M1030-13-84

Application of Physiologically-based Pharmacokinetic Absorption Modeling and Simulations for Biopharmaceutics: Risk Assessment and Control of Critical Quality Attributes for Medical Countermeasure Drug Products

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PURPOSE

- Medical countermeasures (MCMs) drugs include antimicrobial or antiviral drug products that may be used in the event of a bioterrorist attack or a naturally emerging disease.
- Due to the strategic importance of applying MCMs in the public health emergency, a timely assessment and control of the critical quality attributes (CQA) of these drug products is crucial.

OBJECTIVE(S)

- To develop physiologically-based pharmacokinetic (PBPK) absorption models for biopharmaceutics applications for three potential MCM drug products[1].
- To predict the effects of CQAs such as particle size and dissolution specifications on drug-exposure *in vivo*.

METHOD(S)

- Three MCM drugs: balaxovir marboxil (BM, for the treatment of influenza), ciprofloxacin (Cipr, for anthrax), and oseltamivir (OP, for influenza) were selected to determine the effect of CQAs (particle size, dissolution specifications) on the oral absorption and PK[2].
- PBPK absorption models for biopharmaceutics for 3 MCM drugs were developed and validated using available human PK data (GastroPlus™ 9.6).
- Parameter sensitivity analysis (PSA) and virtual bioequivalence (BE) study were applied to study the impact of CQAs on PK.

INFORMATION OF PBPK MODELS AND APPLICATIONS FOR 3 MCMS

Model Parameter	Baloxavir Marboxil (BM-BXA*)	Ciprofloxacin (Cipr)	Oseltamivir (OP-OC*)
Absorption	ACAT™	ACAT™	ACAT™
Dissolution Model	a. Tabulated in vitro dissolution data b. Johnson dissolution model (particle size)		
Disposition Model	PK compartmental model	PK compartmental model	PBPKPlus™ combined with PEAR™
Metabolite Tracking	Yes Use FPE[a]	No	Yes Metabolism module (CES1, Km, Vmax)
Base Model	Monkey & Rat Allometric Scaling to human	Human	Human
Model Validation [b]	External (3) Internal (1)	External (16) Internal (2)	External (10) Internal (2)
Model application	Particle size safe space Dissolution specification		Dissolution specification

• BXA: baloxavir acid (active metabolite of BM); OC: oseltamivir carboxylate acid (OC), active metabolite of OP; CES: Carboxylesterases

a. First pass extraction. b. Model validation was performed both internally and externally. PK data from different formulations and dosages were used for external validations.

RESULT(S)

Balaxovir Marboxil-Balaxovir Acid (BM-BXA, IR)[3]

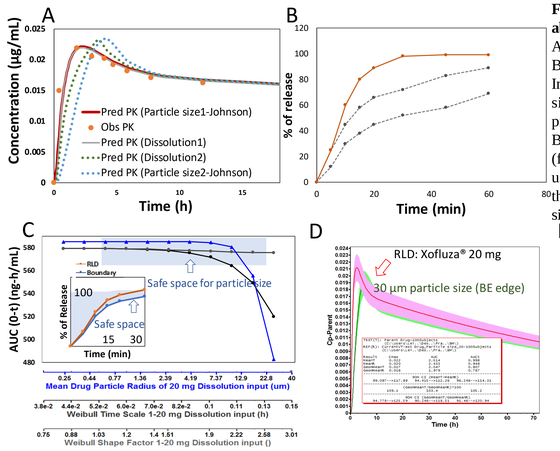

Fig. 1: Development BM-BXA PBPK absorption model for biopharmaceutics. A. Observed and predicted PK data for BXA (BM is not detectable) (20 mg, Immediate Release (IR), variable particle size) using particle size or dissolution profile as model inputs. Larger size in 2. B. In vitro dissolution data (QC method) (for IR with variable particle size) was used as input. Dotted grey curve highlights the range of dissolution with larger particle size (2).

Fig. 2: Application of BM-BXA PBPK absorption model for biopharmaceutics quality control (QC): C. PSA analysis of the effect of 20 mg Xofluza IR tablet particle size (using Johnson Dissolution Model) and Weibull factors (using dissolution data fitted to Weibull functions) on AUC (0-t). Both particle size and dissolution rate are sensitive parameters. D-E. Virtual BE analysis setting the upper bound of particle size for BM (< 30µm) (D) and dissolution safe space (>15%, E) (edge of failing BE). RLD: Reference Listed Drugs

Ciprofloxacin (Cipr, IR & XR)[4]

