Predicting Drug Delivery of Push Pull OROS: A Biorelevant Dissolution and PK Simulation Strategy

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PHYSIOLUTION
Predictive Dissolution Testing

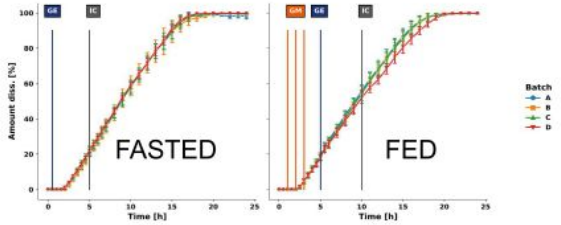
NEXT-GENERATION DELIVERY INNOVATIONS

Aim of the study

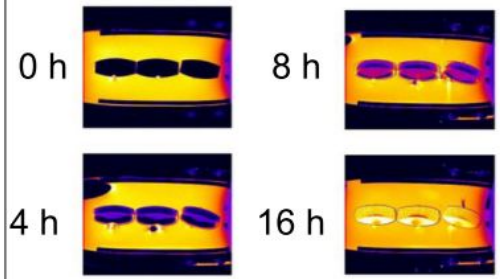
Push-pull osmotic pump tablets characterization

DC - direct compression; WG - wet granulation;
LowPEO - lower viscosity polymer (4,000 kDa); HighPEO - higher viscosity polymer (5,000 kDa)

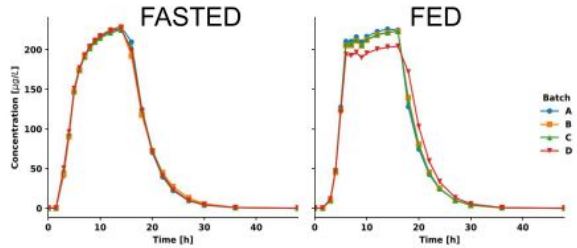
Biopredictive & physiological dissolution tests



MRI analysis

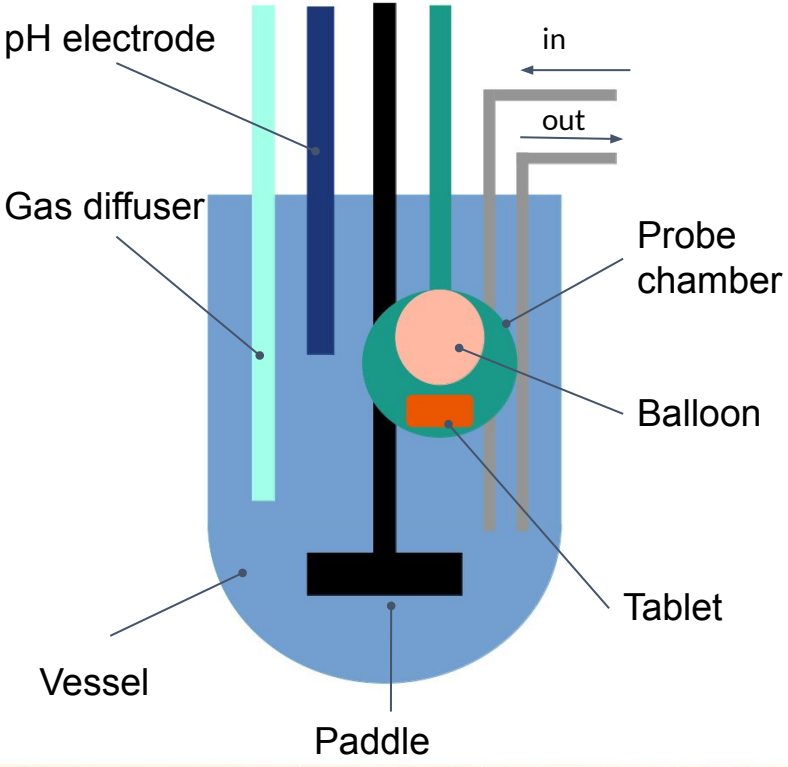


PBBM modeling



DC – direct compression; WG – wet granulation;
LowPEO – lower viscosity polymer (4,000 kDa); HighPEO – higher viscosity polymer (5,000 kDa)

Schematic and photographic representation of the Advanced Modular Platform (AMP)



