#3124. Physiologically Based Pharmacokinetic Modeling for Optimization of Sustained-Release Orthodontic Retainer of Clonidine

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Introduction

Clonidine is approved for therapy of attention-deficit hyperactivity disorder (ADHD) that is one of the most common neurobehavioral problems mainly afflicting children and youth between 6 and 17 years of age with a high modality from 2% to 18% in USA. Current ordinary tablets may produce a burst release after oral administration, leading to a high drug concentration and subsequently severe adverse reactions.

Sustained-release formulations are preferred and orthodontic retainers have the advantage of convenient administration and termination. However, the drug release profiles need to be optimized to ensure suitable exposure in the human body. The purpose of this portion of the work was to use physiologically based pharmacokinetic (PBPK) modeling to predict the pharmacokinetic profiles for these formulations to assist selection of an ideal formulation with a long duration sustained release.

Methods

Clonidine hydrochloride (CH) powders were mixed with other excipients and the mixture was hot-melt extruded to form the filaments that were 3D printed to customizable orthodontic retainers with the fused deposition modeling (FDM) method. To reduce the burst release of the drug, the 3D printed original retainers were coated with polymers to obtain coated retainers, or washed with buffered solutions to obtain washed retainers.

To investigate the drug release, retainers were immersed in PBS (pH 6.8, 100 mL) and oscillated at 37˚ and 150 rpm. An aliquot (2 mL) of the media was withdrawn at predetermined time points for clonidine analysis using an established HPLC method.

A PBPK model of clonidine was developed using Gastroplus® (Simulations Plus, Inc.). Model parameters used in the PBPK model were collected from literature.[1,2] The physiochemical parameters not available in literature[3] were predicted using the ADMET Predictor™ module. The clinical data for clonidine was from clinical studies published in literature, which included the mean concentration-time profiles after both oral and intravenous (IV) administration. The Advanced Compartmental Absorption and Transit (ACATTM) and PBPKPlus™ were used for the simulation of clonidine after IV and oral administration. The simulated pharmacokinetic (PK) profiles of clonidine were compared with observed profiles for evaluation of the model performance. The model was then used to simulate PK profiles after dosing with the sustained release retainers by incorporating the in vitro dissolution data into the model.

Results and Discussion

Personalized retainers were designed and 3D printed, as shown in Figure 1. The three types of orthodontic retainers, including original, coated and washed retainers, showed different clonidine release profiles in PBS. Total drug in the retainer was 30 mg, and the total released amounts within 72 hours were about 5% or less for all three types of retainers. The drug release was expected to continue for longer term (not measured).

Figure 1. Clonidine loaded 3D printed original retainer.

Both the original and coated retainers had significant burst drug release in the early stage because clonidine was freely soluble in water and the retainers had large surface area. The initial burst release from the original and coated retainers may still cause adverse reactions. However, washing out the clonidine from the surface of the retainer significantly reduced the burst release as shown in Figure 2.

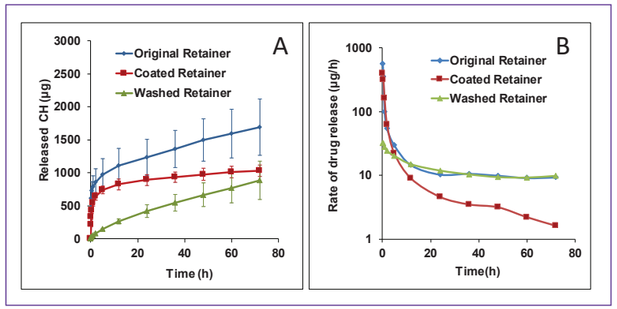

Figure 2. Clonidine release profiles (A) and release rate profiles (B) of 3D printed retainers.

The PBPK model of clonidine was developed based on data collected from literature, and evaluated by comparison to observed clinical data including concentration-time profiles, bioavailability and liver metabolism. Clinical data from two separate publications include both IV doses (0.075, and 0.15 mg) in hypertensive patients and oral doses (0.075, and 0.15 mg) of clonidine in healthy volunteers. Mean concentration-time profiles were collected by digitalization of the plots in the publications. The profiles were then used to validate the PBPK model. The simulated and observed profiles are similar as shown in Figure 3.

The bioavailability was around 60% and overall ~50% of the absorbed drug was metabolized in the liver, consistent with values reported in literature.

