Use of PBBM to Establish Dissolution Safe Space via IVIVR for Concor®

Authors: Joyce S. Macwan[1], Grazyna Fraczkiewicz[1], Mauro Bertolino[2], Phillip Krüger[3], Sheila-Annie Peters[2]

Affiliation: [1]Simulations Plus, Inc, Lancaster, California, USA; [2]Quantitative Pharmacology, Merck KGaA, Darmstadt, Germany ; [3]Manufacturing Science and Technology, Merck KGaA, Darmstadt, Germany

CONTACT INFORMATION: joyce.macwan@simulations-plus.com

PURPOSE

Merck KGaA observed slight differences in the dissolution of Concor® (bisoprolol) batches over the years. The purpose of this work was to assess the impact of *in vitro* dissolution on the simulated PK of Concor® using *in vitro–in vivo* relationship established with available *in vitro* dissolution and corresponding Cp-time data for several bisoprolol batches.

We evaluated potential influences of variability in dissolution of bisoprolol batches on its clinical performance through PBBM and virtual bioequivalence trials.

METHODS

The GastroPlus® 9.6 (Simulations Plus, Inc., Lancaster, CA) Advanced Compartmental Absorption and Transit (ACAT™) model was used in conjunction with the PBPKPlus to build a mechanistic absorption/PBPK model for bisoprolol. The physicochemical and biopharmaceutical properties for bisoprolol were defined using a combination of *in silico* estimates, measured *in vitro* data obtained from the literature and/or Merck, and fitted values.

Human organ weights, volumes, and blood perfusion rates were generated by the Population Estimates for Age-Related (PEAR™) Physiology™ module. All tissues were modeled as perfusion-limited tissues and Kps were calculated using the default Lukacova [1] method. Intravenous plasma data from the literature [2] were used to calibrate Vss. Due to lack of information, Rbp was fitted (1.1) to account for the effect of lysosomal trapping on Vss following intravenous administration. To explain the observed delay in T_{max}, fraction unbound in enterocytes was fitted to 5% to include lysosomal trapping in enterocytes. The total systemic clearance included metabolic clearance in liver and renal excretion. *In vitro* clearance [3] was not predictive of *in vivo* clearance and therefore liver clearance was scaled to match *in vivo* Cp-time profiles. Renal excretion was modeled as fraction of kidney blood flow method, where the fraction of 0.12 was fitted to match urinary excretion of unchanged bisoprolol (~50%) as reported in literature [2].

For the baseline model, the default Johnson model was used to model drug dissolution. For IVIVR and virtual BE trials, single Weibull parameters fitted to *in vitro* dissolution data were used as *in vivo* dissolution input. Clinical batch 5080504 (study ALO-P8-481) was selected as the reference formulation because it is representative of the observed mean dissolution profiles for which Cp-time profiles were available. In the absence of an observed Cp-time profile for batch 231975, which had the slowest observed dissolution, the safe space IVIVR was established by predicting the Cp-time Profile of this batch using an *in vitro* dissolution profile measured at pH 6.8 as input and comparing it to the reference formulation.

Individual subject data from study ALO-P8-481 were used to generate virtual populations with matching mean demographics for virtual BE evaluations. *In vitro* dissolution data of the slow dissolution batch (231975 @ pH 6.8) were first used to assess BE by comparing them to the reference formulation. An expanded safe space was established by extrapolation using the hypothetical dissolution profiles beyond the knowledge space.

RESULTS

The PBPK model was able to reproduce the Cp-time profile following intravenous administration [2] (Figure 1a). The model estimated absolute oral bioavailability of 89%, which agrees with the reported value. The reported urinary excretion profile of unchanged bisoprolol after 20 mg IR solution dosing (47.8% ± 10.5%) was accurately captured by the proposed model (estimated urinary excretion ~42%) (Figure 1b). The model accurately explains the observed oral Cp-time profiles obtained from the literature [2-8] and clinical studies conducted by Merck (Figure 1c–f). Simulated bisoprolol oral Cp-time profiles were within the BE limit of 0.8–1.25 of the clinically observed mean data (results are not shown).

