

Prediction of human pharmacokinetics of subcutaneously administered depot formulation using MBPK model

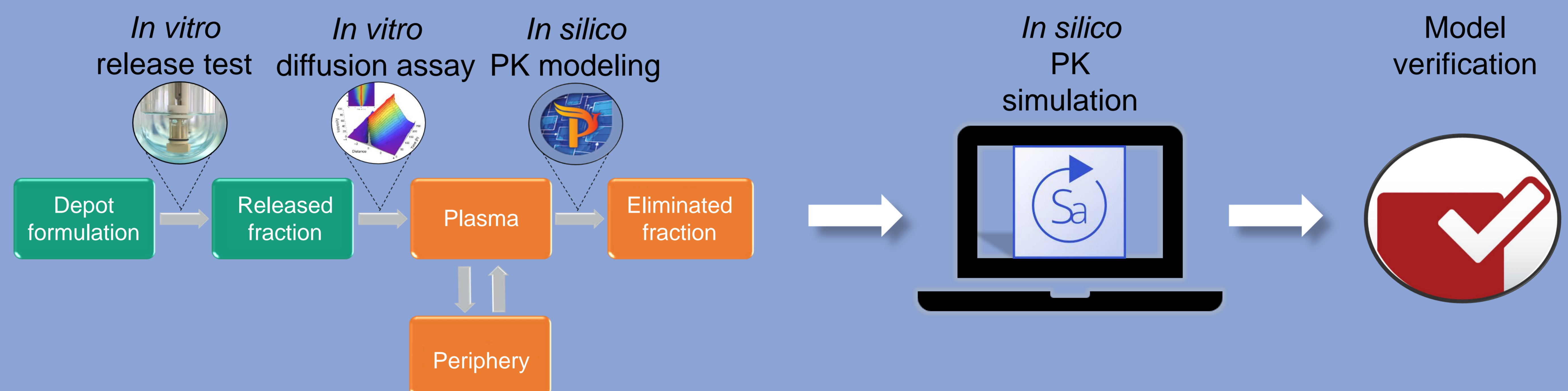
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OBJECTIVES

In silico pharmacokinetic (PK) simulation for subcutaneously administered depot formulation was developed through integrating relevant *in vitro* data into a mechanism-based pharmacokinetic (MBPK) model.

METHODS



RESULTS

In vitro Release

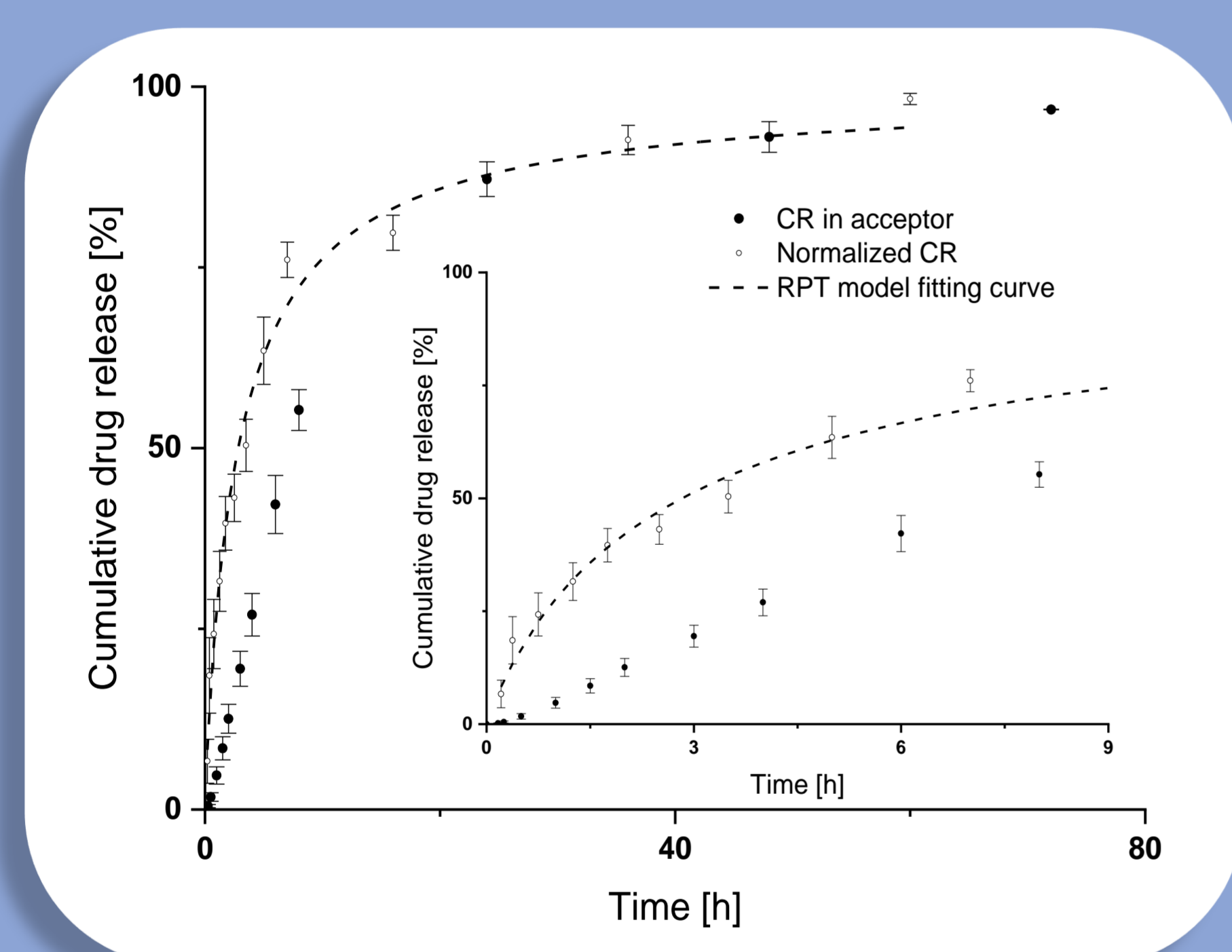


Figure 1. *In vitro* drug release. The release of Provera® was tested using a novel DR technique. The cumulative release was normalized according to the membrane kinetic model and fitted with reciprocal power time (RPT) model.

