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Preparation of rifampicin/lactose microparticle composites by a supercritical antisolvent-drug excipient mixing technique for inhalation delivery

Ober, Courtney A.

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Preparation of rifampicin/lactose microparticle composites by a supercritical antisolvent-drug excipient mixing technique for inhalation delivery

Courtney A. Ober, Lonji Kalombo, Hulda Swai, Ram B.Gupta

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Abstract

Rifampicin (RIF) is precipitated in the presence of inhalable lactose particles using a supercritical antisolvent-drug excipient mixing (SAS-DEM) technique to create RIF/lactose microparticle composites intended to improve the effectiveness of pulmonary tuberculosis treatments by increasing the respirable fraction of RIF. These RIF/lactose microparticle composites are prepared by dissolving RIF in a liquid solvent and spraying the solution into a high pressure vessel containing supercritical CO2 and suspended lactose particles. As the CO2 extracts the liquid solvent, RIF microparticles precipitate to form a microparticle composite mixture with the lactose particles. The effects of solvent, RIF concentration, and RIF to lactose loading are examined. The RIF/lactose microparticle composites are characterized for composition, particle size and surface morphology, crystallinity, thermal behavior, and physicochemical properties. By placing 1000 mg of lactose microfine in the vessel and varying the spraying time of 1 mg/mL and 5 mg/mL RIF in methanol solutions, RIF/lactose microparticle composites of 1.2%, 7.2%, 14.0%, and 25.7% RIF with relative standard deviations of 5.7%, 4.5%, 5.2%, and 2.3%, respectively, are prepared. Based on scanning electron microscopy, homogeneous RIF/lactose composites consisting of spherical particles less than 8 μm in diameter are produced. X-ray diffraction reveals that the SAS precipitation of RIF form I from methanol produces a polymorphic mixture of RIF form I and RIF dihydrate, due to trace water content in the solvent, while both RIF and lactose retain their individual crystalline structures during SAS-DEM processing. Based on differential scanning calorimetry RIF dihydrate converts to amorphous RIF upon heating. Fourier transform infrared spectroscopy demonstrates the absence of chemical interactions between the RIF and lactose proving a physical composite of the two is produced by the SAS-DEM process, and indicating that the therapeutic effectiveness of the drug should be unaffected.

Keywords

Dry powder inhaler; Lactose; Micronization; Rifampicin; Supercritical antisolvent; SAS-DEM