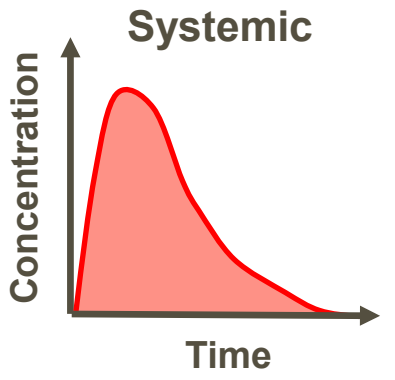
But what if solubilisation and permeation are inter-dependent?

METHODOLOGY – *in vivo*

Fenofibrate example– slides provided by Patrick Augustijns

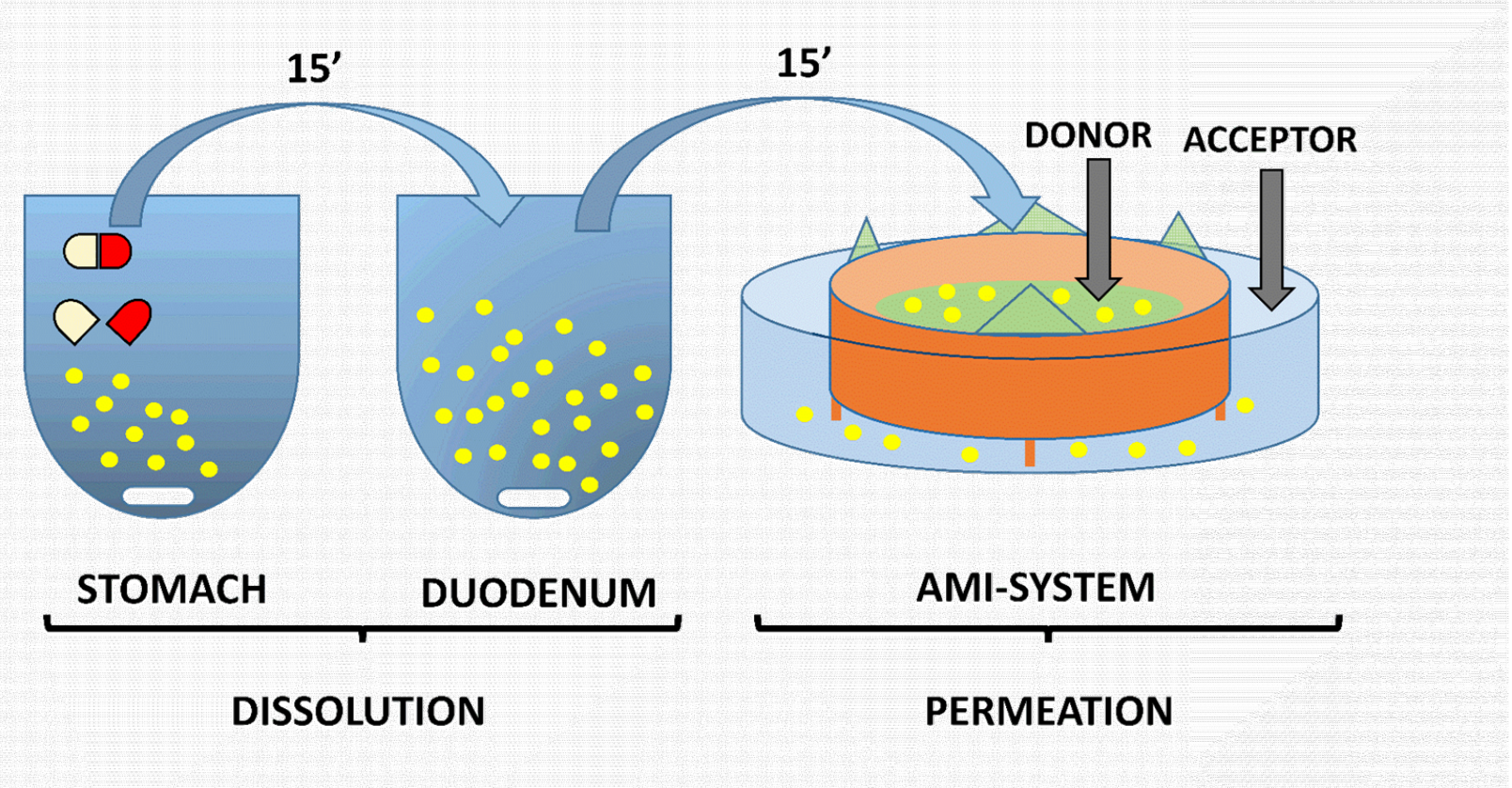






Hens, B., Brouwers, J., Corsetti, M., Augustijns, P., 2015. "Gastrointestinal behavior of nano-and microsized fenofibrate: in vivo evaluation in man and in vitro simulation by assessment of the permeation potential." *European Journal of Pharmaceutical Sciences* 77 (2015): 40-47.

