Interaction of Formulation and Device Factors Determine the *In Vitro* Performance of Salbutamol Sulphate Dry Powders for Inhalation

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ABSTRACT: A variety of capsule-based dry powder inhalers were used to evaluate formulation-device interaction. The *in vitro* deposition of salbutamol sulphate (SS) was compared directly to published data for salmeterol xinafoate (SX). A 3^2 factorial design was used to assess the effect of SS formulations with three blends of different grade coarse lactose supplemented with different levels of fine lactose. These formulations were tested for homogeneity and evaluated for their *in vitro* deposition using Aeroliser, Handihaler and Rotahaler devices. The performance of the SS-lactose formulations differed across the grade of lactose and amount of fine lactose used compared to the same powder compositions blended with SX. SX had a greater fine particle fraction than SS for most of the comparable formulations, probably because of the different cohesiveness of the drugs. A head-to-head comparison of 'matched' SX and SS formulations when aerosolised from the same three devices demonstrated that formulation–device interactions are as critical in determining the *in vitro* deposition of drug–lactose blends as the identity of the active pharmaceutical ingredient. This work has revealed the limitations of the interpretative value of published *in vitro* performance data generated with a single device (even at equivalent aerosolisation force), when designing formulations for a different device. © 2015 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 104:3861–3869, 2015

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INTRODUCTION

Inhaled powder formulations normally consist of micronised active pharmaceutical ingredient (API; <5 μm) and a coarse carrier (approximately 50–200 μm). The coarse carrier is included as a diluent that facilitates powder flow and de-agglomeration of the drug particles, hence improving dispersion of the micronised drug particles into an aerosol upon inhalation.[1] Drug particle dispersion is controlled predominately by the inhalation flow rate of the patient, inhaler design and the interactions between the drug and carrier particle.[2] These parameters need to be considered together to ensure inhaler performance is robust and satisfactory. Despite a general recognition of these principles, the efficiency of most licensed dry powder inhalers (DPIs) is poor with lung deposition *in vivo* typically less than 30%.[3]

Most DPIs utilise lactose as the coarse carrier and employ strategies to improve the efficacy of drug dispersion such as optimising the carrier size,[4] mixing grades of carriers[5] and using lactose carriers with different surface morphologies.[6] Magnesium stearate or leucine can be used to modify the lactose carrier thereby improving the dispersibility of the drug.[7] Fine lactose (<10 μm) also increases drug dispersion.[8] Two major mechanisms of how the fine lactose enhances drug release from the carrier have been suggested. The agglomerate hypothesis suggests that the drug and excipients adhere to each other forming agglomerates that are entrained better into an airstream from a carrier particle than individually adhered particles, but disperse readily after aerosolisation.[9] The active site hypothesis suggests that the carrier surfaces have sites which are more adhesive (higher energy) than other parts of the carrier to which fine particles can adhere and block drug particles, therefore the drug particles are more likely to detach during the aerosolisation process.[10,11]

The addition of fine lactose to formulations of various β_2 agonists with coarse lactose carriers has been shown to increase drug dispersion. This has been demonstrated with salbutamol sulphate (SS)[12,13] and furthermore binary mixtures of salmeterol xinafoate (SX) blended with fine lactose with different particle sizes demonstrated that addition of fine lactose caused an increase in the SX dispersion.[14] Similarly, SS was blended with a range of sizes of lactose and using a design of experiments approach to evaluate the optimum particle size which has been described as a balance between the smaller particle size and the negative effects on the powder flow.[13] Ooi et al.[12] also found that an increase in the carrier size decreased the drug deposition for SS dry powder formulations. These studies were carried out in a systematic manner, although they were completed with different types and sizes of lactose making them difficult to compare directly. Using a range of SX concentrations (1%–5%, w/w), Adi et al.[15] showed that the addition of fine lactose increased drug dispersion and improved dispersion was related to the formation of mixed agglomerates in the powder blend. The authors reported that the redistribution of SX into mixed agglomerates improves the de-agglomeration of SX. It appears that the de-agglomeration of SS-fine lactose blends

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may depend on the device employed.[16] Therefore, accurate comparisons between the effect of formulation design for different β_2 agonists require a directed systematic investigation of the interaction terms for API-device-lactose grade(s).

Interestingly, the addition of fine lactose does not always help to improve the drug deposition. It has been reported that the addition of specific size fractions of fine lactose help to increase drug dispersion, whereas non-cohesive fractions of fine lactose can act as secondary carriers, but do not aid drug dispersion.[17] However, these studies utilised higher proportions of β_2 agonists than commercially orally inhaled products (OIP) which may influence the aerosolisation behaviours of the formulations. Recently, the performance of commercially relevant SX formulations in inhalers of different resistance was reported, although a full analysis of the formulation variables could not be completed because of the limitations imposed by powder mixing, that is, not achieving sufficient content uniformity.[18] The latter finding underlines the need to investigate specific API–lactose blend interactions when interpreting the importance of the addition of fines as a formulation tool.

