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COMMUNICATION

Light-Scattering Method in Particle Size Analysis of Parenteral Emulsions

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ABSTRACT

The use of a light-scattering particle size distribution analyzer has been shown to be a convenient method for characterizing the particle size distribution of parenteral emulsions. However, the concentrations of the samples used were found to have a major impact on the particle size distribution results, particularly for samples with a mean particle size smaller than 0.2 μm. An increase in sample concentration caused a shift to smaller particle sizes as a result of multiple scattering. The blue-light (tungsten lamp) intensity, instead of the He-Ne laser integrity, should be used to control sample concentration within the optimal range for measurement.

INTRODUCTION

In the past, fat emulsions were administered intravenously to patients as nutritional supplements (1). In recent years, fat emulsions have been found to be effective vehicles for the parenteral delivery of water-insoluble drugs (2). The particle size distribution of the oil globules is one of the most important physical characteristics of a parenteral emulsion. The physical instabilities of an emulsion such as coalescence can be monitored by measuring the changes in the particle size distribution. Furthermore, because of clinical safety concerns, there are very stringent particle size distribution requirements for parenteral emulsions. Most intravenous emulsions contain particles in the range of 10 nm–1 μm, while particles above 5 μm are clinically unacceptable because they cause the formation of pulmonary emboli (3).

Various methods have been utilized for particle size analysis of parenteral emulsions (4). The photon correlation spectroscopic method (PCS) is currently the most widely used. It is capable of measuring particle sizes below 1 μm and providing accurate determination of the particle size by using an instrument such as a NICOMP particle sizer (5). However, the index of polydispersity as given by this method provides no detailed information

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regarding the actual particle size distribution of the emulsion.

In recent years, light-scattering particle size analyzers have been used with increasing frequency because of their capability of determining a wide range of measurable particle sizes as well as their unbiased determination of particle size distribution (6). Their optical systems and data treatment methods may vary, depending upon the manufacturer of the instrument. The mie scattering theory is one of the principles upon which the light-scattering particle size analyzer (Horiba LA-900) used in this study is based (7). According to the mie scattering theory, when monochromatic light interacts with a spherical particle, the intensity of scattered light reflected in a certain direction by that particle is determined by the particle size diameter, defined by the ratio of the circumferential length of the sphere to the wavelength of the incident light, and the relative refractive index, which is the ratio of the refractive index of the particle to that of the medium. 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 needed to accurately measure particles under 1.0 μm. A nonlinear iteration procedure is used to calculate the particle size distribution from the light-scattering data. In this study, parenteral emulsions were analyzed using the light-scattering particle size analyzer. The effect of the sample concentration on the particle size distribution results (mean and standard deviation) was also investigated. The results were also compared with those determined using PCS.

MATERIALS

Parenteral emulsions containing 10% soybean oil and 1% drug were used for this study. The emulsions also contain egg lecithin (12 mg/ml) as the emulsifier and glycerol (22.5 mg/ml) as the tonicity adjuster. Four different lots (lots A, B, C, and D) of emulsion samples were used for this study.

METHODS

Light-Scattering Particle Size Analysis

The Horiba LA-900 light-scattering instrument equipped with a personal computer was used for this study. Distilled water which was filtered through a 0.2-μm membrane filter and degassed by sonication was used as the medium for the dilution and subsequent measurement. A 100- to 150-ml quantity of water was transferred into 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 (intensity) was stabilized within a specified range as displayed on the monitor screen of the instrument. The blue-light intensity (transmittance) is shown in the data printout although not displayed prior to sample measurement. The relative refractive index was set at 1.11. The particle size analysis outputs used for this study include a display of a relative size distribution (volume-based) histogram and a cumulative undersize distribution curve, a mean particle size, and the standard deviation of the distribution.

Monodispersed polystyrene latex beads (lot 16392, Duke Scientific) with a nominal size of 0.204 μm were used to calibrate the instrument before sample measurement. Different amounts of each emulsion sample were added to produce four different laser-light and blue-light intensity readings for measurement. At each intensity, triplicate measurements were performed for each of the four samples.

PCS Particle Size Analysis

The NICOMP 370 submicron particle sizer was also used to determine the mean particle size of the four lots of samples. A drop of sample was added into a 100-ml volumetric flask and was subsequently diluted to volume with filtered water and mixed for 1 min. The sample cell filled with the diluted sample was inserted into the instrument. The intensity of the laser light was adjusted to approximately 300 kHz. Particle size output was obtained in 10–15 min. The measurement was performed in triplicate for each sample.

RESULTS AND DISCUSSION

Laser intensity can be read directly from the monitor screen as the emulsion sample is added to the sample mixing chamber of the Horiba instrument, but the blue-light intensity is only shown in the data printout. In this study, the addition of samples was carefully controlled so that a specific laser-light intensity was obtained. Figures 1(a) and (b) display the particle size distributions of sample A, which were determined at laser intensities of 94.5 and 77.0%, with corresponding blue-light inten-

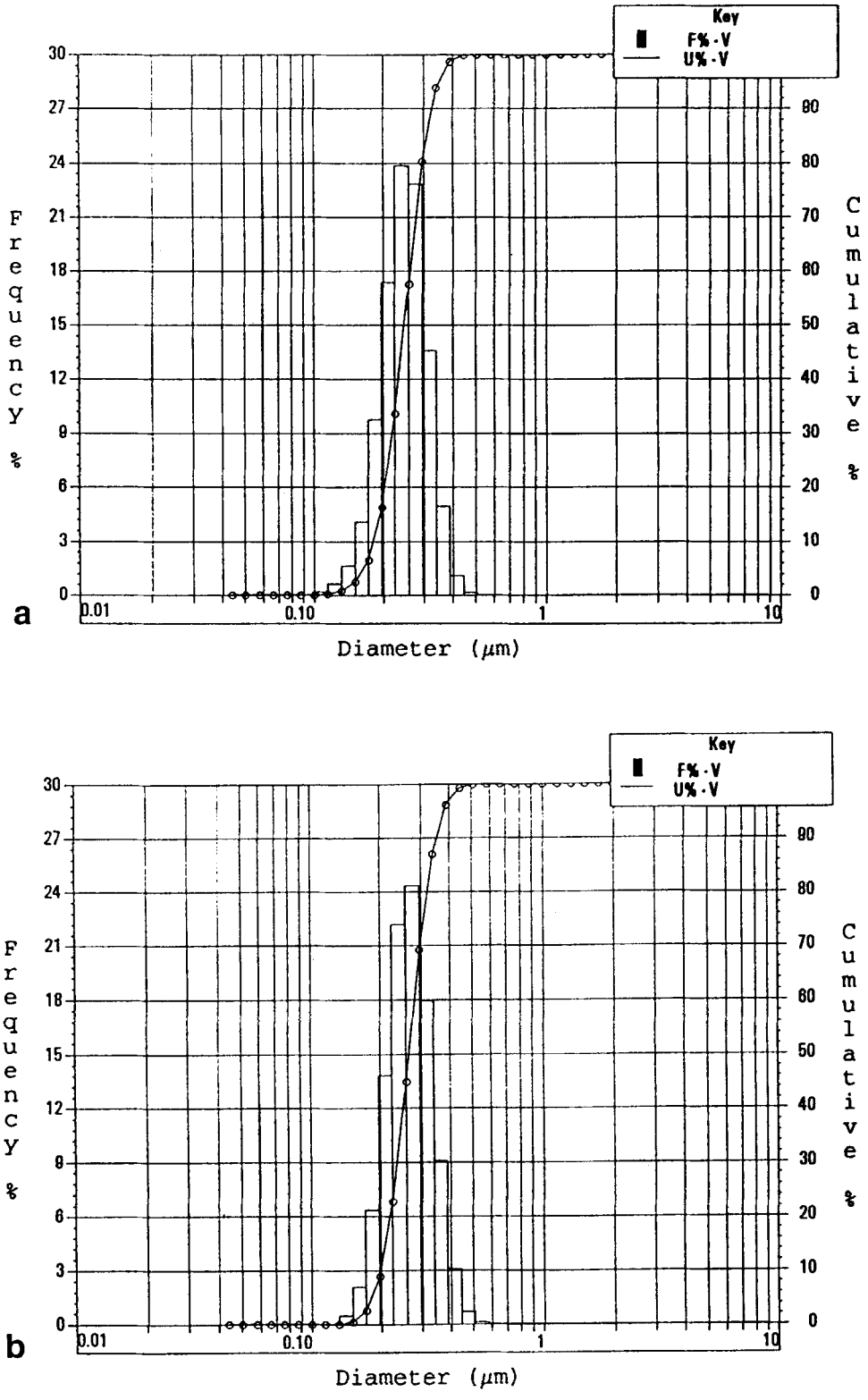

Figure 1. (a) Particle size distribution of sample A measured at a blue-light intensity of 83.40%. (b) Particle size distribution of sample A measured at a blue-light intensity of 41.9%.

