International Journal of Pharmaceutics, 1 (1978) 303–314

Research Papers

PHYSICO-CHEMICAL STUDIES ON AEROSOL SOLUTIONS FOR DRUG DELIVERY III. THE EFFECT OF RELATIVE HUMIDITY ON THE PARTICLE SIZE OF INHALATION AEROSOLS

S.S. DAVIS and M.D. BUBB

Department of Pharmacy, University of Nottingham, University Park, Nottingham NG7 2RD (England)

(Received February 13th, 1978)
(Accepted March 4th, 1978)

SUMMARY

The change in size of aerosol solution particles has been investigated for various humidity conditions at 37°C. The systems studied were water, 20% v/v and 50% v/v propylene glycol in water. Particle size, as determined by cascade impactor, was dependent on relative humidity; the greater the humidity the larger the measured size. The implications of the results for quality control procedures and drug formulation are discussed.

INTRODUCTION

Davis et al. (1978) have described recently the characteristics of aerosols produced from propylene glycol–alcohol–water mixtures. A Venturi-jet blast nebulizer was used and particle size analysis was conducted using a cascade impactor. The ambient laboratory conditions were employed for such measurements: about 20°C and 50–60% relative humidity. When an aerosol is used for the administration of a drug substance the conditions the aerosol will meet within the respiratory tract will be far from those of the laboratory, and current opinion suggests that below the subglottic region the air is at 37°C and at a relative humidity of 99.0–99.8% (Porstendorfer, 1971). Under such conditions hygroscopic aerosol particles will grow in size until the vapour pressure exerted by the droplets equals the vapour pressure of water in the lung (Orr et al., 1958).

If the particle is solid then a dissolution process will also occur. For example, according to the calculations of Zebel (1956) solid sodium chloride particles of radius 0.1 μm increase in size by a factor of approximately 5 at a relative humidity of 99% and by a factor of about 7 at 99.8% relative humidity. Even small non-hygroscopic particles such as carbon black and tobacco smoke can grow by 3–5 fold (Yoshida et al., 1976). These changes in particle size occur very rapidly. The rate of particle growth under sudden

change of moisture content has been investigated by Zebel (1956) and Milburn et al. (1957). They were able to show that the increase in size of small particles upon change of relative humidity was almost complete during the predicted time of residence for a particle in the trachea under normal breathing (75 ms). Yoshida et al. (1976), more recently, have shown, using ultramicroscopic size analysis, that stearic acid and carbon black particles transferred to a supersaturated water atmosphere ranged from a mean size of 0.75 μm and 0.47 μm, respectively, to 1.61 μm and 1.26 μm in 1 ms. Complete growth occurred in less than 1 sec whereupon the final particle sizes were 3.10 and 3.95 μm, respectively.

The rate of growth of hygroscopic particles in high humidity conditions (or for that matter the reversal process of evaporation) is difficult to predict although sophisticated theories and calculations have been presented, especially in the fields of meteorology (Crider et al., 1956; Houghton, 1933), health physics (Green and Lane, 1964) and spray drying (Ranz and Marshall, 1952). Interestingly it has been shown that the rate of particle shrinkage (or growth) is proportional to the diameter of the particle rather than the surface area (Houghton, 1933). Small pure water droplets present an interesting case. These will shrink in size even under conditions of 100% relative humidity. This is due to the lowering of the saturation vapour pressure as the radius of curvature becomes small; the well known Kelvin effect (LaMer and Green, 1952).

The physico-chemical factors defining the rate of condensation of water upon a single droplet have been considered by Byron et al. (1977) and are subject to several perturbations characteristic of the system.

(1) Changing mole fractions of solute and solvent(s) within the droplet as water condenses at its surface.

(2) A progressive increase in temperature of the droplet as condensation occurs.

(3) The difference between the droplet vapour pressure and the vapour pressure observed over a bulk solution of identical composition will decrease with reduction in surface curvature as the droplet size increases.

(4) The boundary conditions governing gaseous diffusion of water vapour may change as the particle descends the respiratory tract.

If instead of a single particle a distribution of hygroscopic particles are considered the problem of growth rate becomes even more complex. Thus the effect of relative humidity on the particle size characteristics of propylene glycol–water systems is best examined experimentally.

EXPERIMENTAL

Materials. Distilled water from an all glass still. Propylene glycol and fluorescein from British Drug Houses.

Aerosol generation. Propylene glycol–water mixtures labelled with 0.1% fluorescein as marker were generated using a Bird Mark III micronebulizer (Bird Corporation, Palm Springs, Calif., U.S.A.). An atomization pressure of 15 psi was used throughout. This gave an air flow of 3.6 l/min through the nebulizer.

Particle size analysis. A cascade impactor, DCI-6 (Delron Research Products, Columbus, Ohio, U.S.A.) was used. This is a six stage device where aerosol samples are collected

on glass plates (Sciarra and Adelman, 1971). The apparatus was supplied calibrated by the manufacturer. For an air flow through the apparatus of 12.45 l/min the top stage collected particles greater than 32 μm. Each subsequent stage gave size levels of a factor of 2 smaller such that the last stage collected particles of 0.5 μm and above. A glass filter pad collected particles greater than 0.25 μm.

Humidity and temperature control. Good control of temperature and humidity are essential requirements when studying changes of aerosol particle size (LaMer et al., 1950). To this end all experiments were carried out inside a humidity/temperature cabinet (Weyco Climatic Cabinet, Fisons Scientific Apparatus, Loughborough).

The experimental arrangement is shown diagrammatically in Fig. 1.

The generated aerosol was fed into the top of the humidity cabinet and drawn through the cascade impactor. The air from the cascade impactor was returned to the cabinet. The cabinet was allowed to reach the required temperature/humidity readings and air was drawn through the cascade impactor to ensure that equilibrium conditions were obtained before the start of each experiment.

The relative humidity inside the cabinet was monitored continuously using a Shaw hygrometer (Shaw Moisture Meters, Bradford). The apparatus and the two probes supplied were calibrated in the usual way using saturated solutions of salts that provided known humidities at 37.0°C.

Determination of aerosol output and mass median diameter. The output of solution and vapour from the nebulizer were determined as before (Davis, 1978) by weighing the nebulizer before and after an atomization. Five ml of aerosol solution was placed in the nebulizer in all experiments. The quantity of fluorescein marker impacting at each stage in the cascade impactor was determined by measuring the fluorescence of suitable dilutions at pH 10.0 using an Aminco-Bowman spectrofluorometer (model 4-8202). The exci-

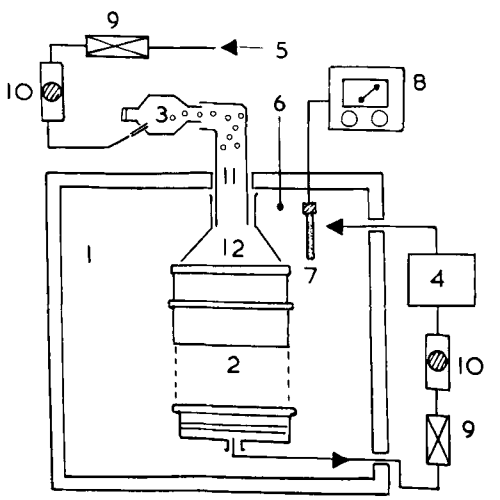


Fig. 1. Apparatus for controlled humidity studies and particle size analysis. 1, humidity cabinet; 2, cascade impactor; 3; Bird micronebulizer; 4, vacuum pump; 5, compressed air cylinder; 6, thermometer; 7, humidity probe; 8, humidity meter; 9, control values; 10, air flow meters; 11, glass throat; 12, glass cone.

tation wavelength was 492 nm and the emission wavelength was 510 nm.

The quality of fluorescein marker in the glass 'throat' and cone arrangement was also determined. All experimental determinations were performed at least twice.

The experimental data were plotted in the form of cumulative percent by weight undersize versus particle size on logarithmic-probability graph paper, since it is generally held that aerosol particles generated using an atomization device will follow a log-normal (or truncated log-normal) particle size distribution (Silverman et al., 1971). Plots are shown in Figs. 2–4. Note that the cumulative weight data refer to the quantity of fluorescein marker in particles of a given size. These data do not necessarily refer to the weight of actual aerosol particles since growth or shrinkage of the particles may have occurred before the particle impacted. The original concentration of fluorescein in the nebulization device was 0.1%; however, the concentration of fluorescein in the impacting droplet may be higher or lower than this depending upon growth or shrinkage. Thus a given quantity of fluorescein may have been delivered by a large number of droplets containing a diluted fluorescein (i.e. droplets that have grown) or by a small number of droplets of the same size range containing a concentrated fluorescein (i.e. droplets that have shrunk in size). Nonetheless, these data provide information relevant to drug therapy. In treatment we wish to know the proportion of drug contained in small particles (usually taken as 5 μm or less) (Byron et al., 1977).

The mass median diameter calculated at the 50% undersize level has been termed an apparent diameter for these reasons.

RESULTS AND DISCUSSION

The effect of relative humidity on mass median diameter

The following systems were studied: water, 20% v/v propylene glycol in water and 50% v/v propylene glycol in water at four humidities, 40, 55 (or 52.5), 70 and 100%.

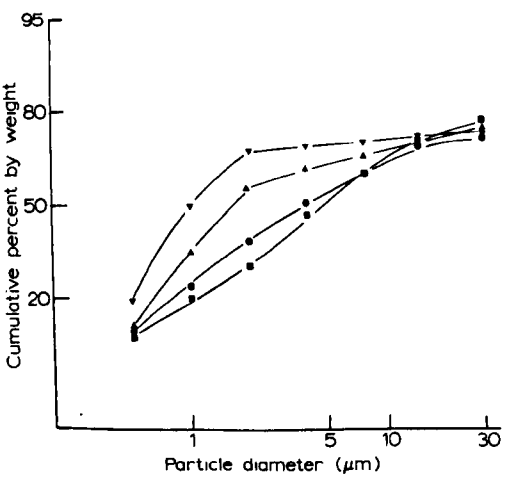


Fig. 2. Log probability plots for water aerosol at different relative humidities. Relative humidity (%): ▼, 40; ▲, 55; ●, 70; ■, 100.

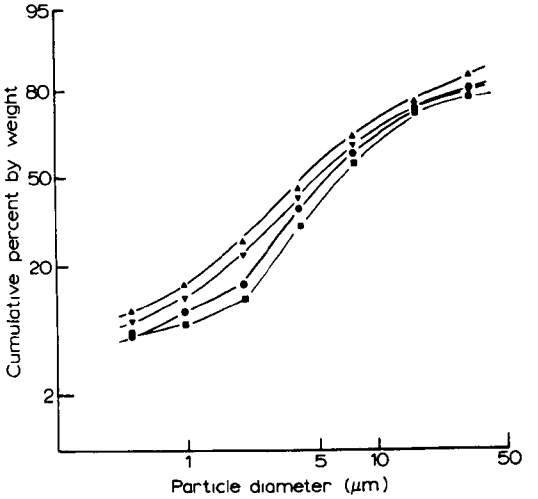


Fig. 3. Log probability plots for 20% v/v propylene glycol aerosol solution at different relative humidities. Relative humidity (%): ▼, 40; ▲, 52.5; ●, 70; ■, 100.

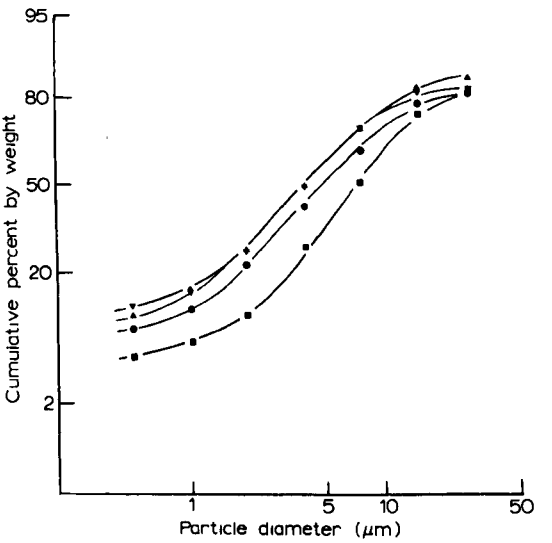
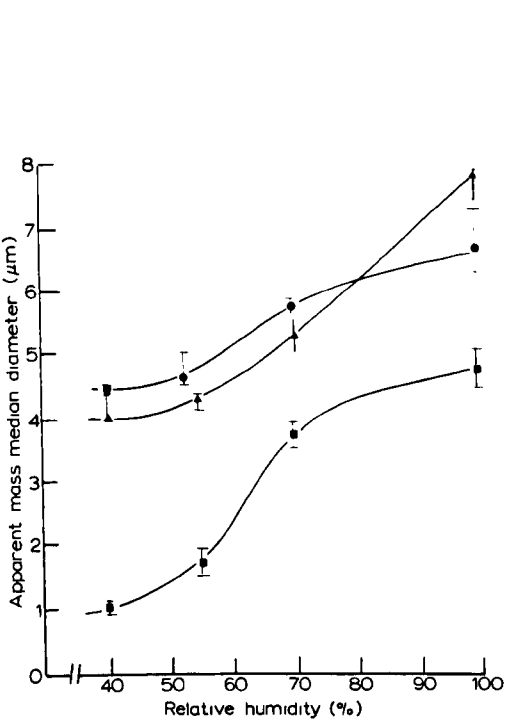


Fig. 4. Log probability plots for 50% v/v propylene glycol solution aerosol at different relative humidities. Relative humidity (%): ▼, 50; ▲, 55; ●, 70; ■, 100.

The log-probability particle size plots are given in Figs. 2–4. Each point represents an average of two determinations.

The profound effect of humidity on the measured particle size distribution is clearly demonstrated for the case of water aerosols (Fig. 2). At 100% relative humidity there will be only a slight change in the size characteristics of the aerosol and the expected log-



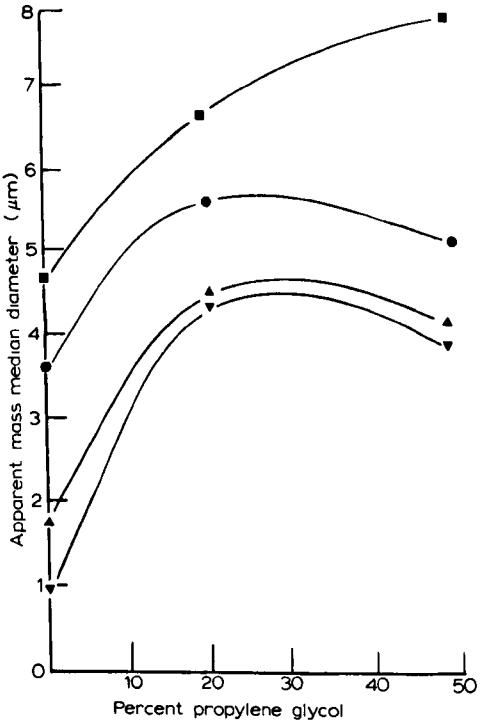


Fig. 5. The effect of relative humidity on aerosol droplet size (37°C). ■, water; ●, 20% v/v propylene glycol; ▲, 50% v/v propylene glycol.

Fig. 6. The effect of propylene glycol content on the mass median diameter at different relative humidities. Relative humidity (%): ▼, 40; ▲, 52.5/55; ●, 70; ■, 100.

normal distribution is obtained. However, at 40% relative humidity considerable particle shrinkage occurs and a highly truncated distribution results.

The change of apparent mass median diameter with relative humidity is shown in Fig. 5. A progressive decrease in measured diameter with decrease in relative humidity is observed. In laboratory investigations of particle size distribution of aerosol particles the normal ambient conditions of about 50% relative humidity and 20°C are normally employed. It is interesting to compare data obtained under such conditions with those more closely related to in vivo conditions (Fig. 6). At low relative humidities a parabolic relation between mass median diameter and propylene glycol content is obtained; however, at 100% relative humidity no maximum is observed and the larger the propylene glycol content the larger the particle size. Davis (1978) has reported that for 50% v/v propylene glycol in water 50% of the aerosol particles were below the generally accepted therapeutic limit of 5 μm. However, under conditions much closer to the 'in vivo' situation: 100% relative humidity and 37°C, only 34% of the fluorescein marker was contained in particles below the therapeutic limit (Fig. 7).

The change in aerosol particle size with relative humidity for the three systems studied can be rationalized in terms of the physical properties of the aerosol, in particular the

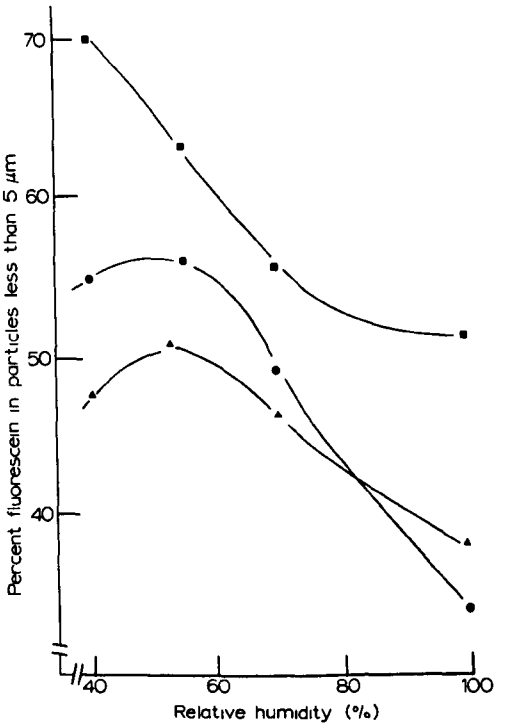


Fig. 7. The quantity of fluorescein marker in particles less than 5 μm. ■, Water; ▲, 20% v/v propylene glycol; ●, 50% v/v propylene glycol.

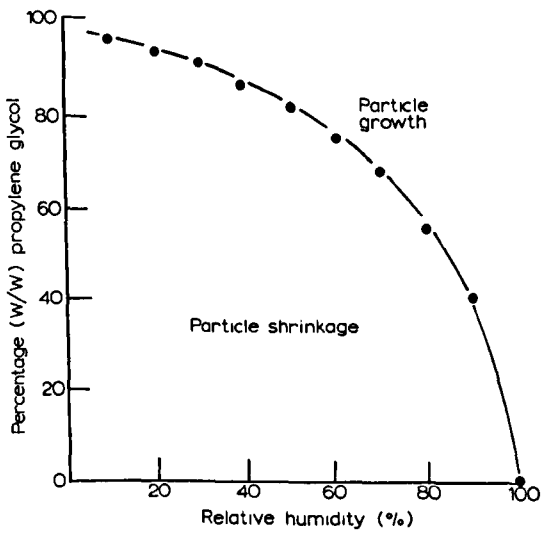


Fig. 8. Propylene glycol solutions in equilibrium with air at various humidities (37°C).

vapour pressure. From vapour pressure data (Davis et al., 1978) we can calculate the equivalent relative humidities (Fig. 8) (the vapour pressure created by a droplet would be *slightly* greater than that for a plane surface; however, such effects can be ignored if the mass mean diameter is greater than 0.5 μm).

Water droplets (formed at 20°C) will be in equilibrium with saturated vapour (100% relative humidity) at ambient temperature. Their transfer to conditions of 37°C and variable relative humidity will result in the evaporation of water from the droplets. Thus the water droplets will shrink at all humidities. At low humidities the droplets would evaporate completely if they contained pure water. However, the marker substance (0.1% fluorescein) will create a definite lowering of vapour pressure and as the droplets decrease in size the concentration of fluorescein will increase. Given sufficient time at low humidities a solid fluorescein particle would result (note, a 22-fold concentration change results when a particle changes in size from 4.7 to 1.0 μm).

It is impossible to set a limiting value for the relative humidity at which complete desiccation occurs because of its dependence on the chemical composition of the dissolved substance(s) in the droplet. In general a droplet will dry out completely when the relative humidity is less than that provided by a saturated solution of the most soluble component (Puck, 1947).

The behaviour of hygroscopic particles exposed to increasing humidity has been described nicely by Green and Lane (1964) as a series of sequential steps:

(i) the particles absorb a few molecular layers of water,

(ii) the particles dissolve to become saturated droplets and at the same time undergo an abrupt increase in size,

(iii) the droplets grow larger and more dilute. If exposed to decreasing humidity the droplets first decrease in size and, at a humidity considerably lower than that at which the particles initially dissolved, they recrystallize while undergoing an abrupt size decrease.

The aerosol droplets containing propylene glycol (20 and 50% v/v) will shrink or grow depending upon the conditions. For example, at 37°C 50% v/v propylene glycol is in equilibrium with 85% relative humidity conditions, and 20% v/v propylene glycol is in equilibrium with 95% relative humidity conditions. Thus at relative humidities below these equilibrium values the droplets will shrink whereas above these values they will grow. The growth potential for a droplet containing 50% propylene glycol will be greater than that for a droplet containing 20% propylene glycol. An aerosol droplet will grow until equilibrium conditions are reached (or when the particle is collected at an appropriate stage in the cascade impactor).

The theoretical relations between particle size at *equilibrium* and relative humidity for different propylene glycol concentrations can be computed. Fig. 9 shows such data calculated after making the following assumptions:

(i) The mean size of droplets leaving the nebulizer was 6.75 μm in all cases (other sizes can be used, indeed Davis (1978) has shown that aerosol particle size is related to propylene glycol content; however the shapes of the resultant curves will be similar).

(ii) The particles reach equilibrium conditions.

(iii) The vapour pressure of propylene glycol can be neglected.

(iv) The particle size distribution is self-preserving.

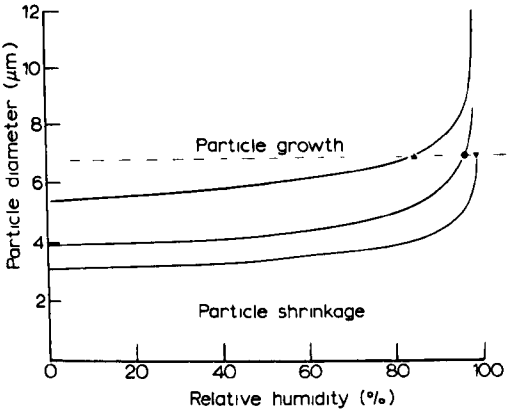


Fig. 9. Change in droplet particle size with relative humidity. Equilibrium conditions. Original droplet size taken as 6.75 μm. ▼, 10% v/v propylene glycol; ●, 20% v/v propylene glycol; ▲, 50% v/v propylene glycol.

We find that the change in size with increase in relative humidity is quite small until high relative humidities are reached, whereupon the particles grow rapidly. The ratios of mean size at ambient humidity (50%) to that at 99% relative humidity are 2.04 and 2.02 for 20 and 50% propylene glycol, respectively. These values can be compared with the experimental values of 1.54 and 1.85.

It should be noted that the rapid change of particle size at high relative humidity creates obvious experimental problems. Experimental values of 99 or 100% relative humidity are difficult to measure accurately to ±1%; however, in this region a difference of 1% in relative humidity can have a marked effect on resultant particle size. An alternative approach would be to measure the aerosol droplet size at various humidities at equilibrium. Using these values it would be possible to calculate particle sizes at other relative humidities provided that the relevant vapour pressure data were available.

Studies on equilibration

Attempts have been made to determine if the particle size of an aerosol system would change if the aerosol was allowed to equilibrate before particle size analysis. An equilibration chamber was constructed. This replaced the glass cone used previously. Humid air gained access to the chamber from the climatic cabinet via a small tube immediately above the chamber. The humidity in the chamber was measured using a small humidity sensor.

For equilibration studies the nebulizer was filled with 5 ml 50% propylene glycol solution. Air at 100% relative humidity was pumped through the chamber and the impactor to allow equilibration of the apparatus. The vacuum pump was then turned off and the aerosol solution was then nebulized for 30 s. The vacuum pump was then either started immediately or 1 min later. The particle size analysis was conducted as before. The material collected in the chamber and connecting tube is referred to as the 'throat' contribution.

Log probability plots for equilibrated and non-equilibrated systems are shown in Fig. 10. The use of the equilibration chamber modifies the results obtained since a large pro-

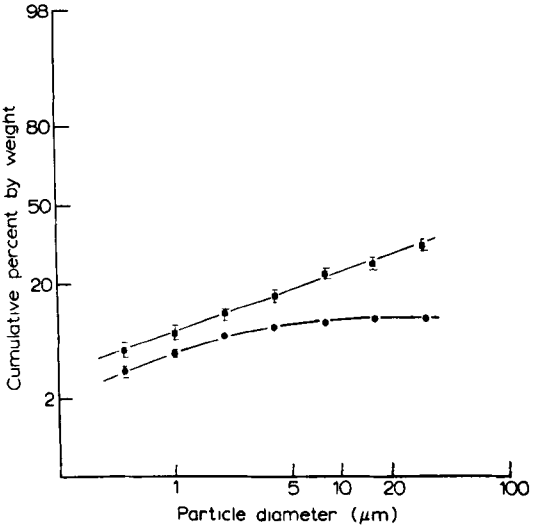


Fig. 10. The effect of 1 min equilibration on the particle size distribution of 50% v/v propylene glycol solution droplets at 100% relative humidity. ■, no equilibration; ●, equilibration.

portion of the aerosol cloud deposits in the chamber. Consequently it is not possible to determine the mass median diameters. However, at each value of particle size one finds a greater cumulative percentage for the non-equilibrated particles. For example after equilibration only 9.5% of the particles are below 5 μm, whereas 17% of the non-equilibrated particles are below this size (Fig. 11). This is as expected since a 50% propylene glycol solution will grow rapidly at 100% relative humidity.

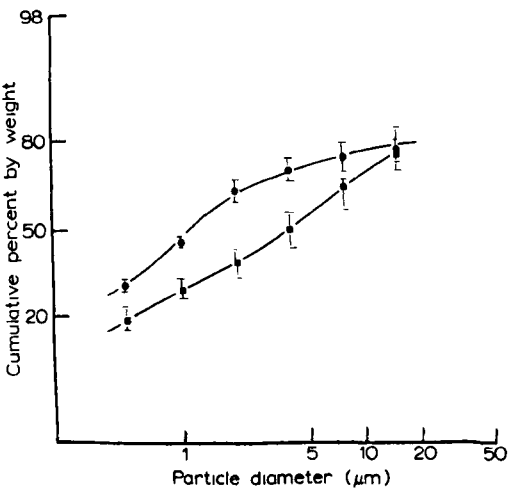


Fig. 11. The effect of 1 min equilibration on the particle size distribution of 50% v/v propylene glycol solution droplets at 100% relative humidity but throat contribution has been ignored. ■, no equilibration; ●, equilibration.

Quantitative comparisons are difficult because of the large proportion of the aerosol that settles in the equilibration chamber. If the data are analyzed ignoring the 'throat' contribution, a particle size analysis of the aerosol cloud entering the impactor is obtained (Fig. 11). For equilibration conditions the mass median diameter is 1.25 μm but for non-equilibration the mean size is greater, 4.2 μm. Thus, a large proportion of the larger particles produced by allowing equilibration for 1 min deposit in the equilibration chamber.

CONCLUSIONS

The size of nebulized aerosol particles can change considerably after atomization depending upon the nature of the aerosol and the conditions of temperature and humidity. Particle size analyses conducted under ambient laboratory conditions may not have particular relevance to the in vivo conditions within the lungs. Moreover, official standards governing the particle size distributions of inhalation aerosols such as those in the British Pharmaceutical Codex (1973) make no demands concerning experimental conditions.

The influence of particles growth warrants careful consideration when one wishes to achieve controlled penetration of the respiratory tract. If penetration into the alveolar region is desired it is essential to generate small particle size without dependence on evaporation since rehydration can occur rapidly in the upper as well as the lower respiratory tract.

We suggest that in the formulation of therapeutic aerosol systems the effects of insoluble films should be considered. It is well known that surface active agents reduce mass transfer if they can form a close packed monolayer of very low compressibility (Blank, 1964). Eisner et al. (1960) stabilized water mists, containing droplets in the size range 2–20 μm radius, using small quantities of fatty alcohol. Droplet life times were increased by factors up to several hundred depending upon ambient conditions. The effect of insoluble films upon the evaporation kinetics of liquid droplets has also been considered by Snead and Zung (1968). In the case of water droplets coated with *n*-decanol evaporation rates were as much as several hundred times slower than those of pure water droplets.

The use of such agents in drug formulations would have to be considered carefully on toxicity grounds but one should not ignore the possibility of using natural surface active agents such as the lecithins.

ACKNOWLEDGEMENTS

The authors wish to thank the Syntex Corporation (U.S.A.) for financial support.

REFERENCES

Blank, M., An approach to the theory of monolayer permeation by gases. J. Phys. Chem. 68 (1964) 2793–2800.

British Pharmaceutical Codex, Pharmaceutical Press, London, 1973, p. 645.

Byron, P.R., Davis, S.S., Bubb, M.D. and Cooper, P., Pharmaceutical implications of particle growth at high relative humidities. Pesticide Sci., 8 (1977) 521–526.

Crider, W.L., Milburn, R.H. and Morton, S.D., The evaporation and rehydration of aqueous solutions. J. Meteorol., 13 (1956) 540–547.

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

Davis, S.S., Elson, G. and Whitmore, J., Physico-chemical studies on aerosol solutions for drug delivery II. Water–propylene glycol–ethanol systems. Int. J . Pharm., 1 (1978) 85–93.

Eisner, H.S., Quince, B.W. and Slack, C., The stabilization of water mists by insoluble monolayers. Disc. Faraday Soc., 30 (1960) 86–95.

Green, H.L. and Lane, W.R., Particulate Clouds, Dusts, Smokes and Mists. 2nd ed., Spon, London, 1964, p. 88.

Houghton, H.G., A study of the evaporation of small water drops. Physics, 4 (1933) 419–424.

LaMer, V.K. and Green, R., A direct test of Kelvin's equation connecting vapor pressure and radius of curvature. Trans. Faraday Soc., 48 (1952) 410–415.

LaMer, V.K., Inn, E.C.Y. and Wilson, I.B., The methods of forming, detecting and measuring the size and concentration of liquid aerosols in the size range of 0.01 to 0.25 microns diameter. J. Colloid Interface Sci., 5 (1950) 471–496.

Milburn, R.H., Crider, W.L. and Morton, S.D., Retention of hygroscopic dusts in human lungs. A.M.A. Arch. Int. Health, 15 (1957) 59–62.

Orr, C., Hurd, F. and Corbett, W.J., Aerosol size and relative humidity. J. Colloid Interface Sci., 13 (1958) 472–482.

Porstendorfer, J., Untersuchungen zur Frage des Wachstums von inhalierten Aerosolteilchen im Atemtrakt. Aerosol Sci., 2 (1971) 73–79.

Puck, T.T., The mechanism of aerial disinfection by glycols and other chemical agents II. An analysis of the factors governing the efficiency of chemical disinfection of the air. J. Exp. Med., 85 (1947) 741–757.

Ranz, W.E. and Marshall, W.R., Evaporation from drops. Chem. Eng. Progress, 48 (1952) 141–146, 173–180.

Sciarra, J.J. and Adelman, D., Determination of particle size of selected aerosol cosmetics II. Cascade impactor. J. Soc. Cosmet. Chem., 22 (1971) 867–877.

Silverman, L., Billings, C.E. and First, M.W., Particle Size Analysis in Industrial Hygiene. Academic Press, New York, 1971, p. 237.

Snead, C.C. and Zung, J.T., The effects of insoluble films upon the evaporation kinetics of liquid droplets. J. Colloid Interface Sci., 27 (1968) 25–31.

Yoshida, T., Kousaka, Y. and Okuyama, K., Growth of aerosol particles by condensation. Ind. Eng. Chem. (Fund), 15 (1976) 37–41.

Zebel, G., Growth and growth velocities of aerosols of soluble substances. Aerosolforsch. Ther., 5 (1956) 263–288.