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Case Study 1

PBBM Best Practices to Drive Drug Product Quality: Regulatory and Industry Perspectives

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Shereeni Veerasingham, MBBS, PhD

A/Manager, Division of Biopharmaceutics Evaluation 3
Bureau of Pharmaceutical Sciences
Pharmaceutical Drugs Directorate

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Outline

- Background, including the question of interest for the PBBM
- Overview of modelling strategy
- Model development challenges and solutions
- Model validation, single simulations
- Model application, virtual bioequivalence to define a safe-space

Background

Problem Statement: Establish a PBBM-based dissolution safe space, determine the *in vitro* dissolution edge of failure, and evaluate if the dissolution specification may be widened.

Question: Can the dissolution specification be widened and still ensure bioequivalent performance?

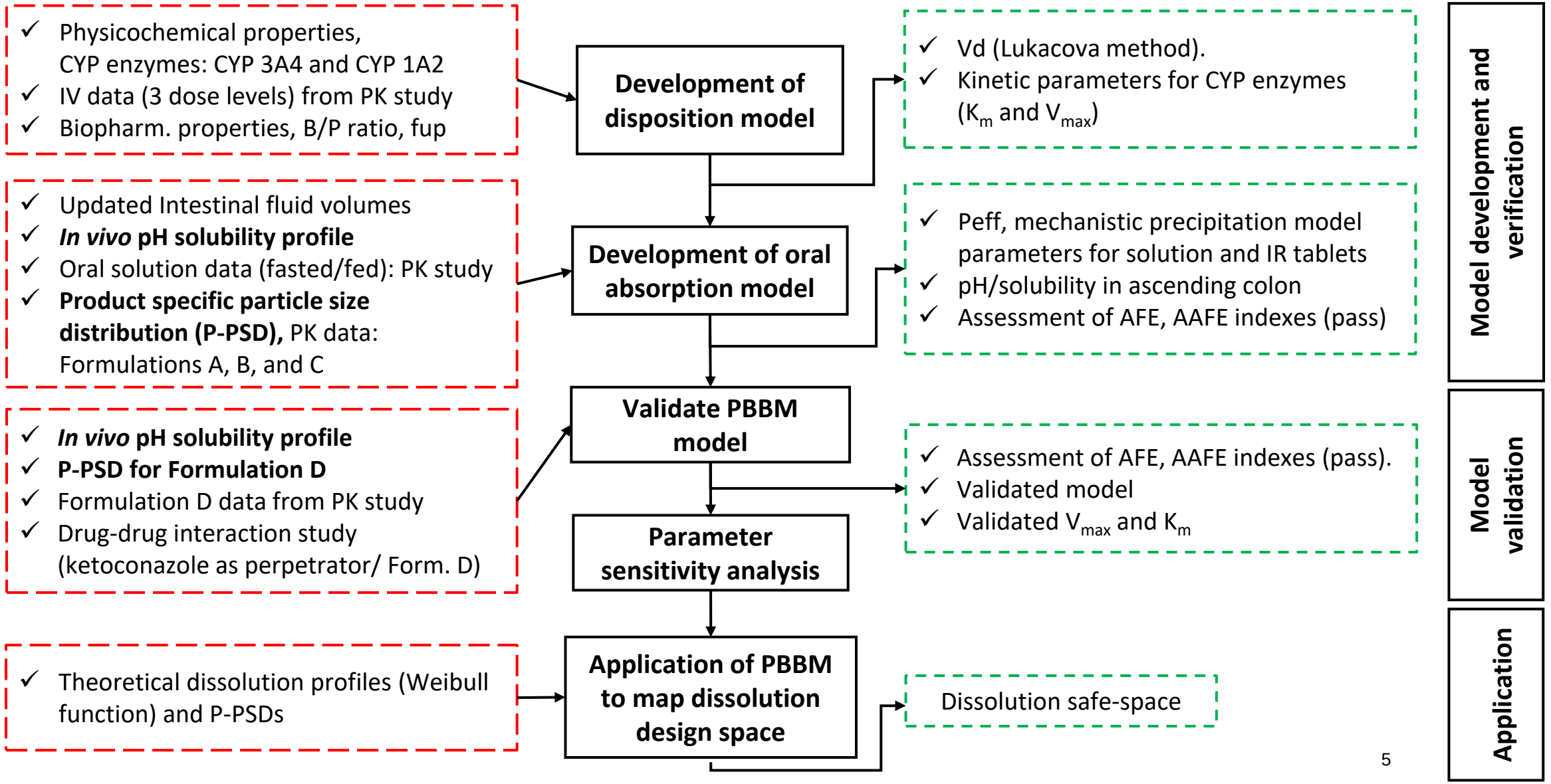
Compound properties

- Weak base
- HCl salt, common Cl^- effect at low pH
- pKa ~ 9.0
- Log D = 4.8 at pH 7.0
- BCS II
- Metabolized by CYP 3A4 and CYP 1A2
