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Measurement of Lactose from Dry Powder Inhalers in Impactors

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Introduction

In vitro testing is a key element in the testing and understanding of dry powder inhalers.[1] The most common excipient used in dry powder inhalers is lactose.[2] 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.[3, 4, 5] 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.[6] 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 LH201, DFE Pharma, Borculo, the Netherlands) with micronized salbutamol sulphate (Turbula blending) were fired into an MSLI. Formulations of LH100 in combination with LH300 or LH210 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 pharmacopeias.6 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 LH300 or LH210) 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 color 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 520, 380, and 330 nm (figure 1).

Lactose in ammonia 5 – 0.1 mg lactose/mL

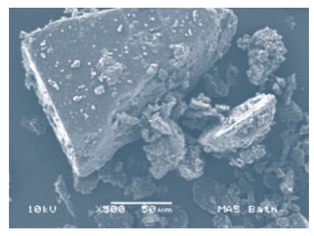
Calibration curves at each absorption maximum were developed (figure 2 for peak at 330-350 nm). A wide range of lactose concentrations can be measured: 0.01-3 mg/mL, ideal for concentrations found for lactose concentration with in-vitro testing. Salbutamol sulphate has UV absorption bands, but it is 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 salbutamol sulphate, was identical for both formulations, only the type of lactose was changed.

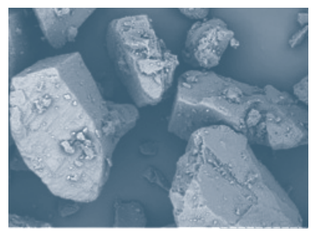
Morphology G3 inspection of samples fired in an NGI of the material on stage 2, showed single particles and small agglomerates. Raman inspection of these particles and agglomerates revealed three types of material: lactose only particles, budesonide only particles, and agglomerates of lactose and budesonide. By changing the type of lactose, the relative amounts of these three changed as is illustrated in figure 4.

Conclusions

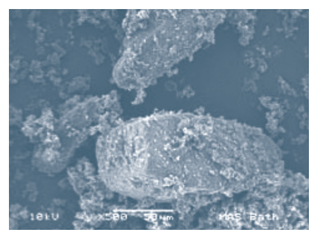
With wet chemical and visualization techniques it is relative easy to measure the amount of lactose in impactors. This additional information gave better insight into the role of lactose. Results reported here showed that upon changes in the deposition of the active, there were changes in deposition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



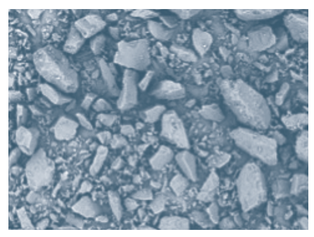
LH100 with 20% LH210



LH100



LH100 with 20% LH300



LH201

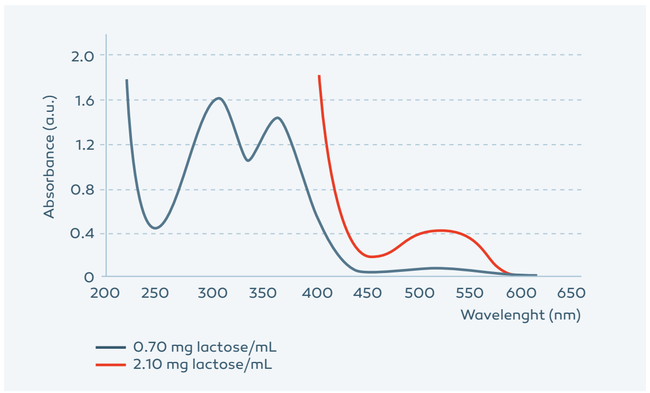


Figure 1: UV/VIS absorption curve lactose and ammonia derivative.

