## Comprehensive Characterization of Raw Simvastatin and Fasudil as Therapeutics in Targeted Pulmonary Drug Delivery for Pulmonary Hypertension

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Pulmonary hypertension (PH) is a progressive disease that leads to increased intraarterial pressure in the pulmonary vasculature and heart failure. Simvastatin and fasudil are novel RhoA/Rho kinase (ROCK) inhibitors that have shown potential in effectively treating pulmonary hypertension via non-invasive, inhalation aerosols and dry powder inhalers (DPIs). Several analytical techniques were comprehensively utilized to characterize the physicochemical properties of the drug powders. Computational methodology was used in predicting physicochemical properties. Karl Fischer titration (KFT) quantified residual water content in the powders. Thermal analysis was employed differential scanning calorimetry (DSC) and imaging in quantifying phase transitions/thermotropic behavior upon heating. Hot stage microscopy (HSM) under cross polarizing lens directly observed the presence or absence of birefringency, a unique characteristic of crystalline materials, as a function of temperature and time. Attenuated total reflectance (ATR)-Fourier-transform infrared (FTIR) spectroscopy and Raman spectroscopy determined the molecular fingerprint of both powders. Gravimetric vapor sorption (GVS) at 25°C quantified water vapor uptake by the drug powders. DSC thermograms showed unique first-order equilibrium order-to-disorder phase transition of solid-liquid melting occurring at different temperatures for each drug. GVS low water vapor uptake as a plateau indicated crystalline powders, as they exist in lowest energy state. Birefringency indicated crystallinity of both drugs. Molecular fingerprinting spectroscopy showed unique chemical spectrum identifications for each drug. This study comprehensively characterized the physicochemical properties of the raw forms of simvastatin and fasudil drugs which are essential for next steps in rationally designing and developing dual drug combination DPIs for targeted pulmonary delivery.