Application of Physiologically Based Absorption Modeling for Amphetamine Salts Drug Products in Generic Drug Evaluation

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ABSTRACT: Amphetamine (AMP) salts-based extended-release (ER) drug products are widely used for the treatment of attention deficit hyperactivity disorder. We developed physiologically based absorption models for mixed AMP salts ER capsules and dextroamphetamine sulfate ER capsules to address specific questions raised during generic drug postmarketing surveillance and bioequivalence (BE) guidance development. The models were verified against several data sets. Virtual BE simulations were conducted to assess BE in various populations other than normal healthy subjects where BE studies are generally conducted for approval. The models were also used to predict pharmacokinetics (PK) for hypothetical formulations having dissolution profiles falling within specification after the development of *in vitro–in vivo* relation. Finally, we demonstrated how to use the models to test sensitivity of PK metrics to the changes in formulation variables. Published 2015. This article is a U.S. Government work and is in the public domain in the USA J Pharm Sci 104:3170–3182, 2015
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INTRODUCTION

Physiologically based absorption modeling and simulation for oral dosage forms has demonstrated its value in various aspects of generic drug evaluation.[1,2] We present a case example where physiologically based absorption modeling and simulation was applied in bioequivalence (BE) guidance development and postmarketing surveillance risk assessment of generic drugs.

Over the last 10 years, the generics share of prescriptions has increased from 54% in 2003 to 84% in 2012 and will likely rise to 87% by 2017.[3] Along with the efforts being devoted to developing and approving generic drugs is the establishment of a strong post marketing surveillance program for generic drugs. The Office of Generic Drugs (OGD) regularly evaluates the adverse events reported for generic drug substitution and analyzes the potential root cause(s). There are many aspects involved in analyzing postmarketing safety signals and searching for the potential root causes, such as drug product quality evaluation, re-evaluation of BE criteria and BE data, and identifying gaps between BE studies and pharmaceutical equivalence data supporting approval and the clinical use of the product. Physiologically based absorption models are valuable tools to identify the potential risks to successful generic substitution because these mechanism-based models integrate drug substance properties, physiological properties, and drug release mechanisms (i.e., formulation properties). For example, virtual BE simulations can be performed based on validated physiologically based absorption models in various patient populations that have not been tested in BE studies. The OGD also routinely develops BE guidance for specific drug products.[4] Physiologically based absorption modeling has also been used to address various questions in guidance development.[5] In the example in this report, physiologically based absorption modeling was used to evaluate the sensitivity of a series of BE metrics to a change in formulation parameters.

Amphetamine (AMP) drug substance refers to the racemic 1:1 mixture of two enantiomers with central nervous system stimulant activity: dextroamphetamine [D-AMP; S-AMP (IUPAC)] and levoamphetamine [L-AMP; R-AMP (IUPAC)]. Mixed AMP salts (MAS) products are nonracemic combinations of four salts in a 1:1:1:1 ratio (by weight): D-AMP sulfate, D-AMP saccharate, AMP aspartate, and AMP sulfate. The ratio of D-AMP salts to L-AMP salts in MAS products is 3:1, whereas the ratio of base D-AMP to base L-AMP is approximately 3.15:1. This combination of AMP salts was approved for the treatment of attention deficit hyperactivity disorder (ADHD). Adderall® (NDA 11522) is an immediate-release (IR) tablet formulation of MAS, and Adderall XR® (NDA 21303) is an oral formulation of MAS consisting of two types of pellets in the ratio of 1:1 (in terms of drug load) in a gelatin capsule: an IR pellet and a delayed-release (DR) pellet.[6] The DR pellets are enteric coated and trigger the release in higher pH environment. The combination of these pellets is considered to be an extended-release (ER) product. Dexedrine® (D-AMP sulfate) ER capsules (NDA 17078), also known as Dexedrine Spansules®, are also indicated for the treatment of ADHD. Its active ingredient is one of the ingredients in MAS products. We conducted physiologically based absorption modeling and simulation for three drug products: two reference listed drugs (Adderall XR® and Dexedrine®), and a generic version of Adderall XR® (referred to as Product Y). The reason for the selection of Product Y for simulation is because it has a similar design as Adderall XR® with two types of pellets, except that the mechanism of the modified-release (MR) pellet is ER instead of DR.

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METHODS

Modeling and Simulation Strategy

The developmental process of the model to predict D-AMP and L-AMP plasma concentrations is based upon the methodology described by Zhang et al.[7] From a chronological perspective, the first models that were developed described D-AMP and L-AMP concentrations following administration of MAS formulations. The models describing pure D-AMP formulations were developed as modifications to the MAS models. Unless indicated, all input parameters/profiles and pharmacokinetic (PK) information were collected from multiple new drug applications (NDAs) and abbreviated NDAs (ANDAs).

