ELSEVIER

International Journal of Pharmaceutics 133 (1996) 203–214

international journal of pharmaceutics

Nebulisation of monodisperse latex sphere suspensions in air-jet and ultrasonic nebulisers

Orla N.M. Mc Callion[a,*], Kevin M.G. Taylor[a], Marian Thomas[b], Anthony J. Taylor[b]

[a]*Department of Pharmaceutics, School of Pharmacy, University of London, 29-39 Brunswick Square, London WCIN IAX, UK*
[b]*Glaxo-Wellcome Research and Development, Department of Respiratory Product Development, Park Lane, Ware, Hertfordshire, SG12 0DP, UK*

Received 27 September 1995; revised 6 December 1995; accepted 30 December 1995

Abstract

Therapeutic steroid suspensions are frequently administered via nebulisation to neonates and young children. We sought to investigate how the size and concentration of model-suspended particles (latex spheres) would influence the physical characteristics of the nebulised aerosol. Suspensions of monodispersed latex spheres [from 0.605 to 11.90 μm: diluted 0.1 to 0.01% (w/v)] were nebulised in three air-jet nebulisers and one ultrasonic nebuliser. Secondary aerosol characteristics were measured with a Malvern 2600C laser diffraction sizer. The residual volumes and percentage outputs of suspension and latex spheres were determined by weight measurements and Coulter Counter analysis. The choice of nebuliser markedly influenced the size, polydispersity and output of the resultant aerosol. No specific correlation existed between the size and/or concentration of the original latex spheres and the size distribution of the nebulised droplets. There was a higher output of smaller spheres, with little or no release of the spheres whose size exceeded the typical mass median diameter of the aerosols. The latex spheres were generally concentrated in the residual fluid due to solvent evaporation, blockage of nebuliser orifice by spheres and/or the refluxing action of the suspension. The ultrasonic nebuliser was less efficient than the jet devices; it degraded the larger spheres and was unable to atomise the 1.16 μm sphere suspensions.

Keywords: Aerosol characterisation; Jet nebuliser; Latex spheres; Suspension; Ultrasonic nebuliser

1. Introduction

Nebulisers are routinely used to deliver β_2 agonists, anti-allergics, anticholinergics, corticosteroids, antibiotics, antivirals, anaesthetics, saline and mucolytics to the respiratory tract (BNF, British National Formulary, 1995). While still in the experimental phase, other agents have been administered by nebulisers: such include protein/peptides (Niven, 1993) and liposomes (Taylor and Farr, 1993). While most of these agents are formulated as solutions, the corticosteroids with intrinsic low aqueous solubility are formulated as suspensions. Suspensions for nebulisation currently available are limited to Becotide® suspension for nebulisation (beclomethasone

* Corresponding author. Current Address: School of Pharmacy, Queen's University, Belfast, 97 Lisburn Road, Belfast, BT9 7BL, UK.

PII S0378-5173(96)04449-3

dipropionate 50 μg/ml) and Pulmicort® respules (budesonide 0.25 mg/ml and 0.50 mg/ml). Since alternative inhalation devices are often unsuitable for neonates and young children, nebulisation is an important technique to administer steroids to such asthmatic/wheezing patients. Little work has been published comparing the nebulisation of solutions and suspensions. Independent studies by Nikander (1993) and Hickey et al. (1994) reported significant differences in the size and output of nebulised solution and suspension aerosols. Literature existing on the nebulisation of respiratory suspensions is generally limited to clinical studies. Conflicting reports on the clinical effectiveness of nebulised beclomethasone dipropionate (BDP) and budesonide have been reported. While Carlsen et al. (1988) noted marked improvement in asthmatic/wheezing patients when treated with nebulised BDP, Webb et al. (1986) and O'Callaghan and Milner (1989) reported nebulised BDP to be less effective than metered dose inhaler or dry powder inhaler formulations of the drug. Budesonide faired more favourably with Godfrey et al. (1987), Hultquist (1989) and De Jongste and Duiverman (1989), all advocating the use of nebulised budesonide. This was largely attributed to the higher dose of budesonide which could be formulated as a suspension, consequently delivering higher doses by nebulisation.

Experimental studies in the aerosolisation of suspensions initially were limited to nebulisation of suspensions of monodisperse latex spheres to generate monodisperse aerosols (Langer and Lieberman, 1960; Keith and Derrick, 1960; Reist and Burgess, 1967; Raabe, 1968). However, in 1972, Stober noted cluster aggregation when latex suspensions were nebulised. More recently, Masinde and Hickey (1993) prepared suspensions of poly (L-lactic acid) microspheres possessing suitable characteristics for nebulisation. The authors reported that jet nebulisation of suspended 2.60 μm microspheres generated aerosols in which more than 80% was respirable (less than 5.8 μm). The main objective of this research was to investigate how the mean size and concentration of a model-suspended particle (latex sphere) would influence the aerosol characteristics obtained upon nebulisation. Stock suspensions of latex spheres were diluted to give final concentrations of 0.01% and 0.10% (w/v). These values were comparable to the drug weight in volume percentages for BDP and budesonide in the Becotide® and Pulmicort® preparations available for nebulisation, i.e. 0.005% (w/v) for BDP and 0.025% and 0.05% for budesonide. Sphere sizes covered the range for commercially available suspended formulations.