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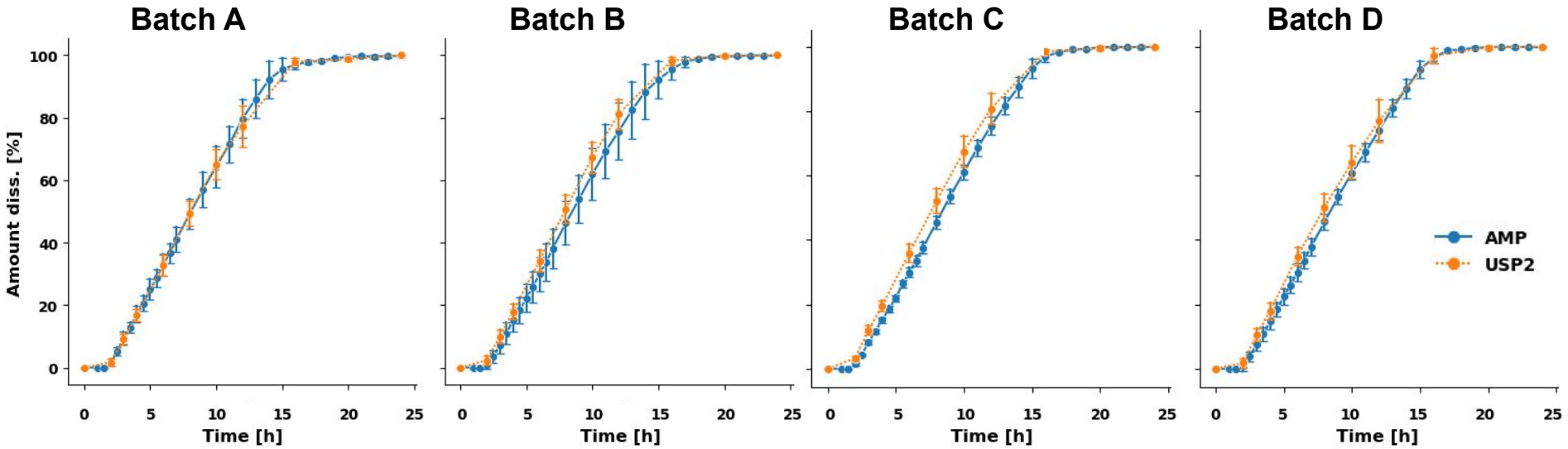
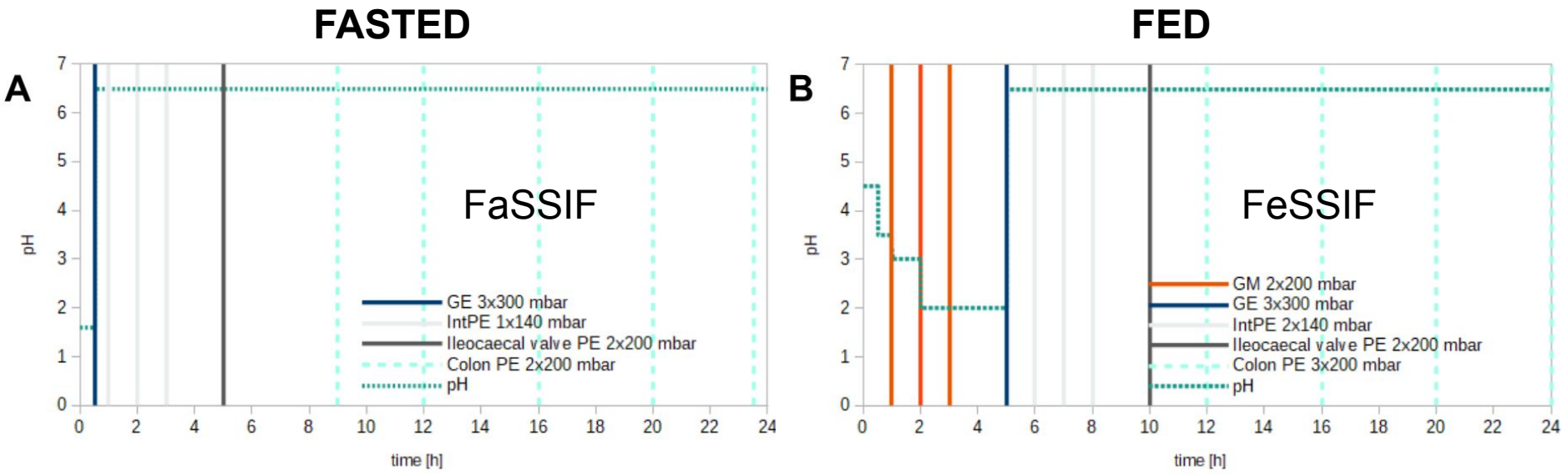
PPOP tablets mechanical robustness confirmed - similar dissolution in USP2 and stress-intensive AMP program

