Nebulization of Fluids of Different Physicochemical Properties with Air-Jet and Ultrasonic Nebulizers

Orla N. M. McCallion,[1,3] Kevin M. G. Taylor,[1] Marian Thomas,[2] and Anthony J. Taylor[2]

Received December 15, 1994; accepted July 18, 1995

Purpose. Empirical formulae relate the mean size of primary droplets from jet and ultrasonic nebulizers to a fluid's physicochemical properties. Although the size selective "filtering" effects of baffling and evaporation may modify the secondary aerosol produced, this research sought to evaluate whether viscosity and surface tension of nebulized fluids influenced the aerosol's size and output characteristics.

Methods. Fluid systems of different surface tension and viscosity (glycerol and propylene glycol solutions [10–50% (v/v)] and a range of silicone fluids [200/0.65 cs – 100cs]) were nebulized in three jet and two ultrasonic nebulizers. Secondary aerosol characteristics were measured with a Malvern 2600C laser diffraction sizer and the nebulization times, residual volumes and percentage outputs were determined.

Results. While the droplet size appeared to be inversely proportional to viscosity for jet nebulizers, it was directly proportional to viscosity for ultrasonic nebulizers. Although fluid systems with lower surface tensions generally produced slightly smaller MMDs, the relationship between surface tension and droplet size was complex. The more viscous fluids required longer nebulization times and were associated with increased residual amounts (lower outputs). The ultrasonic nebulizers did not effectively, and were on occasion unable to, nebulize the more viscous fluids.

Conclusions. It follows that there are cut-off values for viscosity and/or surface tension above or below which ultrasonic devices fail to operate. Moreover, jet nebulizers generated an aerosol with an optimum respirable output from median-viscosity fluids.

KEY WORDS: aerosol; droplet size; jet nebulizer; surface tension; ultrasonic nebulizer; viscosity.

INTRODUCTION

Early studies on airblast atomisation elucidated some of the key factors involved. While the range of variables covered was fairly narrow, it was suggested that droplet-size was inversely proportional to the relative velocity between the air and the liquid and proportional to the liquid's surface tension (for low viscosity liquids); and that viscosity had a decreasing effect on droplet-size as the air/liquid ratio increased. Rizkalla and Lefebvre (1) suggested that the mean drop-size of liquid sprays increased with increases in liquid viscosity and surface tension while the overall effect of liquid density on drop-size was small. Mercer (2) found similar results in his research with nebulizers, stating that the primary droplet distribution was related to:

$$D/D_L = 0.64[1 + 0.011(G_L/G_A)^2] \times [2\gamma/9\rho V^2 D_L]^{0.45}$$

where D = diameter of droplet of average volume, D_L = diameter of liquid inlet orifice, G_L, G_A = mass flow rate of liquid and air, γ = liquid surface tension, ρ = air density and V = air velocity.

Viscosity differences of the magnitude (1–20 cs) were reported to have a negligible effect on average droplet-size (3) and affected mean droplet volume only through the liquid mass flow rate (G_L). Liquid viscosity resists droplet formation at all stages, hence higher viscosities had been expected to increase the size of the droplet. Work by Searls and Snyder (3) revealed that increased viscosity prolonged atomisation time but reduced mean droplet-size. Dorman (4) reported that d_{32} (the volume surface or Sauter mean diameter) was proportional to $\eta^{0.1}$, while Hasson and Mizrahi (5) found that d_{32} was proportional to $\eta^{1/6}$ for values of viscosity from 1–21 cP. However, Hinds *et al.* (6) noted little change in drop-size with increased viscosity. Mercer's equation posits that reducing the surface tension should produce smaller droplets. However, there is insufficient consistent confirmatory research in this area. Walkenhorst and Dautrebande (7) stated that surface tension exerted no real effect on the resultant aerosol, whilst Kouchetov *et al.* (8) reported that, when solutions containing a surface active agent were atomised by high velocity air streams, the resultant droplet-size was similar to water's. However, further studies by Fainerman and Sapiro (9) revealed that surfactant solutions emitted smaller droplets than water.

There have been few previous attempts to assess how medical air-jet atomisers (nebulizers) perform when using solutions of differing physical properties. Maximyst and Bird jet nebulizers were used to nebulize a range of propylene glycol solutions [10% to 60% (v/v)]. Above 20%, MMDs and aerosol output decreased with increased propylene glycol content. Furthermore, as surface tension decreased, the aerosol output increased (10). Newman *et al.* (11) reported than Bird, DeVilbiss and Upmist jet nebulizers tended (though not significantly) to produce smaller droplets from higher-viscosity solutions. They could not, by contrast, demonstrate a clear correlation between droplet-size and the solutions' surface tensions. Medical ultrasonic nebulizers invariably belong to the high frequency (1–3 MHz) piezoelectric type. Two rival theories—the capillary and the cavitation theories—each purport to describe the mechanism of liquid disintegration in ultrasonic devices. The former depicts droplet formation as the result of capillary waves on the excited liquid surface growing in amplitude until the crests break off. Lang (12) observed that the mean drop-size from thin liquid layers was proportional to the capillary wavelength on the liquid surface. Using an experimentally determined factor of 0.34, the drop diameter D was given by the relationship:

$$D = 0.34 \times (8\pi\gamma)^{1/3}/\rho f^2$$

[1] Department of Pharmaceutics, School of Pharmacy, University of London, 29–39 Brunswick Square, London WCIN IAX, United Kingdom.

[2] Glaxo Research and Development, Department of Respiratory Product Development, Park Lane, Ware, Hertfordshire SG12 0DP, United Kingdom.

[3] To whom correspondence should be addressed.

0724-8741/95/1100-1682$07.50/0 © 1995 Plenum Publishing Corporation

where γ = surface tensions; ρ = density and f = excitation frequency. However Sollner's (13) cavitation theory may explain how liquid disintegrates in high frequency nebulizers. This postulates that the liquid is atomised by hydraulic shocks produced by an implosion of cavitation bubbles near its surface. Later research (14,15) using relatively high frequencies (0.5–2.0 MHz) indicated that atomisation was a cavitation-dependent phenomena. Boguslavskii and Eknadiosyants (16) convincingly married these theories when they proposed that drop formation resulted from capillary waves initiated and driven by cavitation bubbles. Thus, if capillary theory contributes in part to ultrasonic atomisation, the droplet-size will be proportional to the surface tension of the liquid and inversely proportional to the liquid's density. Furthermore, variation in liquid properties giving increased threshold amplitude (e.g. increased viscosity) will tend to progressively slow or completely suppress the rate of atomisation.

Boucher and Kreuter (17) reported that solutions with viscosity above 10 cP were difficult to aerosolise with ultrasonic nebulizers. Gershenzon and Eknadiosyants (14) stated that liquid vapour pressure and viscosity were important factors in ultrasonic aerosol output in that liquids with a low viscosity offered less resistance to fountain-disintegration and produced greater "fog" outputs. The rate of ultrasonic nebulization of Alevaire (a drug for mucus clearance) progressively decreased as the viscosity of the drug solution increased (15). Similarly, the output rate of N-acetyl-L-cysteine was increased by 10% when a less viscous solution (10% as opposed to 20%) was nebulized. Furthermore, whilst certain oily/viscous liquids produced a fountain, they did not disintegrate and produced only fountain whirling and foaming with no aerosol generated (15). Variations in air/liquid surface tension may be less significant. Surfactants have been shown to depress nebulization rate, possibly due to a reduction in capillary wavelength causing an increase in the threshold amplitude (17), or to their influence on the diffusion of gas into cavitation bubbles (18).

There are insufficient studies of the effect of formulation variables upon the size and output characteristics of nebulized medical aerosols. This study sought to address this by investigating aerosol characteristics from a diverse range of fluids nebulized in three types of jet nebulizer and two ultrasonic devices.

MATERIALS AND METHODS

Fluids, selected to encompass a wide range of surface tension and viscosity, included deionised water (Whatman WR 50 RO/Deioniser, Whatman U.K.), ethanol, glycerol 10–50% (v/v) solutions, propylene glycol 10–50% (v/v) solutions (B.D.H. Laboratory Supplies, Lutterworth, U.K.) and silicone fluids 200/0.65 cs–200/100 cs (Dow Corning, Reading, U.K.). The surface tension of the fluids tested were determined using the CAHN Dynamic Contact Angle analyser (Scientific and Medical Products Ltd., Manchester, U.K.). The viscosities were determined using a U-tube viscometer and the bulk densities determined using standard density bottles (B.D.H. Laboratory Supplies, Lutterworth, U.K.). These fluids were nebulized to dryness or for (1) 20 min in three jet nebulizers [Pari LC (Pari-Werk GmbH, Starnberg, Germany), Sidestream (Medic Aid Ltd., Pagham, U.K.) and Cirrus (Intersurgical Complete Respiratory Care, Wokingham, U.K.)] driven by compressed air from a gas cylinder at 6 L/min and 8 L/min or (2) nebulized for 10 min in two ultrasonic nebulizers [Medix Electronic and Easimist (Medix Ltd., Lutterworth, Leicestershire)] operated at the midpoint power setting. The Malvern 2600C laser particle sizer (Malvern Instruments, Malvern, U.K.) was used to obtain a continual measurement of aerosol droplet size distribution throughout the entire nebulization period. Readings were taken at 30 sec intervals. Each nebulizer was weighed: (1) when empty, (2) following the addition of the appropriate volume of test fluid (4 to 8 ml) and (3) at the end of the nebulization period. The "dead volume" of the test fluid was calculated from the weight measurements. Optimal alignment of the equipment and background measurements were measured prior to nebulization. The nebulizer was clamped in a vertical position so that the mouth-piece tip was 2.5 cm from the centre of the laser beam. The aerosol was directed through the beam approximately 5 mm in front of the 63 mm Fourier transform lens and was drawn away by extraction into a suction pump. The nebulizers were run at the appropriate flow-rate for 10 sec before measurement in order to achieve a steady output. All experiments were performed in triplicate at ambient temperature (20–25°C) and relative humidity (40–60%). The various parameters relating to aerosol characteristics and nebulization process which were investigated included:

i. The mass median diameter (MMD). Assuming that the nebulized droplets are spherical, it is possible to calculate the aerodynamic diameter from the bulk density values (relative to water) and MMD values.

ii. The percentage of the aerosol droplets less than 5 μm in diameter (i.e. respirable percentage) and the 90% undersize.

iii. The span value. This is a measure of the width of the volume distribution relative to the median diameter.

$$\text{Span} = \frac{90\% \text{ undersize} - 10\% \text{ undersize}}{50\% \text{ undersize}}$$

iv. The time required to nebulize the test fluid to dryness (i.e. the time at which no aerosol could be detected with the sizing equipment) or to a predetermined maximum time.

v. The weight of the test fluid remaining in the device after nebulization. This permitted calculation of the percentage of the initial fluid which remained in the nebulizer and of the total output.

vi. The respirable output (respirable percentage multiplied by the total output percentage) for the appropriate nebulization period.

RESULTS AND DISCUSSION

While empirical formulae relate the mean size of the primary droplets produced by nebulizers to the viscosity, surface tension and density of the fluid, these effects may be masked in the secondary aerosol produced. The marked discrepancies noted in this and other studies between predicted and actual outcomes may be attributable to nebulizer design. Baffle systems are designed to trap more than 99% of the primary droplet mass. This is mostly returned to the reser-

voir, and less than 1% (comprising only the smallest satellite droplets) is emitted at the mouthpiece. The wall of the device may also act as a baffle in small-dimension nebulizers. Consequently, these size-selective "filtering" effects may mask any effects of viscosity and surface tension on the primary droplets produced at the point of atomisation. Furthermore, dependent on the sizing technique adopted, droplet-size may be modified by droplet evaporation (or hygroscopic growth). In this study, drop-sizes were measured by a laser diffraction sizer at a standardised distance of 2.5 cm from the atomiser mouth-piece, since this distance corresponds to the arrival of the aerosol at the patient's respiratory tract. This technique can measure droplets close to their point of generation (before appreciable evaporation or growth can occur) and is therefore an ideal method to characterise aerosols delivered from medical nebulizers. Clark (19) found this a "robust and reliable" technique which allowed him to validate a good correlation between diffraction derived size distribution, gamma camera deposition profiles and the theoretical Rudolph model.

Mass Median Diameter. This study's most prominent finding was the MMD's apparently greater dependence upon the nebulizer fluid's viscosity as opposed to its surface tension (Tables I and II). As fluid viscosity increased, jet and ultrasonic nebulizers exhibited contrary trends in droplet size variation in that MMDs progressively decreased with the former and increased markedly with the latter devices. Reflecting previous findings (20,21), MMDs were consistently smaller when jet nebulizers were operated at the higher flow-rate and the jet nebulizers generated aerosols with appreciably smaller MMDs (0.86–3.69 μm) than the ultrasonics (MMDs: 2.79–6.45 μm—Table I). Both ultrasonic nebulizers were unable to nebulize more viscous solutions of propylene glycol and glycerol than those specified in Table II. The Medix could nebulize the 0.65–5.0 cs silicone fluids while the Easimist could not continuously nebulize any.

Jet Nebulization. Typical findings for jet nebulization are shown by the Pari LC (Table I). The highest MMDs (3.57–2.98 μm at 6 L/min; 3.13–2.55 μm at 8 L/min) occurred with water, silicone fluid 200/0.65 cs, glycerol 10% (v/v) and ethanol. While these fluids differed markedly in their surface tension values (over a range of approximately 55 dyne/cm), they possessed the lowest viscosity values (all below 1.31 cP). By contrast, lower MMDs occurred with fluids which had higher viscosity values but comparable surface tension values. As described by previous studies (10,11) the more viscous fluids tended to produce smaller droplets. Within specific fluid systems, such as glycerol 10%–50% (v/v), propylene glycol 10–50% (v/v) and the 200 grade silicone fluids, MMDs decreased as fluid-viscosity increased. (It is noteworthy that MMD values obtained for the silicone fluid series decreased over the earlier viscosity range whilst the converse was true the more viscous fluids). In the glycerol and silicone fluid series, surface tension did not greatly alter though the effect on the MMD was considerable (3.10–2.47 μm at 6 L/min; 2.90–1.97 μm at 8 L/min: 3.34–1.17 μm at 6 L/min; 2.86–1.06 μm at 8 L/min respectively). These findings suggest that viscosity and MMD were inversely related and that surface tension did not influence the MMD value. However, when the fluid systems were analysed separately a correlation between surface tension and MMDs appeared to exist. In the glycerol and propylene glycol solutions, surface tension was directly proportional to droplet-size, whilst the converse was true for the silicone fluids. Furthermore, although the glycerol and propylene glycol series exhibited similar viscosity values, the propylene glycols possessed lower surface tension values (i.e. 62–45 dyne/cm as opposed to 73–70 dyne/cm) and produced aerosols with much smaller MMDs (circa 40%). While droplets generated

Table I. Mean Mass Median Diameter and Total Output (% of the Initial Amount Released) for a Range of Fluids Nebulized in a Pari LC Nebulizer

Fluid	Viscosity (cP)	Surface Tension (dyne/cm)	Mass Median Diameter (μm)		Total Output (%)	
			6 L/min	8 L/min	6 L/min	8 L/min
Water	1.00	72.80	3.6	3.1	74.3	75.4
Ethanol	1.19	24.10	3.0	2.5	96.6	97.3
Glycerol 10%	1.31	72.90	3.1	2.9	71.5	73.7
Glycerol 25%	2.09	72.21	2.6	2.4	68.1	72.8
Glycerol 50%	6.03	70.00	2.5	2.0	48.4	59.6
P. Glycol 10%[a]	1.50	62.00	1.9	1.6	73.2	75.7
P. Glycol 30%	3.00	52.00	1.6	1.5	70.4	72.1
P. Glycol 50%	6.50	45.00	1.3	1.2	50.8	61.6
S. F. 200/0.65 cs[b]	0.49	15.90	3.3	2.9	98.0	98.4
S. F. 200/1 cs	0.82	17.40	2.4	2.0	89.6	94.6
S. F. 200/5 cs	4.60	19.70	1.6	1.3	87.1	90.5
S. F. 200/10 cs	9.40	20.10	1.7	1.7	79.3	83.4
S. F. 200/20 cs	19.00	20.60	1.7	1.5	76.7	80.0
S. F. 200/50 cs	48.00	20.80	1.2	1.1	62.1	63.7
S. F. 200/100 cs	97.00	20.90	1.4	1.4	24.5	39.2

Each value is the mean of three experiments.
[a] P. Glycol = propylene glycol.
[b] S. F. = Silicone fluid.

Table II. Mean Mass Median Diameter and Total Output (% of the Initial Amount Released) for a Range of Fluids Nebulized in a Medix Electronic Nebulizer

Fluid	Viscosity (cP)	Surface Tension (dyne/cm)	Mass Median Diameter (μm)	Total Output (%)
Water	1.00	72.80	4.5	68.3
Ethanol	1.19	24.10	4.7	92.7
Glycerol 10%	1.31	72.90	4.4	45.7
Glycerol 20%	1.92	72.54	4.5	26.5
Glycerol 25%	2.09	72.21	4.7	19.6
Glycerol 30%	2.74	71.73	4.8	15.8
Glycerol 35%	3.36	71.32	5.3	12.6
Glycerol 40%	4.09	70.61	5.6	8.6
Glycerol 45%	4.94	70.35	6.1	8.2
P. Glycol 10%[a]	1.50	62.00	4.6	65.3
P. Glycol 30%	3.00	52.00	4.7	19.1
P. Glycol 40%	4.32	47.65	4.7	12.6
P. Glycol 45%	5.09	46.00	5.0	12.0
P. Glycol 50%	6.50	45.00	5.6	8.9
S. F. 200/0.65cs[b]	0.49	15.90	2.8	96.8
S. F. 200/1cs	0.82	17.40	2.9	93.5
S. F. 200/1 + 5cs	2.45	18.25	4.1	37.5
S. F. 200/5cs	4.60	19.70	4.8	1.5

Each value is the mean of three experiments.
[a] P. Glycol = propylene glycol.
[b] S. F. = silicone fluid.

from the Sidestream nebulizer were smaller (circa 40%) the trends were, apart from the position of the peak and trough MMDs at specific silicone fluid viscosities, generally congruent with trends obtained with the Pari LC. Aerosols from the Cirrus device displayed comparable MMDs to the Pari LC. Although many of the trends in droplet-size variation correlated with those for the Pari LC, slight differences existed. While MMDs decreased with increasing propylene glycol viscosity, similar values occurred with the 25 and 50% (v/v) glycerol solutions. For silicone fluids trough MMDs were attained at a lower viscosity (5 cs) with a subsequent increase in droplet-size for the higher viscosity members.

Ultrasonic Nebulizers. Unlike the jet nebulizers, the more viscous fluids consistently generated larger droplets with the ultrasonic devices. (Table II). Nebulization of the lower propylene glycol and glycerol solutions in the Medix Electronic gave MMDs similar to water (approximately 4.4–4.6 μm). As the content of propylene glycol was increased from 10% to 50% (v/v), the MMD values progressively increased. Marked increases occurred between the 40%–45% (v/v) and 45%–50% (v/v) solutions. The glycerol solutions behaved similarly—droplet-size increased from 4.79–6.08 μm over the 30–45% (v/v) range. Empirical formula dictate that reducing surface tension should decrease droplet-size. Although surface tension decreased by approximately 25% (for propylene glycols) or remained constant (for the glycerols), the marked increases in MMD highlighted the importance of viscosity and undermined surface tension's role in determining droplet-size. However, when the silicone fluids were considered, such relationships became more complex. MMDs for the 200/0.65 cs and 200/1 cs silicone fluids were low for ultrasonic devices (i.e 2.79 μm and 2.87 μm) and may be partly due to the exceptionally low viscosity (0.49 cP and 0.82 cP respectively) and/or surface tension (15.90–19.70 dyne/cm) of the fluids. MMD values for the other fluid tested increased with increasing viscosity, reaching 4.82 μm for the 200/5 cs fluid (4.60 cP). The Medix was unable to nebulize the higher silicone fluid members. While the low surface tensions may have therefore influenced droplet-size, the higher viscosities appear to have suppressed nebulizer operation. For instance, ethanol (with a low viscosity – 1.19 cP) was readily nebulized, despite having a comparable surface tension (24.10 dyne/cm). Generally, the data obtained for the Easimist device (though restricted to propylene glycol and glycerol solutions) correlated well with those obtained from the Medix nebulizer.

Correlation Figures. An inverse relationship between the viscosity of the nebulizer fluid and the MMD value in jet nebulizers (Fig. 1A) and a direct correlation for the ultrasonic devices (Fig. 1B) were evident. Notable changes in MMD values occurred over the viscosity range 0.5–10 cP. As the viscosity increased to approximately 10 cP, the MMD value for the three jet nebulizers at both flow rates decreased. Thereafter, droplet-size increased with increasing viscosity up to the 97.00 cP value for the Sidestream and Cirrus nebulizers and remained consistent for the Pari LC device. By contrast, higher MMD values were observed when both the Medix and Easimist devices nebulized the more viscous fluids. The relationship between surface tension and MMD was less obvious (Fig. 2A, B). When individual fluid series were examined, a direct relationship appeared to exist between surface tension and droplet-size for propylene glycol and glycerol solutions in jet nebulizers. The opposite seemed true of the silicone fluids where viscosity effects apparently dominate. In ultrasonic nebulizers, MMD and surface tension were inversely related in the case of propylene glycol and glycerol solutions and are directly related in the case of silicone fluids. However, the interplay

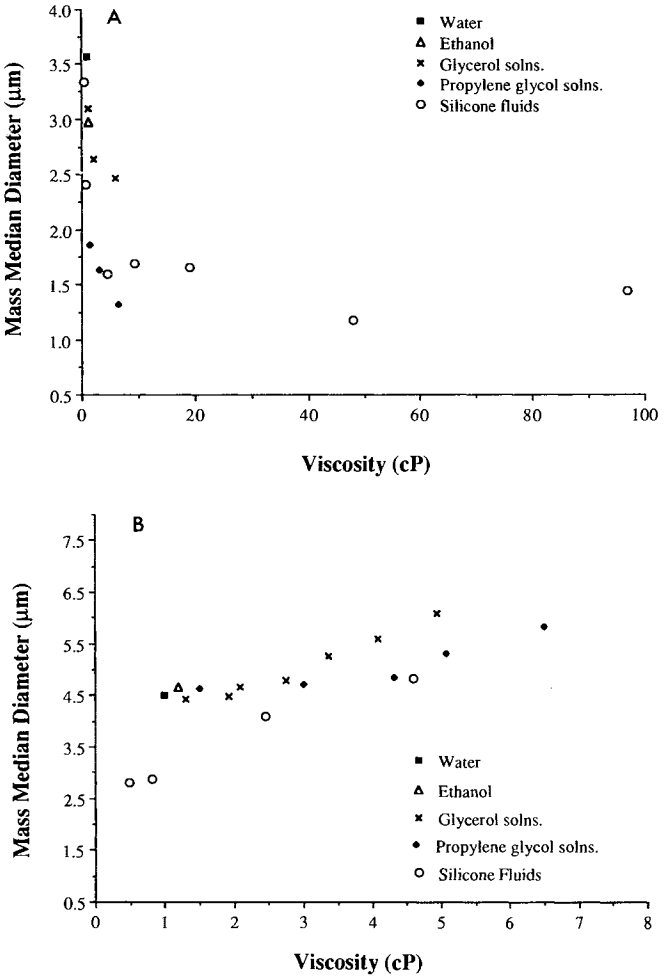

Fig. 1. Correlation plots of droplet-size (MMD) against fluid viscosity for fluids nebulized (A) in a Pari LC jet nebulizer operated at 6 L/min; and (B) in a Medix Electronic ultrasonic nebulizer operated at the mid power setting (n = 3). While the MMDs were inversely related to viscosity over the 1–10 cP range in jet nebulizers, a direct correlation existed for the ultrasonic devices.

