Use of PBPK modelling to evaluate the performance of DissolvIt, a biorelevant dissolution assay for orally inhaled drug products

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Abstract

The dissolution of inhaled drug particles in the lungs is a challenge to model using biorelevant methods in terms of: (i) collecting a respirable emitted aerosol fraction and dose, (ii) presenting this to a small volume of medium that is representative of lung lining fluid, and (iii) measuring the low concentrations of drug released. We report developments in methodology for each of these steps and utilise mechanistic in silico modelling to evaluate the in vitro dissolution profiles in the context of plasma concentration-time profiles. The PreciseInhale® aerosol delivery system was used to deliver Flixotide aerosol particles to DissolvIt® apparatus for measurement of dissolution. Different media were used in the DissolvIt chamber to investigate their effect on dissolution profiles, these were: (i) 1.5% polyethylene oxide with 0.4% L-alphaphosphatidyl choline, (ii) Survanta®, and (iii) a synthetic simulated lung lining fluid (SLF) based on human lung fluid composition. For fluticasone proprionate (FP) quantification, solid phase extraction was used for sample preparation with LC-MS-MS analysis to provide an assay which was fit for purpose with a limit of quantification for FP of 312 pg/mL. FP concentration-time profiles in the flow-past perfusate were similar irrespective of the medium used in the DissolvIt chamber (~0.04-0.07%/min), but these were significantly lower than transfer of drug from air-to-perfusate in isolated perfused lungs (0.12%/min). This difference was attributed to the DissolvIt system representing slower dissolution in the central region of the lungs (which feature non-sink conditions) compared to the peripheral regions which are represented in the isolated lung preparation. Pharmacokinetic parameters (Cmax, Tmax and AUC0-∞) were estimated from the profiles for dissolution in the different lung fluid simulants and were predicted by the simulation within 2-fold of the values reported for inhaled FP (1000 µg dose) administered via Flixotide Evohaler® 250 µg strength inhaler in man. In conclusion, we report methods for performing biorelevant dissolution studies for orally inhaled products and illustrate how they can provide inputs parameters for physiologically based pharmacokinetic (PBPK) modelling of inhaled medicines.