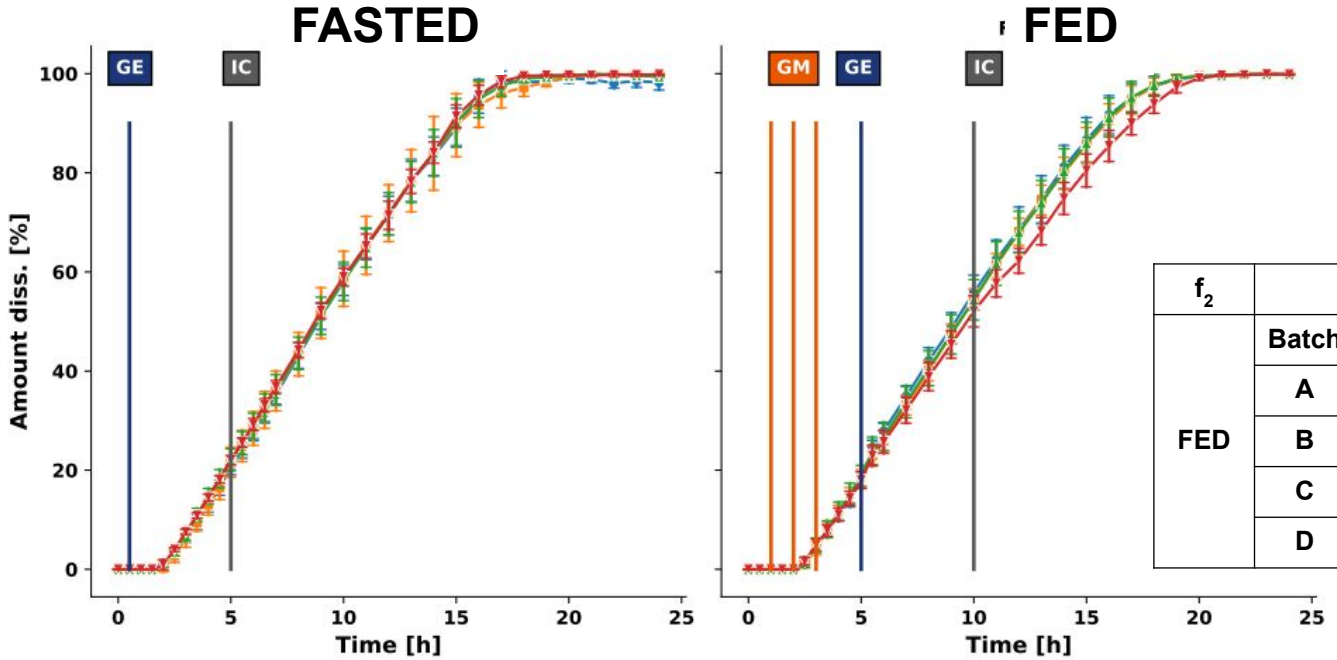


Dissolution profiles of POPP tablets obtained in: AMP (robustness test, blue line); USP apparatus 2 (100 rpm, orange line), medium USP phosphate buffer pH 6.8, given are means of n = 6 ± SD

Fasted and Fed test programs differ in the pH characteristics, timing, and magnitude of stress events



