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Viscosity effects on nebulisation of aqueous solutions

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Abstract

While the viscosity of sucrose and sodium citrate solutions increased with increasing percentage (w/v) of solute, the surface tension largely remained consistent. Water, sucrose (10–60% w/v) and sodium citrate (7–36% w/v) solutions were nebulised in two air-jet nebulisers (Pari LC; Medix A II) operated at 6 l min^{-1} and in an ultrasonic device (Medix Electronic) operated at mid-power setting. A wide variation in nebuliser size and output characteristics existed between the different commercially available models studied. Contrary to atomisation theories for air-jet nebulisation, droplet size was inversely related to solution viscosity (over 1–6 cP). Beyond this critical value droplet size increased as viscosity increased. This anomaly may be due to viscosity acting either directly or through liquid flow-rates. By contrast the ultrasonic device generated droplets of size proportional to viscosity but was unable to nebulise high viscosity fluids (i.e. > 6 cP). The low viscosity solutions offered less resistance to the integral fountain disintegration process, thereby producing smaller droplets and higher outputs.

Keywords: Aerosol characterisation; Nebulisation; Solutions; Viscosity

Nebulisation of liquids is an effective means of aerosol generation for pulmonary drug delivery. Atomisation theories predict that aerosol size and output characteristics are dependent not only upon the operating principles, conditions and mechanical construction of the nebuliser but also upon the physicochemical properties of the nebulised fluids (Mercer, 1981). While different empirical and semi-empirical formulae exist for air-jet and ultrasonic nebulisers, both predict that primary droplet size is proportional to surface tension, inversely related to viscosity and that the effect of density, over the concentration range normally encountered, is negligible. While 'filtering' effects of baffling and solvent evaporation may modify the secondary aerosol produced, previous studies (Boucher and Kreuter, 1968; Davies, 1978; Newman et al., 1987; Mc Callion et al., 1995) have found fluid viscosity to be a major determinant of the aerosol's size and output characteristics.

There are, however, insufficient studies on the effect of formulation variables upon the size and output characteristics of nebulised medical aerosols. This research sought to address this by investigating whether nebulisation of solutions with essentially identical values of surface tension but markedly different viscosities influenced the secondary aerosol characteristics.

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Table 1
Physicochemical properties of sucrose solutions and the MMDs (± S.E.) obtained upon nebulising these solutions in Pari LC, Medix A II and Medix Electronic nebulisers (n = 3)

Conc. (w/v)	Viscosity (cP)	Surf. Tens. (dynes/cm)	Relative density	Mass Median Diameter (μm)		
				Pari LC	Medix A II	Medix Electronic
10%	1.33	72.50	1.038	2.59 (0.03)	3.44 (0.06)	4.32 (0.13)
15%	1.59	72.75	1.059	2.28 (0.05)	3.34 (0.06)	4.42 (0.03)
20%	1.94	73.00	1.081	1.99 (0.05)	3.25 (0.04)	4.56 (0.03)
25%	2.22	73.20	1.104	1.95 (0.03)	3.23 (0.04)	4.52 (0.02)
30%	3.18	73.40	1.127	1.91 (0.10)	3.19 (0.02)	4.56 (0.08)
40%	6.15	74.10	1.176	1.81 (0.06)	3.07 (0.02)	—[a]
50%	15.40	74.85	1.229	1.99 (0.03)	2.62 (0.05)	—[a]
55%	28.35	75.70	1.257	2.04 (0.01)	2.78 (0.13)	—[a]
60%	58.37	76.45	1.286	2.30 (0.05)	—[a]	—[a]

[a]Not nebulised.

Sucrose and sodium citrate were purchased from Sigma Chemicals (Poole, UK). Pari LC nebulisers were supplied by Pari-Werk, GmbH, Starnberg, Germany, while Medix AII and Medix Electronic nebulisers were supplied by Medix Ltd., Catthorpe, UK. Water, sucrose (10–60% w/v) and sodium citrate (7–36% w/v) solutions were nebulised for 10 min in two jet nebulisers (Pari LC and Medix A II) driven by compressed air at 6 l min^{-1} and in the Medix Electronic ultrasonic nebuliser operated at the mid-power setting. The fluids' viscosities ranged between 1 and 56 cP while surface tension lay between 72.50 and 76.45 dynes cm^{-1}. Secondary aerosol characteristics (mass median diameter (MMD), % of droplets < 5 μm, 90% undersize, span) were measured with a Malvern 2600C laser diffraction sizer (Malvern Instruments, Malvern, UK). Nebulisers were clamped in a vertical position such that the mouth-piece tip was 2.5 cm from the centre of the detecting beam. They were weighed pre- and post-nebulization and residual weights ('dead' volumes) measured. All experiments were performed in triplicate at ambient temperature (20–25°C) and relative humidity (40–60%).

