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The use of laser diffraction for the evaluation of the aerosol clouds generated by medical nebulizers

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Abstract

The diffraction method for the measurement of the droplet size distributions produced by medical nebulizers was investigated. The technique was found to be robust and reliable. Correlation of published results obtained from laser diffraction droplet size analysis to characterize the nebulizer clouds with radiolabel deposition profiles and predictions of an empirical deposition model, shows that the diffraction technique measures a size parameter relevant to the clinical situation. The high degree of correlation makes laser diffraction suitable for the predictive assessment of aerosols generated by nebulization of drug solutions.

Keywords: Nebulizer; Particle size; Deposition profile

1. Introduction

Pneumatic and ultrasonic nebulizers are increasingly used in the very young, the elderly, or the chronically sick because other forms of aerosol delivery are generally difficult for these populations to use. The concomitant increase in the number of nebulizer designs requires a reliable in vitro methodology for assessing their performance.

A variety of techniques have been used for performance assessment. For example, Smaldone et al. (1988) reported the use of the Delron DCI5 impactor to size the cloud delivered from four nebulizers used to deliver pentamidine isethionate solution. Clifford et al. (1990) used a twin-beam phase Doppler analyzer to size the cloud delivered from a number of commercially available devices. However, the relevance of some of these techniques must be questioned. For example, there are conflicting reports where the mass median aerodynamic diameter, MMAD, of the aerosol cloud delivered from the same nebulizer apparatus, using similar nebulizer solutions, differs by more than 100%. Smaldone et al. (1988) report the median droplet size generated by the Fisoneb^{TM} and the Respirgard^{TM} to be 2.5 and 0.8 μm, respectively, whereas Thomas et al. (1991a) reported values of 5.2 and 2.1 μm. Both groups were investigating the atomization of pentamidine isethionate solutions. The cause of these difficulties would appear to be the volatile nature of the aqueous droplets generated by nebulizers. The droplets are initially generated inside the atomization chamber of the nebulizer where they are in pseudo-equilibrium with the vapor phase above the re-circulating solution. Immediately on leaving the confines of the nebulizer chamber,

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and exiting the nebulizer mouthpiece, they are exposed to a lower humidity and a higher temperature environment and they start to undergo evaporative loss. As they do so the median droplet diameter of the aerosol cloud changes (Porstendorfer and Gebhart, 1977; Phipps et al., 1987; Gonda and Phipps, 1990). Ultimately, since nebulizer solutions invariably contain dissolved, or suspended, solids, a residual dry powder aerosol is formed. The measurement of the size distribution of the aerosol cloud can therefore take place at any one of a number of indeterminate hydration states and the MMAD obtained can depend on the geometry of the sizing apparatus and the prevailing laboratory conditions.

Because of these difficulties, a large number of investigators have used diffraction analysis for the assessment of nebulizer clouds. The diffraction analyzer offers numerous advantages over the impaction approach. For example, the cloud can be sized at the exit from the mouthpiece before any appreciable evaporation can take place. It therefore determines the 'true' droplet size which would enter the respiratory tract of a patient. It is also much faster than the impaction technique and no chemical or gravimetric determinations of aerosol mass are required. Significantly, the diffraction technique has been used concomitantly in a number of gamma scintigraphy studies (see Table 1). It is therefore possible to develop correlations between diffraction-derived size distributions and deposition profiles.

It is the purpose of this paper to report in vitro investigations into the robustness of the laser diffraction technique, to present data comparing it with the impaction techniques and, with the aid of the published results, to demonstrate that the diffraction technique measures a size parameter which correlates with in vivo deposition patterns. The agreement between the measured deposition patterns and those predicted by the application of a semi-empirical deposition model (Rudolph, 1990) will also be discussed.

2. In vitro validation of the laser diffraction technique

The in vitro investigations were divided into two groups, those designed to assess the robustness of the diffraction technique as applied to nebulizer clouds and those designed to compare the diffraction technique with the more conventional impactor approach. A laser diffraction instrument (MasterSizer X, Malvern Instruments, Malvern, U.K.) and an eight-stage inertial impactor (Non-viable sampler, Andersen Inc., Atlanta, GA) were used throughout.

In the first of these experiments the effect of the optical model (refractive index values) and the positioning of the nebulizer mouthpiece were investigated. The investigations were carried out using both a 'coarse' and a 'fine' droplet size distribution; nominally 6.5 and 2.5 μm volume

Table 1
Summary of studies investigating deposition profiles from medical nebulisers in which diffraction analysis was used to determine droplet size

Authors	Subjects		Nebulisers
	Type	Number	
Clay and Clarke (1987)	mild asthmatics	6	Turret, Up-mist, Inspiron mini-Neb
Ho et al. (1988)	healthy volunteers	10	Turret, Cirrus, Bennett, Neb-U-Mist, Inspiron, Hudson
Johnson et al. (1989)	chronic asthmatics	8	Turret, Bard Inspiron
O'Doherty et al. (1990)	AIDS patients	9	System 22 Mizer, Respirgard II
Thomas et al. (1991a)	AIDS patients	12	Respirgard II, Centimist, System 22 Mizer, Mizer/separator, Mizer/Optimist, Fisoneb, Portasonic, Samsonic
Thomas et al. (1991b)	cystic fibrosis patients	8	System 22, Fisoneb
Hardy et al. (1993)	healthy volunteers	10	Pari Boy, Pari IS-2 Pentasonic, Respiragard II

median diameter (VMD) and 2.2 geometric standard deviation as measured by the Malvern analyzer. These particular aerosol sizes were chosen because they represent the extremes of the VMDs generated by most medical nebulisers (Cipolla et al., 1994).

In the second group of experiments, a comparison of the MMAD measured by the Andersen impactor and the VMD measured laser diffraction analyzer was made. In order to avoid the complex factors associated with droplet evaporation, a non-volatile aerosol of dibutyl phthalate (Aldrich Chemical Co., Milwaukee, U.S.A.) was used.

3. Methods

3.1. Positional experiments

The experimental configuration is presented in Fig. 1. The mouthpiece exit of the nebulizer was initially positioned according to the instrument manufacturer's recommendation; at the maximum X position to avoid vignetting (loss of light scattered at large angles) and at the minimum Y position that would avoid the mouthpiece interfering with the expanded laser beam (20 mm from the lens face and 23 mm from the laser beam axis, respectively). Using normal saline as the droplet medium and a 100 mm receiving lens, the diffraction pattern was averaged over 5000 sweeps (10 s) of the diffraction detector elements. In all cases, inversion of the diffraction pattern was carried out using a model independent fitting routine (Software version BD.01, Malvern Instruments, Malvern, U.K.) and using a value of the real part of the complex refractive index as measured by an Abbe refractometer ($n = 1.33$). For the positional investigations the complex part of the refractive index (absorption) was assumed to be zero (see below). [Mie scattering theory uses complex numbers to represent the refractive index of a material. The real part of the 'complex refractive index' represents the refractive properties of the material, the imaginary part of the complex refractive index represents the absorptive properties of the material. Optical absorption

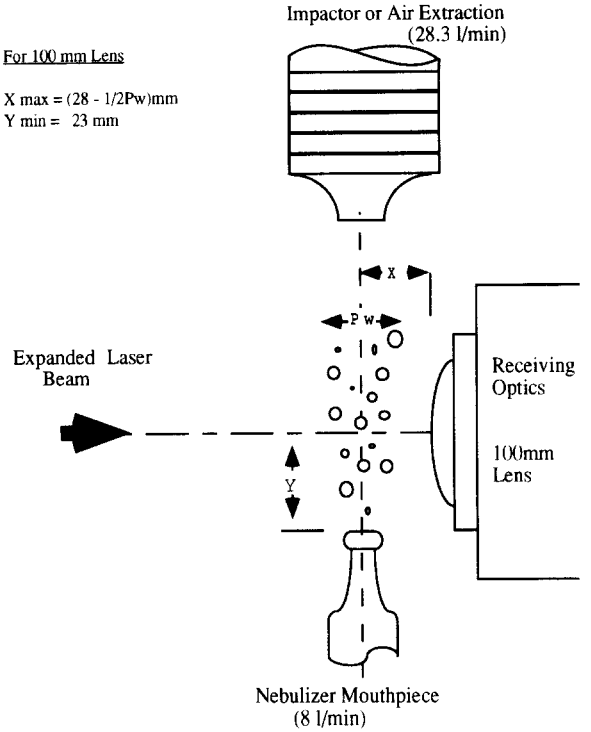

Fig. 1. Experimental configuration for positional and impactor correlation experiments.

in the present context represents the complex component of the refractive index and it is essentially the extinction coefficient of the liquid at the wavelength of the incident laser beam (Kerker, 1969).] After measuring the size distribution in this 'initial' position further measurements were made at a number of X and Y positions. Air extraction (HS3000A, Airfiltronix, Congers, NY) at the rear of the laser sensing zone was employed so as to ensure that the aerosol droplets did not re-enter the laser beam.

3.2. Refractive index

In order to investigate the effect of refractive index a number of computations were performed using the same base diffraction data, but adopting differing values of optical absorption. The computations were performed in this manner because the real part of the complex refractive index of the nebulizer liquid can be assumed to

be fairly close to that of water ($n = 1.33$). The absorption, however, has to be measured experimentally using the bulk liquid and the true absorption of the droplets may be affected by scattering caused by impurities and imperfections on the droplet surface. The diffraction data used for the computations was that generated in initial nebulizer position. Computations were performed using data from both the coarse and fine aerosols.

3.3. Correlation between laser diffraction and inertial impaction

The experimental configuration for the comparative studies is as shown in Fig. 1. The experimental procedure involved the simultaneous measurement of the droplet size distribution of a dibutyl phthalate aerosol, generated from a variety of different jet nebulizers, by the diffraction analyzer and the Andersen impactor. Dibutyl phthalate was chosen because of its low volatility and because a simple UV assay could be used to determine the mass deposited on the stage plates of the impactor. The necessity of using a non-volatile liquid can be seen by reference to the work of Ho et al. (1986) where they showed that an impactor will underestimate median droplet sizes if volatile aqueous aerosols are used for comparative purposes.

The aerosol was passed directly through the Malvern laser beam and drawn into the Andersen impactor. The cloud was measured and the diffraction data averaged by the Malvern during the whole of the sampling period of the Andersen impactor (approx. 10–15 s). The sampling period was chosen to ensure collection of sufficient aerosol for UV spectrophotometric assay without overloading the Andersen stage plates. The impactor was operated at a flow rate of 28.3 l per min and stainless-steel collection plates were used throughout. As with the robustness studies re-

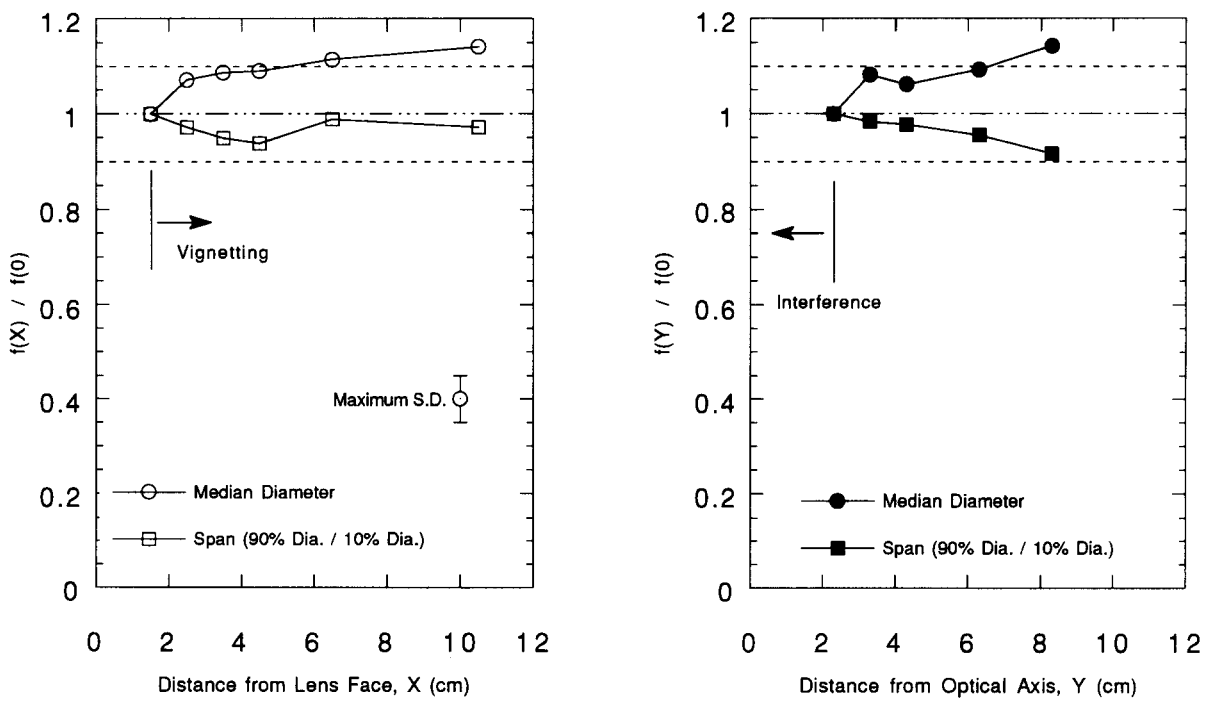

Fig. 2. Effect of plume position upon the calculated median diameter and span for a coarse aerosol of normal saline. (a) Effect of lens face to cloud axis distance upon median droplet diameter and span (median diameter 6.5 μm, span 1.8). (b) Effect of the distance between the optical axis and the mouthpiece exit (median diameter 6.5 μm, span 1.8).

ported above, a 100 mm lens was used for the Fourier collection optics of the Malvern instrument.

