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The influence of surface tension on aerosols produced by medical nebulisers

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Abstract

Nebulisation of liquids is one of the most effective means of aerosol generation for pulmonary delivery. Empirical formulae relate the mean size of primary droplets from jet nebulisers to the surface tension, viscosity and density of a fluid. Although the size selective 'filtering' effects of baffling and evaporation may modify the secondary aerosol produced, viscosity and surface tension may be important determinants of the nebulised aerosol's size and output characteristics. Surfactant systems of different surface tension and similar viscosity (sodium lauryl sulphate, Tween 20, Tween 80 solutions [0.001–1.0% w/v] and sorbitan trioleate dispersions [0.001–0.2% w/v]) were nebulised to dryness or for a 10-min period at room temperature and ambient humidity in three jet nebulisers (Pari LC, Sidestream Durable and Cirrus) driven by compressed air at 6 L/min and in an ultrasonic nebuliser (Medix Electronic) operated at the mid-power setting. Secondary aerosol characteristics (Mass Median Diameter [MMD], % of droplets < 5 μm, 90% undersize, span) were measured with a Malvern 2600C laser diffraction sizer. Nebulisers were weighed pre and post nebulisation and the nebulisation times, dead volumes and percentage outputs were measured. The addition of surfactant to water influenced both the droplet size and output characteristics of the secondary aerosol. Contrary to atomisation theories, an inverse relationship between MMD and surface tension was established for all surfactant solutions/dispersions over the entire concentration range or to a peak value. There was no relationship between this peak value with either a specific surface tension or the critical micelle concentration for the surfactant system. Aerosol output from both Pari LC and Sidestream nebulisers was, however, directly related to surfactant concentration, with decreasing surface tension generating a higher release of aerosol. More variable trends were found for Cirrus and Medix Electronic devices. Trends in respirable output largely concurred with the total output data. The polydispersity of aerosol sizes tended to decrease as MMDs increased; this was evident between different nebulisers and was also observed for surfactant systems nebulised in jet nebulisers.

Keywords: Aerosol; Nebulisation; Output; Particle size; Surface tension; Surfactants

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1. Introduction

Nebulisers convert aqueous solutions or suspensions of drugs into aerosols for inhalation. Their versatility stems from their ability to deliver drugs in large doses, particularly those that cannot, for technical reasons, be formulated as metered dose or dry powder inhalers. Furthermore, since the drug can be administered during relaxed tidal-breathing there are no atomisation/actuation synchronization requirements. Nebulisers may be categorised as jet or ultrasonic and many different designs of both types are commercially available. Therapeutic efficacy depends upon the pulmonary penetration and deposition of the aerosol which is a complex function of several factors, principally the droplet size and mass output of the aerosol product. Respirable fractions are designated as those droplets less than approximately 5 μm which are assumed to penetrate into the peripheral regions of the lung (Stahlhofen et al., 1980). Several factors determine particle size and output characteristics of a nebuliser; these include rate of airflow (Clay et al., 1983; Newman et al., 1987), intrinsic design (Thomas et al., 1991), volume of nebuliser fluid (Phipps and Gonda, 1990) and physicochemical properties of the formulation (Davis, 1978). Nebulisers tend to be inefficient for drug delivery, with between 30–60% of the drug remaining in the device at the end of nebulisation (Clay and Clarke, 1987). This may be improved by increasing the fill volume but at the expense of increasing nebulisation time, thereby possibly reducing patients' compliance.

Empirical and semi empirical equations for both air-jet and ultrasonic nebulisers predict that aerosol quality (size and output characteristics) is dependent not only on the operating principles and conditions, mechanical construction and geometry of nebulisers, but also upon physicochemical properties (notably surface tension, viscosity and density) of the nebulised fluid. An aerosol may be defined in terms of the increase in liquid surface area resulting from nebulisation. The surface area before breakup is simply that of the liquid cylinder as it emerges from the nozzle for jet nebulisers or the free surface of the fluid mass in the chamber of ultrasonic nebulisers. After atomisation, the area is the sum of the surface areas of all the individual droplets. Surface tension is consequently important in nebulisation because it represents the force that resists the formation of new surface area. The minimum energy required for nebulisation is equal to the surface area multiplied by the increase in liquid surface area. Consequently, surface tension forces tend to impair atomisation quality by opposing any distortion or irregularity on the liquid surface, thereby delaying onset of ligament (jet) or fountain (ultrasonic) formation.

Since most of the currently used pharmaceutical nebuliser solutions are aqueous (usually with low solute concentration), the surface tension, viscosity and density may not vary significantly. However, surfactants are required in specific formulations to suspend the drug and these agents will evidently lower surface tension. There is, however, a paucity of published research relating to surfactant effects on aerosolised fluids. Furthermore, although surfactant molecules reduce surface tension, the surface tension at the surface may not be equal to the bulk fluid value. This concept is particularly relevant in nebulisation procedures, since the surfactant molecules may have insufficient time to diffuse to the fluid surface relative to the time required to atomise the fluid, i.e. form the new droplet surfaces.

In extensive studies with air-jet nebulisers, various authors (Dombrowski and Fraser, 1954; Lorenzetto and Lefebvre, 1977; Mercer, 1981) concluded that mean droplet size of liquid sprays was directly related to liquid viscosity and surface tension while the overall effect of liquid density on drop size was small. Kochetov et al. (1965) reported that the presence of a surface active agent (dodecylbenzene sulphonate 0.1–1.0%) influenced the spraying of aqueous solutions; the average drop size decreased by approximately 30% in comparison with water and the polydispersity of the system increased. However, when these solutions were atomised by high velocity air streams, the size of the drops formed and nature of dispersion were comparable to that of water. Further studies by Fainerman and Sapiro (1973) suggested that the efficiency of surfactant addition in the atomisation of liquids by air nozzles depended on relative velocity of air and on the kinetics of surfactant molecule adsorption at the

liquid-gas interface. Atomisation of heptyl alcohol 0.12% (surface tension = 38.5 dynes/cm) generated finer drops than 0.03% ethoxylated dibutylphenol (surface tension = 38.5 dynes/cm) which in turn produced smaller drops than water. Heptyl alcohol was associated with a faster formation of an adsorbed molecule layer than ethoxylated dibutylphenol, and this influenced the resultant drop dispersities.

