Mechanistic *In Vitro-In Vivo* Extrapolation (IVIV_E) of Dissolution within a PBPK Framework: Extrapolation of IR Danazol Dissolution in the USP-2 paddle apparatus to *In Vivo* Dissolution

B. Liu[1], N. Patel[1], S. Pathak[1], A. Rostami-Hodjegan[1,2], M. Jamei[1], D.B. Turner[1]

1.Simcyp Limited (a Certara Company), Sheffield, UK; 2. Manchester Pharmacy School, the University of Manchester, UK

INTRODUCTION

In vitro dissolution studies of oral immediate release (IR) formulations are performed for various reasons including anticipation of *in vivo* behaviour. The hydrodynamics of the USP-2 dissolution apparatus are well-known not to match those of the small and large intestines, the main dissolution sites of IR BCS II/IV drugs. Furthermore, *in vitro* conditions differ from *in vivo* with respect to fluid volumes, pH, [Bile Salts], sink *vs*. non-sink conditions *etc*. Thus, *in general*, direct transfer of USP-2 dissolution rate into *in vivo* simulations may poorly represent *in vivo* dissolution rate. This is complicated where fine particles disperse over time (transit) and thus are dissolving simultaneously in different environments (pH, [Bile Salt] *etc*.). Mechanistic models coupled with appropriate descriptions of the *in vitro* or *in vivo* environments can be assessed/parameterised against *in vitro* dissolution data and applied to *in vivo* simulations with more confidence. In this study we model *in vitro* dissolution of a danazol IR formulation and demonstrate that this can inform the modelling of *in vivo* dissolution, a process referred to as *In Vitro-In Vivo* Extrapolation (*IVIV_E*) of dissolution; validation is via an *IVIVC* approach.

METHODOLOGY

The Simcyp *In Vitro* (data) Analysis (SIVA) toolkit v1.0 was used to model the dissolution of IR danazol (USP-2, 50 and 100 rpm, FaSSIF medium); Table 1 indicates some of the input parameters. The toolkit permits evaluation of dissolution model performance and provides parameter estimation (PE) tools which can, if required, be used to estimate parameters in which there is low confidence and/or a global scalar (*DLMs*) which amongst other factors can account for shape factor effects. PE can be applied to single experiments or simultaneously across multiple experiments (same formulation, different conditions (medium, rpm *etc.*)). Estimated scalars were input into the Simcyp Population-based Simulator to model *in vivo* dissolution taking into account *in vivo* conditions and their regional, temporal and inter-individual variability. The simulated *in vivo* and experimental *in vitro* dissolution profiles were separately correlated with *in vivo* dissolution deconvoluted from the observed plasma-concentration profile using the Simcyp Physiologically-Based *IVIVC* module.

Table 1: Some of the parameters used in SIVA and Simcyp Simulator modelling.

Molecular Weight (g/mol)	337.5	Aqueous diffusion coefficient (10^{-4} cm^2/min)	4.8	Volume of distribution (L/kg) (full PBPK model)	2.0
Solubility in FaSSIF / Intrinsic solubility (µg/mL)	8.4 / 0.74	Particle size (µm) (monodisperse)	22	Clearance: HLM CYP 3A4 CL_{int} (µL/min/mg protein)	42.0
Particle density (mg/mL)	1.2	Dose (mg)	100	Clearance: HLM CYP 2D6 CL_{int} (µL/min/mg protein)	6.8
P_{eff},man (10^{-4} cm/s)	2.05	Log of the Micelle:buffer Partition Coefficient	5.3	Clearance: Additional Undefined Clearance (L/h)*	22.3

* Estimated from an IV clinical study

RESULTS

Mechanistic modelling (1) of *in vitro* danazol dissolution in the USP-2 using SIVA indicated the need to estimate a scaling factor (*DLMs)* (Figure 1); a value of 0.60 (100 rpm study) was obtained. This scalar was input to the *in vivo* dissolution models of the Simcyp Simulator. The *IVIVC* (Figure 2) based upon mechanistic *IVIV_E* of dissolution has an R^2 of 0.94 while those based upon the *in vitro* dissolution profiles were 0.52 and 0.76 (significant deviation from linearity); where the *DLMs* correction (estimated from *in vitro* modelling) was not applied the derived *IVIVC* deviated further from linearity than if the estimated *DLMs* is applied (R^2 is similar).

