EVALUATION OF A MINIMAL WB-PBPK PLATFORM SUPPORTING DIFFERENT ROUTES OF ADMINISTRATION

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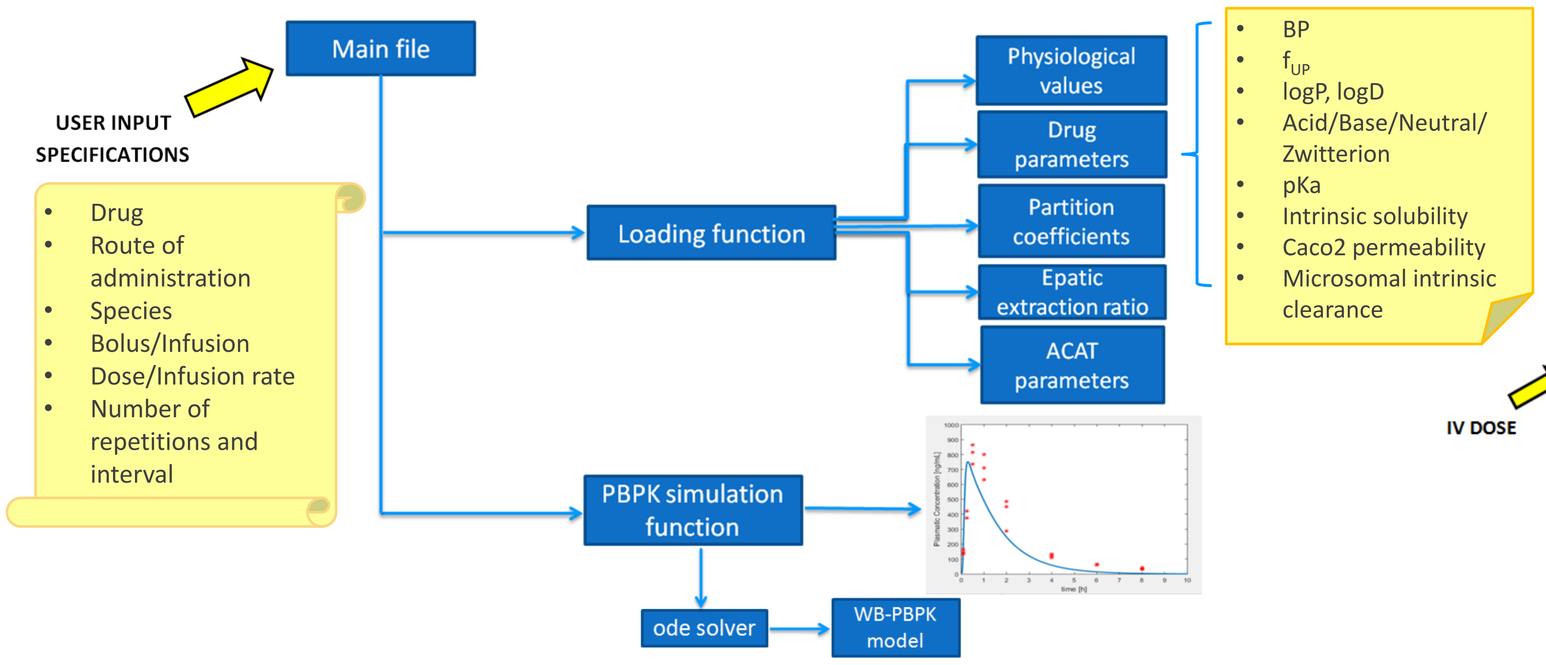
OBJECTIVES*:* to assess in different species a minimal whole-body (WB) PBPK platform, implemented in Matlab from literature information, able to predict, from physiological literature parameters [1] and drug *in vitro* data, concentration-time profiles of drugs administered following two different routes of administration: intravenous (IV) and oral (PO), with single dose or multiple doses schedules.

METHODS*:* the WB-PBPK model was built considering twelve tissue compartments plus the ACAT model to describe the PO administration. No enzymatic reactions were explicitly modelled.