METHODOLOGY – *in vitro*



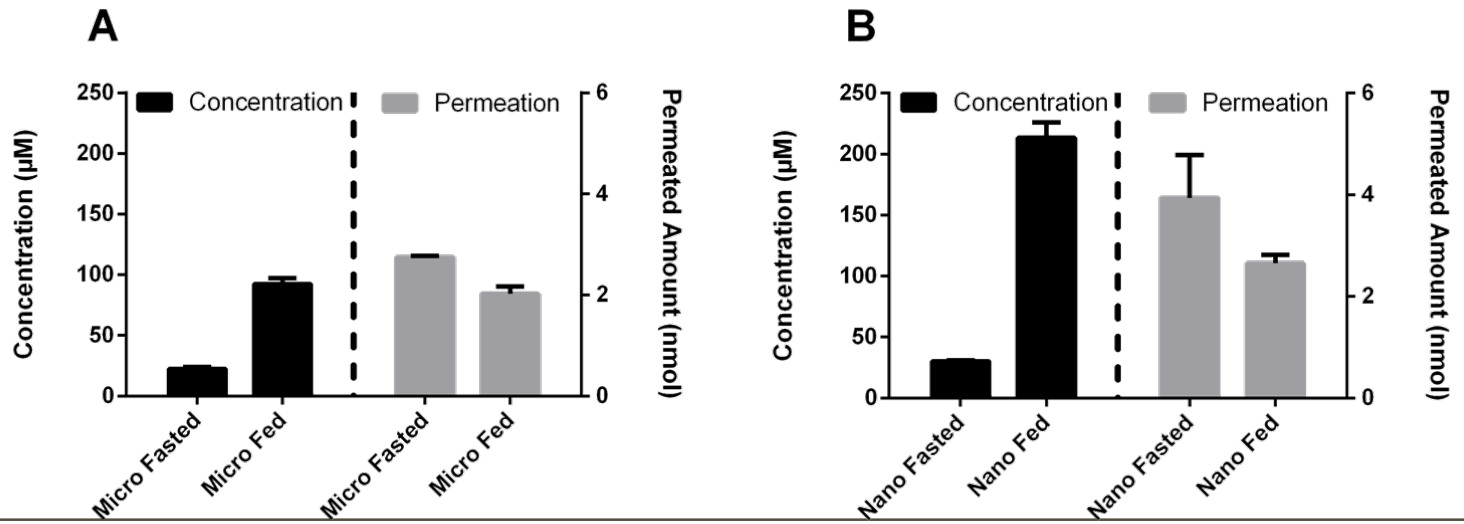
Berben, P., Brouwers, J., Augustijns, P., 2017. The artificial membrane insert system as predictive tool for formulation performance evaluation. Int. J. Pharm. 537, 22-29.

RESULTS – *in vivo & in vitro*

- *In vivo*

	Micro fasted	Micro fed	Nano fasted	Nano fed
Duodenal $AUC_{0\text{-}230min}$ (µM.h)	4.11 ±0.91	41.1 ± 21.2	14.7 ± 5.10	103 ± 37.2
Plasma $AUC_{0\text{-}8h}$ (µM.h)	35.8 ± 12	47.8 ± 13.4	121 ± 12.5	75.7 ± 16.3

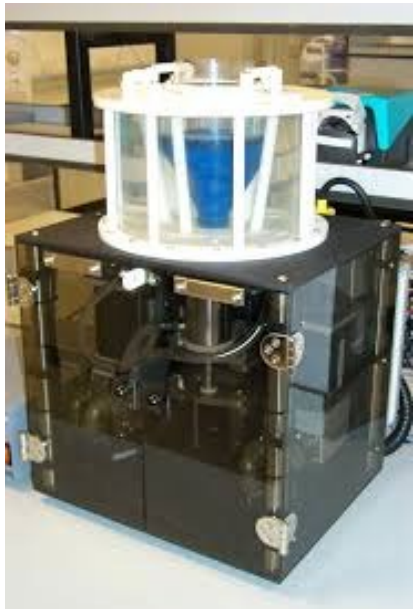
- *In vitro*



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



Dynamic Gastric Model (DGM) from IFR/ Bioneer

TIM-1 and TinyTIM from Triskelion (formerly TNO)

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)

