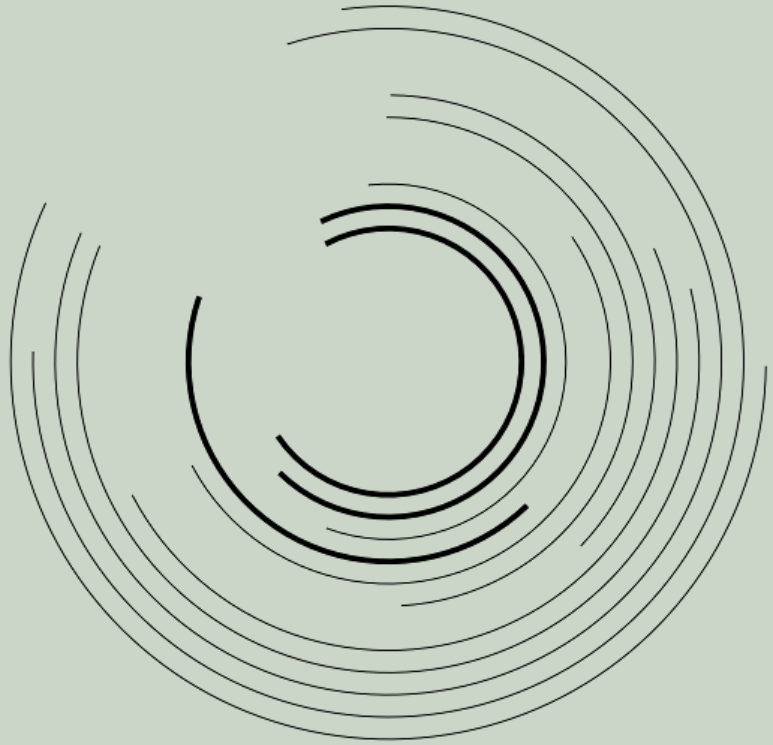
2026 OSP COMMUNITY CONFERENCE

A physiologically based biopharmaceutics modeling (PBBM) framework predicting the particle drift effect on absorption



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Pharmetheus AB

24th of September 2026

Outline

- Background and objectives
- Approach: Particle drift model development
- PBBM application
- Conclusions and outlook

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Director consultant

Other contributing Pharmetheus colleagues:

- Johanna Eriksson
- Erik Sjögren



Background



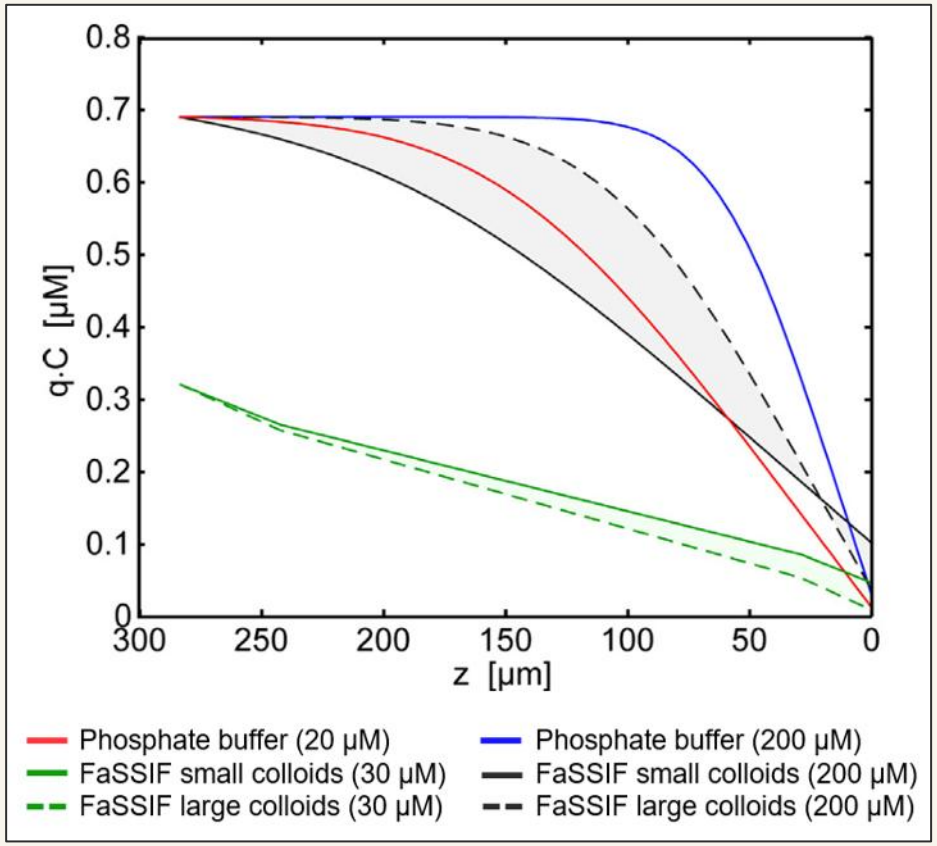
Particle drifting effect may enhance oral absorption

Conventional absorption models tend to under-predict in vivo absorption of nanoparticle formulations, even when accounting for:

- Curvature-increased solubility (*Ostwald-Freundlich*)
- Large Surface area-driven dissolution rate (*Nernst-Brunner*)

The Particle Drift Effect may enhance absorption of nanoparticles by:

- Acting as a “shuttle” aiding drug transport across the intestinal epithelial unstirred water layer (UWL)
- Increasing unbound drug concentration at the intestinal membrane



Simulated concentration gradient of aprepitant at different total concentrations and media.

