Use of Physiologically Based Pharmacokinetic Models Coupled with Pharmacodynamic Models to Assess the Clinical Relevance of Current Bioequivalence Criteria for Generic Drug Products Containing Ibuprofen

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ABSTRACT: Physiologically based pharmacokinetic models coupled with pharmacodynamic (PBPK/PD) models can be useful to identify whether current bioequivalence criteria is overly conservative or venturesome for different drugs. A PBPK model constructed with Simcyp Simulator® using reported biopharmaceutics parameters for ibuprofen was coupled with two published PD models: one for antipyresis and one for dental pain relief. Using products with doses of 400 mg and 10 mg/kg as "reference (R)" drug products, virtual products with doses of 280 mg and 7 mg/kg, respectively, could be interpreted as representing bioinequivalent test (T) drug products, as the point estimate for the ratios T/R are well below the bioequivalence limits. Despite being bioinequivalent in terms of PK, these lower doses were shown to be therapeutically equivalent to the higher doses because of the flat dose–response relationship of ibuprofen. Sensitivity analysis of the PBPK/PD models demonstrated that gastric emptying time, dissolution rate and small intestine pH are variables that influence ibuprofen PK, but do not seem to significantly affect its PD. It was concluded that current bioequivalent guidance might be unnecessarily restrictive for ibuprofen products. © 2014 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 103:3263–3275, 2014
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INTRODUCTION

In 1995, the US Food and Drug Administration (FDA) incorporated the fundamentals of the Biopharmaceutics Classification System (BCS) into its legal framework.[1] Since then, many other regulatory authorities and the World Health Organization (WHO) have published their own guidances related to the BCS-based biowaiver.[2–5] However, the extension of BCS-based biowaiver decisions to drugs belonging to other BCS classes, other than those showing high solubility and high permeability, has not yet reached a consensus among regulators. The most controversial issue is about biowaiving drug products containing weakly acidic drugs that exhibit high solubility at pH 6.8 and are highly permeable, as suggested by WHO.[3] Although it is expected that such drugs would behave like Class 1 drugs in the proximal intestine, as the dose would completely dissolve under intestinal conditions, Class 2 weak acids showed a higher risk for bioinequivalence for C_{max}.[6,7]

Ibuprofen, a widely used nonsteroidal anti-inflammatory drug, is a classic representative of Class 2 weakly acid drugs as it is almost completely absorbed and it has a dose number lower than 1 at pH 6.8 at 37°C.[8,9] A consensus as to whether a BCS-based biowaiver decision is advisable has not yet been reached.[9–13] Some authors have reported that the *in vitro* set of dissolution testing, as required by all BCS-based biowaiver guidelines, was not able to predict the *in vivo* bioequivalence outcome for drug products containing ibuprofen, showing false-positive results (similar dissolution profiles for nonbioequivalent drug products)[11] and a false-negative result (nonsimilar dissolution profile for a bioequivalent drug product).[12] In this context, false-positive results represent the consumer risk, which is the main concern of regulatory authorities, and should be carefully addressed. The two nonbioequivalent results reported were because of C_{max} differences between T and R formulations and not to differences in the extent of exposure,[11] corroborating the conclusions taken in the meeting report of the Workshop "*Bioequivalence, Biopharmaceutics Classification System, and Beyond.*"[6] In 2007, it had already been pointed out that to grant a biowaiver for some Class 2 weakly acid drugs, it would be necessary to widen the bioequivalence limits for C_{max}, if it is not critical to the therapeutic efficacy of the drug, in line with the WHO guidance.[3,6] Given that the bioequivalence criteria were empirically defined, based on the opinions of FDA medical experts that only differences of greater than 20% for C_{max} and AUC_{0-t} would be significant for all drug products,[14] it would not be surprising to find overly conservative scenarios. Owing to the sigmoidicity factor of the dose–response curve, formulation differences in absorption could be either attenuated or magnified in terms of the PD response.[15] When the concentrations resulting from the recommended dosage range are higher than the concentration at which the effect is half-maximal (EC_{50}), formulation differences are expected to be attenuated in terms of PD response.

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Physiologically based pharmacokinetic (PBPK) models coupled with or without *in vitro–in vivo* extrapolation techniques have already been used to justify extending BCS-based biowaiver decisions to some Class 2 drugs.[6,16–19] However, to the best of our knowledge, pharmacokinetic/pharmacodynamic (PK/PD) models have not been applied for this purpose to date.

