



In silico prediction of environmental exposure to fenofibrate micro and nanoparticles

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OBJECTIVES

Aim of the current work was to evaluate possible benefits and risks of active pharmaceutical ingredient (API) nanosizing for patients and environment with regards to pharmacokinetic (PK), ecotoxicology and particle size specific properties¹.

METHODS

PARTICLE CHARACTERIZATION

Two commercially available fenofibrate formulations (Lipidil® and Lipidil One®) were characterized to determine their particle size distribution using Dynamic Imaging Particle Analysis (DIPA) and Nanoparticle Tracking Analysis (NTA) depending on the sample requirements.

IN VITRO DRUG RELEASE

Drug release from both formulations was tested in simulated gastric and intestinal media. To mimic the effect of *in vivo* absorption, the media was supplemented with sodium dodecyl sulfate. Further different hydrodynamic settings were evaluated in terms of consistency with the *in vivo* situation. The resulting profiles were parametrized and implemented in the PBPK model.

MODEL SIMULATION

The model combined a PBPK module calculating the dissolution and absorption processes together with a descriptive distribution and elimination module. As the post-absorption processes were not dependent on the formulation properties, the parameter for elimination and distribution were extracted from human PK data². The PBPK module utilized the drug specific *in vitro* data as well as human physiology parameters. To evaluate the model, predicted plasma profiles were compared to those observed *in vivo*^{3,4}.

ENVIRONMENTAL EXPOSURE SCENARIO

The environmental exposure to fenofibrate were calculated from the *in silico* non-absorbed drug fraction. Further, the eliminated portion of API was divided into excretion as micro and nanomaterial based on an *in vitro* assay mimicking the transit of nanoparticles through the human GI tract. Additionally, the toxicity of fenofibrate and its main metabolite, fenofibric acid, was tested in a fish embryo toxicity test (FET).

RESULTS

Formulation characterization revealed a mean particle size of $2.42 \mu\text{m} \pm 0.97 \mu\text{m}$ for Lipidil® and $162 \text{ nm} \pm 8 \text{ nm}$ for Lipidil One®. In the subsequent release tests the nanoparticle Lipidil One®, exhibited a more rapid drug release rate as well as a higher total release compared to the microproduct Lipidil®. These differences were successfully translated to the *in silico* predictions and accurately reflected the *in vivo* PK profile (AAFE ≤ 1.5). During the *in vitro* GI transit, Lipidil One® showed high stability in the stomach and intestine but a significantly reduced particle concentration ($-57.0\% \pm 4.9$) in the colon compartment. Further, the FET revealed a higher toxicity for fenofibrate (LC₅₀ 29.6 $\mu\text{g/ml}$) compared to its metabolite fenofibric acid (LC₅₀ 53.3 $\mu\text{g/ml}$).

References

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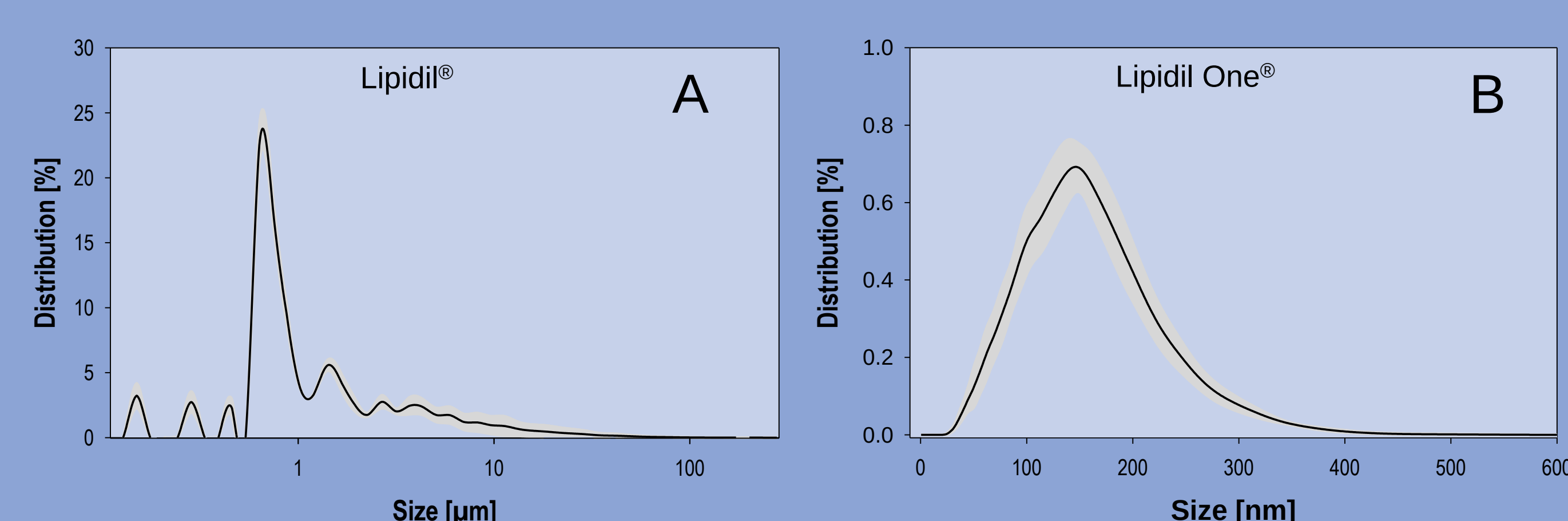


