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Formulating powder–device combinations for salmeterol xinafoate dry powder inhalers

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ABSTRACT

Using salmeterol xinafoate (SX) as an active pharmaceutical ingredient, the effects of carrier lactose particle type, total lactose fines content and device resistance on dry powder inhaler performance were investigated *in vitro*. To mimic drug levels in commercial preparations, interactive mixtures containing 0.58% w/w SX were prepared by low shear tumble mixing. Three types of milled inhalation grade lactose were used (Lactohale® LH 200, Respitose® ML006 and ML001) and the concentration of fine lactose (Lactohale® 300) added was varied. The *in vitro* deposition of each mixture was studied using a next generation impactor and inhaler devices exhibiting different resistances, Rotahaler® < Aerolizer® < Handihaler®. Aerosol performance was evaluated based on the emitted dose (ED), mass median aerodynamic diameter (MMAD) ± geometric standard deviation (GSD) and fine particle fraction (FPF). Increases of up to eight-fold in FPF were observed with increasing intrinsic fine lactose content. The addition of extra fine lactose increased the FPF further, although the effect diminished as more fines were added. The Aerolizer produced the best aerosol performance with any given powder blend, although suitable formulations were identified for each device as defined by the *a priori* success criteria: >80% ED and MMAD ± GSD between 1–5 μm. The results confirmed the factors under investigation to be important determinants of product performance, but demonstrated using realistic conditions how individual factor impact may be enhanced or mitigated by inter-dependency.

1. Introduction

Dry powder inhalers (DPI) are increasingly popular products for delivering drugs to the lungs due to their ease of operation, environmental sustainability and formulation stability (Telko and Hickey, 2005). Historically, DPI have delivered only 20–30% of the emitted dose to the lungs (De Koning, 2001), but more efficient products are emerging (Friebel et al., 2012). Although the scientific literature now provides well-established principles with which to design efficient and effective DPIs (Friebel et al., 2012; Hoppentocht et al., 2014), there is surprisingly little reported regarding the practicalities of formulating powder blends for different inhaler devices.

Drug particles within the respirable size range, 1–5 μm, are generally highly cohesive and tend to form agglomerates, resulting in poor flow properties, non-uniform dispersion and low dose uniformity. Therefore, drug particles are usually blended with coarse carrier particles, typically α-lactose, to help provide bulk and form an ordered mix (Pilcer and Amighi, 2010; Javadzadeh et al., 2012). Since the active drug and lactose powders exhibit different sized particles, the formulation and blending process is important to achieve uniform drug distribution and provide consistency of delivered dose (Pilcer and Amighi, 2010; Saleem and Smyth, 2008). Powders need to be sufficiently adhesive to possess good flow properties without compromising their ability to generate respirable aerosols efficiently and reproducibly (Begat et al., 2004). Powder dispersion can be manipulated by modifying the properties of microparticle drug surface or the carrier's surface morphology and size (Buttini et al., 2008; Pomazi et al., 2013; Zeng et al., 2001; Islam et al., 2004; Zellnitz et al., 2011). A proportion of fine lactose in the

Abbreviations: SX, salmeterol xinafoate; DPI, dry powder inhaler; PSD, particle size distribution; ED, emitted dose; MMAD, mass median eerodynamic diameter; GSD, geometric standard deviation; FPF, fine particle fraction; FPD, fine particle dose.

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formulation, either as intrinsic or added fines, will further improve dispersion and the de-aggregation of the drug particles (Jones and Price, 2006; Beilmann et al., 2007; Kinnunen et al., 2014; Shur et al., 2008; Grasmeijer et al., 2014; Thalberg et al., 2012).

Device properties also determine respirable aerosol generation from a carrier-based powder formulations (Martinelli et al., 2015; Shur et al., 2012). The airflow velocity must also overcome the adhesion forces between the drug and carrier particles to detach the micronized drug particles and disperse them in the aerosol. To aid dispersion, inhaler devices may be engineered with a more tortuous airflow that increases the resistance within the device (Coates et al., 2006; Selvam et al., 2010). Capsule-based inhalers with different resistances are available, which enables the effect of device resistance on dry powder aerosolisation to be investigated.

Although aerosolisation is governed by the powder formulation and the inhaler device design inter-dependently (Frijlink and De Boer, 2004), devices are generally developed as platform technology with which to deliver different drugs to the lungs. Scientific studies aimed at understanding DPI performance often examine the influence of device or formulation as independent variables, or use model systems. For example, effect of adding fine excipient particles has been investigated by looking at the effect of fine lactose on the aerosolisation of salmeterol xinafoate (SX) 1–5% w/w interactive powder mixtures (Islam et al., 2004; Adi et al., 2008). The present study explored the inter-dependency of powder formulation and device factors in typical capsule-based DPI products by varying the carrier particle size distribution and the amount of added lactose fines. Three DPI devices having different intrinsic resistance were employed to aerosolize the SX blends. A 3^2 factorial design was constructed to understand the relative influence of these variables on fine particle fraction (FPF), emitted dose (ED), mass median aerodynamic diameter (MMAD) and the geometric standard deviation (GSD).

