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COMMUNICATION

Particle Size Determination of a Flocculated Suspension Using a Light-Scattering Particle Size Analyzer

A. Bommireddi,* L. C. Li, D. Stephens, D. Robinson, and E. Ginsburg

Advanced Drug Delivery, Hospital Products Division, Abbott Laboratories, Abbott Park, IL 60064-3500

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ABSTRACT

Microscopy is a useful and direct method for measuring the particle size of a suspension because, in addition to the particle size and size distribution, it provides visual detection of the shape and state of aggregation of the particles in the suspension. However, this method suffers from the shortcomings of being tedious and time consuming. In this study, a light-scattering particle size analyzer was used to determine the particle size and size distribution of a flocculated suspension. The sonication of the sample prior to and during measurement was found to be critical in ensuring that data are representative of the size distribution of the primary particles of the suspension. The light-scattering results were further confirmed by data generated using a polarized light microscope equipped with an image analyzer.

INTRODUCTION

Controlled flocculation is the most commonly used approach in formulating pharmaceutical suspensions (1). In a flocculated suspension, particles are attracted to each other, giving rise to scaffoldlike structures called flocs. The sedimentation kinetic of a flocculated suspension is primarily controlled by the size of the floc-aggregates (2). However, the size of the primary particles in a flocculated suspension can be a critical factor affecting the dissolution rate of the suspension and the resultant bioavailability of the product. Therefore, the primary particle size of a flocculated suspension is a key quality control parameter.

The determination of the primary particle size of a flocculated suspension can be performed by microscopic

*To whom correspondence should be addressed.

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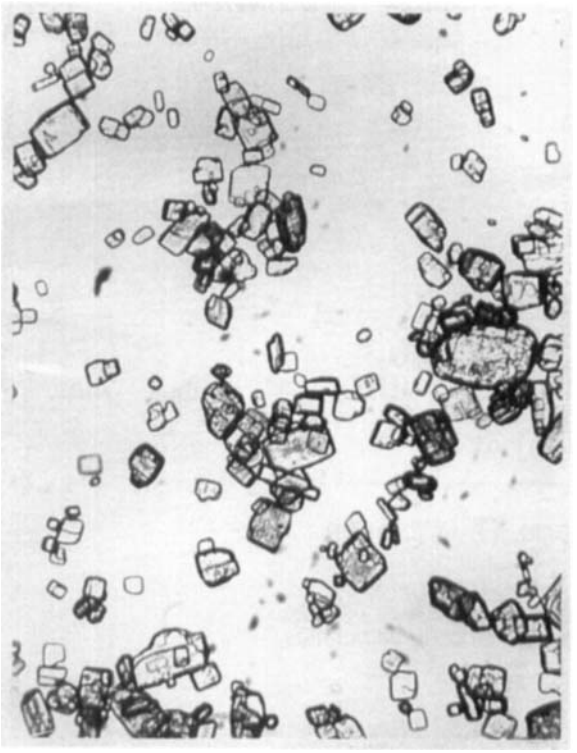

Figure 1. A micrograph (100×) of butamben suspension.

methods, which enable direct viewing of the samples and allow measurement of the primary particles, even in the form of flocs. However, this method can be very tedious and time consuming. The use of automated instrumental particle size analysis methods offers savings in both time and labor. But, the measurement of the primary particle size of a flocculated suspension may be problematic unless a mechanism is provided for the breakdown of the flocs during measurement. This paper describes the measurement of the particle size of a flocculated suspension using a light-scattering particle size analyzer equipped with a sonication function. The results are compared with those obtained by microscopic determination.

MATERIALS AND METHOD

Materials

A suspension consisting, in part, of 5% butamben (butyl-*p*-aminobenzoate) and 0.9% sodium chloride was used for this study. The suspension also contains 0.25% polysorbate 80 and 2.5% PEG 3350. In the presence of a relatively high concentration of electrolyte (NaCl), the suspension is highly flocculated. The zeta potential of the suspension was determined by a microelectrophoretic method (Laser Zee Meter, model 501, PenKem) to be −8.5 mV.

Instrument

The Horiba Model LA900 laser-scattering particle size distribution analyzer used in this study is based on the principle of the mei scattering theory. The optical system of the analyzer consists of three separate detectors, one each for the side and rear scattering and a third detector for the front scattering. The small-angle, front-scattered light from the He-Ne laser (632.8 nm) is detected by the ring detector, and the large-angle, rear-scattered light from the tungsten lamp is detected by the side and rear detectors. Side and rear scattering are necessary to measure particles under 0.1 μm. A nonlinear iteration procedure is used to calculate the particle size distribution from the light-scattering data.

Particle Size Measurement by the Light Scattering Particle Size Analyzer

Distilled water, filtered using a 0.2 μm membrane filter and degassed under sonication and the application of vacuum, was used as a medium for the measurement. A 200–250 ml quantity of water was placed in the sample mixing chamber, stirred, and circulated through the cell. The instrument was blanked for background correction. The sample was subsequently added dropwise into the cell until the laser transmittance was between 85% and 90% as displayed on the computer screen of the instrument. The relative refractive index was set at 1.22. The particle size analysis outputs used for this study consist of a display of a relative size distribution (volume-based) histogram and a cumulative undersize distribution curve, a mean (geometric) particle size, and the standard deviation of distribution.

