BREAKOUT SESSION A DAY 2:

Challenges to predict effects of drug product critical quality attribute changes (e.g. PSD changes) on dissolution and in vivo performance using PBBM. Are the tools ready?

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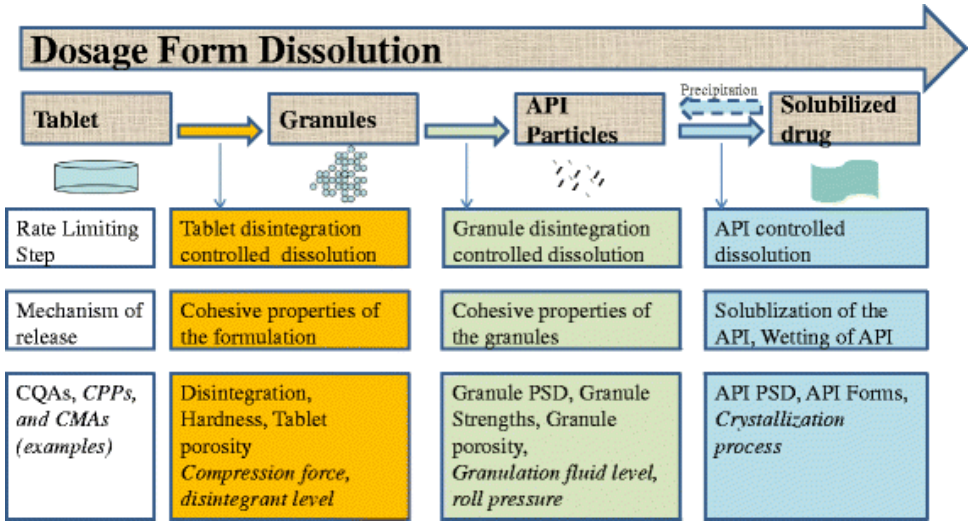
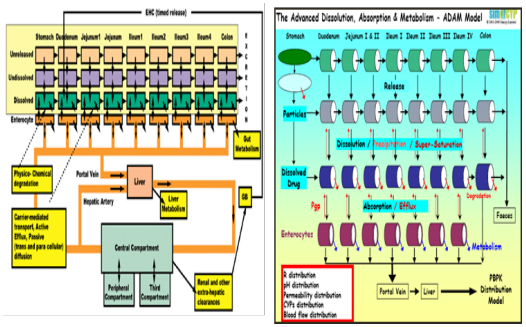
Session Background

Session A/Day 2 covers these two high-level questions

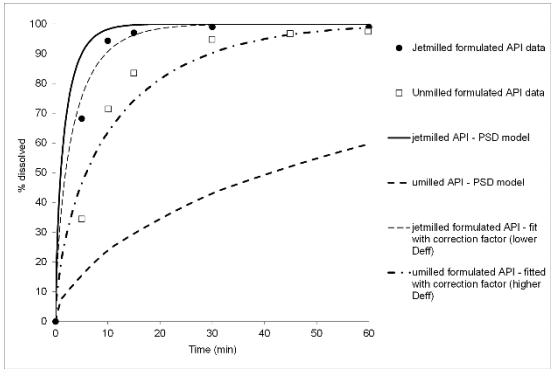
- **Which CQAs/CPPs (individually or combined) can be interrogated by PBBM?**
- **What are the best practices to setup the model for studying impact of CQAs/CPPs on bioavailability?**



Direct Input in PPBM?



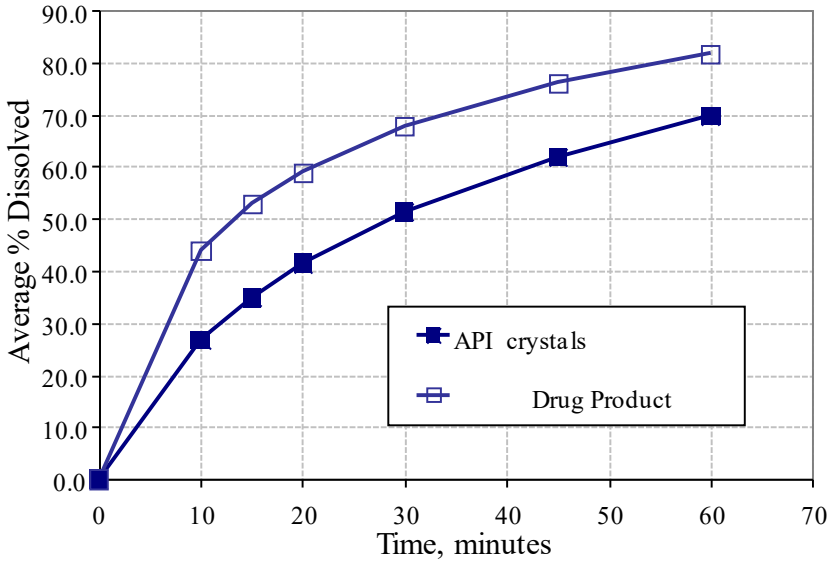
Input via dissolution data/model?



BO Session A, Day 2, Question 1

Given that for most formulated products, dissolution is not dictated by the primary API PSD,

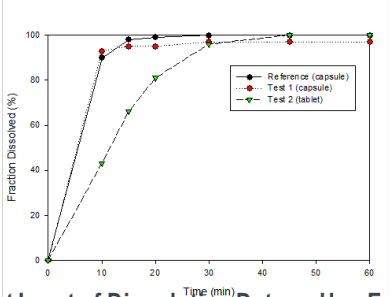
- What is the appropriate use of the PBBM for PSD specifications?
- Which data, modeling assumptions and modeling steps are needed for the meaningful application of these models?