Nebuliser design and principle of operation influenced the droplet size generated, with both air-jet nebulisers producing smaller droplets than the ultrasonic device (Table 1 and Table 2). Many previous studies (Sterk et al., 1984; Phipps and Gonda, 1990) comparing aerosol characteristics between air-jet and ultrasonic nebulisers have reported similar findings. Nebulisation of sucrose and sodium citrate solutions in air-jet nebulisers gave progressively smaller droplets as viscosity increased over the 1–6 cP range. Thereafter MMD increased with increased viscosity. By contrast the MMD initially increased and then plateaued or decreased as viscosity increased in the ultrasonic device. All nebulisers produced consistent MMDs throughout nebulisation, with droplet size tending to alter only in the terminal 'sputtering' phase. During air-jet nebulisation the temperature of the nebuliser fluid fell by approximately 10°C (primarily because the outgoing air became saturated with solvent vapour), while in the ultrasonic nebuliser the temperature rose by approximately 15°C. Although this would be associated with changes in both viscosity and surface tension of the fluid, there was little variation in droplet size during the continous phase of nebulisation. When the MMDs were corrected to mass median aerodynamic diameter values ($\times [\rho_{soln}/\rho_{water}]^{0.5}$), the trends remained consistent.

An inverse relationship exists between MMD and the percentage of droplets < 5 μm, while a direct correlation exists between MMD and 90% undersize. The expected trends were clearly depicted in the results for these related parameters. Span is an index of the aerosol polydispersity. All the nebulised aerosols were polydispersed with span values ranging between 1.93 and 4.88 for jet nebulisers and 1.32 and 1.77 for the ultrasonic device. As expected, the Medix Electronic pro-

Table 2
Physicochemical properties of sodium citrate solutions and the MMDs (± SE) obtained upon nebulising these solutions in Pari LC, Medix A II and Medix Electronic nebulisers. (n = 3)

Conc. (w/v)	Viscosity (cP)	Surf. Tens. (dynes/cm)	Relative density	Mass Median Diameter (μm)		
				Pari LC	Medix A II	Medix Electronic
7%	1.31	72.39	1.048	1.94 (0.02)	3.31 (0.06)	4.13 (0.01)
10%	1.50	72.49	1.071	1.61 (0.01)	3.04 (0.04)	4.26 (0.04)
15%	1.93	72.87	1.110	1.49 (0.03)	2.65 (0.05)	4.32 (0.02)
18%	2.29	73.12	1.133	1.39 (0.03)	2.39 (0.09)	4.46 (0.03)
24%	3.40	73.21	1.181	1.32 (0.01)	2.07 (0.14)	4.01 (0.11)
32%	6.53	73.33	1.249	1.27 (0.02)	1.44 (0.11)	—[a]
36%	9.77	73.41	1.284	3.30 (0.03)	1.84 (0.07)	—[a]

[a]Not nebulised.

duced the least heterodisperse aerosols. The MMD value of an aerosol is generally inversely related to the width of the droplet size distribution (Clay et al., 1983). While both jet nebulisers displayed the expected inverse relation between MMD and span values, a poor correlation existed for the ultrasonic nebuliser.

After nebulisation, a residual amount of fluid remains trapped on the nebuliser walls and baffles. In this study, total output values 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 quantify the residual amounts of sucrose and sodium citrate. The more viscous solutions were associated with in-

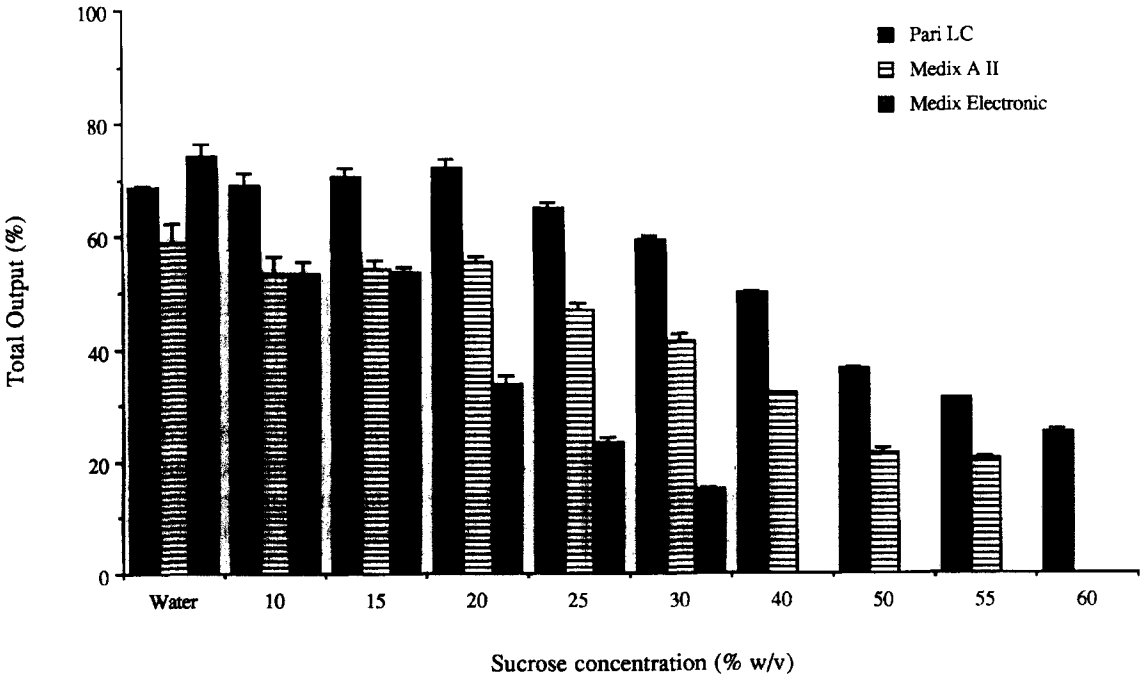

Fig. 1. Total output (%) for water and sucrose solutions (10–60% w/v) nebulised in Pari LC, Medix A II and Medix Electronic nebulisers.

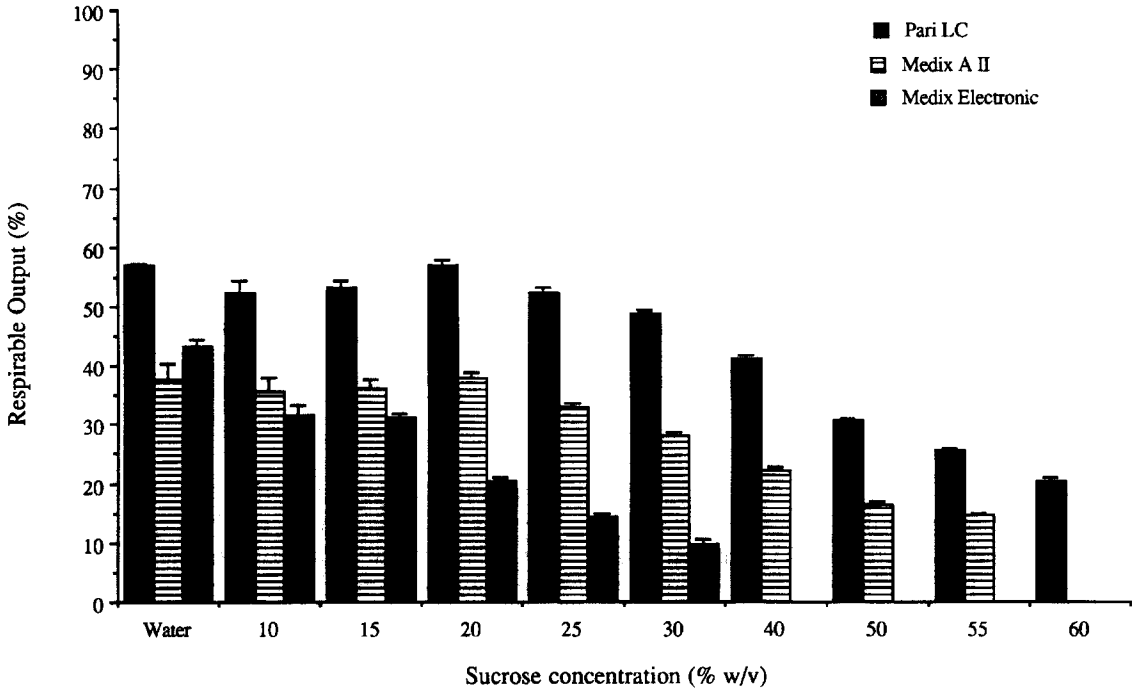

Fig. 2. Respirable output (%) for water and sucrose solutions (10–60% w/v) nebulised in Pari LC, Medix A II and Medix Electronic nebulisers.

creased residual amounts (lower outputs). While both jet nebulisers could aerosolise fluids of high viscosity; the Medix Electronic was unable to nebulise solutions with viscosities exceeding 6 cP (Fig. 1). Respirable output was determined by multiplying the total output by the percentage of droplets < 5 μm. While obviously the absolute values differed from total output values, the trends remained consistent (Fig. 2).

