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# Particle Size of Inhalation Aerosol Systems I: Production of Homogenous Dispersions

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The methods used to size inhalation aerosols and the problems involved in producing an homogenous cloud of aerosol particles are reviewed. Particle size analyses were carried out using a Royco 225/508 particle size analyser. A number of variables such as sensor head position have been examined under conditions of constant temperature and humidity. It is shown that a dilution of the aerosol cloud into a large volume (360 l) gives a satisfactory number of particles in the sample volume. The positioning of the sensor head is not critical provided that adequate air turbulence can be generated using sleeved sintered-bearing fans. The air flow rate must be controlled so that air passes over the sensor at not more than 0.58 $m.s^{-1}$. The length of time required to produce a uniform distribution is shown to be about 10 secs.

## INTRODUCTION

The use of inhalation aerosol devices for the treatment of some respiratory diseases is now routine. Basic standards for maximum particle size and uniformity of dose delivered were introduced into the British Pharmaceutical Codex 1973. It is generally considered that one of the necessary requirements for an inhalation aerosol is the limitation of the maximum size of particles in the cloud produced. However, as suggested by Hatch & Cross (1974) it is not so much the physical size of the particles which is important but their aerodynamic properties. They defined the aerodynamic diameter as the diameter of a sphere of unit density having the same settling velocity as the particle being examined regardless of its shape or density. This size is important because the particles have to pass into the respiratory tract which is effectively a particle classifier (Landhal & Herman (1948); Davies, C.N. (1972)). The respiratory cycle and the separation of particles in the respiratory tract may influence the therapeutic efficacy of the product (Task Group on Lung Dynamics 1966). This latter value is dependent on the size of the particles in the spray and on their degree of flocculation. Therefore any formulation process must include an assessment of the size range of the particles.

Additional studies are required to ensure that the same spray characteristics are produced at each actuation of the device (Davies, C.N. et al (1972)).

There are many documented methods for sizing the aerosol cloud. They include microscopic examination (B.P.C. 1973); sedimentation and subsequent microscopic assessment (Hallworth & Hamilton (1976)); inertial impaction (Bell, Brown & Glasby (1973)); holographic techniques (Gross & Peter (1973)) and light scattering (Dimmick et al (1958)).

The B.P.C. slide deposition method is not entirely satisfactory in that the number of particles deposited on the slide is so great as to prevent adequate examination of any one particle. Sedimentation methods suffer from the disadvantage of taking excessively long time periods and are subject to loss of fine particles (Davies, P.J. et al (1978)), whilst impingement methods would appear to measure aerodynamic properties rather than simple mass or diameter, the efficiency of collection falls with decreasing particle size (Mercer (1962)) and the time required for total assessment can be prolonged.

At the present time holography is a specialised technique and its application is probably restricted to specialist studies, but it does represent a most interesting approach to study of inhalation aerosol particle clouds. Light scattering has been used by several groups of workers (Dimmick (1958), Bell (1976), Davies et al (1978)) and has the advantage of providing rapid counts of large numbers of particles. However difficulties do arise in producing sufficiently dilute non-aggregated suspensions. Also care must be taken to account for the large natural background count due to inherent particle contamination of the atmosphere.

Since light scattering measures a function of projected area it seems reasonable to assume that it provides an approach to assessing the aerodynamic properties of particles. We have used this technique in the present study to examine the problems involved in size analysis of aerosol particles.

## APPARATUS

Particle measurement was carried out using a Royco 225 Particle Size Analyser (Royco Instruments Inc., California, U.S.A. and supplied by Gelman-Hawksley Ltd., Northampton, England). This unit was fitted with a 508 size-selection module, (which also allows for variable sampling time), and a model 241 air-borne particle sensor unit. The counting unit counts particles greater than the selected size sampled over a given period of time. As the particles are drawn through the sensor zone light falling on them is scattered, the light scattered forward in the region 7 - 17° is collected and transmitted to a photodetector. The circuitry and response of the instrument is checked by means of electrical reference pulses and calibrated by means of standard latex aerosol suspensions.

The calibration curve is not linear and shows a discontinuity in the size range 0.8 to 1.1 micrometers (Fig. 1). This could be due to a change in the light scattering process as the size of the particles increases. This may be inconvenient but does not produce insuperable difficulties.

All the experiments were carried out in a modified laminar flow cabinet (Model 2.5 SG, Hepaire (U.K.) Ltd.). A perspex sheet was used to seal the front of the unit to prevent ingress of particles from the air (Fig. 2 and 2a).

Sample distributions within the unit was obtained by use of two sleeved sintered bearing fans (Etri Distribution Fans, Model Nos. 125.RO180 and 126.LF0160, Neuilly-Sue-Seine, France).

The materials used were commercially available inhalation aerosols.

## EXPERIMENTAL AND DISCUSSION

The cabinet volume is important in that sufficient dilution must be obtained to prevent saturation of the electronic counters. This difficulty in the use of light scattering was noted by Davies, P.J. et al (1978) who had difficulty in

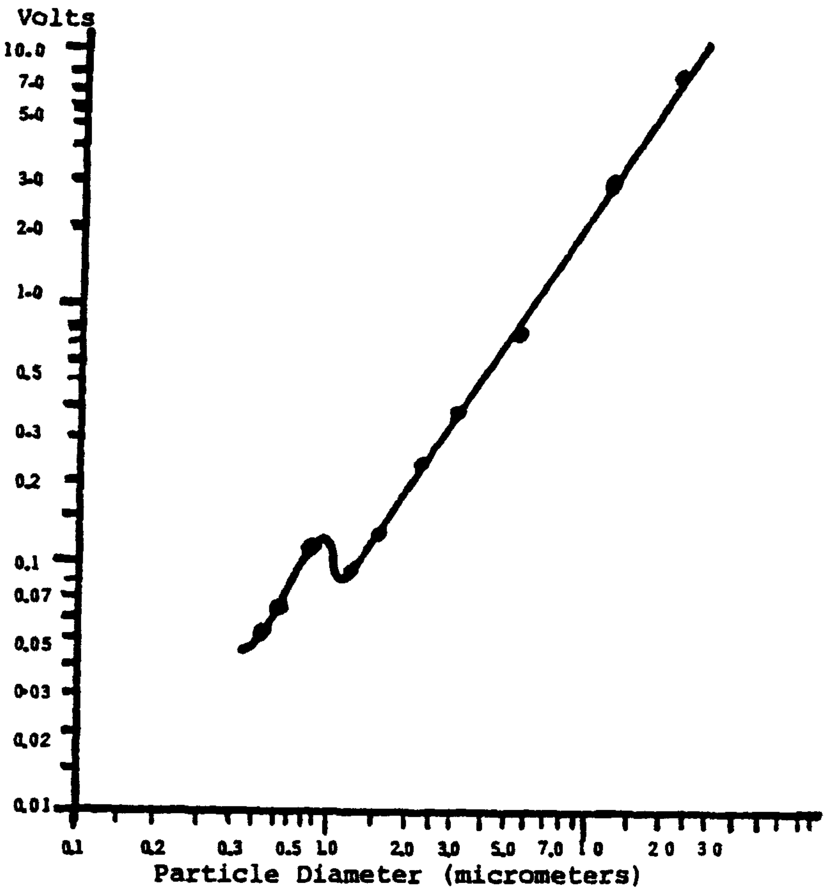


Fig. 1 - Calibration Curve - Royco 225 System with Model 241 Sensor

counting when the chamber volume was 160 litres. This problem has been eliminated in the present study by use of a chamber having a volume of 361.6 litres.

The cabinet air circulator was operated until less than 1000 particles greater than 0.5 μm were recorded in a one minute sample. The air circulator was then switched off and the distribution fans switched on. These produce no measurable increase in the particle count.

The aerosol was actuated into the unit via a port in the front plate and sampled at 0.1 cfm for one minute with a X10 counter sensitivity. At the end of the experiment the unit was cleared of particles before proceeding to the next measurement by means of the cabinet air circulator as indicated above. All experiments were carried out at 30° ± 2° and relative humidity of 40% RH (±5%). Care has to be taken in positioning the sensor in order to get balanced sampling. The air flow rate over the sampling part should not exceed 0.58 $m.s^{-1}$ (Royco

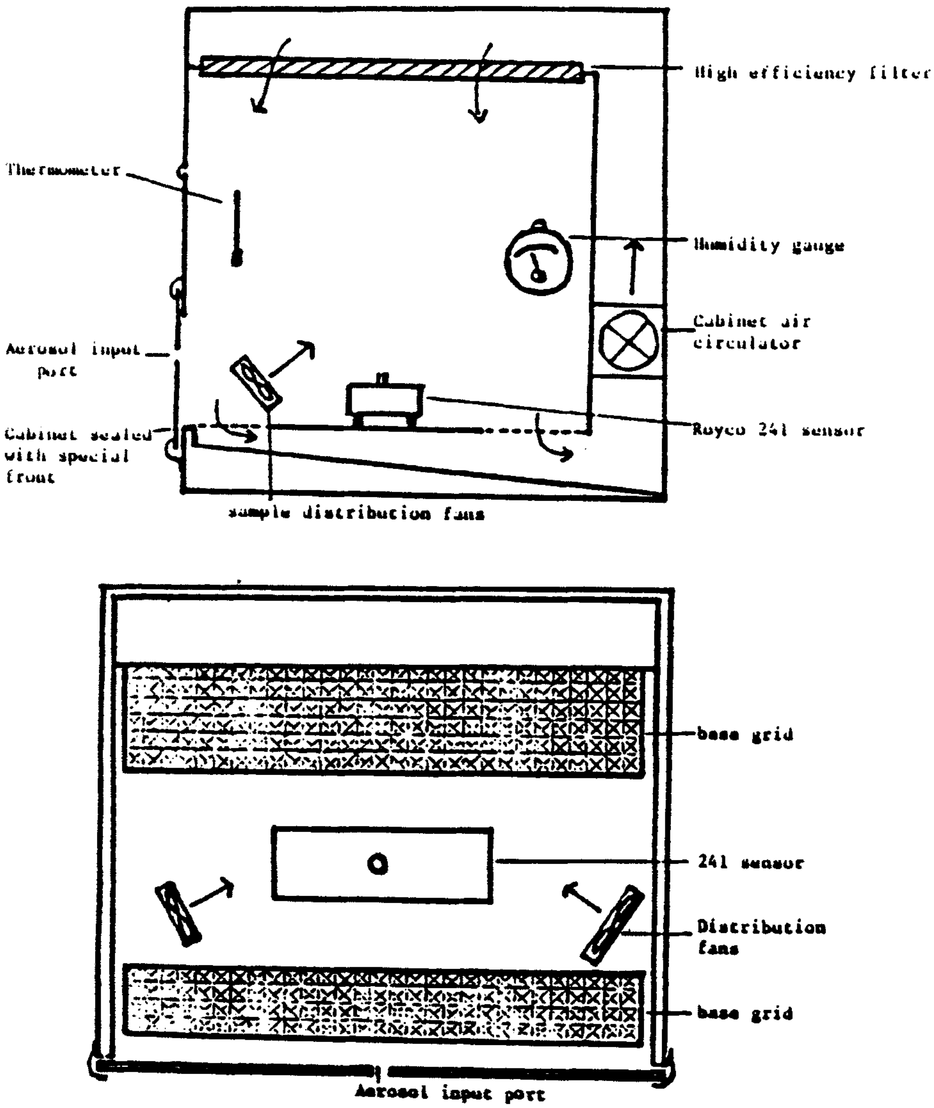


Fig. 2 - Modified Laminar Flow Cabinet for Aerosol Dilution (not to scale)

Instruments Manual). This enables effective sampling of all particles of 10 µm and less. At no time did we detect particles greater than 8 µm although it is possible that some did exist. The average flow rate over the sampling port was 0.25 $m.s^{-1}$ (±20%) measured by means of a Davimeter (Airflow Developments Ltd., England).

The start of sampling time always creates some difficulties. It is essential not only to ensure a uniform distribution of the particles but also to sample before significant changes due to either settling out or possible agglomeration of the system. Data shown in Table 1 indicates that a uniform mix is obtained in about 10 seconds from the time of actuation.

If an homogenous distribution was produced within the mixing period, random placing of the sensor should enable similar results to be obtained. Tests were carried out in ten positions at two levels within the cabinet. Variations of less than ±10% were regarded as acceptable (Table 2).

Table 1. Effect of Time Mixing Before Sampling on the Size Distribution

| Time (s) | Mean Number of Particles Greater than Stated Size (micrometers) for 20 Repeats | | | | | |
|---|---|---|---|---|---|---|
| | 0.5 | 0.7 | 1.5 | 3.0 | 5.0 | |
| 0 | 22939 | 14830 | 7350 | 628 | 27 | |
| 5 | 25414 | 16705 | 8168 | 557 | 19 | |
| 10 | 21399 | 13936 | 6734 | 501 | 18 | |
| 15 | 21412 | 13767 | 6586 | 459 | 15 | |
| 20 | 19473 | 12317 | 5794 | 379 | 12 | |
| 30 | 17485 | 11302 | 5516 | 431 | 14 | |
| Percent Coefficient of Variance | | | | | | Mean |
| 0 | 8.8 | 8.1 | 8.9 | 17.0 | 66 | 21.8 |
| 5 | 9.8 | 13.9 | 18.4 | 32.9 | 52 | 25.6 |
| 10 | 4.2 | 3.9 | 3.9 | 3.6 | 13 | 5.7 |
| 15 | 4.6 | 3.6 | 4.2 | 14.0 | 29 | 11.1 |
| 20 | 4.7 | 4.5 | 4.8 | 8.7 | 52 | 14.9 |
| 30 | 9.0 | 9.1 | 7.9 | 7.1 | 32 | 13.0 |

Table 2. Efficiency of Distribution of Particles After a 10 second Mixing Period

| Sensor Positions | Mean Number of Particles Greater than Stated Size (micrometers) for 20 Repeats | | | | |
|---|---|---|---|---|---|
| | 0.5 | 0.7 | 1.5 | 3.0 | 5.0 |
| Level 1 A | 20288 | 10941 | 5852 | 384 | 11 |
| B | 20550 | 12319 | 5382 | 340 | 8 |
| C | 17732 | 9155 | 4846 | 256 | 6 |
| D | 19217 | 11403 | 5076 | 345 | 8 |
| E | 19534 | 10399 | 5558 | 349 | 9 |
| Level 2 F | 18875 | 9651 | 5044 | 268 | 6 |
| G | 18619 | 9678 | 5087 | 272 | 7 |
| H | 19192 | 10195 | 5521 | 344 | 9 |
| I | 17297 | 8699 | 4565 | 234 | 7 |
| J | 16447 | 8627 | 4636 | 273 | 14 |
| Mean No. | 18775 | 10107 | 5157 | 307 | 7.5 |
| Variation ±% | 10 | 18 | 13 | 25 | 47 |
| Standard Error of Mean | 389 | 358 | 125 | 97 | 2.4 |

## CONCLUSION

The use of a light scattering unit for measuring particle size would appear to offer great applicability to inhalation aerosol systems. Care must be exercised to minimise coincidence of counts or potential agglomeration of particles. This latter parameter is apparently influenced by humidity of the system (Byron (1977)). The choice of operational volume for light scattering studies must allow for adequate space to prevent particles being carried forward and impinging on the walls of the unit. Volume and mixing rate must also be carefully controlled. Light scattering produces a projected area measurement, which may be regarded as a useful aerodynamic measure but it may be necessary to convert data to other distribution formats.

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