Pharmaceutical Research, Vol. 5, No. 1, 1988

Report

Comparison of Output Particle Size Distributions from Pressurized Aerosols Formulated as Solutions or Suspensions

Richard N. Dalby[1] and Peter R. Byron[1,2]

Received June 6, 1987; accepted August 1, 1987

The delivery of particles as small as possible (preferably <5 μm) to the respiratory tract should be the aim of those formulating metered dose inhalers (MDIs). This may be facilitated by the formulation of solution, rather than suspension-type, pressurized aerosol units. Two series of MDIs were compared; one contained suspended micronized disodium fluorescein (0.1%, w/v), while the other contained the same concentration of dissolved salicylic acid. Either oleic acid, L-α-phosphatidylcholine, or sorbitan trioleate was incorporated at 0.15% (w/v) as suspending agent (disodium fluorescein) or solubilizing agent (salicylic acid). The propellant blend was 70% (w/w) Freon 12 and 30% (w/w) Freon 11 in all cases. This exhibited a vapor pressure of 50.6 psig (444.7 kPa) at 21°C. The output particle size distribution of the aerosol reaching the cascade impactor showed a mass median aerodynamic diameter (MMAD) of approximately 4 and 2 μm for the suspension and solution formulations respectively, regardless of the surfactant used. Larger MMADs were observed for solution aerosols formulated with oleic acid (2.32 μm) compared to those containing L-α-phosphatidylcholine (1.93 μm) or sorbitan trioleate (2.07 μm). Possible reasons for these observations are discussed.

KEY WORDS: aerosol; surfactant; particle size; formulation; inhalation.

INTRODUCTION

Frequently, the aim of the oral inhalation aerosol formulator is to deliver the maximum amount of drug to the respiratory tract and minimize deposition in the oropharynx. In order to achieve this goal, stable aerosol particles are required that have small aerodynamic diameters (1–3) and low velocities (3–6). Particles with aerodynamic diameters significantly larger than 8–9 μm are mostly swallowed after impaction in the oropharynx (1–3,7,8), even if they are inhaled slowly. Although particles in the diffusion size range (typically smaller than 0.5 μm) may be pneumatically conveyed from the respiratory tract during the next expiration following use of the metered dose inhaler (MDI), this phenomenon can be minimized by the use of breath holding and is probably insignificant given the relatively small mass of such submicron particles (1,3,8). Practically, therefore, for deep lung penetration, aerosols are required with particles or droplets that are as small as possible.

Most formulations currently on the U.S. market consist of drugs suspended in fluorocarbon propellants [e.g., Brethaire (9)] or drugs dissolved in propellants containing a significant proportion of less volatile solvents [e.g., Norisodrine Aerotrol (10)]. In the first case, the minimum particle size of the output is limited by the size of the drug particles achieved during micronization (1,3,11). However, in the second case, the particle size of the output is governed by the concentration of nonvolatile components in the mixture, the initial droplet size (which depends on such factors as actuator design, spray characteristics, and physicochemical characteristics of the solution being sprayed), and the volatile propellant evaporation rate (1,12). Droplet evaporation rates, however, are limited for solution aerosols containing low-vapor pressure ingredients. Cosolvents such as ethanol are included in present formulations to increase the solubility of polar drug molecules. If the propellant blends in these cases were more volatile, but still able to solubilize the drug, this should lead to an output particle size distribution containing a much higher proportion of respirable particles compared to all current suspension or solution formulations.

The literature describing the effects of pharmaceutically acceptable surfactants to solubilize drugs in nonaqueous systems is sparse. Furthermore, there are relatively few reports (14–16) of well-controlled studies on the effects of formulation variables upon pressurized inhalation aerosol output. This report addresses these two points.

MATERIALS AND METHODS

Preparation of Pressurized Aerosol Units

A series of suspension and solution aerosols was prepared using disodium fluorescein (Fisher Scientific, St. Louis, Mo.) and salicylic acid (Ransdell Company, Louisville, Ky.), respectively. Both series of aerosols used these model drugs at a concentration of 0.1% (w/v). Surfactants were employed at 0.15% (w/v), giving a total nonvolatile content of 0.25% (w/v) in all cases. The same fluorocarbon propellant blend was used throughout.

[1] College of Pharmacy, University of Kentucky, Rose Street, Lexington, Kentucky 40536-0082.

[2] To whom correspondence should be addressed.

