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EVALUATION OF THE DISSOLUTION BEHAVIOR OF ETODOLAC TABLETS USING A PHYSIOLOGICALLY BASED BIOPHARMACEUTICS MODELING (PBBM) APPROACH

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Introduction and Objective

Etodolac is a non-steroidal, anti-inflammatory, acidic molecule (pKa 4.65) with pH-dependent solubility and classified as a BCS class II drug [1]. Due to its low and pH-dependent solubility, the objective of this study was to evaluate the influence of different dissolution test conditions on its bioavailability results using a PBBM approach.

Methods

Experimental dissolution tests were carried out using the Reference Listed Drug (RLD) product in Brazil, Flancox® 400mg tablets (n = 3), using USP apparatus 2 (paddle) 50 rpm, and 1000 mL of 0.05M phosphate buffer (PB) solutions at pH 5.5, 6.0, 6.4, and 6.8 at 37°C.

The PBBM (Figure 1) was built and validated using GastroPlus® version 9.8.3 software. Different PK datasets were extracted from the literature as well the physicochemical/biopharmaceutical properties of the drug. The Cp-time curve of the RLD product in USA, Lodine® 400 mg tablets [2], was used for comparison purposes.

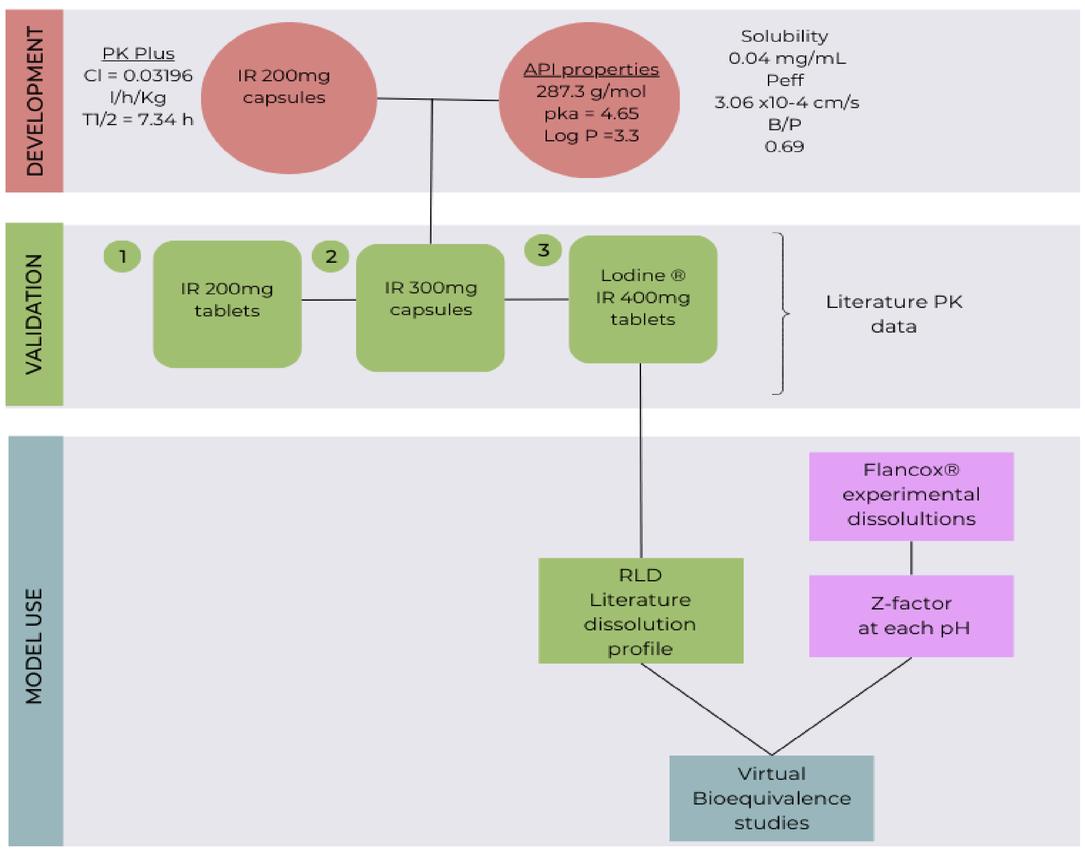

Figure 1. PBBM workflow.

Results

The pH-dependent solubility of etodolac was observed in the dissolution profiles obtained at different pH conditions (Figure 2).

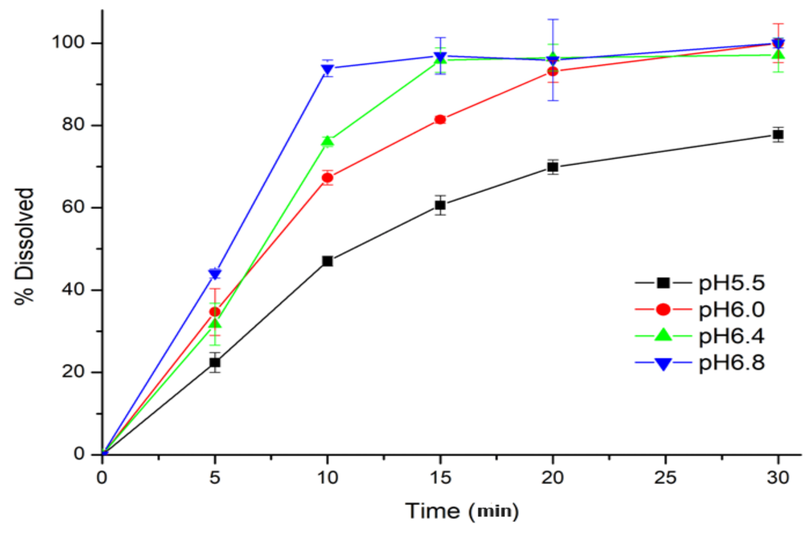

Figure 2. Dissolution profiles of Flancox® 400mg tablets (n = 3), obtained using USP apparatus 2 (paddle) at 50 rpm, and 1000 mL of 0.05M phosphate buffer (PB) solutions at pH 5.5, 6.0, 6.4, and 6.8 at 37°C.

Each dissolution profile (Figure 2) was modeled using the Z-factor dissolution model in GastroPlus®. The obtained Z-factor values and the correspondent solubility of the drug are shown in Table 1.

Table 1. Z-factor values obtained by fitting to each dissolution profile of Flancox 400 mg at pH 5.0, 6.0, 6.4, and 6.8.

pH	*Z- factor* (mL/mg/s)	Solubility (mg/mL)
5.5	1.40×10^{-3}	0.56
6.0	7.40×10^{-4}	1.6
6.4	3.20×10^{-4}	3.9
6.8	1.49×10^{-4}	9.69

A two-compartment PK model was obtained and used in the PBBM to run the simulations. It presented a good fit (Figure 3) to the Cp-time curve of Lodine® 400 mg.

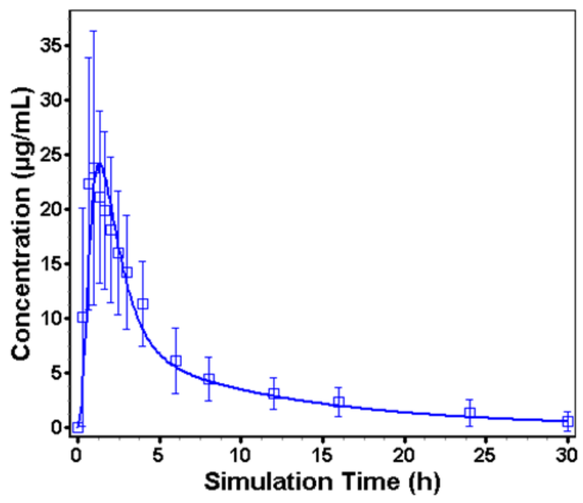

Figure 3. Predicted (line) Cp-time curve using the developed and validated model and observed (squares) Cp-time curve of Lodine 400 mg tables.

Each Z value was incorporated in the model and ten virtual bioequivalences (VBE) were run for each condition in comparison to Lodine®. Table 3 brings a summary of the results found in the VBE.

Table 2. Average VBE results for Z-factor of Flancox (Test) *versus* Lodine (Reference) with 90% CI using dissolution profiles obtained on pH 5.5, 6.0, 6.4 and 6.8.

pH	Cmax Geometric ratio (%) (T/R)	Cmax 90 % CI	AUC_{0-t} Geometric ratio (%) (T/R)	AUC_{0-t} 90% CI
5.5	104	96 - 114	100	91 - 111
6.0	103	95 - 112	100	90 - 111
6.4	99	91 - 107	100	91 - 111
6.8	92	84 - 100	100	90 - 110

The results showed similar predicted in vivo dissolution behavior of the evaluated drug product Flancox® , with high probability to be bioequivalent to the FDA's reference drug product, Lodine ®.

Conclusion

Although etodolac is a BCS class II drug, under pH conditions above its pKa, it behaves as a BCS class I drug, according to the predictions and virtual bioequivalence studies.

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References

[1] Hu, X *et al.*, *Journal of Molecular Liquids*, **volume 316**, page 113779, 2020.
[2] Center for Drug Evaluation and Research. Application number 75054.