The dibutyl phthalate retained on each impaction stage was determined by quantitatively washing each stage plate, and preceding impaction jets, with isopropyl alcohol and measuring the absorbance of the resulting solution at a wavelength of 276 nm. Prior calibration showed that absorbance was linearly related to concentration with an absorptivity of 3.87 cm^{-1} $(mg/ml)^{-1}$ ($r^2 = 0.997$, $n = 12$, over the concentration range 0.01–0.4 mg/ml).

Nine experiments were performed using a variety of nebulizers to generate aerosols with MMDs in the range 2–6.5 μm. The aerosols were all polydispersed and had similar spans (the quotient of the 90% undersize diameter − 10% undersize diameter and the 50% undersize diameter) and geometric standard deviation (σ_g) values (typically 1.8 and 2.3, respectively).

4. Results

4.1. Robustness

The data from the positional experiments are summarized in Fig. 2a and b (coarse aerosol) and 3a and b (fine aerosol). The ordinate is the distance between the nebulizer mouthpiece and the lens face, and the mouthpiece and optical axis, respectively. The abscissa is the ratio of the VMD (volume median diameter) or span measured at position X, Y to that obtained in the initial position ($X = 20$ mm, $Y = 23$ mm). Fig. 2a and 3a show the maximum standard deviation observed at any single position. The standard deviations were independent of position. Also shown are the $\pm 10\%$ levels based on the values obtained at the initial position.

It can be seen from Fig. 2 and 3 that as the distance from the lens face (X) is increased, the computed VMDs increase and the computed

