

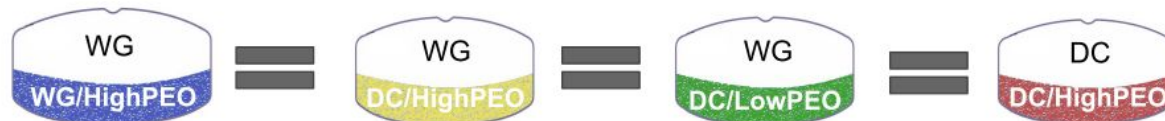
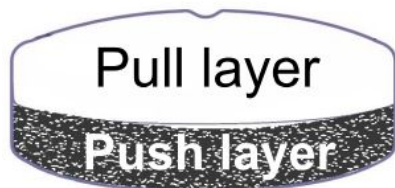
Predicting Drug Delivery of Push Pull OROS: A Biorelevant Dissolution and PK Simulation Strategy

Grzegorz Garbacz

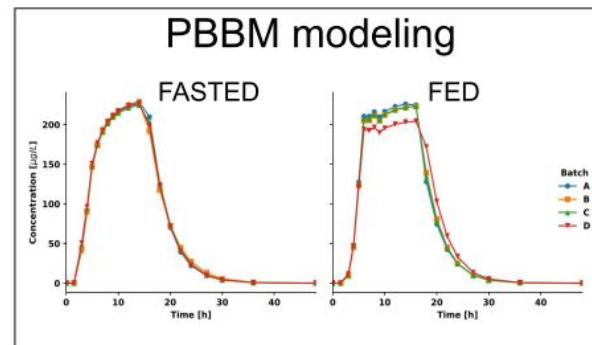
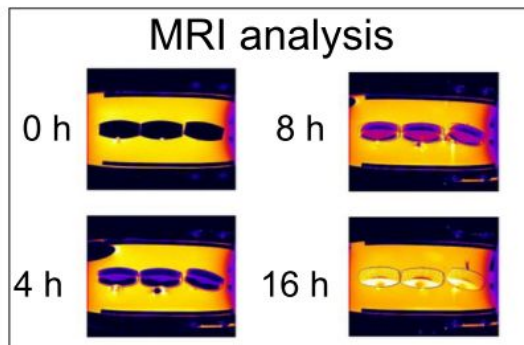
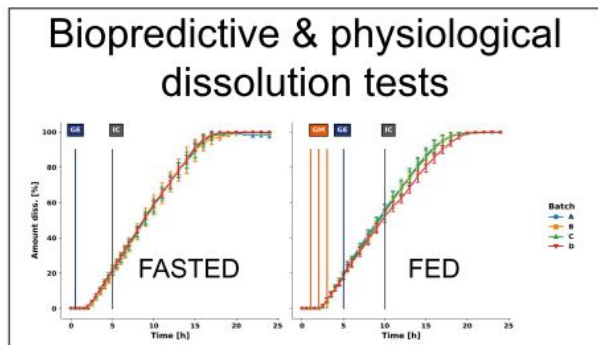
Co-authors: Dorota Danielak, Daria Myslitska, Justyna Dobosz, Michał Smoleński, Jeffrey Gimbel, Jadwiga Paszkowska, Michał Romański, Maciej Winiarski, Marcela Staniszevska, David Ferrizzi, Larry Martin, Ali Rajabi-Siahboomi

