Physiologically Based Absorption Modeling as a Tool to Evaluate the Bioequivalence of Metoprolol ER Products

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Introduction

- Over the last decades, the utilization of generic drugs in US accelerated tremendously which has saved the US health system more than $1.5 trillion. These are generally considered safe and effective as they undergo rigorous bioequivalence (BE) testing.
- The office of Generic Drugs (OGD) at FDA occasionally receives complaints about reduced efficacy/safety following a switch from a brand to a generic drug or a switch between generic drugs. In collaboration with Center for Pharmacometrics and Systems Pharmacology (CPSP) University of Florida, OGD devised a mechanism- and risk-based strategy integrating three different platforms (Bioinformatics, PBPK and PK/PD) to evaluate the reported post-marketed complaints about purported therapeutic equivalence following a brand to generic drug switching.
- From last two decades, Physiologically-Based Oral Absorption (PBOA) modeling has been demonstrated to be more useful than an empirical absorption model as it can provide insights to the key determinants of oral absorption as well as can guide drug product development. Since 2010, FDA assessed 34 new compounds using oral absorption modeling to justify clinically relevant dissolution methods, to investigate quantitative risk associated with drug product specifications and to evaluate bioequivalence.
- The main objective of this study is to evaluate the use of PBOA model to determine the critical quality attributes of Metoprolol ER products that can possibly cause change of relative bioavailability between generic and brand name products.

Methods

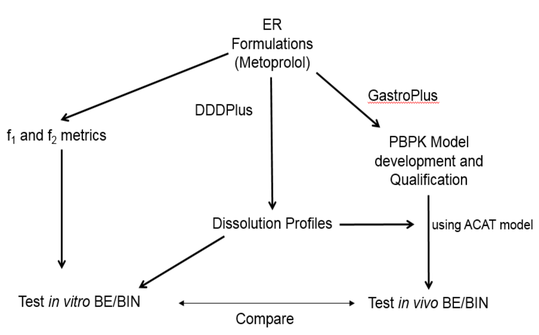

Figure I *General research strategy of the evaluation of the bioequivalence of Metoprolol extended release (ER) products using conventional empirical dissolution based f_1 and f_2 data and PBPK/absorption based model.*

We used a step-wise approach to develop and qualify the PBOA model of Metoprolol using GastroPlus. Once developed and qualified, we performed parameter sensitivity analysis to identify the influential drug-, system- and formulation-specific factors which can possibly cause change of relative bioavailability between generic and brand name products. The method development, qualification and application is described as follows:

1. **Development and Qualification of an Intravenous (IV) Infusion Model:** At first, we deconvoluted pharmacokinetic data from intravenous administration to obtain the disposition model of metoprolol (systemic clearance and volume of distribution. Different structural models were tested and based on the AIC criteria 2 compartment PK model was selected.
2. **Development and Qualification of an Immediate Release (IR) Absorption Model:** In this step, the systemic disposition parameters of metoprolol remained constant and combined with the default ACAT model to characterize the pharmacokinetic properties of metoprolol after oral administration of IR metoprolol tablet.
3. **Development and Qualification of an Extended Release (ER) Absorption Model:** In this step, at first we map out the maximum absorption capacity of the lower gut segments (colon and caecum) by optimizing the ACAT model after the colonic absorption of metoprolol. After that, we combined *in vitro* dissolution profile, disposition parameters and optimized absorption model to define the pharmacokinetic properties of metoprolol after oral administration of ER metoprolol tablet.
4. **Parameter Sensitivity Analysis:** Finally we performed parameter sensitivity analysis (PSA) to identify the key drug- (solubility, particle size/radius etc.), system- (permeability, transit time etc.) and formulation- (drug release exponent (N) and drug-polymer interaction constant (K)) specific factors to guide the next formulation design.

Results

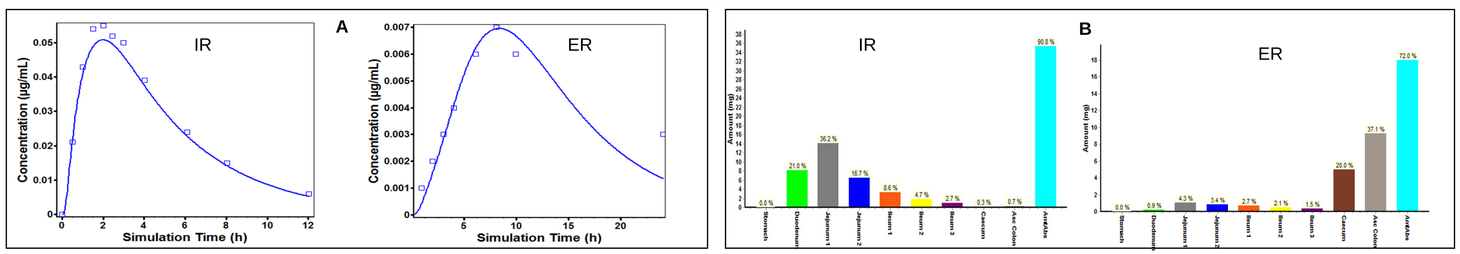

Figure II Panel A: *Physiological-based absorption model development of Metoprolol in IR and ER formulations*. Panel B: *Prediction of absorption of metoprolol IR (a) and ER (b) formulation in different regions: Interaction of Site, Drug and Formulation Specific Properties and Gut Physiology*