- Not a Pg-p substrate

Clinical data used

- Intravenous administration (3 dose levels)
- Oral solution (fasted/ fed state)
- Food effect study for IR tablet
- Drug-drug interaction study
- PK studies evaluating bioequivalence of 3 variants of immediate release (IR) tablet formulations

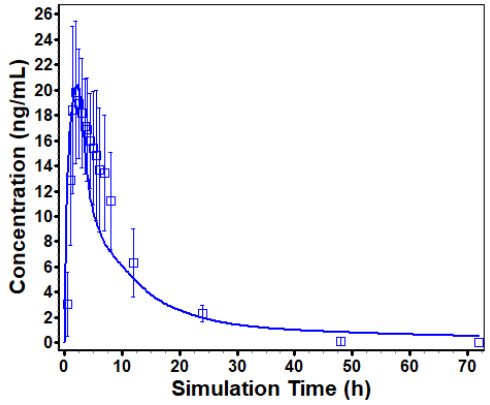
Overview of Modelling Strategy



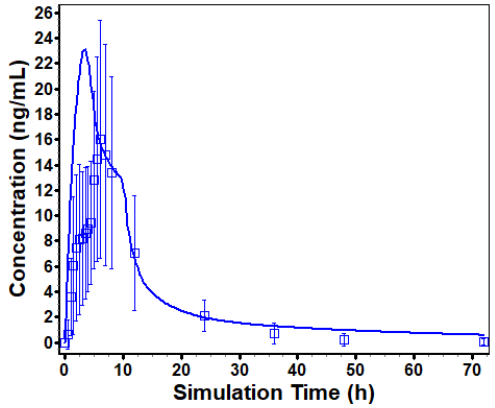
Model Development Challenges and Solutions

Challenges

Oral Solution



IR Tablet

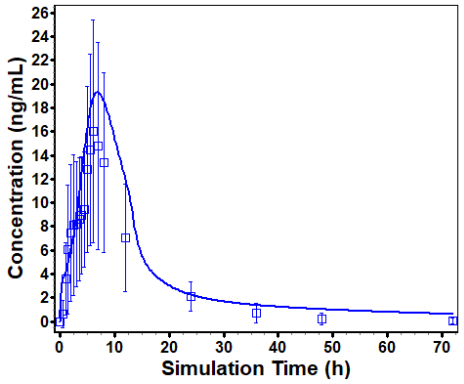


- During oral absorption model development, oral solution PK was reasonably simulated, but not the IR tablet PK profile.
- IR tablet simulations overpredicted C_{max} and underpredicted t_{max}.
- Further model refinement was required.

Solutions

- *In vitro* and *in vivo* pH-solubility profile, calc. using the Henderson-Hasselbalch eq. and *in vivo* chloride ion conc.
- A mechanistic model to account for differences in nucleation & growth rate for oral solution and IR tablet.
- Adjusted pH of ascending colon based on undissolved drug; accounts for micro-environmental pH effects.
- Simulated *in vivo* solubility in the ascending colon.