2. Materials and methods

2.1. Materials

Pari LC nebulisers were supplied by Pari Werk, GmbH, Starnberg, Germany, Medix A II and Medix Electronic nebulisers were supplied by Medix Ltd., Lutterworth, U.K., while PulmoNeb nebulisers were purchased from DeVilbiss Health Care, Heston, U.K. Polystyrene and styrene divinyl latex spheres (0.605–11.90 μm) were purchased from Sigma Chemical Co. (Poole, U.K.); 0.605 and 1.16 μm sphere sizes were verifed using photon correlation spectroscopy (Malvern Instruments, Malvern, U.K.), while laser diffraction analysis (Malvern 2600C) was used to size the 2.97, 6.40 and 11.90 μm spheres). The latex suspensions were supplied in stock concentrations (10% spheres by volume in water) and were stabilised by a proprietary sulphonate surfactant in concentration between 0.1 and 0.5% (w/v).

2.2. Preparation of test suspensions

0.01% and 0.10% (w/v) concentrations of the 0.605, 1.16, 2.97, 6.40 and 11.90 μm stock latex sphere suspensions were prepared by diluting the stock suspensions with deionised water.

2.3. Characterisation of nebulised aerosol

Aerosol characterisation was performed with a Malvern 2600C laser diffraction sizer. Each nebuliser was weighed when empty, following the addition of the appropriate volume of test fluid and at the end of the nebulisation period. Fill volumes for the Pari LC and Medix Electronic were 8 ml; while for the Medix A II and PulmoNeb 4 ml

were used. Jet nebulisers were operated at 6 L/min and the ultrasonic device operated at the mid-power setting for a 10-min period or until dryness, whichever occurred first. The nebulisers were clamped in a vertical position such that the mouthpiece was 2.5 cm from the centre of the Malvern beam. The aerosol was diverted through the beam approximately 5 mm in front of the 63 mm Fourier transform lens and drawn away by extraction into a suction pump. All experiments were performed at room temperature (20–25°C) and relative humidity (40–60%). Five replicates were performed. The various parameters determined included the mass median diameter (MMD), the percentage of the aerosol droplets less than 5 μm ('respirable percentage'), the 90% undersize value, the span value (90% undersize–10% undersize / 50% undersize), the nebulisation time, the weight of the residual fluid following nebulisation and the total and 'respirable output' (total output x 'respirable percentage').

2.4. Electrical resistance technique (Coulter counter determinations)

In order to measure the percentage of latex spheres that remain unnebulised, aliquots of the residual fluid were analysed using a Coulter Counter (Coulter Electronics Ltd., Luton, U.K.). This technique is used to determine the number and size of particles suspended in an electrically conductive liquid. An orifice tube with a 50 μl aperture was used in the analysis of the 0.605 and 1.16 μm spheres, while a 100 μl aperture was used for the larger spheres. Background readings of Steriflex® (0.9% w/v sterile sodium chloride: Fresenius Health Care Group, Basingstoke, U. K.) were measured. A suitable aliquot, ranging between 50 μl and 1.0 ml, of the stock test fluids (i.e. the 0.10% and 0.01% w/v latex sphere suspensions) or an equivalent volume of the residual fluid was added to the Steriflex® and dispersed by stirring. The number of particles within specified size ranges (channels) for a fixed volume of fluid to the Steriflex® was thus determined. By comparing the residual fluid values with those obtained for the related stock test fluids, the proportion of the latex spheres which remained in the 'residual fluid' could be calculated. Consequently, subtracting the residual proportion from the known initial value gave the the proportion of spheres which were nebulised.

3. Results and discussion

3.1. Mass Median Diameters (MMDs) of aerosols

The design and operating principles of the four nebulisers markedly influenced the MMDs for the generated aerosols. Irrespective of the suspension being nebulised, the Pari LC produced aerosols with the smallest droplets, followed by the Medix AII, Medix Electronic and PulmoNeb (Table 1). The droplet sizes produced upon nebulisation of the different latex suspensions in Pari LC, Medix A II and Medix Electronic nebulisers showed small but significant differences ($P < 0.01$: ANOVA). No clear correlation existed between the size and/or concentration of the latex spheres in the nebulised suspensions and the resultant MMD. The small differences observed would not be expected to be of any clinical signifance. These findings concur with studies of nebulised liposomes wherein the MMD and size distribution were largely independent of properties of the liposome being atomised and were determined by the choice of nebuliser and gas flow-rates (Taylor and Farr, 1993). Unlike liposomes, spheres do not generally deform during nebulisation. It is improbable that the spheres affected the performance characteristics of the air-jet nebuliser liquid orifices through attrition since aerosol characterisation remained consistent from the beginning to end of the experiments.

