Methionine offers superior aerosolization stability over leucine for inhalable high-dose spray-dried kanamycin formulation

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Leucine has been widely used to improve aerosolization of high dose spray-dried formulations for inhalation. However, the use of other amino acids such as methionine for the same purpose has not been well established. The aim of this study was to assess the aerosolization stability offered by methionine inclusive formulation. Inhalable particles of kanamycin-methionine (KM) and kanamycin-leucine (KL) were prepared by co-spray drying of the drug with amino acids in 1:1 molar ratio. Solid state characterization was conducted using thermal techniques, microscopy, and Raman spectroscopy. Stability study was performed at 25 °C/<15% relative humidity (RH) and 25 °C/53% RH over 28 days. The Fine Particle Fraction (FPF), determined by Next Generation Impactor with an aerolizer, of the freshly prepared KM and KL formulations were 84% and 85%. Methionine formed a co-amorphous system with kanamycin while leucine crystallized in the co-spray dried in freshly prepared KL. After storage at 25 °C/53% RH for 28 days, the water content of KL and KM were 10.5% and 9.7%, the particles stuck together only in KL, and the methionine in KM crystallized; the FPF of the KL formulation significantly decreased to 79% ($p<0.05$) whereas the FPF of the KM formulation remained unchanged. The decrease in FPF of the KL was possibly due to particle sticking as evident from SEM images. This study suggests that methionine offers better aerosolization stability than leucine at high relative humidity (53%) for kanamycin formulation.