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PHYSICO-CHEMICAL STUDIES ON AEROSOL SOLUTIONS FOR DRUG DELIVERY I. WATER–PROPYLENE GLYCOL SYSTEMS

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SUMMARY

The aerosolization characteristics of two commercial nebulizers have been examined using propylene glycol–water systems. The output of aerosol solution droplets passed through a maximum at 30% v/v propylene glycol; however, an increased output was parallelled by an increased particle size. The quantity of aerosol solution in particles below an arbitrary therapeutic limit of 5 μm was calculated. Viscosity and surface tension were considered to be the two important physico-chemical variables that determine aerosol characteristics. The use of propylene glycol–water vehicles to deliver a dose of a test steroid is considered.

INTRODUCTION

Drugs may be administered by aerosol in a variety of disease conditions, but with few exceptions the therapy is for local rather than systemic effect. Pressure pack devices containing fluorocarbon propellants are widely employed; nevertheless, there is also interest in other forms of aerosol generation, in particular compressed air nebulizers and their use with intermittant positive pressure breathing (IPPB) machines. The present studies were prompted by the need to administer a steroidal compound to the lungs using a conventional nebulizer. The effects of formulation on the output of aerosol particles from two commercial nebulizers and the importance of the various physico-chemical factors (viscosity, surface tension, vapour pressure) have been studied. This first paper will examine water–propylene glycol systems. The second paper will consider propylene glycol–water–ethanol systems and a subsequent publication will describe the effect of relative humidity on particle size and particle deposition.

The properties of pharmaceutical aerosols have been reviewed recently by various authors (Aiache, 1973; Gorman and Hall, 1973; Greene, 1971) and the more general aspects of aerosol science may be found in the standard texts (Dautrebande, 1962; Mercer, 1973; Silverman et al., 1971). Other valuable information about the generation of

small liquid droplets is provided in chemical engineering literature under spray drying (Marshall, 1954; Masters, 1972).

An aerosol for the use in delivering drug substances to the lungs must be of a suitable particle size; however, the published literature and compendial standards are somewhat vague on this point. Most workers have taken an equivalent diameter * of 5 μm as an arbitrary therapeutic limit. Particles below this size will reach the lower airways and will be deposited, provided there is sufficient time for impaction. Very small particles will be exhaled if the subject is breathing normally; however, with the use of medication, patients are normally instructed to take and hold a deep breath. In such a situation all but the very smallest particles will be deposited.

The growth or shrinkage of liquid aerosol droplets in the lungs may be controlled by the addition of solutes that alter the vapour pressure of the system; for example sodium chloride and propylene glycol. Workers concerned with the treatment of cystic fibrosis using mist-tent therapy and administration of water aerosols have discussed such factors at length (Bau et al., 1971; Wolfsdorf et al., 1969). Propylene glycol has also been used widely in aerosol solutions for drug delivery. Dautrebande (1962) has considered the use of propylene glycol and has compared it with glycerol. He concluded that unlike glycerol, propylene glycol was not irritating and did not constrict the airways even when used undiluted with water. Propylene glycol also has the advantage of being a good solvent for a variety of drug species, especially steroidal materials.

The particle size analysis of aerosol systems may be carried out using a variety of techniques ranging from simple impactors or impingers through to laser light scattering and holography (Silverman et al., 1971). However, in all cases one is sizing the aerosol some time after it has left the atomatization device. Moreover, the sizes determined under laboratory conditions may not have direct relevance to the final sizes under the ambient conditions in the lungs.

In the present studies a cascade impactor was used to investigate the particle size distribution of water–propylene glycol aerosols.

The requirements for an aerosol solution for administering drugs using a nebulizer are as follows:

(1) good solubility of the drug in the vehicle;

(2) small dose volume; and

(3) rapid administration.

The important physico-chemical variables have been investigated using two nebulizers and propylene glycol–water mixtures from 0 to 60% v/v.

METHODS

Jet blast nebulizers. A diagram of a typical Venturi-air blast type nebulizer is given in Fig. 1. Air is blown over the top of a small capillary tube, the liquid is drawn up and is atomized. The droplets are further fragmented by baffle arrangements and a fine mist of aerosol droplets are produced from the device. Larger droplets are returned to the solu-

* The equivalent diameter of an aerosol particle would be its diameter if it behaved aerodynamically as a unit density sphere.

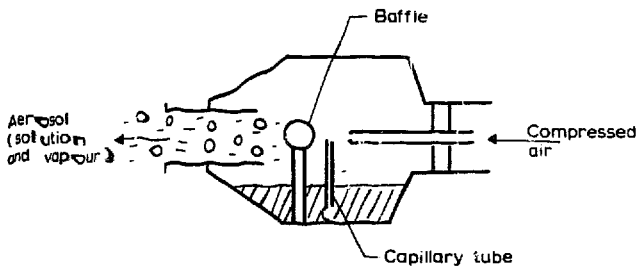

Fig. 1. Schematic diagram of Venturi-type nebulizer.

tion. With some apparatus, for example IPPB equipment, an auxiliary air flow is included.

Two different nebulizers were examined: the Maximyst (Mead Johnson Laboratories, Evansville, Ind.) and the Bird Micronebulizer (Bird Inc., Palm Springs, Calif.). The Maximyst device has a 'finger' valve for controlling air flow. The valve was closed in all experiments. The Bird Micronebulizer has provision for an auxiliary air flow when attached to an IPPB apparatus. This provision was not used and the device was operated as a closed system as shown in Fig. 1. The diameters of the capillaries were 0.50 mm for the Maximyst and 0.55 mm for the Bird Micronebulizer. In all cases the initial volume of solution placed in the nebulizer was 5 ml.

Compressed air supply. A Maximyst Air Compressor (12 psi nominal rating) was used to provide a source of compressed air. The air flow through the Maximyst and Bird nebulizers was 3.5 and 3.6 l/min respectively.

The laboratory nitrogen supply was used for studies on the effect of air pressure on nebulizer characteristics. Pressures were measured using the Bird IPPB pressure gauge. Air flow was determined by a 'Lab-crest' flow meter.

Relative humidity. The relative humidity of the laboratory varied between 40 and 50% during the period of the investigation.

Particle size analysis. The aerosol particle size and particle size distribution were measured using a 6 stage Cascade impactor (CI-6, Delron Research Products, Columbus, Ohio) (Fig. 2). The stages had been calibrated for a flow rate of 12.55 l/min. The aerosol solutions were labelled with 0.1% fluorescein (sodium salt). Fluorescein concentrations were measured with an Hitachi Spectrofluorometer (excitation wavelength 500 nm, emission wavelength 520 nm). The particle size data, expressed as cumulative percent undersize by weight, were plotted in the usual log-probability form, assuming that a log-normal distribution of particle size was present. The reproducibility between separate replicate runs were good. The mass median diameter was read off at the 50% cumulative level.

The standard deviation was determined by drawing the line of best fit through the points lying between 10 and 90% cumulative percentage and taking the ratio of the particle size at 84% to that at 50%. The quantity of aerosol that impacted in the throat arrangement (Fig. 2) was included in the calculation of cumulative weight percent values. If this contribution is ignored a smaller mass median diameter is obtained.

Concentration of aerosol in the nebulizer. During nebulization both solution and solvent vapour will be the output from the nebulizer. Consequently the concentration of drug in the solution will gradually increase. The concentration of the fluorescein label

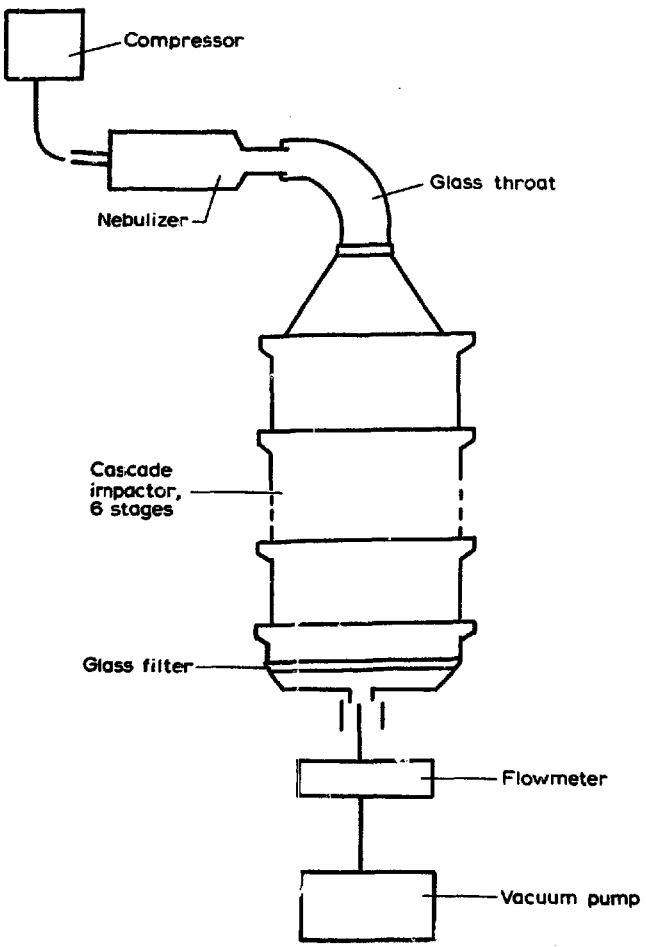

Fig. 2. Schematic diagram of apparatus for particle size analysis of aerosol particles.

was measured at the beginning and end of nebulization, as for the particle size studies above.

Replicates. In all instances at least two determinations were made on each formulation under each set of experimental conditions.

Materials. Propylene glycol from Union Carbide, Fluorescein sodium from Aldrich Chemical Company.

RESULTS

The two devices were studied using water–propylene glycol mixtures.

The factors that influence the delivery of a dose of a drug can be listed as follows:

(1) solubility of the drug in the vehicle;

(2) aerosol output (solution plus vapour);

(3) the increase in the concentration of the aerosol solution;

(4) particle size and particle size distribution; and

(5) the change in the size of the aerosol droplets after nebulization. Droplets will

increase or decrease in size such that the droplet exhibits a vapour pressure to match the relative humidity of ambient conditions (i.e. room or lungs).

In order to assess some of these factors the following were evaluated as indicated.

(1) Total output of aerosol (measured in microlitres of aerosol per litre of air (through jet) (μl/l). To measure this the nebulizer was weighed before and after each study and the volume determined assuming that the density of the solution did not change significantly during the experiment.

(2) Aerosol output is made up from the droplets of aerosol solution and solvent vapour that saturates the outgoing air. This loss of vapour will produce an increase in concentration of the solution in the nebulizer. This concentration effect can be considered in two parts using a drug mass balance analysis: (a) the change in volume effect due to the loss of solution and vapour; and (b) the change in total drug mass due to the loss of solution. Then

$$Ct = \frac{C_0V_0 - St\frac{C_t + C_0}{2}}{V_0 - (S + W)t} \quad (1)$$

where C_t = concentration of solution at time t (g/ml); C_0 = initial concentration of solution; V_0 = initial volume of solution (ml); t = time (min); S = solution output (ml/min) and W = vapour output (ml/min).

Both S and W will change slightly as the solution concentrates, but for the purpose of this analysis they can be assumed to be constant if the change in volume (S + W)t is small and if C_t is only slightly greater than C_0.

$$\text{Since } V_0 - (S + W)\,t = V_t \quad (2)$$

where V_t is the volume at time t, Eqn. 1 can be solved for S and Eqn. 2 for W.

(3) From paragraph (2) above the output of solution and vapour in μl/l or as % of total output can be calculated.

(4) Not all the aerosol solution will be effective therapeutically in the lungs. If the particle size is too large most of the solution will be deposited in the throat and the drug will be absorbed from the gastrointestinal tract and will have a systemic effect. If the particles are too small they may reach the alveolar spaces but can be exhaled again. The optimum size range for maximal local action and minimal systemic action is still the subject of dispute. A generally accepted compromise is to calculate the percentage of aerosol solution droplets below 5 μm. It must be remembered that hygroscopic particles (i.e. those containing more than 10% propylene glycol) will grow in size in the lungs under the conditions of 99% relative humidity at 37°C, below the subglottic region. The percentage of droplets below 5 μm (or any other arbitrary size) can be obtained from the data obtained with the Cascade impactor.

(5) From paragraph (4) above the output of solution (μl/l) or particles below 5 μm can be calculated.

Output of solution and vapour. The change of output of solution and vapour for the two devices is shown in Fig. 3. It can be seen that the Maximyst and Bird nebulizers give similar results. There is a maximum in the total output at around 20% propylene glycol.

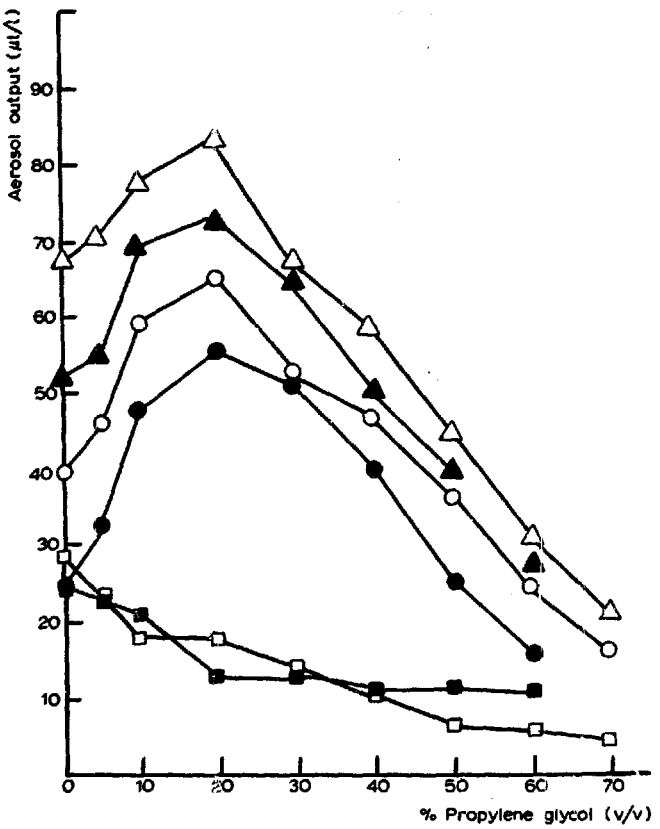

Fig. 3. Nebulization of propylene glycol solutions. The total output (△), solution (○) and vapour (□) outputs with Maximyst and (equivalent filled symbols) Bird nebulizers.

Resolution of the output data into the solution and vapour components shows the vapour output falling progressively as the propylene glycol content increases due, of course, to the effect of the glycol on the local vapour pressure of the system. The output of aerosol solution droplets passes through a maximum at 20% glycol content. The proportions of solution to vapour at any given glycol content can be calculated easily. Above 20% v/v glycol content these proportions are almost constant at 80% solution to 20% vapour. The one major difference between the two nebulizers is the quantity of aerosol lost in the 'throat' arrangement. The Bird nebulizer gives a consistently smaller loss than the Maximyst nebulizer and could be expected to give a much lower dose of the drug systemically when used clinically.

Due to the concentration effect discussed above the output from the nebulizer will not be constant with time but will change as the aerosol solution in the nebulizer concentrates. Below 20% v/v propylene glycol we would expect the output to increase with time but above 20% v/v propylene glycol the output should decrease. For example, the initial rate of output for 50% v/v propylene glycol was 42 µl/l falling to 20 µl/l at 19 min, at which time the output ceased because there was insufficient solution remaining in the nebulizer to give the capillary-Venturi effect.

Particle size analysis. Log-probability plots for 10 and 60% v/v propylene glycol solu-

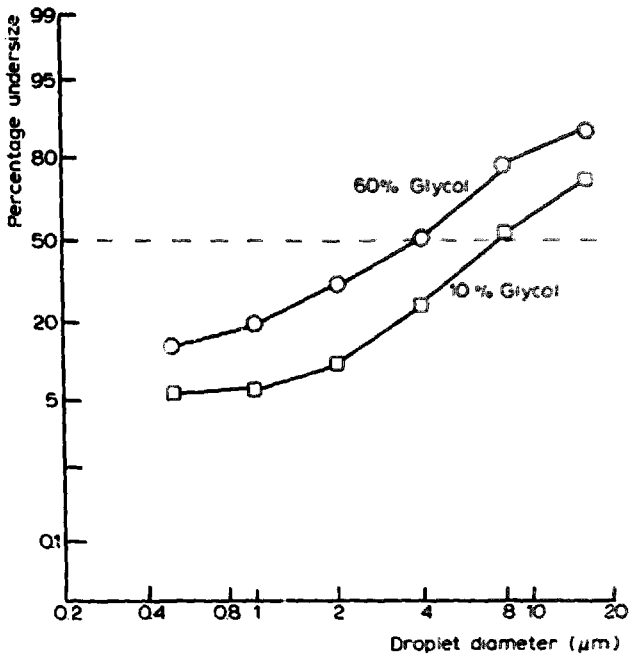

Fig. 4. Particle size analysis of aerosol droplets (log probability plot). ○, 60% propylene glycol; □, 10% propylene glycol.

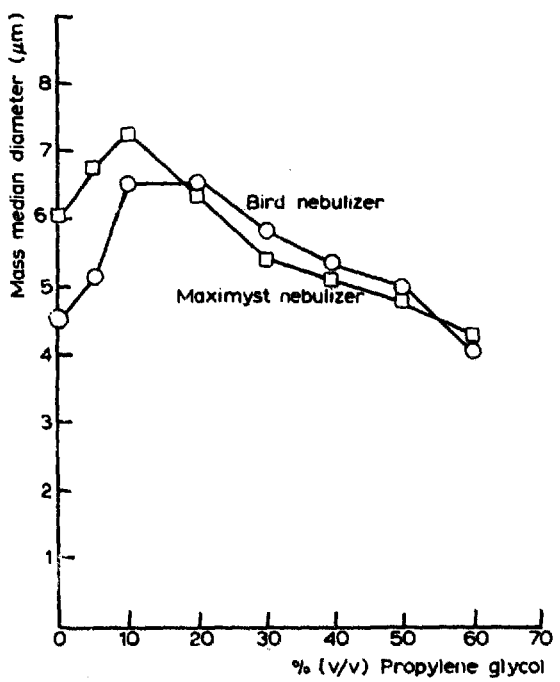

Fig. 5. Relation between aerosol particle size and propylene glycol content. ○, Bird nebulizer; □, Maximyst nebulizer.

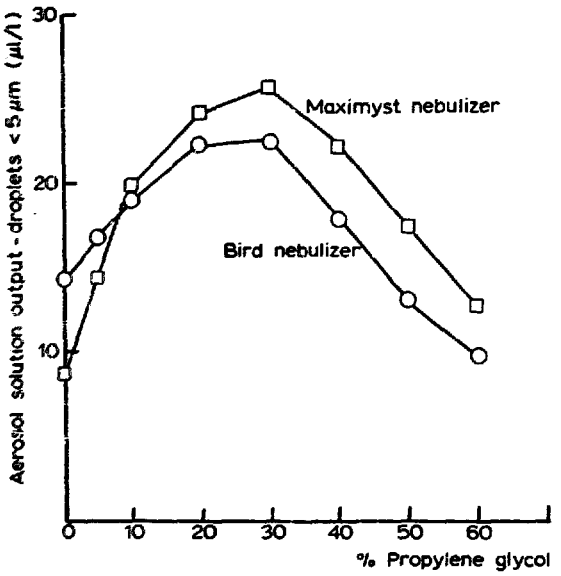

Fig. 6. Effect of propylene glycol content on the output of 'effective' aerosol droplets. ○, Bird nebulizer; □, Maximyst nebulizer.

tions are shown in Fig. 4. As the glycol content increases the mass median diameter falls and the standard deviation increases. The change in mass median diameter with the full range of propylene glycol content is shown in Fig. 5. The mass median diameter passes through a maximum at 10% v/v propylene glycol. This maximum may be an experimental artifact. Below 10% v/v propylene glycol the propylene glycol droplets are not stable and consequently they lose water until the vapour pressure is in equilibrium with the ambient conditions within the Cascade impactor and its sampling arrangement. This suggestion is substantiated by plotting the mass median diameter against surface tension. A linear relation between the two variables breaks down at 10% propylene glycol.

We conclude that the particle size of the aerosol falls as the propylene glycol content increases. The quantity of solution below 5 μm can be determined from the log-probability plots (Fig. 6). A maximum output is found at 30% v/v propylene glycol.

Drug solubility. The solubility of the drug in the vehicle can be of paramount importance and will often play a key role in the selection of the optimum delivery system. In this work we have considered a test steroid, flunisolide (Syntex Pharmaceuticals, Palo Alto, Calif.).

The solubility of flunisolide changes exponentially with propylene glycol concentration (Table 1). In the calculation of delivery times for this drug an arbitrary dose of 1 mg has been chosen. The quantity of aerosol solution containing that dose and the volume of air needed to nebulize that quantity of solution (particles below 5 μm) and the time for nebulization using the Maximyst nebulizer are given in Table 1. It is clear that the time for delivery of a given dose decreases with increase in glycol content. The over-riding factor is the solubility of flunisolide in the vehicle and the system with the maximum output of effective aerosol (30% v/v propylene glycol) is not the best for drug delivery (extrapolation of the experimental data to 70% v/v glycol content indicates that the time for

TABLE 1

NEBULIZATION OF TEST STEROID (FLUNISOLIDE) SOLUTION – MAXIMYST NEBULIZER – DOSE 1 mg

Propylene glycol % (v/v)	Solubility flunisolide [a] (mg/ml)	Quantity of aerosol solution (ml) required	Aerosol solution output (<5 μm) (μl/l)	Volume [b] of air (l)	Time [b] for nebulization [c] (min)
20	0.125	8	24	333	93
30	0.25	4	26	153	43
50	1.00	1	18	56	16
60	2.00	0.5	13	38	11

[a] Poulson, P., personal communication.
[b] Assumed that quantity of drug per unit time is approximately constant due to compensating effects in concentration process.
[c] Airflow = 3.5 l/min.

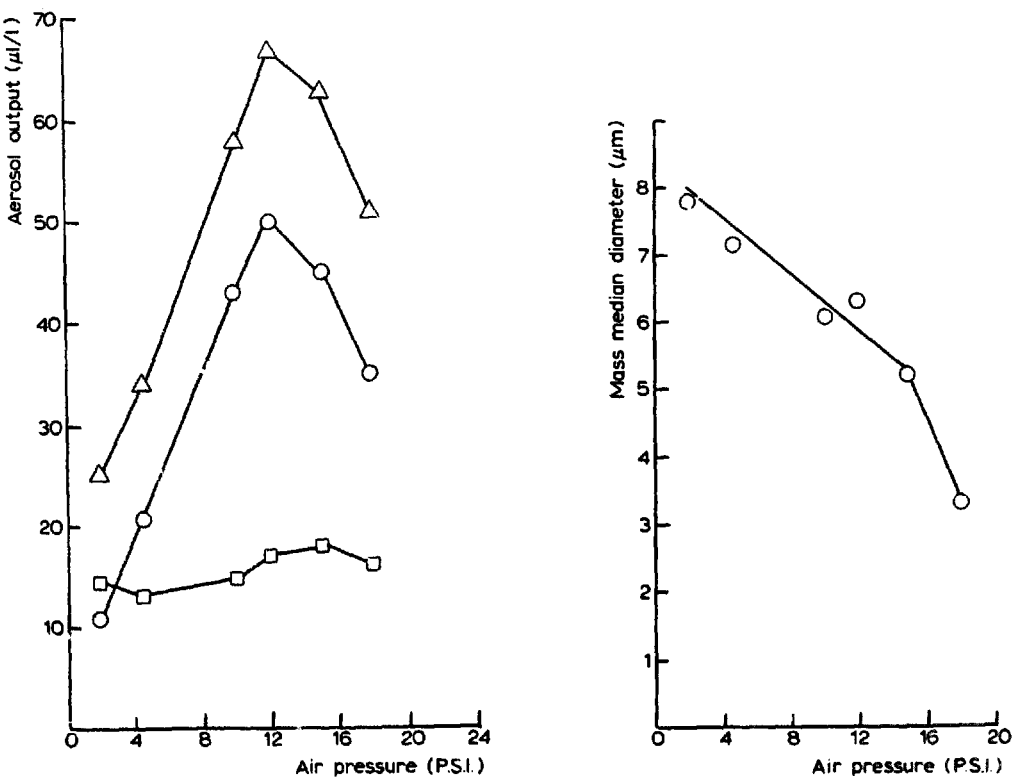

Fig. 7. The effect of air pressure on aerosol output (50% w/v propylene glycol solution). △, total output; ○, solution output; □, vapour output.

Fig. 8. Effect of air pressure on particle size of propylene glycol solution aerosol droplets.

nebulization would be about 14 min). It is concluded that 50 or 60% v/v propylene glycol will provide the best delivery system clinically if one is considering propylene glycol–water systems alone.

In the calculation of the time for dose delivery it has been assumed that the quantity of drug delivered per unit time will remain approximately constant. The increase in the concentration of the aerosol solution will produce a net reduction in output through an increased solution viscosity. However, this effect will be offset by a decreased surface tension which will favour a correspondingly larger output and also a reduction in particle size and the percentage of particles below 5 μm. In addition the nebulized solution will have increased concentration so that the dose per unit volume increases. All things considered there should be little change in the quantity of drug delivered per unit time.

The effect of air pressure. The mass median diameter for 50% v/v propylene glycol using the Bird device under continuous operation was 5 μm. However, the Bird device can be operated over a wide range of air pressures (5–40 psi) and the effect of pressure on aerosol output and particle characteristics was therefore investigated using 50% v/v propylene glycol. In these studies the output may be quoted in two ways since the airflow is not constant: μl/l as before, and μl/min.

The output of aerosol expressed as total aerosol, solution and vapour are shown in Fig. 7 and plotted as μl/l. The solution output reaches a maximum at about 12 psi and then begins to fall. The output of vapour is approximately constant when expressed as μl/l but rises gradually when expressed at μl/min.

The mass median diameter decreases with increased air pressure, reaching approximately 3 μm at 18 psi (Fig. 8). An increase in pressure also results in a more linear log-probability plot and an increased standard deviation.

The percentage of particles less than 5 μm was determined as before and the output of droplets below this size calculated. Expressing the data as μl/l indicates that the output increases in a linear manner with increased pressure until 12 psi and then levels off. However, if the data are expressed as μl/min (a more meaningful parameter for drug delivery) the relation between output and pressure is linear for all values studied. As before, the time required to give a 1 mg dose of flunisolide in 50% v/v propylene glycol can be cal-

TABLE 2

NEBULIZATION OF TEST STEROID FLUNISOLIDE SOLUTION – BIRD IPPB MICRONEBULIZER – DOSE 1 mg 50% PROPYLENE GLYCOL – 1 ml SOLUTION

Administration of particles below 5 μm

Air pressure (psi)	Time to aerosolize 1 ml 50% propylene glycol (min)
2	172
4.5	58
10	21
12	16
15	14
18	12

culated for different air pressures (Table 2). The higher the pressure the lower the delivery time.

DISCUSSION

The output of aerosol droplets from an atomizer is controlled by a variety of factors and the importance of surface tension and viscosity have been discussed by Abramson (1940), Glukhov (1968) and Gorman and Hall (1973) among others. Green and Lane (1957) considered that the mechanism of atomization could not easily be analyzed quantitatively, however, they pointed out that energy was required in order to create new surface and to overcome viscous forces. The Venturi-type nebulizer gave rise to a wide ranging drop size. Empirical equations have related mean droplet size to solution density, surface tension and viscosity. Similar equations have been presented by Glukhov (1968) who has emphasized the importance of surface tension. As surface tension falls the aerosol output increases. Conversely as viscosity rises output falls. The relations between these two variables and propylene glycol content are shown in Fig. 9. Small quantities of glycol produce a considerable lowering in surface tension and we would expect aerosol output to increase. At intermediate glycol concentrations the viscosity begins to rise quite sharply and one would expect the output to be decreased. This competitive effect no doubt affects particle size. Atomization theories suggest that the mean diameter of aerosol droplets will increase as the viscosity increases (Marshall, 1954, Mercer, 1973a). However, we find in the present work that as propylene glycol content is increased the mean size decreases. We note that Mercer (1973b) has commented that the effect of surface tension

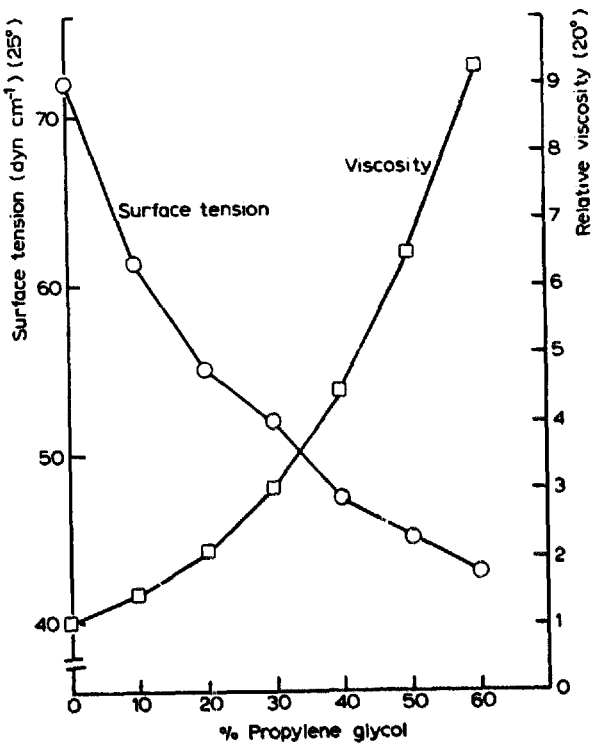

Fig. 9. Physical properties of propylene glycol solution. □, viscosity; ○, surface trension.

on the size distribution of primary aerosol droplets is not always reflected in the distribution of the final aerosol that leaves the nebulizer because of the size-selective characteristics of the nebulizer for retaining primary droplets. In agreement with our findings Searls and Snyder (1936) have reported that an increased viscosity results in a longer atomization time but the mean droplet size falls markedly.

Walkenhorst and Dautrebande (1964) measured various factors influencing the weight, number, flow rate and size distribution of the aerosol particles produced using propylene glycol systems. They noted that 50% glycol had a marked effect on the number of particles produced per ml of solution. They concluded that for their systems lowering of surface tension had no real benefit. The addition of propylene glycol did not alter either the mean size or size distribution but increased considerably the number of particles.

No doubt the exact relationship between aerosol solution output, mean particle size and viscosity and surface tension is a complex function of the design of the nebulizer and its dimensions. Of interest in the present work was a clear relation between total output and particle size. For a given atomization pressure it was found that an increased output was always at the expense of an increased particle size. Thus the net benefit in terms of particles of therapeutic importance (e.g. less than 5 μm) may be quite small.

The propylene glycol concentration for maximal output of small particles was 30% v/v; however, one must temper such an observation with the known properties of the drug molecule, in particular its solubility in the vehicle. We see clearly for the case of a test steroid that the solubility effect dominates all other considerations so that the 50–60% glycol systems provide the shorter times for administration (times too long for clinical situations). The second paper will consider propylene glycol–ethanol–water mixtures where one is able to achieve reasonable solubility of the drug in the vehicle without an unacceptably high solution viscosity.

An increased output together with a reduction in mean particle size can be achieved using an increased atomization pressure. Mercer et al. (1968) have reported similar data to those described in Figs. 7 and 8, namely a fall in particle size with increased pressure and aerosol solution output (expressed as μl/l air) passing through a maximum at 10 psi. The time to administer a dose of test drug can be greatly reduced by increasing the atomization pressure.

CONCLUSIONS

(1) There is little difference in the performance of the Maximyst and Bird nebulizers when used to nebulize propylene glycol–water mixtures.

(2) The maximum output of aerosol solution is at 20% v/v glycol.

(3) The mass median diameter of the aerosol solution reaches a maximum of 7.25 μm at 10% v/v propylene glycol. Further increase in glycol content produces a decrease in particle size.

(4) The output of aerosol solution for particles below 5 μm (a size usually accepted as the upper limit for therapeutic activity) reaches a maximum at 30% v/v propylene glycol.

(5) In delivering a dose of a test steroidal compound the solubility of the drug in the vehicle must be considered. As a consequence the optimum vehicle for drug delivery is 50 or 60% propylene glycol.

(6) An increase in atomization pressure gives rise to an increased output of aerosol droplets up to a maximum at 12 psi and a decreased particle size. The output of aerosol droplets below 5 μm (expressed as l/min) is linearly related to air pressure.

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