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Utility of PBPK Absorption Modeling to Guide Modified Release Formulation Development of Gaboxadol, a Highly Soluble Compound With Region-Dependent Absorption

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ABSTRACT

Given the complexity of controlled release (CR) formulations, selecting the right preclinical tools is important to enable decision making on the *in vivo* performance of these formulations during development. In recent years, with the advancements of absorption/physiologically based pharmacokinetic (PBPK) modeling, such computational approaches play an increasing role in guiding formulation development. Development of PBPK models for CR formulations requires additional information compared with immediate release (IR) products. Perhaps the most important aspect is the need to simulate absorption in the lower intestine. Relatively few publications have investigated the use of PBPK models for compounds with region-dependent absorption. In this manuscript, we use gaboxadol as a model compound with region-dependent absorption. We first explored gaboxadol regional absorption in dogs to develop a PBPK model for absorption in the large intestine. Two matrix-based CR formulations were subsequently developed and tested in minipigs and demonstrated distinctly different pharmacokinetic profiles from the IR formulation. A minipig absorption PBPK model successfully predicted the observed plasma concentration data, with the predictions based on the *in vitro* dissolution being within the observed experimental variability. Finally, we demonstrate the development of an *in vitro–in vivo* correlation for the preclinical data using the same PBPK model.

Introduction

Preclinical evaluation of modified release (MR) formulations historically has been composed of a combination of *in vitro* dissolution testing and preclinical animal models, most commonly studies in dogs. The primary goals of such preclinical studies are to allow for early development of an *in vitro–in vivo* relationship (IVIVR) or an *in vitro–in vivo* correlation (IVIVC) for the dissolution method, investigation of mechanism of release, for example, via imaging, and selection of prototype formulations for further clinical testing.[1] In recent years with the advancements of absorption/physiologically based pharmacokinetic (PBPK) modeling, such computational approaches play an increasing role into guiding formulation development and such models have been successfully demonstrated also for MR dosage forms.[2-4]

Given the complexity of MR formulations, the right selection of preclinical tools is important to enable correct decision making on the *in vivo* performance of these formulations during development. Animal models selected need to accommodate the prolonged release from the formulations. For example, dogs, the most common preclinical species for screening of immediate release (IR) formulations, are known to exhibit significantly shorter small intestinal transit time compared with humans as well as the length of the colon is relatively small.[5] This has led to consideration of minipigs, which have longer intestinal transit times, as an alternative animal model for formulation screening. However, only a few studies have been reported in pigs with MR formulations.[6-9] Similarly, development of PBPK models requires additional information compared with standard PBPK models for IR compounds. The most important aspect is perhaps simulation of absorption in the lower intestine that needs to be taken into account; thus understanding of any region-dependent absorption is critical to the successful development of such models. Again limited reports are available with using PBPK models that account for region-dependent absorption.[3,4]

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Gaboxadol is a $GABA_A$ receptor agonist that was previously in clinical development for treatment of chronic pain and insomnia.[10] It is a zwitterion with pK_a values of 4.3 (acidic) and 8.3 (basic) and log P of −0.61. It is dosed as the hydrochloride (HCl) salt. The compound solubility is more than 30 mg/mL in the physiological pH range. Although gaboxadol exhibits moderate permeability in Caco-2 cells (P_{app} ~ 6–8 × 10^{-6} cm/s),[10] it exhibits high fraction absorbed (84%–93%) in both preclinical species and in humans,[11] thus can be categorized as a Biopharmaceutics Classification System (BCS) Class I compound. Absorption of gaboxadol is rapid with a short T_{max} of approximately 0.5 h and with a half-life of 1.5–2.0 h.[12] Recently, it has been demonstrated that intestinal absorption of gaboxadol is likely mediated by the human proton-dependent amino acid transporter 1 (hPAT1).[10,13] This transporter-mediated uptake can result in region-dependent absorption. Broberg et al.[13] showed that in rats, absorption of gaboxadol from the colon is only 4.2% relative to almost complete absorption (81.3%–91.3%) after administration in the stomach, duodenum, or jejunum. Thus, although the BCS Class I classification would normally be considered positive for the development of a controlled release (CR) formulation, this regional-dependent absorption poses a challenge in optimizing the release profile of a CR formulation.

Given the regional absorption of gaboxadol, it represents an interesting model compound to assess the utility of absorption PBPK modeling in informing possibility of success for CR formulation in a preclinical setting. In this manuscript, we present the development of an absorption model based on preclinical information to project behavior of two matrix-based CR formulations of gaboxadol and comparison of the projections with the outcome of minipig studies evaluating these two formulations with different release rates. Finally, we demonstrate the development of an IVIVC for the preclinical data using the PBPK model.

Methods

Formulations

The formulation used for the dog regional absorption studies was a simple aqueous solution of 0.2 mg/mL gaboxadol. For the minipig studies, CR formulations tested were 15 mg potency hydroxypropyl methylcellulose (HPMC) K100M-based matrix tablets. One of the formulations (fast CR, 15.5% HPMC) was designed with a complete release in approximately 6 h to maximize small intestinal absorption but still allow for reduction of C_{max}. The second formulation (slow CR, 58.5% HPMC) was designed with a prolonged release (complete release post 12 h) to be tested for further model verification. Dissolution for each formulation was measured in 900 mL deaerated water using a United States Pharmacopeia (USP) II apparatus at 50 rpm (Fig. 1). IR formulation was a simple dry filled capsule (DFC). Dissolution profiles in other media (e.g., 0.1 N HCl) resulted in similar differences between tested formulations; given the simplicity of the deaerated water as media, it was selected for the final formulation testing for this study.

Dog Regional Absorption Pharmacokinetic Study

Fasted male Beagle dogs (Marshall Farms, North Rose, NY), weighing approximately 10 kg, with ileal and colonic ports were used of these studies. All animals were housed in an Association for Assessment and Accreditation of Laboratory Animal Care-accredited facility in accordance with United States Department of Agriculture guidelines. The Guide and Animal Welfare regulations were followed in the conduct of the animal studies. Veterinary care was given to any animals requiring medical attention. Formulation dosing studies were conducted under a protocol approved by the Merck Institutional Animal Care and Use Committee (IACUC).

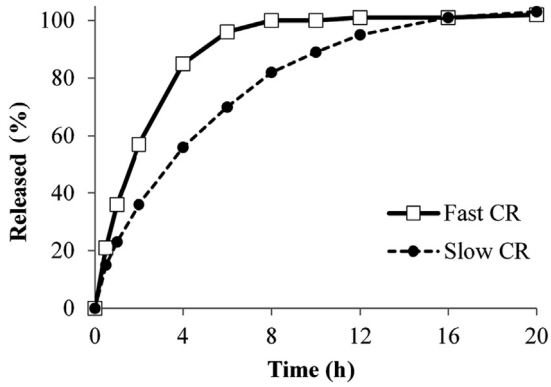

Figure 1. Dissolution of gaboxadol matrix CR formulations.

In the morning of the study, six animals were dosed with 0.2 mg/kg of gaboxadol (1 mL/kg) either orally or via the ileal or colonic port followed by 5 mL rinse with sterile water. Study was a crossover study (i.e., each animal was dosed via all three administration routes) and was completed over a period of 3 weeks (animals were dosed every week). Animals had been fasted overnight prior to dosing and food was returned at 4 h after dosing. Blood was drawn from a 21 g catheter placed into the cephalic vein at pre-dose and 0.25, 0.5, 1, 2, 4, 6, 8, and 24 h after dosing. The plasma was separated by centrifugation (15 min at 2500g) and kept frozen at −70°C until analysis by LC–MS/MS. The analytical method for gaboxadol has been published before.[14] The assay used had a lower limit of quantitation (LOQ) of 0.1 ng/mL for gaboxadol based on 150 μL aliquots of plasma. The calibration curve dynamic range was 0.1 to 1000 ng/mL.

Minipig Formulation Comparison Pharmacokinetic Study

Castrated male, vascular access port implanted Yucatan minipigs (Sinclair Research Center Inc., Auxvasse, MO) weighing approximately 50 kg were used for the study. The Guide and Animal Welfare regulations were followed in the conduct of the animal studies. Veterinary care was given to any animals requiring medical attention. All formulation dosing studies were conducted under a protocol approved by the Merck IACUC. The study design was a full crossover with three periods utilizing eight animals dosed every week. Animals were fasted overnight prior to the day of the study. On the day of the study, animals were dosed orally with 15 mg potency formulations followed by a 3.5 mL/kg water rinse. Water was withheld for 1 h prior to dose to 1 h post-dosing. Food was returned 4 h post-dosing. Blood was collected at pre-dose and 15 min, 30 min, 1 h, 2 h, 4 h, 8 h, 12 h, and 24 h post dosing. The plasma was separated by centrifugation (15 min at 2500g) and kept frozen (−70°C) until analysis by LC–MS/MS.

Pharmacokinetic Analysis

Area under the curve (AUC_{last}), observed maximum plasma concentration (C_{max}), and time of C_{max} (T_{max}) were calculated using a linear trapezoidal, non-compartmental model in Phoenix WinNonlin (Certara USA, St. Louis, MO). As plasma concentrations at 24 h were below LOQ, only data up to 12 h data are used for calculations in this manuscript.