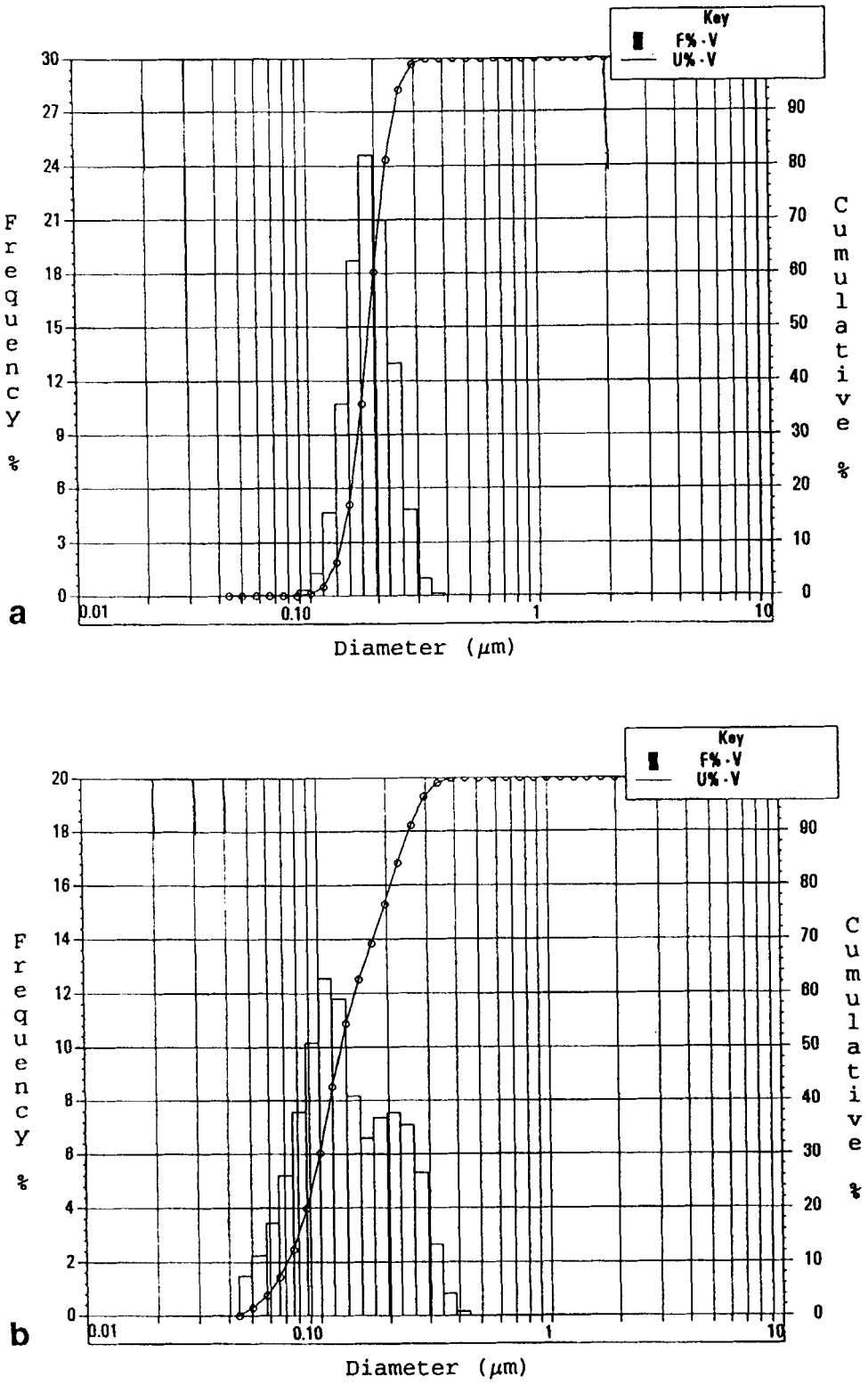

Figure 2. (a) Particle size distribution of sample C measured at a blue-light intensity of 84.2%. (b) Particle size distribution of sample C measured at a blue-light intensity of 39.2%.

sities of 83.4 and 41.9%, respectively. In spite of this marked difference in sample concentration as reflected by the light intensity difference, there was no significant change in the particle size distribution. Thus for this largest sample, multiple scattering was not a problem in the examined concentration range.

Figures 2(a) and (b) show the size distributions of sample C, which were measured at laser intensities of 95.0 and 76.5%, with corresponding blue-light intensities of 84.2 and 39.2%, respectively. As the light intensity was reduced (a higher sample concentration), the distribution shifted to a smaller size; the mean particle size changed from 0.191 to 0.149 μm. In addition, at the lower light intensity, the distribution became broader and showed bimodal distribution characteristics [Fig. 2(b)]. A similar downshift in particle size distribution was also observed for samples B and D when a higher sample concentration was used. Thus for these smaller sized materials, multiple scattering was observed at lower particle concentrations.