Adapted from: Roos C. et al., Eur J Pharm Biopharm. 2018;133:70-76.

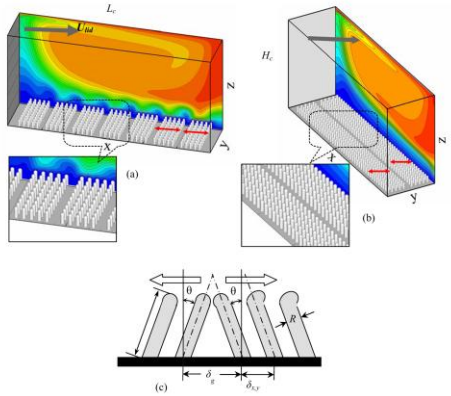
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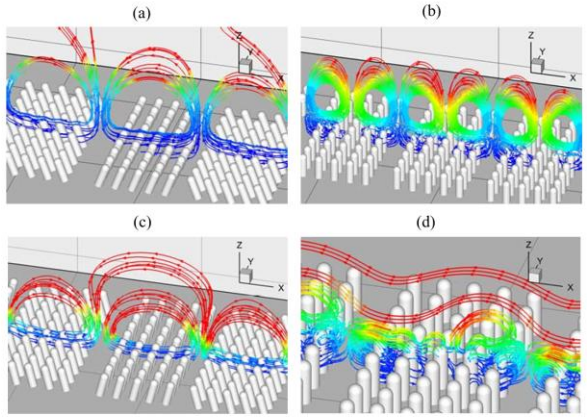
Hydrodynamics of the Intestinal Unstirred Water Layer

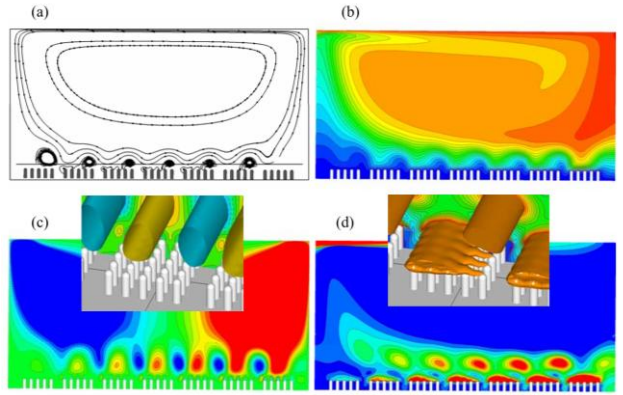
No-slip condition – the relative flow velocity of a viscous fluid is zero at the surface of a solid object

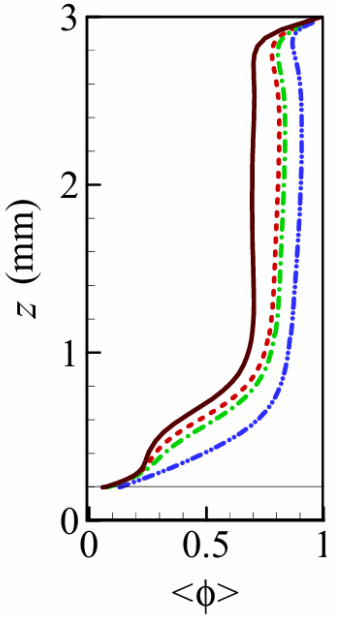
- In a system of flowing fluid this will create a boundary layer of decreasing velocity towards the surface.
- Intestinal motility and villi motions generate highly complex (and time varying) hydrodynamics.
- Different models, simplifications, assumptions have been applied in respect of oral drug absorption.

3D mechanisms of macro-to-micro scale transport and absorption enhancement by gut villi function









Wang Y. et al., Phys Rev E. 2017 Jun;95(6-1):062412

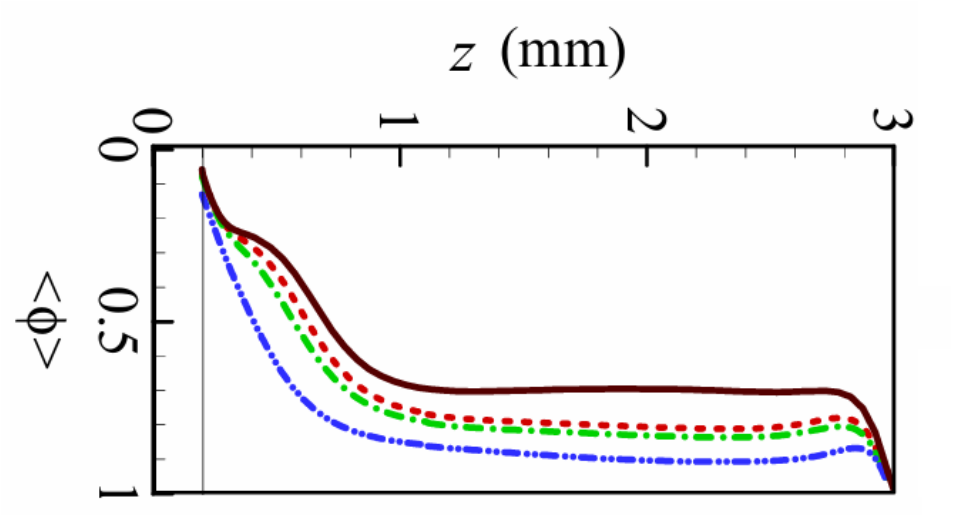
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Leveraging hydrodynamics in PBBM

