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Determination of Zeta Potentials of Polymeric Nanoparticles by the Conductivity Variation Method

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An easy method of measurement of the zeta potentials of sub-50-nm polymeric nanoparticles is suggested. Although zeta potential measurements of nanoparticles or emulsions above 50 nm have been successfully carried out, zeta potentials of emulsions or nanoparticles below 50 nm could not be precisely measured in the region of extremely low conductivity by conventional electrophoresis with a He–Ne laser. However, zeta potentials of sub-50-nm nanoparticles were measured in the region of thin electrical double layers by addition of sodium chloride and zeta potentials in the condition without sodium chloride could be predicted by extrapolation of the measured potentials. The electrophoretic mobility of 150-nm nanoparticles stabilized with sodium dodecylsulfate was the same as that calculated from extrapolation of the measured ones. The zeta potentials of sub-50-nm nanoparticles stabilized with sodium dodecylsulfate could be calculated by the same procedure. **© 2002 Elsevier Science (USA)**

Key Words: **nanoparticles; sodium dodecylsulfate; zeta potential; electrophoresis; electrolyte.**

INTRODUCTION

Polymeric nanoparticles have attracted much attention as a delivery vehicle in biomedical and cosmetic applications due to enhanced permeation, specific cell targeting, and long circulation in blood (1). *In vivo* behavior of nanoparticles or polymeric micelles is mainly dependent upon the size, shape, surface charge, and density of long hydrophilic segments (2). The size and shape of nanoparticles can be characterized by transmission electron microscopy and light scattering. The surface charge (Q) of nanoparticles in the slipping plane can be characterized by zeta potential measurement, which determines the colloidal stability and the practical application (3), as seen in the equation

$$Q = 4\pi\varepsilon\varepsilon_0\zeta r(1+\kappa r). \tag{1}$$

Zeta potential can be determined by the electrokinetic or electroacoustic method. Large nanoparticles above 100 nm are generally correlated with *in vivo* behavior by Doppler microelectrophoresis as an electrokinetic method, while the zeta potentials of nanoparticles below 50 nm have not been measured.

Zeta potentials of polymeric micelles or surfactant micelles below 50 nm can be detected by an argon laser source of wavelength 488 nm (4). However, He–Ne laser light in a conventional electrophoretic instrument cannot detect such systems. Hence, indirect methods such as nanobubble formation and micelle coarcervation using He–Ne laser light have been proposed (5, 6).

This study suggests the possibility of zeta potential measurement of sub-50-nm polymeric nanoparticles by a conventional He–Ne laser of wavelength 633 nm.

MATERIALS AND METHODS

Poly(methyl methacrylate) (PMMA) nanoparticles were prepared by a high-pressure homogenization and solvent evaporation method. The details of these procedures were outlined in a previous article (7). A briefly, methylene chloride solution of PMMA was emulsified in distilled water containing sodium dodecylsulfate to form a crude oil-in-water (O/W) emulsion. The crude emulsion was pumped through the interaction chamber of a M110EH microfluidizer (Microfluidics Corp., Newton, MA) at a pressure of 1000 bar. This process was repeated up to three times.

Particle size distribution and zeta potential were measured by a light-scattering method with a He–Ne laser of 633 nm (Zetasizer 3000HS, Malvern; 10 mW). The scattering angle was fixed at 90° and temperature was maintained at 25°C. The mean diameter was calculated by the Stokes–Einstein relation,

$$D = \frac{k_B T}{6\pi\eta r}, \tag{2}$$

and size distribution was calculated by the CONTIN routine.

The Doppler electrophoretic light scattering measures the electrophoretic mobility of colloid particles in an applied electric field. The velocity of moving nanoparticles is calculated based on Doppler frequency shifts of scattered laser light. Zeta

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potentials (ζ) were calculated from measured electrophoretic mobility by the Dukhin–Semenikhin theory (8). The equation used in the calculation was

$$\mu_D = \frac{3}{2}\zeta_D - \frac{3}{2} \times \frac{\zeta_D|4(1+3m)\sinh^2(\zeta_D/4)+2g_1| + |2(1+3m)\sinh(\zeta_D/2) - 3m\zeta_D + 2g_2|4\ln\cosh(\zeta_D/4)}{\kappa r + 8(1-3m)\sinh^2(\zeta_D/4) - 24m\ln\cosh(\zeta_D/4) + 4g_1}, \quad [3]$$

where μ_{D} is the dimensionless electrophoretic mobility ($3\eta e\mu/2\varepsilon\varepsilon_0 k_{\mathrm{B}}T$), ζ_{D} is the dimensionless zeta potential ($e\zeta/k_{\mathrm{B}}T$), and m is the dimensionless ionic drag coefficient, $m = 2\varepsilon\varepsilon_0 k_{\mathrm{B}} T N_{\mathrm{A}}/(3\eta\Lambda_0)$. The limiting conductance of NaCl in water at 25°C is 0.01265 (S m^2/mol), and the calculated m is 0.1018 (9). Surface conductance was neglected by the functions g_1 and $g_2 = 0$. Each data point for the zeta potential is an average of at least seven measurements.

RESULTS AND DISCUSSION

The oil-in-water polymer solution was passed through high-pressure homogenization for nanoemulsion preparation and solvent evaporation for nanoemulsion hardening, resulting in a nanoparticle suspension. Smaller nanoparticles can be formed by increasing the pressure in a high-pressure homogenizer, as indicated in an earlier study (10). In addition, the size of the nanoparticles was effectively decreased and size distribution became narrow as the cycle number increased, as shown in Fig. 1.

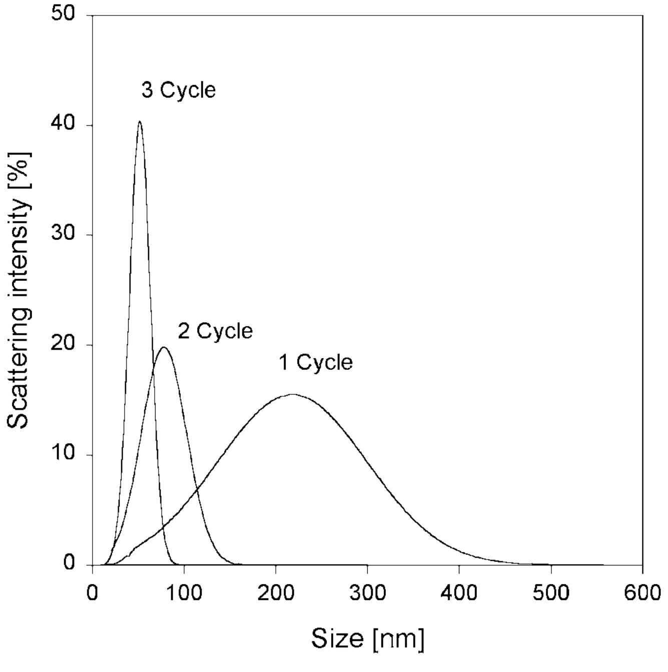

FIG. 1. Size distribution of PMMA nanoparticles stabilized by SDS.

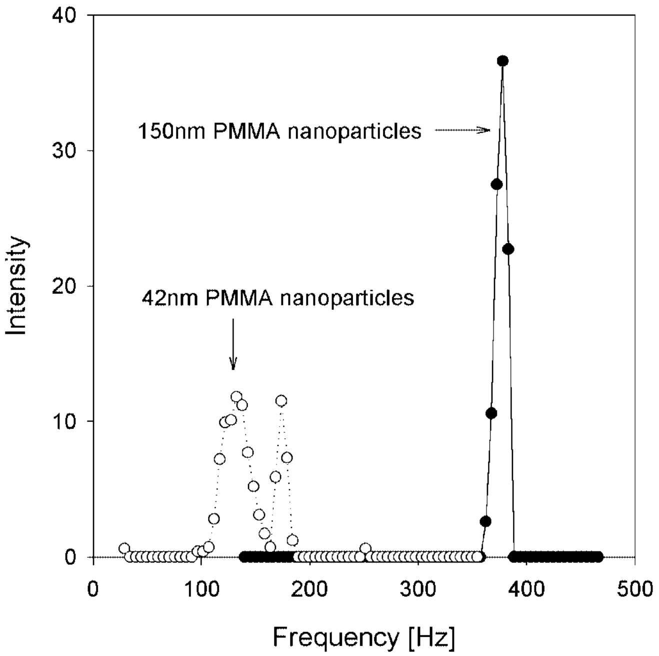

FIG. 2. Doppler spectra of 150-nm and 42-nm PMMA nanoparticles from the conventional electrophoresis method.

The Doppler spectrum of 150-nm nanoparticles at extremely low conductivity was shown in Fig. 2. The reproducible spectrum in each experiment was obtained and the standard deviation of electrophoretic mobility for seven measurements was 0.13, meaning zeta potentials of 150-nm nanoparticles could be accurately determined. However, the Doppler spectrum of 42-nm nanoparticles was not reproducible and gave largely different electrophoretic mobilities in each measurement, meaning the zeta potentials of 42 nm nanoparticles at extremely low conductivity cannot be measured by a He–Ne laser.

Generally, when electrolyte concentration increases, the thickness of the electrical double layer and the corresponding electrophoretic mobility of nanoparticles are reduced due to charge shielding by increased surrounding ions. Likewise, the electrophoretic mobility of 150-nm nanoparticles decreased with NaCl concentration, as shown in Fig. 3. The extrapolation of electrophoretic mobilities at various conductivities to an extremely low conductivity coincided with the measured mobility at the same conductivity. Table 1 presents the calculated electrokinetic radius (κr) corresponding to NaCl concentration, which shows that neither Hückel nor Smoluchowski equations can be applied to evaluate the zeta potential in a nanoparticle system because the equations which are traditionally used can be used in $\kappa r \gg 100$ or $\kappa r \ll 1$ and are too oversimplified to be applied to nanoparticle systems. Hence, the calculation of dimensionless zeta potentials from dimensionless electrophoretic mobilities was carried out by Dukhin–Semenikhin theory for a $1:1$ electrolyte and a thin electrical double layer of spherical particles. Interestingly, the calculated dimensionless zeta potential followed a linear relationship with conductivity, indicating