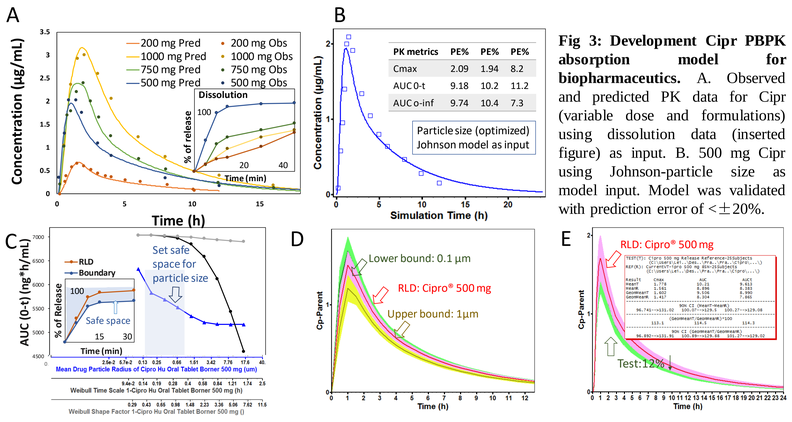

Fig 3: Development Cipr PBPK absorption model for biopharmaceutics. A. Observed and predicted PK data for Cipr (variable dose and formulations) using dissolution data (inserted figure) as input. B. 500 mg Cipr using Johnson-particle size as model input. Model was validated with prediction error of <±20%.

Fig. 4: Application of Cipr PBPK absorption model for biopharmaceutics quality control: C. PSA analysis of the effect of 500 mg Cipro particle size (using Johnson Dissolution Model), Weibull factors (using dissolution data fitted to Weibull functions) on AUC (0-t) of Cipr. Both safe space for particle size and dissolution profile were identified. Virtual BE analysis setting the lower and upper boundaries of particle size (D) and dissolution safe space (E) for Cipro IR 500 mg tablet (edge of failing BE).

Oseltamivir-Oseltamivir Carboxylate acid (OP-OC, IR)[5]

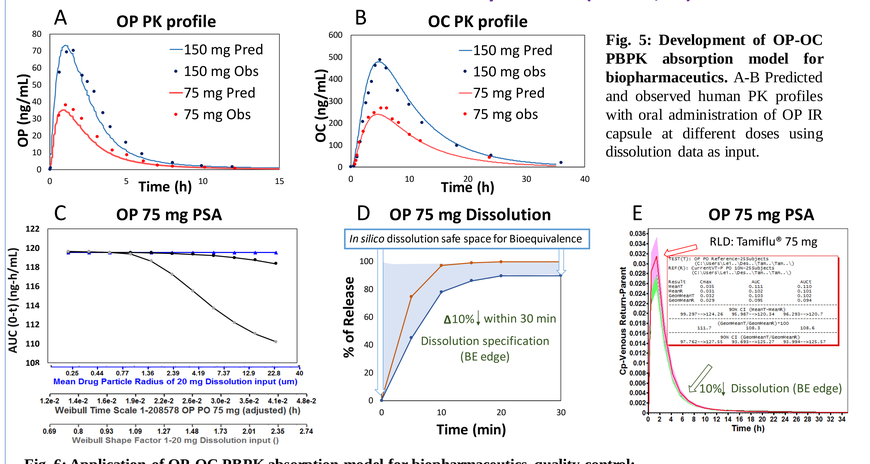

Fig. 5: Development of OP-OC PBPK absorption model for biopharmaceutics. A-B Predicted and observed human PK profiles with oral administration of OP IR capsule at different doses using dissolution data as input.

Fig. 6: Application of OP-OC PBPK absorption model for biopharmaceutics quality control: C. PSA analysis of the effect of OP 75 mg particle size (using Johnson Dissolution Model), Weibull factors (using dissolution data fitted to Weibull functions) on AUC (0-t) of OP. Particle size is not a sensitive parameter for OP. D. In vitro dissolution data of RLD OP capsule, and theoretical safe space for dissolution specification. E. Virtual BE comparison of test batch with 9% decrease of dissolution rate compared to RLD (edge of failing BE criteria).

IN SILICO SETTING OF CLINICALLY RELEVANT SAFE SPACE

Drug	Particle Size (µm, boundary)		Dissolution (% slower, boundary)	
	Pass BE	Fail BE	Pass BE	Fail BE
BM (BXA)	28	30	14	15
Cipr	0.12-0.9	0.10-1.0	11	12
OP-OC	-/-	-/-	9	10

CONCLUSION(S)

- We developed PBPK modeling strategies for multiple MCMs with variable physicochemical properties under different conditions (e.g., parent-metabolites, with sparse human data).
- These PBPK absorption models for biopharmaceutics can be used to set clinically relevant specifications for particle size and dissolution safe space.
- These models can potentially be extended to monitor MCM drug storage and formulation design, etc.

REFERENCES AND ACKNOWLEDGEMENT

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- *This project is supported by FDA MCMi funded Oak Ridge Institute for Science and Education (ORISE) Fellowships. Dr. Lei Miao was supported by an appointment to the Research Participation Program at CDER, administered by ORISE through an interagency agreement between the US Department of Energy and the FDA.*
- *The authors acknowledge Dr Lei Zhang (Deputy Director of ORS) for commenting and modifying the abstract and poster.*

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