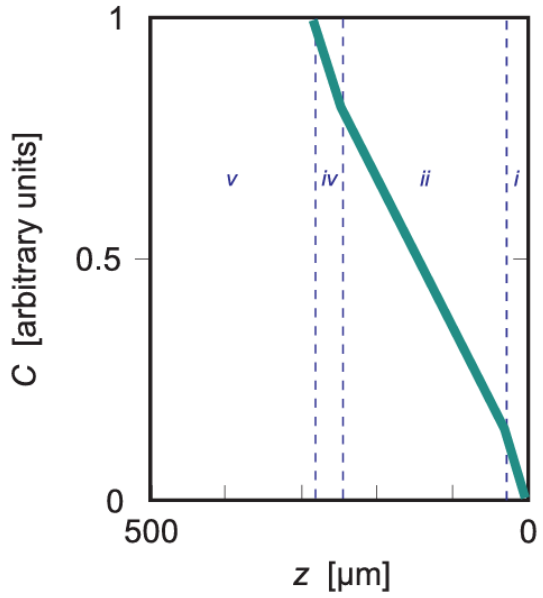
Translating average concentration gradient to hydrodynamic conditions and effective boundary length

Entities and processes will be affected by differences in hydrodynamics

Adapted to a model based on traditional in vitro measurements (S and P)



Simplification:
Well-stirred section removed



Wang Y. et al., Phys Rev E. 2017 Jun;95(6-1):062412

Roos C. et al., Eur J Pharm Biopharm. 2018;133:70-76.

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Objective: Development of a mechanistic PBBM framework for oral nano-formulations aligned to OSP

Quantifying the "particle drift" effect on systemic drug absorption for nano-formulations, using:

- the freely accessible Open Systems Pharmacology Suite (OSPS)
- custom R-based script based on the description by Roos et al. (2018)

Approach



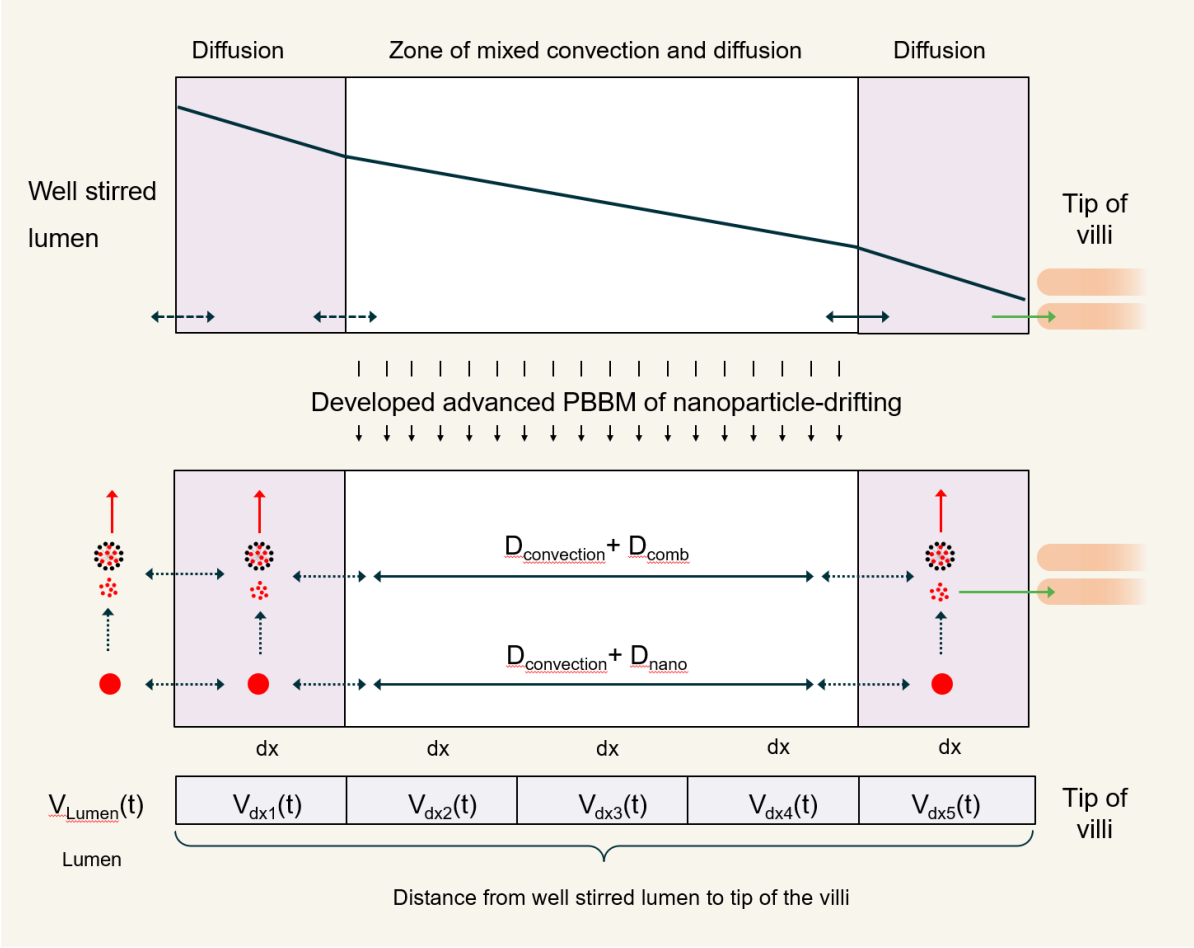
PBBM particle drift model development

An advanced PBBM framework was developed to capture nanoparticle absorption in vivo:

- PK-Sim® (v.11.2) employed for deriving time varying physiological parameters (*t*)
- PBBM implementation developed in R (v 4.2) using the deSolve package (v1.3.4)
- Data and theory from Roos et al. (2018) was used to construct the PBBM:
  - Dissolution, diffusion, convection, absorption, micellar partitioning of solubilized drug, colloidal structures and particles
- Output from PBBM can be used as input to PK-Sim or conventional PK models



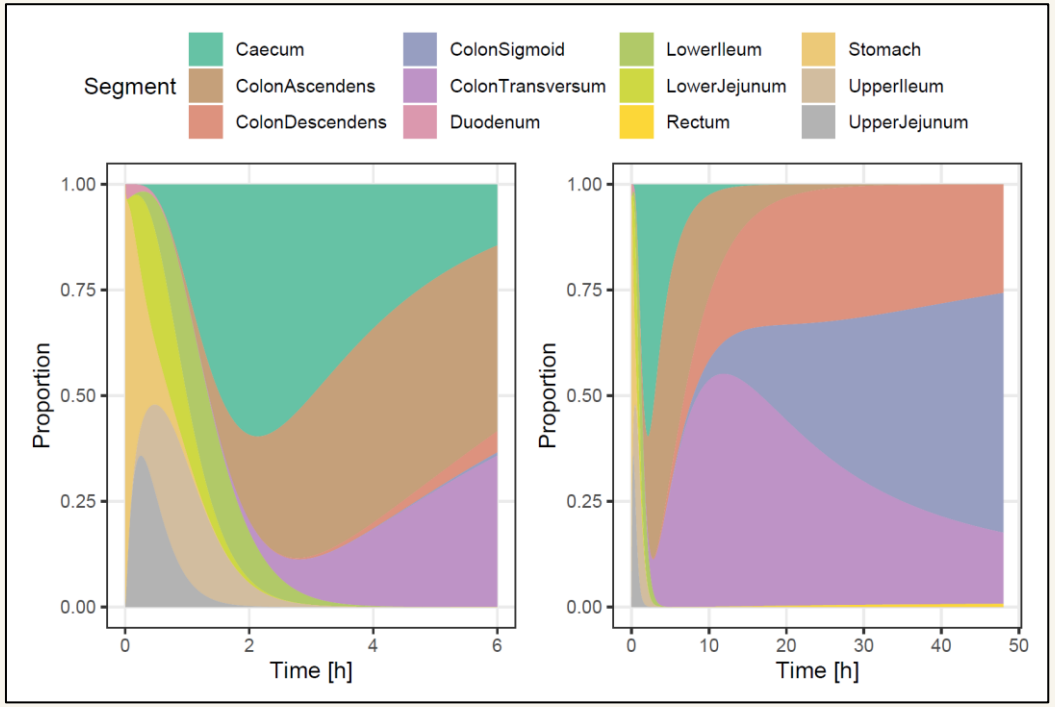
PBBM particle drift model

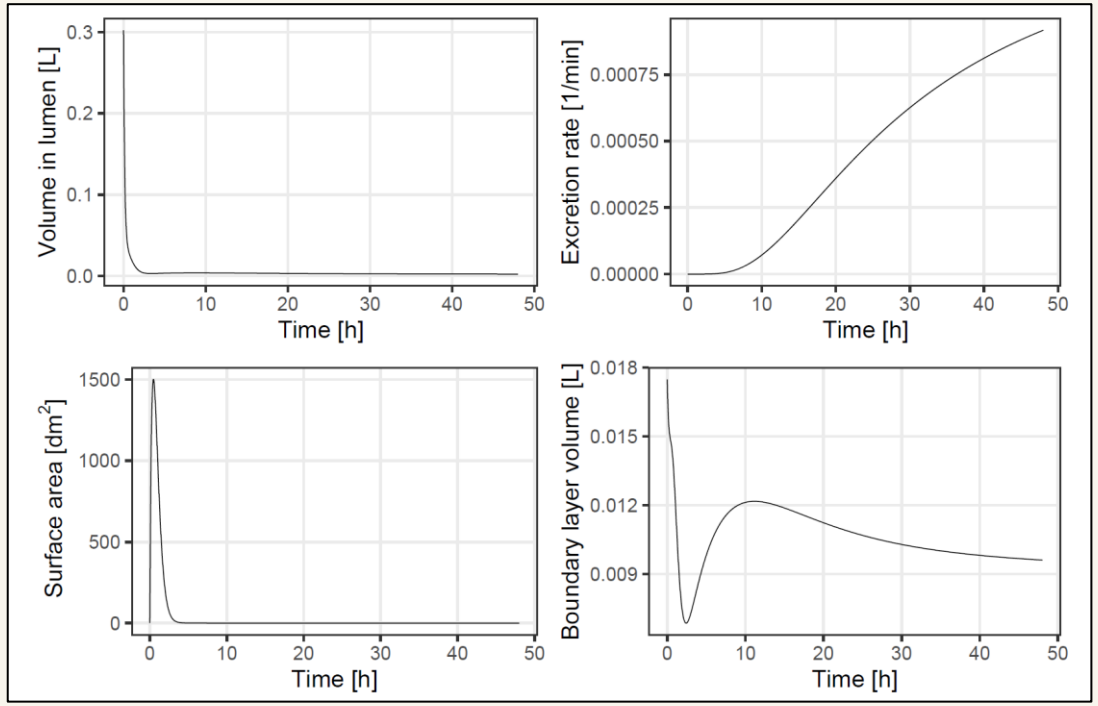


- Entities:
  - Monomers
  - Particles
  - Monomers in colloidal structures
- Input:
  - Membrane permeability
  - Buffer solubility
  - Partition coefficient to colloidal structures
- System:
  - Physiology and Anatomy