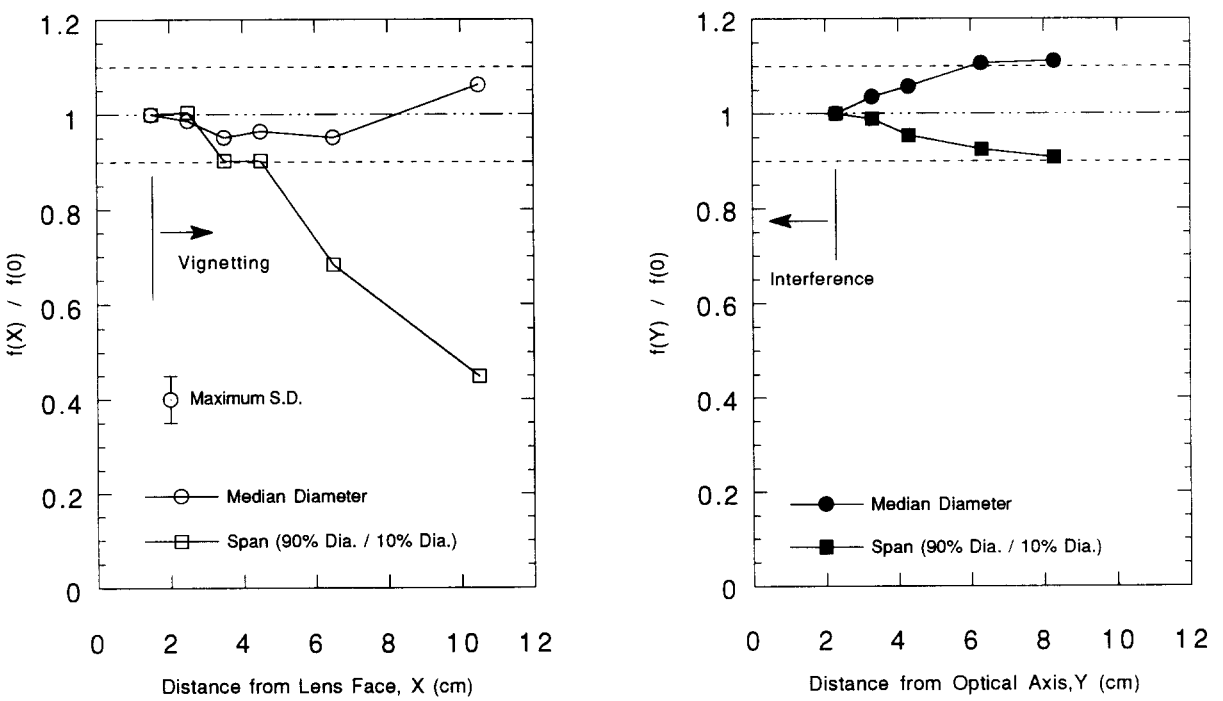

Fig. 3. Effect of plume position upon the calculated median diameter and span for a fine aerosol of normal saline. (a) Effect of lens face to cloud axis distance upon median droplet diameter and span (median diameter 2.5 μm, span 1.75). (b) Effect of the distance between the optical axis and the mouthpiece exit (median diameter 2.5 μm, span 1.75).

spans decrease. In other words, the calculated distribution becomes coarser and narrower. As would be expected the narrowing of the distribution as the distance from the lens face is increased is far more pronounced for the fine aerosol. This is so because; (i) the fine droplets are detected by light scattered at large angles; and (ii) vignetting, or loss of this light at high scattering angles, occurs increasingly with increasing lens to plume spacing. The effect is more marked for the fine aerosol because the computation of its size distribution relies more heavily on the light scattered at larger angles.

It can also be seen from Fig. 2 and 3 that the droplet distribution becomes coarser and narrower as the distance from the optical axis (Y) is increased. In this case, however, the cause is undoubtedly differential evaporation leading to a preferential loss of 'finer' droplets (Porstendorfer and Gebhart, 1977).

These data suggest that it is important to position the nebulizer mouthpiece within the working distance of the lens and as close to the optical axis of the instrument as possible. However, reference to the maximum standard deviation error bars shown in Fig. 2a and 3a shows that changes in the computed size distributions due to position are in fact quite comparable to the experimental variation between measurements at a single position, provided reasonable effort is made to work within the appropriate positional range.

For both aerosols the errors remain within 10% when the mouthpiece is positioned within 4–6 cm of the optical axis and lens face. These results demonstrate that data obtained from the diffraction instrument are fairly robust with respect to position.

Fig. 4 is a normalized plot showing the effect of increased optical absorption upon the computed median droplet diameter and the span of the size distributions for the coarse and fine aerosols. It can be seen that considerable absorption, greater then 10%, has to be assumed before the optical properties have a large affect upon the computed distributions. Most medical nebulizer solutions do not absorb light at the wavelength of the laser used in the diffraction apparatus ($\lambda = 640$ nm); therefore, Fig. 4 again confirms the robustness of the data generated from the diffraction analyzer.

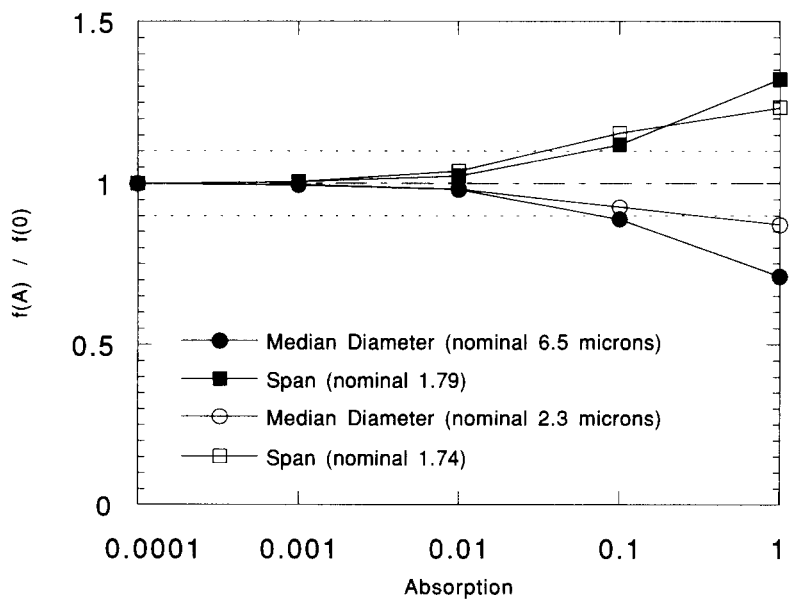

Fig. 4. Effect of absorption upon the calculated median diameter and span for a coarse and fine aerosol.

