Influence of Formulation on Aerosol Particle Size

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Abstract □ A cascade impactor was employed to measure aerosol particle size in a study designed to investigate the influence of several formulation parameters on aerosol particle size. Laboratory data indicate that the size of the aerosol particle may be decreased by reducing the drug particle size, by reducing the drug concentration, by including a surfactant in the formulation, by reducing the spray-orifice diameter, by increasing the propellant vapor pressure, and by increasing the propellant temperature. An aerosol particle size, equivalent to the drug particle size, was obtained only when a high vapor-pressure propellant was employed.

Keyphrases □ Aerosol particle size—formulation effect □ Particle size, aerosols—parameters affecting □ Cascade impacter—aerosol particle size determination □ UV spectrophotometry—analysis

The importance of aerosol particle size[1] in inhalation therapy has been stressed by several researchers (1–6). In view of this observation a study was conducted to investigate the influence of several formulation parameters on aerosol particle size.

The formulation parameters selected for study were: (*a*) drug particle size[2]; (*b*) drug concentration; (*c*) surfactant concentration; (*d*) spray-orifice diameter; (*e*) propellant vapor pressure; and (*f*) propellant temperature. Dexamethasone sodium phosphate NF XII,[3] a water-soluble adrenocortical steroid, was the drug used in this study.

EXPERIMENTAL

Preparation of Aerosols—The "cold-fill" technique was employed to prepare the various aerosols. Concentrates were made by placing dexamethasone sodium phosphate NF XII, dehydrated alcohol, sorbitan trioleate,[4] and glass beads into 120 ml. (4-oz.) plastic-coated glass bottles. The stoppered bottles were placed on a ball mill and the contents were milled for periods ranging from 0.5 to 3 hr. Aliquots of the milled concentrates were transferred into 10-ml. plastic-coated glass bottles. These bottles were cooled in an acetone-dry ice bath and the contents were then brought to a final weight by the addition of cooled, liquefied propellant.[5] A metering valve assembly was attached utilizing a laboratory crimper. The finished aerosols were leak tested by placing them into a hot water bath at 55° for 5 min. The contents of the aerosols had a moisture level[6] of approximately 0.02%. Table I identifies and gives the composition of the aerosols.

Measurement of Drug Particle Size—The drug particle size in these dispersion-type aerosols was determined with a counter.[7] Satisfactory counts (20,000 to 30,000 counts at $t = 3$, an $I = 7$) were obtained on 1 in 20 dilutions of 10 mg. of drug in 100 ml. of electrolyte. The electrolyte consisted of 5% w/v ammonium thiocyanate and 0.1% w/v sorbitan trioleate in isopropyl alcohol. Both 30- and 100-μ aperture tubes were employed. The results of these measurements are expressed in terms of mass median diameters.

Measurement of Aerosol Particle Size—Aerosol particle size was determined with a cascade impactor (7). From 7 to 25 sprays, depending upon the steroid concentration, were introduced into the cascade impactor by means of a glass adapter. Figure 1 is an illustration of the aerosol unit, glass adapter, and first stage of the cascade impactor. Impacted steroid was removed from each glass slide by washing with 10 ml. of distilled water. The aqueous steroid solution was then washed with 10 ml. of methylene chloride to remove sorbitan trioleate and propellant residue which interfered with the subsequent UV assay for dexamethasone sodium phosphate. The quantity of steroid was calculated from the absorbance at the maximum near 242 mμ using absorptivity = 32.8. Figure 2 represents a typical plot of cumulative weight percent dexamethasone sodium

Table I—Identification and Composition of Aerosols[a]

Formulation	Propellant	Concn. of Dexamethasone $NaPO_4$, mg./g.	Concn. of Sorbitan Trioleate, mg./g.
A	20% Dichlorodifluoromethane 80% dichlorotetrafluoroethane	1.43	2.0
B	20% Dichlorodifluoromethane 80% dichlorotetrafluoroethane	0.175	2.0
C	20% Dichlorodifluoromethane 80% dichlorotetrafluoroethane	2.86	2.0
E	20% Dichlorodifluoromethane 80% dichlorotetrafluoroethane	1.43	2.0
F	100% Dichlorodifluoromethane	1.43	2.0
G	100% Dichlorotetrafluoroethane	1.43	2.0
H	20% Dichlorodifluoromethane 80% dichlorotetrafluoroethane	1.43	2.0
J	20% Dichlorodifluoromethane 80% dichlorotetrafluoroethane	1.43	None