In most cases, the MMDs generated upon nebulisation of the latex suspensions (especially respirable sphere sizes [0.605–2.97 μm]), were close to droplet size of water. Evaporation of droplets occurs from droplet formation to detection and thus sizes are highly dependent upon conditions under which the measurements were taken. The laser-sizing technique measured droplet size at a specific distance (2.5 cm) from the nebuliser outlet; this distance was consistent

Table 1
Mean MMDs (± S.E.) obtained upon nebulising suspensions of latex spheres (between 0.605–11.90 μm) in Pari LC, Medix A II, PulmoNeb and Medix Electronic nebulisers for 10 min ($n = 5$)

Fluid	Water	0.605 μm		1.16 μm		2.97 μm		6.40 μm		11.90 μm	
Conc. (w/v)		0.10%	0.01%	0.10%	0.01%	0.10%	0.01%	0.10%	0.01%	0.10%	0.01%
Pari LC	2.37 (0.04)	2.27 (0.02)	2.33 (0.03)	2.35 (0.03)	2.46 (0.03)	2.41 (0.01)	2.34 (0.03)	2.58 (0.04)	2.59 (0.08)	2.49 (0.02)	2.63 (0.02)
Medix AII	3.76 (0.02)	3.70 (0.05)	3.46 (0.05)	3.54 (0.03)	3.59 (0.03)	3.43 (0.03)	3.57 (0.05)	3.66 (0.02)	3.57 (0.07)	3.74 (0.05)	3.83 (0.08)
Pulmo-Neb	4.73 (0.25)	4.67 (0.16)	4.69 (0.14)	4.72 (0.17)	4.84 (0.09)	4.84 (0.23)	4.86 (0.31)	5.35 (0.45)	5.30 (0.14)	4.98 (0.38)	5.26 (0.14)
Medix Elect.	4.38 (0.01)	4.31 (0.01)	4.34 (0.01)	4.49 (0.04)	4.58 (0.03)	4.36 (0.01)	4.37 (0.01)	4.28 (0.02)	4.32 (0.01)	4.30 (0.01)	4.38 (0.02)

for all experiments and equated to the anatomical distance from mouth to back of the throat, thereby correlating well with clinical conditions. Sprayed suspended solids have been shown to produce droplets with median primary droplet sizes greater than solutions (albeit in MDIs) since they are more likely to contain suspended particulates (formed by multiple particle inclusion in single droplets) than those from nebulised solutions (Dalby and Byron, 1988). Furthermore, nebulised latex suspensions have been shown to form aggregates of various number of spheres (Stober, 1972). However, since droplet sizes of the nebulised latex sphere suspensions were generally similar to those of water, aggregation is unlikely to be a major determining factor of droplet size. Furthermore more dilute suspensions would be expected to emit smaller droplets (due to minimal aggregation) but such was not observed in the results. Consequently, nebuliser design and incomplete evaporation largely account for the findings.

3.2. MMD versus time profiles

The MMD versus time profiles for nebulised water and sphere suspensions showed a highly consistent droplet size throughout the entire nebulisation period for the Medix A II, PulmoNeb and Medix Electronic. Profiles for the Medix Electronic (for water and more dilute latex sphere suspensions) increased slightly in the terminal 'sputtering' phases. A marked increase after a precise time (circa 7 min) was observed for the Pari LC data (Fig. 1). The larger MMDs were probably due to reduced efficiency of the Pari LC during this latter stage of operation rather than due to temperature dependent effects. All test fluids were still being nebulised when the experiment was terminated after a 10-min cut-off for the four nebulisers.

3.3. % < 5 μm, 90% undersize and polydispersity

Trends in % of droplets < 5 μm and the 90% undersize values correlated well with the MMDs. The expected inverse relationship between MMD and 'respirable percentage' and the direct relationship between droplet size and 90% undersize were noted. The Pari LC had the highest 'respirable percentage', followed by the Medix A II, Medix Electronic and PulmoNeb (e.g. 78–83%, 62–68%, 57–62% and 47–54%, respectively). Ninety percent undersize values for the Pari LC, Medix A II, Medix Electronic and PulmoNeb, respectively, lay between 6.17 and 6.94 μm, 8.12 and 9.11 μm, 7.84 and 8.74 μm and 10.44 and 11.43 μm for the latex sphere suspensions. It is noteworthy that although the Medix Electronic produced aerosols with larger MMDs than the Medix A II nebuliser, it produced smaller 90% undersize values, indicating that the Medix Electronic produced less heterodisperse aerosols.

