FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

Evaluation of release techniques for nanocarrier on the basis of IVIVC-PBPK modelling

Author: Fabian Jung (1), Lisa Nothnagel (1), Fiona Gao (2), Matthias G. Wacker (1)

Institution: (1) Fraunhofer IME Project Group Translational Medicine and Pharmacology TMP, (2) Institute of Pharmaceutical Technology Goethe University,

OBJECTIVES

Aim of the current work was to compare two methods for testing the drug release from nanoparticles (dispersion releaser (DR) technique and filtration). For this purpose we have employed physiologically based pharmacokinetic (PBPK) model by studying the effect of *in vitro* parameters on the *in silico* profile.

METHODS

IN VITRO RELEASE

To determine the release from nanoparticles, two biorelevant *in vitro* drug release methods were compared with regard to *in vitro* and PBPK modelling results. One method was using a nanofiltration whereas the other was based on a forced dialysis (dispersion release, DR). During release testing, biorelevant media were used to simulate the human gastric and intestinal conditions.

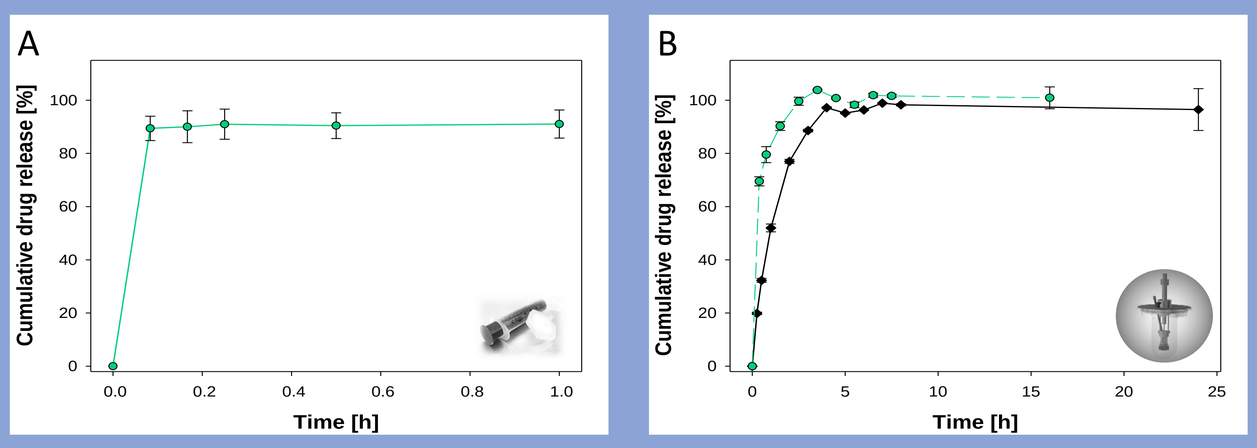

Fig. 1. Flurbiprofen release from PCL nanoparticles: Filtration (A) Dispersion releaser (B)

MODEL VALIDATION

The model consisting of 9 compartments, which was equipped to calculate the drug flux, was developed using Stella Architect® .To validate the model, simulated profile of a marketed flurbiprofen tablet (100mg, Mylan) was compared with its observed *in vivo* profile [2, 3]. Additionally, the simulated and observed non-compartment PK parameters were compared by applying bioequivalence criteria. Standard deviation in the clinical study and bioequivalence criteria are shown as blue background.