Particle Size Measurement by Polarized Light Microscopy

A small amount of suspension sample was placed onto a glass slide, covered with a coverslip, and examined with a Nikon Microphot-SA light microscope using plane and cross-polarized illumination. Color video prints of the samples were taken using a Sony color video camera that was attached to the microscope and interfaced with a Leica Q570 image analyzer. Particles were manually

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measured for the longest length using the image analyzer. A total of 330 particles was measured.

RESULTS AND DISCUSSION

Figure 1 displays a micrograph (100×) of particles in the butamben suspension. Butamben particles were seen linking to each other, giving rise to network structures that are typical of a flocculated suspension. The size distribution profile of the suspension was determined by the light-scattering particle size analyzer using only agitation (Fig. 2). Figure 3 shows the size distribution of the same suspension; it was determined using sonication for 2 min prior to and during measurement. It is apparent that, with the application of sonication, the particle size distribution shifted to a smaller size. This result indicates that the distribution shown in Fig. 2 represents the size of some aggregates of butamben particles in the sample; the breakdown of these aggregates by sonication is evident in the profile presented in Fig. 3.

Table 1 presents the mean and standard deviations of distribution data for measurements performed under four different conditions. These data clearly indicate that 2 min of sonication prior to and during measurement are adequate to yield consistent results representing the particle size distribution of the primary particles of the suspension. Additional results show that a sonication time longer than 2 min did not produce any significant change in size distribution. Therefore, it can be concluded that the particle size data obtained with sonication represent the size distribution of the primary particles of the suspension, and that there was no particle fragmentation as a result of sonication.

Figure 4 shows the log-probability plot of the cumulative undersize volume distribution of the microscopic data. The mean (geometric) of the microscopic data was found to be about 45 μm, which is in close agreement with the mean size (42.4 μm) measured by the Horiba instrument.

The light-scattering particle size analyzer has been shown to provide an acceptable means for measuring the

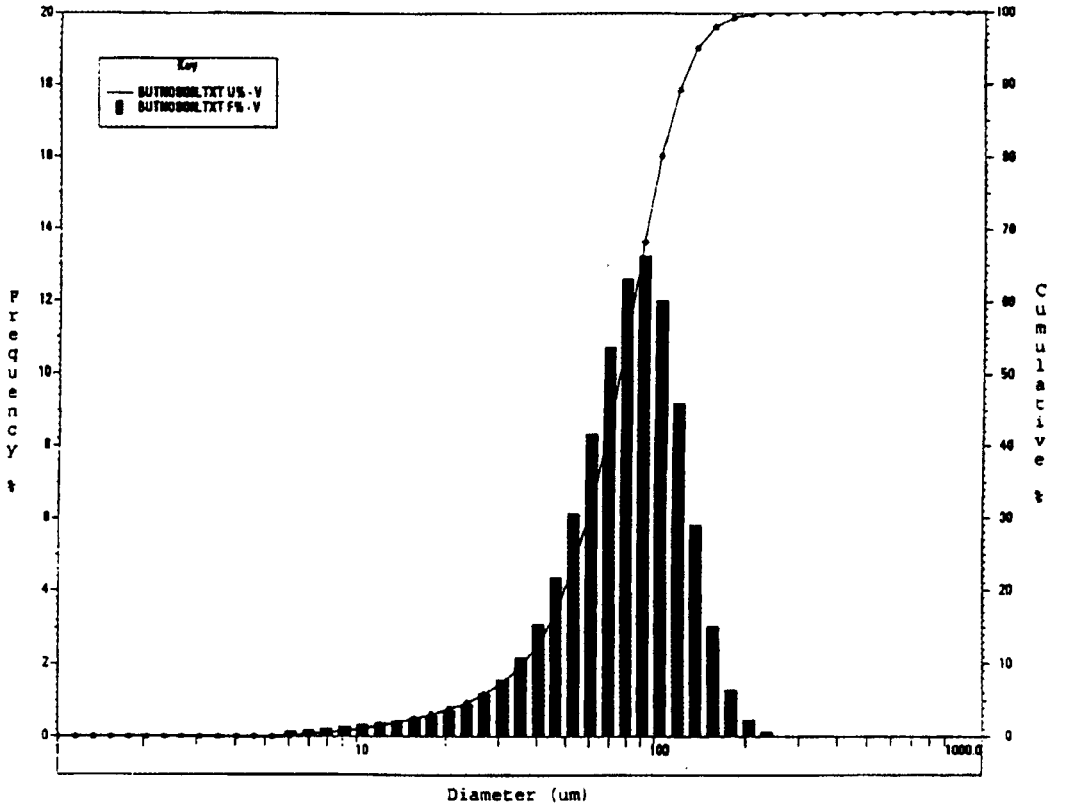

Figure 2. Particle size distribution of butamben suspension measured with agitation.