[a] Drug particle size was 1.4 μ, except for Formulation E, which was 4.3 μ, and Formulation H, which was 5.6 μ. Multiple containers of the same composition were designated as A-1, A-2, A-3, *etc.*

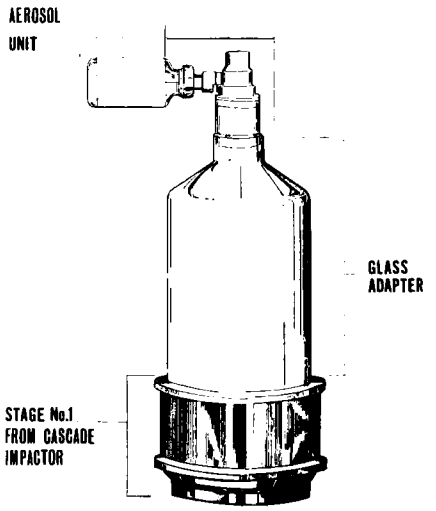

Figure 1—*Illustration of aerosol unit, glass adapter, and first stage of cascade impactor.*

[1] Aerosol particle size refers to the apparent particle size of the drug in the spray from the aerosol.

[2] Drug particle size refers to the apparent particle size of the drug in the formulation, *i.e.*, before spraying from the container.

[3] Dexamethasone sodium phosphate NF XII is dexamethasone 21-(disodium phosphate). Marketed as Respihaler Decadron Phosphate and Respihaler ProDecadron by Merck Sharp & Dohme, West Point, Pa.

[4] Sold as Span 85 by Atlas Chemical Industries, Inc., Wilmington, Del.

[5] Dichlorodifluoromethane is sold as Freon-12 and dichlorotetrafluoroethane is sold as Freon-114 by E. I. du Pont de Nemours and Co., Inc., Wilmington, Del.

[6] Moisture level was determined by a micro Karl Fischer method.

[7] Coulter, Model A.

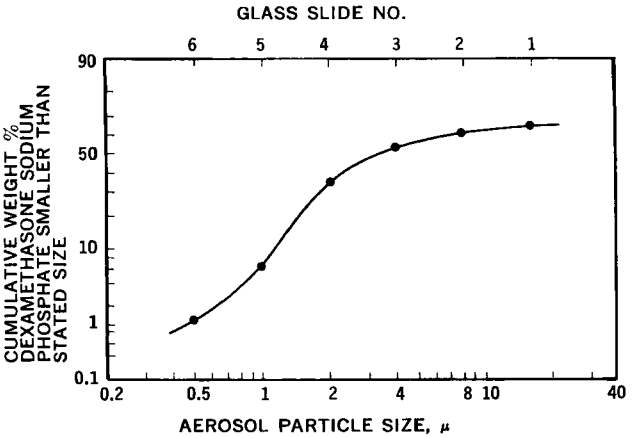

Figure 2—*Aerosol particle size distribution curve (Formulation A).*

phosphate smaller than stated size *versus* aerosol particle size (microns). The mass median diameter is the aerosol particle size at 50 cumulative weight percent. As noted in this figure, the cascade impactor was calibrated so that the cutoff sizes for each of the six jet stages were 16, 8, 4, 2, 1, and 0.5 μ.

Definition of Standard Conditions—In order to evaluate the influence of a formulation parameter on the aerosol particle size, it was necessary to establish a baseline. This baseline, or standard conditions, consisted of Formulation A, an actuator with a spray-orifice diameter of 0.046 cm. (0.018 in.), ambient temperature (approximately 24°), and ambient relative humidity (approximately 30%).

