Introduction

Beagle dogs are widely used in preclinical studies in the assessment of oral formulation behaviour. Simcyp Dog v11.01 is an in silico physiologically-based pharmacokinetic (PBPK) simulator. The model provides a fully mechanistic modelling and simulation (M&S) platform and incorporates in vitro-in vivo extrapolation (IVIVE) techniques to study oral drug absorption, tissue distribution, metabolism and excretion in a 10kg ‘virtual beagle’ dog. The model provides an alternative tool in the drive toward the refinement, replacement and reduction of in vivo studies in beagles.

Purpose

To evaluate the performance of Simcyp Dog, without fitting of model parameters, to predict the PK of Celecoxib (CBX) dosed intravenously (IV), Oral (Polyethylene Glycol (PEG) solution and Immediate Release (IR)) nano-particles stabilized with sodium-1-heptane-sulfonate (SHSO)) and directly to the gastrointestinal (GI) tract: Intra-Gastric (IG) and, via Chronic Intestinal Access Port (CIAP), to the Duodenum, Jejunum and Colon.

Methods

Simcyp Dog v11.01 was used to predict the plasma concentration time (Cp-t) profiles of CBX after an IV dose (5mg/kg PEG solution and IR Capsule) and 10mg/kg oral PEG solution as IG and directly into the Duodenum, Jejunum and Colon via CIAP. The IR capsule was characterized by the solubility profile of CBX in Fasted State Simulated Intestinal Fluid (FaSSIF). A fully mechanistic gut wall permeability model incorporated into the Simcyp Advanced Dissolution Absorption and Metabolism-PBPK Model (ADAM) was used to predict effective regional intestinal permeability (Peff). Model parameters (Gastric Emptying, Peff and SI Transit time) were manipulated to permit the modelling of the direct administration of CBX to the Duodenum, Jejunum and Colon. Key simulation parameters are shown in Table 1.

Results & Discussion

Simcyp Virtual Beagle model was reasonably successful at predicting (without fitting of parameters) CBX Cp-t profiles after administration of IV and Oral formulations. Error in predicting CIAP may be related to failure to account for re-precipitation of drug after CIAP administration. This may have implications with respect to formulations of poorly soluble drugs that are intended to directly deliver drug to specific portions of the GI tract. The fully mechanistic gut wall permeability model in Simcyp Dog is sensitive to differences in site of absorption of the GI tract of the Beagle and can be used to aid study of the regional absorption of drugs from the GI tract.

References: