In Vitro / In Vivo Extrapolation (IVIV_E) of API Dissolution within a PBPK Framework

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Purpose & Background

It is important to have a reliable approach to translate *in vitro* product dissolution assessment to *in vivo* situations. We propose a new mechanistic *In vitro-In vivo* Extrapolation (IVIV_E) approach for low solubility drugs as a way to improve the predictions within a Physiologically based pharmacokinetic (PBPK) modelling framework.

Mechanistic modelling of *in vitro* dissolution experiments can provide assessment of the: (1) validity of the dissolution model and its assumptions for the studied formulation; (2) quality and relevance of input parameters such as particle size; (3) refinement of unknown or uncertain parameters if required. These refined parameters then can be input to PBPK models to predict luminal dissolution with prior knowledge of luminal physiological parameters *viz*. pH, bile salt concentration, fluid velocities and fluid volumes. This approach is a rational framework for translating *in vitro* dissolution to *in vivo* rather than assuming (or requiring) that *in vitro* dissolution rates are equivalent to *in vivo* where the environment is significantly variable and changes as drug product transits down GI tract; 3 examples are given.

Method

The Enhanced Fluid dynamics (EFD) model, implemented in SIVA v1.0 (*Simcyp In Vitro Analysis* toolkit) and the Simcyp Simulator v15, is a mechanistic approach to modelling fine particle dissolution based on fluid dynamics theory[1]. The model is used herein to simulate dissolution in the USP 2 paddle apparatus so as to test its parameters (solubility, particle size, *etc.*) and assumptions prior to using the same structural model for simulations of *in vivo* dissolution while accounting for the different conditions (pH, water volumes, *etc*.) and their population variability *in vivo*. This IVIV_E approach was tested using three model drugs felodipine, digoxin and danazol immediate release formulations.

Results

Felodipine

The EFD model predicted well the dissolution of 13-µm aggregate particles of felodipine in the USP 2 paddle apparatus *only* where a scalar (the Diffusion Layer Model scaler *DLMs)* estimated from the data is applied (*DLMs* = 0.49 @ 25 RPM; 0.31 @ 200 RPM) to account for particle agglomeration (primary particle radius is 3.9 µm). Based on felodipine prediction, the hydrodynamics effect on the dissolution in the USP 2 paddle apparatus is compared with that in the GI tract (Figure 2). The hydrodynamics effect in USP 2 at 50 rpm is similar to that in the stomach.

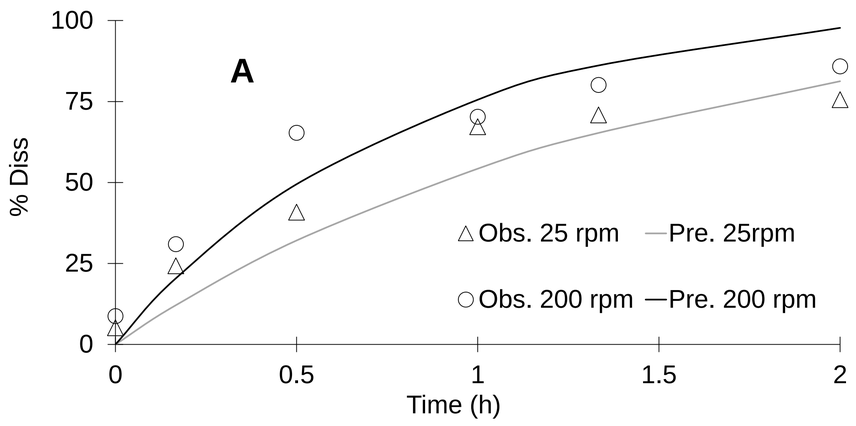

Figure 1: (A) Observed & simulated dissolution profiles of aggregate Felodipine (particle size: 13 µm) at 25 and 200 rpm. (B) observed, simulated and fitted dissolution profiles of primary felodipine (particle size: 3.79 µm) at 25 and 200 rpm. A DLMs of 0.485 and 0.308 were used to fit 25 and 200 rpm, respectively.

