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Insight into pressure drop dependent efficiencies of dry powder inhalers

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ABSTRACT

Purpose: The purpose of this study was to assess the effectiveness of three commercial capsule-based dry powder passive inhalers [Rotahaler® (RH), Monodose Inhaler® (MI) and Handihaler® (HH)] in de-agglomerating salbutamol sulphate (SS) and micronized lactose (LH300) powders and their sensitivity to air flow rate changes and air flow resistance.
Methods: Aerosolisation was assessed in real-time using a laser diffraction method: this approach was possible as only single-component formulations were tested. Volume percent of the aerosolised particles with diameter less than 5.4 μm at air flow rates from 30 to 180 l min^{-1} was obtained with the RH, MI and HH and provided a parameter, relative de-agglomeration (RD), as a measure of de-agglomeration. The pressure drops across the device at various flow rates were obtained from a differential pressure meter.
Results: The relationship between RD of SS and LH300 and air flow rate appeared substantially different between the devices. It was surprisingly found that in some cases RD dropped at the highest air flows: this indicates a device specific maxima in RD occurs, and this may in part be attributed to changes in capsule motion. It is proposed that this relationship between RD and pressure drop provides a patient focussed simple way to assess RD performance. This assessment indicated that MI was the most efficient relative de-agglomerator at lower pressure drops, while HH increases its effectiveness at higher pressure drops.
Conclusion: The approach of measuring RD as a function of pressure drop revealed instructive variations in the aerosolisation performances of different devices. This new approach helps compare device performances with different powders, and hence improve optimisation and consistency of performance.

1. Introduction

Dry powder inhalers rely on patient inspiratory air flow rate to provide energy to aerosolise the powder. In previous studies (Behara et al., 2011a,b), the authors have studied the aerosolisation behaviour of cohesive powders and powder mixtures by characterising the de-agglomeration as a function of air flow to create a profile. In the current paper, the authors have instead focused on the role of the device.

Modern innovative devices exist with many complex designs, with varied levels of air flow resistances, and provide highly complex mechanisms of powder aerosolisation. An "ideal inhaler" should provide uniform de-agglomeration irrespective of air flow rate. The inspiratory muscle strength (Smyth et al., 1984; Wijkstra et al., 1995) of the lung and the resulting inspiratory air flow rate (Coady et al., 1976; Sarinas et al., 1998; Spiro et al., 1992; Wijkstra et al., 1995) are important from a clinical perspective for patients with lung diseases. It has been shown that cystic fibrosis and COPD patients with altered lung capacity can inhale comfortably through dry powder inhaler devices of varying resistances at various air flow rates (Sarinas et al., 1998). The pressure drop and air flow rates ranged from 2.9 – 16.0 kPa (Sarinas et al., 1998; Wijkstra et al., 1995) and 50–400 l min^{-1} (Coady et al., 1976; Sarinas et al., 1998; Wijkstra et al., 1995), respectively for the patients with varied lung disease states. Importantly, Ganderton and Byron (1996) proposed that inhaler devices should be tested at specific pressure drops that were recognised as representing a comfortable inhalation condition for a patient. The inspiration movement is caused by a physical increase in the lung volume, hence generating a pressure differential which drives the air flow. A comfortable pressure differential was believed to be 4 kPa. Hence, pharmacopoeial dry powder inhaler (DPI) testing is based on the air flow rate through a device that corresponds to a pressure differential applied of 4 kPa.

In addition, clinical study has shown that patients tend to inhale through DPIs at higher inspiratory air flow rates than they were trained to do during counselling (Hawksworth et al., 2000). This could lead to either increased or decreased therapeutic effect depending on the properties of the powder, particularly its agglomerate strength distribution and the variability of powder de-agglomeration relative to device and air flow (Behara et al., 2011b). Surprisingly, the influence of the device on the powder

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de-agglomeration relative to the air flow is, in general, poorly understood reflected by a lack of literature reported in this area. It is important to consider that changes in air flow rate can act in opposing ways. Firstly, increased air flow rate has been shown to improve de-agglomeration (Chew et al., 2000; Chew and Chan, 1999; Coates et al., 2005a) and therefore can increase overall drug deposition in the lung (Goldberg and Lourenco, 1973). The basis for this can be proposed as follows. De-agglomeration of cohesive powder is well known to improve as impinging air velocity across the powder increases (Calvert et al., 2009; Wang et al., 2004). In the case of an orifice, the point of maximum air velocity in a device will generally coincide with the point of maximum air resistance. The change in resistance across the devices is reported to result from device design (Meakin et al., 1998), and is a result of a point of constriction in the air flow path (Coates et al., 2005b). Hence it makes logical design sense for this point of constriction (effectively an orifice) providing a maximum resistance to be located at a point which impinges directly onto the powder to be aerosolised. Many different views exist on the actual mechanisms for fluidisation and de-agglomeration of inhaler formulations (Dunbar et al., 1998), and such specifics are not the focus of this project, however in principle it is clear that there is likely to be a relationship between air resistance, the resulting local air velocities and the way in which such local air velocities impinges upon the formulated powder and the aerosolisation performance of the system. However, it is also known that increased air flow rate also increases oro-pharyngeal deposition (via impaction as governed by Stoke's law) for a given aerodynamic particle size, reducing deep lung penetration (Finlay, 2001).