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Time varying intestinal parameters as surrogate for intestinal transit





- Time varying weights used for calculation of averages as surrogate for intestinal transit for intestinal liquid volume, boundary layer volume, fecal excretion rate and surface area

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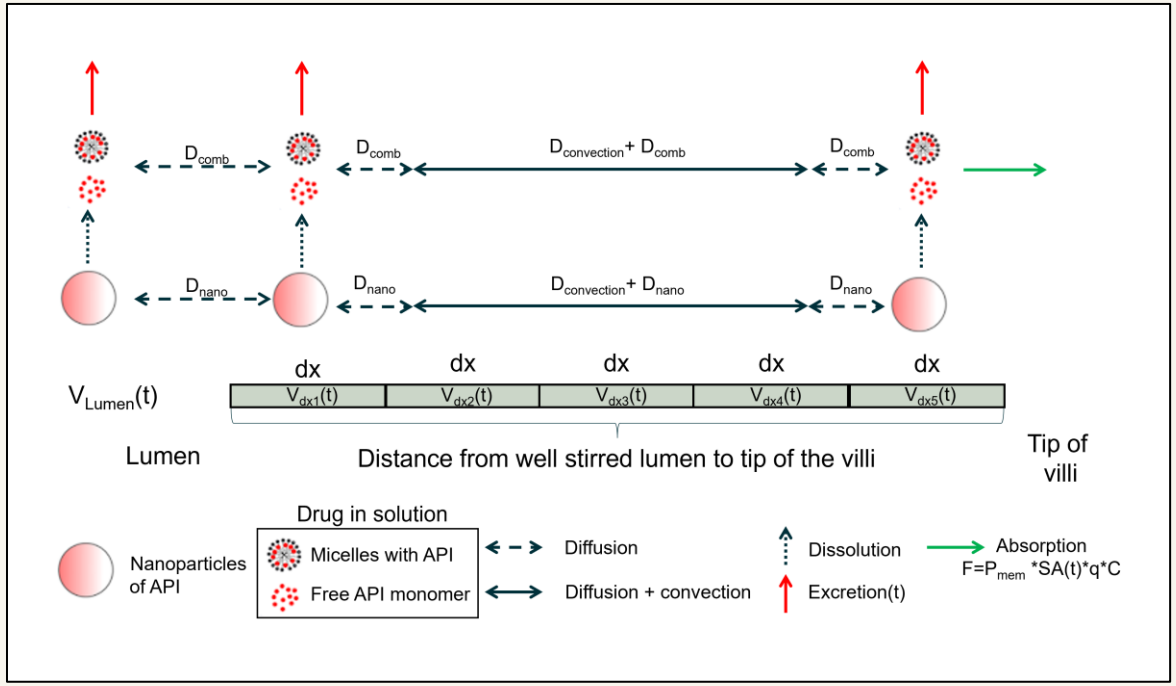
PBBM application



Particle drift model application

- Sensitivity of the model was tested for particle size on drug absorption for formulation:
  - microparticles and low solubility (LP)
  - nanoparticles and low solubility (NP)
  - microparticles and high solubility (ASD)

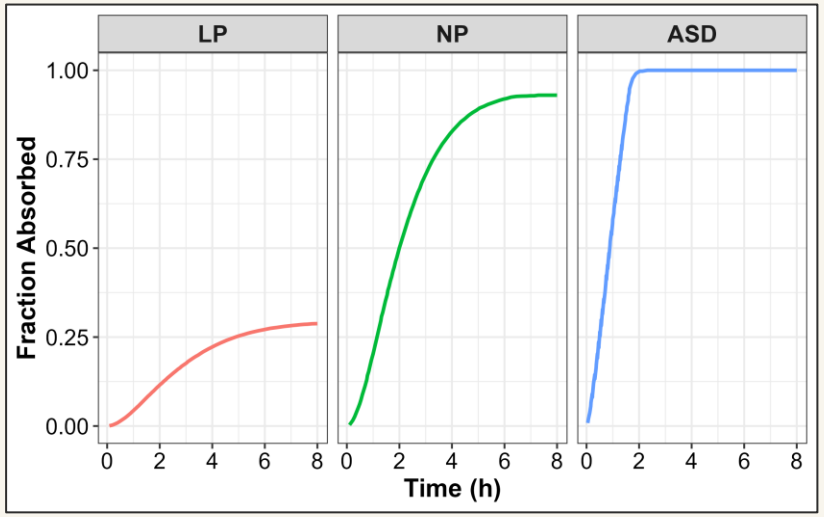
- Model simulations were compared against the observed particle size-dependent oral absorption of fenofibrate