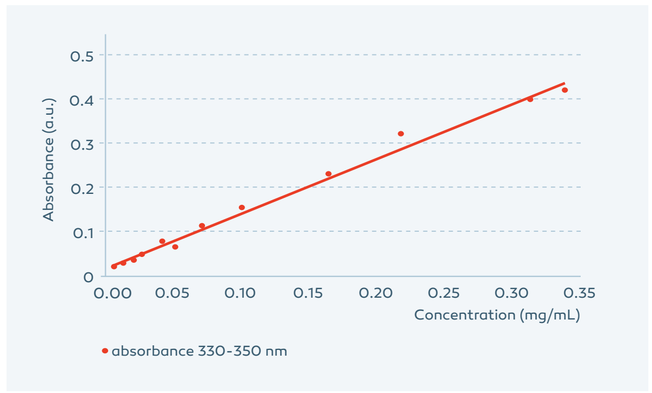
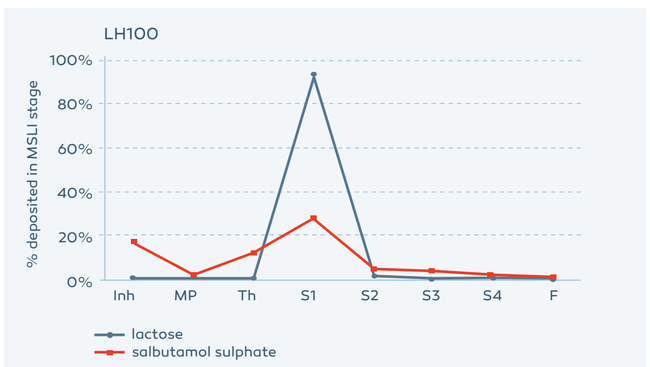


Figure 2: Calibration curve UV/VIS absorption at 330-350nm.



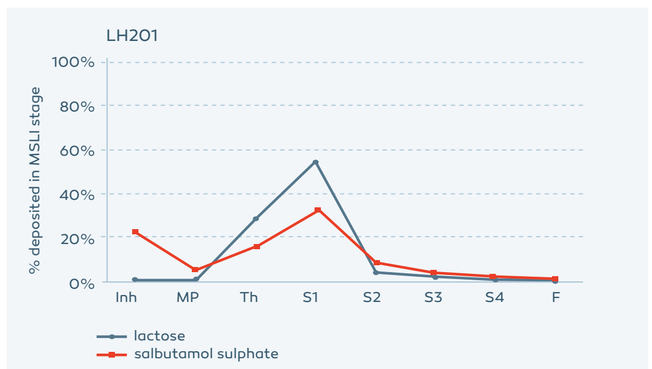


Figure 3: Deposition of lactose and salubutamol sulphate in MSLI after firing from a Cyclohaler. SS was measured by UV spectoscopy, lactose was measured by UV spectoscopy after derivitization with ammonia. (Inh = inhaler; MP = mouth piece; Th = throat; S1-4 = stages 1-4; F = filter)

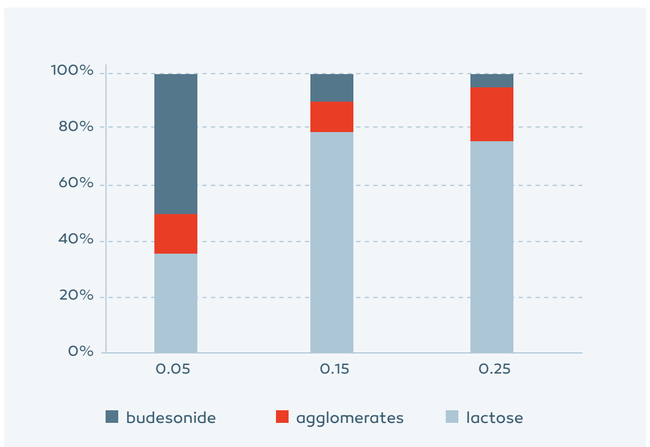


Figure 4: Relative amounts of deposited material on Stage 2 in Next Generation Impactor after firing from Cyclohaler. Particles were characterized by Malvern G3 morphology and found to be pure Budesonide, pure lactose and agglomerates of lactose and budesonide.

References

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