The Use of a Novel Excipient to Enable the Preparation of Stable and Dispersible Dry-powder Aerosol Formulations by Spray Drying

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ABSTRACT

We report the use of a novel proprietary excipient that enables the formation of highly dispersible and stable particles suitable for commercial products. A mechanism is proposed to explain the particle formation phenomenon addressing why this excipient produces particles with superior aerosol properties.

OBJECTIVES

- Design particles with small aerodynamic diameter, which are not cohesive, to be efficiently delivered as a dry powder aerosol.

INTRODUCTION

The use of spray drying to prepare dry powders for inhalation of small molecule drugs (such as antibiotics and antiasthmatics) constitutes a technological challenge mainly because fast drying promotes the formation of amorphous material which is intrinsically cohesive and can be unstable. We describe the one-step preparation of dry powders suitable for inhalation using trileucine. The resulting powders have superior dispersibility and room temperature stability. These powders do not require the use of a carrier, which may represent an advantage when large amounts of powder need to be delivered in a single dose.

METHODS & MATERIALS

Powder Preparation

Dry powders for inhalation for several antibiotic and antiasthmatic drugs were obtained from spray drying of aqueous solution with and without trileucine in a Büchi 190 spray dryer.

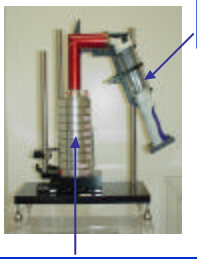
Surface tension of the solutions prior to spray drying was measured using the Wilhelmy plate method using a Krüss model K-12 Tensiometer.

Powder Characterization

SEM was used to monitor particle morphology. Powder surface composition was determined by X-ray Photoelectron Spectroscopy (XPS). Surface energy was calculated from acetone and octane adsorption isotherms at 25°C, which were gravimetrically determined in a DVS.

Aerosol Characterization

The powders' aerosol performance was characterized by their *in vitro* emitted dose (ED) and their fine particle mass less than 3.3 µm (FPM<3.3µm), determined by using a Nektar Pulmonary Delivery System (PDS) and an Andersen Cascade Impactor (ACI), respectively, under controlled ambient conditions (21°C and 40% RH).

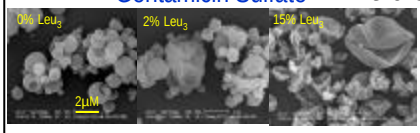


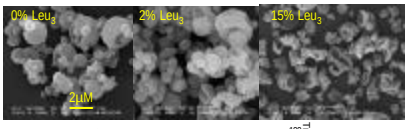
$$ED = \frac{M_{filter}}{M_{blister}}$$

$$FPM = \frac{M_{\leq 3.3m}}{M_{blister}}$$

RESULTS

Gentamicin Sulfate **Antibiotics** Netilmicin Sulfate





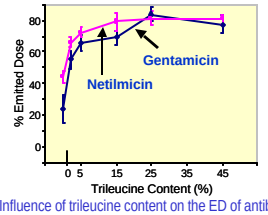


Figure 1. Influence of trileucine content on the ED of antibiotics. ED for a 3 mg blister package tested using the Nektar PDS.

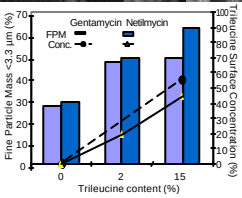
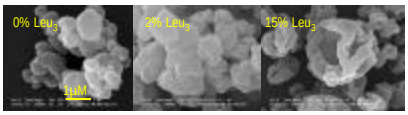


Figure 2. Influence of trileucine content on the fine particle mass <3.3 µm by Andersen Cascade Impactor and Surface Concentration by XPS.

Albuterol **Asthmatic Therapeutics** Cromolyn

Powders contain 2% Albuterol



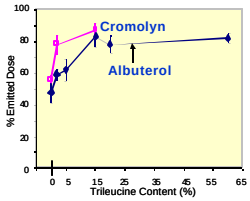


Figure 3. Influence of trileucine content on the ED of anti-asthmatics. ED was for a 3 mg blister package tested using the Nektar PDS. 2% albuterol powders contain raffinose and trileucine.

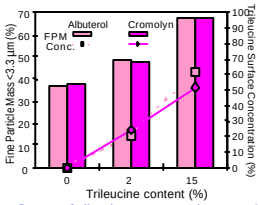


Figure 4. Influence of trileucine content on the FPM <3.3 µm by Andersen Cascade Impactor and Surface Concentration by XPS. 2% albuterol powders contain raffinose and trileucine.

Surface energy, γ_s, of Albuterol/Raffinose/Trileucine powders decreases as trileucine coverage increases

Trileucine concentration (% w/w)	ED (%)	γ_s^d (mNm^{-1})	γ_s^p (mNm^{-1})	γ_s (mNm^{-1})
5	62	30.0	2140.3	254
20	78	30.9	1194.2	192
60	82	30.7	974.4	173

'Formulations contain 2% albuterol, indicated amount of trileucine and the rest is raffinose

Where,

$\gamma_s = (\gamma_s^d \gamma_s^p)^{1/2}$,

γ_s^d is the dispersive (non polar), and

γ_s^p is the polar components of the surface energy

Particle Formation Mechanism

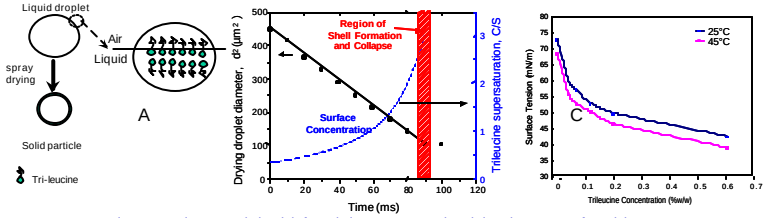


Figure 5. During spray drying (A), formulation components in solution observe a preferential precipitation inversely proportional to their aqueous solubility (B). In addition, trileucine surface activity (C) promotes the formation of a non-polar, low-energy surface.

CONCLUSIONS

- Addition of small amounts of trileucine to the formulation produces dry powders for inhalation with superior FPM and ED of otherwise difficult-to-formulate antibiotics and asthmatic therapeutics.
- Three- to ten-fold enrichment of trileucine on the surface of the spray-dried powders correlates to its high surface activity in aqueous solutions.
- Trileucine containing particles are more "wrinkled" and have low surface energy, which significantly improves aerosol performance.

ACKNOWLEDGMENTS

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