Journal of Pharmaceutical Sciences xxx (2016) 1-10

Contents lists available at ScienceDirect

Journal of Pharmaceutical Sciences

journal homepage: www.jpharmsci.org

Pharmaceutics, Drug Delivery and Pharmaceutical Technology

# Assessment of Bioequivalence of Weak Base Formulations Under Various Dosing Conditions Using Physiologically Based Pharmacokinetic Simulations in Virtual Populations. Case Examples: Ketoconazole and Posaconazole

Rodrigo Cristofoletti [1, 2], Nikunjkumar Patel [3], Jennifer B. Dressman [2, *]

[1] Division of Therapeutic Equivalence, Brazilian Health Surveillance Agency (Anvisa), Brasilia, Brazil
[2] Institute of Pharmaceutical Technology, Johann Wolfgang Goethe University, Frankfurt am Main, Germany
[3] Simcyp Limited (a Certara Company), Blades Enterprise Centre, Sheffield, UK

ARTICLE INFO

*Article history:*
Received 30 August 2016
Revised 12 October 2016
Accepted 13 October 2016

*Keywords:*
dissolution
physiologically based pharmacokinetic modeling
bioequivalence
disease states
Biopharmaceutics Classification System

ABSTRACT

Postabsorptive factors which can affect systemic drug exposure are assumed to be dependent on the active pharmaceutical ingredient (API), and thus independent of formulation. In contrast, preabsorptive factors, for example, hypochlorhydria, might affect systemic exposure in both an API and a formulation-dependent way. The aim of this study was to evaluate whether the oral absorption of 2 poorly soluble, weakly basic APIs, ketoconazole (KETO) and posaconazole (POSA), would be equally sensitive to changes in dissolution rate under the following dosing conditions—coadministration with water, with food, with carbonated drinks, and in drug-induced hypochlorhydria. The systems-components of validated absorption and PBPK models for KETO and POSA were modified to simulate the above-mentioned clinical scenarios. Virtual bioequivalence studies were then carried out to investigate whether formulation effects on the plasma profile vary with the dosing conditions. The slow precipitation of KETO upon reaching the upper part of the small intestine renders its absorption more sensitive to the completeness of gastric dissolution and thus to the gastric environment than POSA, which is subject to extensive precipitation in response to a pH shift. The virtual bioequivalence studies showed that hypothetical test and reference formulations containing KETO would be bioequivalent only if the microenvironment in the stomach enables complete gastric dissolution. We conclude that physiologically based pharmacokinetic modeling and simulation has excellent potential to address issues close to bedside such as optimizing dosing conditions. By studying virtual populations adapted to various clinical situations, clinical strategies to reduce therapeutic failures can be identified.



## Introduction

Even though the term pharmacokinetics (PK) was coined in 1953, many pivotal articles on this subject had already been published.[1] For instance, the work on kinetics of drugs can be tracked back to the remarkable Torsten Teorell,[2,3] who pioneered the development of mathematical models to represent the distribution of xenobiotics administered intravascularly or extravascularly. The model comprised 5 physiologically defined compartments and it has been recognized as the first physiologically based pharmacokinetic (PBPK) model.[4-6] The number of scientists interested in studying the time course of drug concentrations in biological fluids and tissues grew considerably in the subsequent years; nevertheless, the research mostly centered around developing empirical compartmental models. Despite being useful for data description and interpolation, empirical models are of limited use for extrapolation, because the compartments do not represent real physical spaces or physiological tissues.[4,7] Thus, it is difficult to anticipate how drug concentrations will change when the underlying physiology is modified by intrinsic and/or extrinsic factors. To overcome this difficulty, Bischoff and Dedrick resumed the development of comprehensive PBPK models,[8,9] based on mass conservation principles and contemporary knowledge about anatomy, physiology, and biochemistry of the human body. Since then, a number of PBPK models have been developed for various purposes.[10,11]

* *Correspondence to:* Jennifer B. Dressman (Telephone: +49 69 7982 9680; Fax: +49 69 7982 9724).
*E-mail address:* dressman@em.uni-frankfurt.de (J.B. Dressman).

http://dx.doi.org/10.1016/j.xphs.2016.10.008
0022-3549/

Given that PBPK models can account for differences among biological systems, they have been extensively used by toxicologists in the risk assessment of hazardous substances since the early 1980s. In this application, xenobiotic disposition can be extrapolated from animal tissue data to humans, avoiding the need to directly expose the latter to potentially toxic chemicals.[12-14] Utilization of PBPK models by pharmaceutical scientists is by comparison quite recent, with the bulk of the work appearing in the literature over the last decade.[10] The rapid growth in pharmaceutical application of PBPK has paralleled the development of (1) dynamic absorption models, like the mixing-tank model which was further used to derive the compartmental absorption and transit model[15-18]; (2) QSAR models to predict blood-tissue partition coefficients and drug disposition[19-21]; (3) *in vitro-in vivo* extrapolation methods, whose state-of-the-art was revised elsewhere[22]; and (4) user-friendly modeling and simulation tools.[23] Additionally, the acceptance of PBPK models to support regulatory submissions has indisputably been a powerful driving force for the expanding utilization of PBPK models among pharmaceutical companies.[24] Indeed, in the regulatory environment, through running "predict-learn-confirm" cycles, one can use PBPK models not only to mechanistically understand available clinical observations, but also to predict untested clinical scenarios via simulations, thus filling in missing information in the clinical dataset. For example, by means of carrying out *in silico* investigations on the effect of various intrinsic and extrinsic factors on drug exposure following application of a given formulation, sponsors can make decisions about the need for further clinical pharmacology studies.[25,26]

