A new particle population balance model (PPB) for PBPK modelling of orally dosed drugs accounting for two solid states

Dan Liu*, Masoud Jamei, David B. Turner
Certara UK Limited, Simcyp Division, Level 2-Acero, 1 Concourse Way, Sheffield, S1 2BJ, United Kingdom

FDA project: NIH-003-absorption
Email: dan.liu@Certara.com

Background

Population balance equations (PBEs) have been developed to model the evolution of particles or cells in various fields, such as the drying process when producing pharmaceutical tablets, crystallization to emulsions in food processing, and cell growth in biological systems [1], This work describes the development a new particle population balance model (PPB) for mechanistic modelling of oral drug absorption of particulate formulations and integration of the PBEs into the existing Simcyp ADAM model [2] to improve the description of particle distribution and dissolution rate during transit within the Gastrointestinal (GI) tract while retaining mass balance.

Methods

1. In the new PPB model, PBEs, describing how particle size distribution (PSD) changes over time, were integrated into the ADAM model as an alternative to the existing approach for handling dispersed API particles:
   - The new model can account for two solid states of a formulation viz. handling two forms with two different solubility, such as different crystalline forms or a crystalline and amorphous form. Each solid state of the drug can have a separate PSD, which can be either mono- or poly-dispersed, different intrinsic solubility and thus dissolution rate. In addition to Immediate Release (IR) formulations, the model can handle API particles released from various formulations, such as Controlled/Modi¬fied Release (CR, MR), Enteric Coated Granules and Enteric Coated Tablets.
   - The model allows precipitation to a different solid state to that of the dosage form or to two solid states simultaneously, and includes a nucleation (particle birth) model.
2. The differences between PPB and its predecessor the Mass Balance Only (MBO) are summarised in Table 1. Also particle handling mechanisms for these two methods are illustrated in Fig. 1.
3. The PPB model simulation results are compared to those of the MBO model using 9 cases with an IR formulation:
   - 3 cases using Midazolam as a model drug
   - 6 cases using a hypothetical neutral compound A, with a low intrinsic solubility of 0.005 mg/mL

   For these initial assessments *only,* it is assumed the drugs do not precipitate (no supersaturation was observed), are not metabolised and are not transporter substrates. Different oral doses were given with 250 mL water in all 9 cases; other parameters are summarized in Table 2.
4. MBO simulations were run using the Population Representative of the Healthy Volunteer population in Simcyp V17. Results with the PPB were generated using Matlab because the PPB is currently being implemented in Simcyp simulator V18 (not yet available).

Results

Figure 2 is a comparison of Tmax, Cmax, and AUC24h of enterocyte concentration in different GI segments between the MBO and PPB model for the 9 cases (Table 2). PPB results were used as baseline. In summary:

1. For formulations which dissolve rapidly in the stomach, and as expected, the difference between PPB and MBO is small (cases 1 and 2) .
2. The dissimilarity becomes more noticeable once particles do not rapidly dissolve in the stomach and are transferred into small intestine (cases 3-9).
3. Undissolved masses at a given time are higher with the PPB and hence luminal and enterocyte concentrations are different.
4. In most cases, the original MBO model predicted higher luminal and enterocyte concentrations compared to those of the PPB model because dissolution is more rapid in the former case.
   - For example, in cases 5, 6 and 9, the MBO predicted a 40-50% higher Cmax (enterocyte) compared to that of the PPB model from Jejunum I to colon. This is because in the MBO, fixed particle numbers are maintained throughout the simulation (Fig. 1). Consequently, the MBO model predicts higher dissolution rates for a given mass of undissolved API.
5. The differences are more apparent in the distal GI tract as the impact of over-estimation o.f dissolution rate accumulates.

Table 1 Summary of the main features of the MBO and PPB model in the Simcyp simulator

ADAM	MBO	PPB
Mass balance	Yes	Yes
Particle count	Fixed	Varied mechanistically due to dissolution and birth
Particle bin handling (Polydispersed)	Discrete with gaps	Discrete without gaps
Maximum number of bins	10 (V17), 1000 (V18)	1000
Multiple PSDs	No	Yes
Two solid states	No	Yes
Excipient	Yes	Yes
pH & Bile micelle mediated solubility	Yes	Yes
Particle surface solubility	Yes	Yes
IR/EC-tablet/EC-granule/MR/CR	Yes	Yes
Segregated transit time model	Yes	Yes
First order precipitation	Yes	Yes
Mechanistic Particle Growth (DLM)	No	Yes
Precipitation to a different solid state	No	Yes
Nucleation	No*	Yes
Luminal degradation	Yes	Yes

•Possible, but not implemented in the Simcyp simulator.

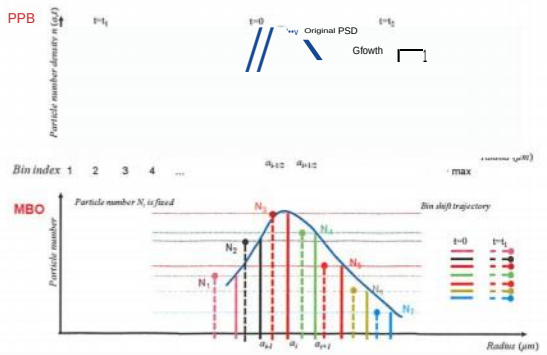

Figure 1, Illustration of the particle handling mechanisms in MBO and PPB model

Table 2, Summary of the settings for the 9 case examples

Case	Compound	IR Formulation	Dose (mg)	Radius PSD (pm)	Petr (cm/s)
1	Midazolam	Polydispersed	5	Norm(10, 2.5%CV)	default
2	Midazolam	Polydispersed	100	Norm(10, 2.5%CV)	default
3	Midazolam	Polydispersed	100	Norm(100, 2.5%CV)	default
4	Comp A	Polydispersed	10	Norm(10, 0.5%CV)	5 x 10'4
5	Comp A	Polydispersed	10	Norm(10, 0.5%CV)	0.0001 x10'4
6	Comp A	Monodispersed*	10	10	0.0001 xio-4
7	Comp A	Monodispersed*	100	10	0.0001 xio-4
8	Comp A	Polydispersed	100	Norm(100, 2%CV)	5 x 10'4
9	Comp A	Polydispersed	100	Norm(100, 2%CV)	0.0001 x 10-4

*In PPB a discrete PSD (0.04pm step-size) was used to approximate the monodispersed MBO-ADAM.

Conclusions

1. A new PPB model has been developed to enhance mechanistic oral dissolution modelling including handling two solid states of an API at the same time. This model maintains both mass and particle population balance.
2. The current studied cases reveal that the new PPB model can predict significantly lower dissolution rate compared to the original ADAM model.
3. Further work is needed, once fully implemented into Simcyp v18, to quantify differences between the MBO and PPB in terms of PK outcomes and to qualify the PPB model.

[1] Kolewe, et al., Biotechnol Bioeng 109(2) (2012) 472-82. [2] Jamei et al., AAPS J 11(2) (2009) 225-37

Figure 2, Relative difference of Tmax, Cmax, and AUC24h for ***enterocyte drug concentration*** at different GI segments between MBO vs PPB.