Axial Ratio Measurements for Early Detection of Crystal Growth in Suspension-Type Metered Dose Inhalers

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INTRODUCTION

Crystal growth in suspension-type metered dose inhaler (MDI) formulations leads to a decrease in the amount of respirable drug available to the patient. Such growth is not always easy to determine by aerodynamic testing (1). During formulation development, it is possible to detect changes in crystal size distribution, as a manifestation of physical instability, while the drug is suspended in nonaqueous propellant. We have shown that micronization and the presence of surface active agents can promote the crystal growth of a model compound in a traditional propellant (2). This was determined by monitoring changes in volume median diameter, D_{vm}, of methylprednisolone suspended in trichloromonofluoromethane (CFC-11) using forward laser light scattering. However, the detection of finite changes in D_{vm} required that measurements were performed over a period of 120 days.

We have also observed, in stored albuterol formulations containing alternative propellant blends, that changes in both the axial ratio (AR = length/width) and the crystal size had occurred (Fig. 1). Micronized albuterol crystals before (Fig. 1A) and after storage in a CFC-based formulation (Fig. 1B) had similar crystal habits and sizes (mean diameter $\approx$ 1.5 μm, AR $\approx$ 1). However, after approximately 12 months in an alternative propellant blend, the crystals grew into fine needles (Fig. 1C). We hypothesized that for drugs such as albuterol, which are known to have substantial axial ratios in their unmicronized form (3), a change in AR may provide an early indication of crystal growth before significant changes can be detected by measurements of D_{vm} or mass median aerodynamic diameters. To test this hypothesis we sized crystals of salicylic acid (SA) suspended in a CFC propellant blend as a function of time. Axial ratios were determined simultaneously. Acicular crystals of salicylic acid had been grown previously in CFC-11, in which the drug has an unusually high solubility (4).

METHODS

SA (City Chemical Corp., New York) was micronized using a Jet-O-Mizer fluid energy mill (Model 00, Fluid Energy Processing and Equipment Co., Hatfield, PA) operated at 70 psig using dry air. The size of the micronized SA was assessed by optical microscopy (Optiphot Microscope, Nikon, Tokyo). Suspensions were prepared by weighing the micronized SA into 4-oz plastic-coated glass containers (Wheaton Glass, Mays Landing, NJ). CFC-11 (Dupont Wilmington, DE) was added and bottles were crimped with continuous valves (BK356 metering valve modified to continuous, Bespak Inc., Cary NC). CFC-12 was subsequently added via a pressure burette (30-ml pressure burette, Model 35B, Aerosol Laboratory Equipment, Walton, NY) to give a propellant blend ratio of 1:1 by weight and a SA concentration of 1% (w/w). All formulations were stored in a water bath (Model mgw RMS Lauda) maintained at 25 ± 0.1°C. Suspensions were filtered at fixed times through a 25-mm stainless-steel filter holder containing an 0.22-μm filter (Millipore GVWP filter, Millipore, Bedford, MA) as described previously (4). The filter holder was disassembled and a sample of SA crystals captured on the filter transferred to a microscope slide for observation at 400 or 600×. Photomicrographs were also obtained. Particles were measured along their longest axis using a calibrated eyepiece graticule (CFW 10XCM eyepiece, Optiphot, Nikon, Japan). A minimum of 2500 particles in at least 10 fields of view was measured from each sample in order to develop a histogram describing the crystal size distribution. Particles were grouped into those with lengths <1, 1 through <3, 3 through <5, 5 through <10, and 10 through <15 divisions and those which were >15 divisions, where 1 division at ×600 equals 1.67 μm. Axial ratios were determined by taking the ratio of crystal length along the longest axis to greatest crystal width for a minimum of 250 particles for each sample. The mean AR was determined by $(\Sigma n_i AR_i)/n_T$, where AR_i is a particular ratio of length to width, n_i is the number of crystals having that ratio, and n_T is the total number of crystals measured. Standard deviations were calculated by $[\Sigma n_i(AR_i - \text{mean}AR)^2/(n_T - 1)]^{1/2}$.

RESULTS AND DISCUSSION

Microscopy is the only method that examines the shape and appearance of the individual particles (5). It was used to grossly quantify the crystal growth of micronized SA suspended in the propellant blend. The monograph for metaproterenol sulfate inhalation aerosol (6) suggests that microscopy be performed by actuating the formulation onto a microscope slide held 5 cm from the mouthpiece. Results from our laboratory indicate, however, that less than one-third of the total output from a typical albuterol MDI formulation is impacted into a slide held at that distance. To prevent irregular sampling and the likelihood of counting recrystallized SA particles formed from evaporated solution droplets con-