Several intrinsic and extrinsic factors can affect systemic drug exposure in a postabsorptive fashion, for example, increased plasma volume and protein binding changes during pregnancy, or altered drug biotransformation due to liver disease.[27,28] The effects elicited by such factors on extent and peak of drug exposure are assumed to be dependent on the active pharmaceutical ingredient (API). From the perspective of the bioequivalence (BE) testing, systemic fraction is expected to be similarly affected regardless of whether the API was released from a generic/test (T) or a reference (R) formulation. Indeed, this is the scientific principle supporting the extrapolation of BE results obtained in healthy volunteers to populations for which the reference drug product is approved. According to the European Medicines Agency, the healthy adult model "is regarded as adequate in most instances to detect formulation differences."[29] Nonetheless, this statement foresees that the healthy adults may not always be an adequate model. Indeed, it has already been demonstrated that extrapolating BE results from adults to pediatrics may not be as straightforward when the rate-determining step for oral drug absorption is different in children than in adults.[30,31] Likewise, hypochlorhydria (a condition in which acid secretion in stomach is reduced, leading to elevated gastric pH) may affect preabsorptive events. Dissolution, which is the rate-limiting step to the absorption of poorly soluble but highly permeable APIs, is initiated in the stomach. Especially for poorly soluble, weakly basic APIs, an elevation of the gastric pH by means of intrinsic (e.g., disease state, aging, and race) or extrinsic (e.g., co-medication) factors often leads to significantly impaired absorption.[32-37] Furthermore, the magnitude of the effect of hypochlorhydria on drug absorption may be formulation-dependent. Mitra et al. compared the bioavailability of 2 different formulations containing "compound A," a poorly soluble-free base (F1), and its hydrochloride salt (F2) in dogs pretreated with pentagastrin (i.e., with low gastric pH) or famotidine (i.e., drug-induced hypochlorhydria). In pentagastrin-pretreated dogs the $C_{max}$ and $AUC_{0\text{-}t}$ ratios (F2/F1) were 1.36 and 0.96, whereas in famotidine-pretreated dogs the ratios were 14.75 and 9.02, respectively.[38] Therefore, it seems the hypochlorhydric dogs were a more sensitive model to detect formulation differences than the dogs which were not pretreated with famotidine.

In this context, the aim of this research was to use the previously developed and validated PBPK models by our group[39] to mechanistically investigate whether the oral absorption of ketoconazole (KETO) (subject to slow intestinal precipitation)[40] and posaconazole (POSA) (subject to significant and rapid precipitation after gastric emptying),[37,41] both classical representatives of class 2 of the Developability Classification System (DCS),[42] would be sensitive to changes in dissolution rate under hypochlorhydria and normal gastric pH scenarios.

## Experimental

The first step was to establish reliable PBPK models for KETO and POSA in healthy adults (presumed to have low gastric pH) by updating previously established models[39] to account for (1) the pH at the dissolving surface ($pH_0$) and (2) known precipitation characteristics. The simulations with the updated models were then compared with PK data. The next step was to create PBPK models to address administration of KETO and POSA under the following conditions: (1) subjects with hypochlorhydria, (2) subjects who are administered the antifungal agents with an acidic cola drink and (3) administration of the drugs in the fed state. Additionally, the sensitivity of the simulated plasma profiles to parameters such as particle size of the drug and pH of the stomach was investigated. Virtual BE studies were then carried out to determine under which dosing conditions the plasma profile is most sensitive to formulation effects. All substance-related properties, unless otherwise stated, were taken from the literature and are summarized in Table 1.

### *Absorption and PBPK Models for Oral Administration of KETO and POSA in the Fasted and Fed States to Healthy Subjects*

Previously developed absorption and PBPK models for KETO and POSA in healthy adults[39] were used as the starting points for running subsequent "predict-learn-confirm" cycles in order to arrive at models which would better reflect the state-of-the-art scientific knowledge and fit the purposes of this research. Specifically for POSA, the precipitation rate constant ($k_{prec}$), the maximum supersaturation ratio (MSR), and particle size were updated according to the latest literature data. As input parameters we therefore used an average $k_{prec}$ of 12 $h^{-1}$, an MSR of 10, and particle size of 0.7 μm.[41,50,51] Diffusion coefficients ($D$) of the free monomers were calculated as $D = 9.9 \times 10^{-5} \times MW^{-0.453}$,[52] where MW is molecular weight. Furthermore, the micelle:buffer partition coefficient ($\log K_m$:$w$) for the POSA neutral species was manually adjusted to 5.0 to fit the experimental solubility measured in aspirated fasted state human intestinal fluid.[47]

Given that the latest released version of the Simcyp® Simulator (i.e., v15.1; Simcyp Ltd., Sheffield, UK) does not consider the effect of $pH_0$ on the dissolution of weak bases, it was necessary to adapt the simulation to account for this parameter correctly in the model. First, we estimated the $pH_0$ for KETO and POSA using the equation derived by Ozturk et al.[53] Then, the impact of replacing $pH_{bulk}$ by $pH_0$ on the model fit was investigated. For example, to investigate a scenario in which $pH_{bulk} \approx 2.0\text{-}2.5$, the gastric pH in the simulator screen was set at 4.2, the equivalent $pH_0$ for dissolving particles containing KETO.[43]

To predict plasma profiles after administration in the fed state conditions, all built-in parameters representing the fed state in