Drug Development and Industrial Pharmacy, 26(8), 895–900 (2000)

COMMUNICATION

Particle Size Determination of a Three-Component Suspension Using a Laser-Scattering Particle Size Distribution Analyzer

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ABSTRACT

In this study, a rapid and accurate particle size determination method using a light-scattering particle size analyzer was developed to measure the particle size and size distribution of a suspension containing three solid components: clotrimazole, triamcinolone, and sarafloxacin, which have different refractive indices. To ensure that data represent the size distribution of the primary particles of the suspension, the optimal sonication prior to and during measurement was determined. It was found that the results obtained using the average relative refractive index (RRI) of the three components agreed with the results obtained using three individual RRIs. In addition, the results from two analysts demonstrated good reproducibility of this method. The size distribution data of the suspension were also compared to those of the bulk drugs. The results showed that the median particle size of this three-component suspension is relatively close to that of clotrimazole, which accounts for 80% of solid particles in the suspension. Furthermore, the results obtained using the light-scattering technique were comparable to those obtained using a polarized light microscope equipped with an image analyzer, indicating acceptable accuracy of this technique.

Key Words: *Particle size determination; Suspension.*

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INTRODUCTION

Measuring particle size and the size distribution is a routine and essential part of quality control of suspensions in the pharmaceutical industry. The particle size of a suspension can be a critical factor affecting its sedimentation volume and rate, dissolution rate, and resultant bioavailability. The determination of the primary particle size of a suspension can be performed by a microscopic method that provides direct observation of the samples. Microscopy allows measurement of the primary particles and provides information on size, shape, and degree of aggregation of the particles (1). However, this method is very time consuming. The use of automated instrumental particle size analysis methods can save both time and labor. In recent years, many methods capable of measuring particle size have become readily available and are of particular interest to the pharmaceutical industry (2). Quasi-elastic light scattering has been widely used as a method for assessing the particle size distribution of suspensions. A study by Bommireddi et al. (3) showed that the particle size and size distribution of the primary particles can be obtained by subjecting the suspensions to sonication prior to and during the measurement using a laser light-scattering particle size analyzer.

This study investigated the use of a laser light-scattering particle analyzer equipped with a sonication function to measure the particle size of a three-component suspension. The goals of this study were to investigate whether the average relative refractive index (RRI) of the three RRIs can be used instead of the individual RRIs and to show the reproducibility of this technique. In addition, the accuracy was determined by comparing the results generated by this technique to those obtained by a microscopic method.

EXPERIMENTAL

Materials

A suspension consisting of three micronized active ingredients (clotrimazole, triamcinolone acetonide, and sarafloxacin HCl) in phosphate buffer (0.02 M, pH 7) was used in this study. The formulation is given in Table 1. Clotrimazole was from Fabbrica Italiana Sintetici (Vicenza, Italy), triamcinolone acetonide was from Sicor (Milano, Italy), and sarafloxacin HCl was an Abbott Laboratories (Abbott Park, IL) product. Tween 20 was purchased from Aldrich (Milwaukee, WI); sodium chloride was from EM (Gibbstown, NJ); and EDTA, sodium carboxymethylcellulose (CMC), and other reagents were from Sigma (St. Louis, MO).

Table 1

Ingredients of the Three-Component Suspension

Ingredient	Concentration
Triamcinolone	1.1 mg/ml
Sodium CMC	0.35% (w/v)
Sodium chloride	1% (w/v)
EDTA	0.1% (w/v)
Tween 20	0.02% (w/v)

Instrument

The Horiba model LA920 laser light-scattering particle size distribution analyzer (Horiba Instrument, Irvine, CA) used in this study measures the particle size distribution by an angular light-scattering technique with an assumption that the particles are spherical. The optical system consists of 13 separate sets of detectors, 12 for wide-angle and back scattering and 1 for the forward scattering. The small-angle, forward-scattered light is conventionally produced by the helium-neon laser and is detected by the ring detector array. To measure very small particles, the wide-angle and back-scattered light is given by the tungsten lamp (405 nm)/laser (632.8 nm) combination and is detected by individual photodiodes located at larger angles from the forward detector array.