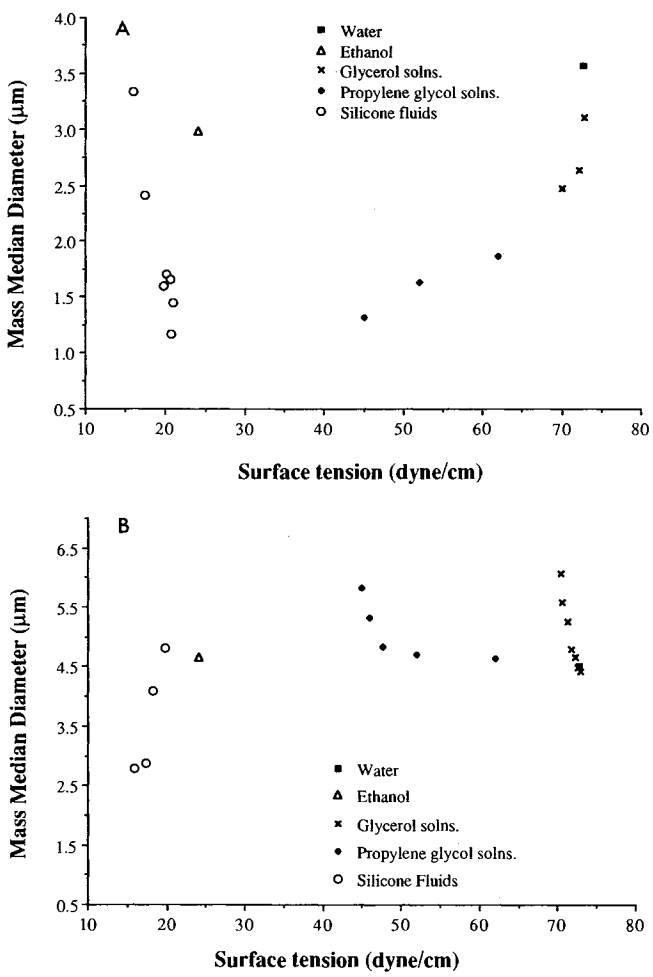

Fig. 2. Correlation plots of droplet-size (MMD) against fluid surface tension for fluids nebulized (A) in a Pari LC jet nebulizer operated at 6 L/min; and (B) in a Medix Electronic ultrasonic nebulizer operated at the mid power setting (n = 3). In jet nebulizers, while an inverse relationship existed between MMD and surface tension for silicone fluids, a direct correlation was noted for the propylene glycol and glycerol solutions. By contrast, MMD and surface tension were directly related for silicone fluids in ultrasonic nebulizers, with an inverse correlation existing for the propylene glycol and glycerol solutions.

between viscosity and surface tension may, in combination with other factors, serve to complicate data interpretation.

The MMDs were largely consistent throughout the nebulization period and tended to alter only during the "sputtering" phase. During air-jet nebulization, the temperature of the nebulizer fluid falls by approximately 10°C, primarily because outgoing air becomes saturated with solvent vapour and in ultrasonic nebulizers temperature increases by up to 15°C. Although this would normally be associated with changes in both viscosity and surface tension of the fluids, there was little variation in drop-size during the continuous phase of nebulization in the systems studied (Fig. 3).

Percentage of Droplets < μm, 90% Undersize and Size Distribution. The percentage of droplets less than 5 μm was used to define the respirable percentage. The MMD value and the % of droplets < 5 μm are inversely proportional while the 90% undersize is directly proportional to the MMD value. The results correlated well with MMD values for all three jet and both ultrasonic nebulizers. The span gives a measure of the width of the volume distribution relative to the median diameter. The heterodispersity of aerosols produced from ultrasonic nebulizers was less than those produced from jet nebulizers. All the nebulized aerosols were polydisperse with span values ranging between 1.74–5.61 for jets and 1.36–2.34 for ultrasonics. Although higher flowrates have previously been reported to produce more heterodisperse aerosols (20), span values were not found to be consistently higher for aerosols produced at higher flow rates (8 L/min). Within specific fluid systems, trends of increased span value with decreasing MMD values were sometimes noted, particularly with the Pari LC and Cirrus but these findings were not conclusive. For the ultrasonic nebulizers studied, a good correlation existed between the physicochemical properties of the nebulizer fluid and the span. Trends of decreasing span with increasing MMD were observed for the three fluid series.

Nebulization Time and Fluid Output. When the fluid

was nebulized to dryness, nebulization time was taken as the time at which aerosol emission/detection ceased. As expected, the more viscous fluids nebulized more slowly and fluids in jet devices nebulized more quickly at the higher flow-rate. Certain fluids (ethanol, silicone fluids 200/0.65 cs to 200/10 cs) were nebulized in such a short period that the fill volume had to be increased. Nebulization times (2–8 min) were shortest for the silicone fluids 200/0.65 cs, 200/1 cs and for ethanol (irrespective of nebulizer type). Water, glycerol 10% (v/v) and propylene glycol 10% (v/v) solutions exhibited comparable nebulization times (6–16 min). The more viscous fluids required considerably longer times to nebulize to dryness, typically exceeding the predetermined maximum. After nebulization, a residual amount of fluid remains trapped on the nebulizer walls and baffles. In this study, the total output values, as a percentage of the initial amount of fluid, were calculated from simple weight measurements since inclusion of tracer compounds may have altered the physicochemical properties and there was no suitable analytical technique to measure the residual amount of these test fluids. The more viscous solutions were associated with the highest residual amounts and consequently gave the lowest output values (Tables I and II). While between 98.4–96.6% of silicone fluid 200/0.65 cs and ethanol were nebulized in jet devices, the more viscous fluids were less efficient with much larger residual amounts and exceptionally low outputs. Whilst viscosity largely explains these findings, it does not explain the anomalous position of the earlier silicone fluids (particularly 200/5 cs). Even though the 200/5 cs fluid possesses a viscosity (4.60 cP) roughly comparable to those of the higher concentration glycerols and propylene glycols (2–6 cP and 3–6.5 cP respectively), it was associated with a much lower residual amount (approximately 2 to 3 fold less). This may in part be due to the lower surface tension which facilitated a more efficient aerosol delivery.

The outputs for equivalent fluids differed markedly between the jet and ultrasonic nebulizers. The ultrasonic nebulizers were unable to efficiently nebulize viscous fluids and were associated with exceptionally low outputs. In some cases aerosol emission was poor in the initial stages while for other fluids nebulization rate appeared to be suppressed towards the end of the nebulization period. The Medix was unable to nebulize silicone fluids beyond the 200/5 cs silicone fluid (and could only aerosolise 1.5% of this fluid in 10 min). The Easimist was worse, being unable to consistently nebulize any silicone fluid for more than 5–7 sec. It is possible that surface tension may play a role here—although silicone fluid had viscosities comparable to some of the nebulized propylene glycols and glycerols, it could not operate efficiently with such a low surface tension. By contrast, jet nebulizers could nebulize 20 to 40% of even the most viscous silicone fluid studied, 200/100 cs (albeit in 20 min). Similar trends were established for both propylene glycol and glycerol solutions. Output rates from ultrasonic nebulizers often exceed those from jet nebulizers. However, the ultrasonic devices generally retained larger volumes of the test fluids than did the jet nebulizers.

Respirable Output. Respirable output was dependent upon the percentage of droplets less than 5 μm and the total output. It was consistently higher for jet nebulizers when operated at higher flow-rates. While the total output percentages were comparable for the three jet nebulizers, respirable output percentages varied. Respirable percentages were as follows: Pari LC: 6 L/min = 21.5–71.2%, 8 L/min = 34.8–77.3%; Sidestream: 6 L/min = 18.5–87.5%, 8 L/min = 29.0–91.9%; Cirrus: 6 L/min = 19.9–73.8%, 8 L/min = 27–85.0%. The Sidestream generated aerosols with higher respirable percentages than Pari LC and Cirrus which was attributable to its smaller associated MMD values. As the viscosity increased (between 0.5–10/20 cP), smaller droplets were produced (though at the expense of reduced total output). Generally, as the fluid viscosity increased, the respirable output decreased with the most obvious reduction occurring between the more viscous members of the fluid series.

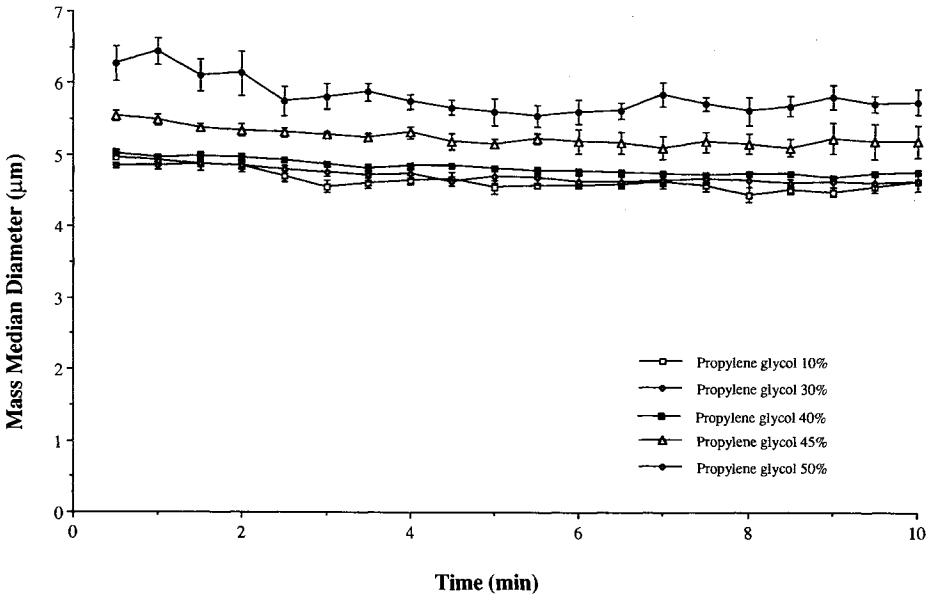

Fig. 3. The MMD (±SE) time profiles for propylene glycol solutions [10–50% (v/v)] nebulized in an Easimist ultrasonic nebulizer operated at the mid power setting for 10 min. (n = 3).