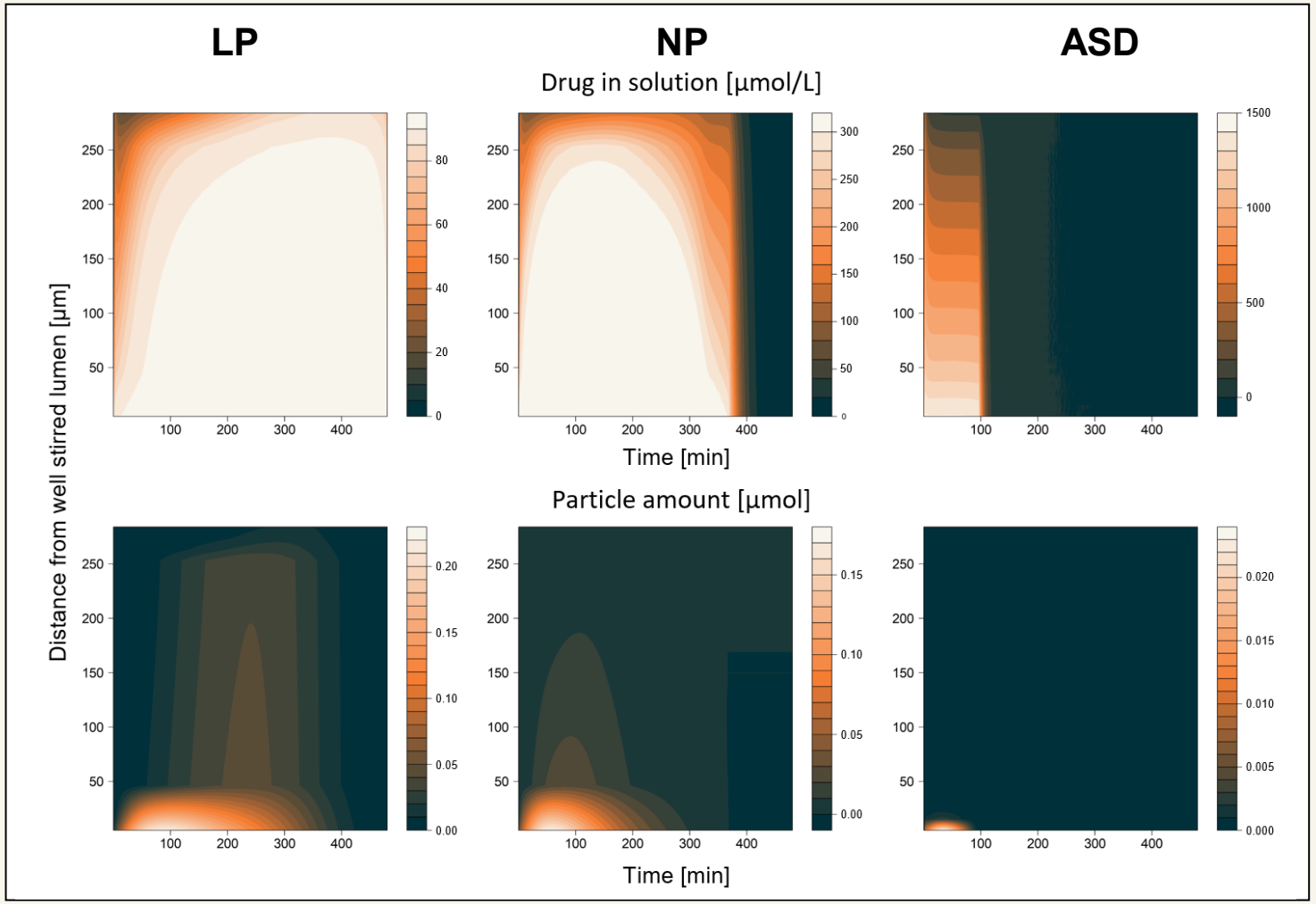


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Simulated concentration of drug in solution and particle amount along the UWL over time

- High solubility formulations lead to high drug concentration in the UWL at early time points
- Low solubility formulations only reach high concentrations in the UWL when particle sizes are small