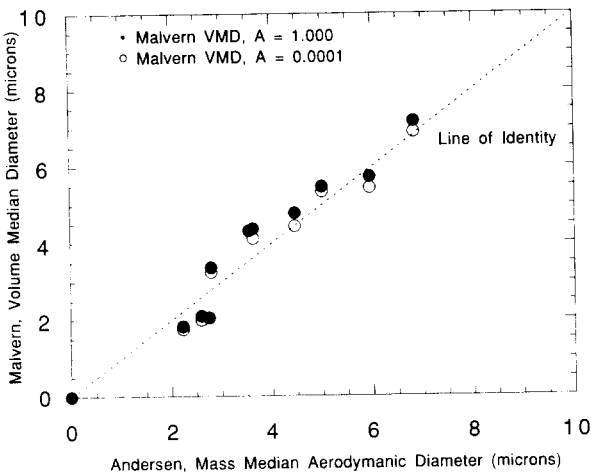

Fig. 5. Comparison of the median diameter obtained from the Andersen impactor and the Malvern Mastersizer using aerosols of dibutyl phthalate.

4.2. Equivalence of VMD as measured by the Malvern Mastersizer to MMAD measured by the Andersen impactor

Fig. 5 presents a plot of the MMAD determined by the Andersen impactor vs the VMD determined by the Malvern Mastersizer. Two computed diameters are shown for each Malvern determination, one assuming an optical absorption of 10^{-3}, the other assuming an absorption of 1. In contrast to the data using saline aerosol, presented above, it can be seen that the computed diameters show very little dependence upon absorption. This is so because the absorption term of the complex refractive index is less important for higher real refractive index droplet (scattering is proportional to the square of the absolute value of the sum of the real and imaginary parts of the refractive index). It can be seen from Fig. 5 that the agreement between the two methods is excellent. However, this agreement should perhaps not be viewed as too surprising: the droplets measured by the Malvern are nearly spherical, due to their small size and the relatively high surface tension, the cloud is homogeneous and the density of dibutyl phthalate is approx. 1. These factors lead to the theoretical and practical equivalence of MMAD and VMD.

Unfortunately, it did not prove possible during the experiments to vary the σ_g or span of the aerosols independently of the MMAD, and so no direct effect of varying the width of the aerosol distribution could be studied. However, the clouds generated by medical nebulizers are polysdisperse with σ_g values and spans very similar to those studied above. It is therefore believed that, despite the fact that the data was obtained with a higher refractive index medium than most drug solutions, the correlation presented in Fig. 5 is generally applicable to the measurement of the aqueous droplets generated by medical nebulizers. The size distribution determined by the diffraction analyzer at any particular instance should therefore be equivalent to the aerodynamic size distribution. Further, if the size distribution is measured close to the mouthpiece of the nebulizer the distribution should reflect the aerodynamic size distribution of the inhaled aerosol.

5. Conclusions and discussion

The validation experiments reported above have demonstrated that the diffraction technique is robust and determines, at least for a non-volatile aerosol, a diameter which is equivalent to MMAD. Since it can also measure droplets close to their point of generation, i.e. at the exit of the mouthpiece of the nebulizer before appreciable evaporation can occur, it should be ideal for characterizing the clouds delivered by medical nebulizers.

However, it remains, to be shown that a diameter measured in this way has a relevance to the clinical situation. The data to demonstrate this fact can be found in the published literature. A number of investigators have used gamma camera techniques to evaluate the deposition fraction and deposition profiles of the aerosols delivered from nebulizer devices. Some have also used the diffraction technique to assess the droplet size produced by the nebulizer that they tested. If the diffraction technique does indeed measure a clinically relevant size parameter, it would be expected that a correlation would be found between

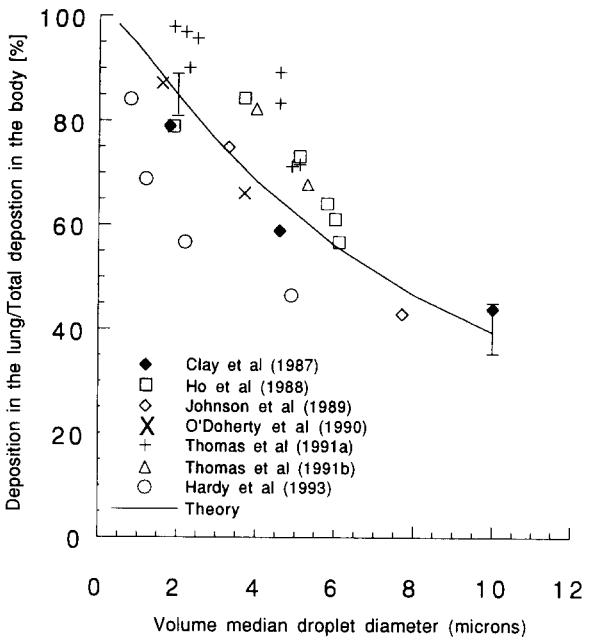

Fig. 6. Correlation between the volume median diameter of a nebuliser cloud, measured by laser diffraction analyser, and % thoracic deposition.

the deposition results and the diffraction derived droplet sizes.