In silico Simulation

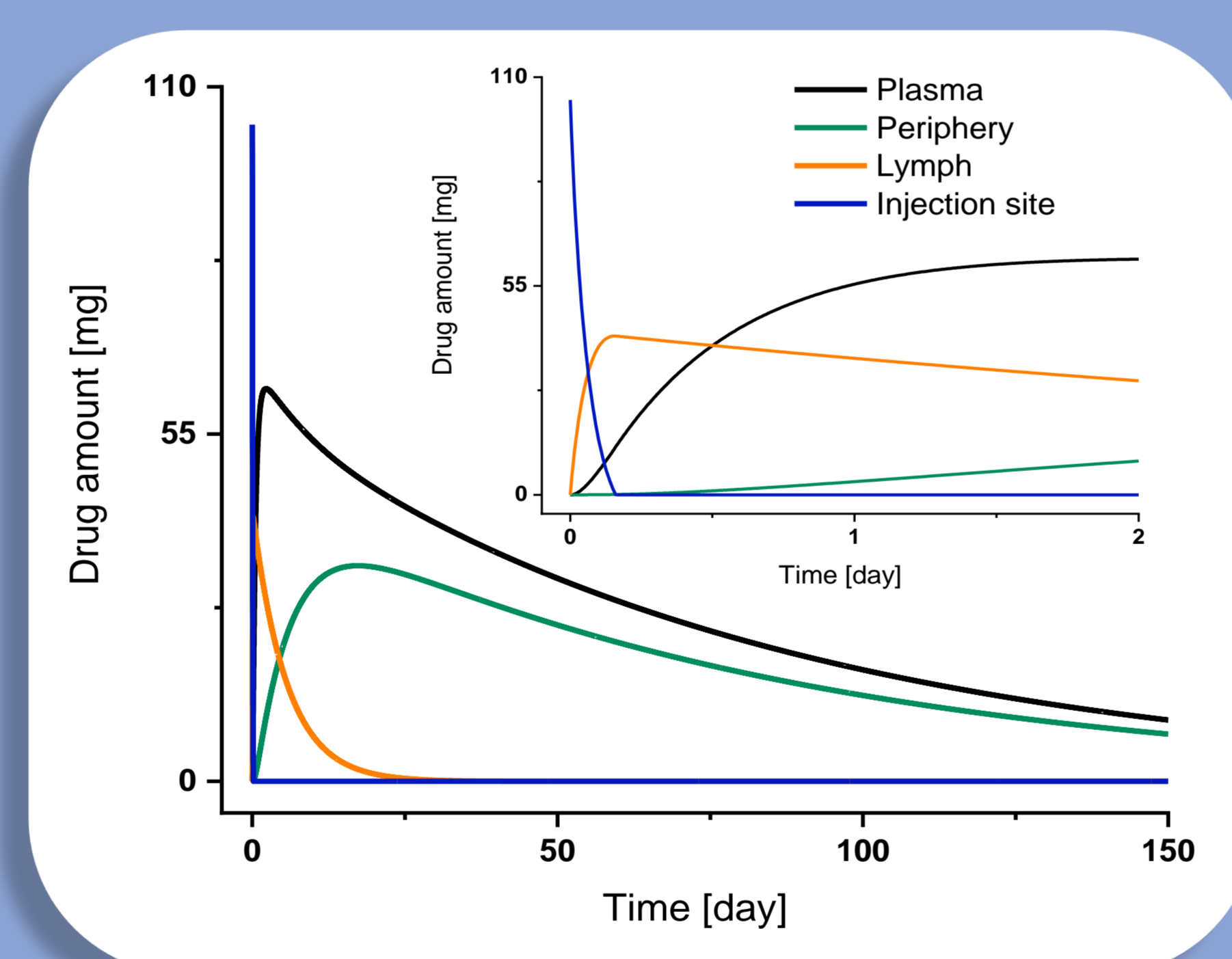


Figure 2. *In silico* simulated PK profiles. The whole process from drug injection to drug elimination was simulated with STELLA software. The amount of drug in different compartments at different time points after injection were predicted.

