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ScienceDirect
International Journal of Pharmaceutics 339 (2007) 103–111
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

The influence of fluid physicochemical properties on vibrating-mesh nebulization

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Received 11 December 2006; received in revised form 20 February 2007; accepted 23 February 2007
Available online 6 March 2007

Abstract

In this study, the effect of fluid physicochemical properties and the vibrating-mesh mechanism on the aerosols generated from vibrating-mesh nebulizers have been evaluated using fluids having a range of viscosity, surface tension and ion concentration. Two nebulizers were investigated: the Omron MicroAir NE-U22 (passively vibrating) and the Aeroneb Pro (actively vibrating) mesh nebulizers. For both devices, the total aerosol output was generally unaffected by fluid properties. Increased viscosity or ion concentration resulted in a decrease in droplet volume median diameter (VMD) and an increase in fine particle fraction (FPF). Moreover, increased viscosity resulted in prolonged nebulization and reduced output rate, particularly for the Omron nebulizer. Both nebulizers were unsuitable for delivery of viscous fluids since nebulization was intermittent or completely ceased at >1.92 cP. The presence of ions reduced variability particularly for the Aeroneb Pro nebulizer. No clear effect of surface tension was observed on the performance of nebulizers employing a vibrating-mesh technology. However, when viscosity was low, reduced surface tension seemed advantageous in shortening the nebulization time and increasing the output rate, but for the Omron nebulizer this also increased the droplet VMD and decreased the FPF. This study has shown that vibrating-mesh nebulization was highly dependent on fluid characteristics and nebulizer mechanism of operation.

Keywords: Aerosol; Ions; Nebulizer; Surface tension; Viscosity

1. Introduction

Traditionally, nebulizers have been classified into two main types: air-jet (pneumatic) and ultrasonic devices. Recently, a third type, vibrating-mesh nebulizers has been commercialized (Dhand, 2002; Newman and Gee-Turner, 2005).

Air-jet nebulizers convert liquid into aerosols by means of a high velocity gas passing through a narrow "venturi" nozzle. The fluid in the nebulizer reservoir is drawn up a feed tube and emerges as fine filaments that collapse into aerosol droplets due to surface tension (O'Callaghan and Barry, 1997). In ultrasonic nebulizers, a high frequency vibrating piezoelectric crystal is employed to generate the aerosol. A fountain of fluid is produced at the air–fluid interface. Small droplets are generated from the lower regions of the fountain whilst large droplets are generated from the apex (O'Callaghan and Barry, 1997; Taylor and McCallion, 2002). In both air-jet and ultrasonic nebulizers, baffles in the nebulizer trap and recycle the large (primary) aerosol droplets, whilst small (secondary) droplets are released for inhalation (O'Callaghan and Barry, 1997).

In air-jet nebulizers, the aerosol output comprises aerosolized droplets and solvent vapour which saturates the outgoing air (Ferron et al., 1976; Dennis et al., 1990; Smye et al., 1992). This induces cooling of the nebulizer fluid and increases solute concentration in the residual volume (Cockcroft et al., 1989). Ultrasonic nebulizers are generally unsuitable for delivery of suspensions (Taylor and McCallion, 2002) and liposomes (Elhissi and Taylor, 2005), and due to heat generation during atomization they may degrade labile substances such as proteins (Niven et al., 1995). Vibrating-mesh nebulizers may overcome the drawbacks of air-jet and ultrasonic nebulizers. Vibrating-mesh devices employ perforated plates which vibrate in order to generate the aerosol (Dhand, 2002). These nebulizers do not heat the fluid during atomization (Fink et al., 2001a), and have been shown to be suitable for delivery of suspensions (Fink et al., 2001b; Yoshiyama et al., 2002; Eskandar et al., 2003;

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doi:10.1016/j.ijpharm.2007.02.035

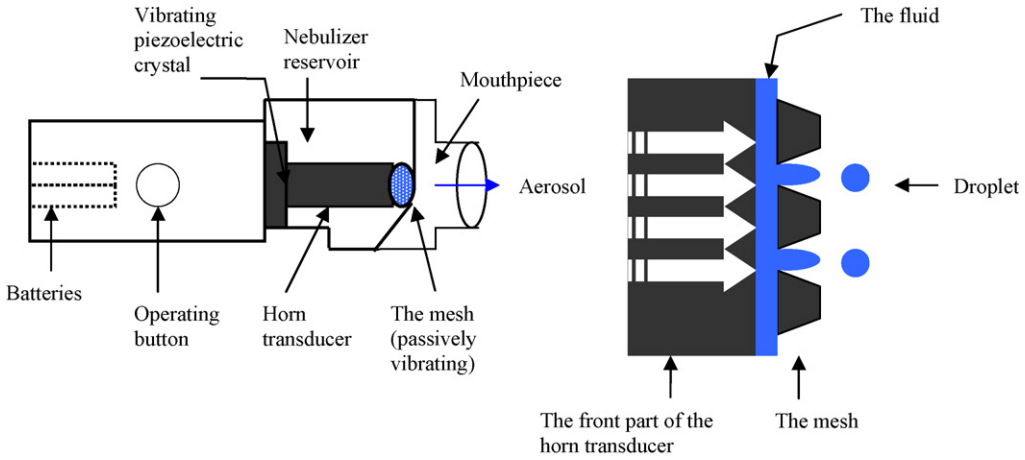

Fig. 1. A schematic diagram of the hand-held Omron MicroAir NE-U22 nebulizer (left). The vibrations of the piezoelectric crystal are transmitted via a horn transducer which induces passive vibrations of the mesh positioned in front of it. This results in the extrusion of the nebulizer fluid through the mesh pores in order to generate the aerosol droplets (right).

Fink and Simmons, 2004), and delicate structures such as liposomes (Elhissi and Taylor, 2005; Elhissi et al., 2006; Wagner et al., 2006) and nucleic acids (Lentz et al., 2006). Moreover, the Aeroneb Pro vibrating-mesh nebulizer in particular is recommended for the delivery of drugs during mechanical ventilation (Fink et al., 2001a; Pedersen et al., 2006).

Vibrating-mesh nebulizers are divided into passively and actively vibrating-mesh devices (Newman and Gee-Turner, 2005). Passively vibrating-mesh devices (e.g. Omron MicroAir NE-U22 nebulizer, Fig. 1) employ a perforated plate having up to 6000 tapered holes, approximately 3 μm in diameter. A vibrating piezoelectric crystal attached to a transducer horn induces "passive" vibrations in the perforated plate positioned in front of it, resulting in extrusion of fluid through the holes and generation of the aerosol (Fig. 1). Actively vibrating-mesh devices (e.g. Aeroneb Pro nebulizer, Fig. 2) may employ a "micropump" system which comprises an aerosol generator consisting of a plate with up to 1000 dome-shaped apertures and a vibrating element which contracts and expands on application of an electric current. This results in upward and downward movements of the mesh by a few micrometres, extruding the fluid and generating the aerosol (Dhand, 2002) (Fig. 2).

In pulmonary delivery, the generation of particles smaller than approximately 5 or 6 μm is considered necessary to achieve deposition as the fine particle fraction (FPF) (i.e. in the respiratory bronchioles and alveolar region) (O'Callaghan and Barry, 1997). However, for nebulizers, other properties such as total output and output rate are also important. Previous studies on solutions have shown that the properties of aerosols generated from air-jet and ultrasonic nebulizers are dependent on fluid physicochemical properties such as viscosity and surface tension (McCallion et al., 1995; Steckel and Eskandar, 2003). In this study, the effect of fluid viscosity, surface tension and ion concentration on the aerosol properties and nebulization performance were investigated using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers. Findings of this study were compared with literature findings for air-jet and ultrasonic devices.

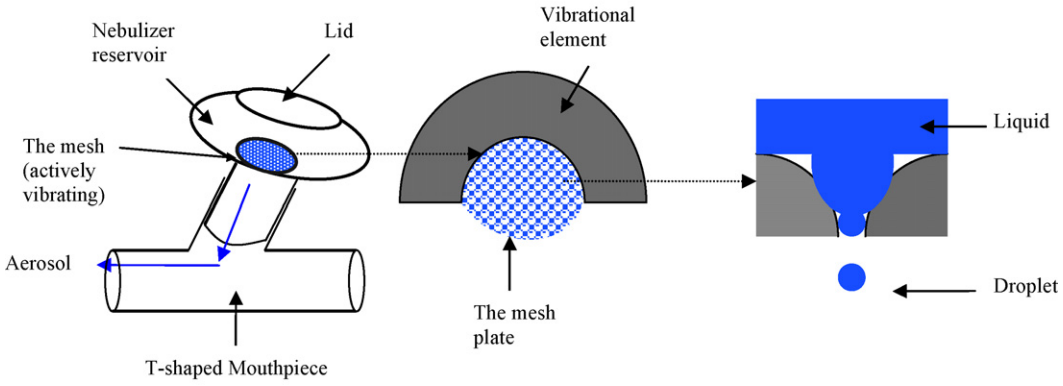

Fig. 2. A schematic diagram of the hand-held Aeroneb Pro nebulizer attached to a T-shaped mouthpiece (left). The mesh at the bottom of the nebulizer reservoir is surrounded by a vibrational element (middle) which expands and contracts at very high frequency. This produces a "micropump" action which extrudes the liquid through dome-shaped apertures and generates the aerosol droplets (right).

2. Materials and methods

2.1. Materials

Glycerol and absolute ethanol were both AnalaR grade and purchased from BDH, UK. Silicone fluid (SF) 200/0.65 and SF 200/5+1cs were supplied by Dow Corning, UK. Sodium chloride (NaCl) was supplied by Sigma–Aldrich, UK. Deionized water was high performance liquid chromatography (HPLC) grade and purchased from Fisher Scientific Ltd., UK. The Omron MicroAir NE-U22 nebulizer was supplied by Omron Healthcare, UK and the Aeroneb Pro nebulizer was supplied by Nektar, CA, USA.

2.2. Methods

2.2.1. Preparation of nebulizer fluids

A range of fluids was selected or prepared to provide nebulizer solutions having different viscosities, surface tensions or ion concentrations. Glycerol solutions were prepared in deionized water to yield 5, 10, 20 or 30% (v/v) concentrations. NaCl was dissolved in deionized water to provide 0.3 0.6, 0.9 or 9.0% (w/v) solutions. Silicone fluids and deionized water were used as received.

2.2.2. Measurement of fluid viscosity and surface tension

The viscosity of solutions was measured using a U-tube viscometer BS/U size A (BDH, UK) clamped vertically in a water bath at 20 °C. Surface tension measurements were performed using a Wilhelmy plate method by employing the CAHN Dynamic Contact Angle Analyzer (DCA-312, Scientific and Medical Products Ltd., UK) at 20 °C. Deionized water was used as a reference for all of the fluids investigated.

2.2.3. Determination of total aerosol output and aerosol output rate

Fluid (5 ml) was placed in the nebulizer directed towards a vacuum line, positioned horizontally. The reservoir and mouthpiece of the Omron nebulizer were both parallel to the ground (Fig. 1), whilst the reservoir of the Aeroneb Pro device was positioned perpendicular to the surface and attached to a Nektar T-shaped mouthpiece (Fig. 2). Nebulization was commenced to "dryness" (i.e. when aerosol generation completely ceased) and the time required determined. Total aerosol output was calculated gravimetrically by measuring the weight of the nebulizer before and after nebulization. The aerosol output rate was calculated at "dryness" as ml/min after converting the mass of the fluid nebulized to volume.

2.2.4. Laser diffraction size analysis of aerosol droplets

The size distribution of aerosol droplets at midway during nebulization was analyzed using a Malvern 2600c laser diffraction size analyzer with 63 mm lens (Malvern Instruments Ltd., UK). Laser diffraction is well established for size analysis of nebulized droplets and has shown good correlation with pulmonary deposition findings (Clark, 1995). Fluid (5 ml) was added to the nebulizer which was previously clamped 2.5 cm from the centre of the laser beam and adjusted to permit the aerosol cloud to traverse the beam at a distance of 2.5 cm from the lens of the instrument. A vacuum was applied to draw the aerosol through the beam. The size of the aerosol droplets was expressed as the volume median diameter (VMD). FPF was calculated as the volume fraction of the aerosol falling below 5.21 μm multiplied by the total aerosol output. This figure was selected because it was the closest to 5 μm of the size fractions determined by the instrument employed. The instrument employed does not detect particles which are smaller than 0.5 μm.

2.3. Statistical analysis

All experiments were performed in triplicate. Statistical analysis was performed using the one-way analysis of variance (ANOVA) for comparison of more than two results and the Student's *t*-tests for comparison of two sets of results.

3. Results and discussion

3.1. Droplet size, total aerosol output and FPF

Table 1 shows that aerosol droplet size, total aerosol output and FPF were all dependent on nebulizer type and fluid physicochemical properties. The Omron nebulizer generated aerosols with slightly larger ($P < 0.05$) droplet size and similar or smaller FPF when compared with the Aeroneb Pro nebulizer (Table 1). This indicates that whilst the droplets emitted from the Omron nebulizer were larger than from the Aeroneb Pro, they were less polydispersed. Using a liposome formulation we have shown that the Omron nebulizer generated the least polydispersed aerosol when compared with a range of air-jet and vibrating-mesh nebulizers (Elhissi et al., 2006). Moreover, for all fluids except for ethanol, the Omron nebulizer produced significantly ($P < 0.05$) higher total aerosol output than the Aeroneb Pro device (Table 1). Very high aerosol outputs (i.e. low residual volumes) have previously been reported for the Omron MicroAir NE-U22 nebulizer (Yoshiyama et al., 2002; Kishida et al., 2003; Ismail and Chrystyn, 2004; Elhissi and Taylor, 2005; Newman and Gee-Turner, 2005; Elhissi et al., 2006).

Glycerol solutions (0–30%, v/v) were employed to investigate the effect of fluid viscosity, since the increase in glycerol concentration increased the viscosity with minimal change in surface tension (Table 1). Fluid viscosity was inversely proportional to the VMD of the aerosol droplets, which was statistically significant ($P < 0.05$) only for the Omron nebulizer (Table 1; Fig. 3a). Literature findings for air-jet and ultrasonic nebulizers have yielded conflicting results, probably due to the employment of different nebulizer designs or operating parameters. For instance, Davis (1978) and McCallion et al. (1995) have shown that when fluid viscosity was increased, the median droplet size decreased for air-jet nebulizers and increased for ultrasonic nebulizers. In another study, McCallion and Patel (1996) have shown that the median size of droplets generated from air-jet nebulizers was inversely proportional to fluid viscosity up to a critical viscosity value above which droplet median size started to increase. Steckel and Eskandar (2003) have reported an increase in the droplet size at the

Table 1
Size, total output and FPF of aerosol droplets generated from fluids with different physicochemical properties using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers ($n = 3 \pm$ S.D.)

Fluid	Physicochemical properties		Aerosol generated using the Omron MicroAir NE-U22 nebulizer			Aerosol generated using the Aeroneb Pro nebulizer		
	Viscosity (cP)	Surface tension (dyne/cm)	VMD (μm)	Total aerosol output (%)	FPF (%≤5.21 μm)	VMD (μm)	Total aerosol output (%)	FPF (%≤5.21 μm)
Deionized water	1.00[a]	72.80[a]	6.43 ± 0.87	91.24 ± 3.11	30.23 ± 6.36	5.94 ± 1.66	58.06 ± 22.22	28.05 ± 16.51
Glycerol (5%, v/v)	1.21 ± 0.00	71.17 ± 0.12	5.82 ± 0.20	95.80 ± 0.64	41.00 ± 1.68	4.74 ± 0.13	74.02 ± 2.07	41.46 ± 2.67
Glycerol (10%, v/v)	1.31 ± 0.02	70.30 ± 0.17	5.83 ± 0.08	95.89 ± 0.63	42.13 ± 0.60	4.60 ± 0.06	74.28 ± 1.70	42.43 ± 0.81
Glycerol (20%, v/v)	1.92[a]	69.90 ± 0.10	4.69 ± 0.22	95.67 ± 0.29	53.35 ± 2.34	4.23 ± 0.04	77.95 ± 4.61	48.65 ± 2.57
Glycerol (30%, v/v)	2.74[a]	69.10 ± 0.10	No aerosol generated			4.09 ± 0.03	81.79 ± 1.65	52.14 ± 0.93
NaCl (0.3%, w/v)	1.02 ± 0.01	72.3 ± 0.10	5.99 ± 0.03	94.19 ± 0.85	39.40 ± 0.21	4.70 ± 0.07	75.62 ± 1.64	43.08 ± 1.45
NaCl (0.6%, w/v)	1.02 ± 0.00	72.47 ± 0.15	6.03 ± 0.15	94.46 ± 0.83	39.26 ± 0.92	4.63 ± 0.07	75.18 ± 2.16	43.45 ± 1.01
NaCl (0.9%, w/v)	1.02 ± 0.00	72.63 ± 0.06	5.58 ± 0.08	93.52 ± 0.70	43.08 ± 0.65	4.55 ± 0.04	75.21 ± 2.50	43.96 ± 1.08
NaCl (9%, w/v)	1.1 ± 0.00	74.57 ± 0.21	4.88 ± 0.10	93.78 ± 0.52	51.36 ± 0.67	4.35 ± 0.50	81.54 ± 4.80	49.36 ± 9.25
Absolute ethanol	1.19[a]	24.10[a]	4.39 ± 0.04	94.52 ± 3.40	58.47 ± 1.71	4.32 ± 0.10	90.98 ± 1.28	57.30 ± 2.34
SF (200/0.65cs)	0.49[a]	15.60 ± 0.10	7.31 ± 0.17	95.74 ± 0.40	37.02 ± 1.19	4.20 ± 0.40	84.33 ± 2.61	50.14 ± 2.20
SF (200/1+5cs)	2.45[a]	17.93 ± 0.15	No aerosol generated			No aerosol generated		

[a] From McCallion et al. (1995).

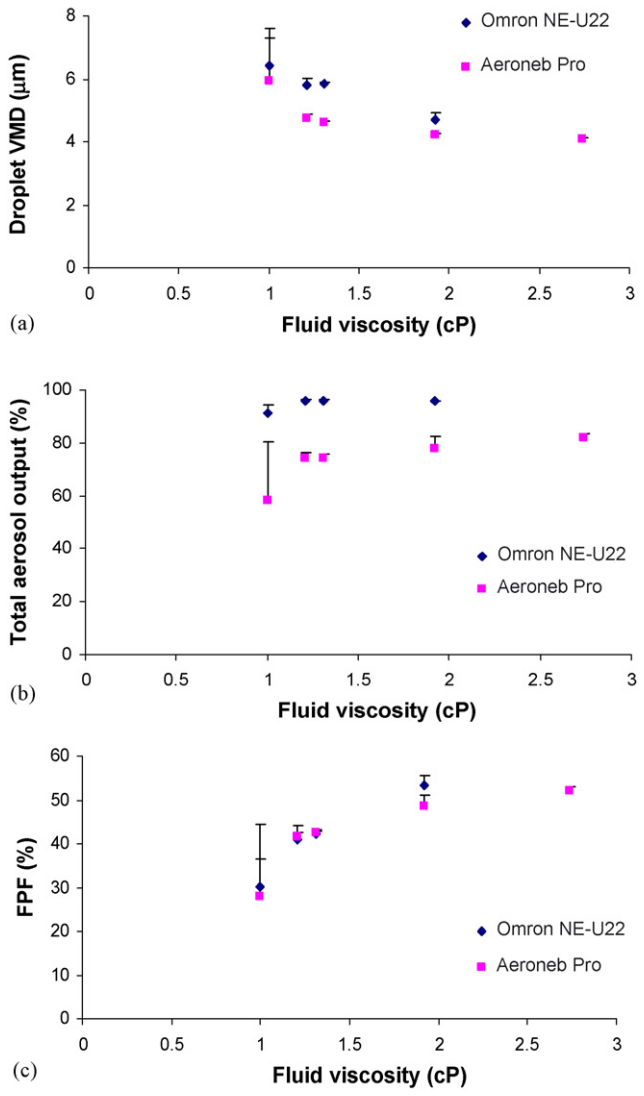

Fig. 3. The relationship between fluid viscosity and (a) droplet VMD, (b) total output and (c) FPF of the aerosols generated using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers for glycerol 0, 5, 10, 20 and 30% (v/v) solutions ($n = 3 \pm$ S.D.).

beginning of jet nebulization, which was attributed to increased formulation viscosity due to solvent evaporation and subsequent cooling. However, Finlay et al. (2000) have shown an inverse relationship between viscosity and droplet size for an ultrasonic nebulizer, though the relationship between viscosity and droplet size was dependent on nebulizer design for air-jet devices.

The total aerosol output for the Omron nebulizer was minimally but significantly ($P < 0.05$) affected by fluid viscosity, with higher outputs produced by glycerol inclusion compared with deionized water (Table 1; Fig. 3b). For the Aeroneb Pro nebulizer, this effect was not statistically significant ($P > 0.05$) due to the large variability in the total output produced when deionized water was employed (Table 1; Fig. 3b). For both devices, the FPF was significantly increased ($P < 0.05$) when the glycerol concentration was increased (Table 1; Fig. 3c). In addition, low concentrations of glycerol enhanced the reproducibility of the aerosol properties (Table 1; Fig. 3). However, when glycerol (30%) was employed (i.e. the highest viscosity fluid), no aerosols were generated from the Omron nebulizer (Table 1) whilst intermittent nebulization was observed for the Aeroneb Pro device. This indicates that when vibrating-mesh nebulizers were employed, increased viscosity was desirable up to certain limit beyond which nebulization became intermittent or completely ceased. Cessation of aerosol generation was evident for the Omron nebulizer, which may be related to the low energy input for atomization since the vibrations of its mesh are passive, compared to the active vibrations of the mesh generated within the Aeroneb Pro nebulizer. According to these findings, both nebulizers are not recommended for delivery of solutions having a viscosity value higher than 1.92 cP. The ceased or intermittent nebulization observed for the vibrating-mesh devices as a result of increasing the viscosity has been previously reported for ultrasonic nebulizers which are also considered unsuitable for generating aerosol from viscous fluids (McCallion and Patel, 1996; Finlay et al., 2000). For ultrasonic nebulizers, the viscosity values above which aerosol generation ceases have been reported to be similar (Finlay et al., 2000) or higher (McCallion and Patel, 1996) than those observed in this study for the vibrating-mesh devices. However, air-jet nebulizers have been shown capable of generating aerosols from highly viscous solutions (McCallion and Patel, 1996; Finlay et al., 2000).

NaCl solutions (0–9%, w/v) have similar surface tension and viscosity values but the concentration of ions derived from NaCl was different (Table 1). This permitted investigation of the effect of ion concentration on nebulization. The VMD of the aerosol droplets was inversely proportional to NaCl concentration (Table 1; Fig. 4a). This relation was statistically significant ($P < 0.05$) for the Omron nebulizer and a trend was observed for the actively vibrating-mesh (Aeroneb Pro) device. Statistical analysis showed that total aerosol output was unaffected by ion concentration ($P > 0.05$) (Table 1; Fig. 4b). However, NaCl inclusion enhanced reproducibility and tended to increase total aerosol output particularly for the Aeroneb Pro nebulizer. FPF was enhanced as NaCl concentration was increased, which was again statistically significant ($P > 0.05$) only for the Omron nebulizer (Table 1; Fig. 4c). This suggests, in general, that ions have played a role in the process of aerosol generation from vibrating-mesh nebulizers. Using an AERx soft mist inhaler, aerosol generation improved and variability was reduced when formulations were prepared in NaCl solution compared with lactose solution (Deshpande et al., 2002). This device employs a nozzle array comprising laser-drilled holes through which liquid is passed to generate the aerosol (Placke et al., 2002), suggesting a similar principle of operation to that of vibrating-mesh nebulizers. Using the AERx device, it was hypothesized that a small electrolyte concentration would increase the electrical conductivity and subsequently suppresses the high electrostatic charge present in pure water. This would decrease water adhesion to the internal device surfaces by repulsion of charge towards the bulk fluid and reducing the droplet surface charge (Rosell et al., 2000; Deshpande et al., 2002). Thus in our study, the ions present in solution may prevent water adhesion to the internal surfaces and mesh pores of the nebulizers, resulting in enhanced aerosol properties and reduced variability between experiments. It is also

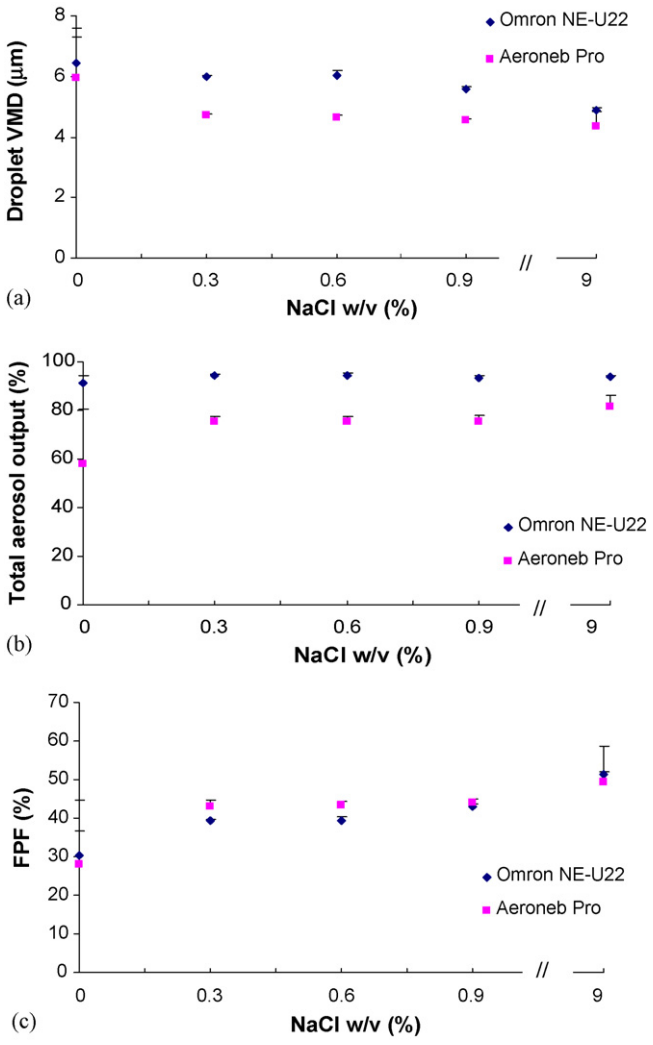

Fig. 4. The relationship between NaCl concentration (i.e. ions concentration) and (a) droplet VMD, (b) total output and (c) FPF of aerosols generated using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers ($n = 3 \pm$ S.D.).

possible that the effect of NaCl on the generation of aerosols is related to the tendency of chloride anions to be present at the air–water interface whilst sodium cations migrate to the bulk liquid of the droplet (Garrett, 2004). Further work is required to explain the effect of ion type and concentration on the aerosols generated using this type of nebulizer.

SF (200/0.65cs) was employed to provide a formulation having low surface tension and viscosity, whilst ethanol was used to provide a formulation with low surface tension and a viscosity value similar to those of most fluids investigated (Table 1). For the Aeroneb Pro nebulizer, SF (200/0.65cs) produced aerosols having similar aerosol properties to all fluids studied (Table 1). By contrast, the aerosol droplets generated from the Omron nebulizer using this fluid were the largest amongst the fluids investigated and consequently the FPF was low (Table 1). The employment of ethanol with this nebulizer resulted in the generation of aerosols having similar properties to the other fluids (Table 1). Thus, the large droplet size and reduced FPF for this nebulizer using the SF (200/0.65) is likely to result from the reduced viscosity rather than reduced surface tension, again indicating the inverse relation between viscosity and droplet size. When SF (200/1+5cs) was employed in an attempt to increase viscosity and retain low surface tension, no aerosol was generated from either nebulizer (Table 1), indicating that viscosity is the prime determinant of the aerosol properties and nebulizer performance. Using air-jet or ultrasonic nebulizers, the effect of surface tension on droplet size was minor when compared to the effect of viscosity (McCallion et al., 1995), which agrees with the present findings for vibrating-mesh devices. For air-jet and ultrasonic nebulizers, surface tension and droplet size were inversely related as reported by McCallion et al. (1996) whilst directly related as reported by Steckel and Eskandar (2003) and Steckel et al. (2003).

When ethanol was employed, the Aeroneb Pro nebulizer produced slightly smaller droplets compared with other fluids, and both total output and FPF were relatively high (Table 1). This trend was not observed for glycerol (5%) which has similar viscosity to ethanol (Table 1). Thus, such small changes in the aerosol properties for this nebulizer are likely to be due to the low surface tension of ethanol. Using air-jet nebulizers, total aerosol and FPF have been reported to increase when ethanol content in water/polymer-based formulations was increased, and this was attributed to an ethanol-induced lowering in surface tension (Davis et al., 1978). It has been also reported that aerosol output from a jet nebulizer may be increased by lowering the surface tension of the formulation (Smye et al., 1990; Coates et al., 1997). Recently, liposome-based formulations have been shown to increase the FPF of bronchodilators compared with liposome-free drug solutions using air-jet (Aboudan et al., 2004) or vibrating-mesh (Aboudan et al., 2004; Elhissi et al., 2005) nebulizers. This was attributed to a phospholipid-induced reduction in surface tension using the liposomal formulation (Elhissi et al., 2005).

3.2. Nebulization time and aerosol output rate

For both nebulizers, the time required to complete nebulization and the aerosol output rate differed significantly ($P < 0.05$) between the different fluids (Table 2). Although the Omron nebulizer produced higher total aerosol outputs (Table 1), it generally required longer time to achieve “dryness” compared with the Aeroneb Pro nebulizer (Table 2). Thus, aerosol output rate is an important consideration for evaluating the efficiency of these devices. The aerosol output rate was generally higher for the Aeroneb Pro nebulizer compared with the Omron device (Table 2). Nebulizers utilizing the Aerogen micropump vibrating-mesh technology, as is the case here, have previously been shown to produce higher output rates than the Omron MicroAir NE-U22 nebulizer (Fink et al., 2003; Elhissi et al., 2006). This can be attributed to the higher energy input for atomization in the Aeroneb Pro nebulizer as the vibrations of the mesh are active, permitting a more efficient ability to overcome the resistance of fluids to the shear forces applied.

Using glycerol (0–30%, v/v), a direct relationship between fluid viscosity and time required to reach “dryness” was evident for the Omron nebulizer (Table 2; Fig. 5a). For the Aeroneb

Table 2
Time of nebulization and output rate of aerosols generated from fluids with different physicochemical properties using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers ($n = 3 \pm$ S.D.)

Fluid	Physicochemical properties		Aerosol generated using the Omron MicroAir NE-U22 nebulizer		Aerosol generated using the Aeroneb Pro nebulizer	
	Viscosity (cP)	Surface tension (dyne/cm)	Time of nebulization to "dryness" (min)	Aerosol output rate (ml/min)	Time of nebulization to "dryness" (min)	Aerosol output rate (ml/min)
Deionized water	1.00[a]	72.80[a]	26.11 ± 4.57	0.18 ± 0.04	13.82 ± 6.87	0.26 ± 0.16
Glycerol (5%, v/v)	1.21 ± 0.00	71.17 ± 0.12	24.40 ± 2.47	0.20 ± 0.02	10.70 ± 0.16	0.35 ± 0.01
Glycerol (10%, v/v)	1.31 ± 0.02	70.30 ± 0.17	35.27 ± 6.41	0.14 ± 0.02	12.88 ± 3.08	0.30 ± 0.07
Glycerol (20%, v/v)	1.92[a]	69.90 ± 0.10	51.91 ± 5.27	0.09 ± 0.01	13.71 ± 2.86	0.30 ± 0.07
Glycerol (30%, v/v)	2.74[a]	69.10 ± 0.10	No aerosol generated		17.96 ± 0.68	0.23 ± 0.00
NaCl (0.3%, w/v)	1.02 ± 0.01	72.3 ± 0.10	24.07 ± 1.11	0.19 ± 0.01	10.29 ± 0.22	0.37 ± 0.01
NaCl (0.6%, w/v)	1.02 ± 0.00	72.47 ± 0.15	22.78 ± 1.52	0.21 ± 0.01	10.33 ± 0.03	0.37 ± 0.01
NaCl (0.9%, w/v)	1.02 ± 0.00	72.63 ± 0.06	23.35 ± 1.25	0.20 ± 0.01	12.13 ± 1.83	0.32 ± 0.04
NaCl (9%, w/v)	1.1 ± 0.00	74.57 ± 0.21	23.35 ± 2.51	0.21 ± 0.02	18.34 ± 2.19	0.22 ± 0.04
Absolute ethanol	1.19[a]	24.10[a]	29.70 ± 6.40	0.16 ± 0.03	10.43 ± 0.23	0.45 ± 0.02
SF (200/0.65cs)	0.49[a]	15.60 ± 0.10	3.78 ± 0.17	1.32 ± 0.03	5.21 ± 0.02	0.83 ± 0.03
SF (200/1+5cs)	2.45[a]	17.93 ± 0.15	No aerosol generated		No aerosol generated	

[a] From McCallion et al. (1995).

Pro nebulizer the difference between the fluids was not statistically significant ($P > 0.05$) but a trend of a direct relationship was observed if deionized water (0% glycerol) was ignored (Table 2; Fig. 5a). Prolongation of nebulization time resulting from increased fluid viscosity has been reported for air-jet (Newman et al., 1985; McCallion et al., 1995; Finlay et al., 2000) and ultrasonic (McCallion et al., 1995; Finlay et al., 2000) nebulizers. The aerosol output rate decreased as viscosity was increased, and this was statistically significant ($P < 0.05$) only for the Omron nebulizer (Table 2; Fig. 5b). Thus, the reduced droplet size and increased FPF due to increased fluid viscosity (Table 1; Fig. 3) were counteracted by the prolonged nebulization and reduced output rates, particularly when the vibrations of the mesh were passive as in the case of the Omron nebulizer (Table 2; Fig. 5).

When considering NaCl solutions (0–9%, w/v) to study the effect of ions on nebulization time and output rate, no effect ($P > 0.05$) of NaCl concentration was found for either device (Table 2; Fig. 6a and b). However, the presence of ions reduced

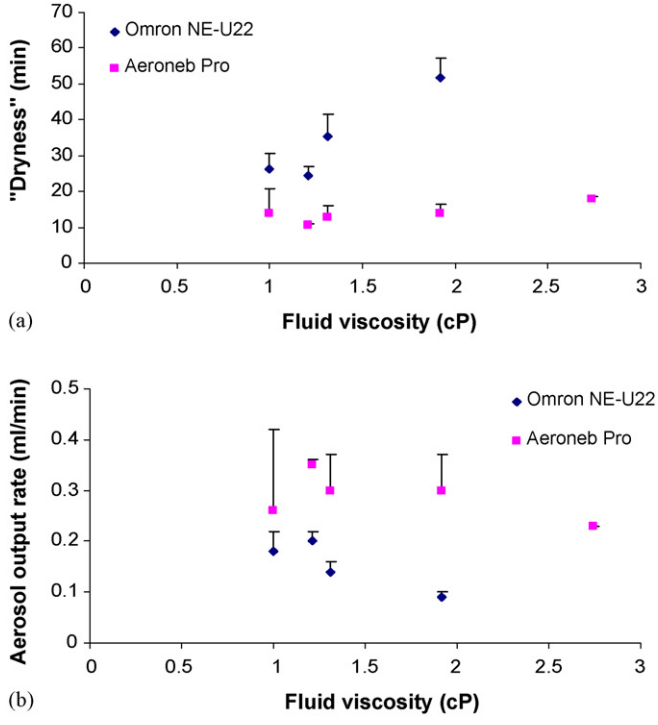

Fig. 5. The relationship between fluid viscosity and nebulization (a) time to "dryness" and (b) output rate for aerosols generated using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers for glycerol 0, 5, 10, 20 and 30% (v/v) solutions ($n = 3 \pm$ S.D.).

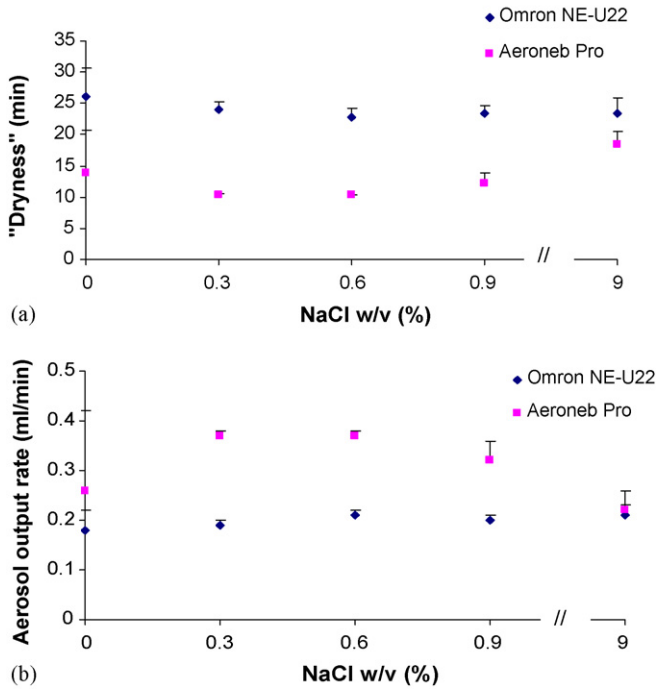

Fig. 6. The relationship between NaCl concentration (i.e. ions concentration) and (a) time of nebulization to "dryness" and (b) output rate of the aerosols generated using Omron MicroAir NE-U22 and Aeroneb Pro vibrating-mesh nebulizers ($n = 3 \pm$ S.D.).

the variability of the output rate and the time required to complete nebulization of deionized water (Table 2; Fig. 6), indicating that the effective performance of vibrating-mesh nebulizers, particularly the Aeroneb Pro, requires the presence of dissolved electrolyte. The Aeroneb Pro nebulizer required longer to nebulize NaCl (9%, w/v) solution with a subsequent low output rate compared to the other NaCl solutions (Table 2; Fig. 6a and b), which may be attributed to the slightly higher surface tension of this formulation (Table 2). Surface tension has been reported to be directly proportional to the time required to complete air-jet (Newman et al., 1986; Davis et al., 1978; McCallion et al., 1995) and ultrasonic (McCallion et al., 1995) nebulization. Thus, it was expected that nebulization time would be very short and the output rate would be particularly high for SF (200/0.65cs) owing to its very low surface tension (Table 2). However, such short nebulization times and high output rate might also be attributed to the reduced viscosity of this fluid (Table 2). Ethanol required a much longer time to reach "dryness" although its surface tension was low, and this may be attributed to its high viscosity compared to SF (200/0.65cs) (Table 2). No aerosols were generated from the highly viscous SF (200/1+5cs) although its surface tension was low. Overall, this suggests that reduced surface tension might help in shortening nebulization time although it is not a prime influence. The low viscosity and surface tension of SF (200/0.65cs) greatly enhanced the performance of the Omron nebulizer since it completed nebulization in a shorter time ($P < 0.05$) and produced higher output rate ($P < 0.05$) than the Aeroneb Pro device when this fluid was employed (Table 2).

4. Conclusions

A range of fluids with different physicochemical properties were nebulized using the Omron MicroAir NE-U22 (passively vibrating) and the Aeroneb Pro (actively vibrating) mesh nebulizers. The aerosol performance was dependent on both the fluid characteristics and the particular vibrating-mesh technology. For all fluids, the Omron nebulizer generated aerosols with slightly larger droplet size and similar or smaller FPF than the Aeroneb Pro device. The total aerosol output was generally independent of fluid properties. However, increased fluid viscosity resulted in a decrease in droplet size and a consequent increase in the FPF, but the nebulization time was prolonged and output rate decreased. A further increase in viscosity resulted in cessation of nebulization from the Omron nebulizer and intermittent aerosol generation from the Aeroneb Pro device, indicating that vibrating-mesh technology may be inappropriate for nebulizing highly viscous fluids. The presence of low ion concentrations in the nebulizer fluid was desirable as it enhanced the aerosol generation and reduced the variability of droplet size and aerosol output. Increased ion concentration also resulted in a decrease in droplet size and a subsequent increase in the FPF, particularly for the Omron nebulizer. No clear relationship was observed between fluid surface tension and aerosol properties. However, when viscosity was low, low surface tension seemed desirable as this dramatically shortened the nebulization time and increased the aerosol output rate, particularly for the Omron nebulizer, though for the Omron nebulizer this also increased the droplet size and slightly decreased the FPF. In general, the Omron nebulizer was superior to the Aeroneb Pro device in generating very high total aerosol outputs from the fluids investigated. On the other hand, the Aeroneb Pro nebulizer was superior in terms of completing nebulization in shorter times and producing higher aerosol output rates especially when the viscosity was increased. This study has also shown that vibrating-mesh nebulizers are affected by fluid properties in a manner different from that of air-jet and ultrasonic devices.

Acknowledgements

We wish to thank Nektar, USA for supplying us with the Aeroneb Pro nebulizer and Omron Healthcare, UK for supplying us with the Omron MicroAir NE-U22 nebulizer.

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