



Assessment of bioequivalence outcomes of oral formulations containing racemic ibuprofen through a chiral physiologically-based pharmacokinetic model

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INTRODUCTION AND OBJECTIVES

Since ibuprofen enantiomers exhibit different pharmacokinetics [1-4], the characterization of the time course of R- and S-ibuprofen can be useful in the selection of the most sensitive analyte in bioequivalence assays [5]. Physiologically based pharmacokinetic (PBPK) modelling and simulation represents an efficient methodology to virtually assess bioequivalence outcomes [6,7]. Therefore, the objective of the present work was to evaluate the sensitivity of ibuprofen enantiomers to assess bioequivalence outcomes of oral formulations containing racemic ibuprofen.

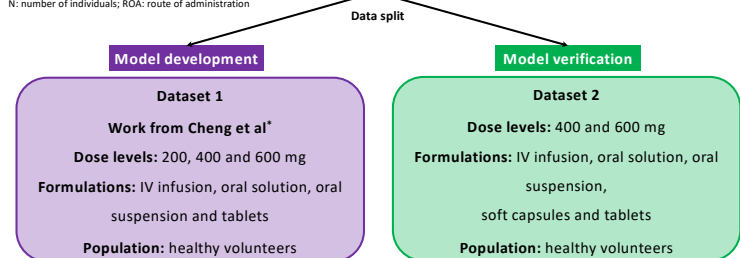
MATERIAL AND METHODS

Data analysis

Table 1. Experimental dataset from 11 independent Phase I clinical trials.

Study	N	Female proportion (%)	ROA	Formulation	Dose (mg)	R-ibuprofen observations	S-ibuprofen observations	Additional information
A	24	50	IV	Infusion	600	381	390	Infusion time: 15, 20 and 30 min
			ORAL	Solution	600	376	384	Arginine salt
B	24	50	IV	Infusion	600	390	394	Infusion time: 30 min
			ORAL	Solution	600	400	404	Arginine salt
C	24	33	IV	Infusion	400	376	384	Infusion time: 30 min
			ORAL	Solution	400	374	384	Arginine salt
D	35	48	IV	Infusion	400	672	698	Infusion time: 30 min
			ORAL	Solution	400	692	720	Arginine salt
E	14	0	ORAL	Suspension	200	481	516	2% oral suspension
F	23	0	ORAL	Suspension	400	1062	1079	2% and 4% oral suspension
G	30	52	ORAL	Soft gelatine capsule	400	31	31	Lysine salt; mean profiles
H	26	54	ORAL	Soft gelatine capsule	400	984	1000	
I	24	50	ORAL	Tablet	600	33	36	Mean profile
J	24	33	ORAL	Tablet	600	877	904	
K	30	0	ORAL	Tablet	600	-	-	Only PK exposure parameters

N: number of individuals; ROA: route of administration



*Cheng et al. Pharm. Res., 1994, 11(6):824-830

Modelling strategy

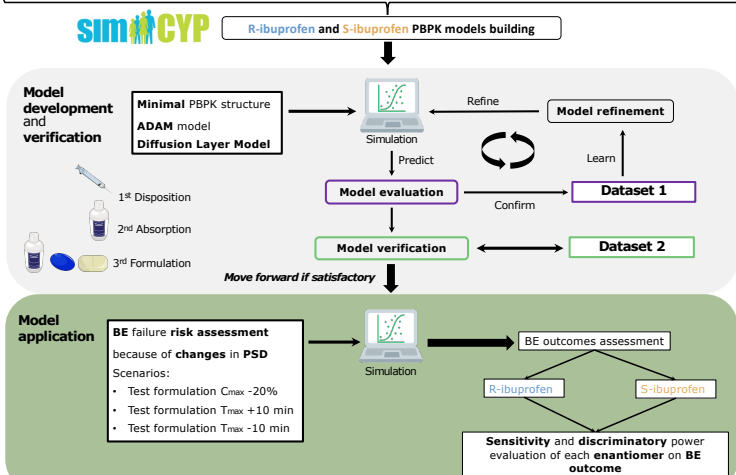
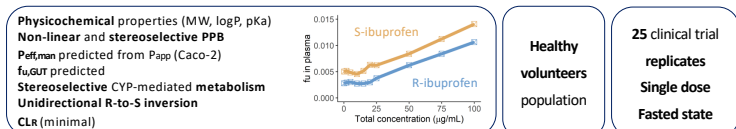