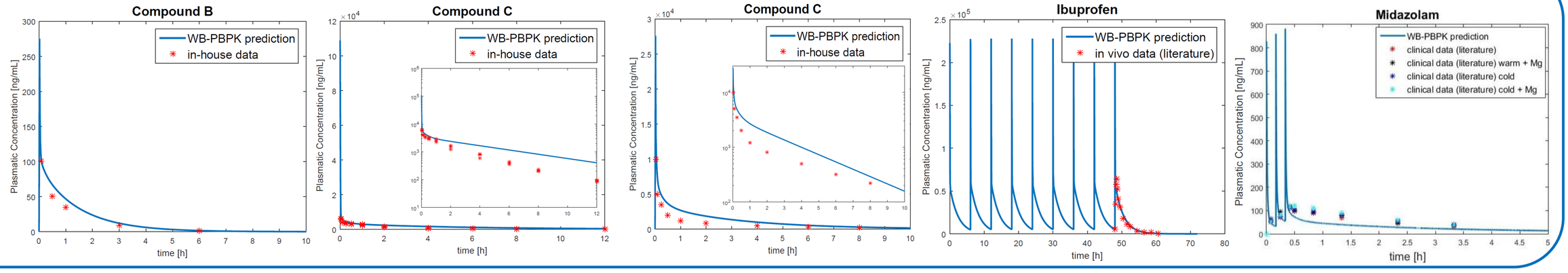
The tool implemented allows three main tasks: simulation, estimation and sensitivity analysis. In the main file the user can specify the information to perform a new experiment, in a drug file the drug-related parameters.

Two different strategies to calculate the partition coefficients were considered and are available: one based on the work of Poulin et. al [2] and the other based on Rodgers et al. [3],[4]. The value of the Caco2 permeability must be specified to allow the calculation of the absorption parameters of the ACAT model. A function to compute the hepatic extraction ratio using the intrinsic microsomal clearance as input value is also included.

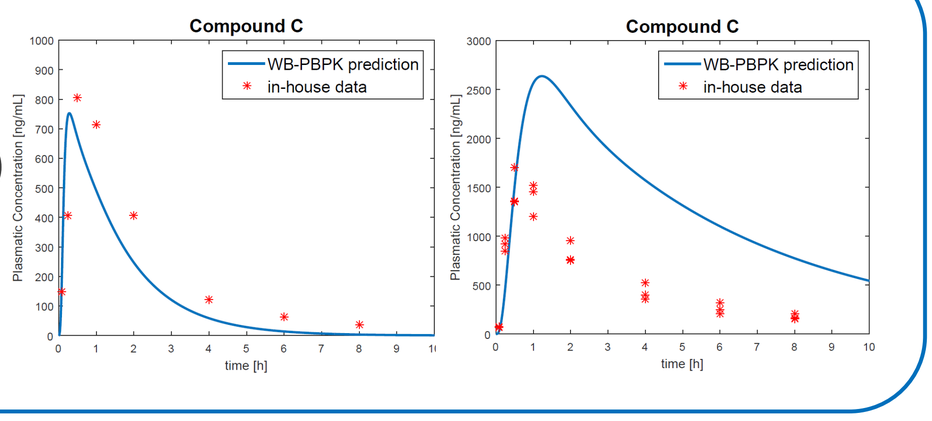


RESULTS: the platform was assessed on 14 different compounds, with different physico-chemical characteristics and pharmacodynamic action, given IV and PO to rats, dogs and humans, by using in-house data and several clinical studies available in the literature, some of them report both *in vivo* measurements and *in silico* profiles, certain obtained with the GastroPlus software.

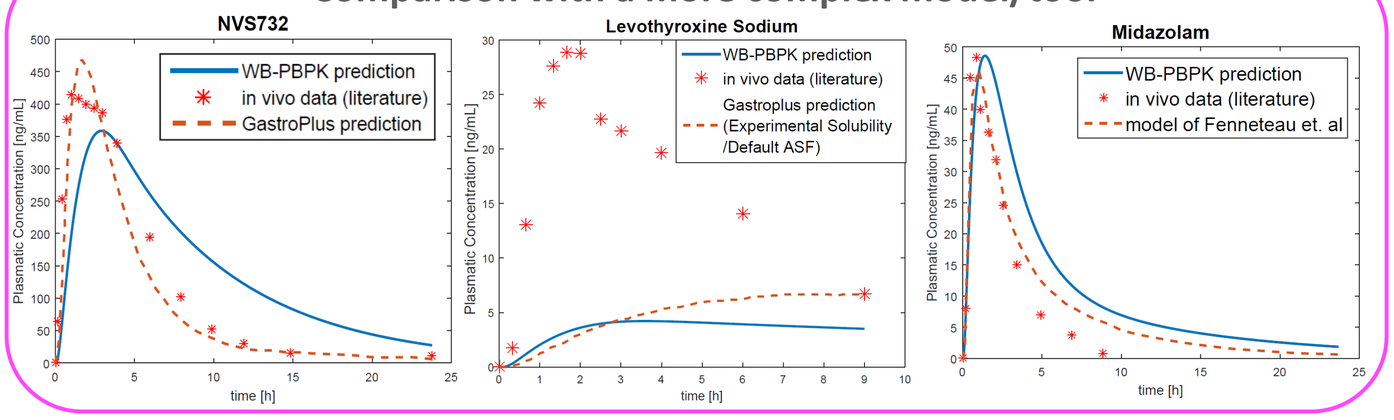
IV



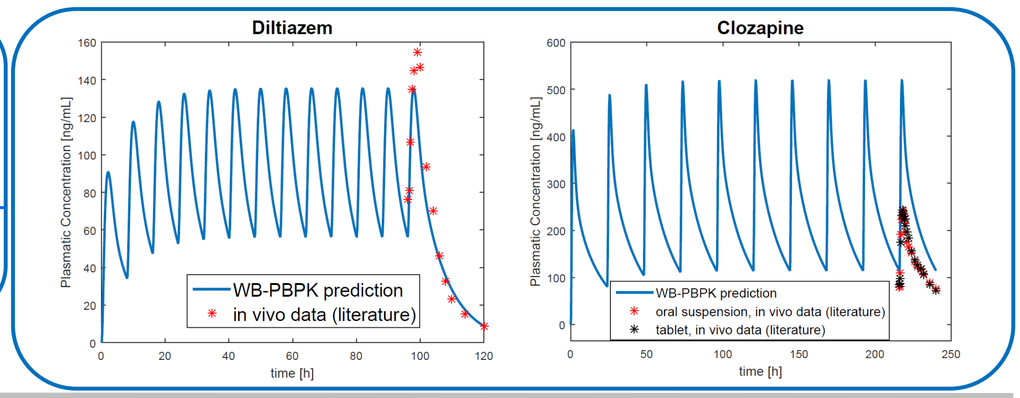
PO



Comparison with a more complex model/tool



Number of compounds	Acids	Bases	Neutrals	Zwitterions	Compounds whose **AUC is in the two-fold range**	Compounds whose **Cmax is in the two-fold range**
14	1	9	1	3	11/14	9/14



CONCLUSIONS: the implemented minimal WB-PBPK platform, while requiring few basic *in vitro* information for simulating a new experiment, is able to reasonably describe both the in-house data and those reported in the selected literature studies. Moreover its performances are comparable, for the cases examined, to those of a more sophisticated PBPK model and modelling tool, such as GastroPlus.

REFERENCES: [1] Brown R.P et al., Physiological parameter values for physiologically based pharmacokinetic models. Toxic and Ind Health (1997)
[2] Poulin P., Theil FP., Prediction of pharmacokinetics prior to in vivo studies: I. Mechanism-based prediction of volume of distribution. J Pharm Sci (2002)
[3] Rodgers T. et al., Physiologically based pharmacokinetic modeling: predicting the tissue distribution of moderate-to-strong bases. J Pharm Sci (2005)
[4] Rodgers T., Rowland M., Physiologically based pharmacokinetic modelling: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. J Pharm Sci (2006)