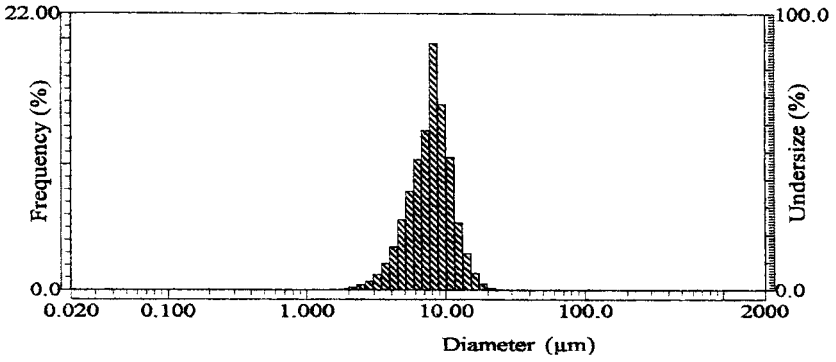

Figure 1. A typical particle size distribution profile of the suspension generated by the laser light-scattering particle size analyzer.

Table 2

Volume-Based Particle Size Distribution Data of a Three-Component Suspension Measured by Laser Light Scattering Particle Size Distribution Analyzer With and Without 2-minute Sonication at Various Power Levels

Sonication Power	Median (μm)	<90% (μ)
0	10.83	18.68
	10.14	16.12
	12.01	19.31
Average ± SD	10.99 ± 0.95	18.04 ± 1.69
2	8.03	14.26
	5.28	8.63
	8.87	15.53
Average ± SD	7.39 ± 1.88	12.81 ± 3.67
7	8.17	15.75
	5.06	8.60
	9.25	16.92
Average ± SD	7.49 ± 2.18	13.76 ± 4.50

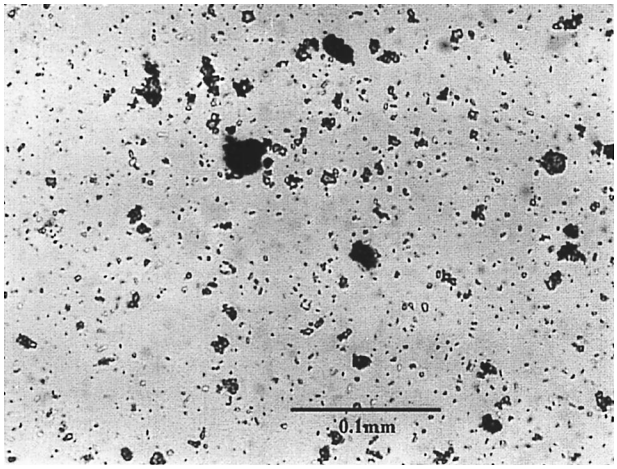

Figure 2. A photomicrograph of the suspension.

Table 3

Number-Based Particle-Size Distribution of a Three-Component Suspension Obtained by Laser Light Scattering Particle-Size Analyzer and Light Microscopy with Automated Image Analysis

Method	Average Median ± SD (μm)
Laser light scattering	4.05 ± 0.69
Light microscopy[a]	3.29 ± 1.15

[a] Number of particles measured = 906.

The Horiba instrument is capable of determining particles with a size range from 0.02 to 2000 μm.

Methods

Particle-Size Measurement by the Light Scattering Particle Size Analyzer

A buffer solution saturated with three drugs containing Tween 20 (0.02% w/v) was used as a dispersant for the measurement. The dispersant (150–200 ml) was placed in the sample mixing chamber, stirred, and circulated through the cell. The instrument was blanked for background correction. The sample was added dropwise into the sample chamber until the laser transmittance was stable between 70% and 95%, as displayed on the computer screen. The RRI was set at a predetermined value. The sample was sonicated prior to and during the measurement to break down the aggregates. The particle size analysis output was presented as volume-based relative size distribution unless stated otherwise. A median particle size and the 90% undersize measure were reported.