Less information has been published concerning factors which influence droplet size for ultrasonic nebulisation. A hybrid of the capillary and cavitation theories (as proposed by Boguslavski and Eknadiosyants, 1969) may most readily explain droplet formation from such devices. Thus, if capillary theory contributes in part to ultrasonic atomisation, the droplet size will be proportional to the surface tension of the liquid (Lang, 1962). The surface tension of any liquid may be reduced by the addition of surfactants. These agents have been shown to depress nebulisation rate in ultrasonic devices which may be due to a reduction in capillary wavelength causing an increase in the threshold amplitude (Boucher and Kreuter, 1968), or to their influence on the diffusion of gas into cavitation bubbles (Kapustina, 1969).

There are insufficient studies of the effect of surface tension upon the size and output characteristics of nebulised medical aerosols. This study sought to address this by investigating aerosol characteristics from a number of surfactant systems nebulised in three air-jet nebulisers and one ultrasonic nebuliser.

2. Materials and methods

2.1. Materials

Sodium lauryl sulphate, Tween 20, Tween 80 and Sorbitan trioleate (Span 85) were purchased from Sigma Chemicals (Poole, Dorset, U.K.). Pari LC nebulisers were supplied by Pari-Werk GmbH, Starnberg, Germany, Sidestream (Durable) by Medic-Aid Ltd., Pagham, U.K., Cirrus by Intersurgical, Wokingham, U.K. and Medix Electronic by Medix Ltd., Lutterworth, U.K.

2.2. Determination of nebuliser fluid physicochemical properties

The surfactants were added to deionised water (concentrations ranging from 0.0001–1.0% w/v). Surface tensions were determined using the CAHN Dynamic Contact Angle analyser (CAHN Inst. Inc., Cerritos, California), viscosities by Ostwald U-tube viscometer and densities using standard density bottles (B.D.H., Lutterworth, U.K.) at room temperature (20–25°C) and ambient humidity (40–60%).

2.3. Characterisation of nebulised aerosol

The experimental methods were described in detail in a previous publication (Mc Callion et al., 1995). The test fluids were nebulised to dryness or for 10 min, whichever occurred first, in three jet nebulisers (Pari LC, Sidestream, Cirrus) driven by compressed air at 6 L/min and in an ultrasonic nebuliser (Medix Electronic) operated at mid-setting. Fill volumes (jets: 4 ml and ultrasonic: 8 ml) were dependent on the dimensions of the device. Experiments were conducted at room temperature and ambient humidity and performed in triplicate. Secondary aerosol characteristics (Mass Median Diameter [MMD], % of droplets < 5 μm, span) were measured with a Malvern 2600C laser diffraction sizer (Malvern Instruments, Malvern, U.K.). Nebulisers were weighed pre- and post-nebulisation and the nebulisation times and residual amounts of fluids measured.

3. Results

3.1. Physicochemical properties of test fluids

The surface tensions ranged between 32.00–72.80 dynes/cm, kinematic viscosities between 1.00–1.0675 and relative densities between 1.00–1.001 for the fluids tested.

3.2. Mass Median Diameter (MMD)

The different brands of nebulisers studied generated aerosols with appreciably different droplet

Table 1
MMD (± S.E.) for surfactant solutions/dispersions nebulised for 10 min in Pari LC, Sidestream, Cirrus and Medix Electronic nebulisers [SLS = Sodium lauryl sulphate; T 80 = Tween 80; T 20 = Tween 20; S 85 = Span 85].

Solution	Surface tension(dynes/cm)	Mass Median Diameter ± S.E. values (/m/m)			
		Pari-LC	Sidestream	*Cirrus	Medix
Water	72.80	2.49 ± 0.04	2.08 ± 0.01	3.66 ± 0.07	4.73 ± 0.02
SLS 0.0001%	65.70	2.64 ± 0.02	2.01 ± 0.01	3.70 ± 0.03	4.83 ± 0.04
SLS 0.001%	60.60	3.00 ± 0.03	2.38 ± 0.04	4.34 ± 0.02	4.97 ± 0.02
SLS 0.01%	56.00	2.99 ± 0.05	2.39 ± 0.01	4.52 ± 0.02	4.32 ± 0.02
SLS 0.1%	43.80	2.30 ± 0.02	2.11 ± 0.04	3.74 ± 0.15	4.31 ± 0.01
SLS 0.25%	39.30	—	—	3.37 ± 0.10	—
SLS 1.0%	37.10	2.62 ± 0.06	1.92 ± 0.04	—	4.28 ± 0.01
T 80 0.0001%	65.17	2.41 ± 0.01	2.35 ± 0.01	3.43 ± 0.23	4.43 ± 0.03
T 80 0.001%	55.56	2.62 ± 0.02	2.39 ± 0.08	3.55 ± 0.20	4.48 ± 0.02
T 80 0.01%	50.54	2.77 ± 0.01	2.46 ± 0.04	3.81 ± 0.07	4.86 ± 0.06
T 80 0.1%	45.27	2.96 ± 0.04	2.29 ± 0.02	4.10 ± 0.05	4.96 ± 0.06
T 80 0.25%	44.14	—	—	3.92 ± 0.03	—
T 80 1.0%	43.20	3.24 ± 0.02	2.22 ± 0.02	—	4.73 ± 0.01
T 20 0.0001%	66.90	2.48 ± 0.03	2.24 ± 0.06	3.29 ± 0.06	4.47 ± 0.03
T 20 0.001%	60.56	2.58 ± 0.03	2.23 ± 0.02	3.29 ± 0.03	4.68 ± 0.01
T 20 0.01%	48.44	2.85 ± 0.02	2.36 ± 0.02	3.43 ± 0.06	5.01 ± 0.09
T 20 0.1%	42.40	3.14 ± 0.07	2.27 ± 0.06	3.67 ± 0.06	5.33 ± 0.02
T 20 0.25%	40.60	—	—	3.74 ± 0.06	—
T 20 1.0%	39.60	3.14 ± 0.01	2.11 ± 0.05	—	4.58 ± 0.02
S 85 0.0001%	56.90	2.44 ± 0.03	2.18 ± 0.01	4.10 ± 0.12	4.67 ± 0.01
S 85 0.001%	50.90	2.48 ± 0.01	2.24 ± 0.02	4.44 ± 0.06	4.69 ± 0.02
S 85 0.01%	35.40	2.65 ± 0.04	2.29 ± 0.02	4.65 ± 0.07	4.74 ± 0.02
S 85 0.1%	32.50	2.79 ± 0.04	2.35 ± 0.05	4.93 ± 0.06	5.09 ± 0.05
S 85 0.2%	31.80	2.88 ± 0.03	2.17 ± 0.04	4.98 ± 0.03	5.95 ± 0.02

*The Cirrus nebuliser was unable to nebulise 1% solutions of SLS, T 80 and T 20 due to foaming and bubble formation; weaker surfactant solutions (0.25%) were used.

sizes and all three jet nebulisers generated droplets with smaller MMDs than the ultrasonic device. Irrespective of the solution being nebulised, the Sidestream produced aerosols with the smallest droplets, followed by the Pari LC, Cirrus and Medix Electronic respectively (Table 1). Marked differences were noted in MMD values between devices and in the trends for droplet size at specific surfactant concentration. For the Pari LC, the MMD values increased as the concentration of surfactant (Tween 80, Tween 20 and Span 85) increased. However, the other three devices generally exhibited a trend of increasing MMD to a peak value followed by a decrease in size. The MMDs of aerosols nebulised in the four devices differed significantly for different concentrations of the same surfactant (ANOVA: $P < 0.05$). Compared to water, aerosols generated from the surfactant solutions tended to have larger MMDs; this was more apparent in the jet nebulisers.

In the Pari LC, nebulised water was generally associated with a lower MMD than that for any of the nebulised surfactant solutions/dispersions. All the non-ionic surfactant solutions/dispersions studied showed an incremental increase in droplet size as the surfactant concentration increased (i.e. as the surface tension decreased). MMD values increased between 2.41–3.24 μm, 2.48–3.14 μm and 2.44–2.88 μm for increased concentrations of Tween 80, Tween 20 and Span 85 solutions/dispersions. These surfactant solutions/dispersions attain their CMCs at relatively low concentrations

and will contain micelles at concentrations of approximately 0.01–0.001%. The anionic surfactant studied (sodium lauryl sulphate) exhibited a unique profile of an initial increase in MMD to a plateau, followed by a decrease between 0.01–0.1% and thereafter an increase. This surfactant CMC occurs at higher concentration ($\approx 0.2\%$). In the Sidestream nebuliser, all the surfactant solutions studied showed an increase in MMD to a peak value (generally at the 0.01% concentration) and thereafter decreased. Sodium lauryl sulphate, Tween 80 and Tween 20 solutions and Span 85 dispersions produced aerosols with MMDs ranging from 1.96–2.46 μm. Most surfactant MMDs were larger than that obtained for water (2.08 μm). Overall, there was a narrow range of MMD values which may indicate the overlying importance of the nebuliser design in determining aerosol size.

Both sodium lauryl sulphate and Tween 80 solutions showed an increase in MMD to a peak value (at 0.01 and 0.1%, respectively) followed by a decrease when nebulised in the Cirrus. By contrast, Tween 20 and Span 85 solutions exhibited a progressive increase in MMD as the surfactant concentration increased. Water generated MMDs of 3.66 μm, which tended to be smaller than most of the surfactant solutions/dispersions nebulised. The largest droplets were produced from the Span 85 dispersions, which attain CMC at the lowest concentration ($\approx 0.001\%$) and thus contain micelles. In the ultrasonic nebuliser, the sodium lauryl sulphate and Tween 20 and 80 solutions showed an increase in MMD to a peak value with a subsequent decrease. Most of these values were close to or slightly lower than the MMD obtained for water, namely 4.73 μm. The Span 85 dispersions showed a incremental increase in MMD as the surfactant concentration increased, most notably between 0.1–0.2%.

3.3. MMD versus time plots and nebulisation times

The time profiles gave highly consistent MMDs throughout the entire nebulisation period for the Medix Electronic and the Cirrus nebulisers. Profiles for the Sidestream nebulisers tended to increase only slightly in the terminal 'sputtering' phase, while a marked increase after a precise time (related to a prolonged 'sputtering' phase) was observed for the Pari LC data. Typical plots are illustrated in Fig. 1 and Fig. 2. The low S.E. values throughout suggested good reproducibility of the data. All test fluids were still being nebulised at the 10 min cut-off in the Pari-LC, Cirrus and Medix devices. In the Sidestream, while sodium lauryl sulphate solutions had nebulisation times exceeding 10 min, the Tween 80 and 20 solutions and the Span 85 dispersion had nebulisation times between 9 and 9.5 min.

3.4. Percentage of droplets < 5 μm

An inverse relationship exists between MMD and percentage of droplets < 5 μm; this was clearly depicted in the results. Reciprocal trends of the MMD data were found for the respirable data and differences between nebuliser types and between surfactant groups were maintained. The ultrasonic nebuliser, the Medix Electronic had the lowest percentage of droplets < 5 μm, followed by the Cirrus, Pari LC and the Sidestream (e.g. 54.5%, 65.7%, 78.8% and 91.2%, respectively, for water).

3.5. Size distribution of aerosols

The span (90% undersize — 10% undersize / 50% undersize) gives a measure of the width of the volume distribution relative to the median diameter. Of the nebulisers studied, the Medix produced aerosols with the smallest span, followed by the Cirrus, Sidestream and Pari LC nebulisers (e.g. span values for nebulised water were 1.64, 1.88, 1.97 and 2.39, respectively). For the jet nebulisers, the trends in span values appeared to be inversely related to the MMD data. By contrast, no such relationship was established for the ultrasonic device.

Span values (2.18–2.51) were consistently higher with the Pari LC nebuliser than with any of the other devices studied. Within surfactant systems, the absolute values did not vary appreciably to that obtained for water. For sodium lauryl sulphate, Tween 80 and 20 span values

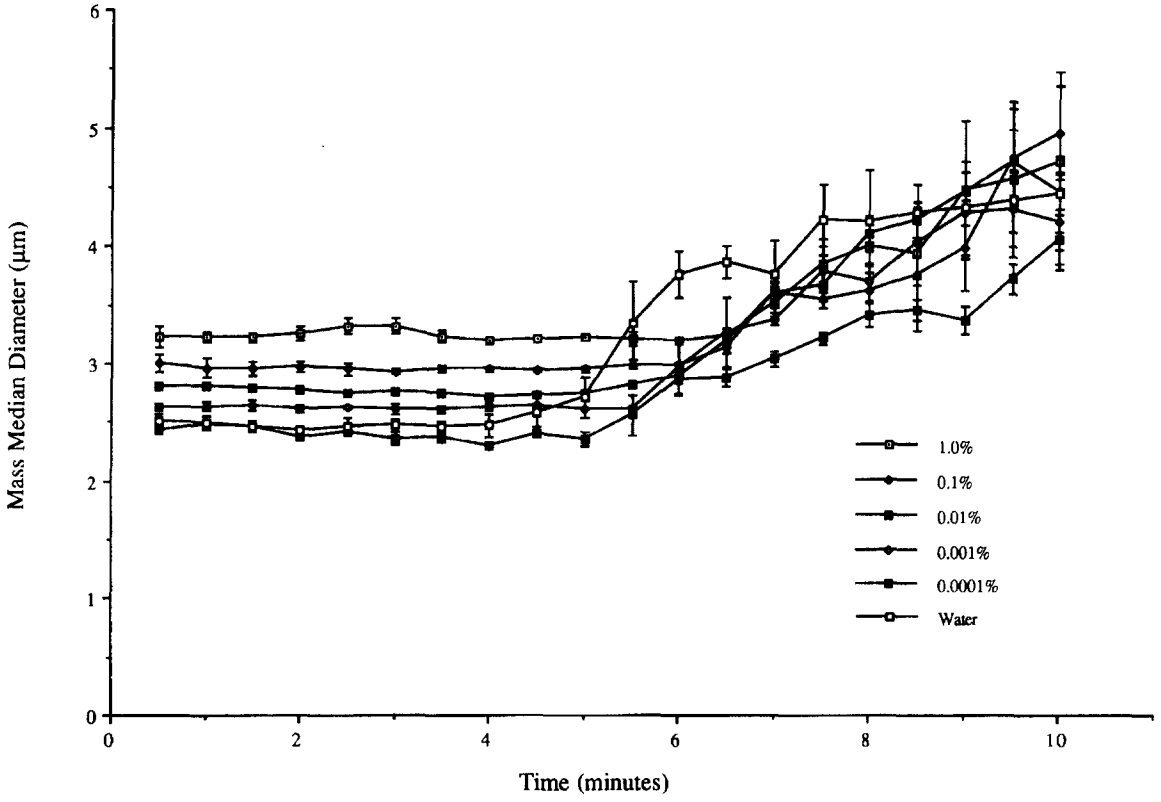

Fig. 1. MMD (± S.E.) versus time for Tween 80 solutions and water nebulised in a Pari LC nebuliser (6 l/min).

decreased to a trough value and thereafter increased. Span 85 dispersions had progressively lower span values as the surfactant concentration increased. These trends in span values were inversely related to MMD findings. Akin to the Pari LC results, the span data for the Sidestream produced reciprocal images of the corresponding MMD data. For all surfactant systems studies, there was an initial decrease in span value followed by an increase as the surfactant concentration increased. Span values for sodium lauryl sulphate, Tween 80, Tween 20 and Span 85 ranged between 1.67 and 2.11. Most of the span values obtained were lower than that for water.

Trends in span values varied between the different surfactant groups nebulised in the Cirrus device and the inverse relationship with MMD did not exist for the Span 85 dispersions. Span values for sodium lauryl sulphate and Tween 80 and 20 solutions decreased to a trough value and thereafter increased. Span values for the Span 85 dispersions (1.74–1.80) were lower than those obtained for water and for the other surfactant systems (1.73–2.00). The Medix Electronic nebuliser produced the least heterodisperse aerosols, with span the values ranging between 1.50 and 1.75. With such a narrow range, there was only a slight deviation from the value obtained for water and clear trends were not evident. For sodium lauryl sulphate solutions, the span initially decreased, then increased and fell slightly as surfactant concentration increased. Both Tween 80 and 20 exhibited an increase to a peak value with a subsequent decrease. Span 85 dispersions showed a progressive increase in span from 1.50–1.75, with a decrease between the 0.1 and 0.2% concentrations to 1.60.

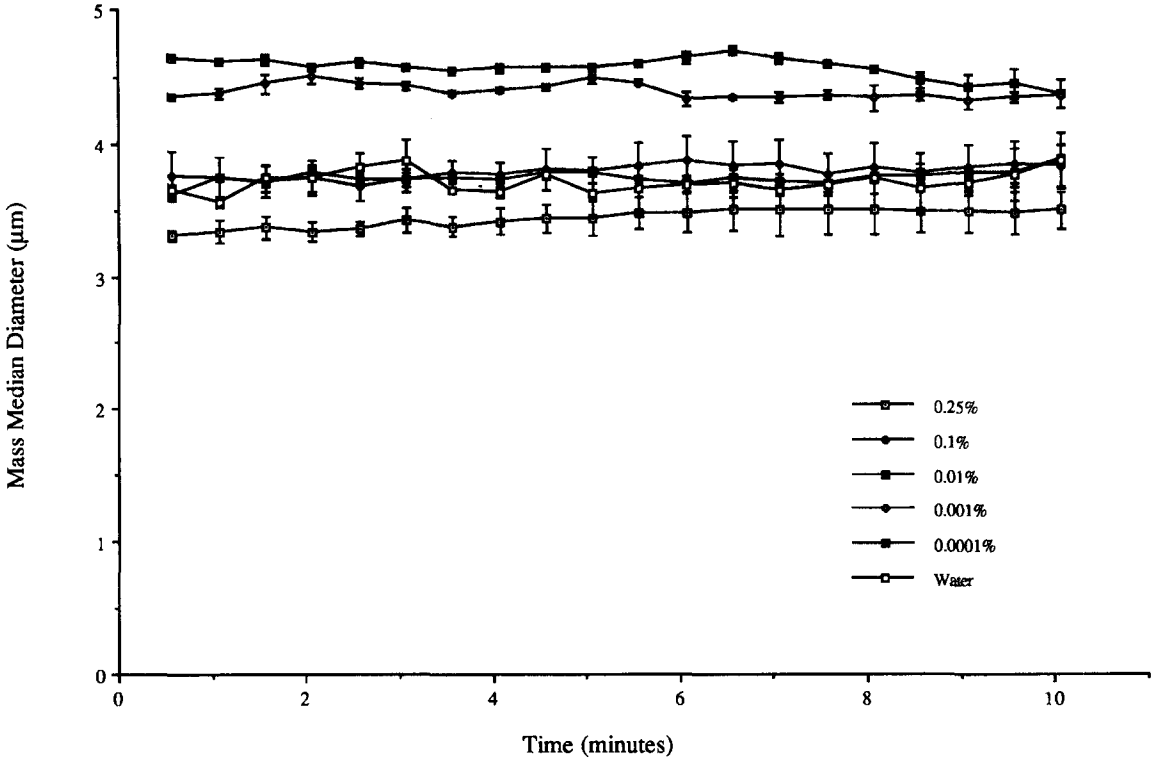

Fig. 2. MMD (± S.E.) versus time for sodium lauryl sulphate solutions and water nebulised in a Cirrus nebuliser (6 l/min).

3.6. Total output

The percentage of the fluid nebulised (total output) in a 10-min period was determined from weight measurements. As clearly shown in Table 2, the different nebuliser types varied markedly in their capability to nebulise the fluids (e.g. for water, total outputs of 54%, 70%, 70% and 84% were noted for Cirrus, Medix, Pari LC and Sidestream nebulisers, respectively).

There was a progressive increase in total output as the concentration of all four surfactants increased when nebulised in the Pari LC and the Sidestream nebulisers. Compared to water, the total output values obtained for all surfactant solutions/suspensions nebulised in the Pari LC, increased appreciably as the surface tension of the fluids decreased. However, for the Sidestream most of these values were comparable to the output obtained with water. The trends in total output variability differed markedly for the surfactant systems nebulised in the Cirrus nebuliser. For sodium lauryl sulphate, Tween 20 and Span 85, there was an initial decrease followed by an increase in total output as surfactant concentration increased. Tween 80 solutions produced a progressive increase in output over the concentration range 0.0001–0.1%, with a slight decrease for the 1.0% solution. While total outputs obtained for sodium lauryl sulphate and Tween 80 tended to exceed that for water, the outputs from Tween 20 and Span 85 were similar to or less than the water value. In the ultrasonic nebuliser, most of the total output values obtained with surfactant systems were comparable to the water value. Sodium lauryl sulphate and Tween 80 and 20 solutions generally showed an initial decrease in output with a subsequent rise as the surfactant concentration increased. By contrast, the total output obtained from the Span 85 dispersions tended to decrease as surfactant concentration increased, with marked reduction occurring be-

Table 2
Total Output (± S.E.) surfactant solutions/dispersions nebulised for 10 min inPari LC, Sidestream, Cirrus and Medix nebulisers [SLS = Sodium lauryl sulphate; T 80 = Tween 80; T 20 = Tween 20; S 85 = Span 85].

Solution	Surface tension (dynes/cm)	Total Output ± S.E. values (%)			
		Pari-LC	Sidestream	* Cirrus	Medix
Water	72.80	70.30 ± 0.74	83.85 ± 1.21	53.97 ± 3.07	69.77 ± 0.35
SLS 0.0001%	65.70	69.70 ± 0.60	79.23 ± 0.84	59.11 ± 1.27	67.96 ± 2.02
SLS 0.001%	60.60	69.93 ± 2.51	79.13 ± 1.28	49.74 ± 0.50	62.98 ± 2.75
SLS 0.01%	56.00	72.07 ± 1.66	79.37 ± 0.47	54.88 ± 0.57	68.73 ± 1.52
SLS 0.1%	43.80	80.80 ± 0.89	82.97 ± 0.78	69.24 ± 2.61	71.87 ± 1.09
SLS 0.25%	39.30			63.93 ± 3.64	—
SLS 1.0%	37.10	83.40 ± 2.51	88.42 ± 0.44	—	76.14 ± 0.41
T 80 0.0001%	65.17	73.48 ± 2.91	82.40 ± 0.68	55.21 ± 1.13	68.00 ± 1.38
T 80 0.001%	55.56	80.12 ± 1.82	83.20 10.74	58.91 ± 1.13	63.46 ± 1.22
T 80 0.01%	50.54	86.66 ± 0.48	85.49 ± 0.55	65.47 ± 1.11	62.97 ± 0.88
T 80 0.1%	45.27	90.55 ± 0.05	87.90 ± 0.51	67.28 ± 1.28	73.13 ± 3.22
T 80 0.25%	44.14			66.84 ± 1.87	—
T 80 1.0%	43.20	90.72 ± 0.60	88.71 ± 0.31	—	74.97 ± 0.37
T 20 0.0001%	66.90	75.25 ± 2.93	84.03 ± 0.59	56.88 ± 1.12	69.80 ± 0.59
T 20 0.001%	60.56	80.72 ± 0.47	84.86 ± 0.46	54.86 ± 1.78	70.10 ± 1.11
T 20 0.01%	48.44	83.99 ± 0.78	85.57 ± 0.46	54.54 ± 0.68	64.93 ± 2.06
T 20 0.1%	42.40	90.44 ± 0.11	88.69 ± 0.49	51.55 ± 0.98	61.78 ± 1.84
T 20 0.25%	40.60			58.31 ± 0.20	—
T 20 1.0%	39.60	92.28 ± 0.60	89.36 ± 0.43	—	69.17 ± 1.11
S 85 0.0001%	56.90	65.63 ± 0.19	76.89 ± 0.85	52.79 ± 3.73	72.38 ± 1.37
S 85 0.001%	50.90	68.94 ± 0.97	79.43 ± 0.34	49.44 ± 0.77	69.79 ± 2.39
S 85 0.01%	35.40	78.34 ± 1.83	79.97 ± 0.30	48.90 ± 2.25	66.73 ± 0.75
S 85 0.1%	32.50	82.27 ± 0.77	80.27 ± 0.69	48.21 ± 1.87	68.57 ± 1.31
S 85 0.2%	31.80	81.97 ± 0.25	80.52 ± 0.84	49.16 ± 0.96	47.11 ± 1.89

*The Cirrus nebuliser was unable to nebulise 1% solutions of SLS, T 80 and T 20 due to foaming and bubble formation; weaker surfactant solutions (0.25%) were used.

tween the 0.1–0.2% concentration. Most of the surfactant systems showed a significant difference in the aerosol output depending upon the concentration of surfactant undergoing nebulisation in all four devices (ANOVA: $P < 0.05$). The only exceptions were noted for Span 85 dispersions nebulised in a Cirrus nebuliser and Tween 20 nebulised in the Medix Electronic.