Table 1 presents the mean particle size and standard deviation of distribution for the four emulsion samples measured at four different light intensity ranges. A comparison between the laser and blue-light intensities clearly indicates that the blue-light intensity is much more sensitive to the sample concentration than the laser intensity. This can probably be explained by the fact that particles smaller than 1 μm scatter the blue light much more effectively than does the laser, which has a much longer wavelength. These data support the conclusion that the blue-light intensity is a much more sensitive indicator for monitoring the concentration of submicron samples used in light-scattering particle size analysis. It is critical to monitor the blue-light intensity in order to avoid the interference of multiple scattering.

Although multiple scattering is the most plausible explanation for the downshifting of the particle size distribution at high sample concentration (reduced light intensity), it is interesting to note that this effect is less apparent for samples with a particle size larger than 0.2 μm (sample A). The data given in Table 1 show that the downshift of the mean particle size for the other three samples (B, C, and D) occurred at a blue-light intensity of less than 70%. The width of the distribution as indicated by the standard deviation also changed to a higher value as the blue-light intensity fell below 70%. Therefore, when submicron particles are measured, the amount of sample used should be controlled at a blue-light intensity above 70% or preferably, 80%. This controls the measurement in the effective range on the analyzer so that underestimation of particle size due to multiple scattering can be avoided.

Table 1

Particle Size Distribution Parameters Determined at Different Light Intensities[a]

Sample	Laser Intensity (%)	Blue-Light Intensity (%)	Mean Size (μm)	Standard Deviation (μm)
A	94.2 (0.44)	82.5 (1.29)	0.218 (<0.0010)	0.048 (0.001)
	88.0 (0.15)	66.0 (0.06)	0.224 (<0.0010)	0.049 (0.001)
	85.6 (0.85)	59.8 (2.08)	0.224 (0.0012)	0.052 (0.001)
	78.4 (1.25)	44.6 (2.40)	0.228 (0.0012)	0.059 (0.001)
B	95.3 (0.42)	84.7 (0.85)	0.202 (<0.0010)	0.045 (0.001)
	86.8 (2.30)	67.5 (1.07)	0.204 (0.0012)	0.045 (0.001)
	84.7 (0.47)	57.3 (0.96)	0.170 (<0.0010)	0.048 (<0.001)
	80.1 (0.47)	47.9 (1.00)	0.169 (<0.0010)	0.081 (<0.001)
C	95.1 (0.46)	84.5 (1.67)	0.191 (<0.0010)	0.038 (0.001)
	91.3 (0.70)	72.8 (2.05)	0.189 (0.0015)	0.041 (0.001)
	85.2 (0.31)	56.6 (0.50)	0.153 (<0.0010)	0.060 (0.001)
	76.0 (0.76)	38.2 (1.59)	0.149 (<0.0010)	0.071 (0.001)
D	94.8 (0.50)	83.1 (1.80)	0.186 (<0.0010)	0.039 (0.001)
	92.3 (0.31)	75.0 (0.72)	0.182 (<0.0010)	0.041 (<0.001)
	89.0 (0.78)	65.9 (2.61)	0.150 (<0.0010)	0.057 (<0.001)
	76.0 (0.32)	38.5 (1.22)	0.144 (<0.0010)	0.072 (<0.001)

[a]Each data point is the mean of three measurements and the standard deviation is in parentheses.

Table 2

Comparison Between Light-Scattering Analyzer and PCS Results

	Laser Scattering		PCS	
Sample	Mean (μm)	SD (μm)	Mean (μm)	SD (μm)
A	0.218	0.048	0.221	0.070
	0.218	0.047	0.223	0.053
	0.218	0.048	0.222	0.058
B	0.202	0.045	0.190	0.051
	0.202	0.045	0.196	0.047
	0.202	0.045	0.192	0.046
C	0.191	0.038	0.187	0.048
	0.191	0.038	0.187	0.046
	0.191	0.039	0.186	0.044
D	0.185	0.039	0.183	0.045
	0.186	0.039	0.185	0.059
	0.186	0.040	0.181	0.046

The mean particle sizes for these samples were also determined by PCS. The PCS results are listed with the light-scattering analyzer data (at a blue-light intensity greater than 80%) in Table 2. The close agreement between these two groups of data further verifies the accuracy of the results generated using the light-scattering analyzer at an optimal sample concentration.

CONCLUSION

The results of this study indicate that controlling the sample concentration within the proper range of laser-light intensity as displayed on the monitor screen of the instrument may not be adequate, particularly for samples with a mean particle size below 1 μm. The concentration of the sample should be controlled at a blue-light intensity above 70% to avoid underestimation of particle size as a result of multiple scattering. When an optimal sample concentration is used, accurate particle size results can be generated by the light-scattering analyzer. Because of the simplicity and speed of the testing procedure, such an analyzer can be a valuable quality control tool.

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