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Short communication

Physiologically based *in silico* modeling of a model BCS class II antipsychotic drug following oral administration

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Introduction

The oral drug absorption from immediate release (IR) solid dosage form is determined by many factors such as solubility of the active ingredient, dissolution rate and the intestinal membrane permeability. When it comes to drugs that belong to the Biopharmaceutics Classification System (BCS) class II, solubility and dissolution rate are the limiting factors to oral absorption. Deeper insight into the influence of a particular factor or set of factors on drug absorption profiles can be obtained using the physiologically based *in silico* modeling. Physiologically based models can provide quantitative predictions of a drug pharmacokinetics in vivo based on the interrelationships among key physiological, biochemical and physico-chemical factors using mathematical equations (Jeffrey and Zhoumeng, 2020).

The aims of this study were: (i) to develop a drug-specific physiologically based model for the prediction of a BCS class II atypical antipsychotic bioperformance following intravenous (IV) and peroral (PO) administration, and (ii) to identify the key parameters affecting the rate and extent of this drug absorption after oral administration.

Materials and methods

The model was constructed using GastroPlus™ software (version 9.8.2000, Simulations Plus Inc., USA). The selected input dataset included literature data on the drug physico-chemical/biopharmaceutical properties (molecular weight, pKa, LogP, Caco-2 permeability, solubility, effective particle radius, plasma protein binding). For those parameters for which we could not find literature data, default software values (drug density, precipitation time, blood:plasma concentration ratio) or the software calculated values (drug diffusion coefficient, human jejunal permeability) were used. The software integrated PKPlus module was used to select the appropriate pharmacokinetic compartmental model and fit the pharmacokinetic parameters values. The model was first developed for the 2 mg IV infusion with infusion time of 0.25 h. After that, using the Advanced Compartmental Absorption Transit (ACAT) human fasted model, a PO absorption model was developed for the 5 mg IR tablet formulation. Both IV and PO models were verified based on the work of Boulton et al. (2008) which provided drug plasma concentrations versus time profiles under single dosing conditions. Graphical data from literature data were digitized using DigIt™ program (version 1.0.4, Simulations Plus, Inc., USA). Parameter sensitive analysis (PSA) was conducted to identify the critical factors that influence the in vivo pharmacokinetic performance of the drug. The percent prediction error (%PE) for maximum plasma concentration (C_{max}) and area under the plasma concentration-time curve (AUC) were calculated based on the equation given below:

$$\%PE = \frac{observed - predicted}{observed} x\ 100$$

Results and discussion

Literature data:

The drug of interest is a weak base with pKa of 7.46 (EMEA, 2005). It is practically insoluble in water and shows pH-dependent solubility with the highest solubility at acidic region (solubility at pH 1.2 is 0.53 mg/mL) and the lowest solubility at pH around 7 (solubility at pH 7.0 is 0.01 mg/mL) (Zhou et al., 2021). Moreover, the drug

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exhibits polymorphism, which might influence its biopharmaceutical properties (Otsuka, 2002). The values for LogP and permeability through Caco-2 cells indicate that the drug is highly permeable and crosses the intestinal membrane via passive diffusion (FDA, 2002). Drug bioavailability after oral administration has been determined to be 87%, which indicates nearly complete absorption and minimal presystemic metabolis (EMEA, 2005). Following intravenous administration of a 2 mg dose, the drug plasma concentration declines in a multiphasic manner and is measurable for up to 99 hours post dose.

In silico *simulations*

Using the PKPlus module, we analyzed the literature plasma concentration data and found out that the two-compartmental pharmacokinetic model best described the distribution and clearence of the drug. The relevant pharmacokinetic parameters were fitted accordingly, and the resultant plasma concentration-time profiles following IV administration nicely matched the in vivo data (Boulton et al., 2008). The simulated and observed values for $AUC_{0-\infty}$ and C_{max} following IV administration were 556 ng-h/mL vs. 620 ng-h/mL for $AUC_{0-\infty}$ (PE= 10%) and 19.20 ng/mL vs 16.9 ng/mL for C_{max} (PE= -13%).

The predicted drug bioavailability (F) following PO administration was 97%, which coincides with literature values. The predicted pharmacokinetic parameters i.e., $AUC_{0-\infty}$ and C_{max} were also similar to the in vivo observed values (1372.5 ng-h/mL vs. 1290 ng-h/mL, PE= -6.4% and 17.7 ng/mL vs. 19.9 ng/mL, PE= 11%, respectively), while there was a certain difference in the predicted vs observed t_{max}. Namely, the model slighly prolonged the time needed to achieve the maximum plasma concentration with t_{max} of 4.5 h, while the mean in vivo observed value was 2.75 h. Neverthless, this discrepancy can be accepted, considering large interindividual variability in this parameter (1.5-6.0 h) (Boulton et al., 2008). The regional absorption distribtuion of the drug was also evaluted. Because the drug is a weak base, absorption will most likely occur in the gastrointestinal (GI) region(s) where the drug residence time is sufficient for the drug to be absorbed into membrane and where the medium pH yields sufficient concentration of the drug to be present in an non-ionized form. According to the simulation results, after PO administration the largest amount of drug will be absorbed in the caecum (approximately 42%).

The PSA was preformed for drug solubility, dose, effective particle radius and mean precipitation time in order to assess the importance of the selected input parameters in predicting the percent of drug absorbed. The obtained results indicate that the extent of drug absorption mainly depends on drug solubility and effective particle radius.

Conclusion

The presented results demonstrate the value of physiologically based *in silico* modeling. The simulation outcomes indicate that the predicted drug plasma exposure following oral absorption is sensitive to drug solubility and particle radius. Such data are in accordance with the fact that this drug is a BCS class II compound with poor and pH-dependent solubility. Therefore, the solubility of a chosen polymorphic form and drug particle size distribution should be carefully considered during formulation development. In addition, investigation of the effect of drug dissolution on the expected bioavailability for IR tablets should be assessed, as planned for our future studies.

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