Aim of the study

Push-pull osmotic pump tablets characterization

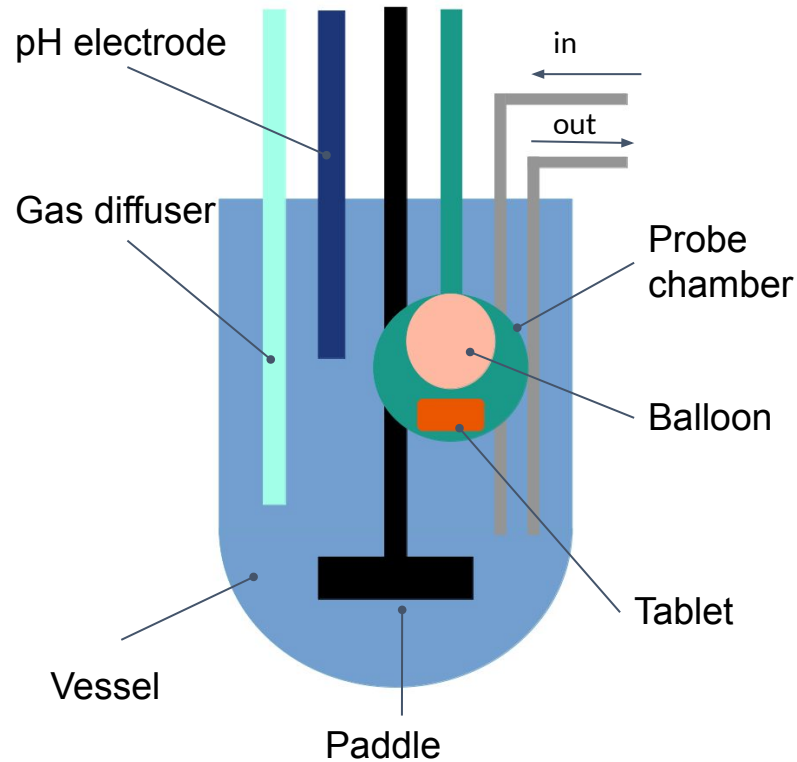


DC - direct compression; WG - wet granulation;
LowPEO - lower viscosity polymer (4,000 kDa); HighPEO - higher viscosity polymer (5,000 kDa)



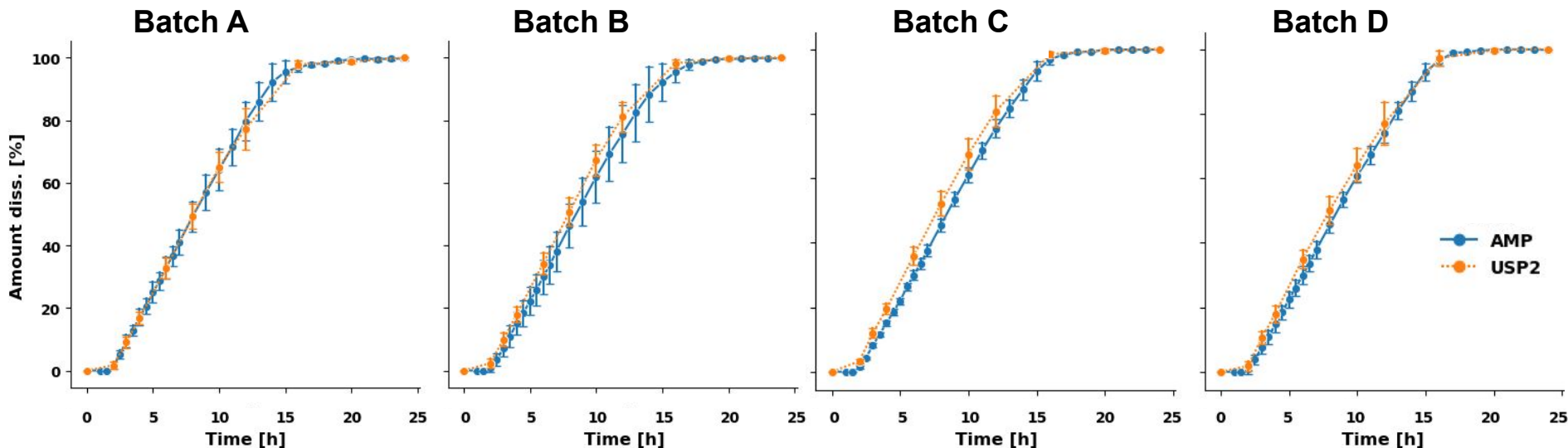
DC – direct compression; WG – wet granulation;
LowPEO – lower viscosity polymer (4,000 kDa); HighPEO – higher viscosity polymer (5,000 kDa)

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



©Physiolution Polska

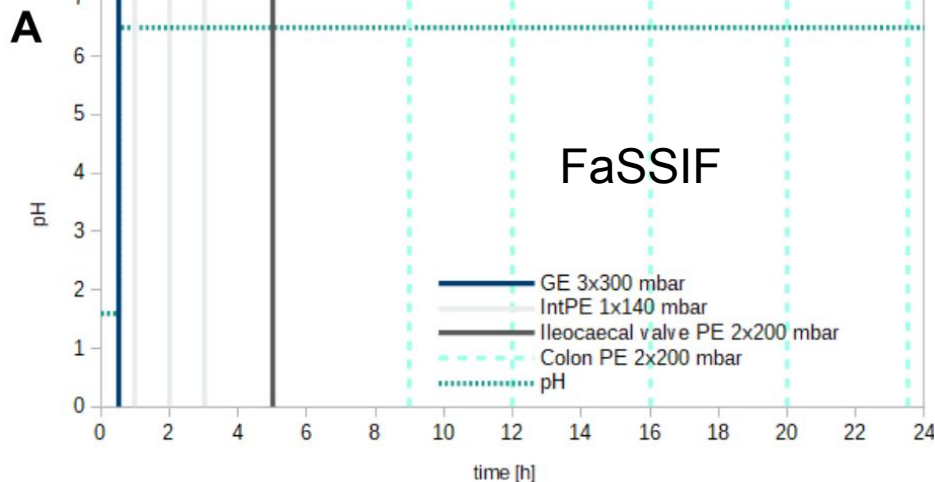
PPOP tablets mechanical robustness confirmed - similar dissolution in USP2 and stress-intensive AMP program



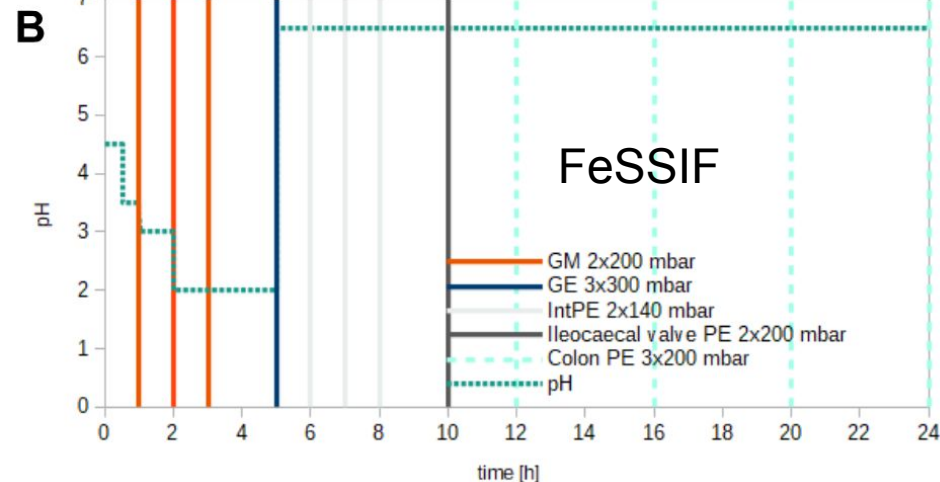
Dissolution profiles of POPP tablets obtained in: AMP (robustness test, blue line); USP apparatus 2 (100 rpm, orange line), medium USP phosphate buffer pH 6.8, given are means of $n = 6 \pm \text{SD}$

