A MECHANISTIC PHYSIOLOGICALLY-BASED PHARMACOKINETIC (PBPK) MODEL TO PREDICT THE PHARMACOKINETICS OF R/S-OXAZEPAM AFTER ORAL DOSING

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Introduction:

R/S-Oxazepam (**OXZ, Figure 1**) is a well-known benzodiazepine used to treat anxiety disorders or alcohol withdrawal symptoms. It is primarily metabolised by several UDP-glucuronosyltransferase (UGT) enzymes. OXZ is a moderately soluble (intrinsic solubility 22 μg/mL), weakly basic drug (pKa 1.5) which may be susceptible to precipitation in the duodenum potentially impacting its rate/extent of absorption.

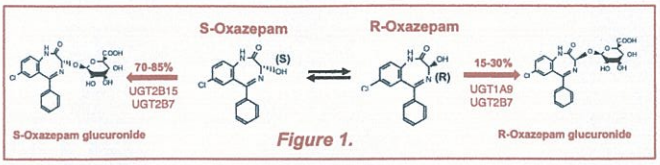

Figure 1.

Objectives:

1. Develop a mechanistic PBPK model to predict the PK of OXZ after oral administration of a 15 mg immediate release (**IR**) dosage form.
2. Evaluate the influence of drug-formulation properties: supersaturation ratio (**SSR**), precipitation rate constant (**PRC**) and particle size distribution (**PSD**) on the predicted PK of OXZ using the mechanistic PBPK model.

Methods:

- Simcyp Simulator Version 14 (Sheffield, UK) which incorporates PBPK models of absorption and disposition was used for simulations and sensitivity analysis (**SA**). The 'MechPeff' model included in the Advanced Dissolution, Absorption and Metabolism (ADAM) model was used to predict effective regional intestinal permeability (x 10^{-4} cm/s) as follows: Duodenum: 3.23; Jejunum I: 8.67; Jejunum II: 5.20; Ileum I-IV: 1.5; Colon: 0.88. Simulated plasma concentration time profiles (10 trials x 30 subjects) were compared with clinical data from He *et al.*, 2009 [1].
- Trial design specifics and model input parameters are shown in **Table 1**.

Table 1. Trial design specifics and model input parameters

PARAMETER	VALUE
Mol. Wt. (g/mol)	287
log $P_{O/W}$	2.37
pKa (type)	1.5 (basic)
Blood-to-plasma ratio	1.11
Plasma fu	0.048
V_{SS}, predicted (L/kg)	0.53 (Rodgers & Rowland method)
Solubility @ pH 7.4 (mg/mL)	0.022
Particle size range (μm)	3 - 25 (arith. mean = 11)
Regional gut wall permeability ($P_{eff,man}$) (10^{-4} cm/s)	Predicted using 'MechPeff'
Fraction unbound in gut enterocyte	0.034 (Prediction model in Simcyp v14)
Renal clearance (L/h)	0.38
$CLint_{UGT2B15}$ (S) (μL/min/mg protein)	3.67
$CLint_{UGT2B7}$ (S) (μL/min/mg protein)	0.034
$CLint_{UGT2B7}$ (R) (μL/min/mg protein)	0.084
$CLint_{UGT1A9}$ (R) (μL/min/mg protein)	0.428
Trial Design	Healthy Male Volunteers; 10 Trials x 30 Subjects; Age 18-45 years [1]
Formulation	IR [1]
Trial Duration (h)	48
Fluid with dose	250 mL water [1]
Fasted / Fed Status	Fasted Gut Physiology (pH, bile salts, gastric emptying, basal fluid volumes) [4]

Intrinsic Clearance (CLint) obtained using the retrograde approach and utilising clinical metabolic and renal clearance values[2-3].

- To evaluate the influence of the drug-formulation properties (SSR and PRC) on the predicted PK of OXZ, SA was performed within the following ranges for the respective parameters: SSR: 1-20 with PRC: 4 or 0.01.
- OXZ simulations were also run with monodispersed particle size of 11μm to evaluate the need to model polydispersity.

