

INTRODUCTION AND OBJECTIVES

Physiologically-based pharmacokinetic (PBPK) models predict drug exposure but often overlook formulation differences [1]. Physiologically-based biopharmaceutics models (PBBM) address this by integrating *in vitro* dissolution data into PBPK frameworks, creating an *in vitro-in vivo* (IVIV) link [2,3]. These PBBM/PBPK models can enhance *in vitro* testing, predict *in vivo* bioequivalence (BE), and define safety margins for drugs like ibuprofen. Therefore, the aims of this study are:

- Optimizing the variability of an existing PBPK model [4] for ibuprofen using data from BE studies.
- Developing a PBBM model for ibuprofen integrating *in vitro* dissolution data at different conditions.
- Identifying the safe space of dissolution parameters through virtual BE (VBE) simulations under different study designs.

MATERIALS AND METHODS

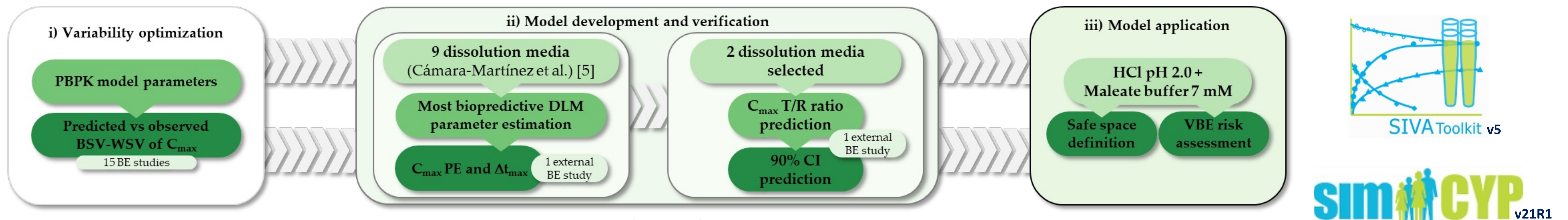


Figure 1. Workflow strategy followed.

RESULTS

i) Variability optimization

Selected parameter	Variation (CV (%))	Minimum limit	Parameter value	Maximum limit	Optimized
Fasted MRT stomach fluid	150	0.01	0.12	12	✓
Fasted MRT SI fluid	150	0.5	3.4	12	✓
pH fasted duodenum	16	0	6.4	15	
pH fasted jejunum 1	13	0	6.5	15	
pH fasted jejunum 2	11	0	6.6	15	
pH fasted ileum 1	10	0	6.8	15	
pH fasted ileum 2	10	0	7	15	
pH fasted ileum 3	7	0	7.1	15	
pH fasted ileum 4	6	0	7.3	15	
pH fasted colon	13	3.18	6.6	9.8	
Initial volume of stomach fluid fasted	30	20	50	1000	
Total Jej1 Ile4 volume fasted	30	10	105	1000	
Colon volume fasted	0	1	13	250	
V _{ss} (user input) treatment 1	10	0.05	0.09	1000	✓
V _{ss} (user input) treatment 2	10	0.05	0.09	1000	✓
Fasted MRT stomach fine particles trt 1	150	0.01	0.27	12	✓
Fasted MRT SI fine particles trt 1	150	0.5	3.4	12	✓
Fasted MRT stomach fine particles trt 2	150	0.01	0.27	12	✓
Fasted MRT SI fine particles trt 2	150	0.5	3.4	12	✓

Table 1. Parameters selected for within-subject variability.

Variability	Enantiomer	IV	Solution		Suspension		Soft gelatin capsules		Tablets			
			Obs	Pred	Obs	Pred	Obs	Pred	Obs	Pred		
WSV	R		15.63	16.73	15.63	19.73	14.25	14.65	16.05	15.55	14.90	15.83
	S		16.93	17.98	16.93	20.05	13.35	14.95	16.00	15.55	12.15	16.60
BSV	R		17.05	16.63	22.03	23.68	25.10	23.30	18.20	23.80	21.90	19.93
	S		16.23	19.43	19.38	24.55	22.30	22.70	18.35	23.35	20.40	21.67

Table 2. Observed and predicted variabilities of C_{max} for each ibuprofen enantiomer and dosage form.

ii) Model development and verification

Pretreatment	Treatment	Reference Product				Test Product				
		Medium	Particle Surface pH	r ²	C _{max} PE	Δ t _{max} (%)	Particle Surface pH	r ²	C _{max} PE	Δ t _{max} (%)
None	PB50		5.71	0.93	0.96	50	5.71	0.95	1.14	-40
HCl (pH 1.2)	PB50		6.29 *	0.91	1.13	25	6.25 *	0.95	1.24	-50
HCl (pH 2.0)	PB50		6.30 *	0.94	1.13	25	6.20 *	0.95	1.24	-50
None	PB5		5.81	0.97	1.01	50	5.58	0.96	0.99	-30
HCl (pH 1.2)	PB5		6.28 *	0.92	1.13	25	5.30 *	0.96	0.80	-7
HCl (pH 2.0)	PB5		6.25 *	1.00	1.12	25	5.42 *	0.95	0.89	-20
None	MB7		5.64	0.97	0.93	75	5.40	0.91	0.87	-20
HCl (pH 1.2)	MB7		6.33 *	0.94	1.13	25	5.49 *	0.95	0.93	-20
HCl (pH 2.0)	MB7		6.02 *	0.99	1.09	25	5.57 *	0.98	0.98	-30

Table 3. Estimated particle surface pH for reference and test products at different experimental *in vitro* conditions and the corresponding C_{max} prediction error and t_{max} difference (%).