While not equivalent to geometric standard deviation, the span values served as an index to the polydispersity of the aerosols. For specific nebuliser types, the span values varied only slightly for different sizes and concentrations of the latex sphere suspensions, thereby implying that polydispersity was largely unaffected by the presence of the suspended spheres in the suspensions tested. By contrast, the span values were influenced markedly by the choice of nebuliser. Of the nebulisers studied, the Medix Electronic produced aerosols with the smallest span, followed by the PulmoNeb, Medix AII and the Pari LC (span values lay between 1.61–1.71, 1.89–2.04, 2.03–2.17 and 2.20–2.44, respectively). MMD 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 Pari LC — Medix A II — Medix Electronic — PulmoNeb nebulisers, span values may be expected to follow a reciprocal trend. While an irregularity occurred between the Medix Electronic and PulmoNeb nebulisers, the inverse relationship between MMD and span existed.

3.4. Total and respirable outputs

Total aerosol output was determined from weight measurements. The different nebuliser types varied significantly in the ability to nebulise the fluids ($P < 0.01$: ANOVA). Total output values of 66 to 78%, 37 to 71%, 41 to 57% and 22

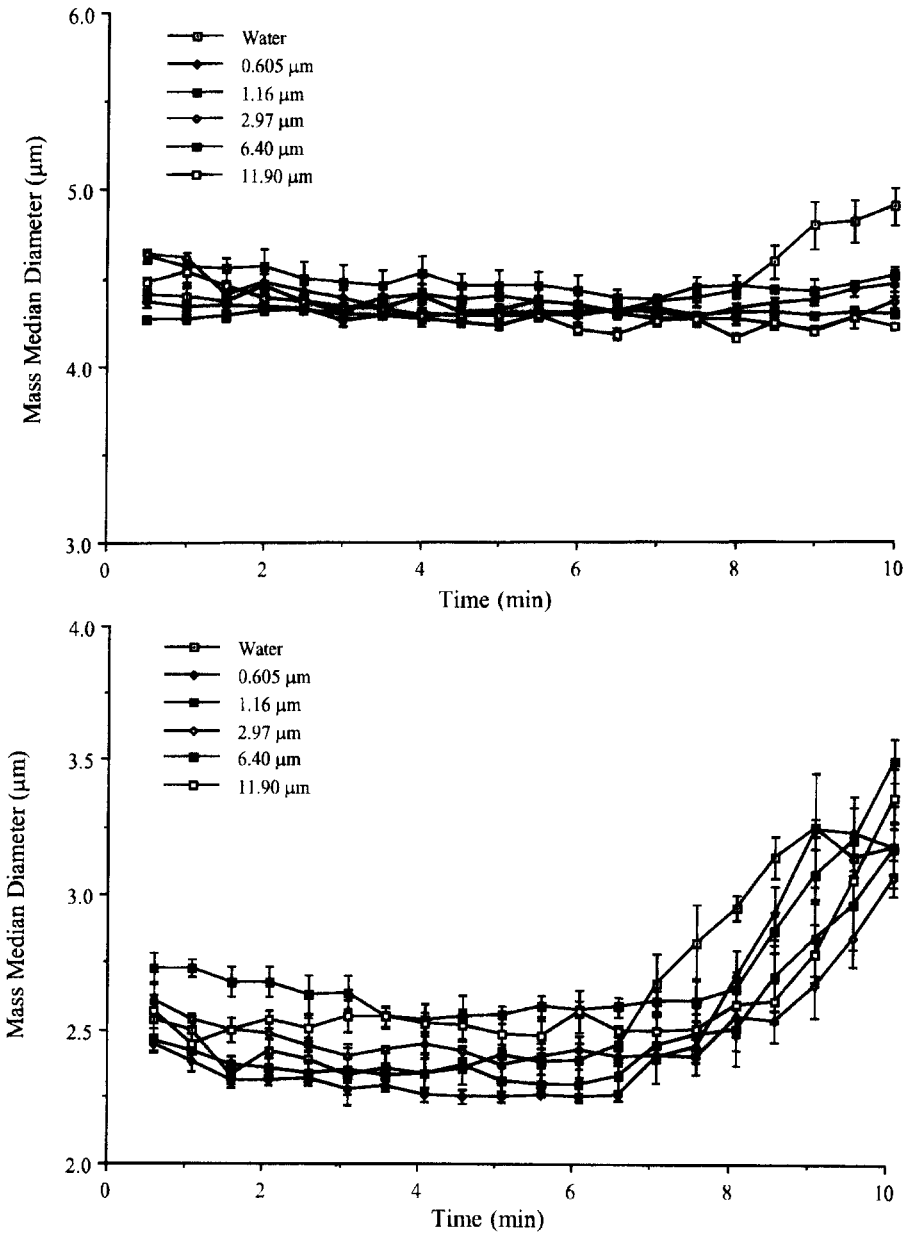

Fig. 1. MMD (± S.E.) time profiles for suspensions of latex spheres (0.10% w/v) nebulised in (A) a Medix Electronic nebuliser, and (B) a Pari LC nebuliser.