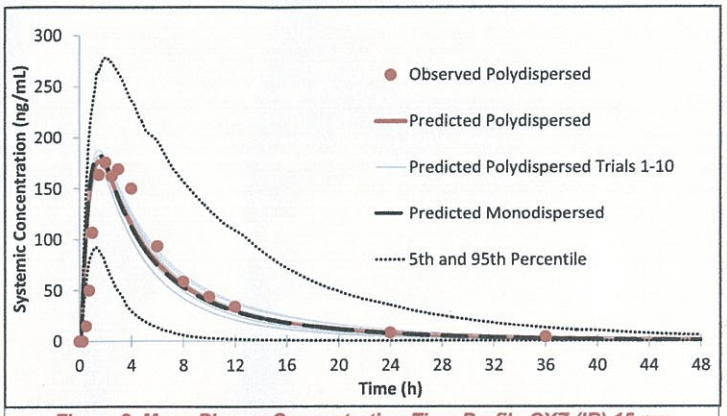

Figure 2. Mean Plasma Concentration-Time Profile OXZ (IR) 15 mg

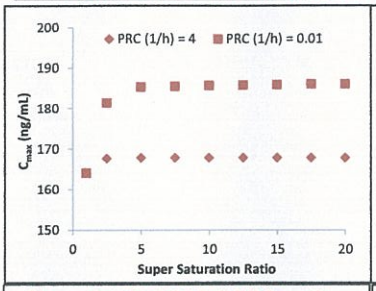

Figure 3. SA of SSR & PRC on C_{max}

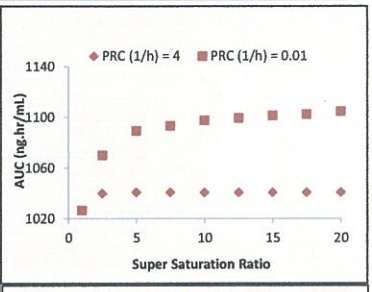

Figure 4. SA of SSR & PRC on AUC

Table 2. PK parameters for an IR formulation of OXZ

OXZ Formulation	T_{max} (h)	C_{max} (ng/mL)	AUC_{0-t} (ng.h/mL)
Observed (Polydispersed 3-25 μm; IR)	2.16	179	1401
Predicted (Polydispersed 3-25 μm; IR)	1.65	186 (174-195)	1306 (1049-1503)
Predicted (Monodispersed 11 μm; IR)	1.55	192 (180-203)	1276 (1031-1471)

Results: Predicted OXZ plasma concentration time profiles for the polydispersed IR formulation were in good agreement with observed profiles (**Table 2 & Fig. 2**). Simulations also indicated that changing the formulation model from a polydispersed (3-25 μm) to a monodispersed PSD (11 μm) did not significantly affect the predicted concentration time profiles (assessed via T_{max}, C_{max} & AUC). SA on OXZ parameters SSR and PRC indicated that the PK parameters C_{max} and AUC were not sensitive to variation in magnitude of these parameters (**Figs. 3 & 4**).

Conclusions: The PBPK model successfully predicted the plasma concentration-time profile of OXZ IR 15 mg formulation with a polydispersed PSD. Simulations also indicate that, although OXZ is sparingly soluble, a change in the formulation from a polydispersed PSD to a monodispersed particle size does not significantly affect the plasma PK profile of OXZ. At least for this dose of OXZ the PK parameters C_{max} and AUC are not sensitive variations in the supersaturation and precipitation rate.

References:

[1] He *et al.*, Br. J. Clin. Pharmacol. (2009) 68:721–730; **[2]** Sonne *et al.*, (1988) Eur. J. Clin. Pharmacol. 35:385-389; **[3]** Murray *et al.*, *Clin. Pharmacol. Ther.* (1981) 30:805-809; **[4]** Jamei *et al.*, (2009) *AAPS Journal* 11:225-237.