0724-8741/88/0100-0036$06.00/0

Disodium fluorescein was milled prior to use using a Trost Gem T research jet mill (Garlock Inc. Plastomer Products, Newtown, Pa.) operated at 70 psig with dry air, and the resulting powder sized by optical microscopy (Reichert "Zetopan" Large Research Microscope, Vienna, Austria). All other reagents and materials were used as supplied. Two hundred milligrams of either jet-milled disodium fluorescein or salicylic acid was manually levigated using a spatula and plate-glass sheet to a smooth, uniform paste with 300 mg of either, oleic acid (Chem Service, West Chester, Pa.), sorbitan trioleate (Span 85, Fluka AG, Ronkonkoma, N.Y.), or L-α-phosphatidylcholine (egg lecithin, Calbiochem, La Jolla, Calif.). Aliquots of 150 mg of the resulting pastes were each transferred to a 120-ml plastic-coated glass pressure-resistant bottle (Wheaton Glass, Mays Landing, N.J.) and fitted with a 50-μl/actuation, inverted metered dose valve (Valois DF 10, BLM Packaging Inc., Greenwich, Conn.). Sixty milliliters (84.68 g) of a propellant blend consisting of 70% (w/w) fluorocarbon 12 and 30% (w/w) fluorocarbon 11 (Dymel 12 and 11, Du Pont, Wilmington, Del.), which had a calculated vapor pressure of 50.6 psig (444.7 kPa) at 21°C, was filled through the valve. Valve crimping and propellant filling were performed using Pamasol small-scale aerosol pressure packing equipment (Pfaffikon, Switzerland). Each assembled aerosol unit was then tumble mixed using a Turbula mixer (Model T2C, Glenn Mills Inc., Maywood, N.J.) operated at maximum speed for 1 hr. Investigations were performed on each aerosol unit within 2 days of manufacture.

Determination of Output Particle Size Distributions

Each aerosol unit was shaken vigorously for 30 sec by hand and successively fitted with the same Valois IN1 actuator (BLM Packaging Inc., Greenwich, Conn.), which contains a 0.4-mm orifice designed for suspension-type aerosols. The complete unit was fitted into the aerosol inlet port of an evaporation chamber located atop a calibrated cascade impactor (Delron Research Model DCI-6, Powell, Ohio) through which air was drawn at 12.45 liters/min. The actuator, evaporation chamber, and first stage of the cascade impactor are described with their critical dimensions in Fig. 1. The aerosol was discharged manually 5 times for disodium fluorescein suspension aerosols and 10 times for salicylic acid solution aerosols (for reasons of assay sensitivity), with 2–3 sec between actuations. The actuator, the evaporation chamber, each slide, and the terminal filter of the impactor were washed with pH 7.4 phosphate buffer or 0.01 *M* sodium hydroxide solution for the fluorescein and salicylic acid aerosols, respectively. The washings were immediately analyzed spectrophotometrically (Cary 219, Varian Instrument Division, Palo Alto, Calif.) at 488.5 or 292 nm for fluorescein and salicylic acid, respectively. Calibration curves were linear (correlation coefficient, >0.9999) and unaffected by the presence of the surfactants employed. Ten replicates of each experiment were performed.

RESULTS AND DISCUSSION

Experiments were performed to compare the size distributions of suspension and solution aerosols containing the same concentration of nonvolatile ingredients by weight. In the case of the suspension aerosol, the drug concentration (0.1%, w/v) was selected so that the aerodynamic diameter of the product should be similar to that of the primary particles (11). In more concentrated systems, the inclusion of more than one particle in each nebulized droplet is believed to produce aerosols of larger sizes because of the formation of clusters or aggregates in the spray. Total model drug output per actuation was assessed for both suspension and solution aerosols by discharging under liquid as described by Moren (14). The mean dose per actuation was 50.98 μg (SD = 3.45) for the solution and 52.62 μg (SD = 4.23) for the suspension aerosols. Disodium fluorescein was readily suspended by all surfactants but remained insoluble. Conversely, salicylic acid was readily solubilized by oleic acid and lecithin at 21°C but required warming to 37°C when sorbitan trioleate was the surfactant (the unit was cooled to 21°C before use where the solution was supersaturated. Precipitation was noted if the formulation was allowed to stand for more than 3 hr at 21°C).