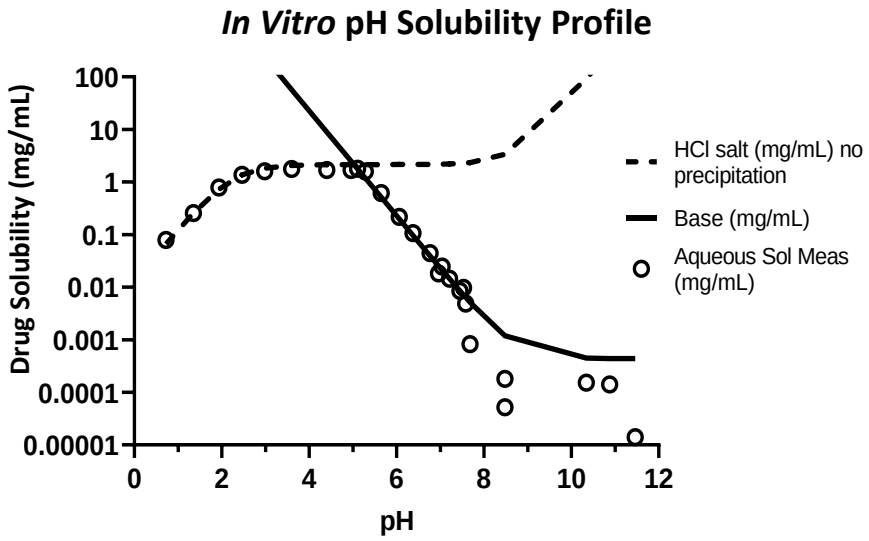
IR Tablet: Validated Model



Model application: establish a dissolution safe-space and evaluate widening of the dissolution specification.

Common Chloride Ion Effect

- Aqueous solubility of the drug (HCl salt) decreases in the presence of Cl^- due to common ion effect.
- The *in vivo* pH solubility profile was assumed to be specific for each formulation and prandial state.
- Stomach: low pH and high chloride concentration
  - decreases drug solubility and dissolution rate
  - varies with volume of water administered with product and/or the prandial state.



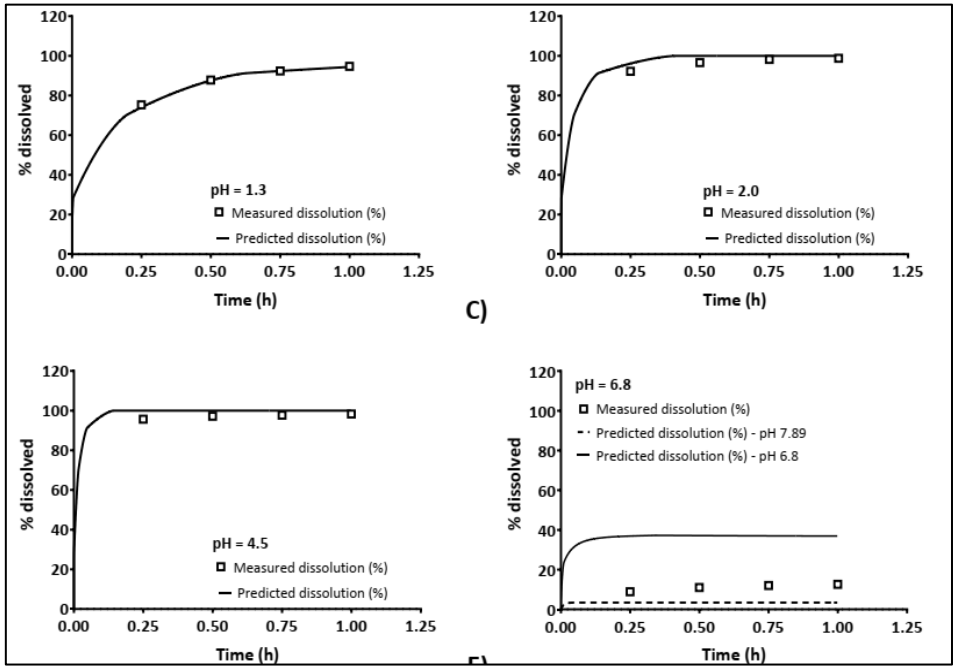
- Cl^- concentration is high through the GI tract until the colon, unfavorable for dissolution.
- Colon: longer residence time and low chloride concentration allows for drug dissolution. pH obtained from *in vitro* experiment was used to account for the estimated amount of undissolved drug (changed from 6.8 to 4.86).