Table II—Influence of Drug Particle Size on Aerosol Particle Size

Sample	Mass Median Diam. of Drug Particles, μ	Mass Median Diam. of Aerosol Particles, μ
H-2	5.6	9.0
E-1	4.3	6.0
A-2	1.4	3.2

RESULTS AND DISCUSSION

Drug Particle Size—This parameter was evaluated by formulating aerosols with steroid solid having mass median diameters over the range 1.4 to 5.6 μ. The data are presented in Table II. In all three samples, the mass median diameters of the aerosol particles were larger than the mass median diameters of the drug particles. Also, a direct relationship was observed between drug particle size and aerosol particle size. The mass median diameter of the aerosol particles decreased from 9.0 to 6.0 to 3.2 μ as the mass median diameter of the drug particles decreased from 5.6 to 4.3 to 1.4 μ. Data are presented later illustrating a formulation which produced aerosol particles which had the same mass median diameter as the drug particles.

Drug Concentration—Aerosols formulated with steroid concentrations ranging from 0.175 to 2.86 mg./g. were employed in evaluating this variable. Table III summarizes the data. The mass median diameter of the aerosol particles did not change when the steroid concentration was increased from 0.175 to 1.43 mg./g. However, the

Table III—Influence of Drug Concentration on Aerosol Particle Size

Samples	Concn. of Dexamethasone Sodium Phosphate, mg./g.	Mass Median Diam. of Aerosol Particles, μ
B-2	0.175	3.2
A-2	1.43	3.2
C-2	2.86	18.0

Table IV—Influence of Surfactant Concentration on Aerosol Particle Size

Sample	Concn. of Sorbitan Trioleate, % w/w	Mass Median Diam. of Aerosol Particles, μ
J-1	0.0	4.6
A-2	0.2	3.2

mass median diameter of the aerosol particles increased from 3.2 to 18.0 μ when the steroid concentration was increased from 1.43 to 2.86 mg./g. The following factors which probably account for the observed increase in aerosol particle size are: (*a*) decreased efficiency of spray orifice to break-up agglomerates; (*b*) decreased efficiency of expansion chamber; and (*c*) decreased ratio of propellant concentration to steroid concentration.

Surfactant Concentration—Aerosols containing no surfactant and 0.2% surfactant were tested to investigate the influence of surfactant concentration. The mass median diameter of the aerosol particles decreased from 4.6 to 3.2 μ when the sorbitan trioleate concentration was increased from 0 to 0.2%. Table IV summarizes these data.

Spray-Orifice Diameter—Valve actuators, having orifice diameters of 0.046, 0.061, and 0.076 cm. (0.018, 0.024, and 0.030 in.), were utilized to study the influence of spray-orifice diameter. Table V contains the pertinent data. The mass median diameter of the aerosol particles remained unchanged, *i.e.*, 11.0 μ, when the spray-orifice diameter was decreased from 0.076 to 0.061 cm. (0.030 to 0.024 in.). However, further reduction in the spray-orifice diameter from 0.061 to 0.046 cm. (0.024 to 0.018 in.) was accompanied by a decrease of the mass median diameter of the aerosol particles from 11.0 to 3.2 μ. It is interesting to note that the spray-orifice area of the valve actuator with a 0.046-cm. (0.018-in.) spray-orifice diameter is

Table V—Influence of Spray-Orifice Diameter on Aerosol Particle Size

Sample	Spray-Orifice Diam., in.	Spray-Orifice Area $\times 10^2$ in.^{2}	Mass Median Diam. of Aerosol Particles, μ
A-3	0.030	7.07	11.0
A-3	0.024	4.52	11.0
A-2	0.018	2.54	3.2

only 36% of the spray-orifice area of the valve actuator with a 0.076 cm. (0.030 in.) spray-orifice diameter.

Propellant Vapor Pressure—Propellants having different vapor pressures were used alone and in combination for the evaluation of this parameter. These data are summarized in Table VI. An inverse relationship was observed between propellant vapor pressure and aerosol particle size. The mass median diameter of the aerosol particles decreased from 11.0 to 3.2 to 1.3 μ when the vapor pressure was increased from 16 to 31 to 77 psig. Of special significance is the observation that the aerosol particle size, *i.e.*, 1.3 μ, was the same as the drug particle size, *i.e.*, 1.4 μ, when the propellant vapor pressure was high, *i.e.*, 77 psig.

