Prediction of Diclofenac Pharmacokinetics using Early Drug Discovery *In Vitro* Data in a Mechanistic Dog Physiologically-Based Pharmacokinetic Model - 'Simcyp Dog'.

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Introduction

Beagle dogs are used as a surrogate for human testing in toxicity of drugs and chemicals and specifically as a model for assessing oral drug absorption. ***Simcyp Dog V3.0*** is an *in silico* physiologically based absorption, distribution, metabolism and excretion Simulator. The model provides a platform and database for mechanistic modelling and simulation of the processes of oral absorption, tissue distribution, metabolism and excretion of drugs in a ***10kg 'virtual' beagle dog***. It combines experimental data generated routinely during preclinical drug discovery and development from *in vitro* enzyme and cellular systems, and relevant physicochemical attributes of compound and dosage form to predict the fate of the drug *in vivo* in beagle dogs used routinely as a pre-clinical model in drug discovery.

Purpose

To evaluate the performance of ***Simcyp Dog V3.0*** to predict the ***Plasma Concentration-Time Profile*** of ***Diclofenac*** using Physico-Chemical and ***In Vitro Dog Liver Microsomal Metabolism Data***.

Methods

Simcyp Dog V3.0 was used to predict the Plasma Concentration-Time profiles for an Orally administered Immediate Release formulation of Diclofenac in a 10kg 'virtual' beagle dog. The simulated trial was based on an *in vivo* trial[1] comprising *n*=6 beagle dogs orally administered a conventional diclofenac tablet. Simcyp Dog V3.0 utilised *In Vitro* Dissolution data (Figure 1) at pH 4 and pH 6.8 provided within the *in vivo* study with the Advanced Dissolution Absorption and Metabolism model (ADAM), the Physico-Chemical data for diclofenac such as LogP used to predict drug absorption and tissue distribution (Rodgers & Rowland Method), and kinetic metabolic data 'intrinsic clearances (CL_{int}) generated in Dog Liver Microsomes. This data is routinely generated in an Early Drug Discovery setting and the principle of *In Vitro In Vivo* Extrapolation *(*IVIVE)[2] was applied. A gastric pH of 5.3 used within the dog model was the value measured within the *in vivo* trial. The other key simulation parameters are provided in Table 1.

Table 1. Key Simulation Parameters

Parameter	Description/Value
Dose (mg)	37.5mg, Single
Dose Route	Oral
Log P	4.5
fup	0.003
B/P	0.61
Log P predicted Dog P_{eff} (Jejunum I) (10^{-4} cm/sec)	4.08
ADAM - Formulation	Immediate Release
ADAM – Dissolution Profile	Gastric and SI profiles (Fig 1).
Vss - PBPK – Method 2 (L/kg)	0.159
CL_{po} (CL_{iv}/F) (mL/min)	11.69
Microsmal CL_{int} (uL/min/mg)	237
Gastric pH	5.3
Gastric Emptying Rate (h)	0.87
SI Transit (h)	2.39

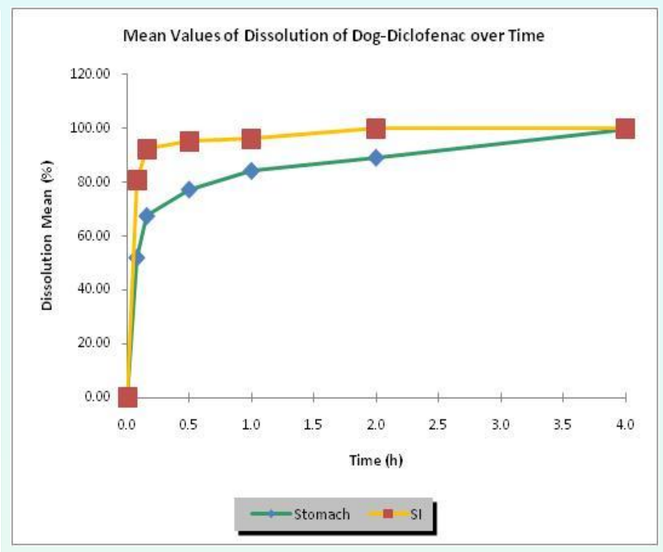

Figure 1. *In vitro* dissolution profiles for both stomach (pH 4) and small intestine (SI) (pH 6.8) used within the ADAM model in Simcyp Dog simulations.

Results

Figure 2 shows that simulations utilising an *in vivo* CL_{po} (CL_{iv}/F) and microsomal CL_{int} (IVIVE), successfully capture the *in vivo* profiles and that these profiles fall within the variability (deviation bars) of the *in vivo* study. The majority of the *in vivo* time points fall within the 5th and 95th centiles simulated by Simcyp dog.

The predicted PK parameters fall between a range of 0.83 and 1.33 fold different to those values calculated *in vivo* (table 2) for both *in vivo* CL_{po} and microsomal CL_{int} simulations, with the Mic CL_{int} simulation providing an AUC 0.96 fold that of the *in vivo* trial. Using only *in vitro* data routinely generated in an early drug discovery setting, the Mic CL_{int} simulation shows that it is possible to predict an *in vivo* diclofenac concentration time profile in a 'virtual' beagle dog successfully.