In silico – *in vivo* Correlation

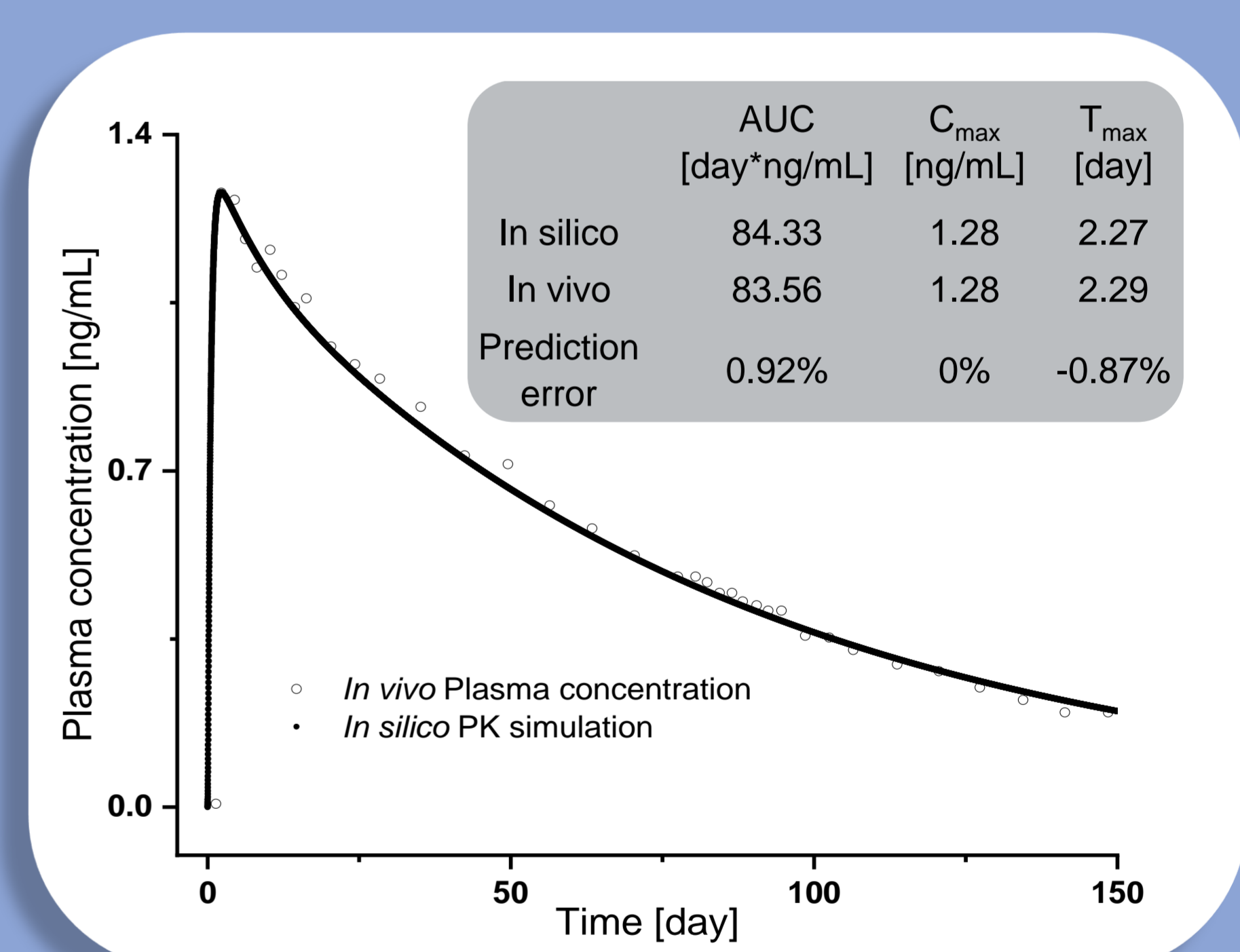


Figure 3. *In silico* – *in vivo* correlation. The simulated plasma concentration profile was compared with *in vivo* clinical data. AUC, C_{max} and T_{max} were also calculated to determine the *in silico* – *in vivo* correlation.

CONCLUSIONS

The release test with the patented Dispersion Releaser and agarose gel based diffusion assay were useful *in vitro* techniques to provide reliable parameters for PK modeling and simulation. The described multiple compartment MBPK model based simulation was able to predict the *in vivo* drug release, absorption, distribution, and elimination with high precision.

PERSPECTIVES

The market of subcutaneous depot formulation are quickly expanding, especially for the application of biopharmaceuticals. For detailed physiologically based pharmacokinetic (PBPK) modeling and simulation regarding these formulations, more PK processes should be described in appropriate mathematical language, such as degradation at injection site, diffusion through different pathway and even lymphatic uptake, etc.

REFERENCES

Janas, C., et al., *The dispersion releaser technology is an effective method for testing drug release from nanosized drug carriers.* Eur J Pharm Biopharm, 2017. 115: p. 73-83.