Propellant Temperature—Aerosols containing various propellants were equilibrated at several temperatures to study the influence of propellant temperatures. Table VII summarizes these data. An inverse relationship was observed between propellant temperature and aerosol particle size. With dichlorotetrafluoroethane as the propel-

Table VI—Effect of Propellant Vapor Pressure on Aerosol Particle Size

Sample	Propellant	Vapor Pressure, psig.	Mass Median Diam. of Aerosol Particles, μ
G-1	Dichlorotetrafluoroethane	16	11.0
A-2	20% Dichlorodifluoromethane and 80% dichlorotetrafluoroethane	31	3.2
F-1	Dichlorodifluoromethane	77	1.3

Table VII—Effect of Propellant Temperature on Aerosol Particle Size

Sample	Propellant	Temp. of Propellant, °C.	Vapor Pressure, psig.	Mass Median Diam. of Aerosol Particles, μ
G-1	Dichlorotetrafluoroethane	24	16	11.0
G-1	Dichlorotetrafluoroethane	37	30	2.8
A-2	20% Dichlorodifluoromethane and 80% dichlorotetrafluoroethane	24	31	3.2
A-3	20% Dichlorodifluoromethane and 80% dichlorotetrafluoroethane	37	51	2.1
A-4	20% Dichlorodifluoromethane and 80% dichlorotetrafluoroethane	49	75	1.8
F-1	Dichlorodifluoromethane	5	38	2.1
F-1	Dichlorodifluoromethane	24	77	1.3

lant, the mass median diameter of the aerosol particles decreased from 11.0 to 2.8 μ as the propellant temperature was increased from 24 to 37°. The propellant vapor pressure increased from 16 to 30 psig. over this temperature range. With 20% dichlorodifluoromethane and 80% dichlorotetrafluoroethane as the propellant system, the mass median diameter of the aerosol particles decreased from 3.2 to 2.1 to 1.8 μ as the propellant temperature was increased from 24 to 37 to 49°. The propellant vapor pressure increased from 31 to 51 to 75 psig. over this temperature range. When dichlorodifluoromethane was the propellant, the mass median diameter of the aerosol particles decreased from 2.1 to 1.3 μ as the propellant temperature was increased from 5 to 24°. The propellant vapor pressure increased from 38 to 77 psig. over this temperature range.

SUMMARY

An investigation of the influence of several formulation parameters on aerosol particle size was conducted. Sample aerosols were prepared by the cold-fill technique. A Coulter counter was employed to measure drug particle size, *i.e.*, the apparent particle size of the drug in the formulation. A cascade impactor was employed to measure aerosol particle size, *i.e.*, the apparent particle size of the drug in the spray from the aerosol. Laboratory data are presented which indicate that aerosol particle size may be decreased by reducing the drug particle size, by reducing the drug concentration, by including a surfactant in the formulation, by reducing the spray-orifice diameter, by increasing the propellant vapor pressure, and by increasing the propellant temperature. An aerosol particle size, equivalent to the drug particle size, was obtained only when a high vapor pressure propellant was employed.

With this type of preformulation knowledge, the industrial pharmacist is better equipped for his role in the development of an inhalation aerosol with optimum biological activity.

REFERENCES

(1) W. Findeisen, *Arch. Ges. Physiol.*, **236**, 367(1933).

(2) H. D. Landahl and R. Hermann, *J. Ind. Hyg.*, **30**, 181(1948).

(3) H. D. Landahl, T. Tracewell, and W. H. Larsen, *AMA Arch. Ind. Hyg.*, **3**, 359(1951).

(4) L. Dautrebande, "Studies on Aerosols," University of Rochester Atomic Energy Project Report UR-530, 1958.

(5) R. I. Mitchell, *Am. Rev. Respirat. Diseases*, **82**, 627(1960).

(6) H. W. Lovejoy, Jr., H. Constantine, and L. Dautrebande, *Proc. Soc. Exptl. Biol. Med.*, **103**, 836(1960).

(7) R. I. Mitchell and J. M. Pilcher, *Ind. Eng. Chem.*, **51**, 1039 (1959).

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