The Model Drug Substances

All AMP salts are considered to be highly soluble drugs according to the criteria of the Biopharmaceutical Classification System[8] (Table 1). The apical-to-basolateral (A–B) and basolateral-to-apical (B–A) permeability rates of D-AMP sulfate through Caco-2 at pH 7.4 was reported to be 79.7×10^{-6} and 33.9×10^{-6} cm/s, respectively.[9] The values of these rates and a significant favoring of transport in the A–B direction are suggestive of complete gastrointestinal (GI) absorption, that is, AMP is a highly permeable drug substance. The metabolic pathway for AMP is not well-established; however, AMP is known to be a substrate of CYP2D6 that catalyzes its conversion to 4-hydroxy-AMP.[10] The major metabolite is alpha-hydroxy-AMP, where the molecule and its derivatives account for 50% of the administered dose recovered in urine and AMP itself accounting for 30%–40% in urine. AMP has a half-life of 9.77–11 h (D-AMP) and 11.5–13.8 h (L-AMP). Intestinal metabolism of AMP as well as hepatic first-pass effect (FPE) has not been evidenced. It is assumed that FPE has minor impact on absolute bioavailability and as such, it was neglected in model building. Other physiochemical properties of D-AMP and L-AMP used in simulations are provided in Table 1.

The PK Model—MAS

No data from an intravenous dose of MAS is available. Rather, PK data after oral administration of 30 mg Adderall® IR tablets under fasting conditions were fit in the PKPlus™ module of GastroPlus™ with Hooke and Jeeves Pattern Search method with unity weighting of the objective function to determine the appropriate compartmental model for D-AMP and L-AMP as determined by optimal Akaike Information Criterion (AIC) values. The average subject weight of 79.28 kg (or 174.78 lbs) was inputted into the module for each isomer. With a 30-mg dose of Adderall®, it was calculated that in a single tablet, there is 14.247 mg D-AMP base and 4.523 mg L-AMP base.

The Absorption/Advanced Compartmental Absorption and Transit Model—MAS

Because the PK model parameters were derived from oral data, the volumes of distribution and systemic clearances (CL) were only apparent values, as the PK model did not account for the bioavailability of the Adderall® tablet dose. The conventional PK model from PKPlus™ was reoptimized in the context of the Advanced Compartmental Absorption and Transit (ACAT) model of GastroPlus™ along with an optimization of the effective human permeability (P_{eff}), which was a parameter initially estimated from the ADMET Predictor module of GastroPlus™ (Table 2). All physiological parameters are provided in Tables S1–S3 in the Supporting Information. For the simulations, both paracellular transport model (suggested by GastroPlus™) and bile salt effect were included in the model. The "Opt log *D* Model SA/V6.1" option was selected for absorption scale factor determination. MAS formulations contain four active pharmaceutical ingredients (APIs) that account for the two active enantiomeric moieties. Each AMP salt has different solubility properties and it is not possible to determine in the available PK data what portion can be attributed to each salt. In order to simplify this model, two drug records were produced in GastroPlus™: one for D-AMP and one for L-AMP. It was assumed that the compound/API for that record was either a theoretical salt of D-AMP or L-AMP. Similar solubility values were observed with D-AMP sulfate and AMP sulfate, whereas D-AMP saccharate and AMP aspartate showed higher levels of solubility. As the predicted solubility and experimental solubility of the AMP salts were high, the impact of that parameter on the simulation was minimal. As such, the ADMET predictor values were chosen for the simulation, which were similar to the D-AMP sulfate and AMP sulfate values (Table 1). The applicability of this solubility assumption was evaluated with a parameter sensitivity analysis (PSA). The dosage form "IR: Tablet" was selected and the default human fasted physiology or human fed physiology was selected in GastroPlus™ with no deviations from default values.

For b.i.d. dosing of Adderall® tablets every 4 h (q4h), "Mixed Multiple Doses" was selected as the dosage form where a single dose is given at the start of the simulation and an additional dose is given 4 h into the simulation. In one simulation (Simulation 1), the switch to the human fed physiology model was the only modification made; and in the other simulation (Simulation 2), to account for the different population, the one-compartmental PK parameters were reoptimized.

Adderall XR® (MAS) ER capsules contain a blend of IR and DR pellets with a ratio of 1:1 in terms of drug load and exhibits a multiphasic release profile.[6] The IR pellets begin to dissolve immediately after administration in the stomach, whereas the DR pellets only begin to dissolve following the disintegration of the enteric coat once the individual pellet has transited from the stomach. As the DR portion does not transit through the stomach as a monolith, enteric-coated pellets behave more similarly to ER formulations because the pellets continuously trickle out of the stomach into the duodenum.[11] For pelleted enteric formulations in GastroPlus™, the "DR:MultiPart EntCoat" dosage form is the most appropriate as it treats the transit of each pellet from the stomach to the small intestine individually and drug is released from the pellet only once it has entered the small intestine using the dissolution model set in GastroPlus™. We directly mimicked the Adderall XR® formulation with a "Mixed Multiple Doses" dosage form with equal dosings of "IR: Solution" and "DR: MultiPart EntCoat." The IR pellets were described by "IR: Solution" instead of "IR: Capsule" or "IR: Tablet" because: (1) all three IR formulations can be expected to behave similarly because of the high solubility and high predicted permeability of AMP; and (2) only a single dissolution model can be specified in a GastroPlus™ record and the dissolution model necessary for the DR portion could not be used to describe IR release rates. The dissolution from the DR pellets after exiting the stomach was described with the Z-factor (Takano) model,[12] where dissolution rate was controlled via optimization of the Z-factor parameter (Table 2). Previous optimization runs poorly