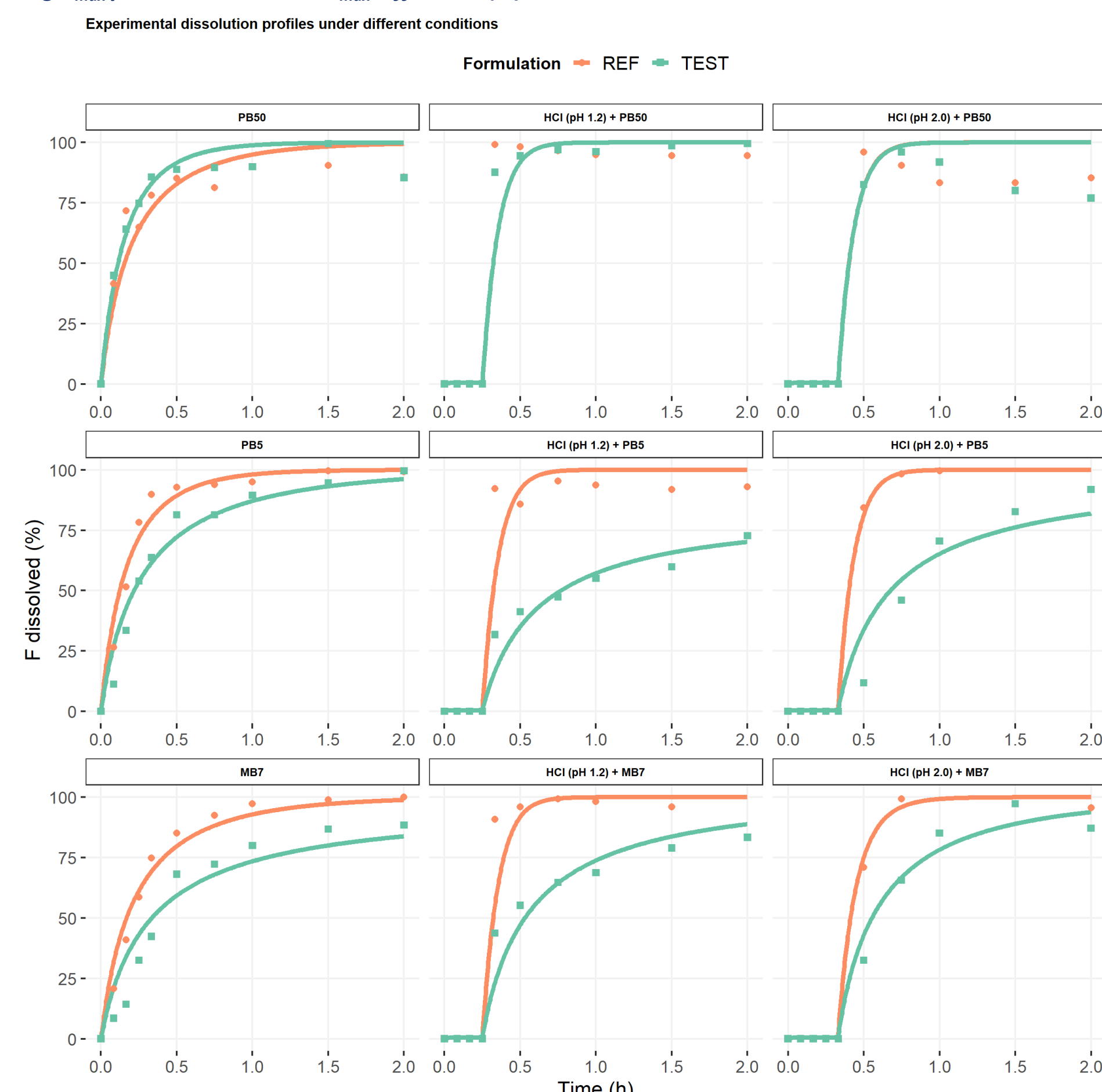


Figure 2. Individual fitting of mean dissolution data throughout different experimental conditions.

iii) Model application

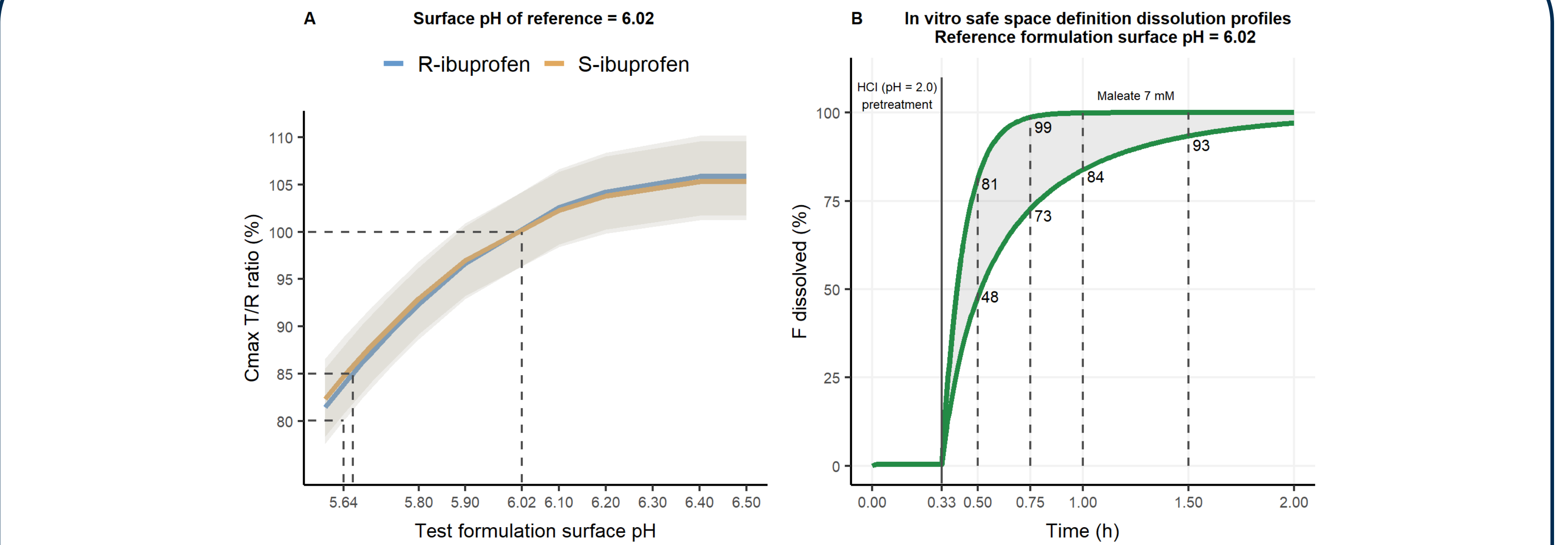


Figure 3. (A) Effect of particle surface pH on C_{max} T/R GMR (orange and blue solid lines) with the corresponding 90% CI (grey band); (B) Safe space for test products of IR tablets of 200 mg racemic ibuprofen.

