

## **Engineering of inhalable microparticles containing terbinafine for management of pulmonary fungal infections**

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Terbinafine is a broad-spectrum antifungal agent with potential therapeutic value in management of pulmonary aspergillosis. The aim of this work was to engineer a dry powder inhalation formulation of terbinafine hydrochloride by nano spray drying. A factorial experimental design was constructed to study factors influencing characteristics of formulations prepared by nano spray drying. The experimental design involved two excipients (mannitol and lactose), different spray solvents (hydroethanolic and aqueous), different spray nozzles, and different drying gas inlet temperatures. The nano spray drying products were characterized mainly in terms of the yield, the crystallinity using differential scanning calorimetry, the disintegration/dissolution behaviour in a bronchial/alveolar fluid surrogate, and the aerodynamic performance using a Next Generation Impactor with Cyclohaler® as an inhalation device at 100 L/min. Factors influencing characteristics of nano spray drying products were identified. The influence of the spray solvent was most interesting: a spray solvent composed of 50.5 % w/w ethanol in water was found, compared to water, to result in smaller particles with up to 3.5-fold higher respirability, i.e. higher fine particle fractions. The influence is attributed to the dependence of the size of spray droplets generated by the vibrating-mesh atomizer on the spray solution viscosity. The formulations exhibited partial (< 40 %) drug dissolution within 2 minutes of dispersion in a bronchial/alveolar fluid surrogate. Undissolved drug particles were smaller than 160 nm in diameter, suggesting they have potential to avoid clearance by alveolar macrophages and mucociliary escalation and to thus provide prolonged local action.