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

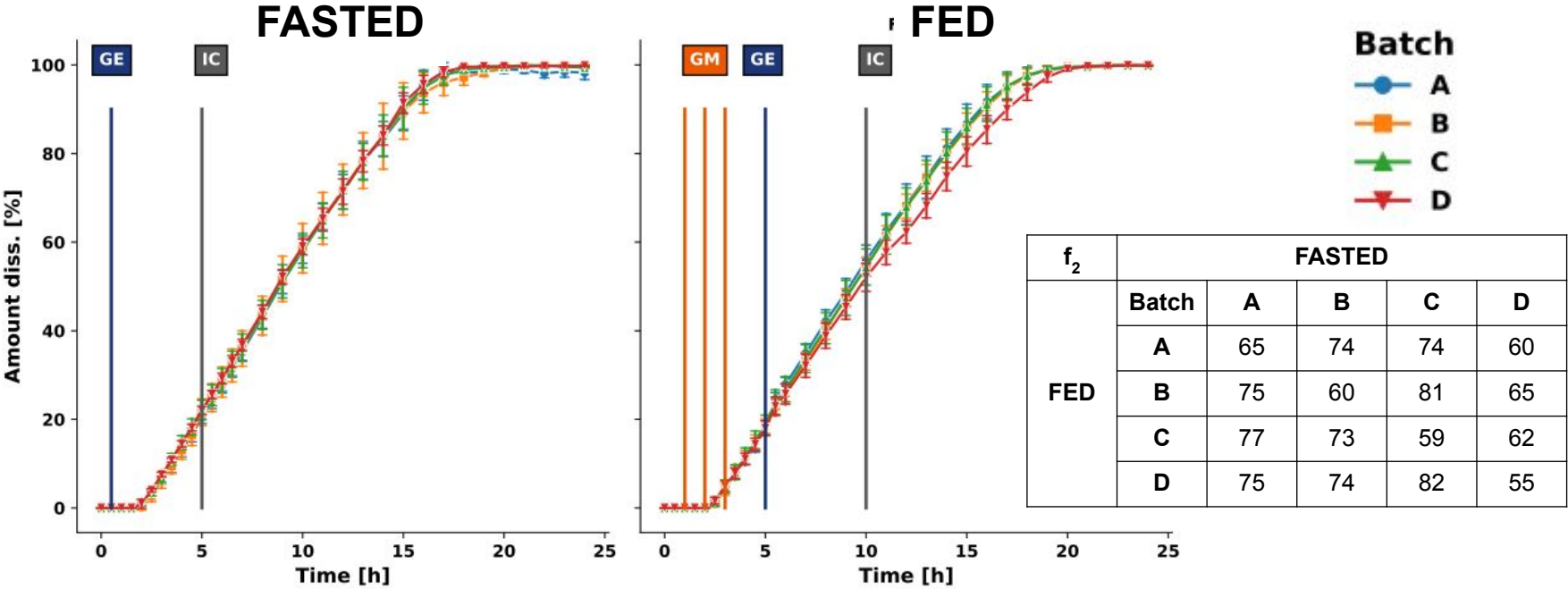
FASTED



FED



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



Dissolution of POPP tablets obtained in AMP under the simulated fasted and fed intake conditions, given are means of $n = 6 \pm \text{SD}$

LADMEos2 - innovative web app for PK simulations and modeling

LADMEos2.0 An Interactive Explorer for LADME data - LADMEos2 [ver. 0.1.0]

Liberation, absorption,
distribution, metabolism and
excretion Operating Software
System

Disintegration in PhysioCell

Disintegration

Pharmacokinetics index

Wiki article

Upload new diso data:

Wybierz plik Disint...ta.csv

Upload PhysioCell flow:

Wybierz plik Flow...m.csv

Set dose [mg]:

100

PhysioCell setup:

configuration: closed loop

StressCell [mL]: 34

CollectVessel [mL]: 500

IS duration [min]: 1.667

GE duration [min]: 4

GE flow [mL/min]: 20

solid transfer: yes

sampling site: vessel

Set disintegration model:

time_wise_first_order

k disint points: 2

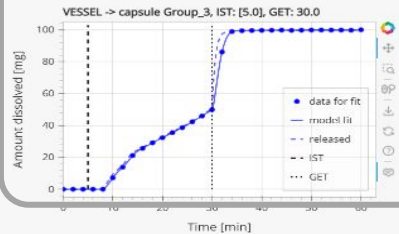
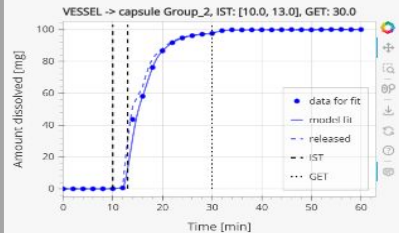
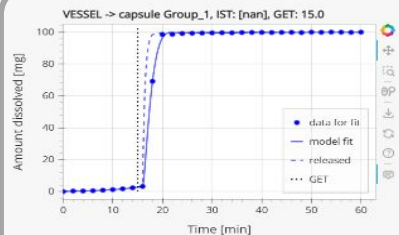
Return to dissolution

Select PK mode:

Average subject, fasted

Go to PK simulation

RUN NEW CALCULATIONS



An Interactive Explorer for LADME data - LADMEos2 [ver. 1.1.0]

Set dose [mg]:

11.2

Set flag [h]:

Formulation_1 est X nan

Formulation_2 est X nan

Formulation_3 est X nan

Formulation_4 est X nan

Set dissolution model:

mixed Q1 order

Set switchpoint [%]:

Formulation_1 switch point 95.0

Formulation_2 switch point 95.0

Formulation_3 switch point 95.0

Formulation_4 switch point 95.0

Upload new data:

Wybierz plik Nie...o pliku

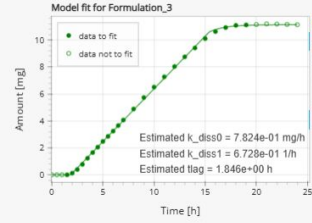
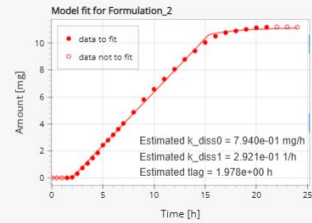
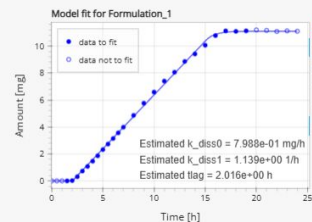
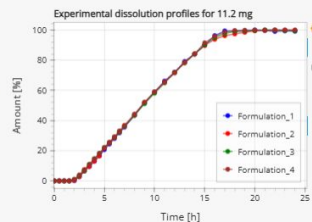
Download Disso_data_fasted

Go to PK simulation

RUN NEW CALCULATIONS

Download disso_fit_data.csv

Download disso_fit_table.csv



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

0117

7

LADMEos2 - PK simulation for an average subject

≡ LADMEos 2.0 An Interactive Explorer for LADME data - LADMEos2 [ver. 1.1.3]

Liberation, absorption,
distribution, metabolism and
excretion Operating Software
System

Fasted administration

Average subject, fasted

Pharmacokinetics index

Wiki article

Optimize
study
design

Investigate
gastric emptying
influence

Clinical study design:

Dose [mg]

11.2

☒ Use nominal dose

Sampling time list [h]

0, 1.5, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 18, 20, 22, 24, 27

☐ Dense mesh instead of sampling times

Gastric emptying setup:

V water [mL]

240

kGE [1/h]

8

GET [h]

0.5

colon res. [h]

24

absorp. [%]

100

Typical PK values:

P [10⁻⁴cm/s]

2.409

CL/F [L/h]

3.3863

V1/F [L]

4.4

Q2/F [L/h]

9.7037

V2/F [L]

