Measurement of Lactose from Dry Powder Inhalers in Impactors

Introduction

In vitro testing is a key element in the testing and understanding of dry powder inhalers. The most common excipient used in dry powder inhalers is lactose. Besides the role of lactose as diluent to aid in filling of devices, capsules or blisters, lactose plays an important role during the inhalation event. Here we will discuss two methods to measure the lactose deposited during in vitro testing in the impactor. The first is a wet-chemical method, where lactose is labeled with ammonia in order to allow for colorimetric determination of the content. The second method is based on Raman spectroscopy in order to distinguish between lactose and other ingredients of the formulation.

Materials and methods

Formulations of lactose (Lactohale (LH) LH100, LH200, and LH210, DFE Pharma; Borculo, the Netherlands) with micronized salbutamol sulphate (Turbula blending) were fired into an MSLI. Formulations of LH100 in combination with LH210 or LH200 with Budesonide as active were fired in an NGI from a Cyclohaler.

Lactose content was tested after reaction with ammonia according to a method described in the pharmacopoeia. The procedure was as follows: lactose was dissolved in water and an equivalent amount of 25% ammonia solution was added. The resulting solution was heated on a water bath at 80°C for 15 minutes. After cooling, the UV-VIS absorption spectrum of the solution was recorded.

Formulations of lactose (blends of LH100 with LH210 or LH201) with micronized budesonide were fired from a Cyclohaler in an NGI. Material from stage 2 was collected and particle sizes, shapes and chemical composition were determined by aid of a Malvern Morphology G3-ID by Raman imaging.

Results and Discussion

The role of lactose solutions that have been treated with ammonia at 80°C is pink to red, dependent on the initial lactose concentration. In the UV spectrum three maxima can be observed at 250, 360, and 310 nm (Figure 1). Calibration curves at each absorption maximum were developed (Figure 2). The curve at 330 nm is linear in a concentration range between 0.01 and 3 mg/mL, ideal for concentrations found for lactose concentration with in-vitro testing. Substituted sulphate has UV absorption bands, but it is relatively easy to distinguish between these absorption bands and of the lactose derivative.

In Figure 3, two examples of in-vitro data were depicted. The composition, lactose versus substituted sulphate, was identical for both formulations, only the type of lactose was changed. Morphology G3 inspection of samples fired in an NGI of the material on stage 2, showed single particles and small agglomerates. Raman inspection of these particles and agglomerates revealed three types of material: lactose only particles, budesonide only particles, and agglomerates of lactose and budesonide. By changing the type of lactose, the relative amounts of these three changed as is illustrated in Figure 4.

Conclusions

With wet chemical and visualization techniques it is relative easy to measure the amount of lactose in impactors. This additional information gave better insight into the role of lactose. Results reported here showed that upon changes in the deposition of the active, there were changes in deposition of lactose and agglomerates as well. The correlation between these is currently under investigation.

References