In Vitro Dissolution as a Tool for Formulation Selection: Telmisartan Two-Step IVIVC
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Purpose
In-vivo predictive dissolution methods (iPD) can be useful tools during product development in order to ensure the bioequivalence of new formulations in the clinical phases or the generic ones after patent expiration. The validation of the predictability of the in vitro test requires its comparison with human in vivo results. In this work an exploratory two-step level A in vitro in vivo correlation (IVIVC) was developed for three Telmisartan oral immediate release formulations, the reference product Micardis and two generic formulations. One of the generic formulations (X2) demonstrated in vivo bioequivalence (BE) while the other (X2) failed to show BE due to the lower limit of the 90% confidence interval on Cmax being outside the acceptance limits.

Methods
Individual plasma profiles of Telmisartan for all the formulations were deconvoluted by Loo-Riegelman method to obtain the individual fractions absorbed (fa). The average of the individual fa versus time profiles was calculated for each formulation. Fractions dissolved (fdiss) were obtained in several conditions in USP II and USP IV apparatus. The apparatus and conditions showing the same rank order than in vivo were selected for further refinement of conditions. Levy plot was constructed to estimate the time scaling factor.

Results
Figure-1 shows in the top panel the fractions dissolved versus time on the original time scale obtained in the US IV apparatus with a three-step pH change (from 1.2 to 4.5 and 6.8) and 0.05% of tween 80, superimposed with the fractions absorbed versus time. Bottom panel shows the same variables (fa and fdiss profiles) with the time scaled for the fraction dissolved. None of the USP II conditions were able to match the in vivo behavior. Figure 2 displays the level A IVIVC. Fa versus fdiss correlation showed a linear trend with a good correlation coefficient. Nevertheless, the in vivo prediction error on Cmax was slightly higher than 15%.

Conclusion
Telmisartan is a low solubility weak base for which in vivo dissolution is determined by physiological variables as pH changes during intestinal transit and the presence of natural surfactants. On the other hand, in vivo dissolution seems to be the limiting factor for its absorption. In this work a more physiological dissolution set up in USP IV apparatus, allowing to simulate the pH gradient and the presence of surfactants, is able to show the formulations differences in dissolution that were previously observed in vivo in one successful and one failed BE study. Even if the dissolution conditions will need further refinement to fulfill regulatory requirements for a biowaiver claim, they could be used as a risk-analysis tool for formulation selection in future BE trials.

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