Table 1 lists deposition studies where both deposition and diffraction droplet sizes were obtained. The main problem with these studies is that the deposition fractions are presented in different ways and it is therefore very difficult to find a common way of expressing the data. For example, Clay and Clarke (1987) summarize their data as lung deposition as percentage of the total deposition in the body, whereas O'Doherty et al. (1990) summarize their data in terms of the percentages of the total dose placed in the nebulizer. Clay and Clarke's presentation turns out to be the only common form in which the collective data can be expressed. Fig. 6 therefore presents a plot of the percentage of aerosol deposited in the lung as a percentage of that deposited in the body versus the volume median diameter of the inhaled aerosol for all the studies listed in Table 1. It can clearly be seen that a good correlation exists between the VMD, as measured by Malvern analyzer, and the percent depositing in the thoracic region. This correlation may, at first sight, be quite surprising since the volunteers in these studies possessed varying degrees of airways obstruction. However, since the data represents the fractionation of the cloud between the oropharynx and the lung, it is quite consistent, in that diseased airways would not be expected to have a major effect upon oropharyngeal filtering. The theoretical line presented in the figure was calculated using the empirical model described by Rudolph et al. (1990). For the purpose of calculation the aerosols generated by the nebulizers were assumed to be log normal with a standard deviation of 2.2. Sensitivity calculations using a range of MMDs and σ_g values showed that geometric standard deviations in the range 2–2.5 have very little effect on the calculated deposition fractions. The best fit to the deposition data was obtained by assuming a tidal volume of 1000 ml and an inhalation flow rate of 300 ml/s. (It should be noted that the actual breathing patterns used in the cited studies could not be used for the calculations because they were not reported. However, the above best fit pattern would seem reasonable.) Also shown in Fig. 6 is the magnitude of the effect of varying the inhalation flow rate by ± 100 ml/s and the tidal volume by ± 250 ml. It will be seen that the magnitude compares favorably with the spread in the experimental data. It should also be remembered that large intersubject variability would be expected (Rudolph, 1990).

Also of interest would have been the correlation between VMD and the deposition profile within the lung. However, the data presented in the above papers were obtained using different definitions of penetration index. As with total thoracic deposition, it was therefore difficult to find a common method of data presentation. For this reason Fig. 7 shows only the alveolar deposition fraction as a function of VMD as determined by Thomas et al. (1991a). Thomas et al. used 24 h retention of ^{99m}Tc colloidal human serum albumin. The theoretical line shown in Fig. 7 was calculated using the model and parameters described above. It can be seen that there is very good agreement. This agreement however, should perhaps not be viewed as to surprising since the data used to develop the semi-empirical deposi-

tion model of Rudolph were derived using 24 h retention data. However, the data do stress the value of the droplet size data obtained using the diffraction technique.

It may be noted here that despite the problems with data interpretation encountered in the above analysis, it is still interesting to compare the penetration index (PI) measurements. For example, in mild asthmatics (Johnson et al., 1989) and in 'healthy' AIDS patients all of the PI measurements were close, or relatively close, to 1. With the cystic fibrosis patients (Thomas et al., 1991b), however, the PIs were of the order of 4. While this may in part be due to differences in the definition of PI between the studies, some of the difference is undoubtedly due to high central airways deposition caused by the high degree of airway obstruction experienced by the CF volunteers. This conclusion emphasizes the fact that the alveolar correlation reported above is only directly applicable to normal airways or airways with very limited obstruction.

Having 'validated' the relationship between the diffraction derived size distribution, the gamma camera deposition profiles and the Rudoph model it is instructive to draw some conclusions from the full predictions of the empirical model. Fig. 8 presents the calculated deposition fraction, in the oropharynx, the conducting airways and the alveolar region of the lung, as a fraction of the inhaled dose. The calculations were performed for aerosols with median diameters ranging from 0.5 to 10 μm and a geometric standard deviation of 2.2. It will be seen that oropharyngeal deposition decreases monotonically with decreasing median diameter, falling from 60% of the inhaled dose at 10 μm to nearly zero at 1 μm. Central airway deposition peaks at 6–7 μm and peripheral airway deposition at 2–3 μm. It can be seen that from 10 μm down to 4 μm the increased lung deposition as a fraction of the dose deposited in the body (Fig. 6) is the result of decreasing oropharyngeal deposition and increasing lung deposition. However, below 4 μm total lung deposition decreases and the continued increase in lung fraction is the result of decreasing oropharyngeal deposition only. Peripheral airway deposition shows a similar trend, but the size dependency is enhanced by decreasing central airway deposition below 6–7 μm. It is interesting