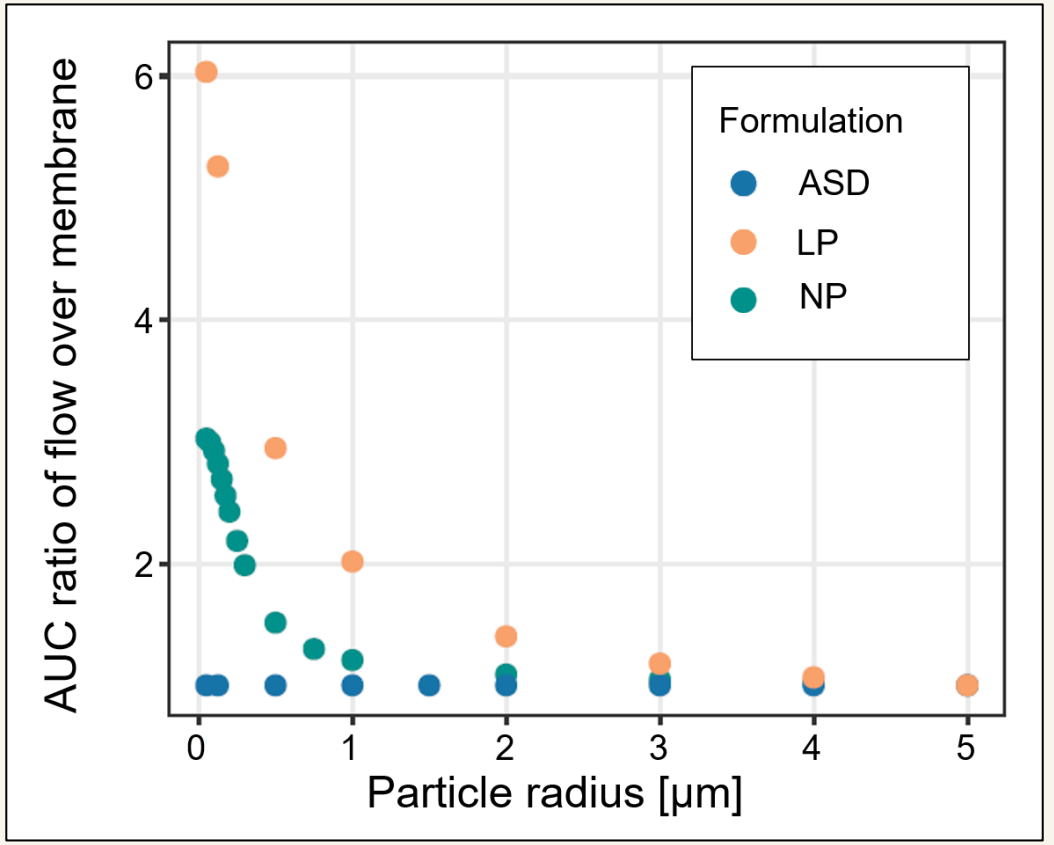




Intestinal membrane drug flow is particle size dependent

Sensitivity analysis of particle size shows:

- Particle size reduction: increased overall exposure, magnitude was drug solubility and dose dependent
  - High solubility formulations (ASD) already show high absorption and did not benefit from reducing particle sizes
  - Low solubility formulations (NP and LP) showed a strong increase when administered as a nano-formulation



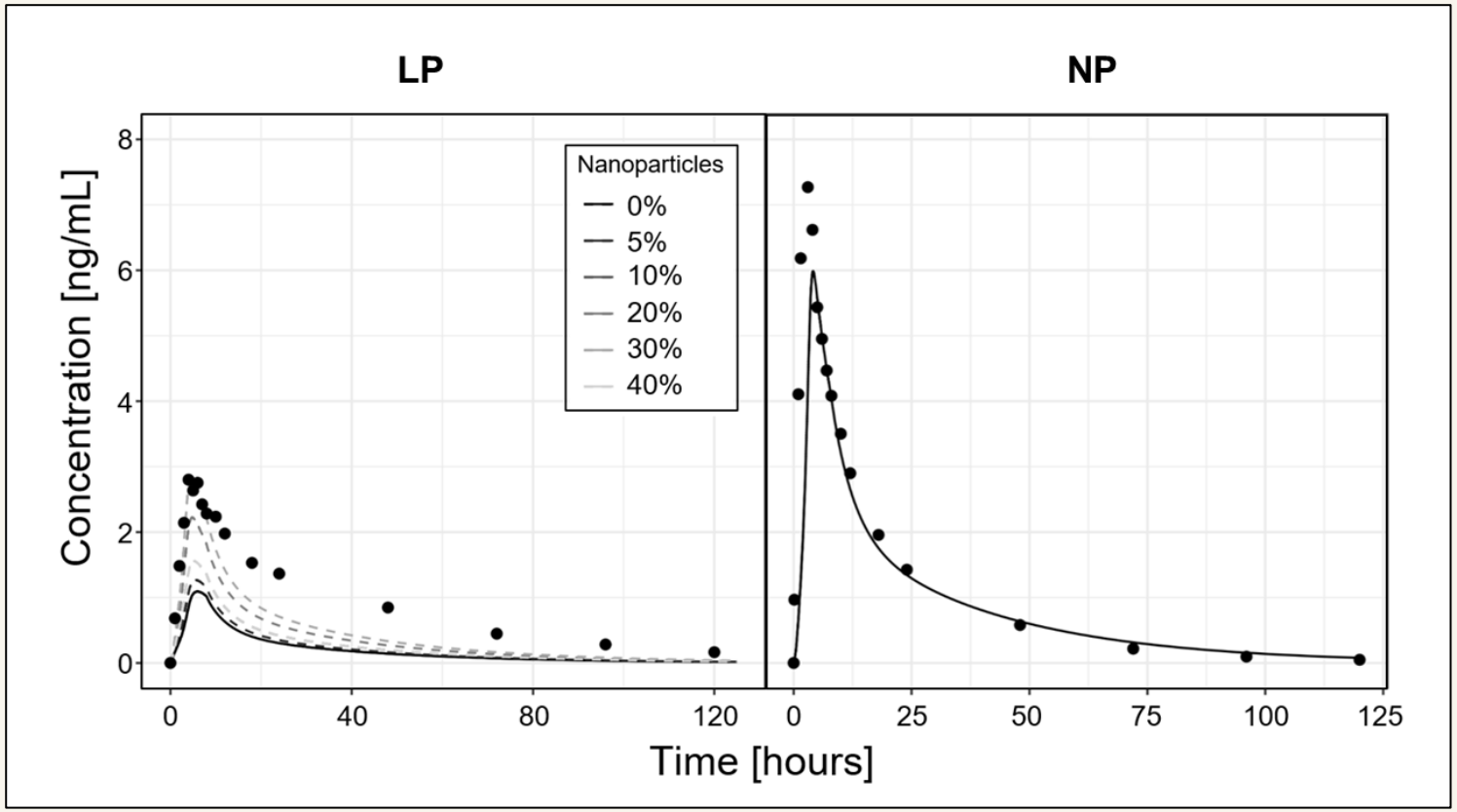
Note: Different solubility was adopted for ASD, LP and NP