Figure 1. Modelling workflow for the development of R-ibuprofen and S-ibuprofen PBPK models. V_d: volume of distribution at steady-state; PPB: plasma protein binding; P_{eff,man}: effective human jejunal permeability; P_{app}: apparent permeability; f_{u,GUT}: fraction unbound into the enterocyte; CLR: renal clearance; ADAM: advanced dissolution, absorption and metabolism; BE: bioequivalence; PSD: particle size distribution.

Model evaluation

- ✓ **Graphical:** observed versus predicted plasma concentration-time profiles
- ✓ **Numerical:**
 - ✓ Numerical predictive check
 - ✓ Error metrics:

$$PE = \frac{Pred_i}{Obs_i}$$
$$AAFE = 10^{\frac{1}{n} \sum \log \left| \frac{Pred_i}{Obs_i} \right|}$$
$$PPE(\%) = Mean \left(\left| \frac{Pred_i - Obs_i}{Obs_i} \right| \times 100 \right)$$
$$AFE = 10^{\frac{1}{n} \sum \log \left| \frac{Pred_i}{Obs_i} \right|}$$

RESULTS

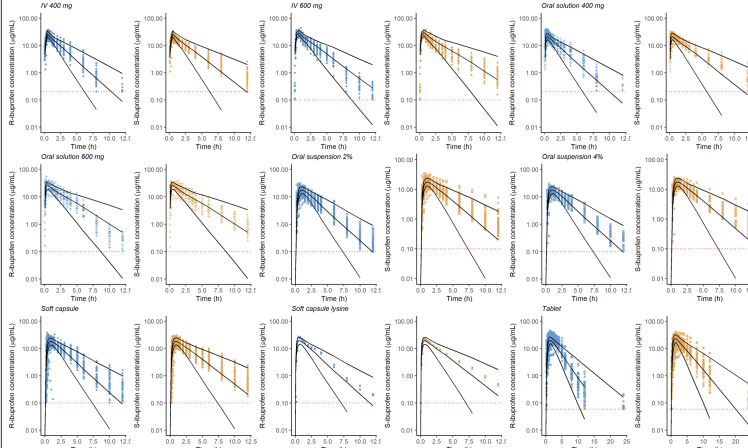


Figure 2. Observed versus predicted plasma concentration-time profiles in the model verification step. Black profiles indicate 5th, 50th and 95th of the simulated profiles. Horizontal dotted red lines indicate lower limit of quantification.

Table 2. Numerical assessment of the PBPK model for R-ibuprofen and S-ibuprofen.

