Establishment of Virtual Bioequivalence via DoE-PBBM Model: A Donepezil Case Study

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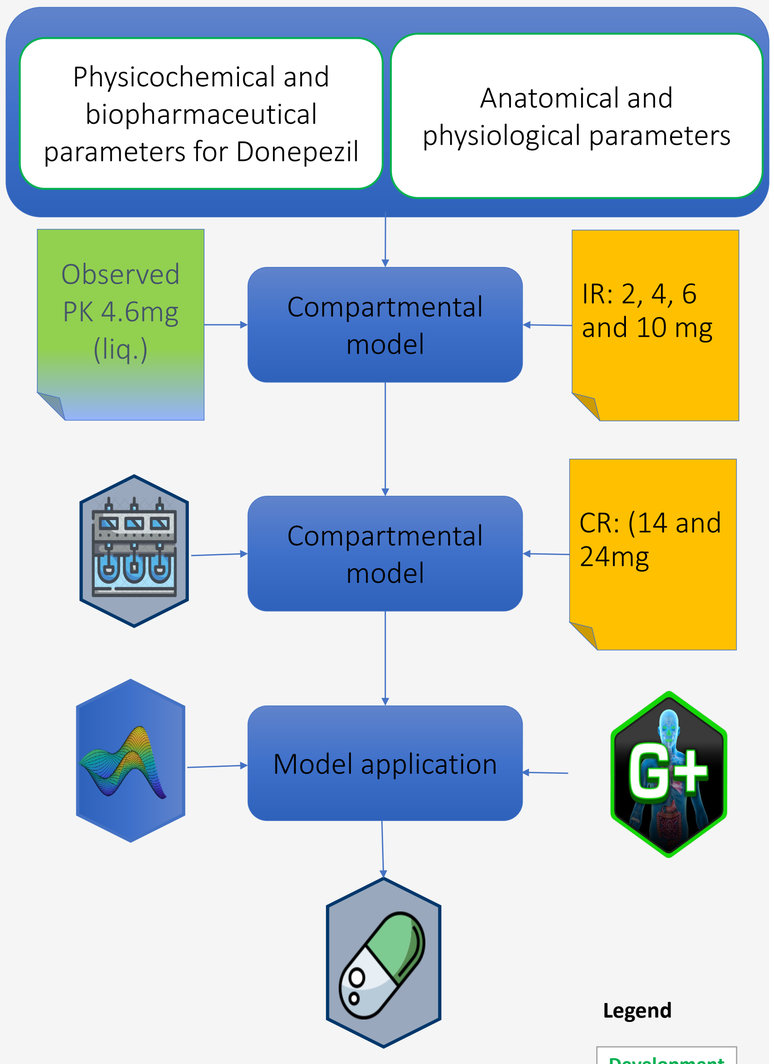
PURPOSE

Donepezil (DZP) is a medication used to treat Alzheimer's disease. It works by inhibiting the breakdown of acetylcholine in the brain, which is a neurotransmitter important for memory and cognitive function. The immediate release (IR) tablets of donepezil (Aricept) were approved by the Food and Drug Administration in 1996, and an extended release (SR) formulation was approved in 2010. The SR tablet is different from the IR formulation in that it has a slower time to peak concentration following oral ingestion. One way to deliver drugs over an extended period through oral consumption is to use hydrophilic matrix tablets, which are made by incorporating water-swellable polymers that quickly expand and form a gel layer around the dry core, regulating the rate of drug release as it moves through the gastrointestinal tract.

OBJECTIVES

The goal of this work was to develop a new formulation of donepezil SR that performs as well as the commercial product. To achieve this, the researchers used Design of Experiments (DoE) and Physiologically Based Biopharmaceutics Modeling (PBBM) to predict the effects of formulation changes on *in vivo* pharmacokinetics during the early stages of SR tablet development. This approach could potentially save time and resources required for the development of SR formulations.

METHODS



RESULTS

Figure 1: Dissolution profile of all formulations studied compared with Aricept SR.