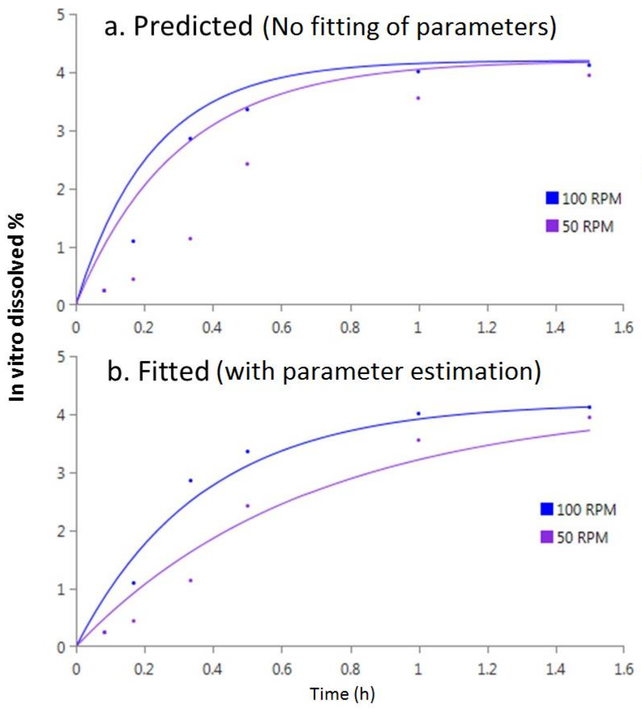

Figure 1 (left): *In vitro* dissolution rate in the USP-2: a) Simulated profiles; b) Simulated profiles with an estimated *DLMs* scalar.

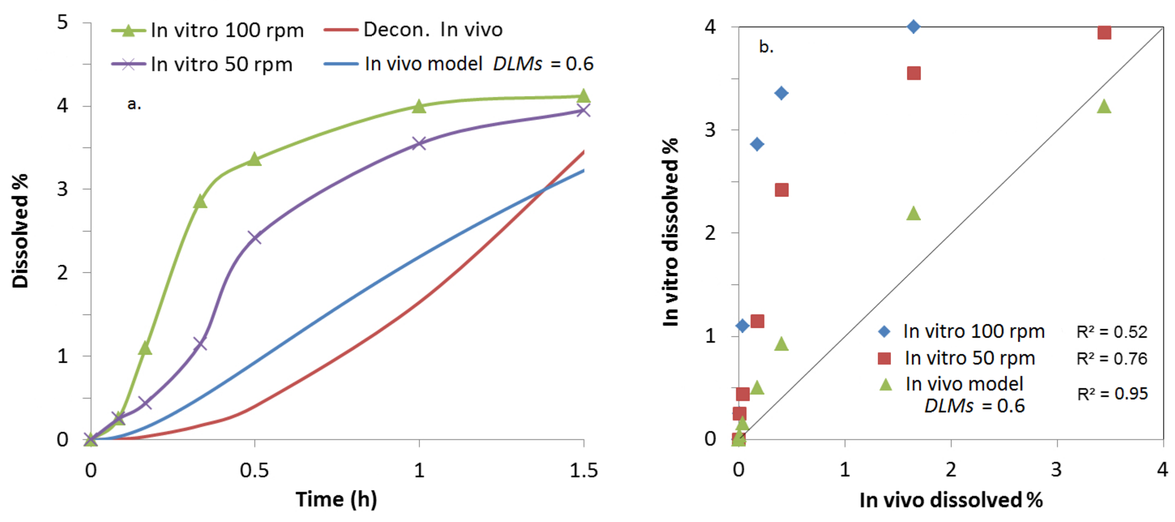

Figure 2: a) *In vitro* and in vivo dissolution profiles; b) IVIVC analysis with squared correlation coefficients between a profile deconvoluted from clinical data and the in vitro and in vivo predicted profiles.

These results demonstrate that, for the studied formulation, the *In Vitro-In Vivo Extrapolation* (*IVIV_E*) approach to modelling *in vivo* dissolution provides significantly better results (assessed via *deconvolution* from clinical data) than direct input of *in vitro* dissolution profiles to *in vivo* simulations. A scalar (the *DLMs*) derived from *in vitro* modelling improves *in vivo* prediction.

SUMMARY:

The described approach, referred to as *IVIV_E* of dissolution within a PBPK framework, can be used to account for known differences between *in vitro* and *in vivo* hydrodynamics, fluid volumes, pH, [Bile Salts], sink vs. non-sink conditions *etc*. An example has been provided based upon an immediate release formulation of the BCS II drug danazol. This approach can be used to add value to USP 2 dissolution studies routinely carried out within the pharmaceutical industry potentially obviating the need for more complex *in vivo*-like *in vitro* experimental set-ups. However, further work with a wide range of compounds is required to validate the approach.

References: 1) B. Liu, M. Jamei, A. Rostami-Hodjegan, D.B. Turner; Toward 'translating' in vitro dissolution to in vivo dissolution: a particle motion model to predict drug dissolution rate in the USP 2 paddle apparatus; 9th World meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, 2014, Lisbon; **2)** Liu *et al.* ms. In preparation.

orbito Innovative Tools for Oral Biopharmaceutics

imi innovative medicines initiative efpia