When aerosols were discharged for sizing, quantities of model drug were retained in the actuator, evaporation chamber, and cascade impactor (Fig. 1). Table I shows the distribution of aerosol output in these three categories as a function of aerosol formulation. Similar quantities of model drug (about 17–20% of the dose) were retained by the actuator in all cases. Material retained by the evaporation

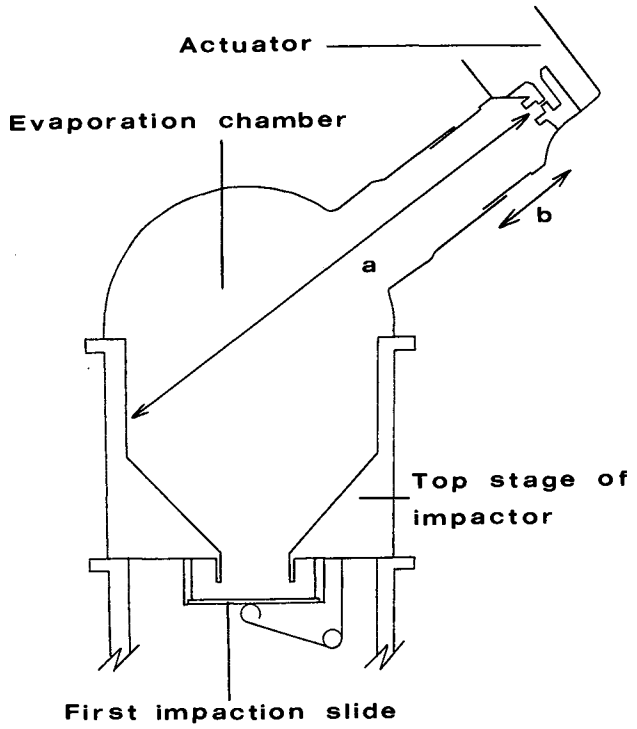

Fig. 1. Scale diagram of the evaporation chamber and first impaction stage of the particle sizing apparatus. The actuator was fitted tightly into the aerosol inlet port of the evaporation chamber atop a cascade impactor before discharging the aerosol. The evaporation chamber volume was 380 ml and its diameter was 8.4 cm. The distance between the actuator nozzle and the opposite inner wall of the impaction chamber (dimension a) was 15.0 cm, while the distance from the nozzle to the end of the mouthpiece (dimension b) was 2.75 cm. The orifice diameter of the actuator nozzle was 0.4 mm.

Table I. Distribution of Aerosol Output Among Actuator, Evaporation Chamber, and Cascade Impactor (N = 10; SD in parentheses)

Formulation	% in actuator	% in evaporation chamber	% in impactor[a]
	Disodium fluorescein (suspension)		
Oleic acid	17.87 (2.38)	37.93 (6.28)	44.21 (4.53)
Lecithin	17.34 (2.42)	39.72 (4.15)	42.95 (3.95)
Span 85	18.87 (1.03)	36.02 (1.49)	45.13 (1.19)
	Salicyclic acid (solution)		
Oleic acid	19.34 (3.00)	29.79 (1.64)	50.86 (3.55)
Lecithin	17.48 (0.69)	26.62 (4.42)	55.91 (4.45)
Span 85	19.45 (1.14)	19.87 (3.20)	60.68 (2.79)

[a] Percentage of aerosol output penetrating the first stage of the cascade impactor (aerodynamic diameter, <11.2 μm).

chamber probably consisted of particles that had a large stopping distance (17), because of either their large aerodynamic diameters or their high exit velocities from the actuator nozzle (1). Such particles may or may not have mass median aerodynamic diameters >11.2 μm (the 50% cutoff diameter of the first stage of this cascade impactor), but in either case they would almost certainly be retained by a patient's oropharynx during oral inhalation. The statistically significant difference (Table I, $P < 0.001$) between the percentage of solution aerosol (mean of pooled data = 26.05, SD = 5.08) and that of suspension aerosol (mean of pooled data = 38.02, SD = 4.58) deposited in the evaporation chamber could be due to several factors. Sprayed suspended solids are known to produce droplets with median primary droplet sizes greater than solutions (12) and these primary droplets are more likely to contain suspended particulates than the smaller satellites (1,3). Particulate aggregates may be sprayed intact if they were present in the original liquid suspension or they may be formed by multiple particle inclusion in single droplets (11). The presence of surfactants at the droplet–air interface is known to moderate the evaporation rate of volatile droplet components (18,19). It is unlikely, however, that the presence of the different surfactants, in either the suspension or the solution systems, altered evaporation rates sufficiently to produce differences in retention within the evaporation chamber. The minor changes observed in evaporation chamber retention for both solution and suspension aerosols containing different surfactants could equally well be explained by variations in droplet surface tension, viscosity (12), or random error between the formulations.

The fourth column in Table I presents the percentage of model drug penetrating the first stage of the impactor. All of this material had an aerodynamic diameter <11.2 μm, and although each size particle would be retained by different regions of the respiratory tract to different degrees, at least a fraction of each size range is potentially respirable following slow oral inhalation (8). Statistically significant increases ($P < 0.001$) in the percentage of dose reaching the impactor were noted for solution as compared to suspension aerosols.