Enantiomer	Formulation	N	Dose (mg)	N 0.9-1.11 (%)	N 0.8-1.25 (%)	AFE	AAFE	PPE (%)
R-ibuprofen	AUC _{0-t}							
	IV infusion	6	400, 600	3 (50%)	6 (100%)	1.09	1.12	13
	Oral solution with arginine	6	400, 600	3 (50%)	6 (100%)	1.03	1.12	12
	Oral suspension	5	200, 400	5 (100%)	5 (100%)	1.01	1.02	2
	Soft capsule with lysine	2	400	0 (0%)	1 (50%)	0.79	1.26	21
	Soft capsule	2	400	0 (0%)	2 (100%)	0.85	1.18	15
	Tablet	6	600	2 (33%)	6 (100%)	0.97	1.13	12
	C _{max}							
	IV infusion	6	400, 600	5 (83%)	6 (100%)	0.98	1.07	7
	Oral solution with arginine	6	400, 600	1 (16.6%)	4 (66.6%)	0.82	1.21	17
	Oral suspension	5	200, 400	5 (100%)	5 (100%)	0.98	1.05	4
	Soft capsule with lysine	2	400	0 (0%)	0 (0%)	0.65	1.53	35
Soft capsule	2	400	0 (0%)	2 (100%)	0.80	1.26	20	
Tablet	6	600	1 (16%)	3 (50%)	0.77	1.30	22	
S-ibuprofen	AUC _{0-t}							
	IV infusion	6	400, 600	3 (50%)	5 (83%)	1.11	1.11	11
	Oral solution with arginine	6	400, 600	5 (83%)	6 (100%)	0.96	1.09	8
	Oral suspension	5	200, 400	4 (80%)	5 (100%)	0.94	1.07	7
	Soft capsule with lysine	2	400	0 (0%)	2 (100%)	0.87	1.15	13
	Soft capsule	2	400	2 (100%)	2 (100%)	0.95	1.05	5
	Tablet	6	600	4 (67%)	6 (100%)	0.95	1.06	6
	C _{max}							
	IV infusion	6	400, 600	5 (83%)	6 (100%)	1.06	1.07	7
	Oral solution with arginine	6	400, 600	3 (50%)	6 (100%)	0.89	1.13	11
	Oral suspension	5	200, 400	5 (100%)	5 (100%)	0.98	1.03	3
	Soft capsule with lysine	2	400	0 (0%)	2 (100%)	0.82	1.23	18
Soft capsule	2	400	1 (50%)	2 (100%)	0.90	1.11	10	
Tablet	6	600	4 (67%)	6 (100%)	0.92	1.09	8	

N: total number of scenarios; N 0.9-1.11: number of prediction errors between 0.9-1.11; N 0.8-1.25: number of prediction errors between 0.8-1.25; AAFE: average fold error; AAFE: absolute average fold error; PPE: percent prediction error.

Table 3. Deterministic assessment of bioequivalence outcomes as a consequence of changes in particle size distribution.

Scenario	Enantiomer	Formulation	C _{max} (%)	T _{max} (%)	AUC _{0-t} (%)	AUC _{0-tmax} (%)
Test C _{max} 80%	S-ibuprofen	Suspension	80.00	184.15	104.12	36.69
		Soft capsule	80.00	180.72	103.97	36.28
		Tablet	80.00	160.00	105.15	45.72
		Suspension	77.27	184.15	100.30	36.59
Test T _{max} 50 min	R-ibuprofen	Soft capsule	77.53	150.00	100.20	41.93
		Tablet	79.21	160.00	102.70	44.74
		Suspension	101.40	80.20	99.70	110.67
		Tablet	101.01	80.00	99.85	106.56
Test T _{max} 70 min	S-ibuprofen	Suspension	97.19	118.81	100.78	77.47
		Soft capsule	98.75	120.48	100.47	82.54
		Tablet	90.13	120.00	101.41	67.45
		Suspension	96.74	118.81	100.25	77.22

T/R: test over reference formulation ratio as percentage; Test C_{max} 80%: test formulation with a 20% lower C_{max} compared to the C_{max} of the reference formulation; Test T_{max} 50 min: test formulation with a T_{max} equal to 50 min (~20% decrease on T_{max}); Test T_{max} 70 min: test formulation with a T_{max} equal to 70 min (~20% increase on T_{max}); AUC_{0-t}: area under the concentration-time profile from zero to last observation; AUC_{0-tmax}: area under the concentration-time profile from zero to median T_{max} of the reference formulation.

CONCLUSIONS

The deterministic bioequivalence risk assessment has revealed R-ibuprofen (distomer) as the most sensitive analyte to detect differences in PSD for oral formulations containing a racemic mixture of ibuprofen. The evaluation of AUC_{0-t} ratios suggests it is the most sensitive parameter for test formulations with changes in PSD causing a lower dissolution and absorption rate, whereas T_{max} is more discriminative to detect formulation changes resulting in an increase in absorption rate. No significant changes in AUC_{0-t} nor C_{max} are anticipated when T_{max} is varied by 20%. These results suggest achiral bioanalytical methods would increase type II error and declare non-bioequivalence for formulations that are bioequivalent for S-ibuprofen (eutomer).

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