The Importance of Lysosomal Trapping for Setting Clinically Relevant Product Specifications for Dextromethorphan Immediate Release Dosage Forms

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Purpose
Physiologically based pharmacokinetic (PBPK) in silico models are increasingly used by the pharmaceutical industry and regulatory authorities in the development of new drug products. PBPK models use a ‘‘bottom-up’’ approach by mechanistically describing the physiology of a biological system. A drug’s blood concentration profile in different tissues is estimated depending on its physiochemical properties, route of administration and metabolic events in the different tissues. Dextromethorphan (DEM) undergoes different extents of metabolism in different populations. The current study developed a PBPK model for DEM and its metabolite dextrophan (DXO) which includes the effect of lysosomal trapping in extensive (EM) and poor metabolisers (PM). Lysosomal trapping appears when a weak base diffuses into the lysosomes of an enterocyte. The pH within a lysosome is lower compared to the cytoplasm. Therefore, the drug molecule gets ionized in the lysosome and is now more hydrophilic and needs more time to partition out of the lysosome. The study shows how clinically relevant product specifications can be set using this PBPK model.

Methods
Gastroplus™ 8.5 (Simulation Plus, Inc.) Advanced Compartmental Absorption and Transit (ACAT™) model and PBPK plus modules were used to build the dextromethorphan model for absorption, distribution, and excretion. Physiological and biochemical parameters were either obtained from literature or were predicted using ADEMET Predictor™ 7.1 (Simulation Plus, Inc.). Human organ weights, volume, and blood perfusion rates were generated by the Population Estimate of Age Related (PEAR™) data-base. The metabolic clearance of DEM was estimated from in vitro enzyme kinetic values of CYP2D6 and CYP3A4. The model was tested and validated with different pKa, Log P values reported in literature and lysosomal trapping was added to the model. Simulations were performed using a 30 mg immediate release (IR) tablet in EM and PM populations and compared with the reported values in healthy volunteers.

Results
There was a significant difference in DEM plasma profiles between EM and PM simulations. Different Log P and pKa values significantly affected the plasma profile in EM and PM due to significant differences in plasma protein binding that vary from 13% to 48%. The plasma protein binding effected metabolism in the liver. Lysosomal trapping influenced the plasma profile by prolongation of tmax. In PM a higher Cmax, longer tmax, and larger AUC0-24 of DEM was observed in comparison to EM. Accordingly, EM showed a higher Cmax, longer tmax and larger AUC0-24 for the metabolite DXO compared to PM. Both EM and PM plasma profiles of DEM and its metabolite DXO matched well with the reported clinical study. The model shows that DEM is fast absorbed into the enterocytes but the drug and it metabolite only appear slowly in the plasma due to lysosomal trapping. The PBPK model showed that the absorption of DEM was permeability controlled. Parameter sensitivity analysis showed that a particle size of less than 11 um ensures sufficient dissolution without changing any PK parameters like tmax, Cmax, or AUC0-24. Therefore, particle size control together with a disintegration test are suggested as relevant product specifications.

Conclusion
The validated in silico PBPK model was able to simulate the plasma profile of DEM and DXO in PM and EM. The mechanistic model helps to understand the different physiochemical and biological factors affecting the plasma profiles in pharmacogenomically different populations. Lysosomal trapping was identified as main factor for the slow appearance of the drug in plasma. If the absorption of a drug is permeability controlled then particle size and disintegration can be sufficient product specifications to ensure clinical relevant product performance.