

# Trileucine Improves Aerosol Performance and Stability of Spray-Dried Powders for Inhalation

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**ABSTRACT:** For particles to be useful medicinal aerosols, not only their aerodynamic diameter has to be on the order of a few micrometers but also they have to be chemically and physically stable. Manufacture of respirable particles is a technical challenge because as particles are reduced in size by conventional milling techniques, their cohesiveness greatly increases and physical and chemical stability is often compromised by the formation of amorphous material. In the present study, we describe the use of trileucine for the preparation of dry powders suitable for inhalation via spray drying of a wide range of drugs (i.e., asthma therapeutics such as albuterol and cromolyn, and anti-infectives such as netilmicin and gentamicin, as well as therapeutic proteins and peptides such as human growth hormone and salmon calcitonin). The glass transition of spray-dried trileucine is dependent on the pH and can be correlated with the proportion of the anion, cation, and zwitterion concentration in solution. Trileucine glass transition is relatively high ( $\approx 104^{\circ}\text{C}$ ) enabling long-term room temperature stability. The solubility of trileucine is dependent on the pH and is lowest at neutral pH ( $\approx 6.8$  mg/mL). Trileucine's low aqueous solubility enables the formation of low-density corrugated particles and promotes the formation of trileucine coated spray-dried particles, resulting in superior aerosol performance. Trileucine is surface active and promotes the formation of spray-dried powders with a reduced cohesiveness as demonstrated by a decrease in the measured surface energy which correlates with an observed improvement in aerosol performance. Additionally, trileucine competes with the protein on the air/water interface resulting in an additional depression of surface tension in solution which correlates with a decreased denaturation and aggregation in the solid state. © 2007 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci