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Aerodynamic size distribution, hygroscopicity and deposition estimation of beclomethasone dipropionate aerosol

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Aerodynamic size distribution and aerodynamic mass per dose of beclomethasone dipropionate aerosol were measured at 24 and 95% relative humidity. At high humidity, the count median aerodynamic diameter was unchanged, mass median aerodynamic diameter increased from 2·01 μm to 2·68 μm, particle number/dose from $41{\cdot}3 \times 10^6$ to $78{\cdot}3 \times 10^6$, and aerodynamic mass per dose from 23·7 to 60·0 μg. The quantity of active ingredient estimated to be in the 23·7 μg aerodynamic mass at low humidity was 19·7 μg. From data previously available describing average deposition fraction as a function of aerodynamic diameter, 6·7 μg or 13% of the total dose of 50 μg produced by the metered dose canister would be expected to deposit in the lower respiratory tract.

Beclomethasone dipropionate dispensed as a micronized powder from a fluorocarbon-charged metered-dose canister is widely used as for bronchial asthma (Brown et al 1972; Davies et al 1977). The efficacy of aerosol therapy depends upon retention and distribution of the aerosol particles in the respiratory tract. If aerosol aerodynamic size distribution is known, respiratory tract deposition can be estimated using theoretical and experimental data relating deposition fraction to particle aerodynamic diameter (Da) (Task Group on Lung Dynamics 1966; Lippmann 1977). However, estimation of deposition is complicated when particles grow or shrink because of water condensation or evaporation as a result of humidity changes. Morrow (1974) suggested that, for most therapeutic aerosols, particle growth in the respiratory tract could be expected. There is little information documenting or quantitating this predicted effect of exposure to high humidity on therapeutic aerosols.

We have measured the aerodynamic size distribution of beclomethasone dipropionate (BDP) at ambient and airway humidity. The measurements were made using the single particle aerodynamic relaxation time (SPART) analyzer (Mazumder & Kirsch 1977; Hiller et al 1978). We also used the aerodynamic size distribution of BDP to estimate respiratory tract deposition.

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MATERIALS AND METHODS

The SPART analyzer measures the aerodynamic diameter (Da) of individual particles over a size range of 0·10–10·0 μm but its resolution is better in the 0·3 to 6·0 μm size range in which it was calibrated for the present studies. The instrument can count and size particles at a maximum rate of 200 s^{-1}. The aerosol is drawn from an environmental chamber into the analyzer and across the measuring site called the "sensing volume", which is formed by the intersection of two laser beams of slightly different frequencies. Here it is subjected to acoustic oscillation at 24·25 kHz and this causes a Doppler shift in the frequency of the light which the particles scatter. This scattered light is detected by a photomultiplier that generates a frequency-modulated (FM) signal. The acoustic field oscillation is detected by a microphone. Particle motion lags behind acoustic field oscillation and this delay, termed "phase lag" is directly related to Da. The demodulated FM signal which represents particle oscillation is compared electronically with the microphone signal output representing acoustic excitation to determine the phase lag. A microprocessor determines Da from phase lag and stores Da for each particle in a 128 channel file for computer processing.

The stored data is processed by minicomputer to determine count median aerodynamic diameter (CMAD), mass median aerodynamic diameter (MMAD), geometric standard deviation, and total number of particles counted, and also to plot the following distributions: (1) derivative of number with

respect to log Da, (2) derivative of volume (referred to later as "aerodynamic mass", which is the mass in the measured size range assuming particle density of 1 g cc^{-1}) with respect to log Da, (3) cumulative number, and (4) cumulative volume.

The minicomputer was also programmed using the following equations which closely describe the deposition curve Lippmann (1977) reported for the pulmonary deposition (gas exchange area) of aerosols inhaled by mouth. Where p_d is pulmonary deposition:

For Da $> 10\,\mu$m,
$p_d = 0$.
For $7 <$ Da $\leqslant 10$,
$p_d = 1{\cdot}88\ (\log Da)^2 - 3{\cdot}89\ (\log Da) + 2{\cdot}01$.
For Da $\leqslant 7\,\mu$m,
$p_d = -0{\cdot}95\ (\log Da)^4 - 0{\cdot}75\ (\log Da)^3 + 0{\cdot}47\ (\log Da)^2 + 0{\cdot}47\ (\log Da) + 0{\cdot}24$.

The minicomputer was also programed to calculate estimated deposition in conducting airways using the model described by the Task Group on Lung Dynamics (1966).

A 200 litre insulated Plexiglas chamber with heat strips and a digital thermometer, was used to control environmental conditions. A variable-speed fan inside the chamber provided thermal and aerosol mixing. The chamber was humidified by bubbling air through a heated water bath at a flow rate necessary to attain the desired humidity.

Environmental conditions in the chamber were monitored at ambient and high humidity using a hygrometer. The humidity of the efflux from the sensing chamber was monitored during the high humidity studies (using a digital humidity probe, Model HM-111, Weathermeasure Corp., Sacramento, Ca.) to insure that no drop in humidity occurred during measurement. Humidity monitoring devices were calibrated with saturated electrolyte solutions known to provide a specific humidity at a defined temperature. Eight studies were done each at ambient and high humidity. For studies at ambient humidity, temperature was maintained at 36·8 s.d. 0·4 °C, and relative humidity at 23·6 s.d. 1·4 %. For studies at airway humidity, temperature was 37·1 s.d. 0·4 °C and humidity at 96·4 s.d. 0·2 %.

The analyzer samples at the rate of 55 cc min^{-1}. The sensing volume is $1{\cdot}3 \times 10^{-6}$ cc and the quantity of aerosol passing through it is $1{\cdot}3 \times 10^{-2}$ cc^{-1}. Coincidence loss with the analyzer is less than 2% when the counting rate is 40 particles s^{-1} or less. At the sampling rate we use, this was accomplished by maintaining aerosol concentration in the environmental chamber at less than 3000 particles $cc.^{-1}$

When appropriate environmental conditions were attained, the BDP was injected into the chamber. The count rate as measured by the analyzer was used to assess aerosol concentration and to determine the number of valve actuations of the canister necessary to bring the environmental chamber to approximately 3000 particles cc^{-1}. These were delivered in succession and, after a 15 s mixing period, sampling was initiated and continued for 5 min. The environmental chamber was located directly over the analyzer, and a 6 mm diameter sampling tube aspirated aerosol via a flared opening 20 cm above the floor of the chamber. The aerosol travelled vertically to maintain laminar flow and minimize particle loss from impaction in the sampling tubing.

RESULTS

The properties which describe BDP aerosol measured at low and high humidity are shown in Table 1. The size distribution curves at low and high humidity shown in Fig. 1 are computerized summations of all studies at low and high humidity. There was no significant increase in count median aerodynamic diameter at high humidity but mass median aerodynamic diameter was significantly increased. 11% of the particles by number and 63% of the mass of the aerosol at low humidity were in the 1–5 μm size range.

The mass per dose and particle number per dose in the measured size range is shown in Table 2. Total mass in the size range measured is 47% of the quantity of active ingredient which the manufacturer claims is dispensed with each dose. Particle number increased 1·9 fold ($P < 0{\cdot}001$) at high humidity.

The total mass estimated to deposit in the respiratory tract is the sum of that estimated to deposit in

Table 1. Physical properties of beclomethasone dipropionate aerosol produced by commercially available metered-dose device

Relative humidity (%)	CMAD[a] μm	MMAD[b] μm	σg[c]
24	0·62 s.d. 0·02	2·01 s.d. 0·59	2·11
95	0·63 s.d. 0·02	2·68 s.d. 0·51	2·15
p[d]	$> 0{\cdot}05$	$< 0{\cdot}05$	

[a] Count median aerodynamic diameter with standard deviation.
[b] Mass median aerodynamic diameter with standard deviation.
[c] Geometric standard deviation.
[d] P value using Student's t-test to compare means of low and high humidity studies (8 trials).

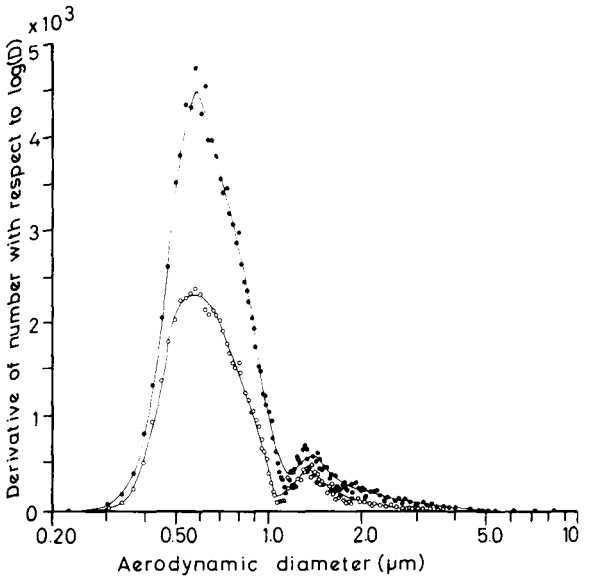

FIG. 1. Aerodynamic particle size distributions of beclomethasone dipropionate aerosol at low and high humidity in the measured size range. Each symbol represents one size channel of the 128 channel file in the SPART analyzer.

Table 2. Number of particles and total mass aerosolized in the measured size range per dose by beclomethasone dipropionate metered-dose device.

Humidity	Particles/dose ($\times 10^6$) (with s.d.)	Mass/dose (μg) (s.d.)	Active ingredient per dose (μg)*
24	41·3 s.d. 2·3	23·7 s.d. 6	50 μg
95	78·3 s.d. 20·0	60·0 s.d. 21	50 μg
P†	< 0·001	< 0·001	

* Quantity of active ingredient dispensed per dose as indicated by manufacturer.

† P value using Student's t-test to compare means of low and high humidity studies (8 trials each).

gas exchange areas and that predicted to deposit in conducting airways. Gas exchange area deposition, calculated using the deposition curves of Lippmann (1977), was estimated at 28·5%. Conducting airway deposition, based on Task Group on Lung Dynamics (1966) deposition curves, was estimated at 5·2%. Deposition below the larynx then would be approximately 33·7% of the active ingredient in the aerosolized mass. The quantity of active ingredient aerosolized per dose in the respirable size range can be estimated from the measured aerodynamic mass (Table 2). Probably not more than 10% of the total mass is inactive ingredient (Dr M. D. Yudis, Schering Corp., personal communication). If 10% is subtracted from 23·7, 21·3 μg active ingredient remains. The aerodynamic mass (Ma) shown in Table 2 is determined assuming density (ρ) = 1. Ma must be converted to actual mass (Mp) as follows: $Mp = Ma/\rho^{\frac{1}{3}}$. The density of beclomethasone dipropionate is not known but probably is close to 1·17 cc^{-1} which is reported for other steroids. Using that figure, Mp is 19·7 μg and estimated deposition below the larynx is 33·7% or 6·7 μg.

DISCUSSION

These data indicated that the count median aerodynamic diameter of BDP was 0·62 μm, the mass median aerodynamic diameter 2·0 μm, and the σg 2·1 μm when the aerosol was studied at 24% RH. Total mass aerosolized in the respirable size range was approximately 40% of the total mass of active dispensed ingredient from the metered dose device and this mass was contained in approximately 4×10^7 particles. When the aerodynamic size distribution of this aerosol was used along with the deposition curves of Lippmann (1977), and the Task Group on Lung Dynamics (1966), 6–7 μg or 13% of the total dispensed mass of active ingredient was estimated to deposit in the lower respiratory tract. When the aerosol was exposed to high humidity, the count median aerodynamic diameter was unchanged but mass median aerodynamic diameter increased to 2·7 μm. At high humidity, aerodynamic mass per dose increased to 60 μg and total particles per dose to $7{\cdot}8 \times 10^7$.

The mass median aerodynamic diameter measured in this study for BDP at low humidity is similar to that reported by Hallworth & Hamilton (1976) and Hallworth & Andrews (1976), who, using three cascade impactors and two different delivery techniques with each impactor, reported it to be in the range of 2·5 μm to 3·6 μm. They found that, depending on delivery technique and cascade impactor used, the mass below 4 μm ranged from 56 to 77%. From the culmulative distributions based on the present data, 81% of the mass is in particles smaller than 4 μm. There are at least two possible reasons for the slightly larger mass fraction below 4 μm found by us. (1) The aerosol deposited in stage 1 of the impactors (each with equivalent cut-off diameters of about 12·5 μm) used by Hallworth & Andrews (1976) added sufficient mass in the larger size ranges in which SPART resolution is less. (2) The size of the aerosol sample analysed by the cascade impactor is much larger than that analysed by the SPART instrument. This difference may be significant for particles larger than 5 μm.

The measured value of the average number of particles aerosolized per metered dose of BDP in our study was $41{\cdot}3 \times 10^6$, which is larger than the $5{\cdot}3 \times 10^6$ reported by Hallworth & Hamilton (1976) using microscopic techniques and the $16{\cdot}3 \times 10^6$ reported by Davies et al (1978) using an optical counter. The relatively larger number of particles observed using the SPART analyzer compared with microscopic techniques may be attributed in part to the relatively greater ability of that instrument to count submicron particles compared with microscopic techniques. Particles in the 0·1 to 1·0 μm size range, especially those below 0·5 μm, are difficult to collect for microscopic sizing since such particles are less likely to be deposited by either impaction or sedimentation, therefore techniques such as electrostatic precipitation are used. Larger particles, those greater than 10 μm, are not counted by the analyzer but are so few that their loss does not appreciably decrease the total count. Further aggregation and wall loss of small particles, both of which are enhanced by the longer residence time and higher concentration, may significantly affect the measured size distribution. Since a smaller chamber was used for the microscopic studies compared with the SPART studies, and because of the relatively short aerosol residence time before sampling used by us, these biasing effects were less significant. For these reasons, the count median aerodynamic diameter found by us is smaller than that reported by Hallworth & Hamilton (1976). The difference in particle number between the present study and that of Davies et al (1978) is small and can also probably be attributed to differences in sampling technique and differences in sensitivity for sizing submicron particles. It is necessary to recognize that the distributions of active ingredients relative to particulate distributions has not been measured. Although the BDP content of small particles is not clear, such particles contribute a relatively small quantity to total mass.

The mass of particles recovered at high humidity, 60·0 μg, is greater by 2·5 fold than that at low humidity, 23·7 μg. This is similar to the increase in mass which would be seen if a monodisperse aerosol with a similar MMAD, 2·01 μm, increased to 2·68 μm; such a change would result in a 2·4 fold increase in mass. Thus the MMAD observed is compatible with the increase in mass. An increase in particle number of 1·9 fold was seen at high humidity compared to low humidity. This increase was primarily in the small size range and thus would not contribute greatly to the increase in mass noted at high humidity. The reason for the observed increase in particle number at high humidity is not clear. We hypothesize that particles smaller than the resolution range of the SPART analyzer at low humidity grow at high humidity into the measureable size range leading to the observed increase in particles per dose.

The mass measured per dose, 23·7 μg, of which approximately 21·3 μg is estimated to be active ingredient, is less than the 50 μg dispensed by the metered dose device. The difference is less when the approximately 5 mg/dose retained in the oral adaptor is considered (Hallworth & Andrews 1976). A greater difference is probably accounted for by particles larger than the SPART analyzer's range. Such particles, while contributing little to particulate concentration by number, constitute a sizable portion of the total aerosol mass. This is demonstrated by impactor studies (Hallworth & Andrews 1976) in which approximately 15–25 μg are recovered from the throat and first stage of various impactors. Such particles are for the most part larger than the "respirable" size range and so would be expected to deposit above the larynx during inhalation by human subjects. The mass measured by the SPART analyzer probably represents most of the mass aerosolized in the 'respirable' size range, i.e., those particles of a size most likely to pass the larynx. If it is assumed that the active ingredient is proportionally similar in particles of all sizes, it is possible to estimate deposition in the lower respiratory tract.

Predicted deposition of the aerosol in the non-ciliated region of the lung in this study is based on comparison of the measured aerodynamic size distribution curves from the SPART analyzer to deposition data for oral deposition (Lippmann 1977). Using this method, 13% of the total dispensed, or 6–7 μg, is estimated to deposit in these regions. If 5 μg is retained in the mouthpiece adaptor as shown by Hallworth & Andrews (1976), then 15% of the remaining 45 μg dose would be estimated to deposit in non-ciliated lung regions. This is the quantity (15%) estimated to deposit in these regions by Hallworth & Andrews (1976) using a size selective air sampler.

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REFERENCES

Brown, H. M., Storey, G., George, W. H. S. (1972) Br. Med. J. 1: 585–590

Davies, G., Thomas, P., Broder, I., Mintz, S., Silverman, F., Leznoff, A., Trotman, C. (1977) Ann. Intern. Med. 86: 549–553

Davies, P. U., Muxworthy, E. M., Pickett, J. M., Smith, G. A. (1978) J. Pharm. Pharmacol. 30: (suppl) 40P

Hallworth, G. W., Hamilton R. R. (1976) Ibid. 28: 890–897

Hallworth, G. W., Andrews, U. G. (1976) Ibid. 28: 898–907

Hiller, C., Mazumder, M., Wilson, D., Bone, R. (1978) Am. Rev. Resp. Dis. 118: 311–317

Lippmann, M. (1977) in: Lee, D. H. K., Falk, H. L., Murphy, S. D., Geiger, S. R. (eds) Reactions to Environmental Agents. Bethesda, American Physiological Society, pp 213–232

Mazumder, M. K. (1970) Appl. Phys. Lett. 16: 462–464

Mazumder, M. K., Kirsch, K. J. (1977) Rev. Sci. Instrum. 48: 622–624

Martin, L. E., Harrison, C., Tanner, R. J. N. (1975) Postgrad. Med. J. 51: (suppl. 4) 11–20

Morrow, P. E. (1974) Am. Rev. Respir. Dis. 110: 88–99

Task Group on Lung Dynamics. (1966) Health Phys. 12: 173–208