2. Materials and methods

Micronised SX was supplied by Vamsi Labs Ltd., Maharashtra, India. Milled inhalation α-lactose monohydrate grades (Respitose® ML006, Respitose® ML001, Lactohale® LH 200 and Lactohale® 300) were obtained as samples from DFE Pharma (Veghel, Netherlands). Size 3 hard gelatin capsules were acquired from Farillon Limited, (Romford, UK). Rotahaler®, Aerolizer® and Handihaler® devices were retrieved from commercial products. HPLC grade methanol and hexane and laboratory grade disodium hydrogen orthophosphate dodecahydrate were supplied by Fisher Chemicals (Loughborough, UK). Magnesium stearate and analytical grade citric acid monohydrate were supplied by Sigma–Aldrich Company Limited (Dorset, UK) while silicone oil was obtained from VWR International Limited (Lutterworth, UK).

2.1. Internal resistance of inhaler devices

Each DPI inhaler was loaded with an empty pierced capsule and attached to the dosage unit sampling apparatus (Copley Scientific Limited, Nottingham, UK) connected to a high-capacity vacuum pump (Model HCP5, Copley Scientific Limited, Nottingham, UK) *via* a critical flow controller (Model TPK, Copley Scientific Limited, Nottingham, UK). For each inhaler device, triplicate measurements of the pressure drop were recorded across the flow rate range of 30–100 L min^{-1} at 10 L min^{-1} intervals. A linear plot of the square root of the mean pressure drop against flow rate was obtained and the internal resistance of the DPI device was defined as the slope of the linear plot (Clark and Hollingworth, 1993).

2.2. Lactose particle size

To characterise the coarse lactose carriers, an amount of each α-lactose grade (60 mg) was dispersed in 15 mL of propan-2-ol with the aid of sonication for 1 min. The particle size distribution (PSD) of each lactose grade was characterised in terms of D_{v10}, D_{v50} and D_{v90} values (the volume diameter of 10%, 50% and 90% of aerosol droplets respectively); measured using a Spraytec® (Malvern Instruments, Malvern, UK), equipped with a wet-cell dispersion unit. The span value provided an indication of the width of PSD and the percentage of particles with an equivalent volume diameter of less than 10 μm was also determined.

2.3. SX blends preparation

Based on a 3^2 factorial design, nine interactive mixtures, each containing 0.58% w/w SX and 0.08% w/w of magnesium stearate (to aid mixing), were prepared in 50 g batches with 10% overage, using different powder components (Table 1). The binary interactive mixtures consisted of SX particles and coarse carrier. Coarse lactose (2 g) was first used to 'sandwich' SX and the powders were mixed using a Spinmix Vortexer (Gallenkamp, Loughborough, UK). Coarse lactose was subsequently added in multiple stages (2.5 g, 5 g, 10 g, 10 g, 10 g and 10.21 g) and the powder mixture blended using a Turbula® T2F shaker-mixer (Willy A. Bachofen AG, Basel, Switzerland) for 30 min at 67 rpm. The ternary interactive mixtures were three-component blends of SX particles, coarse carrier and added fines. The fine lactose and half of the coarse lactose were pre-blended for 30 min at 67 rpm, followed by the addition of the other half of the coarse lactose. This was blended for a further 30 min, before mixing with SX, similarly to the preparation of the binary mixtures, by gradual addition of the coarse-fine lactose pre-blend to the SX blends and mixing for 30 min at 67 rpm between each addition of the pre-blend.

Table 1
Composition of each interactive mixture prepared in accordance to the 3^2 factorial design, each containing 0.58% w/w salmeterol xinafoate and 0.08% magnesium stearate.

Interactive mixture	Concentration of fine lactose added (%w/w)	Coarse lactose grade
M6F0	0	Respitose® ML006
M6F5	5	Respitose® ML006
M6F10	10	Respitose® ML006
M1F0	0	Respitose® ML001
M1F5	5	Respitose® ML001
M1F10	10	Respitose® ML001
LHF 0	0	Lactohale® LH200
LHF 5	5	Lactohale® LH200
LHF 10	10	Lactohale® LH200
LHF 20[a]	20	Lactohale® LH200

[a] Additional mixture prepared to investigate poor blend homogeneity.