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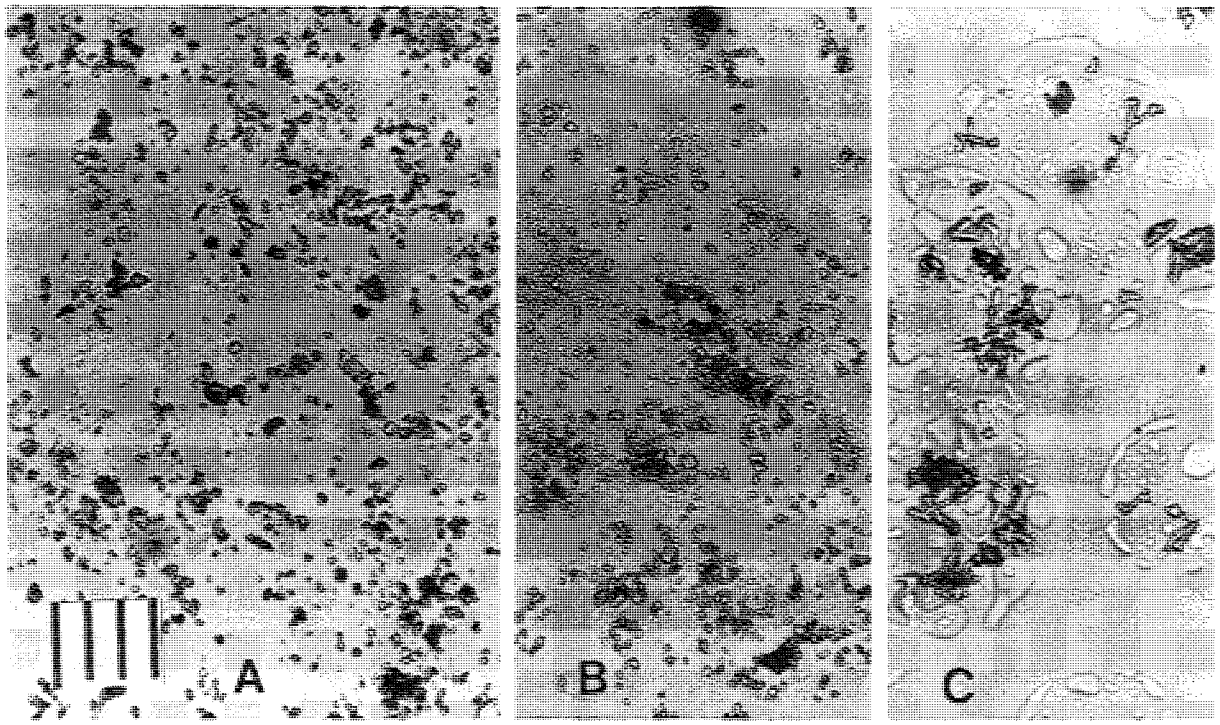

Fig. 1. Micronized albuterol before (A) and after 12 months of storage in suspension formulations containing CFC 11, CFC 12, and oleic acid (B) or propellant A-17, dimethyl ether, and oleic acid (C). Photographs were taken at the same magnification. The distance between the hatch marks is equivalent to 10 μm.

taining dissolved drug, SA crystals were sampled following filtration. Figure 2 shows histograms representing the distribution of SA crystals prior to (t = 0) and after (3 and 31 days) formulation. Initially, 99% of the micronized SA was less than 8.4 μm. After day 31 in suspension, only 88% of the SA particles were less than 8.4 μm.

Micronization at high operating pressures usually results in particles with axial ratios approaching 1 (3). In the case of micronized SA the initial mean AR was 1.3. The axial ratio of micronized SA crystals was also evaluated after 3 days, 12 days, and 38 weeks in suspension. Cumulative frequency versus axial ratio at these time points is plotted in Fig. 3. Table I, however, compares the mean AR of micronized SA, SA crystals filtered from suspension at the various time points, and unmicronized SA. There was a change in AR after only 3 days (Table I), a time at which it would be difficult to show convincing evidence of crystal growth unless extremely large numbers of particles were carefully sized (Fig. 2). Volume and mass median diameters are known to be much less sensitive to growth than the number-based frequency distributions shown in Fig. 2. The form of the cumulative frequency versus AR plot (Fig. 3) best illustrates the rapid diagnostic sensitivity of AR to early crystal growth and the significant increase in AR after only 3 days. The mean AR changed dramatically between preformulation and 12 days (1.3 to 2.3, respectively). After that time, although the crystals continued to grow, the AR did not change. SA crystals filtered from suspension after 38 weeks still had an AR less than that of the unmicronized crystals.

Crystal habit is the description of the outer appearance of the crystal (7). Factors affecting crystal habit include the degree of supersaturation (8), rate of cooling (9), degree of solution agitation (10), nature of the solvent, presence of cosolvent, and constancy of environmental conditions. In the case of the SA and albuterol it has been demonstrated that the nature of the solvent affected the crystal habit of the material. Albuterol, which was apparently physically stable in the CFC propellant blend, experienced a dramatic change in crystal habit in a more polar alternative propellant (Fig. 1). We have also observed that SA crystals grown in pure CFC-11 had a much larger AR than those grown in the less polar CFC-12.