Fig. 1. Particle distribution with SD of the microproduct Lipidil® (A) and the nanoparticle Lipidil One® (B)

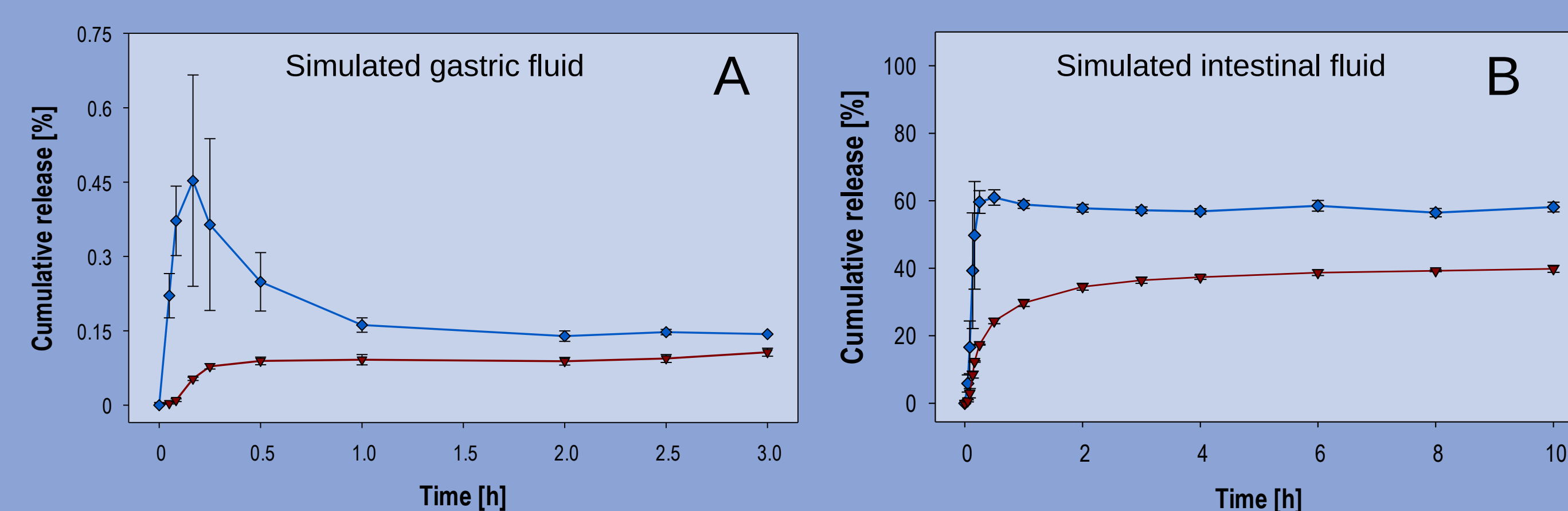


Fig. 2 Release test in biorelevant gastric (A) and intestinal (B) media for Lipidil® (red) and Lipidil One® (blue)