Here, the effect of fine lactose particles on the *in vitro* deposition in the next generation impactor (NGI) of SS formulations in inhaler devices of different resistance is reported. A full 3^2 factorial design was used to assess the effect of commercially relevant formulations (different levels of added fine lactose with three different coarse lactose carriers blended with 0.58%, w/w, SS). Formulation–device interactions were investigated by using inhalers with different device resistances.[14] The influence of active drug was explored by utilising SS in experiments directly comparable to previously reported results for SX.[18]

METHODS

Materials

Micronised SS was a gift from Cipla Ltd., Mumbai, India. HPLC grade methanol, hexane and Whatman™ nylon filter (pore size 0.2 μm, diameter 47 mm) were obtained from Fisher Scientific Ltd., Loughborough UK. Silicone oil was purchased from Sigma–Aldrich Ltd., Poole, UK and size 3 gelatin capsules were acquired from Meadow Laboratories Ltd. (Romford, UK). The three coarse lactose products (Respitose® ML001, Respitose® ML006 and Lactohale® LH200) and the single fine lactose (Lactohale® LH300) were supplied by DFE Pharma (Sutton, UK).

Particle Size Characterisation

Particle size measurements for the coarse lactose and SS were performed on a Sympatec HELOS/RODOS (Sympatec GmbH, Clausthal-Zellerfield, Germany) with a R3 lens (0.9–175 μm). This equipment was verified using silicone carbonate P600–09 standard provided by the manufacturer. Samples were filled into a glass vial and expelled through the machine at a pressure of 4 bar. This was repeated three times. Particle size distribution (PSD) was characterised using Fraunhofer theory, analysed using WINDOX 4.0 software and reported as D_{v10}, D_{v50}, D_{v90} and volume mean diameter. D_{v50} is the median particle volume diameter (i.e., the 50% point on the cumulative undersize PSD). D_{v10} and D_{v90} report represent the diameter corresponding to the 10th and 90th percentile of the cumulative undersize PSD. Intrinsic fines content was calculated as the percentage of the particles <10 μm.

Dispersibility of Salbutamol Sulphate

The critical primary pressure (CPP) of SS was calculated by performing particle size measurements using a Sympatec HELOS/RODOS with a R3 lens and a rotating table.[19] The equipment was also verified using the silicone carbonate P600–09 standard provided by the manufacturer. SS was hand-filled into a u-shaped groove of the rotating table and the powder sample was transferred under a plough scraper and roller to remove any excess. The SS was then drawn up into the dispersing line via the protruding aspiration tube. Throughout the sample delivery, the rotating table remained at a constant rotation setting of 20%. When the optical concentration (C_{opt}) exceeded 1.1% the measurement was set to activate; however, the measurement stopped when the C_{opt} was below 1% for 5 s. A forced stability of '4' was used for this set of experiments with a timebase of 100 ms. The primary pressure (PP) was set manually in the range of 0.2–4.5 bar and at each PP, three measurements were taken with a fresh powder sample.

Critical primary pressure was calculated using a difference ratio between the D_{v50} and two consecutive PPs (PP_1 and PP_2), when the particle size-PP profile achieved a plateau (Eq. (1)). This is shown to represent the pressure required to overcome the interactive forces which held the most cohesive agglomerates in the micronised powder together.

$$d_r = \frac{D_{v50}PP_1 - D_{v50}PP_2}{D_{v50}PP_1} \quad (1)$$

Powder Formulations

Nine interactive mixtures were manufactured with different coarse lactose carriers and amounts of fine lactose (Table 1). These interactive mixtures contained 0.58% (w/w) SS. Magnesium stearate (0.1%) was added to the blends to aid mixing and mirrored the formulation approach of Hassoun et al.[18] The binary interactive mixtures were composed of SS and a coarse lactose carrier. The coarse lactose carrier was added in multiple stages (2, 2.5, 5, 10, 10, 10, and 10.21 g) and blended using a Turbula® T2F blender between each addition for approximately 30 min at 67 rpm. Ternary interactive mixtures were a mixture of SS, a coarse lactose carrier and fine lactose. The method of making ternary interactive mixtures differed slightly from the binary mixtures. The fine lactose and half of the coarse lactose were pre-blended for 30 min at 67 rpm which was followed by the addition of the other half of the coarse lactose.

Table 1. Powder Formulations Containing 0.58% (w/w) Salbutamol Sulphate, 0.1% (w/w) Magnesium Stearate and Combinations of Different Coarse Lactose and Amount of Added Fine Lactose

Interactive Mixture	Type of Coarse Lactose	Amount of Fine Lactose Added (%)
M6F0	Respitose® ML006	0
M6F5	Respitose® ML006	5
M6F10	Respitose® ML006	10
M1F0	Respitose® ML001	0
M1F5	Respitose® ML001	5
M1F10	Respitose® ML001	10
LHF0	Lactohale® LH200	0
LHF5	Lactohale® LH200	5
LHF10	Lactohale® LH200	10

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