A Model- and Systems-Based Approach to Assess Impact of Potential Pharmacokinetic Differences on Pharmacodynamics and Questions Regarding Generic Substitution "A Case Study on Metoprolol Extended-Release Tablets"

Sarah Kim[1†], Vishnu D Sharma[1†], Karthik Lingineni[1], Nashid Farhan[1], Lanyan (Lucy) Fang[2], Liang Zhao[2], Joshua D. Brown[3], Rodrigo Cristofoletti[1,4], Valvanera Vozmediano[1], Sihem Ait-Oudhia[1], Lawrence J. Lesko[1], Mirjam N. Trame[1], Stephan Schmidt[1*]

[1] Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Orlando, FL, USA
[2] Office of Research and Standards, Office of Generic Drugs, Center for Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD, USA
[3] Department of Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, USA
[4] Division of Therapeutic Equivalence, Brazilian Health Regulatory Agency (Anvisa), Brasilia, Brazil
[†] Contributed equally to this work
[*] Corresponding author's email: SSchmidt@cop.ufl.edu

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INTRODUCTION

- Generic drugs account for almost 90% of all prescriptions in the U.S. and saved the U.S. health system more than $1.79 trillion over the last decade.
- Model based approaches can address questions related to bioequivalence and generic substitution[1].
- Example: in 2014, Wockhardt and Dr. Reddy's Laboratories recalled several batches of both the 25 and 50 mg generic metoprolol extended-release (ER) formulations due to failed dissolution testing. → Modeling and simulation can assess the risk that a dissolution change may lead to bio-in-equivalence (BIN).

OBJECTIVES

- To evaluate the impact of changes in formulation of metoprolol ER tablets on *in vitro* dissolution, *in vivo* pharmacokinetic (PK), and exercise-induced heart rate (EIHR) using a combined physiologically-based absorption pharmacokinetic (PBA-PK) and population pharmacokinetic / pharmacodynamic (PopPK/PD) modeling and simulation approach

METHODS

Impact of formulation on *in vitro* dissolution

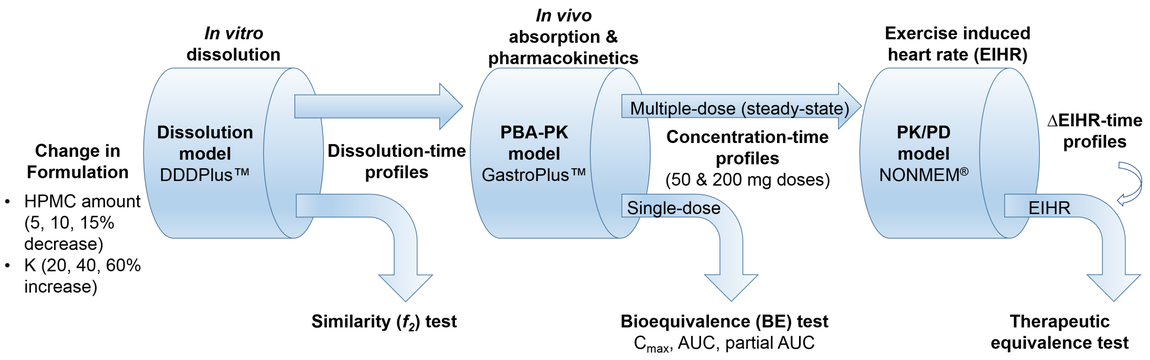
- We assessed **the impact of changes in formulation properties** using the release controlling polymer hydroxypropylmethylcellulose (HPMC) content & quality as a surrogate **on dissolution** using the Korsmeyer-Peppas algorithm[2] as implemented in DDDPlus™ (version 5) for 50 and 200 mg of metoprolol ER tablets.
- **Similarity** of dissolution profiles was assessed using the f_2 **test**.

Impact of formulation on *in vivo* PK

- Simulated *in vitro* dissolution profiles were then used to predict *in vivo* absorption and PK in a virtual population of 200 subjects using **a PBA-PK model** previously developed in GastroPlus™ (version 9.5)[3].
- **Bioequivalence (BE)** was declared when the 90% confidence interval for the ratio of the population geometric means of the PK measures for test to reference fell within 80% to 125%[4].

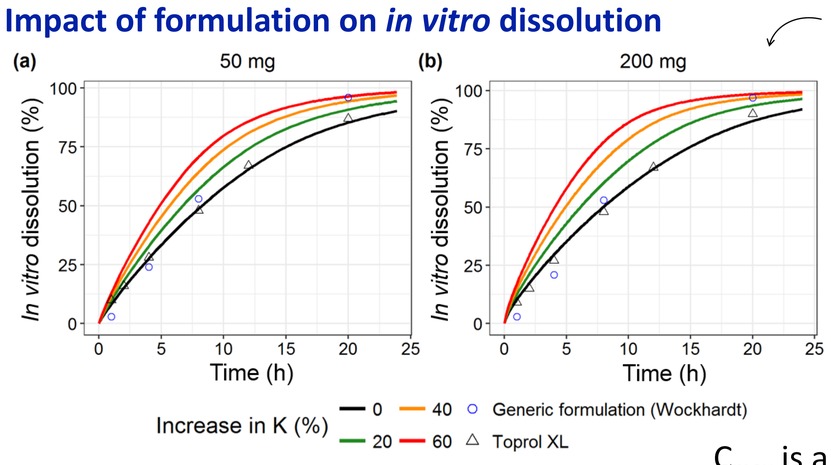
Impact of formulation on ΔEIHR

- Simulated plasma profiles were then used to drive the simulation of ΔEIHR, which is a well-established clinical risk-marker for hypertension, at steady-state using **a PopPK/PD model** which was newly developed in NONMEM® (version 7.3) based on literature data.
- **Therapeutic equivalence** was declared when the model predicted EIHR was within 50 to 85% of the average maximum EIHR of healthy 30-year-old subjects.



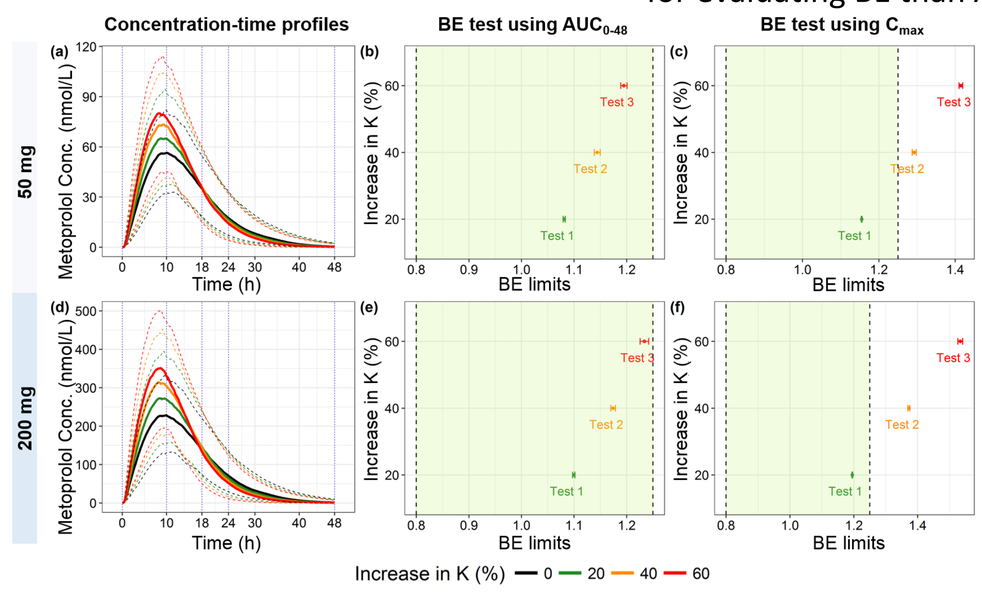
RESULTS

Impact of formulation on *in vitro* dissolution



A 40% or more increase in K resulted in dissimilarity in the dissolution profiles based on the f_2 test and BIN in PK for both, 50 and 200 mg strength metoprolol ER tablets.

Impact of formulation on *in vivo* PK



C_{max} is a more sensitive measure for evaluating BE than AUC_{0-48}.

Impact of formulation on ΔEIHR

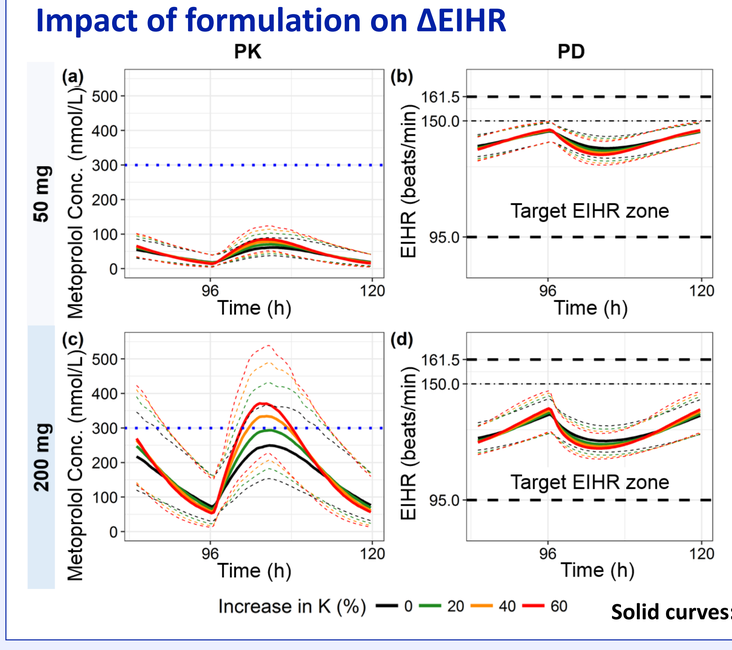


Figure (c) shows that following repeated administration of 200 mg metoprolol ER, corresponding peak plasma concentrations at steady-state, particularly for increased drug release from its ER formulation, are high enough to exceed to the threshold for β1 selectivity (300 nmol/L)[5].

BIN in PK does not translate into therapeutic inequivalence.

Solid curves: median, Dashed curves: 5th and 95th percentiles.

CONCLUSIONS

- Qualitative and quantitative differences in HPMC can lead to batch-to-batch variability which may lead to BIN of metoprolol ER products.
- However, they do not lead to therapeutic inequivalence if EIHR is used as PD biomarker, which may not be necessarily true. This is because, EIHR may not be sensitive enough to detect changes in PK of metoprolol ER products. This supports the current reliance on PK profiles as being most sensitive to detect formulation differences.

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UF College of Pharmacy UNIVERSITY of FLORIDA

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