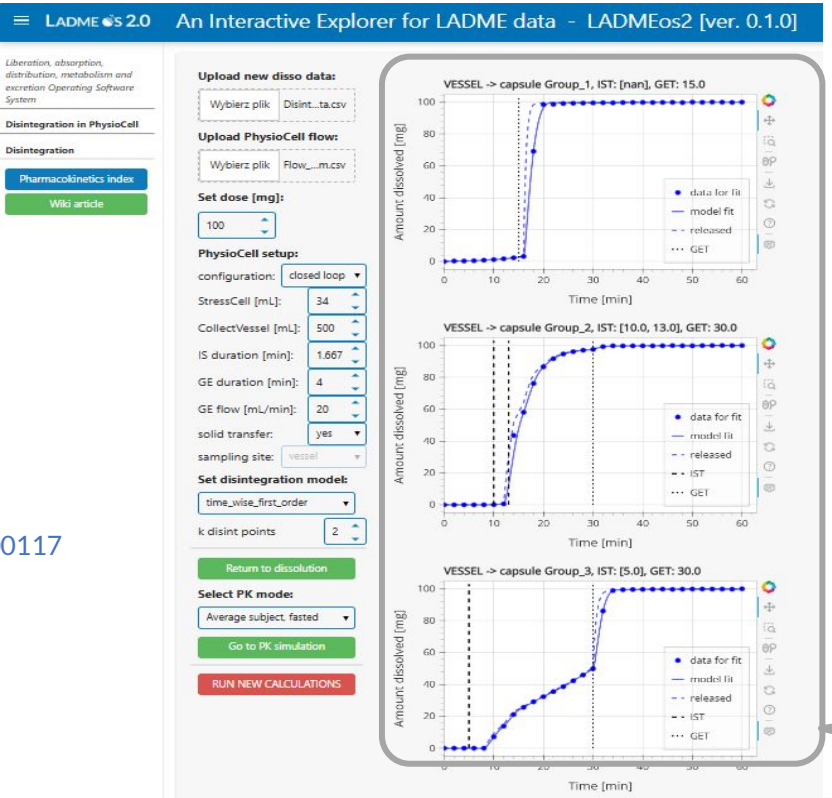
Well-aligned dissolution profiles for all batches obtained in the AMP under both fasted and fed intake conditions

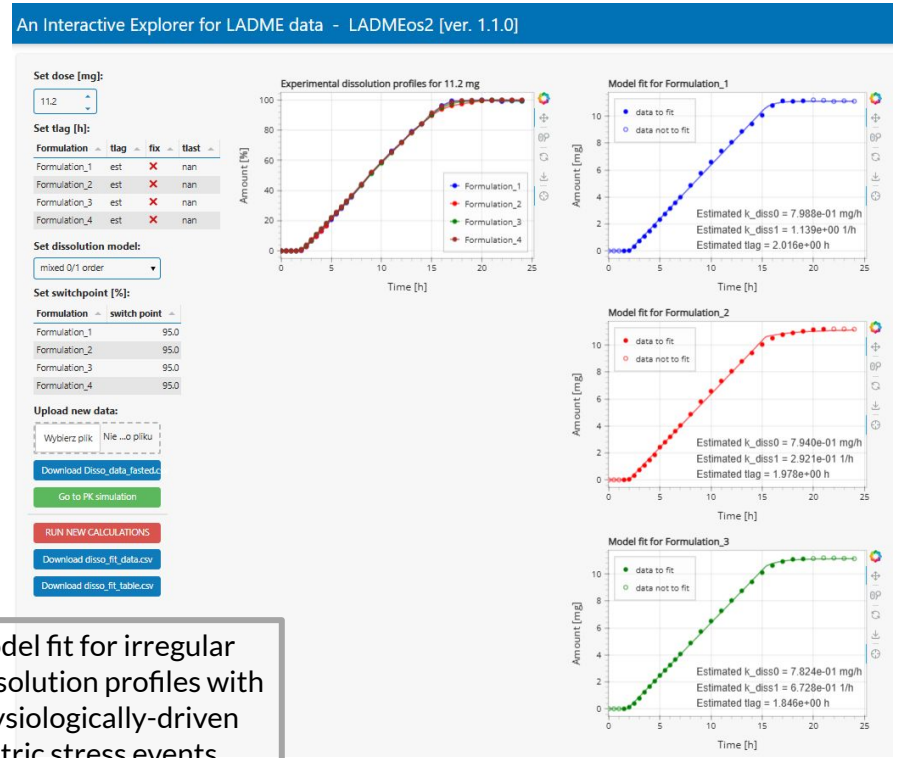


f_2	FASTED				
	Batch	A	B	C	D
FED	A	65	74	74	60
	B	75	60	81	65
	C	77	73	59	62
	D	75	74	82	55

Dissolution of POPP tablets obtained in AMP under the simulated fasted and fed intake conditions, given are means of n = 6 ± SD

LADMEos2 - innovatiwe web app for PK simulations and modeling





Model fit for irregular dissolution profiles with physiologically-driven gastric stress events