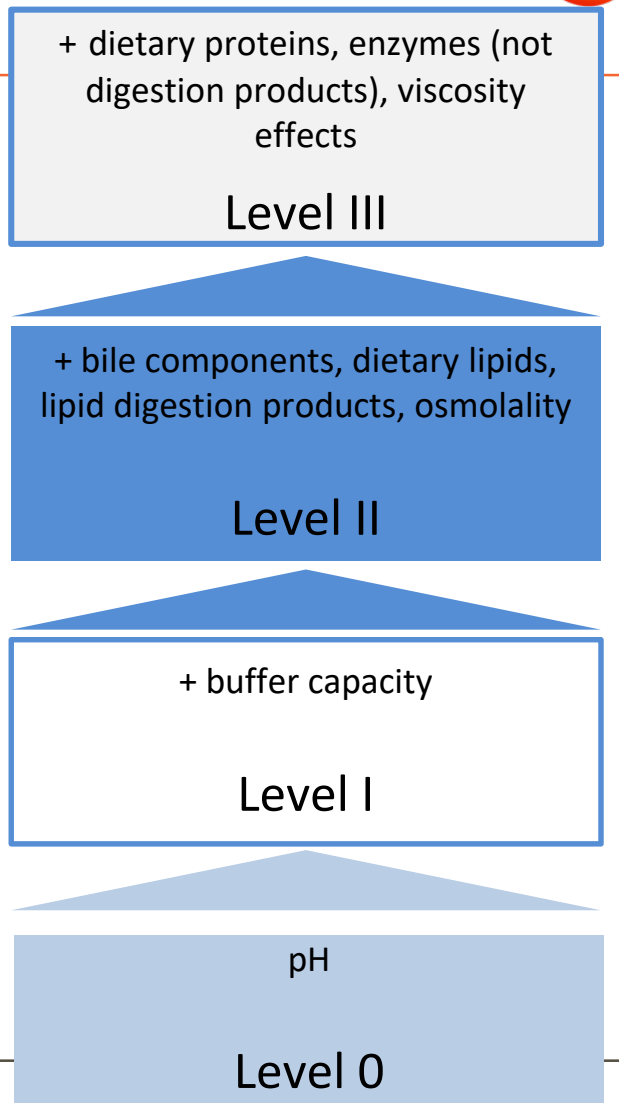
API	Formulation	Meal type	*In vivo* fed/fasted ratio	TIM *in vitro* fed/fasted ratio	Publication TIM data
Danirixin	DNX HBr	High fat meal	0.64 ($AUC_{0\text{-}inf}$)	0.9 (TIM-1)	Bloomer et al. 2017
Diclofenac	Cataflam IR	Ensure Plus	1.0 ($AUC_{0\text{-}8h}$)	1.0 (TIM-1)	Van den Abeele et al 2017
Ciprofloxacin	Ciproxin ER	High fat meal	1.0 (AUC)	1.2 (TIM-1) 1.0 (tiny-TIM)	Verwei et al. 2016
Acetaminophen	Paracetamol IR	High caloric meal	0.94 ($AUC_{0\text{-}inf}$)	1 (TIM-1)	Souliman et al. 2006
Acetaminophen	Sinaspril **crushed*	Infant formula	No food effect	No food effect (tiny-$TIM_{pediatrics}$)	Havenaar et al. 2013
Fosamprenavir	Telzir IR	Scandi-shake Mix	No food effect AUC Effect on disintegration	No food effect bioacc. Effect on disintegration (TIM-1)	Brouwers et al. 2011
Celecoxib	Celebrex	High fat meal	1.6 ($AUC_{0\text{-}inf}$)	2.0 (TIM-1)	Lyng et al. 2016
Posaconazole	Noxafil Suspension	Coca-cola	1.7 (AUC)	1.5 (TIM-1 & tiny-TIM)	Verwei et al. 2016
Nifedipine	Adalat XL MR	High fat meal	1.7 ($AUC_{0\text{-}9h}$)	3.5 (TIM-1) 3.6 (tiny-TIM)	Verwei et al. 2016
Posaconazole	Noxafil Suspension	High fat meal	4 ($AUC_{0\text{-}72h}$)	13.8 (TIM-1) 12.9 (tiny-TIM)	Verwei et al. 2016

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



See Markopoulos, Constantinos, et al. "In-vitro simulation of luminal conditions for evaluation of performance of oral drug products: choosing the appropriate test media." *European Journal of Pharmaceutics and Biopharmaceutics* 93 (2015): 173-182.

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)

Summary

- 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

EFPIA (industry) and academic collaborators in IMI OrBiTo - especially contributors to the in-vitro tools work-package (WP2)

Questions?