Advanced PBBM prediction show good agreement with observed particle size-dependent oral absorption of fenofibrate

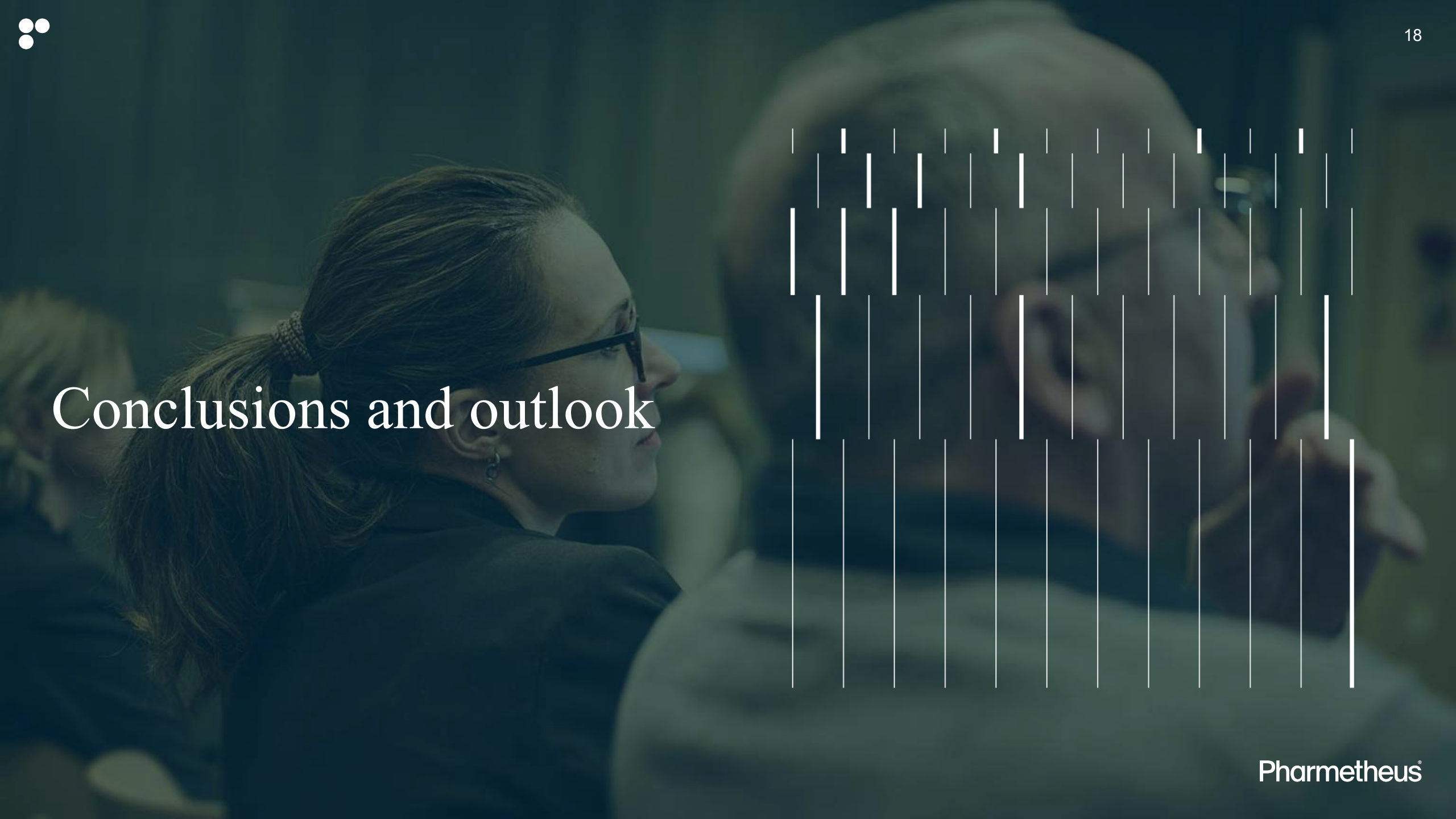
Fenofibrate
- 145 mg
- Particle size: 0.2/1.1 µm
- Solubility: 13.7 µg/mL
- Partitioning to micelles: 0.98
- Caco-2 permeability: 2.1×10^{-4} cm/sec

Data and PK model according to Sjögren at al. 2013

Sjögren E et al. (2013), doi:10.1016/j.ejps.2013.05.019



Different fractions of nanoparticles in the micronized formulation were tested as in vitro dissolution experiments were inconsistent with the measured particle size



Conclusions and outlook

Conclusions and outlook

Advanced PBBM framework developed linking the particle drifting effect to *in vivo* drug exposure

- Can be used to predict plasma concentration profiles for drugs administered as a nano-formulation
- Prospectively assess potential absorption enhancement by switching to a nano-formulation
- Compatible with OSP and R
  - Enables translatability between species and populations
  - Leverage open-source platforms

Future improvements

- Extend models to include **binding to formulation polymers**, for ASDs
- Mechanistic extrapolation method to estimate **intestinal membrane permeability** from *in vitro* data
- Dynamic levels of colloidal structures
- Expand on solubility/dissolution


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