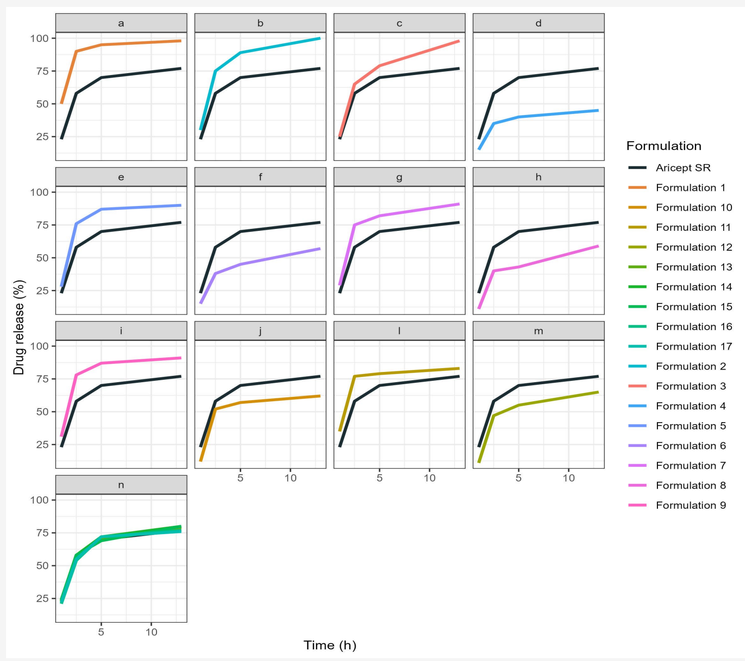


Figure 2: Response Surface Plot Showing the Influence of HPMC and NaCMC on donepezil release at 1, 2.5, 5 and 13 h.

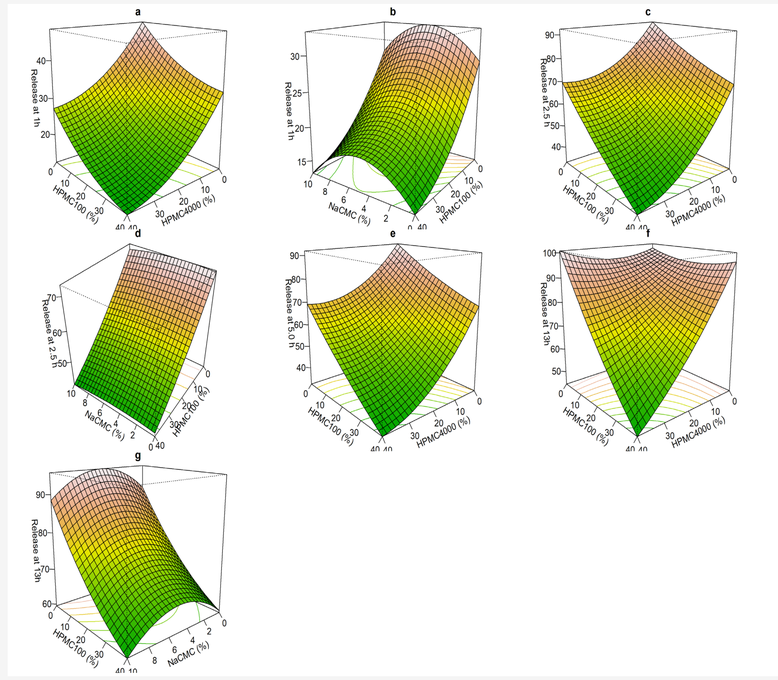


Figure 3: Gel strength profiles of investigated products by texture analyzer in different swelling time

