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B8

EVALUATION OF THE DISSOLUTION BEHAVIOR OF THE LYSOSOMOTROPIC DRUG AMLODIPINE USING PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODELING (PBBM)

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INTRODUCTION

Amlodipine (AML) is a weak base drug (pKa 9.1, lop=2.96) belonging to class I of the BCS and therefore a candidate for biowaiver. However, different studies have been carried out to determine the release of AML besylate tablets using diverse dissolution conditions such as those of the FDA, WHO, and ICH M9, and the results are discordant[1]. Considering that compendial/pharmacopeial dissolution methods may not be biorelevant, reports of false-positive or false-negative outcomes of the BCS procedure and the importance of appropriate dissolution tests to request a waiver of BE trials from *in vitro* data (%dissolved), the objective of this research was to evaluate the dissolution behavior of AML and relate it with its in *vivo* performance through Physiologically based biopharmaceutics modeling (PBBM)[2].

METHODS

Modeling approach

The model was built and validated using GastroPlus® version 9.8.3. All oral PK profiles were of the innovator product Norvasc®. Due to AML characteristics lysosomal trapping was evaluated with MembranePlus™.

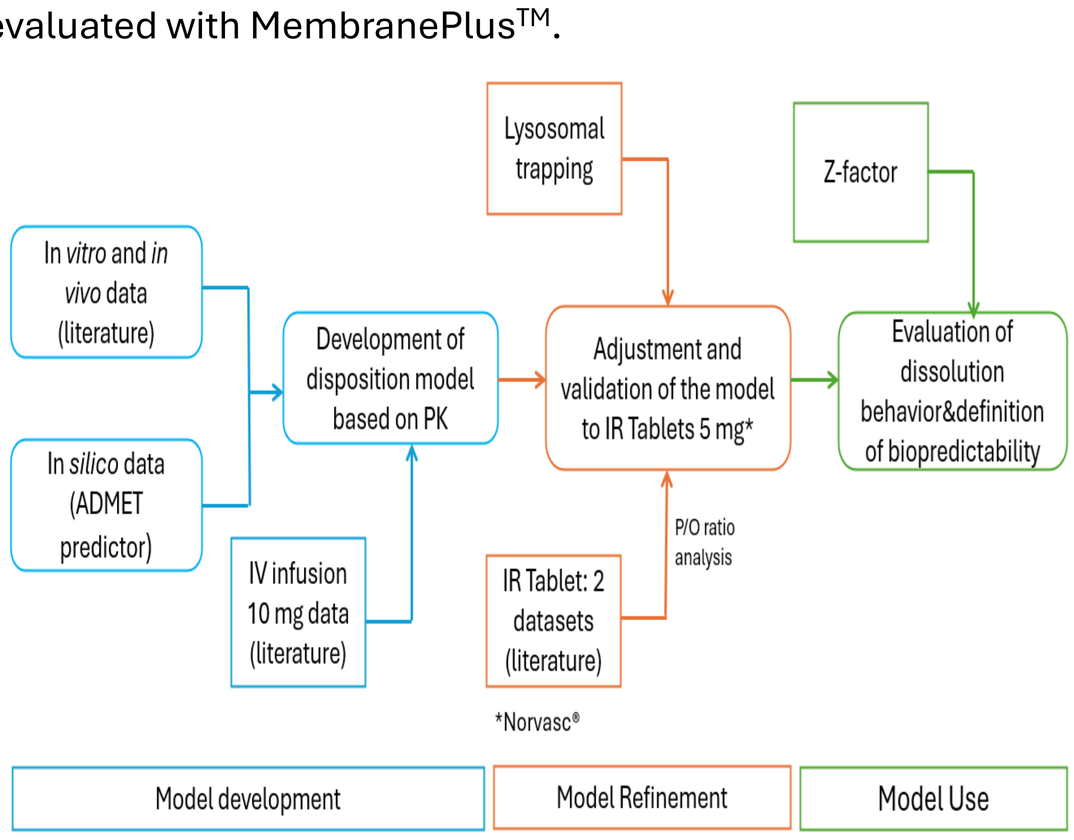

Figure 1. PBBM Workflow for Amlodipine.

In vitro dissolution

Experiments of dissolution were performed with Norvasc IR Tablet 5 mg under the following conditions: apparatus 2 (paddle) at 50 rpm, and 900 mL of buffered media at pH 1.2, 4.5 and 6.8 for 10, 20 and 30 min[4].

RESULTS AND DISCUSSION

The two-compartment model exhibited a good fit with all datasets examined (IV and oral routes), as represented by Figure 2, and the predicted/observed (P/O) ratio values for C_{max}, $T_{max,}$ and AUC were within the 0.8-1.25 acceptance criteria (table 1).