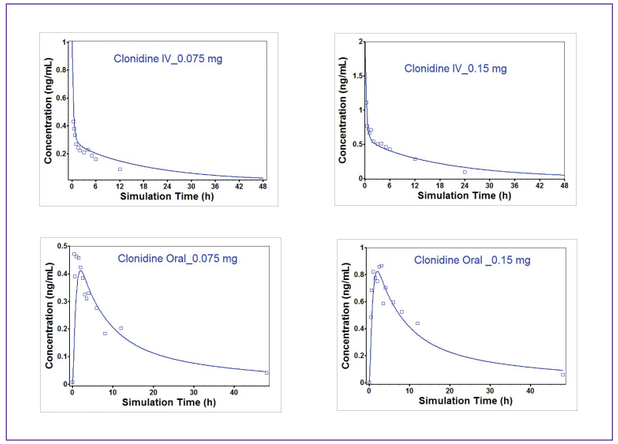

Figure 3. Simulated and observed clonidine concentration-time profiles after 0.075 and 0.15 mg IV administration and oral 0.075 and 0.15 mg administration.

Model simulated drug dissolution and absorption profiles are shown in Figure 4. Simulated in vivo dissolution profiles were consistent with those observed from in vitro studies due to the high solubility of the drug. The incomplete absorption was probably due to low permeability of the drug, which was classified as a BCS III compound.

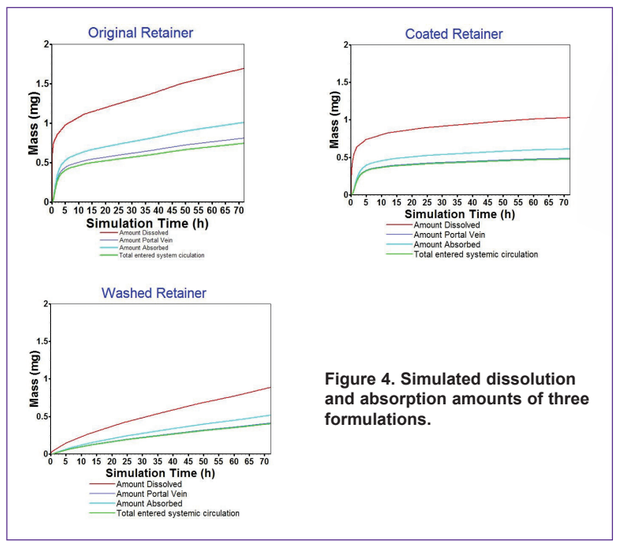

Figure 4. Simulated dissolution and absorption amounts of three formulations.

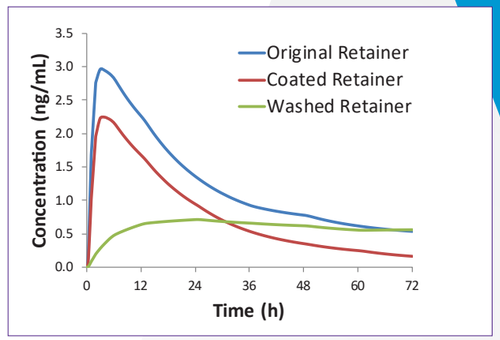

Figure 5. Predicted concentration-time profiles for the three types of retainers.

As shown in Figure 5, the simulated clonidine concentration-time profiles showed the initial high concentrations after administration of original and coated retainers due to the burst clonidine release. Clonidine plasma concentrations slowly increased from the beginning of administration of washed retainers; however, more importantly, there was no burst clonidine release. At 7 h post-administration, a suitable clonidine concentration of 0.5 ng/mL was reached. After then, stable concentrations (0.5-0.7 ng/mL) were maintained up to 72 h. The concentration range is close to the reported effective therapeutic concentration of clonidine.

Conclusions

A PBPK model was developed to support optimization of clonidine-loaded sustained release orthodontic retainers. The model predicated pharmacokinetic profiles indicated that the washed retainers may provide sufficient exposure long term with lower risk due to minimal burst release. The PBPK model provides evidence for formulation and preparation process screening of sustained release retainers of clonidine. This work demonstrated that PBPK modeling could be applied to optimize formulations to achieve desired pharmacokinetic profiles.

References

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Presented at SOT 2019

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