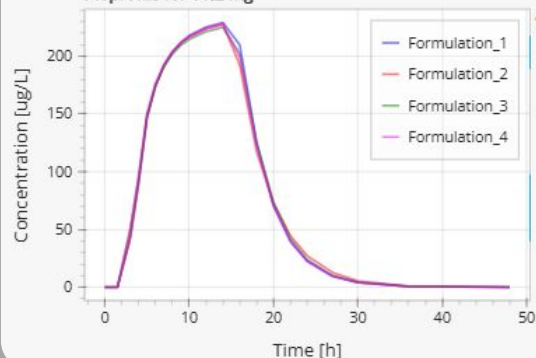
4.722

Check dissolution profiles

RUN NEW CALCULATIONS

Describe PK
properties

PK profile for 11.2 mg



Investigate
the results

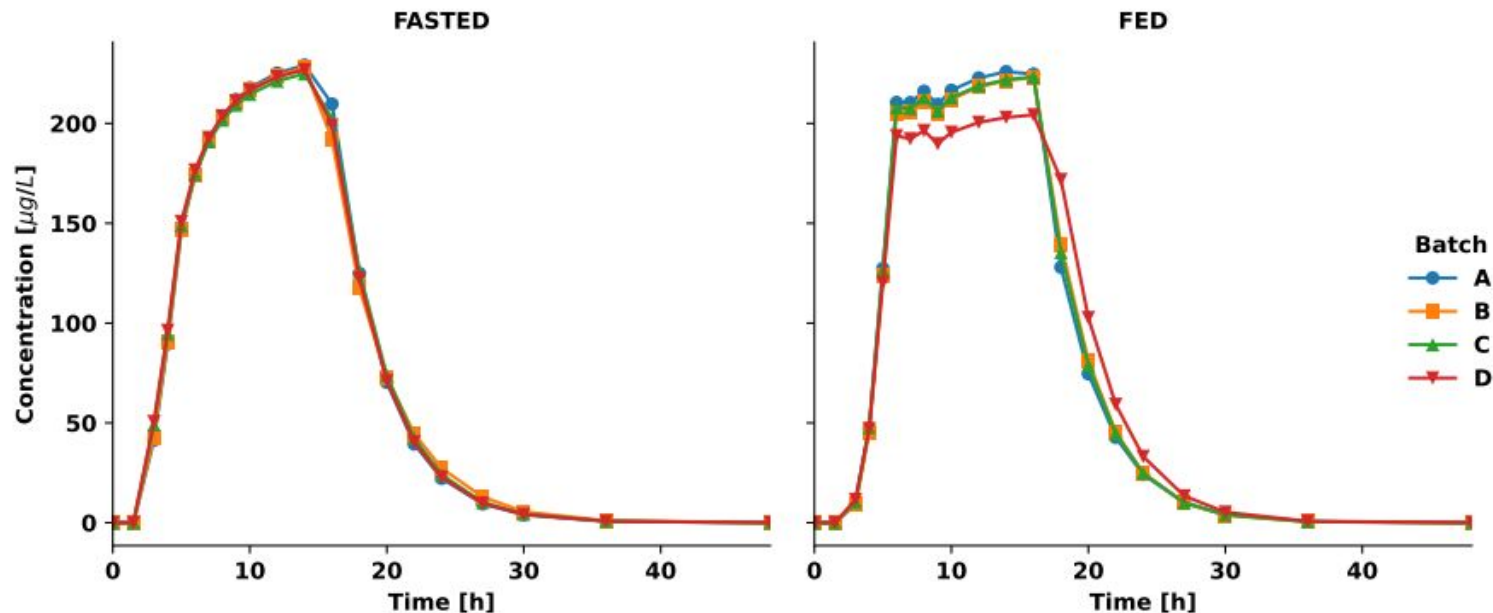
NCA Parameters

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	228.95	14.0	3297.82

NCA Parameter Ratios

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	0.9887	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.





Thank you for your attention!

Michał
Smoleński