3.7. Respirable Output

Respirable output was determined by multiplying the total output by the percentage of droplets < 5 μm. While obviously the absolute values differed from the total output values, the trends largely remained consistent. Lowest respirable outputs were found for the Cirrus, with increasing outputs for the Medix, Pari LC and Sidestream (e.g. for water, respirable outputs were 35.5, 38.0, 55.4 and 76.5%, respectively). The respirable outputs for different surfactant concentrations nebulised in all four nebulisers differed significantly (ANOVA: $P < 0.05$). This difference in respirable output for the four nebulisers was apparent from Fig. 3. which shows the respirable output obtained upon nebulising Span 85 dispersions.

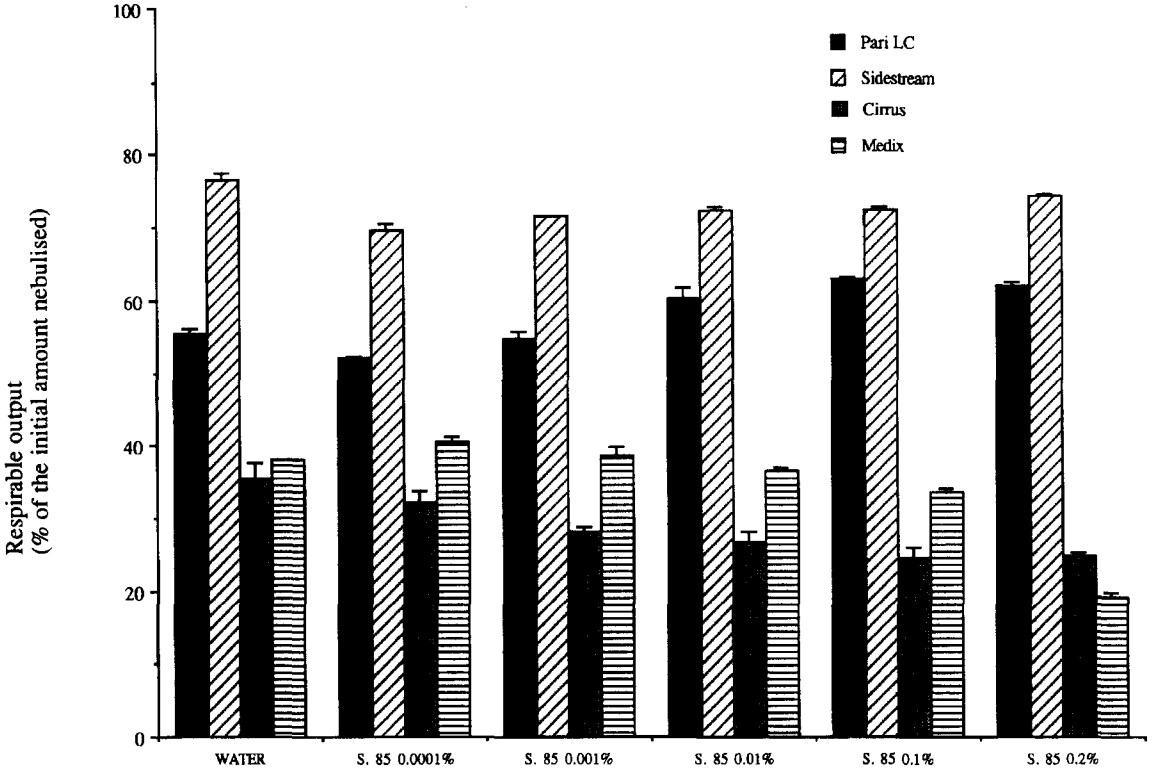

Fig. 3. Respirable output (± S.E.) for Span 85 dispersions (0.0001–0.2%) and water nebulised for 10 min in Pari LC, Sidestream, Cirrus and Medix Electronic nebulisers.

Generally, an increase in respirable output with a small terminal decrease was observed upon nebulising surfactant solutions/dispersions in the Pari LC nebuliser. For sodium lauryl sulphate, Tween 80 and Span 85 respirable outputs ranged between 51.03–65.50%, 58.51–66.33% and 52.06–62.73%. Tween 20 solutions tended to give increased respirable output with increased concentration, despite a small decrease at mid concentrations (60.52–64.92%). Respirable outputs obtained with surfactant solutions/dispersions, particularly at high concentration, were greater than those associated with water. In the Sidestream nebuliser, the surfactant systems all exhibited a general increase in respirable output as the surfactant concentration increased (i.e. with lower surface tension). For sodium lauryl sulphate, Tweens 80 and 20 and Span 85, respirable outputs increased from 69.67–83.18%, 73.29–79.86%, 75.23–81.34% and 69.60–73.99%. Most of these values differed only slightly to the respirable output obtained for water.

The respirable output versus surfactant concentration profiles differed between each surfactant system for the Cirrus. For sodium lauryl sulphate, Tween 20 and Span 85, it generally decreased to a base value, with a subsequent increase as surfactant concentration increased. Tween 80 solutions tended to give increased respirable output with increased surfactant concentration (38.15–41.69%). Respirable output values obtained for sodium lauryl sulphate and Tween 80 and 20 solutions were usually comparable to or higher than that for water, whereas the Span 85 values were much smaller (approximately 30% reduction). When nebulised in the Medix Electronic, the sodium lauryl sulphate, Tween 80 and Tween 20 surfactant solutions exhibited an initial decrease in respirable output with increased surfactant concentration; trough values occurred at

0.001%, 0.01% and 0.1%. Thereafter, an increase in respirable output was noted (i.e. 36.00–31.96–47.30%, 40.99–33.06–40.60% and 41.75–28.49–39.18% respectively). The Span 85 dispersions gave progressively lower respirable outputs with increased surfactant concentration, with a marked decline between 0.1–0.2% concentration (40.62–19.03%). Most respirable outputs did not differ appreciably from that of water.

4. Discussion

4.1. MMD

4.1.1. Nebuliser differences

Jet and ultrasonic nebulisers have different operating principles and vary markedly in design and dimensions; this is reflected in the different size and output characteristics of the aerosols produced. Typically, ultrasonic nebulisers have produced aerosols with larger mean sizes and less polydispersed than jet nebulisers (Mercer, 1981). Such findings were apparent in the present study. In all cases (except sodium lauryl sulphate 0.01%), the Medix Electronic produced aerosols with the largest droplets. These values contrasted markedly with the much smaller droplets generated from the two open-vent jet nebulisers, Pari LC and Sidestream, and with droplets emitted from the traditional venturi nebuliser, the Cirrus. It was apparent that marked variation existed in the droplet size distribution for each of the three jet nebulisers. The design and geometric relationship of the constituent parts of jet nebulisers in part determines the speed of the air jet, the rate at which the solution is entrained and the efficiency of impaction and filtration of the aerosol produced (Dennis and Hendrick, 1992). Both the Pari LC and Sidestream had lower MMDs than the Cirrus device. This highlights the improved efficiency in a higher respirable fraction which can be obtained (at relatively low flow-rates) with the new open-vent jet nebulisers.

