Predicting the Higher Bioavailability Observed for Oxybutynin’s OROS Formulation Compared to the Immediate-Release (IR) Tablet Using a Novel Simplified Absorption PBPK Model

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Purpose
A new model that describes the small intestinal transit time using a reduced number of small intestinal compartments has been recently proposed [1]. This model, or minimal Segmented Transit and Absorption model (mSAT), was combined with a new method to parametrize human intestinal permeability (P_peff) in order to predict regional gastrointestinal (GI) absorption (fa) [1]. The aim of this study was to extend such a model and to apply it for the prediction of the oral bioavailability (F) and pharmacokinetics of oxybutynin (OXY) when administered as IR and Controlled-release (CR) OROS formulations, and to explain the higher relative bioavailability observed for the OROS formulation [2].

Methods
The mSAT model was extended to predict OXY’s pharmacokinetics. The model describes the human GI tract by five compartments: stomach, duodenum, jejunum, ileum and ascending-colon [1]. The drug can be modelled either in the solid state or the dissolved state. For the extension of the model, OXY’s dissolution was implemented and predicted using a diffusion layer model[3] employing drug’s segmental solubility, calculated based on segmental differences in pH, bile-salts and water volumes. Segmental drug absorption was predicted from Peff and mucosal surface area differences (Method 3 described in [1]). Enterocytic compartments were implemented to predict segmental intestinal first-pass metabolism using OXY’s intrinsic clearance (CLint), CYP3A abundance and villous blood flows. OXY’s disposition and systemic clearance was described by a semi-physiological three compartment model, including a liver compartment, implemented within the mSAT model. All the drug-related and physiological parameters were taken from the literature, with the exception of OXY’s disposition parameters and CLint, which were derived from fitting OXY’s disposition model to the intravenous data described in [4]; assuming a 100% hepatic and CYP3A4-mediated clearance. The model was implemented in Matlab® 2014a. Finally, the pharmacokinetics of oxybutynin after oral administration of three 5 mg IR tablets and one 10 mg OROS formulation were mechanistically predicted using OXY’s physicochemical and biopharmaceutical properties and the mSAT model.

Results
The predicted pharmacokinetics of OXY administered as IR and OROS formulations are shown in Figure 1. The predicted F for the IR formulation was 9.5%, close to the reported value of 6.2% [4]. For the OROS formulation the predicted F was 17.5%, in agreement with the data suggesting that the OROS formulation shows higher bioavailability than the IR counterpart [4]. The observed and predicted main pharmacokinetic parameters for OXY (IR and OROS) are summarized in Table I. From the model predictions it can be noticed that the higher bioavailability observed for the OROS formulation is mainly attributable to differences in intestinal first-pass metabolism (FG) rather than due to a higher fa. The predicted fa was 1.00 and 0.50 for the IR and OROS formulations, respectively, whereas the predicted FG was 0.16 and 0.88 for the IR and OROS formulations, respectively.

Conclusion
The extended mSAT model was able to predict the OXY’s pharmacokinetics and bioavailability differences after oral administration for both the IR and the OROS formulations. These results provide further support to the hypothesis of an increased FG as the main factor responsible to explain the higher bioavailability observed for OXY’s OROS formulation vs the IR [4, 5].

References