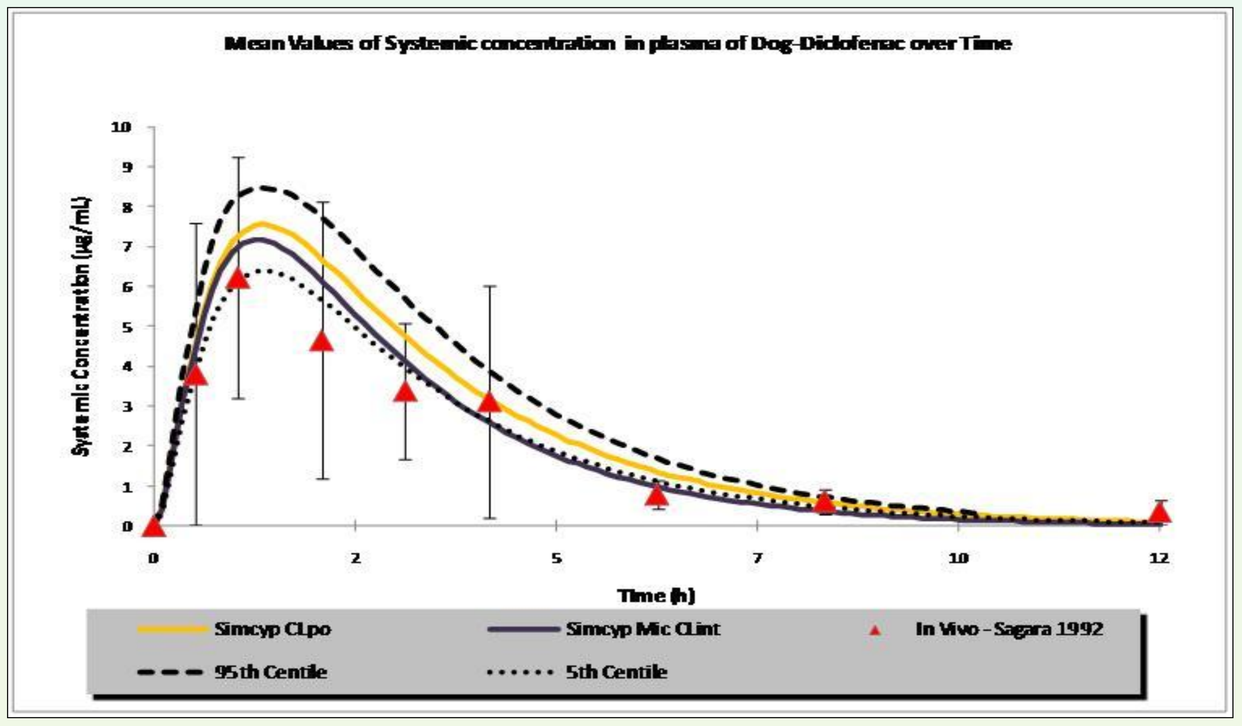

Figure 2. Diclofenac plasma concentration time profiles for the *in vivo* study (triangles) and Simcyp Dog simulations using oral clearance (Simcyp CL_{po}, yellow line) and intrinsic clearance ($CL\text{-}_{int}$) from dog liver microsomes (Simcyp Mic CL_{int}, purple line), the - - - - dashed line, reflects the 95th centile profile for Simcyp dog simulations (*n*=6) and the ····· dotted line, reflects the 5th centile profile for Simcyp dog simulations (*n*=6). Each *in vivo* point reflects the mean ± standard deviation.

Table 2. Summary of pharmacokinetics parameters for the *in vivo* study and Simcyp Dog simulations using oral clearance (Cl_{po}) and intrinsic clearance (CL_{int}) from dog liver microsomes (and CV% (within parentheses) .

	T_{max} (h) (CV%)	Fold (*In Vivo*/Simcyp)	C_{max} (µg/mL) (CV%)	Fold (*In Vivo*/Simcyp)	AUC (µg/mL/h)	Fold (*In Vivo*/Simcyp)
In Vivo	**1.6 ± 1.3 (81%)**	**-**	**8.1 ± 3.4 (42%)**	**-**	**23.6 ± 7.7 (33%)**	**-**
Simcyp - CL_{po}	**1.3 ± 0.09 (7%)**	**1.23**	**7.56 ± 0.94 (12%)**	**1.07**	**28.6 ± 3.81 (13%)**	**0.83**
Simcyp - Microsomal CL_{int}	**1.2 ± 0.13 (11%)**	**1.33**	**7.17 ± 0.89 (12%)**	**1.13**	**24.6 ± 3.28 (13%)**	**0.96**

References

1. Sagara *et al* 1992, *Chem Pharm Bull*, 40(12), 3303-3306
2. Gibson G. G. & Rostami-Hodjegan 2007, *Xenobiotica*, Oct-Nov; 37 (10-11): 1013-1014.