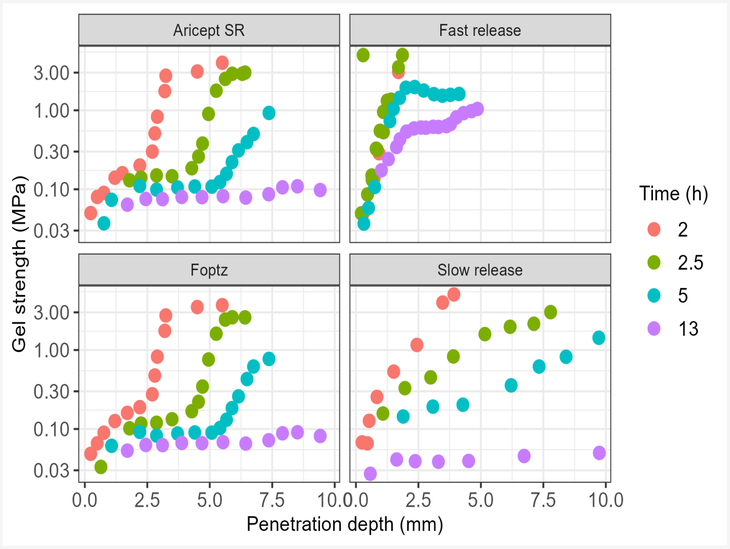


Figure 4: Hydration and weight loss of matrix tablets during dissolution at different agitation speed.

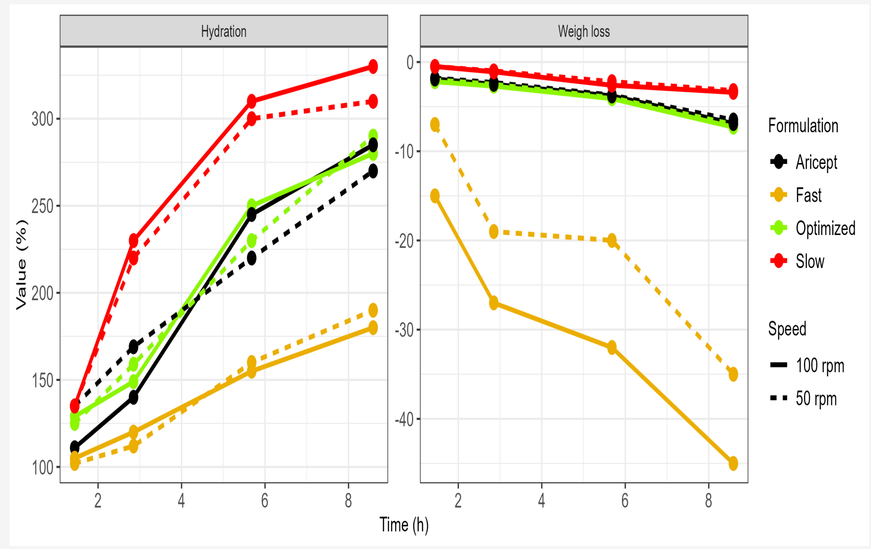


Figure 5: Simulation vs observed PK from different sources and doses.