4.1.2. MMD variations with increasing surfactant concentrations

Altering the surface tension of nebuliser fluids by surfactant addition should influence the size and output characteristics of the aerosol produced. In the current research, the surface tension decreased with increased surfactant concentration until the critical micelle concentration (CMC) was attained. The CMCs for sodium lauryl sulphate, Tween 20, Tween 80 and Span 85 are 0.23%, 0.006%, 0.0014% and $< 0.001\%$, respectively. All four surfactant solutions/dispersions reached the CMC over the concentration range (0.0001–1.00%) studied, with surface tension ranging between 65.70–37.10, 65.17–43.20, 66.90–39.60 and 56.90–31.80 dynes/cm for sodium lauryl sulphate, Tween 80, Tween 20 and Span 85, respectively. The expected direct relationship between MMD and surface tension was not observed for any of the surfactant solutions/dispersions in any of the nebulisers. Indeed an inverse relationship could more plausibly summarise the findings. The results concurred with previous research which also reported inconsistent and conflicting experimental findings. Kochetov et al. (1965) stated that when solutions of a surface active agent (dodecylbenzene sulphonate) were dispersed by high velocity air streams, the size of the drops formed were independent of presence of the agent. Furthermore, Newman et al. (1987) reported that dropsizes for drug solutions (saline, mucolytic, antibiotics) of different surface tension and viscosity released from nebulisers did not correlate with either physical property. Mercer (1973) commented that the effect of surface tension on the size distribution of the primary aerosol droplets was not always reflected in the secondary aerosol because of size-selective characteristics of the nebuliser for returning primary droplets. Research verifying the theories appear limited to studies by Fainerman and Sapiro (1973). These authors reported that finer (smaller) drops were produced upon atomising surfactant solutions of ethoxylated dibutylphenol and heptyl alcohol than for water. In studies with Maximyst and Bird atomisers, Davis (1978) noted a rise in MMD as propylene glycol content of test solutions rose from 0–20%, with a subsequent decrease in MMD as propylene glycol content rose between 20–60% (with a corresponding decrease in surface ten-

sion). While MMD and surface tension appeared to be directly related in the latter phase, viscosity effects were noted to be a major contributing factor to the increased MMDs.

The current findings may, however, be explained in terms of surface tension effects on satellite droplet formation. When fluid ligaments are sheared by high velocity gas jets to produce primary droplets an excess fluid 'waist' is formed at the nozzle outlet from which satellite droplets (typically 5–40% the size of the primary droplets) are produced. Efficient baffling prevents the emission of the larger primary droplets (circa 20 μm) such that only the smaller satellite droplets leave the nebuliser to constitute the respirable aerosol. Atomisation theories predict only a direct relationship between fluid surface tension and primary droplet size. While reducing surface tension theoretically decreases the size of the primary droplet, it may concurrently increase the fluid mass in the 'waist' area, thereby inadvertently increasing the size of the satellite droplets (i.e. the emitted aerosol). Similar effects may also arise in the ultrasonic device, though the mechanism is less precise.

4.1.3. Variations in MMD between different nebulisers and at different surfactant concentrations

For particular brands of nebulisers the MMDs varied significantly ($P < 0.05$) upon nebulising specific surfactant solutions and the trends of droplet size variation over a range of surfactant concentrations differed. Compared to water, the surfactant solutions tended to generate aerosols with larger MMDs; this was more apparent in the jet nebulisers. When the non-ionic surfactants (Tween 80, Tween 20 and Span 85) were nebulised in Pari LC nebulisers, a consistent increase in MMD with decreased surface tension was observed; this directly contradicts theory predictions. Sodium lauryl sulphate solutions gave an irregular pattern, with no correlation apparent. The other three nebulisers generally exhibited a trend of increasing MMD to a peak value followed by a decrease in size. The Sidestream device was associated with a narrow range of droplet size, attributable more to a highly efficient nebuliser design and operation than to properties of the test fluid. Nebuliser design of the Cirrus restricted the range of surfactant concentration which could be atomised; 1.0% solutions of sodium lauryl sulphate, Tween 80 and Tween 20 foamed such that bubble formation prevented analysis — consequently 0.25% dispersions with essentially identical surface tensions were used.

Contrary to atomisation theory, the droplet sizes appeared to be inversely related to surface tension over the entire concentration range studied or to a peak value. This value was related to neither a specific surface tension nor to the CMC value for the surfactant systems, thereby indicating that droplet size was independent of micelle development.

4.1.4. Variation between surfactant groups

Generally the size of droplet produced from sodium lauryl sulphate, Tween 80 and Tween 20 were comparable regardless of which nebuliser was utilised. These three surfactant solutions showed comparable surface tension variation over the concentration range and hence similar results may be expected. By contrast, the Span 85 data differed more dramatically both in its surface tension values (attaining CMC at lower surfactant concentration) and in the associated MMD values and their trends. In the Pari LC, lower MMDs were typically found for nebulised Span 85 dispersions compared to the other three surfactant solutions, while larger droplets were produced in the Cirrus. MMD values for Span 85 aerosols in Sidestream and Medix nebulisers were largely comparable with other surfactants.

4.1.5. MMD versus time profiles

During nebulisation the temperature of fluid in the nebuliser chamber of jet nebulisers typically decreases (by approximately 10°C) while in ultrasonic nebulisers, temperatures may increase by 20°C. [Changes in viscosity of aqueous solutions over the temperature range of interest were small (< 1 cP) and unlikely to influence the size or output data]. With decreased temperature, the surface tension of fluids increase and vice versa. Atomisation theories, therefore, imply that temperature variations associated with nebulisation

may influence MMDs produced. However, such effects were not apparent. MMD versus time plots were consistent throughout the entire nebulisation period for both Cirrus and Medix Electronic devices. The Sidestream nebuliser exhibited slight increases in droplet size for some test fluids during the terminal 'sputtering' phase. A marked and prolonged increase in droplet size was observed in Pari LC devices generally after 5 min (which correlated with the 'sputtering' phase). The larger MMDs observed are probably due to reduced efficiency of the Pari LC during this latter stage of operation rather than due to temperature dependent effects.