None of the aerosol entering the impactor showed a particle size distribution that could easily be fitted to a normal or log-normal distribution (20). For this reason no attempt was made to determine a geometric standard deviation for any of the aerosol distributions. The size distributions of the aerosols are shown in Fig. 2. The area under each of the normalized histogram blocks is directly proportional to the percentage of the total model drug penetrating the first stage of the impactor in each of the size fractions. Therefore the total area under the histogram represents 100% of the drug penetrating the impactor (17). The gross differences between the solution series, A, and the suspension series, B, are summarized in Table II, in which the data are presented as mass median aerodynamic diameters (MMAD). Statistically significant differences ($P < 0.001$) in MMAD were observed between solution and suspension aerosols containing the same surfactant. Similar levels of significance were also observed when comparing the mass median aerodynamic diameters of disodium fluorescein suspension aerosols formulated with lecithin and sorbitan trioleate and when comparing salicylic acid solution aerosols formulated with oleic acid to those containing either lecithin or sorbitan trioleate. All other differences were not significant at this level. It is likely that the major differences between the solution and the suspension formulations, with pooled mean mass median aerodynamic diameters of 2.11 μm (SD = 0.19) and 4.00 μm (SD = 0.25), respectively, can be explained by the fact that suspension aerosols can have a MMAD no less than that of the original particles used in their formulation (11). Microscopic sizing of the jet-milled disodium fluorescein, prior to nonaqueous suspension manufacture, showed count median and volume median diameters of 2.6 and 4.9 μm, respectively, assuming sphericity. If allowances are made for various complications associated with shape, density (17), surfactant coating (11), and segregation of the distribution prior to entry into the impactor, the values quoted for MMAD of suspension aerosols (Table II) are probably consistent with the collection of coated, dry, micronized particles. The equilibrium MMAD of the solution aerosols, however, depends on the initial droplet sizes and the concentration of nonvolatile ingredients in the solution. It has been shown that a typical actuator produces

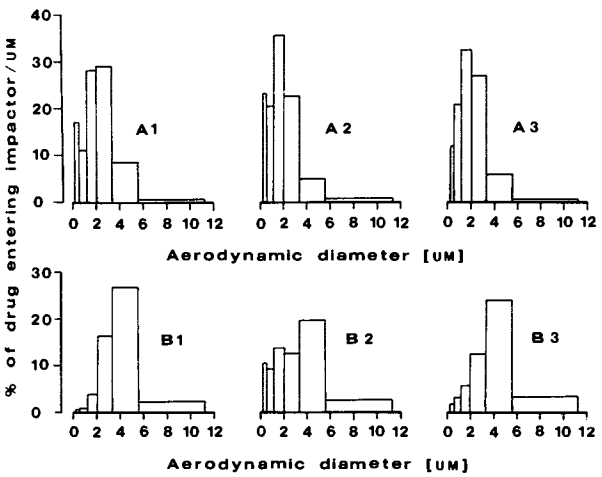

Fig. 2. Particle size distributions of the aerosol output escaping the actuator and evaporation chamber. The salicylic acid solution (A series) and the disodium fluorescein suspension (B series) aerosols contained either oleic acid, lecithin, or sorbitan trioleate (1, 2, and 3, respectively).

Table II. Mass Median Aerodynamic Diameter (MMAD) of Aerosol Output Escaping Actuator and Evaporation Chamber (N = 10)

Model drug	Surfactant	Aerosol type	Mean MMAD (SD) (μm)
Disodium fluorescein	Oleic acid	Suspension	4.00 (0.22)
	Lecithin		3.77 (0.19)
	Span 85		4.22 (0.10)
Salicyclic acid	Oleic acid	Solution	2.32 (0.08)
	Lecithin		1.93 (0.07)
	Span 85		2.07 (0.10)

droplets of between 20 and 40 μm in diameter (1,16) which leave the actuator nozzle at a high velocity [up to 50 ms^{-1} (21)]. For a solution with a nonvolatile content of 0.25% (w/v) this would be expected to yield particles with an aerodynamic diameter of between 2.5 and 5.0 μm assuming a particle density of 1.2 g cm^{-3}. These values are consistent with the data presented above for salicylic acid solution aerosols after the initial loss of large droplets and particulates in the actuator and evaporation chamber. The finer differences in MMAD of the solution aerosols may be explained by differences in droplet evaporation rates. Droplet evaporation can occur not only in the evaporation chamber (Fig. 1), but also during passage through the cascade impactor; smaller droplets escaping capture on the upper stages having longer to evaporate than their larger counterparts. Some of the data presented in Fig. 2 and Table II may therefore be evidence that the use of different surfactants in nonaqueous formulations is capable of moderating droplet evaporation kinetics. The significantly larger MMAD observed when comparing salicylic acid solution aerosols formulated with oleic acid to those formulated with lecithin or sorbitan trioleate may, for example, be explained by the ability of oleic acid to form a condensed film at the droplet–air interface (22) more easily than either lecithin or sorbitan trioleate, both of which are cumbersome as far as molecular packing is concerned, due to their multiple hydrophobic chains and large polar head groups (23).