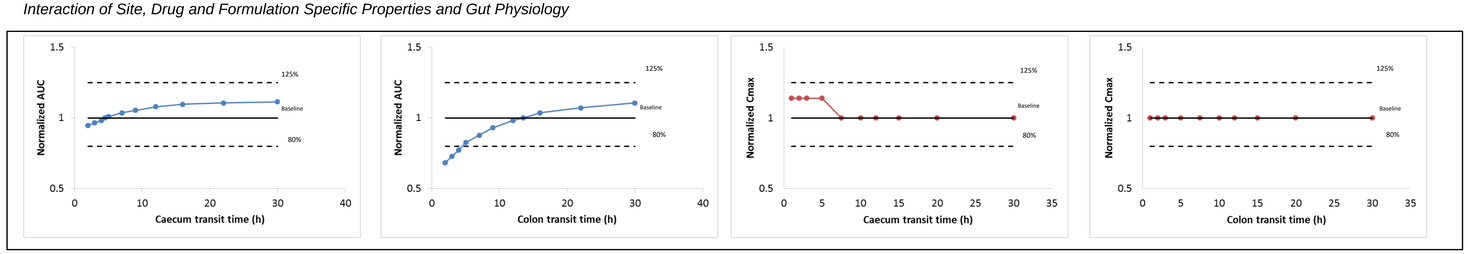

Figure III *Impact of changes in transit time (stomach, small intestine, colon and caecum) on pharmacokinetic parameters (AUC and C_{max}) of Metoprolol ER formulation.*

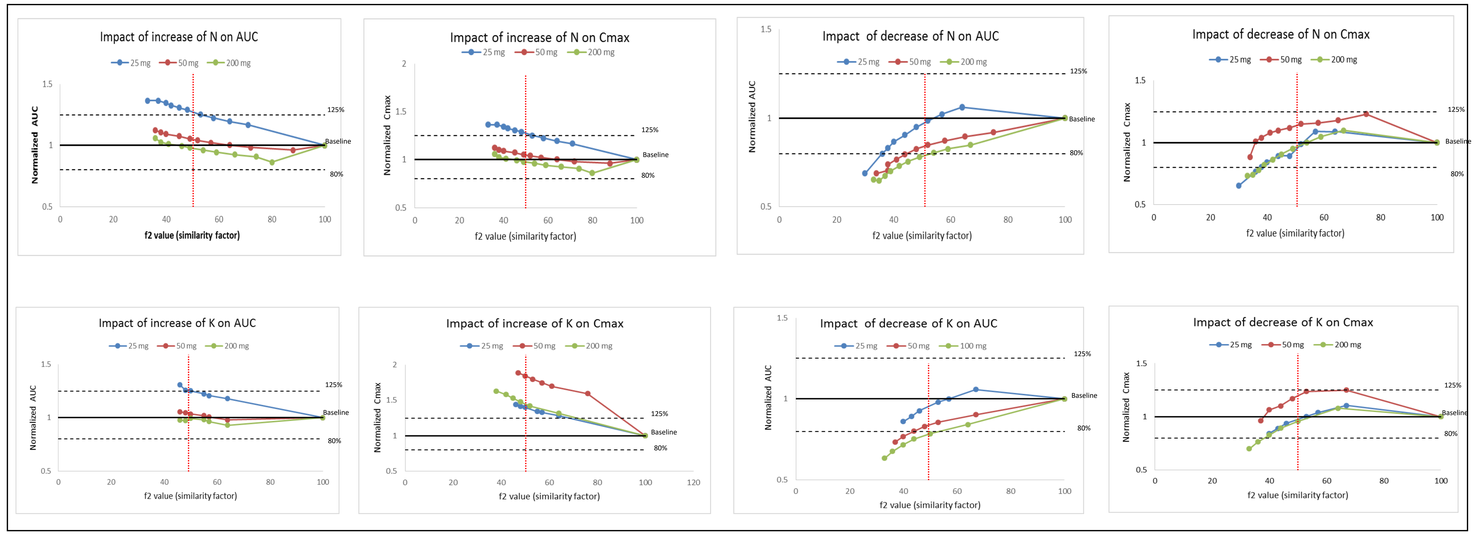

Figure IV *Impact of changes in the drug release exponent (N) and drug-polymer interaction (K) on the in vitro dissolution shown as f_2 factor as well as BE parameters (AUC and C_{max}) of Metoprolol ER formulation.*

Conclusions

- We have demonstrated that PBPK models (using metoprolol ER as an example) can facilitate identify possible reasons for reported complaints of in vivo bioinequivalence in the context of switching from brand to generic drugs. Among all the factors, we found that formulation-specific factors like drug release exponent (N) and drug-polymer interaction (K) are the most significant one which might cause changes in relative bioavailability in reference and test formulations.
- Our physiological based absorption model can be utilized as an ideal platform which can be linked with the PK/PD model of metoprolol ER which will be employed to determine whether the changes in relative bioavailability can increase the risk of therapeutic inequivalence resulting in reduced efficacy or increased rate of adverse effects.

Acknowledgement

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References

1. Babiskin et al., JPS 2015, 2. Chow et al., AAPS 2015, 3. Zhang et al., AAPS 2011.