The goal of the present analysis was to fit PBPK/PD models for ibuprofen into Simcyp Simulator®, using published biopharmaceutics, PK and PD data, to evaluate whether the bioequivalence criteria would indeed be clinically significant for such a drug. The clinical indications considered were fever reduction in children and dental pain relief in adults, for which PD models have already been established.[20,21] In this context, the risks of waiving *in vivo* bioequivalence studies for immediate-release oral dosage forms containing ibuprofen were also assessed.

EXPERIMENTAL

Computer Hardware and Software

Simcyp Simulator® version 12.2 (Simcyp Ltd., Sheffield, UK) was run using a DELL computer with Intel Core™ i5 processor (DELL, Hortolândia/SP, Brazil).

Virtual Populations

An effect of age on the PK of ibuprofen has been proposed by some authors,[22,23] but this could not be substantiated by other authors.[20,24–26] However, it has been reported that the PD response elicited by ibuprofen is age dependent.[26,27] For these reasons, the age range of the virtual population was selected to closely match those of the subjects enrolled in two clinical trials: (1) children aged from 2 to 11 years for the antipyretic model and (2) adults aging 18–40 years for the dental pain relief model.[21,24]

Data Used for Simulations of PD Response of Ibuprofen

All physicochemical properties, biopharmaceutics, PK and PD parameters of ibuprofen, unless otherwise stated, were taken from the literature and are summarized in Table 1.

PBPK Model

Absorption

The oral absorption of ibuprofen was predicted using the advanced dissolution, absorption, and metabolism (ADAM) model, which divides the gastrointestinal tract (GI) into nine segments.[33] Negligible absorption from the stomach was assumed and the default settings of the software for gastric emptying time (GET; based on first-order emptying with a half-life of 16.6 min), small intestine transit time (based on a Weibull probability distribution function), and GI pH (default pH values: duodenum = 6.4; jejunum I = 6.5; jejunum II = 6.6; ileum I = 6.8; ileum II = 7; ileum III = 7.1; ileum IV = 7.3; and colon = 6.5) were used to establish the absorption model.[33]

The effective permeability in humans ($P_{eff,man}$) of ibuprofen was estimated using the mechanistic P_{eff} model in ADAM and data obtained from an *in vitro* permeability study in Caco-2 cells, in which 36 different compounds using the same experimental protocol were investigated, including internal standards of high (e.g., propranolol) and low (e.g., cimetidine) permeability.[28,33] Because ibuprofen permeability values throughout the small intestine are not statistically different

Table 1. Parameter Values Used for Ibuprofen Simulations in the Simcyp Simulator®

Parameters	Value	Reference/Comments
Molecular weight (g/mol)	206.27	
log P	3.23	9
Compound type	Monoprotic acid	9
Solubility at pH 1.2 (mg/mL)	0.038	9
pKa	4.5	9
Absorption		
Model	ADAM	
$P_{eff,man}$(10^{-4} cm/s)	6.309	Predicted using the MechP_{eff} model
$P_{app,Caco\text{-}2}$ (10^{-6} cm/s)	53	28
Fraction absorbed	0.99	Based on MechP_{eff} prediction
k_a (h^{-1})	2.596	Based on MechP_{eff} prediction
Distribution		
Model	Full PBPK	
V_{ss} (L/kg)	0.120	Predicted using the Rodgers and Rowland method
Fraction unbound plasma	0.01	29
Blood to plasma coefficient (B:P)	0.55	30
k_p	0.45–0.55	
Elimination	Enzyme Kinetics	
HLMs (μL/min.mg protein)		
CYP3A4 2-OH	12.93	31
CYP2C8 2-OH	2.41	31
CYP2C9 2-OH	10.52	31
CYP2C19 2-OH	2.12	31
CYP2E1 2-OH	1.20	31
CYP2C9 3-OH	61.37	31
CYP3A4 3-OH	2.67	31
CYP2C19 3-OH	1.33	31
UGT supersomes (μL/min.mg protein)		
UGT1A3	0.40	32
UGT1A9	2.20	32
UGT2B4	0.30	32
UGT2B7	8.90	32
Antipyretic PD Model		
E_{max}	−0.04	20
EC_{50} (mg/L)	6.18	20
Baseline temperature (T_0; °C)	39.10	20
Sigmoidicity (n)	2.71	20
k_{out} (h^{-1})	1.17	20
k_{in} (h^{-1})	45.40	20
Dental Pain Relief PD Model		
P_{max}	1.54	21
k (h^{-1})	1.26	21
E_{max}	1.80	21
EC_{50} (mg/L)	10.20	21
k_{e0} (h^{-1})	1.49	21
Sigmoidicity (n)	2.00	21