The Use of Novel Excipients to Enable the Preparation of Stable and Dispersible Dry-Powder Aerosol Formulations by Spray Drying

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ABSTRACT SUMMARY

We report the use of a novel proprietary non-sugar 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 superior particles.

Keywords: Spray-dried powders, stability, dispersibility, DPI

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 unstable.

We describe the one-step preparation of dry powders suitable of inhalation using a non-sugar proprietary excipient (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.

EXPERIMENTAL METHODS

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 as described in ref 1. Netilmicin sulfate, gentamicin sulfate, and sodium cromolyn were formulated neat and with various amounts of trileucine. A 2 percent albuterol sulfate formulation was formulated with various amounts of trileucine and raffinose. 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 gross morphology. Each sample was coated with a 15nm layer of Au:Pd using a Desk II sputter coater prior to analysis. SEM images were acquired under high vacuum with a Philips XL 30 Scanning Electron Microscope using an accelerating voltage of 20kV and a beam current of 33 mA.

Powder surface composition was determined by X-ray Photoelectron Spectroscopy (XPS). A monochromatic Al X-ray (1486.7 eV, 300W) with a known take-off angle of 45° was directed to a spot size of 2x3 mm on the sample. Survey and high-resolution spectra were collected with a Physical Electronics PHI 5000 Series Spectrometer.

Aerosol Characterization

The powders aerosol performance were characterized by their in vitro emitted dose (ED) and their fine particle mass less than 3.3 µm ($FPM_{<3.3\mu m}$), determined by using a Nektar™ Pulmonary Delivery System (PDS) and on Andersen Cascade Impactor (ACI), respectively, under controlled ambient conditions (21°C and 40% RH).

RESULTS AND DISCUSSION

The morphology of a spray dried particle (Figure 1) is largely influenced by the drug's solubility and its propensity to crystallize from solution, given by its glass transition temperature and molecular symmetry. A typical morphology of a water soluble molecule is presented in Figure 1 A, which is in striking contrast with the morphology observed when it is formulated with trileucine (Figure 1B)

Powders containing the antibiotic or antiasthmatic drug and a sugar as bulking agent presented low ED and large $FPM_{<3.3\mu m}$ when compared to those prepared with trileucine. For example, the ED of an albuterol/raffinose formulation was improved from 30% to more than

80% with the addition of 20% w/w of trileucine. Similarly, the ED of a gentamicin formulation was improved from 35% to more than 75% with the addition of as little of 5% w/w and ED > 90% were achieved with 25%w/w of the trileucine (Figure 2).

Improvement on the ED was observed to correlate to the amount of the trileucine on the surface of the particles. Such correlation achieved a maximum ED at a concentration that was formulation dependent. The surface concentration correlates with the surface tension of the solution before spray drying suggesting a competing surface enrichment mechanism (Figure 3).

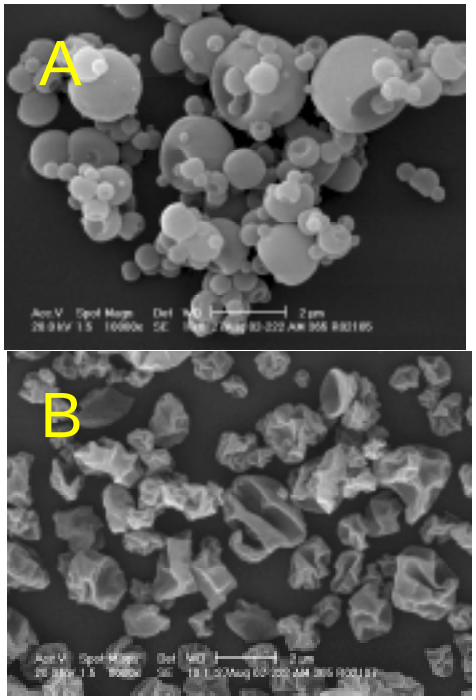

Figure 1: Particle morphology of spray-dried netilmicine, neat (A) and with 15% trileucine (B).

CONCLUSIONS

Addition of small amounts of tri-leucine to the formulation produces dry powders for inhalation with superior FPM and ED of otherwise difficult-to-formulate antibiotics and antiasthmatics. Three- to ten-fold enrichment of trileucine on the surface of the spray-dried powders correlates to its high surface activity in aqueous solutions. This enrichment of trileucine on the surface results in more wrinkled particle morphology and significantly improves the aerosol performance.

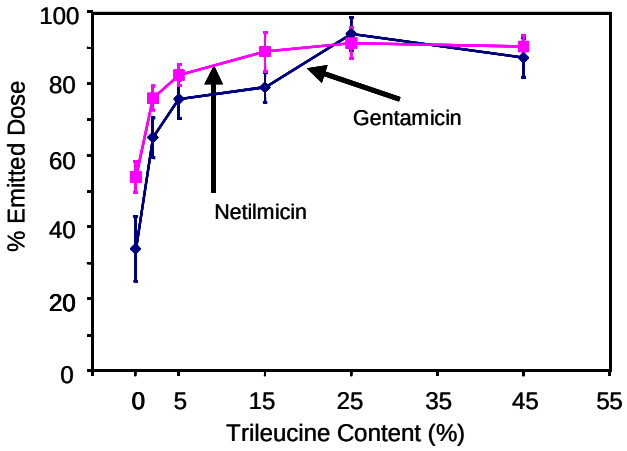

Figure 2: Influence of trileucine content on the emitted dose of antibiotics. Emitted dose from a 3 mg blister package tested using a Nektar™ Pulmonary Delivery System.

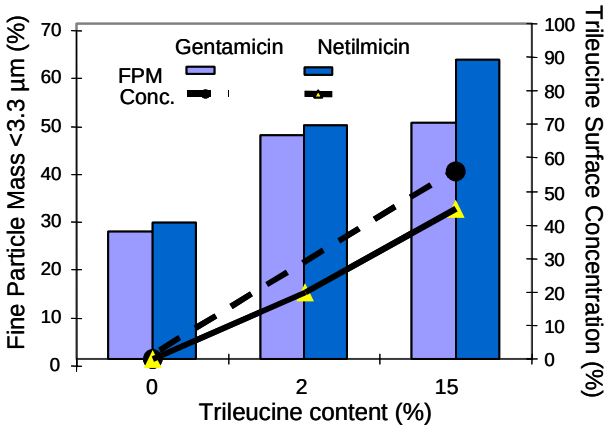

Figure 3: Influence of trileucine content on the fine particle mass < 3.3 µm by ACI analysis and surface concentration by XPS.

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REFERENCES

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