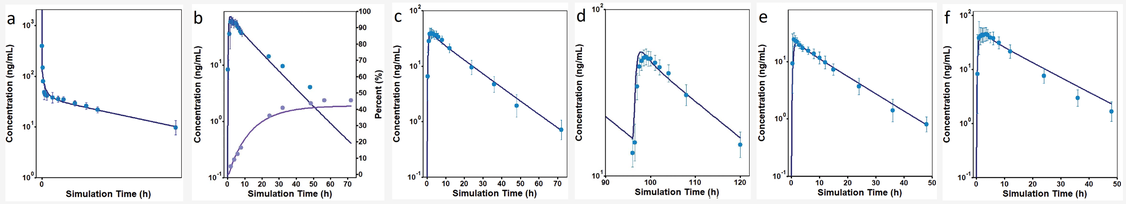

Figure 1 Mean observed (symbols) and simulated (lines) bisoprolol plasma concentrations in the fasted state following (a) 10 mg intravenous bolus dose[2], (b) a single oral dose of 20 mg solution[2], (c) a single oral dose of a 10 mg IR tablet (Merck study ALO-P8-481), (d) once-a-day doses of a 10 mg IR tablet for 5 days (Merck study ESO-P0-180), (e) a single oral dose of a 10 mg IR tablet (Merck study EMR200006-001), and (f) a single oral dose of a 10 mg IR tablet (Merck study CAEP 43.001.15)
(b) Cumulative amount excreted in urine (purple) are shown as percent of the administered dose (y axis on the right) for literature [2] mean observed (symbols) and simulated (lines) bisoprolol urine concentrations.

The crossover virtual trials demonstrated that the point estimates and 90% CIs of the GMR of the simulated PK of the batch with slow dissolution [(231975 @ pH 6.8) results are not shown] and the fast-dissolving batch (229619 @ pH 6.8) were within the BE limits of 0.8–1.25 of the observed PK parameters of the clinical batch used in ALO-P8-481 (Table 1).

Table 1 Point estimates and 90% CIs for PK of batch 229619 @ pH 6.8 (fast-dissolving batch) and hypothetical dissolution profiles from a single crossover virtual trial

Dissolution Profiles	C_{max} (ng/mL)		AUC_{0-t} (ng.h/mL)[b]		AUC_{0-inf} (ng.h/mL)	
	Point estimates[a]	90% CI	Point estimates[a]	90% CI	Point estimates[a]	90% CI
Batch 229619 @ pH 6.8 (fast)	92.36	87.04 - 98.73	107.70	100.72 - 113.11	106.80	99.75 - 112.13
Hypothetical: Example 1	87.05	82.11 - 92.29	108.70	102.74 - 114.97	107.40	101.50 - 113.59
Hypothetical: Example 2	85.86	80.69 - 91.82	108.40	101.42 - 113.89	107.00	99.98 - 112.42
Hypothetical: Example 3	84.10	78.96 - 89.95	107.30	100.29 - 112.61	105.80	98.78 - 111.07

a Calculated (Geometric mean Test/Reference)*100, b t=72 h

The hypothetical profiles had a mean dissolution of 72%, 70%, and 69% (example 1, 2, and 3, respectively) at 15 min and 81%, 79.5%, and 78% (example 1, 2, and 3, respectively) at 30 min (Figure 2). The hypothetical profile with 70% and 79.5% dissolved at 15 and 30 min, respectively (example 2), was the slowest dissolution profile that was within BE criteria, and the hypothetical profile - example 3 was marginally outside of the BE limits (Table 1). These simulations suggest that provided the shapes of the profiles are comparable, minimum 70% dissolution in 15 min and 79.5% at 30 min is sufficient for new batches to be bioequivalent with the current formulation.

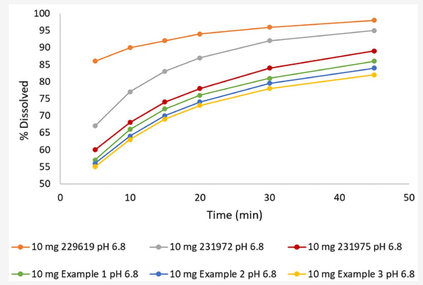

Figure 2 Experimental (the three fastest) and hypothetical examples (the three slowest) of the dissolution profiles for a 10 mg immediate release tablet

CONCLUSION

The validated PBBM model, which was used to run several crossover virtual BE trials, demonstrated that differences in dissolution of fast-dissolving and slow-dissolving batches did not impact the PK of bisoprolol. This work demonstrated the possibility of developing an approach for requesting a biowaiver for a bisoprolol drug product that exhibits varied release properties. This analysis suggests that extrapolation outside the knowledge space may be extended to other BCS class I compounds with well-defined dissolutions (e.g., rapid dissolution) and well-characterized absorption properties (e.g., no change in excipients) because the risk for lack of *in vivo* performance similarity is very low.

REFERENCES

1. Lukacova et al. In. AAPS Annual Meeting. Atlanta, GA; 2008
2. Leopold G, et al. J Clin Pharmacol. 1986; 26:616-621
3. Horikiri Y, et al. Life Sci.1998; 63:1097-1108
4. Dutta A, et al. Clin Pharmacol. 1994; 34:829-836
5. Buś-Kwaśnik K, et al. Kardiol Pol. 2017; 75:48-54
6. Kirch W, et al. Clin Pharmacokinet. 1987; 13:110-117
7. Kirch W, et al. Clin Pharmacol. 1986; 31:59-62
8. Ding L, et al. J Pharm Biomded Anal. 2007; 44:520-525