Particle Size Measurement by Polarized Light Microscopy

A small amount of suspension was placed on a glass slide, covered with a coverslip, and examined with a Ni-

Table 4

Volume-Based Particle Size Distribution of the Suspension Determined by Two Analysts as Shown by Reproducibility of the Method

Analyst	Median (μm)	<90% (μm)
1	8.46	12.48
	8.32	12.90
	8.04	11.64
	7.76	11.08
	8.73	14.05
	6.84	9.46
	8.98	16.53
	8.61	13.27
	7.85	11.19
	8.06	11.97
Average ± SD	8.17 ± 0.61	12.46 ± 1.93
2	8.58	14.55
	8.33	13.29
	6.25	8.61
	8.47	12.96
	8.69	13.99
	8.82	14.17
	8.98	14.41
	10.76	22.58
	8.73	15.66
	8.63	16.01
Average ± SD	8.62 ± 1.02	14.62 ± 3.28

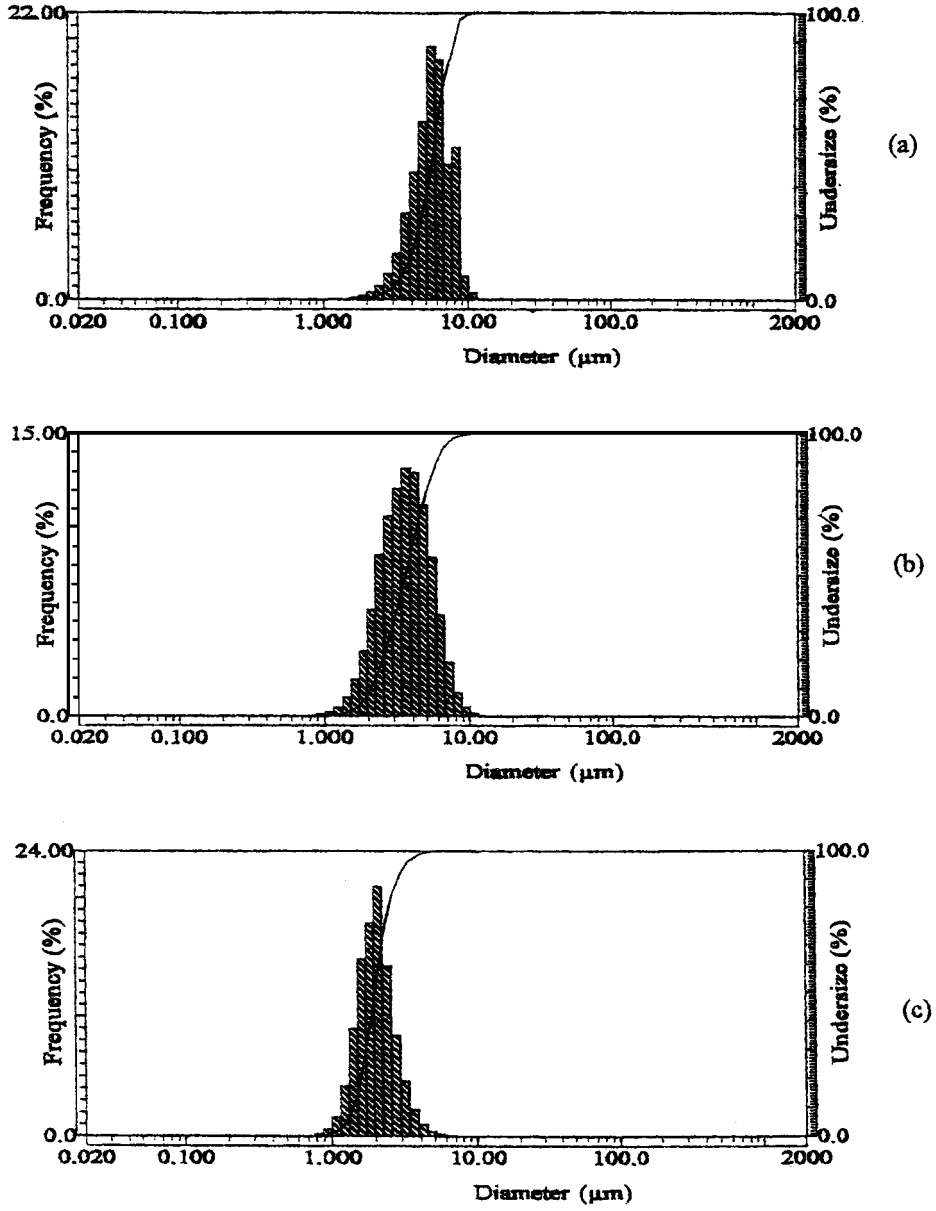

Figure 3. Typical particle size distribution profiles of (a) clotrimazole, (b) triamcinolone acetonide, and (c) sarafloxacin HCl generated by the light-scattering particle size analyzer.

kon® Microphot-SA light microscope equipped with 40× and 100× lenses and a Leica® Q550IW image analyzer and automated routine.