to 72% were noted for the Pari LC, Medix A II, PulmoNeb and Medix Electronic, respectively, over the entire range of latex sphere suspensions studied. Open vent air-jet nebuliser systems, incorporating inhalation and exhalation valves, have been developed, which allow for enhanced generation of aerosol during the inspiratory phase of breathing and reduced release of aerosol during the expiratory phase (Knoch et al., 1993). The Pari LC has an open-vent system and consequently produced greater total outputs than either the Medix AII and PulmoNeb devices (traditional

venturi nebulisers) or the ultrasonic Medix Electronic. Output rates from ultrasonic nebulisers often exceed those from jet nebulisers (Mercer, 1981; Sterk et al., 1984), and indeed the ultrasonic nebuliser had a greater output efficiency than the traditional air-jet devices in this study. The performance of the ultrasonic nebuliser was highly dependent on sphere size and concentration of the suspension; it experienced considerable difficulty nebulising the larger latex spheres and the more concentrated suspensions. For jet nebulisers, the total output varied randomly and generally, except for the 11.90-μm suspensions in the Medix A II and PulmoNeb, appeared independent of latex sphere size and concentration of the suspension.

The 'respirable output', determined by multiplying the total output by the percentage of droplets < 5 μm, was inherently dependent on the total output data and the forementioned trends largely remained consistent (Fig. 2). The contribution of the respirable percentage factor reinforced the differences between the nebuliser types, and clearly highlighted the marked efficiency of the Pari LC device over the other nebulisers tested.

3.5. Percentage of latex spheres that remained unnebulised

While significant differences ($P < 0.01$: ANOVA) existed between the nebulisers in their ability to atomise the latex sphere suspensions (Fig. 3), latex sphere size determined the proportion of spheres nebulised. Modern air-jet nebulisers tend to generate aerosols in which the primary droplets are approximately 20 μm in diameter and satellite droplets range between 1 and 8 μm (Byron, 1987). Efficient baffling ensures that only the smaller satellite droplets leave the nebuliser to constitute the respirable aerosol. Consequently, the 11.90-μm spheres would not be nebulised. However, all latex spheres with diameters between 0.605 and 6.40 μm, could be incorporated into the liquid filaments and subsequently into either primary droplets or the satellite droplets. Those latex spheres contained within the satellite droplets could then be released from the device. Such was evident in the findings of the study, with a incremental increase in the percentage of latex spheres nebulised as the sphere size decreased (e.g. 50–60% of the 0.605 μm spheres were nebulised in the three jet devices, while only 7–40% of the 6.40 μm spheres were released).

The ultrasonic device gave less efficient and more erratic results. While ultrasonic nebulisation could release approximately 27–33%, 20–25% and 7–8% of the 0.605 μm, 2.97 μm and 6.40 μm latex suspensions, respectively, it was unable to nebulise any of the 1.16 μm latex suspension and appeared to degrade the 11.90 μm latex spheres to produce smaller particles. While approximately 40–50% of the original 11.90 μm latex spheres remained unchanged in the residual fluid, particles of smaller sizes (between 2–10 μm) were found, possibly due to deformation of the larger 11.90 μm latex spheres. As expected, the smaller latex spheres (with the exception of the 1.16 μm spheres) were more readily nebulised with progressively higher percentages being released. The anomaly for the 1.16 μm spheres may suggest that the operating frequency of the ultrasonic nebuliser was unable to atomise suspended particles of a specific size, concentration and/or density.

3.6. Efficiency (ratio of latex spheres:suspension nebulised)

The ratio of latex spheres:suspension nebulised relates the total output and the proportion of latex spheres nebulised. The latex sphere concentration generally increased in the residual fluid for the nebulisers (Table 2). This may be due to loss of vehicle by evaporation in the nebuliser (Cockcroft et al., 1987), physical blockage by spheres of nebuliser orifice, and/or refluxing action of the suspension. Alternatively, the polymer density (1.05 g/ml) may account for the reduced release of spheres relative to water, particularly in the ultrasonic device. While data for the Pari LC and Medix A II concurred with expected values (namely more fluid than solid spheres were nebulised and that efficiency increased as sphere size decreased), irregular findings were noted for the PulmoNeb and Medix Electronic. In the Pul-