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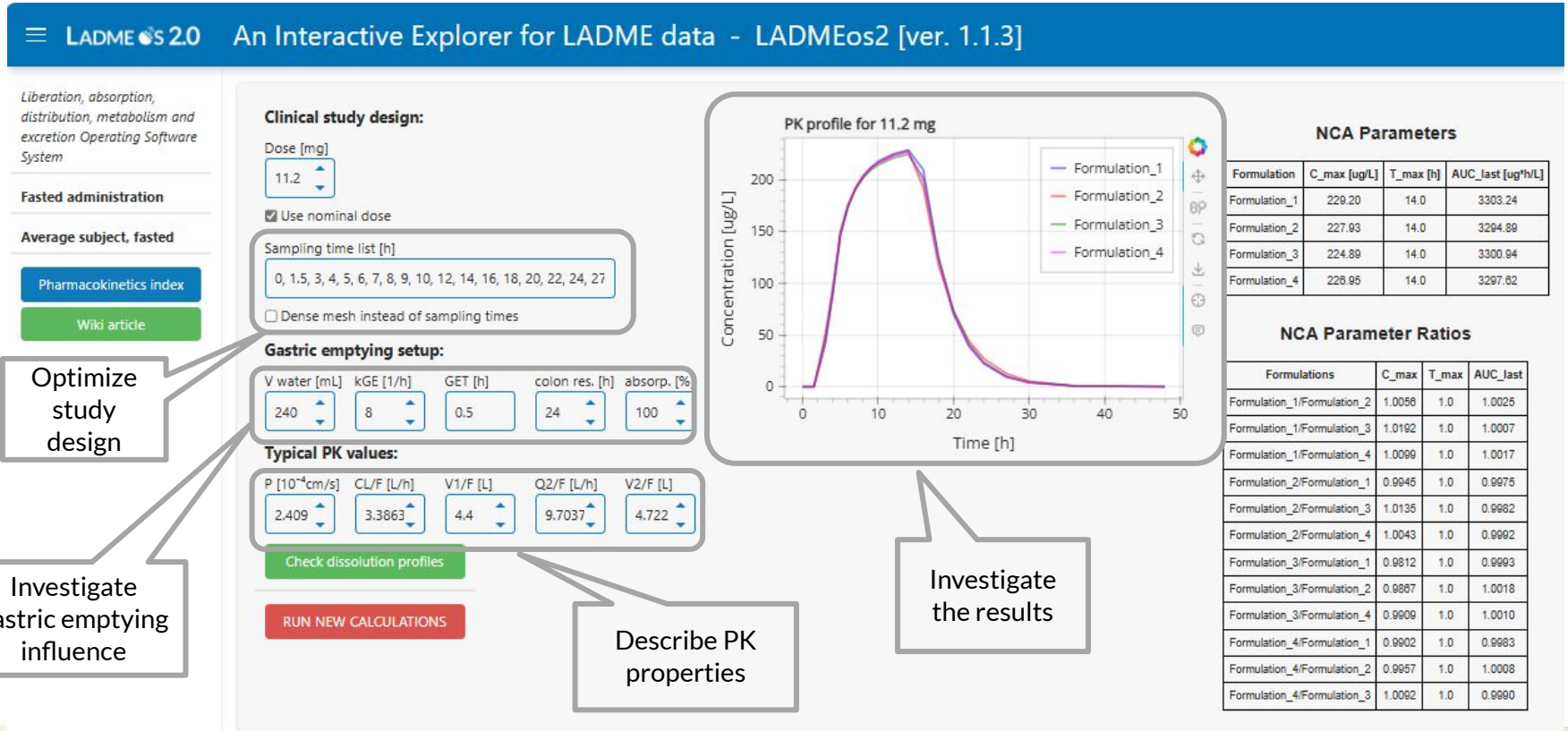
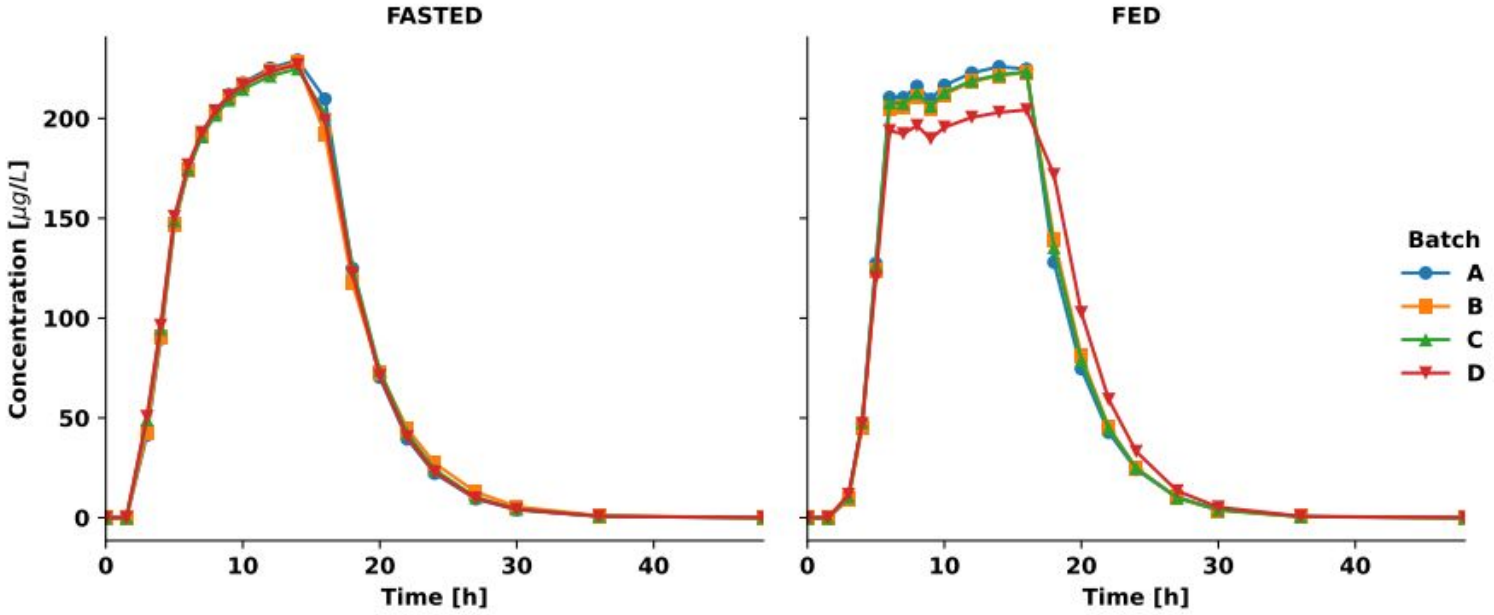
LADMEos2 - PK simulation for an average subject