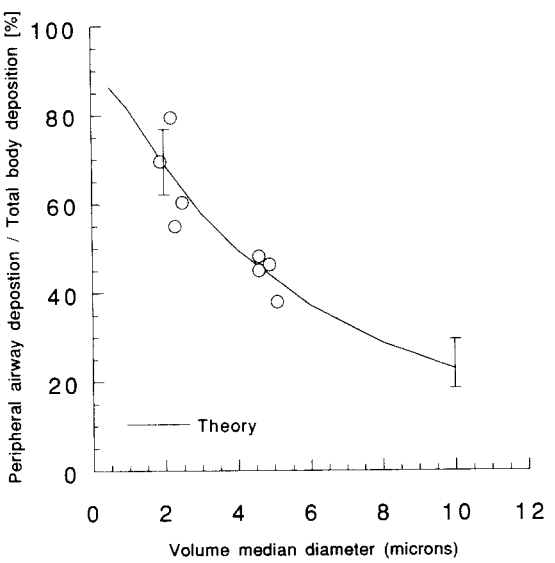

Fig. 7. Peripheral airway deposition from a nebuliser cloud as a function of volume median diameter as measured by laser diffraction analyser (as determined by Thomas et al. (1991b) using 24 h retention of ^{99m}Tc-labeled human serum albumin).

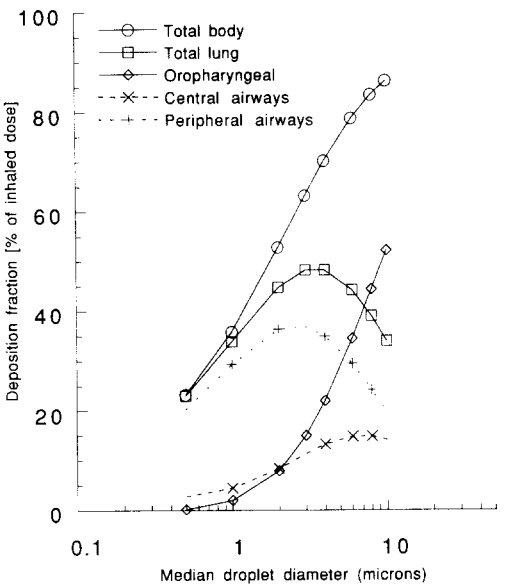

Fig. 8. Deposition profiles for an inhaled nebulizer cloud with a geometric standard deviation of 2.2 as predicted by an empirical deposition model (Rudolph et al., 1990).

to note that dose reaching the peripheral airways, as a fraction of that inhaled, varies by less than 8% over the median droplet diameter range 1–5 μm. That is to say, over this size range the dose deposited in the peripheral airway is only weakly dependent upon median droplet diameter. The cause of the increase in peripheral airway deposition fraction (Fig. 7) is therefore the reduction in both oropharyngeal and central airway deposition and not an increase in the dose deposited in the peripheral airways. With large median diameter the aerosol is deposited in the mouth wereas with small median diameters a high proportion of the aerosol is exhaled. It would appear that the main benefit of using aerosols with median diameters smaller than 5 μm is to reduce oropharyngeal and central airway deposition. This could be important for drugs such as corticosteroids whose upper and central airway deposition is associated with adverse reactions. In healthy airways using fine aerosols will not increase the dose reaching the lower airways. Of course, it may also be necessary to use fine aerosols when a high degree of airway obstruction is present since the curves presented in Fig. 8 would be moved to the left by higher impaction in the cental upper airways of these patients.

Finally, it should be remembered that the above discussion relates to lung deposition as a function of the inhaled dose. Obviously, in order to apply the full predictive power of the diffraction methodology/empirical model, a reliable method of measuring the inhaled dose that would be delivered from a nebuliser must be developed.

In summary, it has been demonstrated that the laser diffraction technique is both a robust and reliable method for determining the droplet size of the aerosol clouds delivered from medical nebulizers. The correlation found between this method and both theoretical and in vivo deposition patterns makes laser diffraction a suitable tool for the assessment of aerosols generated by nebulization of drug solutions.

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