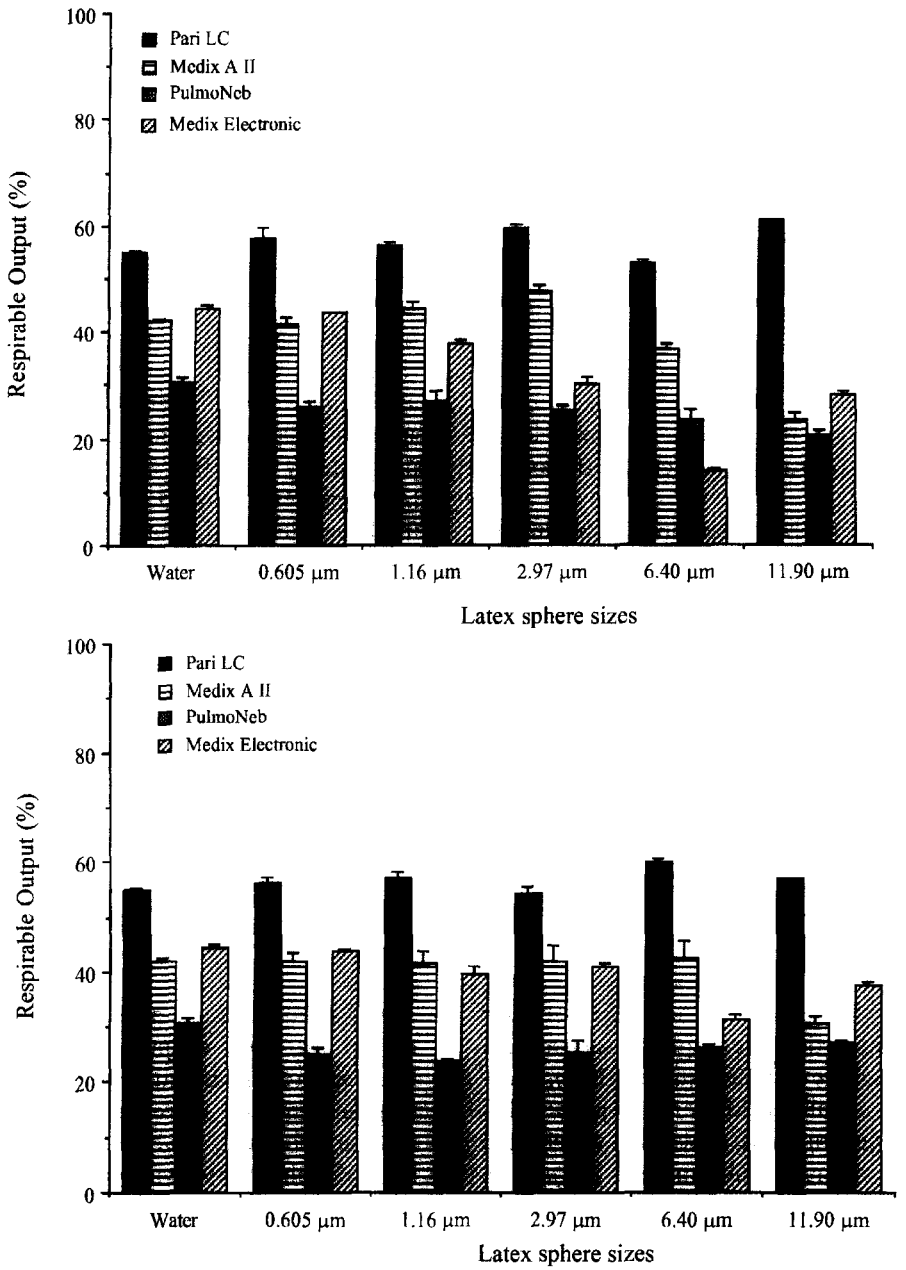

Fig. 2. Mean respirable outputs (± S.E.) obtained upon nebulising suspensions of latex spheres for 10 min in Pari LC, Medix A II, PulmoNeb and Medix Electronic nebulisers. Suspensions were diluted to a final concentration of (A) 0.10% w/v and (B) 0.01% w/v.

moNeb, a higher percentage of the original latex spheres relative to the original suspension was nebulised for some latex suspensions (mainly for the 0.01% (w/v) concentration). It is feasible that the droplets (being the largest produced for the four nebulisers) contained more than one sphere (i.e. sphere aggregation) with the concomitant effect of releasing a higher proportion of latex