RESULTS AND DISCUSSION

Figure 1 displays a typical particle size distribution profile of the suspension obtained from the laser light-scattering particle size analyzer. To measure the primary particle size distribution of the suspension, sonication was used to break down the aggregates. The optimal sonication power required for the measurement was determined. Table 2 gives the particle size distribution results for a typical sample exposed to various levels of sonication power prior to and during measurement. Without sonication, the medians were the measurement of the aggregates. After 2 min sonication at power 2, the median

particle size was reduced. Increasing the sonication power to 7 did not result in further reduction of the particle size. Therefore, high-power sonication, which generates more heat and noise, is not necessary. It was determined that 2 min of sonication at power 2 prior to and during measurement is adequate to yield consistent results representing the primary particle size distribution of the suspension.

Figure 2 shows a photomicrograph of the suspension. The number-based particle size distribution of the suspension obtained by the laser light-scattering particle size analyzer with a median size of 4.05 μm was comparable to that obtained by the light microscopy and automated image analysis (3.29 μm) (Table 3). This result indicates that the accuracy of the laser light-scattering particle size analyzer is acceptable, and that this method is reliable for the measurement of the particle size distribution of a three-component suspension.

The reproducibility of this method was also evaluated. Particle size distribution results obtained by two analysts for the suspension were compared. The median determined by analyst 1 was 8.17 μm, compared to 8.62 μm obtained by analyst 2 (Table 4). Both median and <90% undersize determined by the two analysts were very close, suggesting that this method is reproducible.

Typical particle size distribution profiles of the three bulk drugs obtained by the laser light-scattering particle size analyzer are shown in Fig. 3. The median particle size of clotrimazole, triamcinolone acetonide, and sarafloxacin HCl were 6.7, 3.7, and 2.1 μm, respectively (Table 5). The median particle size of the suspension containing three drugs (8.2 μm) was relatively close to that of clotrimazole, which is the most concentrated ingredient (10 mg/ml), accounting for more than 80% of the total solid particles in the suspension.

The RRIs of clotrimazole, triamcinolone acetonide, and sarafloxacin HCl were 1.26, 1.18, and 1.20, respectively. The RRI used in the measurement was an average of the RRIs of the three bulk drugs. The average RRI was 1.21; however, due to the limitation of the instrument, the RRI of 1.20 was chosen for this experiment. The particle size distribution data of the three-component suspension obtained using an average RRI and the three different RRIs are given in Table 6. The close agreement between these results indicates that the average RRI can be used

Table 6

Volume-Based Particle Size Distribution Data of the Three-Component Suspension Calculated Using Relative Refractive Indices of Three Individual Drugs

RRI	Median[a] (μm)	<90%[a] (μm)
1.20	8.17 ± 0.61	12.46 ± 1.93
1.18	8.36 ± 0.99	13.78 ± 2.80
1.26	8.17 ± 0.94	13.53 ± 2.86

[a] Average of 10 independent measurements ± SD.

Table 5

Volume-Based Particle Size Distribution Data of the Three Individual Active Ingredients

Ingredient	Median (μm)	<90% (μm)
Clotrimazole (RRI = 1.26)	5.58	8.06
	6.02	8.52
	8.47	14.45
Average[a] ± SD	6.69 ± 1.56	10.34 ± 3.57
Triamcinolone acetonide (RRI = 1.18)	3.90	6.34
	3.63	5.71
	3.62	5.88
Average[a] ± SD	3.72 ± 0.16	5.97 ± 0.33
Sarafloxacin HCl (RRI = 1.20)	2.17	3.27
	2.00	2.89
	2.18	3.19
Average[a] ± SD	2.12 ± 0.10	3.12 ± 0.20

[a] Average of 3 independent measurements.

in particle size determination of the suspension containing three drugs with refractive indices that are not significantly different.

In conclusion, the light-scattering particle size analyzer provided an acceptable means of measuring the particle size and size distribution of a three-component suspension. Sonication prior to and during measurement was required for the determination of primary particle size. The accuracy, precision, and reproducibility of this method were also demonstrated. In addition, the average RRI can be used for the particle size determination of the suspension containing three drugs as their refractive indices were not significantly different.

ACKNOWLEDGMENT

We would like to thank Joseph Neilly and Joyce House for their assistance in the microscopic measurements.

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