We have emphasized the benefits of formulating high-volatility solution, rather than suspension, aerosols in order to achieve better respiratory tract penetration after oral inhalation therapy with metered dose inhalers. Previous work by Bell *et al.* (24), who found that commercial isoproterenol solution aerosols produced less respirable material than suspension systems, emphasizes the importance of volatility for all liquid ingredients; however, their solution formulations contained significant proportions of nonvolatile cosolvents. With the emergence of dimethyl ether (DME) as an acceptable propellant for pharmaceutical use and the use of nonaqueous solubilizing agents, the potential for dissolving drugs, as opposed to merely suspending them, has been greatly increased. The usefulness of DME is due to the increased polarity of this propellant compared to most fluorocarbon and hydrocarbon propellant blends (13). The present use of suspension aerosols restricts the possibilities for design variation in existing actuators owing, for example, to the likelihood of orifice blockage if nozzles are made too small. Some of our future work will focus on possible device modifications to best exploit high-pressure solution systems.

ACKNOWLEDGMENTS

The donation of actuators and valves from BLM Packaging Inc. and glass, pressure-resistant aerosol bottles from Wheaton Glass Inc. is gratefully acknowledged.

REFERENCES

1. P. R. Byron. *Pharm. Tech.* 11:42–56 (1987).
2. I. Gonda and P. R. Byron. *Drug Dev. Ind. Pharm.* 4:243–259 (1978).
3. P. R. Byron. *Drug Dev. Ind. Pharm.* 12:993–1015 (1976).
4. S. P. Newman. In S. W. Clarke and D. Pavia (eds.), *Aerosols and the Lung: Clinical and Experimental Aspects,* Butterworths, London, 1984, pp. 197–224.
5. S. P. Newman, G. Woodman, S. W. Clarke and M. A. Sackner. *Chest* 89:551–556 (1986).
6. P. König. *Chest* 88:276–284 (1985).
7. I. Gonda. *J. Pharm. Pharmacol.* 33:692–696 (1981).
8. P. R. Byron. *J. Pharm. Sci.* 75:433–438 (1986).
9. *Physicians Desk Reference* (41st ed.), Medical Economics Company, Oradell, N.J., 1987. p. 951.
10. *Physicians Desk Reference* (41st ed.), Medical Economics Company, Oradell, N.J., 1987, pp. 540–541.
11. I. Gonda. *Int. J. Pharm.* 27:99–116 (1985).
12. N. Dombrowski and G. Munday. In N. Blakebrough (ed.), *Spray Drying in Biochemical and Engineering Sciences,* Academic Press, London, 1968, pp. 209–320.
13. L. J. M. Bohnenn. *Aerosol Age* Sept:30–32 (1986).
14. F. Moren. *Int. J. Pharm.* 1:205–212 (1978).
15. F. Moren. *Int. J. Pharm.* 1:213–218 (1978).
16. F. Moren and J. Andersson. *Int. J. Pharm.* 6:295–300 (1980).
17. P. C. Reist. *Introduction to Aerosol Science,* Macmillan, New York, 1984, pp. 13–15, 40–49, 75–77.
18. C. C. Snead and J. T. Zung. *J. Coll. Interface Sci.* 27:25–30 (1968).
19. Y. Otani and Y. S. Wang. *Aerosol Sci. Tech.* 3:155–166 (1984).
20. T. Allen. *Particle Size Measurement* (2nd ed.), Chapman and Hill, London, 1975, pp. 74–112.
21. R. W. Rance. *J. Soc. Cosmet. Chem.* 25:545–561 (1974).
22. D. J. Shaw. *Introduction to Colloid and Surface Chemistry* (3rd ed.), Butterworths, London, 1980, pp. 98–105.
23. P. H. Elworthy, A. J. Florence and C. B. MacFarlane. *Solubilization by Surface-Active Agents,* Chapman and Hall, London, 1968, pp. 314–322.
24. J. H. Bell, K. Brown, and J. Glasby. *J. Pharm. Pharmacol.* 25 (Suppl.):32–36p (1973).