The Impact of Particle Size in the Delivery of Drugs by Inhalation

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**Objectives:** To assess the effect of the particle size in-silico when delivering mometasone directly to the lung in a rodent model of lung inflammation by adding a deposition module to Merck’s multi-scale mechanism-based integrated computational lung platform [1].

**Methods:** The deposition module is based on the typical path lung model [2] and considers three deposition mechanisms: diffusion, sedimentation, and inertial impaction based on drug particle properties such as density and diameter. Parameters associated with dissolution, absorption, transport, distribution, and partition [1] were calibrated to describe the observed plasma and lung exposure profiles of IT-delivered mometasone in rats exposed to allergen lipopolysaccharide (data not shown). Given these PK parameters, PD parameters were calibrated with the neutrophil response after same allergen and inhaled mometasone for 7 doses, assuming a particle diameter of 3 um as calculated using gravimetric and analytical data [1]. The baseline error was defined as the mean square error of the fit w.r.t. the PD response for all doses. Fixing all other parameters, the increase in the error of the fit was computed w.r.t. the baseline error when varying the particle diameter.

**Results:** The deposition fractions changed for varying particle diameters (Fig.1A) with systemic and lung concentration profiles and PD response changing accordingly (Fig.1B and C). The error of the fit increased more than 100% and 50% when the particle diameter was 1 and 5 um, respectively, versus the diameter of 3 um (Fig.1D), all other parameters fixed.

**Conclusions:** Our computational platform was qualified using existing IT and inhaled literature data on mometasone, providing an in-silico option to predict local lung concentration and PD response profiles that are generally difficult to measure. The strong dependency of deposition fractions (and therefore, of PK and PD profiles) with particle size was illustrated.

**Impact of particle diameter** The deposition fractions in the NOPL (nasal cavity, oral cavity, pharynx and larynx), TB (tracheobronchial), and P (pulmonary) regions depend on the particle diameter (A). The plasma and lung PK and PD profiles for diameters of 1, 3 and 5 µm are shown in (B) and (C), respectively. The percentage error increase in the PD fit with respect to the error for a diameter of 3 µm is also shown (D).