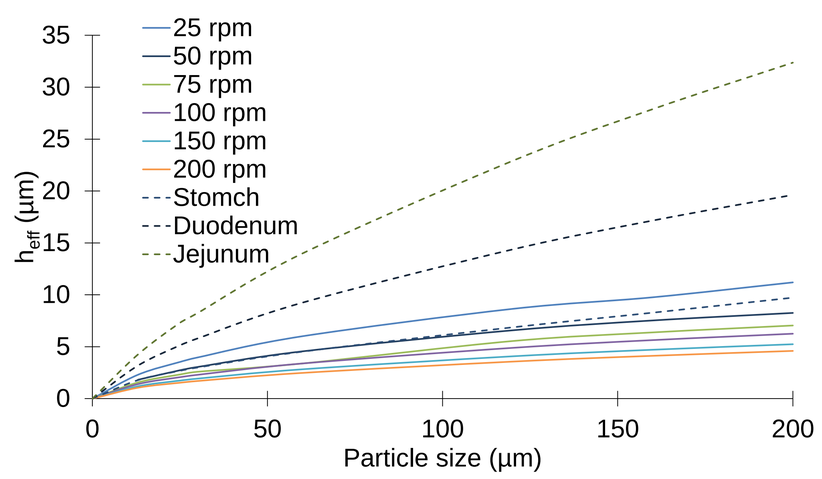

Figure 2: Simulated diffusion layer thickness (h_{eff}) in USP 2 paddle apparatus and *in vivo* stomach, duodenum and jejunum vs. particle size using an EFD model.

Digoxin

With digoxin the experimental *in vitro* dissolution profile in 0.1 M HCL at pH 1.2 at 100 rpm in the USP 2 paddle apparatus is accurately predicted with prior knowledge of particle size and solubility without parameter estimation (Fig. 3). This figure illustrates the mean simulated and observed dissolution profile of digoxin in aqueous buffer pH 1.2, indicating that the EFD model can be used to predict drug dissolution in the USP 2 paddle apparatus. Digoxin degrades in an acid environment, hence the observed % dissolved (69%) is lower than the predicted (94%) after 30 mins. This instability of digoxin is likely partly the reason for the high variability (CV=20%) of the observed *in vitro* dissolution profiles. The predicted *in vivo* dissolution profile based on the EFD model is comparable to the mechanistic deconvoluted *in vivo* dissolution profile from the observed digoxin plasma concentration.

Acknowledgments

The authors wish to acknowledge the clinical danazol data provided by Anette Mullertz, Department of Pharmacy, University of Copenhagen, Denmark

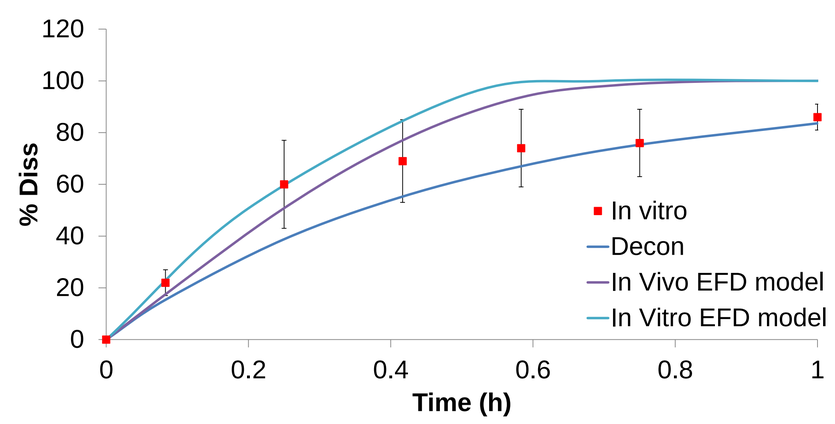

Figure 3: Deconvoluted in vivo dissolution profile from observed drug plasma concentration, observed in vitro dissolution profile at 100 rpm, simulated in vitro dissolution profile using EFD model and simulated in vivo dissolution profile using EFD model.

Danazol

The danazol study required a *DLMs* of 0.18 to model the *in vitro* profile due to the significant time associated with breakdown/disintegration of the capsules which is not independently characterised from particle dissolution. The predicted danazol C_{max} and $AUC_{0\text{-}24}$ are 0.02 mg/L and 0.13 mg/L.h respectively, which is comparable to the observed average C_{max} of 0.03 mg/L and $AUC_{0\text{-}24}$ of 0.14 mg/L.h. However, the predicted C_{max} and $AUC_{0\text{-}24}$ are 0.02 mg/L and 0.18 mg/L.h, if the *DLMs* is 1.

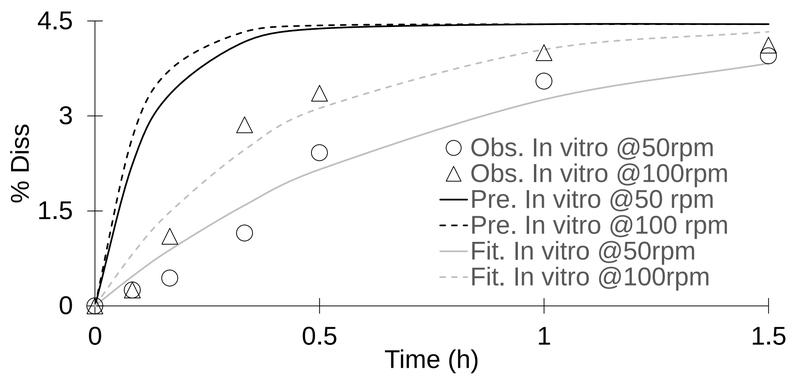

Figure 4: Danazol dissolution in USP 2 paddle apparatus in FaSSIF dissolution medium at 50 and 100 rpm

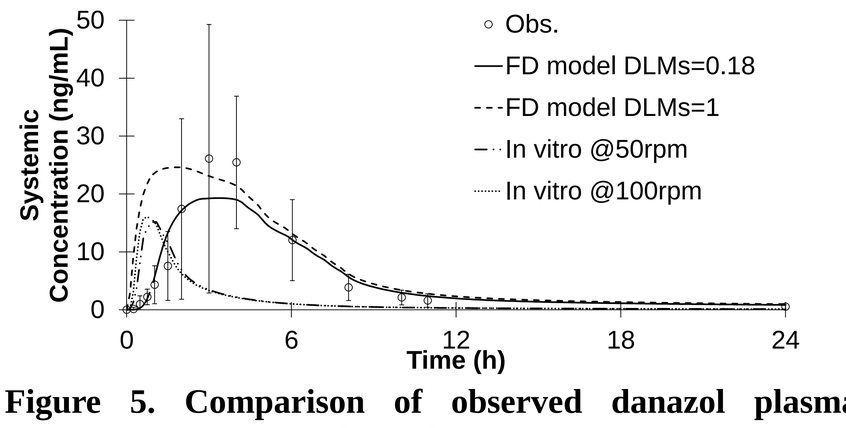

Figure 5. Comparison of observed danazol plasma concentration and predicted by EFD model with DLMs of 0.18 and 1 as well as predicted data using dissolution profile in USP 2 paddle apparatus at 50 and 100 rpm as input function of PBPK model.

Conclusion

This study suggests that *in vitro* dissolution profiles in the USP 2 apparatus can be modelled well with the EFD provided that disintegration and/or particle agglomeration do not play a significant role. In these cases it would be useful to have experimental characterisation of these two aspects in order separate out the processes in a non-ambiguous manner. However, parameters estimated or verified from the *in vitro* studies can improve predictions of *in vivo* dissolution within a PBPK model framework thus providing a step toward better IVIVE of dissolution.

Reference: Liu, B et al. ms. in preparation.