These results suggest that for a crystalline compound having an acicular crystal habit in the propellant vehicle of choice, physical instability may be detected shortly after incorporation by measuring the axial ratio of the micronized drug particles filtered from the suspension. The advantage of this simple technique is that changes in the physical stability of the formulation may be detected soon after formulation using a simple technique. While it is recognized that particle characterization (size and shape) can be labor intensive and subject to operator variability and fatigue, the process can be automated or combined with image analysis to reduce errors and increase sample throughput. Average axial ratios can also be determined more easily, and on fewer particles, than is the case with microscopic particle size determinations. Automated microscopy has been proposed as a compendial test for examining particulates in parenteral solutions (11). We suggest that a microscopic technique should be used to determine axial ratios of crystals filtered from nonaqueous suspension formulations in order to detect physical instability at early stages in MDI formulation development.

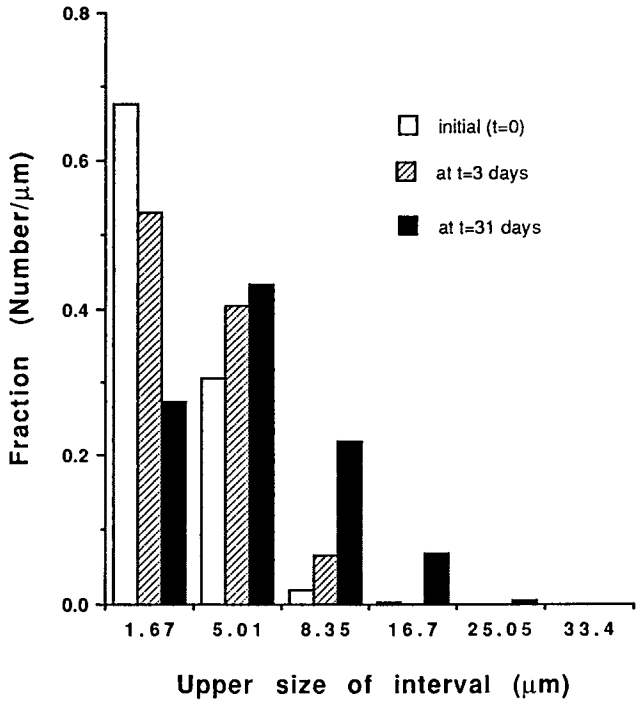

Fig. 2. Crystal growth of micronized SA suspended in a 1:1 blend of CFC 11:CFC12. Crystal sizes are lengths measured along the longest axis.

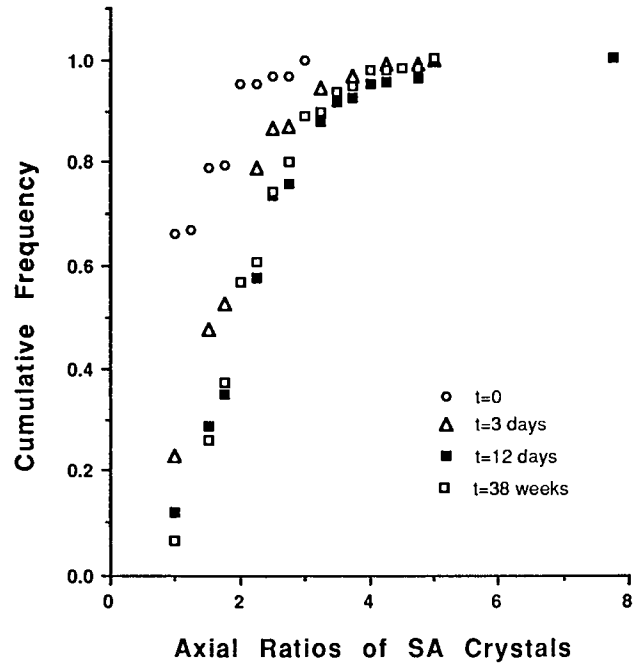

Fig. 3. Cumulative frequency versus axial ratio of SA crystals suspended in CFC 11:CFC 12 over 38 weeks. Data for $t = 0$ shows micronized crystals prior to formulation.

Table I. Mean Axial Ratios of SA Crystals Before and After Suspension in a 1:1 CFC11:CFC12 Propellant Blend

SA crystals	Mean AR[a]	SD[a]
Micronized	1.3	0.5
t = 3 days	1.8	0.8
t = 12 days	2.3	1.0
t = 38 weeks	2.2	0.8
Unmicronized[b]	2.8	1.4

[a] See Methods for definition of mean AR and standard deviation (SD).
[b] Included for comparison.

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