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The effects of suspension particle size on the performance of air-jet, ultrasonic and vibrating-mesh nebulisers

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ABSTRACT

Using latex microspheres as model suspensions, the influence of suspension particle size (1, 4.5 and 10 μm) on the properties of aerosols produced using Pari LC Sprint (air-jet), Polygreen (ultrasonic), Aeroneb Pro (actively vibrating-mesh) and Omron MicroAir NE-U22 (passively vibrating-mesh) nebulisers was investigated. The performance of the Pari nebuliser was independent of latex spheres particle size. For both Polygreen and Aeroneb Pro nebulizers, total aerosol output increased when the size of latex spheres increased, with highest fine particle fraction (FPF) values being recorded. However, following nebulisation of 1 or 4.5 μm suspensions with the Polygreen device, no particles were detected in the aerosols deposited in a two-stage impinger, suggesting that the aerosols generated from this device consisted mainly of the continuous phase while the dispersed microspheres were excluded and remained in the nebuliser. The Omron nebuliser efficiently nebulised the 1 μm latex spheres, with high output rate and no particle aggregation. However, this device functioned inefficiently when delivering 4.5 or 10 μm suspensions, which was attributed to the mild vibrations of its mesh and/or the blockage of the mesh apertures by the microspheres. The Aeroneb Pro fragmented latex spheres into smaller particles, but uncontrolled aggregation occurred upon nebulisation. This study has shown that the design of the nebuliser influenced the aerosol properties using latex spheres as model suspensions. Moreover, for the recently marketed mesh nebulisers, the performance of the Aeroneb Pro device was less dependent on particle size of the suspension compared with the Omron MicroAir nebuliser.

1. Introduction

There are several factors affecting aerosol deposition in the respiratory airways, such as the physicochemical properties of the drug and formulation, type and design of the delivery device, breathing pattern of the patient and clinical condition of the lung (Labiris and Dolovich, 2003; Tronde et al., 2003). The size of inhaled particles is considered to be the most important physical property affecting particle deposition in the airways (O'Callaghan and Barry, 1997). Particles with a diameter less than 5 μm are likely to deposit in the lower respiratory tract (i.e. respiratory bronchioles and alveolar region); these particles are considered to be "respirable" or in the "fine particle fraction" (FPF). By contrast, particles larger than 12 μm are regarded unsuitable for pulmonary delivery as they are likely to deposit in the extrathoracic region (i.e. mouth and throat) (Stahlhofen et al., 1980; O'Callaghan and Barry, 1997).

Amongst devices used in pulmonary drug delivery, nebulisers are recommended for delivery of large liquid volumes. Two types of nebuliser have been commercially available for decades, namely air-jet nebulisers and ultrasonic nebulisers. Air-jet nebulisers operate by passing a high velocity gas through a narrow "venturi" nozzle in order to convert the liquid into aerosols (O'Callaghan and Barry, 1997; Hess, 2000). The outgoing air is saturated with solvent vapour; this reduces the temperature of nebuliser fluid (O'Callaghan and Barry, 1997; Hess, 2000). By contrast, ultrasonic nebulisers generate aerosols by employing a high frequency vibrating piezoelectric crystal (McCallion and Taylor, 2002). Ultrasonic nebulisers are generally unsuitable for delivering suspensions

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(McCallion and Taylor, 2002), large liposomes (Elhissi and Taylor, 2005) and other delicate structures such as some macromolecules, (Niven et al., 1995) due to the heat generated during atomization, causing instability of the processed materials.

More recently, a third type of nebulisers, known as vibrating-mesh nebulisers, has been introduced (Dhand, 2002; Newman and Gee-Turner, 2005). Vibrating-mesh nebulisers employ perforated plates that vibrate to generate aerosols. There are two types of vibrating-mesh nebuliser; these are passively vibrating and actively vibrating-mesh nebulisers. An example of passively vibrating-mesh devices is the Omron MicroAir NE-U22 nebuliser which employs a perforated plate with around 6000 tapered holes of approximately 3 μm diameter. A vibrating piezoelectric crystal is attached to a transducer horn that transmits the vibrations to the perforated plate, resulting in fluid extrusion through the holes of the "passively" vibrating mesh to produce the aerosol (Newman and Gee-Turner, 2002; Ghazanfari et al., 2007). An example of actively vibrating-mesh devices is the Aeroneb Pro nebuliser which employs a "micropump" system consisting of a plate with up to 1000 dome-shaped apertures. An electric current is applied to a vibrating element which contracts and expands, causing the mesh to move up and down by a few micrometres to extrude the liquid and generate the aerosol (Dhand, 2002; Ghazanfari et al., 2007). Studies with vibrating-mesh nebulisers have shown that, unlike ultrasonic devices, they do not heat solutions during atomisation (Dhand, 2002). Using liposome suspensions nebulised with the Omron MicroAir device, the temperature of the fluid was measured at time intervals and found to be around $25 \pm 1\,^{\circ}C$ (data unpublished). Moreover, only a slight increase in fluid temperature was reported when poly(lactide-co-glycolide; PLGA) nanoparticles were nebulised using the Aeroneb Pro nebuliser (Beck-Broichsitter et al., 2012). This might be the reason behind the suitability of vibrating-mesh nebulisers for delivering heat-sensitive materials such as proteins (Maillet et al., 2008). In addition, mesh nebulisers are suitable for delivering suspensions (Yoshiyama et al., 2002; Fink and Simmons, 2004), liposomes (Elhissi and Taylor, 2005; Elhissi et al., 2006; Kleemann et al., 2007; Elhissi et al., 2011) and nanoemulsions (Amani et al., 2010). Compared with air-jet nebulisers, vibrating-mesh devices exert less damaging effects on liposomes (Elhissi et al., 2006; Elhissi et al., 2007; Kleemann et al., 2007), and using single phase solutions, the residual volume left after completed nebulisation can be negligible when low viscosity solutions are used (Ghazanfari et al., 2007). Aerosolisation of siRNA–chitosan polyplexes using the Aeroneb Pro did not undermine the gene silencing activity in mice lung (Luo et al., 2012). This nebuliser was also found to deliver high proportions of aerosol to the lungs of healthy volunteers compared to a model jet nebuliser (De Andrade et al., 2012).

The effects of nebuliser design and formulation characteristics on the properties of generated aerosols have been investigated. For example, the inhaled mass of budesonide suspension was influenced by the type of nebuliser, while the inhaled mass of terbutaline sulphate solution was less dependent on nebuliser type; thus suspensions are generally more difficult to nebulise compared to solutions (Nikander et al., 1999). Using monodispersed latex microspheres as model suspensions, McCallion et al. (1996) investigated the effect of size and concentration of the spheres on the aerosol performance using three air-jet nebulisers and an ultrasonic nebuliser. They reported that the aerosol performance was dependent on the type of nebuliser and the mechanism of its operation.

In this study, latex microspheres (1, 4.5 and 10 μm) were used as model rigid suspension particles for nebulisation, using passively and actively vibrating-mesh nebulisers and modern air-jet and ultrasonic nebulisers. The influence of sphere size and nebulisation mechanism on the aerosol performance was explored and critically discussed following appraisal of the relevant literature findings. This is the first study that evaluates the role of suspension particle size on the performance of vibrating-mesh nebulisers.

2. Materials and methods

2.1. Materials

Omron MicroAir NE-U22 (passively vibrating-mesh) nebuliser (Omron Healthcare, Japan) was purchased from Evergreen, Lancashire, UK. Aeroneb Pro (actively vibrating-mesh) nebuliser was supplied by Aerogen Ltd., Ireland. Pari Turbo-Boy S compressor and Pari LC Sprint (air-jet) nebuliser (Pari GmbH, Germany) were purchased from Pari Medical Ltd., UK. Polygreen KN-9210 (ultrasonic) nebuliser was manufactured and supplied by K-Jump Health Co., UK. Polystyrene latex spheres (1, 4.5 and 10 μm spheres; 2.5% w/v) were supplied by Alfa Aesar, UK, and phosphate buffered saline (PBS) tablets were purchased from Sigma–Aldrich, UK.

2.2. Methods

2.2.1. Preparation of nebuliser suspensions

0.10% (w/v) concentration of the 1, 4.5 and 10 μm latex sphere suspensions 2.5% (w/v) were prepared by dilution with PBS solution. Particle size analysis for 1, 4.5 and 10 μm latex suspensions (before nebulisation) using the Malvern Mastersizer 2000 (Malvern Instruments Ltd., UK) confirmed that the latex microspheres were of the size stated by the supplier with narrow size distribution (i.e. low polydispersity) (data not shown).

2.2.2. Aerosol output and size analysis of microspheres delivered to two-stage impinger

A two-stage impinger (Copley Scientific, UK) was assembled and set up by filling its lower stage with 30 ml and its upper stage with 7 ml deionised water and by setting the flow rate at 60 l/min (Hallworth and Westmoreland, 1987). Following pipetting the suspension (5 ml) into the nebuliser reservoir, the mouthpiece of the nebuliser was directed towards the "throat" of the impinger and nebulisation was performed to 'dryness' (i.e. when aerosol generation ceased completely), and the time taken was recorded. Nebulisers were weighed whilst empty, after loading with microsphere suspension and after achieving "dryness". Aerosol mass output (%) was calculated by measuring the weight difference of nebuliser before and after nebulisation. The aerosol output rate was determined as the mass of liquid nebulised per unit time (g/min). Suspensions were collected from the lower impinger, upper impinger and nebuliser reservoir for particle size analysis using the Malvern Mastersizer 2000 (Malvern Instruments Ltd., UK). Volume median diameter (VMD), 90% undersize, 10% undersize and span of the microspheres were calculated automatically by the instrument's software. Span is a term introduced by Malvern Instruments to express the size distribution (polydispersity) of the particles; Span = (90% undersize - 10% undersize)/VMD.

2.2.3. Size analysis of aerosol droplets using laser diffraction

Malvern Spraytec laser diffraction size analyzer (Malvern Instruments Ltd., UK) was used to determine the size and size distribution of aerosol droplets produced by each nebuliser. The nebuliser loaded with microsphere suspension was positioned for aerosols to pass across the laser beam of the laser diffraction instrument. A vacuum with a flow rate of 60 l/min was applied to draw the aerosol cloud across the beam. Volume median diameter (VMD), 90% undersize, 10% undersize and span values were determined for the generated aerosol from each nebuliser. FPF was calculated by multiplying the percentage of aerosols $\leq$5.41 μm (fraction recorded by the instrument closest to 5 μm) by aerosol output. Alveolar and