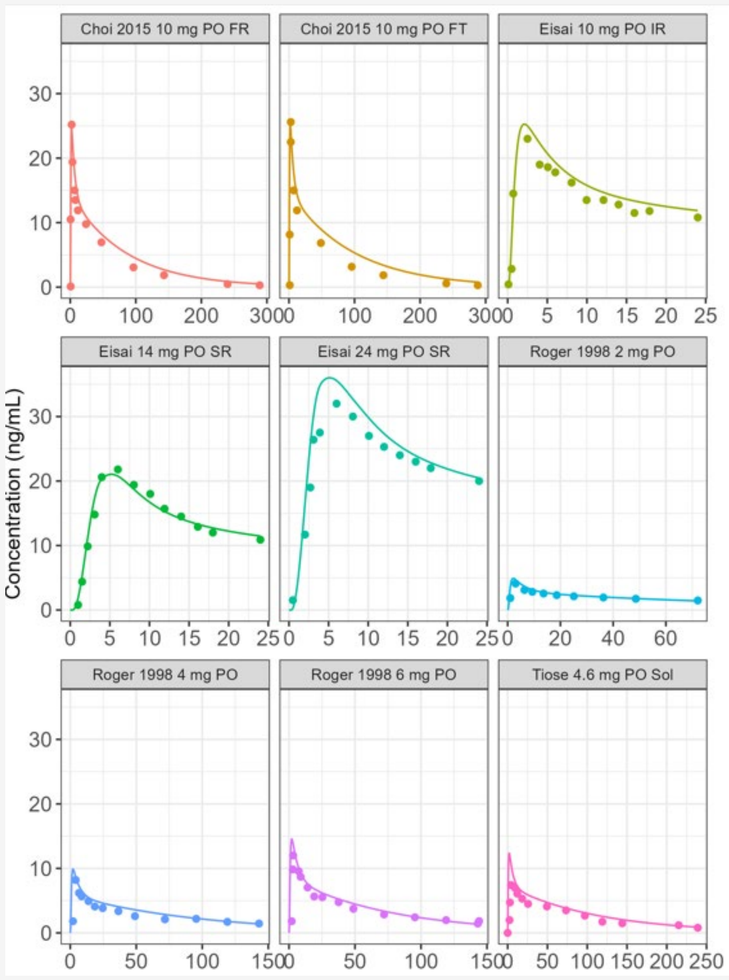
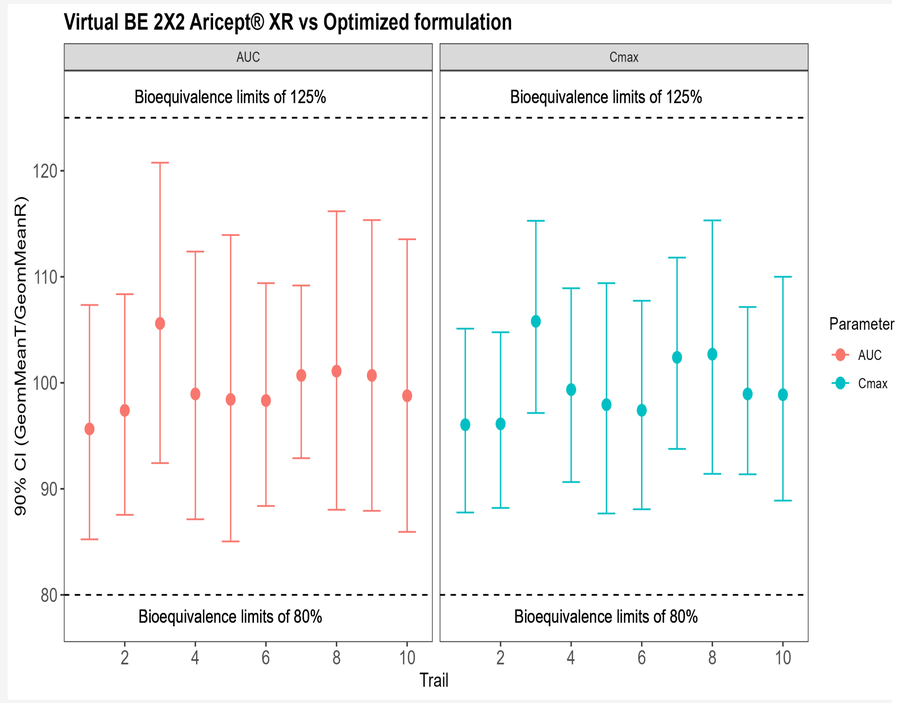


Figure 7: Virtual bioequivalence between optimized formulation and market product Aricept SR.



A stepwise procedure was employed to estimate and confirm biopharmaceutical parameters, enabling the prediction of drug dissolution profiles in the case of donepezil. These data were subsequently inputted in the model to predict *in vivo* response. In the absence of DZP IV PK data, the PBBM model was constructed by adjusting parameters derived from PO data. The accuracy of the model was evaluated based on its capability to align with plasma PK profiles obtained from observed PO PK studies, and its consistency across diverse in vivo dissolution conditions.

CONCLUSION

In conclusion, the application of the DoE-PBBPM has proven to be highly successful in optimizing and assessing the likelihood of bioequivalence (vBE) between two donepezil sustained-release (XR) formulations. The formulation containing 40% HPMC and 5% NaCMC demonstrated a high likelihood of bioequivalence with Aricept XR. However, it is worth noting that future investigations focusing on tablet compression force could significantly contribute to the development of formulation specifications. Overall, the DoE-PBBM approach has exhibited great potential as an alternative method for both complementary formulation development and bioequivalence studies.

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