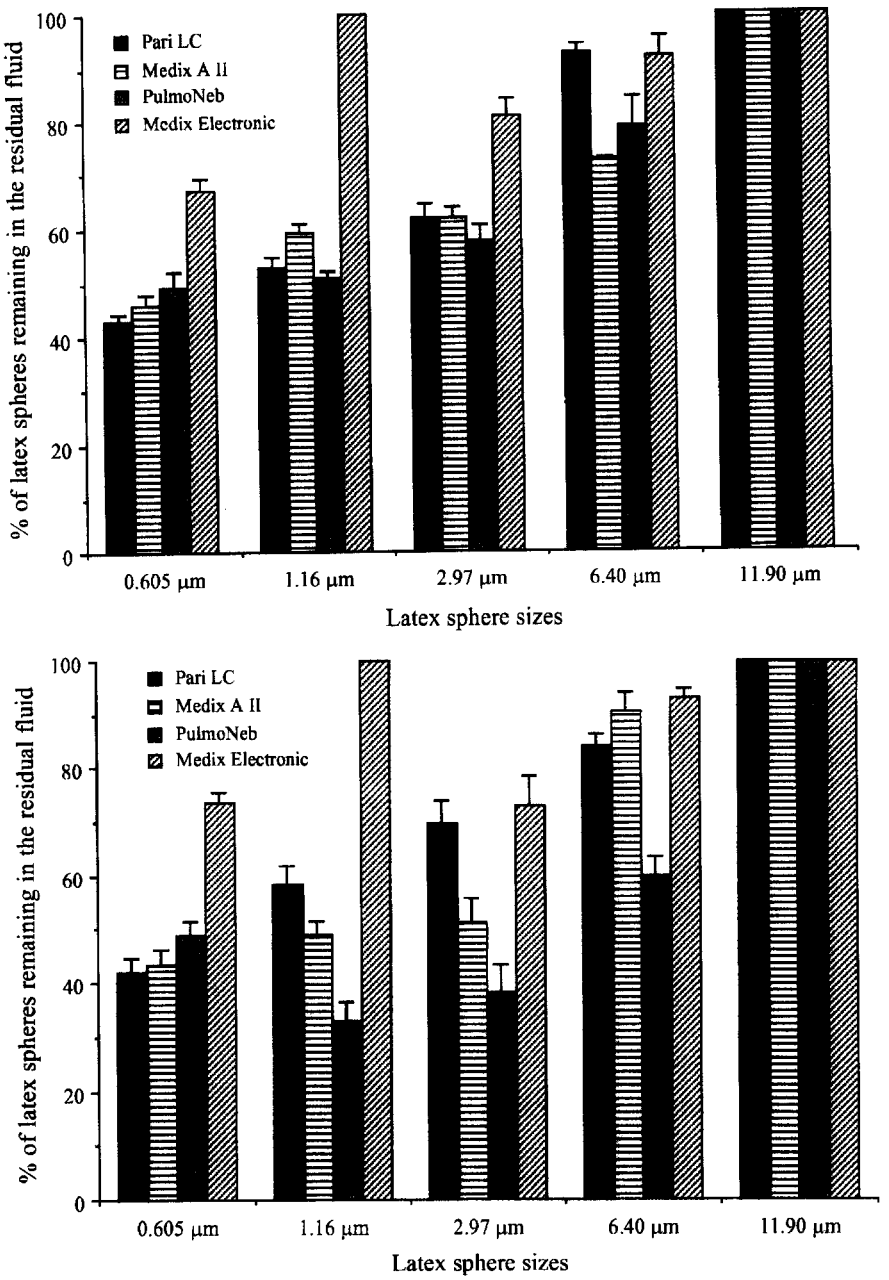

Fig. 3. Mean percentage (± S.E.) of latex spheres remaining in the residual fluid after 10 min nebulisation in Pari LC, Medix A II, PulmoNeb and Medix Electronic nebulisers. Suspensions were diluted to a final concentration of (A) 0.10% w/v and (B) 0.01% w/v.

spheres. Findings for the Medix Electronic were highly irregular, with deformation and non-aerosolisation of certain sphere suspensions. A higher mechanical energy than that produced by the piezoelectric crystal may be required to effectively atomise the heavier latex spheres. Consequently, the use of ultrasonic nebulisers to generate aerosols from latex sphere (and possibly therapeutic) suspensions would not be advocated.

Table 2
The mean efficiency [ratio of latex spheres/fluid nebulised] (± S.E.) obtained upon nebulising suspensions of latex spheres (between 0.605–11.90 μm) in Pari LC, Medix A II, PulmoNeb and Medix Electronic nebulisers for 10 min (n = 5)

Suspension Conc. (w/v)	0.605 μm		1.16 μm		2.97 μm		6.40 μm		11.90 μm	
	0.10%	0.01%	0.10%	0.01%	0.10%	0.01%	0.10%	0.01%	0.10%	0.01%
Pari LC	0.82 (0.04)	0.84 (0.04)	0.68 (0.02)	0.58 (0.05)	0.51(0.04)	0.45 (0.06)	0.11 (0.02)	0.21 (0.03)	0.00	0.00
Medix AII	0.84 (0.01)	0.91 (0.01)	0.62 (0.01)	0.84 (0.08)	0.54 (0.03)	0.77 (0.06)	0.47 (0.01)	0.14 (0.05)	0.00	0.00
PulmoNeb	1.06 (0.06)	1.10 (0.05)	0.98 (0.05)	1.48 (0.10)	0.86 (0.04)	1.29 (0.10)	0.43 (0.12)	0.74 (0.08)	0.00	0.00
Medix Electronic	0.46 (0.03)	0.36 (0.02)	0.00	0.00	0.38 (0.06)	0.54 (0.08)	0.22 (0.14)	0.14 (0.09)	0.00[a]	0.00[a]

[a] Ultrasonic nebulisation degraded approximately 50% of the 11.90 μm spheres to produce smaller particles (2–10 μm).

4. Conclusions

No specific correlation existed between the size and/or concentration of the latex spheres and the size of the nebulised droplets. The droplet size distribution was determined by the nebuliser design and incomplete solvent evaporation, thereby highlighting the importance of design and experimental conditions in determining aerosol size characteristics. While aerosol polydispersity was largely unaffected by particle size and concentration of the suspensions tested, the span values were influenced markedly by the choice of nebuliser. Dispersity of aerosols, assessed by span, was smallest for the ultrasonic device and tended to decrease as the MMDs rose for the jet nebulisers.