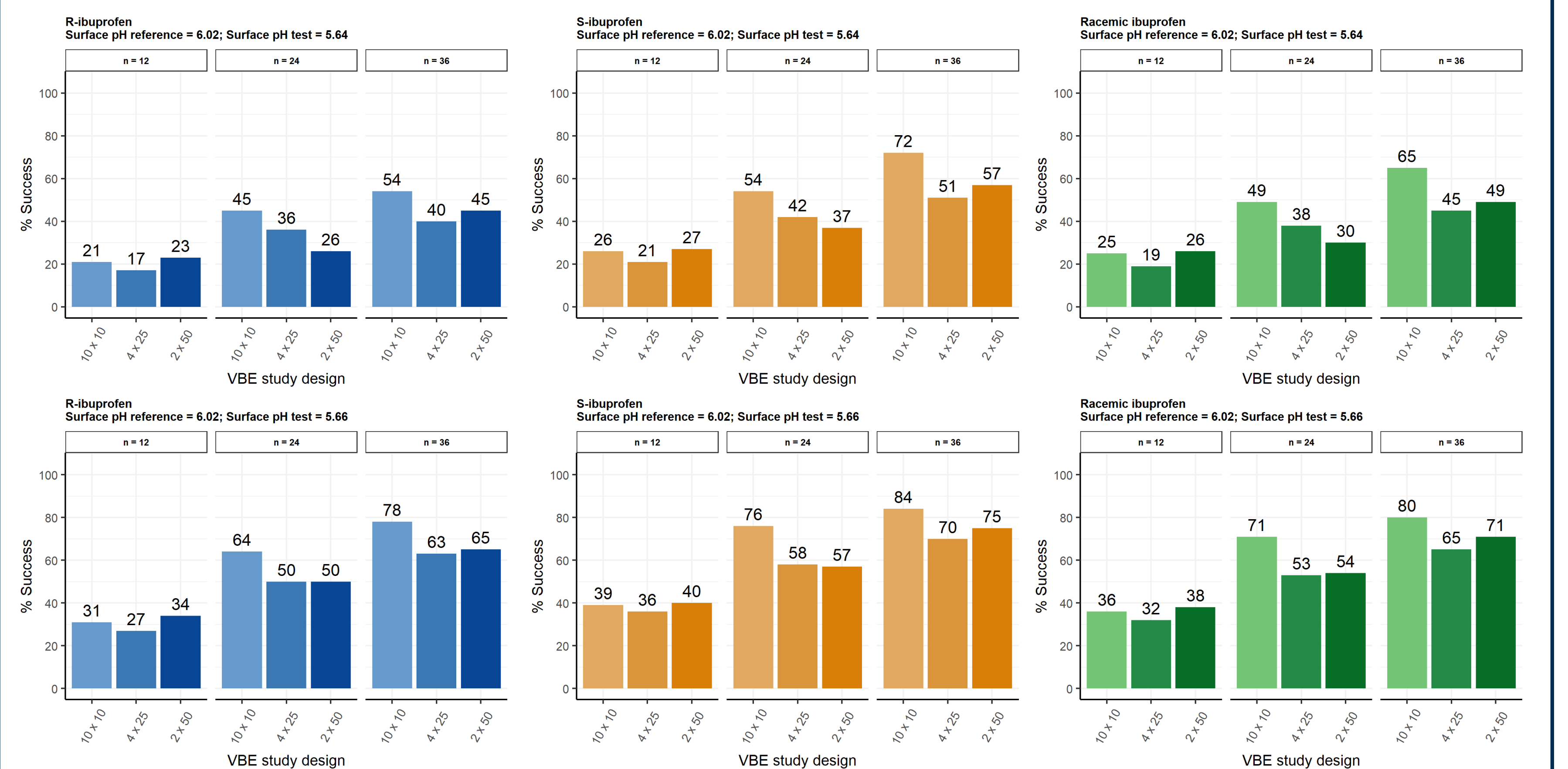


Figure 4. VBE success rate for ibuprofen enantiomers and racemic mixture under different sample size, test formulation particle surface pH of R-ibuprofen, and number of runs and trial replicates.

CONCLUSIONS

- PBPK model variability was optimized to better reflect that observed in BE studies across different dosage forms and dose levels.
- Ibuprofen particle surface pH has been identified as the *in vitro* parameter governing dissolution in maleate buffer 7 mM with HCl pH 2.0 pretreatment.
- This allowed to establish an *in vitro* safe space useful for calculating sample sizes and to evaluate the BE success rate through PBBM/PBPK model-informed VBE simulations.

REFERENCES

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ACKNOWLEDGEMENTS