Product Specific - Particle Size Distribution (P-PSD)

Dissolution was assumed to be controlled by the diffusion of the drug through a stagnant film layer surrounding the dissolving particle as described by Pepin *et al*., 2019.

- *In vitro* dissolution rates were fitted to P-PSD.
- Validated by using the P-PSD to predict dissolution at different pH.
- At pH 6.8, the P-PSD and bulk pH/solubility overpredicted dissolution rate.
- Using surface pH/solubility at pH 6.8 improved the prediction (calc. solubility is 10x lower)
- The P-PSD was used as input to simulate the *in vivo* dissolution for the ACAT model.

Predicted Dissolution Profiles using P-PSD



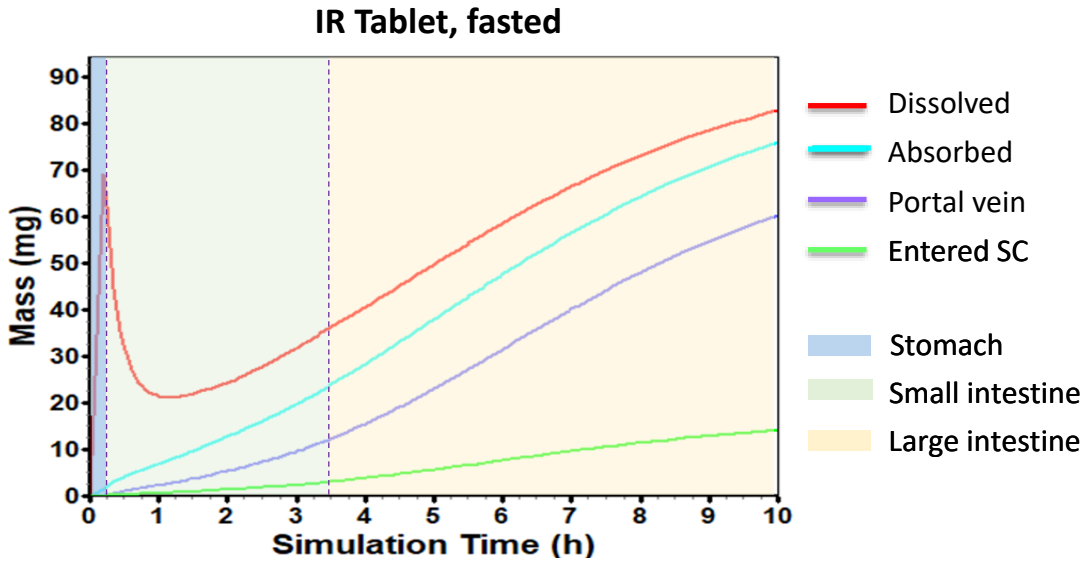
Pepin X.J.H. *et al*., Eur. J. Pharm. Biopharm., 2019. 142: p. 421 – 434

Regional GI Tract Absorption

Based on simulations:

- Consistent with IR tablet, ≈ 80% of the dose dissolves in the stomach (0 – 0.25 h).
- ≈ 50 mg drug precipitates at pH > 6.0 in the small intestine, then slowly redissolves.
  - Supported by low solubility at pH 6.0 – 7.4 and slow *in vitro* dissolution in pH 6.8.
- Some drug remains undissolved, decreases pH as it reaches the ascending colon.
- The shift in pH promotes drug ionization, increases dissolution and absorption.
  - Consistent with low bioavailability, long T_{max}

PSA, impact on C_{max} and AUC:
small intestine transit times,
small intestine and colon fluid volumes,
and ascending colon pH.