Respirable outputs for the ultrasonic nebulizers were as follows: Medix: 2.54–51.40% for non-silicone fluids, 0.79–74.21% for silicone fluids; Easimist: 2.74–39.13% for non-silicone fluids. Viscosity increases were associated with a marked reduction in MMD values and a decreased aerosol output. These acted in concert to reduce the respirable output. Consequently, the least viscous fluids produced aerosols with the highest respirable outputs.

CONCLUSIONS

In jet nebulization the droplet-size appeared to be inversely proportional to viscosity (at least between the 0.5–20 cP range), while in ultrasonic devices it was proportional to viscosity. No clear overall correlation was established between droplet-size and surface tension. The more viscous fluids required longer nebulization periods and were associated with increased residual amounts (lower outputs). While fluids of high viscosity produced aerosols with smaller MMDs in jet nebulizers, they may not be entirely suitable for clinical application due to poor patient-compliance (longer nebulization times) and low efficiency. Unlike jet nebulizers, ultrasonic devices efficiently generated aerosols (with optimum respirable output) from low viscosity fluids and indeed experienced difficulty or were unable to nebulize the more viscous fluids. Ultrasonic nebulizers were more adversely affected by variations in the physicochemical properties of nebulizer fluids than were jet nebulizers. Moreover, jet nebulizers generated an aerosol with an optimum respirable output (low MMD and high output) from median-viscosity fluids.

REFERENCES

1. A. A. Rizkalla and A. H. Lefebvre. Influence of liquid properties on air-blast atomizer spray characteristics. *ASME Gas Turbine Conference* Paper No. 74-GT-1, 1–5 (1974).
2. T. T. Mercer. Production of therapeutic aerosols. *Chest* **80**: 813–817 (1981).
3. E. M. Searls and F. M. Snyder. Relation of viscosity to dropsizes. *J. Econ. Entomol.* **29**:1167–1170 (1936).
4. R. G. Dorman. The atomization of liquids in a flat spray. *Br. J. Appl. Physiol.* **3**:189–192 (1952).
5. D. Hasson and J. Mizrahi. The drop size of fan spray nozzles. *Trans. Instn. Chem. Engrs.* **39**:415–422 (1961).
6. W. C. Hinds, J. M. Macher, and M. W. First. Size distribution of aerosols produced by the Laskin aerosol generator using substitute materials for DOP. *Am. Ind. Hyg. Ass. J.* **44**:495–500 (1983).
7. W. Walkenhorst and L. Dauterbande. New studies on aerosols, 23 Experimental observations on various factors influencing weight, number, flow-rate and size distribution of aerosol particles. *Arch. Int. Pharmacodyn.* **150**:264–294 (1964).
8. V. I. Kouchetov, E. S. Klepikov and R. M. Garaishin. Effect of surface active agents on spraying of a liquid. *Colloid J. USSR* **27**:203–206 (1965).
9. V. B. Fainerman and V. S. Sapiro. Dispersion of aqueous surfactant solutions by air-atomizing nozzles. *Colloid J. USSR* **35**:392–394 (1973).
10. S. S. Davis. Physico-chemical studies on aerosol solutions for drug delivery. 1. Water-propylene glycol systems. *Int. J. Pharm.* **1**:71–83 (1978).
11. S. P. Newman, P. G. D. Pellow, and S. W. Clarke. Dropsizes from medical atomisers (nebulizers) for drug solutions with different viscosities and surface tensions *Atomization and Spray Technol.* **3**:1–11 (1987).
12. R. J. Lang. Ultrasonic atomization of liquids. *J. Acoustic Soc. Am.* **34**:6–8 (1962).
13. K. Sollner. The mechanism of the formation of fogs by ultrasonic waves. *Trans. Faraday Soc.* **32**:1532–1536 (1936).
14. E. L. Gerhenzon and O. K. Eknadiosyants. The nature of liquid atomization in an ultrasonic fountain. *Sov. Phys. Acoust.* **10**:156–162 (1964).
15. B. I. Il'in and O. K. Eknadiosyants. Nature of liquid atomization in an ultrasonic fountain. *Sov. Phys. Acoust.* **12**:310–318 (1966).
16. Y. Y. Boguslavskii and O. K. Eknadiosyants. Physical mechanism of the acoustic atomization of a liquid. *Soviet Phys. Acoust.* **15**:14–21 (1969).
17. R. M. G. Boucher and J. Kreuter. The fundamentals of the ultrasonic atomization of medicated solutions. *Ann Allergy* **26**:591–600 (1968).
18. O. A. Kapustina. Effect of surface active substances on bubble growth kinetics in a sound field. *Soviet Phys. Acoust.* **15**:110–111 (1969).
19. A. R. Clark. The use of laser diffraction for the evaluation of the aerosol clouds generated by medical nebulizers. *Int. J. Pharm.* **115**:69–78 (1995).
20. M. M. Clay, D. Pavia, S. P. Newman, and S. W. Clarke. Factors influencing the size distribution of aerosols from jet nebulizers. *Thorax* **38**:755–759 (1983).
21. S. P. Newman, P. G. D. Pellow, and S. W. Clarke. In vitro comparison of DeVilbiss jet and ultrasonic nebulizers. *Chest* **92**:991–994 (1987).