The ultrasonic nebuliser had a greater output efficiency than the traditional air-jet devices, though less than the open-vent Pari LC jet device. It was, however, more adversely affected by physicochemical properties of the test suspensions and experienced difficulty in nebulising the larger latex spheres and the more concentrated suspensions. It was unable to nebulise the 1.16 μm spheres and appeared to degrade the larger 11.90 μm spheres. By contrast, the total output generated from suspension nebulised in air-jet devices varied randomly and was not influenced by the size and/or concentration of the suspended latex spheres. Respirable output trends mirrored those of total output, though the differences between devices were more pronounced. The design and operating conditions of nebulisers limit the maximum droplet size; hence restricting the size of latex spheres which can be nebulised. As expected, the smaller spheres were more readily nebulised, with progressively higher percentages being released. For most devices (except the PulmoNeb), the latex spheres were concentrated in the residual fluid, possibly due to loss of vehicle by evaporation in the nebuliser, physical blockage by spheres of nebuliser orifice, refluxing action of the suspension and/or the heavier polymer density (1.05 g/ml).

References

British National Formulary, No. 29. British Medical Association and Royal Pharmaceutical Society of Great Britain, London, 1995.

Byron, R.P., Pulmonary targetting with aerosols. *Pharm. Technol.*, 11 (1987) 42–56.

Carlsen, K.H., Leegard, J., Larsen, S. and Orstavik, I., Nebulised beclomethasone dipropionate in recurrent obstructive episodes after acute bronchiolitis. *Arch. Dis. Child*, 63 (1988) 1428–1433.

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.

Cockcroft, D.W., Hurst, T.S. and Gore, B.P., Importance of evaporative water losses during standardised nebuliser inhalation provocation tests. *Chest*, 96 (1987) 505–508.

Dalby, R.N. and Byron, R.P., Comparison of output particle size distribution from pressurised aerosol formulated as solutions or suspensions. *Pharm. Res.*, 5 (1988) 36–39.

De Jongste, J.C. and Duiverman, E.J., Nebulised budesonide in severe childhood asthma. *Lancet*, i (1989) 1388.

Godfrey, S., Avital, A., Rosler, A., Mondelburg, A. and Uwyyed, K., Nebulised budesonide in severe infantile asthma. *Lancet*, ii (1987) 851–852.

Hickey, A.J., Kuchel, K. and Masinde, L.E., Comparative efficiency of solution and suspension output from jet nebulisers. *Respirat. Drug Deliv.*, IV (1994) 259–263.

Hultquist, C., Nebulised budesonide in severe childhood asthma. *Lancet*, i (1989) 380.

Keith, C. and Derrick, J., Measurement of particle size distribution and concentration of cigarette smoke by the 'Conifuge'. *J. Colloid Sci.*, 15 (1960) 340–356.

Knoch, M., Wunderlich, E. and Geldner, S., A nebulizer system for highly reproducible aerosol delivery. *J. Aerosol Med.*, 9, Suppl. (1993) 73.

Langer, G. and Lieberman, A., Anomalous behaviour of aerosol produced by atomization of monodisperse polystyrene latex. *J. Colloid Sci.*, 15 (1960) 357–360.

Masinde, L.E. and Hickey, A.J., Aerosolized aqueous suspensions of poly (L-lactic acid) microspheres. *Int. J. Pharm.*, 100 (1993) 123–131.

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

Nikander, K., Drug delivery systems. *J. Aerosol Med.*, 16 Suppl. (1993) 85.

Niven, R.W., Delivery of biotherapeutics by inhalation aerosol. *Pharm. Technol.*, 7 (1993) 72–82.

O'Callaghan, C. and Milner, A.D., Inhaled steroids and recurrent wheeze after bronchiolitis. *Lancet*, i (1989) 1458.

Raabe, O., The dilution of monodisperse suspensions for aerosolisation. *Am. Ind. Hyg. Assoc. J.*, 29 (1968) 439–443.

Reist, P.C. and Burgess, W.A., Atomization of aqueous suspensions of polystyrene latex particles. *J. Colloid Interfac. Sci.*, 24 (1967) 271–273.

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

Stober, W., Dynamic shape factors of nonspherical aerosol particles. In Mercer, T.T., Morrow, P.E. and Stober, W. (Eds.), *Assessment of airborne particles*, Thomas, Illinois, 1972, pp. 249–289.

Taylor, K.M.G. and Farr, S.J., Liposomes for drug delivery to the respiratory tract. *Drug Dev. Indust. Pharm.*, 19 (1993) 123–142.

Webb, M.S.C., Millner, A.D., Hiller, E.J. and Henry, R.L., Nebulised beclomethasone dipropionate suspension. *Arch. Dis. Child*, 61 (1986) 1108–1110.