Comments on Model Development

- Approach for modelling *in vivo* drug solubility profiles:
  - Increased complexity of the model balanced by improved predictions.
  - Focus on most impacted GI tract regions (stomach and colon) to reduce model complexity.
  - Uncertainty regarding the degree of change in ascending colon pH.
  - Precipitation is a key consideration; experimental data is recommended.
- Peff: a fitted value is adequate for a high permeability drug.
  - Fitted to PK data for oral solution, fasting condition; verified by simulation, fed conditions.
  - Experimental Papp data from *in vitro* permeation assays is preferred.
- The P-PSD underpredicts dissolution at pH 6.8, despite correction for surface pH.
- Drug physicochemical properties (log D, pKa) indicate possible lysosomal trapping.
  - Volume of distribution was accurately predicted; compared to IV PK data at 3 dose levels.

Model Validation

Method validation employed:

- Datasets were independent from those used in model development.
- P-PSD and *in vivo* pH solubility profile specific for Formulation D.
- Single simulation comparisons to observed PK profiles from three clinical studies.
- Additional validation from food effect study (low-fat and high-fat meals) and a drug-drug interaction study (ketoconazole as perpetrator).

Acceptance criteria were met for most studies, except for AUC in one PK study (AFE 1.35), and C_{max} for the low-fat, low-calorie simulation (AFE 1.27).

Overall, model validation was considered adequate for the intended use of the model.

AFE: Average Fold Error, satisfactory if the AFE is between 0.8 – 1.25

Model Application – Dissolution Safe Space

- Theoretical dissolution profiles were generated by altering Weibull Ph1 fraction (f1).
  - As f1 decreases, dissolution is slower with an increase in P-PSD, PK simulations display a correspondingly lower C_{max}.
- Virtual BE trials: simulated PK for theoretical profiles compared to reference tablet.
  - For the slowest f1 profile (f1-slow), 1 of 10 virtual trials did not meet BE criteria, C_{max} ratio 90% CI < 0.8.
  - All f1 profiles faster than f1-slow were bioequivalent to the reference tablet.
- A dissolution safe-space was defined based on the results of the virtual BE trials.

Comments on Model Application

- Variability of the virtual subjects was not fully representative of that observed in clinical trials.
  - Mean inter-subject variability for AUC and C_{max} across 10 trials mimicked the observed variability.
  - However, probability contours cover the observed variability at 95% prediction interval in 5/10 trials.
  - Conservative criteria for bioequivalence were set: all 10 trials need to meet BE criteria.
  - Tablet variant with slower dissolution, not BE to target profile: 1/10 trials did not meet BE criteria. Concerns regarding predictive ability of the model for the non-BE tablet.
- Model complexity/software limitations led to unsuccessful trial simulations for some subjects.
  - 42 virtual subjects were included, only the first 32 completed subjects for the reference formulation and corresponding subject simulation for the test formulation were used for the analysis.
- Model risk was considered low per the credibility assessment framework.*
- Virtual BE supports the defined safe-space, could permit widening of dissolution specifications.

* Kuemmel C. *et al*., CPT: Pharmacomet. & Syst. Pharmacol., 2020, 9: p. 21 – 28

Summary

- PBBM for a weak base compound, with a mechanistic approach to *in vivo* pH solubility profiles that considered common chloride ion effects and precipitation.
- Assumptions about precipitation should be supported by experimental data.
- Some limitations were noted related to the model complexity.
  - Focus on most impacted GI tract regions (stomach and colon)
  - Unsuccessful trial simulations for some subjects
- Validation based on single simulations was considered adequate, but some concerns were noted for the virtual BE trials (variability, prediction of non-BE tablet variant).
- Model risk was considered low. The dissolution specification can be widened within the defined safe-space while maintaining bioequivalent product performance.

Acknowledgements

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