Temperature has a comparatively small effect on micellar properties of ionic surfactants, e.g. for sodium lauryl sulphate (with a minima of 8.1 mM at 25°C in the CMC vs temperature plot) an increase in temperature from 25 to 40°C or a decrease from 25 to 10°C will only raise the CMC to 8.7 mM. For non-ionics surfactants, temperature increases up to the cloud point are associated with an increase in micellar size and a corresponding decrease in CMC. The general failure to detect a minima in curves for non-ionics could conceivably be a consequence of lack of data at sufficiently high temperature (measurements not being feasible at elevated temperatures due to phase separation). However, while temperature changes are associated with changes in micellar properties of the fluids, there was little variation in droplet size during the continous period of nebulisation for any surfactant system in any of the nebulisers studied, thereby implying that droplet size is not influenced by micelle development.

4.2. Size distribution of aerosols

Ultrasonic nebulisers are generally associated with less polydispersed aerosols than jet nebulisers (Mercer, 1981). In this study, the Medix Electronic had the lowest span values (ranging between 1.50–1.75), indicating a narrow scatter of droplet size distribution. The three jet nebulisers exhibited higher span values, 1.73–2.51. Mass Median Diameter values are inversely related to the width of the droplet size distribution (Clay et al., 1983). Since MMD values for fluids studied typically increased from Sidestream — Pari LC — Cirrus — Medix Electronic nebulisers, span values may be expected to follow a reciprocal trend. While an irregularity occurred between the Sidestream and Pari LC nebulisers, the inverse relationship between MMD and span existed. Furthermore, when the individual surfactant systems are studied in the three jet nebulisers, span values appeared to be inversely related to the MMD values. No such relationship was established for the ultrasonic device.

4.3. Total and Respirable Output

The exact relationship between aerosol output, mean droplet size and physicochemical properties of the fluid is a complex function of design of the nebuliser and its dimensions. Aerosol output was determined from weight measurements. While this is not the most accurate technique (since it does not consider the solute concentrating effect), it served as an adequate method in these experiments; insufficient fluid remained post nebulisation for analytical assay and tracer agents were avoided to prevent altering physicochemical properties of the test fluids.

4.3.1. Inter-nebuliser varaitions

Open vent systems, incorporating inhalation and exhalation valves, have been developed; these devices allow for enhanced generation of aerosol during the inspiratory phase of breathing and reduced release of aerosol during the expiratory phase. The Pari LC and Sidestream have open vent systems and both these nebulisers had greater total and respirable outputs than either the Cirrus (a traditional venturi nebuliser) or the Medix Electronic (an ultrasonic nebuliser). While the ultrasonic nebuliser had lower output than the two open vent system devices, it did have a greater output efficiency than the traditional venturi device. Output rates from ultrasonic nebulisers often exceed those from jet nebulisers (Mercer, 1981; Sterk et al., 1984). This appeared to be verified when comparing the Medix Electronic against the Cirrus nebuliser but did not hold when compared with the newer, more efficient open vent system devices.

4.3.2. Surfactant addition

Both Pari LC and Sidestream devices nebulised higher proportions of the test fluids with increased surfactant concentration (i.e. as surface tension decreased). Output values for the 1.0% surfactant solutions were observed to have increased by 20–25% from the output values for the most dilute (0.0001%) solution for the Pari LC nebulisers and by 6–11% for the Sidestream nebuliser. Since the output values for water or most dilute surfactant solutions were high (approximately 70%) in the Sidestream nebuliser, further increases were limited. Similar findings were found by Davis (1978); he stated that as the surface tension of the fluid (water — propylene glycol solutions) decreased, the aerosol output increased. Previous workers (Walkenhorst and Dautrebande, 1964; Glukhov, 1969) had also reported that surface tension had a profound effect not only on droplet size but also upon the aerosol output. More recently, Smye et al. (1990) reported that jet nebulisation of fluids with lower surface tension would increase the mass of solution released. Nebulisation of three solutions with surface tensions of 7.2×10^{-3} and 3.1×10^{-3} was reported to have significantly increased the efficiency (mass released/initial mass) from 49 to 69%. By contrast, the Cirrus nebuliser exhibited an irregular pattern with no definite link between output and surface tension of the nebulised fluid. This was predominantly a function of nebuliser design and poorer inter-nebulisation reproducibility. The output from the Medix Electronic initially decreased as the surfactant concentration increased, reaching trough values at 0.001%, 0.01% and 0.1% for sodium lauryl sulphate, Tween 80 and Tween 20, respectively. Thereafter, output increased with increased surfactant content (lower surface tension). It is notable that the Medix was the only nebuliser to experience difficulty in nebulising 0.2% Span 85 dispersion.

Despite the contributing factor of the respirable percentages, respirable output values were largely determined by those of total output with trends in respirable output largely remaining consistent with those obtained for total output. The Sidestream nebuliser was the most efficient device producing aerosols with the highest respirable output, followed by the Pari LC, Medix Electronic and Cirrus nebuliser. Consequently, the choice of nebuliser, as previously reported by Newman et al. (1985), is paramount in ensuring a high respirable output and efficient drug delivery.

5. Conclusions

The addition of surfactant to water influenced both the droplet size and output characteristics of the secondary aerosol emitted from both jet and ultrasonic nebulisers. Contrary to atomisation theories, an inverse relationship between MMD and surface tension was established for all surfactant solutions/dispersions over the entire concentration range or to a peak value. This value was not related to specific surface tension values or indeed to the critical micelle concentration for the surfactant system, thereby indicating that droplet size was independent of micelle formation or presence of such structures. The results may suggest that fluid surface tension is inversely related to the size of the emitted satellite droplets, thereby accounting for the increased MMD observed as the fluid surface tension decreased. Aerosol output from both Pari LC and Sidestream nebulisers was, however, directly related to surface tension, with decreasing surface tension generating a higher release of aerosol. More variable trends were found for Cirrus and Medix Electronic devices. The surfactant output values obtained for the ultrasonic device were generally comparable to the water value and were lower than for the two open-vent jet nebulisers. Trends in respirable output largely concurred with the total output data. Dispersity of aerosols, assessed by span, tended to decrease as the MMDs increased. This was clearly evident between different nebulisers and was also observed for surfactant systems nebulised in jet nebulisers.

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