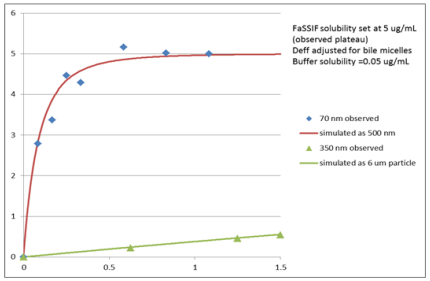
BO Session A, Day 2, Question 2

What criteria should be used to evaluate appropriateness of the approach to input drug product properties/dissolution data for PBBM?

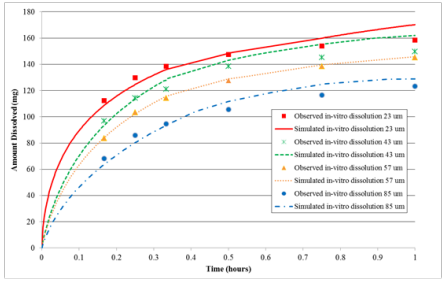
- Is it ever appropriate to enter dissolution data “as is” (i.e. assume 1:1 in vitro – in vivo correlation)? If yes, what scenarios may be acceptable?



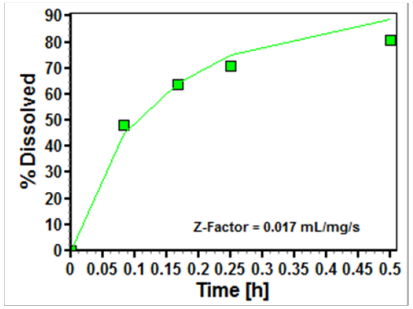
Direct Input of Dissolution Data or Use Empirical Function (i.e. 1-1 IVIVC)



Estimate an “Effective” PSD from Dissolution Data



Use API-PSD model incorporating a scaling correction factor



Use a composite dissolution parameter (z-factor)

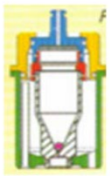
BO Session A, Day 2, Question 3

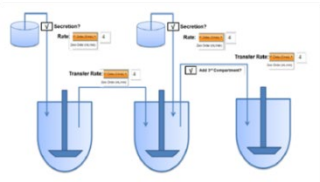
What type of dissolution data (e.g. biorelevant, biopredictive, with discriminating ability) are appropriate to be used as input for PBBM?

- How should each of these data be entered?
- Can we rely only on in silico simulated dissolution?

Biorelevant: designed to closely mimic a relevant biological fluid and a physiological environment
Biopredictive: capable of predicting pharmacokinetic profiles. These are typically based on classical or mechanistic IVIVC
With Discriminating Ability: able to differentiate drug products manufactured under target conditions vs. drug products that are intentionally manufactured with meaningful variations


USP II

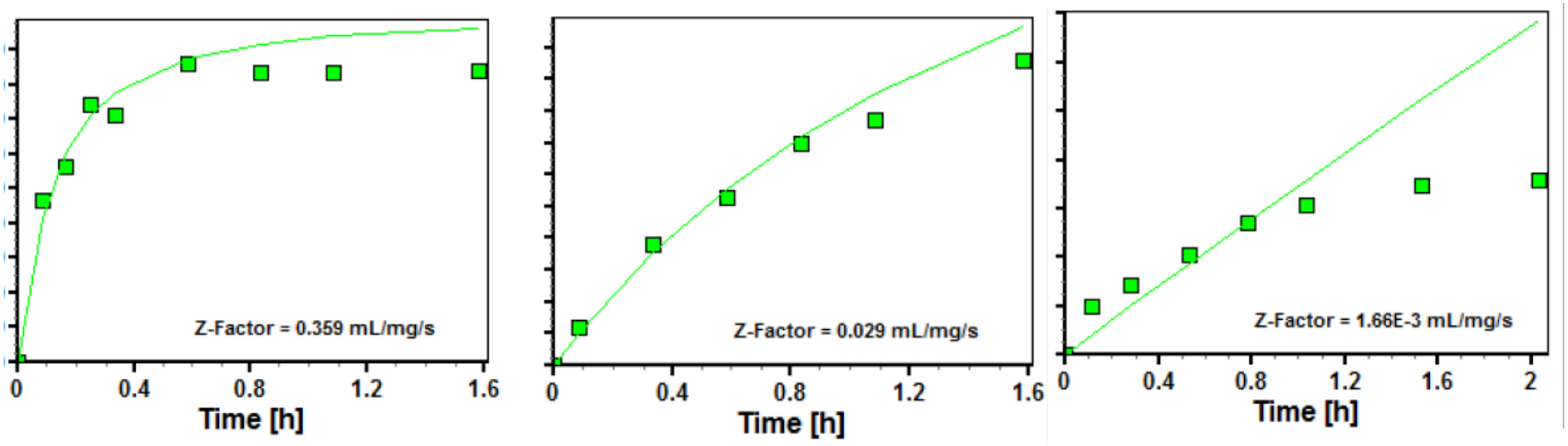

USP IV


Transfer Experiments

BO Session A, Day 2, Question 4

What constitutes adequate fitting of dissolution data for input into PBBM?

- If e.g. z-factor is used what is important to be captured, the beginning, the end, or the entire dissolution curve?



BO Session A, Day 2, Question 5

Under what scenarios (e.g. for which type of formulations/compounds) are the models ready to be used for informing CPPs and CQAs?

- How should one go about linking those to the model for IR drug products?
  - What are the gaps in knowledge and challenges?
  - What are some potential collaboration pathways to fill in the gaps?
- How should one go about linking those to the model for MR drug products?
  - What are the gaps in knowledge and challenges?
  - What are some potential collaboration pathways to fill in the gaps?