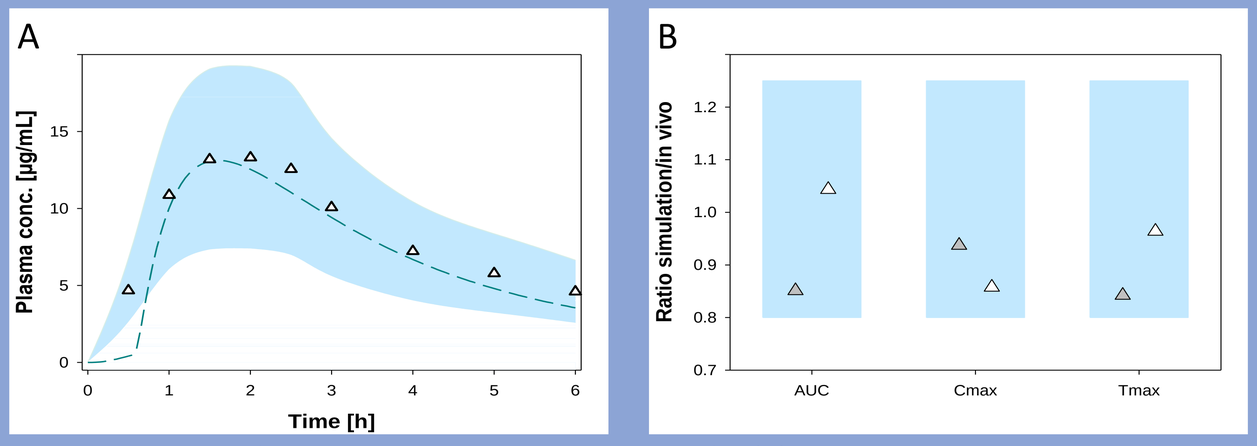

Fig. 2 Comparison of simulated and observed plasma profile (A) and evaluation according to bioequivalence criteria with additional parameters from the FDA approval (B)

PREDICTION AND SENSITIVITY ANALYSIS

To predict the PK of PCL nanocarriers, the results of both techniques were evaluated using the PBPK model. Further, a partial sensitivity analysis was conducted by varying the release rate (±10%).

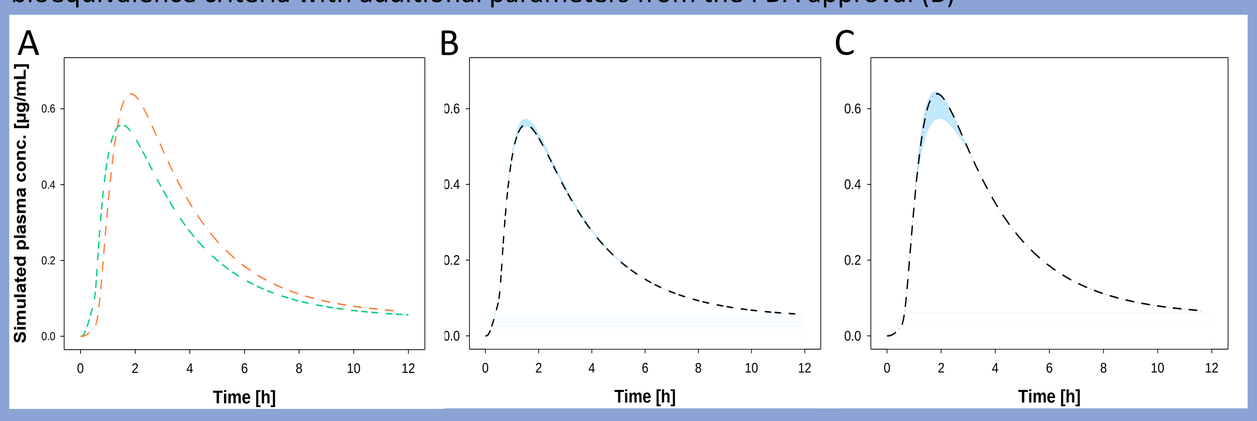

Fig. 3. Prediction for both techniques (A) and sensitivity of the PBPK model for *in vitro* changes: Filtration (B) and (C) Dispersion releaser

RESULTS

In *in vitro* studies, both methods led to a substantial drug release i.e. 91.0 ± 5.3 % for filtration and 100.9 ± 4.1 % for the DR technique respectively. During validation, the PBPK model was able to reflect the *in vivo* situation when compared with mean profile and bioequivalence criteria. Although with the *in silico* model, both techniques produced similar results, the release data obtained with the DR technique revealed higher sensitivity *in vitro* and in the simulated profiles as compared to filtration technique.

CONCLUSION

In summary, the filtration technique enables a rapid testing with suitable simulations in the early stages of research whereas the DR based simulations detected changes in the release rate more efficiently throughout the process. Therefore based on our results the DR technique proved to be more appropriate in formulation development and quality control as compared to the filtration technique. Furthermore PBPK modeling demonstrates itself as a useful tool to estimate the influence of minor changes in *in vitro* results on the actual *in vivo* performance.

References

[1] Fabian Jung and Lisa Nothnagel et al., A comparison of two biorelevant *in vitro* drug release methods based on advanced physiologically-based pharmacokinetic modelling, Eur J Pharm Biopharm , 2018 (in revision)

[2] A. Suri, B.L. Grundy, H. Derendorf, Pharmacokinetics and pharmacodynamics of enantiomers of ibuprofen and flurbiprofen after oral administration, Int J Clin Pharmacol Ther, 35 (1997) 1-8.

[3] U.S.F.a.D. Administration, Ansaid® (flurbiprofen tablets, USP) 50 mg and 100 mg in, 2010.