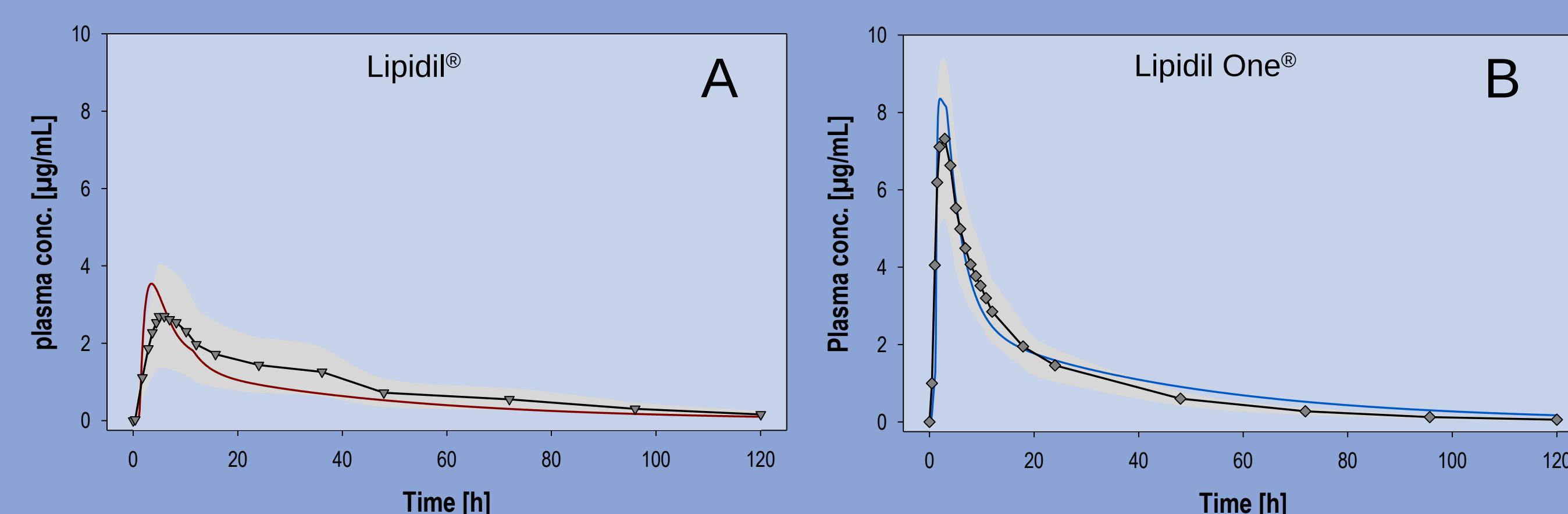


Fig. 3. Comparison of *in silico* (straight line) and *in vivo* (line and symbols) profiles with SD of Lipidil® (red) and Lipidil One® (blue)

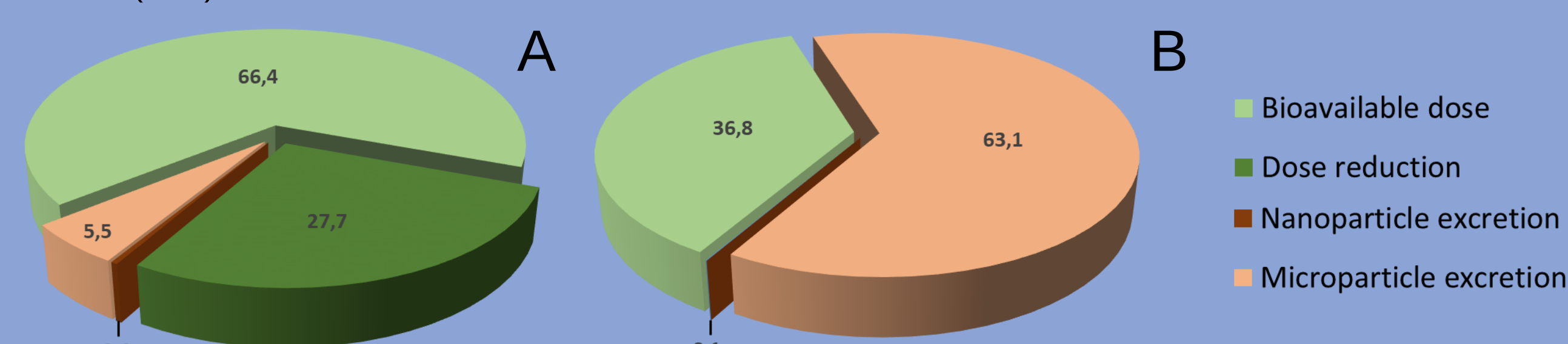


Fig. 4. Environmental exposure scenario for Lipidil® (A) and Lipidil One® (B) in percent

CONCLUSION

The particle distributions of two formulations were precisely characterized which enabled their classification as nano and microproduct. The *in silico* model reliably predicted the pharmacokinetics *in vivo* and allowed calculation of potential environmental exposure to the amount of fenofibrate as well as its particulate form. The model revealed superior pharmacokinetic properties of Lipidil One® and also demonstrated benefits for the environment due to the reduced dose. At the same time the excretion of fenofibrate was shifted from the more toxic API to its less toxic metabolite. In the future, our model could be used to evaluate possible benefits of nanosizing for other APIs as well.

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