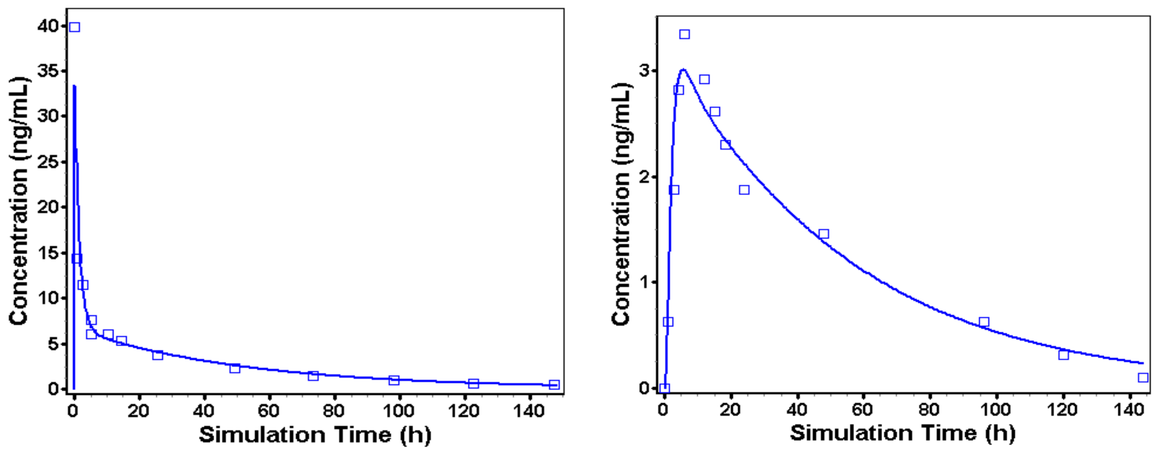

Figure 2. Observed (squares) and predicted (line) mean plasma concentration (Cp)-time profiles of Amlodipine after 10 mg IV infusion (left) and 5 mg IR Tablets (right)[4,5].

Table 1. Predicted (Pred) and observed (Obs) PK values of IV infusion and IR tablet 5 mg administration of AML, and the respective P/O ratio.

PK parameter	IV infusion			IR Tablet		
	Obs	Pred	P/O	Obs	Pred	P/O
C_{max} (ng/mL)	39.88	33.408	0.837	3.349	3.0068	0.897
T_{max} (h)	0.166	0.166	1	6.1458	5.58	0.907
AUC_{0-t} (ngh/mL)	349.11	363.37	1.04	165.13	161.26	0.976
$AUC_{0-\infty}$ (ngh/mL)	378.14	383.79	1.014	167.47	173.71	1.037

At the validated model, the *in vitro* dissolution profiles were modeled in GastroPlus® using the calculated Z-factor, for each pH.

Table 2. Calculated Z-factor values and solubility concerning the assessed pH.

pH	Z- factor (mL/mg/s)	Solubility (mg/mL)
1.2	4.98×10^{-4}	3.853
4.5	4.05×10^{-4}	3.323
6.8	4.96×10^{-4}	1.583

The results indicated that the three dissolution test conditions evaluated can be used as biopredictive since similar predicted *in vivo* behavior was observed independent of the dissolution profile used in the model. On the other hand, AML is trapped by lysosomes, with a fraction unbound to the enterocytes (Fuen)t of 1.3% (Figure 3), according to the parameter sensitivity analysis (PSA).

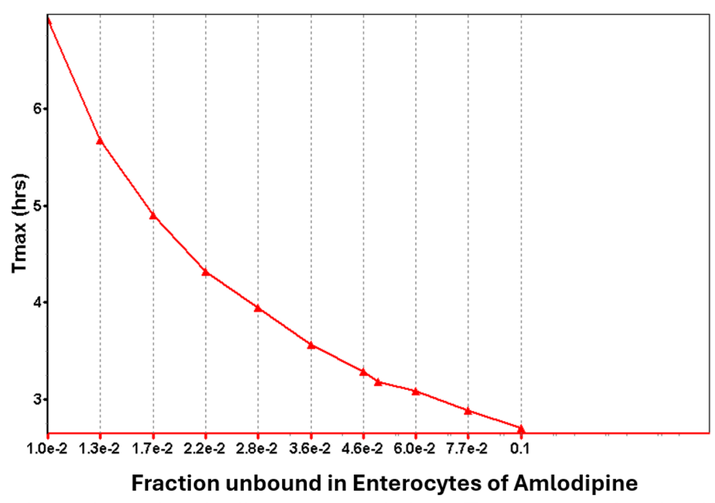

Figure 3. PSA showing the influence of the Fuent on Amlodipine T_{max}.

CONCLUSION

The PBBM model was able to predict the Cp-time profile of AML and lysosomal trapping was responsible for the long T_{max} (>6 h), being the main factor for the slow appearance of the drug in plasma. Similar Z-factor values were found for different dissolution profiles reported in the literatura for pH 1.2, 4.5 and 6.8, and similar predictions were obtained based on these dissolution profiles. These three dissolution test conditions can be considered biopredictive, and as evidenced in this study, the *in vitro* dissolution test did not present a great relevance in the case of Amlodipine, a BCS class I drug, subjected to lysosomal trapping.

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REFERENCES

[1] Cook H *et al*., *Trop J Pharm Res* **17**, 1685, 2018.

[2] Cristofoletti R *et al., J. Pharm. Sci,* ***102***, 3136, 2013.

[3] Sharp S *et al.*, *The AAPS Journal, **20**, 93*, 2018.

[4] Zaid A et al. *The AAPS Journal,* **68,** 625, 2018.

[5] Faulkner and Gibney.*Br. J. clin. Pharmac*, **22**,21, 1986.