A recent study demonstrated that the difference in in vitro drug deposition from inhalers of different designs when aerosolised at the same air flow rate was due to the design of the powder inhaler (de Boer et al., 1996). However, this study (de Boer et al., 1996) used a wide range of different devices with different formulations making direct comparison and hence a simple analysis is not possible. Similarly, a range of devices and commercial formulations were aerosolised by Mendes et al. (2007) where correlation between fine particle fraction and pressure drop was shown at 60 l min^{-1}. Nevertheless, at an air flow rate of 60 l min^{-1} these devices show different pressure drops and therefore a comparison between devices at a specific pressure drop could not be obtained. In addition, the amount of fines suitable for inhalation between formulations varies greatly and the effect of excipient size alters the de-agglomeration mechanism (Adi et al., 2008). Furthermore, clinical response as a function of air flow rate has been demonstrated to show substantial variation using low (Auty et al., 1987; Pedersen, 1986; Richards et al., 1988), medium (Nielsen et al., 1997; Zanen et al., 1992) and high (Pedersen et al., 1990) resistance devices. Consequently, there appears a lack of simple methodology that is relevant to the patient's ability to inhale, which is demonstrated to enable the efficiency of aerosolisation of a given device to be assessed, and compared to another device.

It is evident from coincident views of clinicians and device engineers that inspiratory air flow rate and device resistance are very important in lung deposition. These factors are both related to the pressure drop (or air flow resistance) across the device. Therefore comparison between devices with the same formulation over a range of pressure drops appears to be an appropriate approach.

This investigation focused on three inhaler devices of low (Rotahaler®) (RH), medium (Monodose Inhaler®) (MI) and high (Handihaler®) (HH) resistance. The geometry of these devices is presented in Table. 1. For the RH, the capsule is split into two sections, allowing the majority of the powder to empty from one half of the body of the capsule as it tumbles freely and chaotically with air flow inside the main device chamber. For the MI, the capsule is pierced at either end and it is held in a circular chamber with tangential air impingement. This causes the capsule to spin and empty the powder by centrifugal force through the holes at either end of the capsule. With the HH, the capsule is held in a chamber which permits just enough movement for it to precess and rattle about its position. In this case the capsule is pierced close to the centre, and via both rattling movement and the pressure difference from the air flow, powder aerosolisation occurs. Consequently, the capsule movements during operation were notably different for RH, MI and HH: i.e. random tumbling, spinning, and precession rattling, respectively. This study was directed to an understanding of the relative behaviour of the inhaler devices and their sensitivity to air flow rates/pressure drops with the powders (SS and LH300) that were known to exhibit different micro-structures (Behara et al., 2011b).

2. Materials and methods

2.1. Materials

SS (Combrex Profarmaco, Milan, Italy) and LH300 (Borculoingredientsdomo, Borculo, The Netherlands) were used in this study. The inhaler devices, RH (GSK, Middlesex, UK) and the HH (Boehringer Ingelheim, Germany) were purchased from a local pharmacy (Priceline Pharmacy, Brunswick, VIC, Australia) and the MI was a kind gift from NanoMaterials Technology Pte Ltd., Singapore.

2.2. Initial processing of the materials

Micronized SS and LH300 samples were agitated to simulate the energy input and disruption of a blending event using a previously validated method (Alway et al., 1996) to ensure a standard powder condition prior to aerosolisation of the powders, and one which standardises the mechanical movement and tribology of a shear blend process. Five gram batches were prepared by placing the powder in a glass bottle containing three ceramic beads (10 mm diameter) which was shaken vigorously for a minute, and then tapped for 15 s to remove powder adhered to the corners (Behara et al., 2011a,b). This process was repeated four times.

2.3. Primary particle size distributions

The primary size distributions of processed SS and LH300 were determined by laser diffraction (Mastersizer® S, Malvern Instru-

Table 1
Illustrations of design geometry of the marketed inhaler devices.

Description	Rotahaler®	Monodose Inhaler®	Handihaler®
Inhalation port length (mm)	22.0	29.2	31.3
Mouthpiece orifice diameter (mm)	13.9 × 20.1	10.5	5.1
Piercing pin diameter (mm)	5.2 × 2	1.0 × 2	1.5 × 2
Mesh diameter (mm)	21.3	9.6	9.9
Number of voids	80	32	67
Void dimension (mm)	0.95 × 1.00	0.98 × 1.00	0.82 × 0.79
Capsule rotating chamber volume (ml)	11.576	2.784	0.762
Chamber air inlet area (mm^2)	81.4	38.0	8.6