A wide variation in nebuliser size and output characteristics existed between the different commercially available models studied. Contrary to atomisation theories, MMD was inversely related to the viscosity of fluids (over 1–6 cP) when nebulised in jet nebulizers. However, beyond this critical value the trend reversed with larger droplets being generated as viscosity increased. Viscosity may influence the droplet size either directly or through liquid flow-rates. When the parameter $[2\eta^2/\rho D]$, where η = fluid viscosity, ρ = liquid density and D = diameter of liquid inlet orifice, is less than 0.01 viscosity affects the mean droplet size only through the mass flow-rate (Mercer, 1981). Only when this term exceeds 0.01, does viscosity directly influence the droplet size. Consequently, it is feasible that when solutions with viscosities between 1 and 6 cP are nebulised in Pari LC or Medix A II devices, droplet size is influenced by liquid flow-rates. As the viscosity increases, the flow through the capillary orifice is reduced. With constant energy supply (from air-jets) and less fluid presented at the nozzle orifice, more energy is supplied per unit fluid volume, thereby resulting in smaller droplets. However, when the critical value is reached, droplet size will be determined by fluid viscosity. Consequently nebulisation of high viscosity fluids would generate larger droplets. Such was apparent in the present study. The reduced liquid flow for more viscous fluids would also account for their associated reduced outputs.

While the ultrasonic device generated droplets

of size proportional to viscosity, it was unable to nebulise high viscosity fluids (i.e., > 6 cP). In ultrasonic nebulisation, droplet formation is thought to result from crests breaking from capillary waves initiated and driven by cavitation bubbles (Boguslavski and Eknadiosyants, 1969). At sufficiently high ultrasonic intensities, a fountain of liquid is formed from which larger droplets are emitted from the apex and a 'fog' of smaller (respirable) droplets is emitted from the lower part. The threshold amplitude for generation of the capillary waves is directly proportional to the liquid viscosity and hence higher viscosities would be expected to suppress the atomisation process. This was clearly depicted in the present findings; high viscosity solutions presented greater resistance to the integral fountain disintegration process, thereby producing not only lower outputs but also larger droplets.

References

Boguslavski, Y.Y. and Eknadiosyants, O.K., Physical mechanism of the acoustic atomization of a liquid. *Soviet Phys. Acoust.*, 15 (1969) 14–21.

Boucher, R.M.G. and Kreuter, J., The fundamentals of the ultrasonic atomization of medicated solutions. *Ann. Allergy*, 26 (1968) 591–600.

Clay, M.M., Pavia, D., Newman, S.P. and Clarke, S.W., Factors influencing the size distribution of aerosols from jet nebulisers. *Thorax*, 38 (1983) 755–759.

Davies, S.S., Physicochemical studies on aerosol solutions for drug delivery. I. Water-propylene glycol systems. *Int. J. Pharm.*, 1 (1978) 71–83.

Mc Callion, O.N.M., Taylor, K.M.G., Thomas, M. and Taylor, A.J., Nebulization of fluids with different physicochemical properties in air-jet and ultrasonic nebulizers. *Pharm Res.* 12 (1995) 1682–1688.

Mercer, T.T., Production of therapeutic aerosols. *Chest*, 80 (1981) 813–817.

Newman, S.P., Pellow, P.G.D. and Clarke, S.W., Dropsizes from medical atomisers (nebulisers) for drug solutions with different viscosities and surface tensions. *Atom. Spray Tech.*, 3 (1987) 1–11.

Phipps, P.R. and Gonda, I., Droplets produced by medical nebulisers. Some factors affecting their size and solute concentration. *Chest*, 97 (1990) 1327–1332.

Sterk, P.J., Plomp, A., van der Vate, J.F. and Quanjer, P.H., The physical properties of aerosols produced by several jet and ultrasonic nebulisers. *Bull. Eur. Physiopathol. Resp.*, 20 (1984) 65–72.