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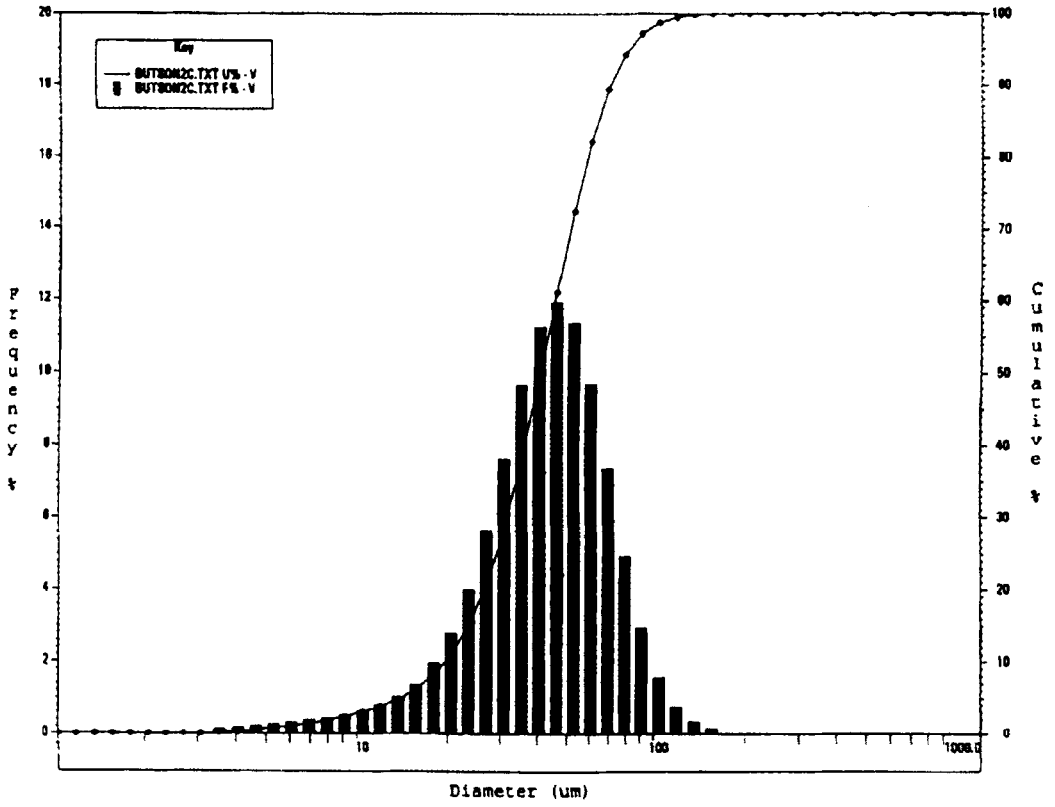

Figure 3. Particle size distribution of butamben suspension measured with 2 min of sonication prior to and during measurement.

Table 1

Particle Size Distribution Parameters

Measurement Conditions	Mean (μm)	Standard Deviation (μm)
No Sonication	75.8	33.1
	81.4	41.9
	75.9	36.9
Sonication during measurement	52.8	28.1
	54.0	30.6
	66.0	30.0
Sonication 1 min prior to and during measurement	43.1	21.3
	41.5	20.1
	42.9	21.2
Sonication 2 min prior to and during measurement	44.5	22.4
	42.8	20.7
	42.4	20.7

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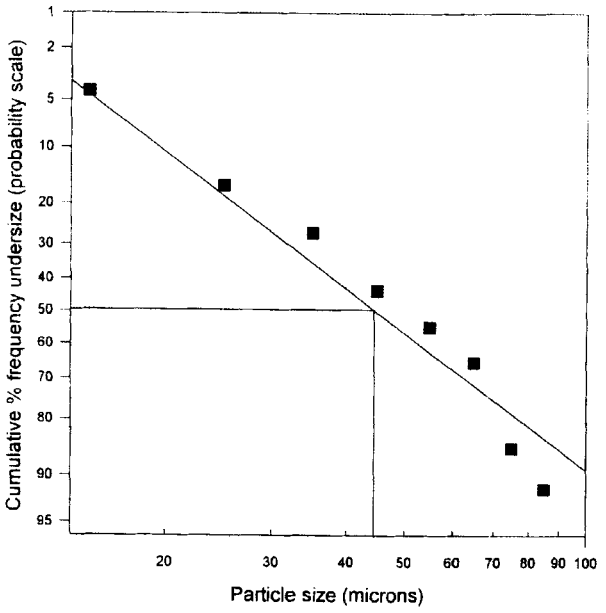

Figure 4. A log-probability plot of the microscopic volume distribution data.

particle size of a highly flocculated suspension. Sonication prior to and during measurement was found to be critical in determining the size of the primary particles of the suspension. The reproducibility and accuracy of this method have also been demonstrated. The relatively simple operation procedures of this method make it very attractive for routine quality control of suspension dosage forms.

ACKNOWLEDGMENT

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