Formulation	C_max [ug/L]	T_max [h]	AUC_last [ug*h/L]
Formulation_1	229.20	14.0	3303.24
Formulation_2	227.93	14.0	3294.89
Formulation_3	224.89	14.0	3300.94
Formulation_4	226.95	14.0	3297.62

Formulations	C_max	T_max	AUC_last
Formulation_1/Formulation_2	1.0056	1.0	1.0025
Formulation_1/Formulation_3	1.0192	1.0	1.0007
Formulation_1/Formulation_4	1.0099	1.0	1.0017
Formulation_2/Formulation_1	0.9945	1.0	0.9975
Formulation_2/Formulation_3	1.0135	1.0	0.9982
Formulation_2/Formulation_4	1.0043	1.0	0.9992
Formulation_3/Formulation_1	0.9812	1.0	0.9993
Formulation_3/Formulation_2	0.9867	1.0	1.0018
Formulation_3/Formulation_4	0.9909	1.0	1.0010
Formulation_4/Formulation_1	0.9902	1.0	0.9983
Formulation_4/Formulation_2	0.9957	1.0	1.0008
Formulation_4/Formulation_3	1.0092	1.0	0.9990

Simulated individual drug plasma concentration-time profiles for an average subject under both fasted and fed intake conditions were generated using LADMEos2.



Simulated drug plasma concentration-time profiles for an average subject fasted and fed intake conditions

Conclusions

1. PPOP tablets demonstrated robustness against physico chemical and mechanical conditions characteristic for fasted and fed states.

2. Manufacturing method and polymer molecular weight in the push layer had minimal impact on tablet performance.

3. Biopredictive in vitro testing, including mechanical agitation and the use of biorelevant media supported by PK modeling confirms the comparable drug delivery performance of the tested formulations.

Michał
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