Sensitivity Analysis

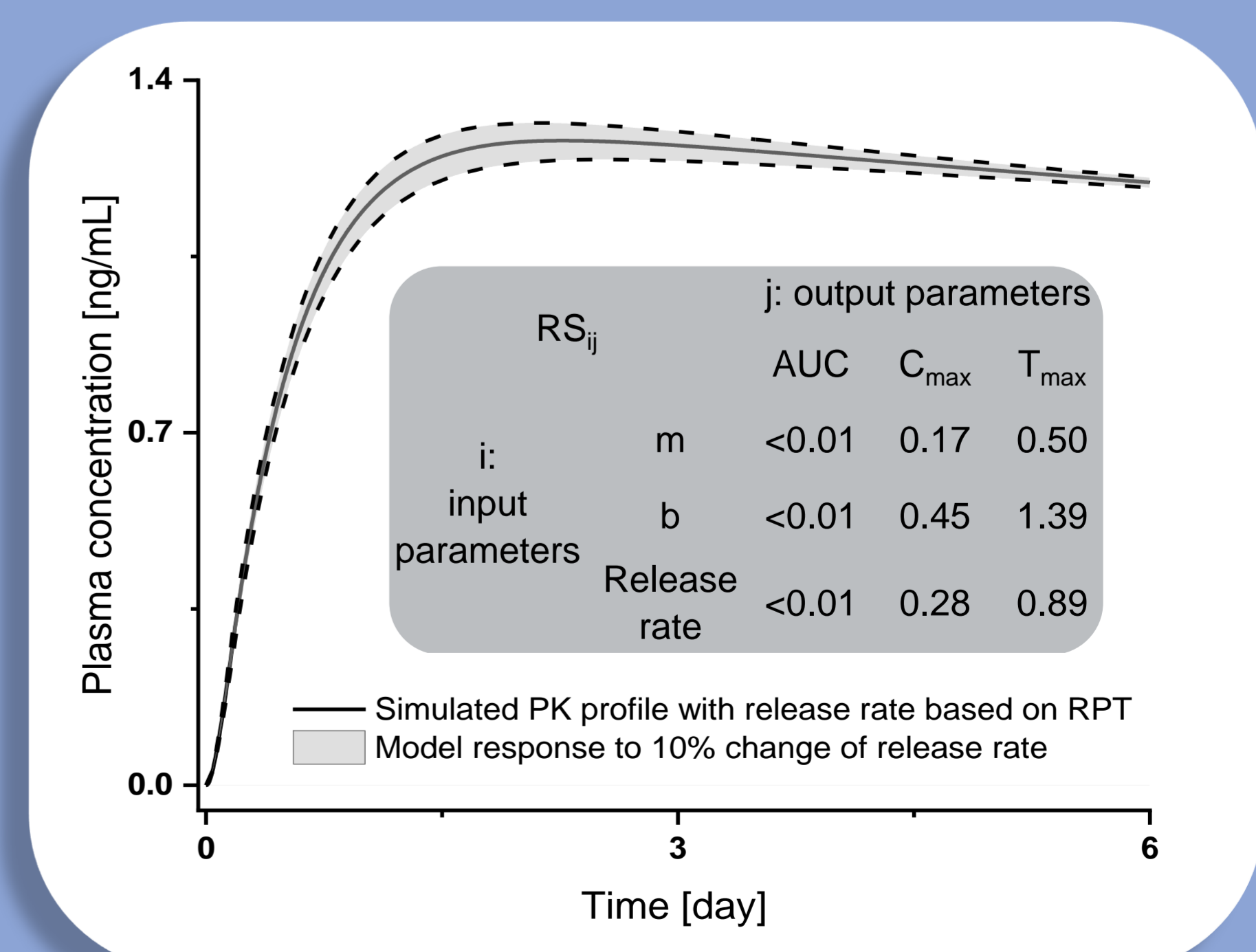


Figure 4. Local sensitivity analysis. The impact of release relevant parameters on PK was investigated. The normalized sensitivity coefficients were calculated using central difference method for sensitivity derivative. A relative sensitivity value of output parameter j to the input parameter i of less than 0.1 indicates insignificant influence.