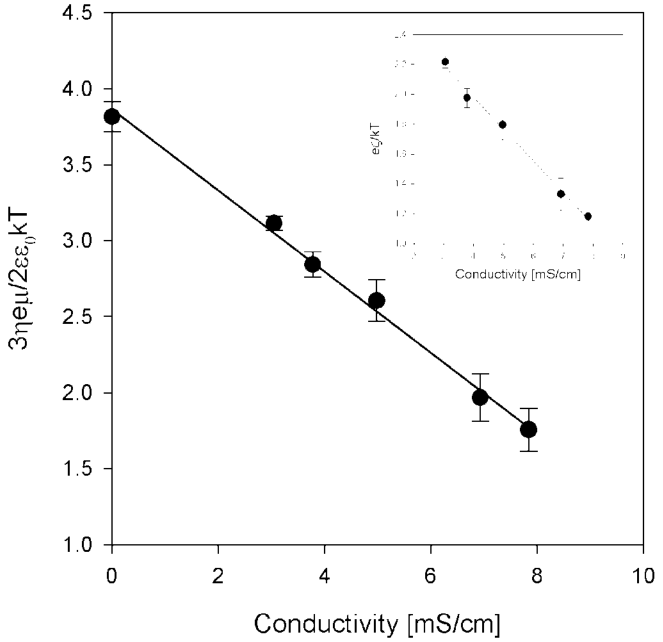

FIG. 3. Dimensionless electrophoretic mobility of 150-nm PMMA nanoparticles according to conductivity.

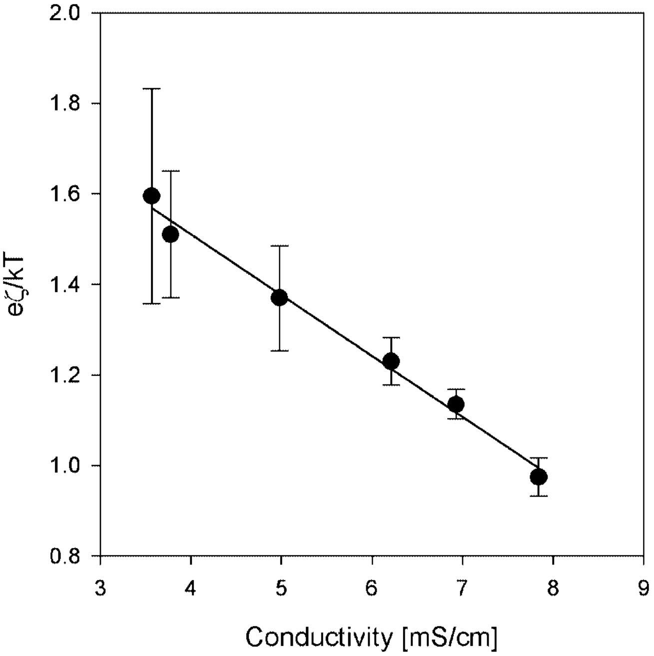

FIG. 4. Dimensionless zeta potential of 42-nm PMMA nanoparticles according to conductivity.

that the zeta potential at an extremely low conductivity can be predicted by a simple extrapolation. The predicted zeta potential in the condition without NaCl was −72.7 mV, but it could not be compared with the experimental one because the Dukhin–Semenikhin equation is not applicable in regions of small electrokinetic radius.

This behavior gives an important clue to the determination of the zeta potentials of 42-nm nanoparticles because the electrophoretic mobility of 42-nm nanoparticles could not be measured in the region of low conductivity.

The measurement of the electrophoretic mobility of 42-nm nanoparticles at elevated conductivity was successfully carried out by adding NaCl, showing a standard deviation of 0.357 for nine measurements (NaCl: 0.03 M, κr: 11.94). The electrophoretic mobilities above 0.03 M of NaCl were also successfully measured in the same way. The dimensionless electrophoretic mobility of 42-nm nanoparticles showed a linear relationship with conductivity according to the same principle as for 150-nm nanoparticles. Hence, the zeta potential at extremely low conductivity can be determined by extrapolation as shown in Fig. 4 because the dimensionless zeta potentials showed the same tendency. The zeta potential of 42-nm nanoparticles was calculated to be −52.7 mV by extrapolation.

Why the measurement of electrophoretic mobility is possible with increasing concentrations of electrolyte is obscure in the current state; however, it can be suggested that interparticle flocs are formed by thinner electrical double layers and that the scattering by nanoparticles with an enlarged effective diameter of flocs is detectable in a coherent light beam. Therefore, Doppler frequency shifts in the scattered light are used for the determination of electrophoretic mobility. Practically, electrolyte concentrations below 0.1 M NaCl did not show apparent precipitation, maintaining transient stability of interparticle flocs. However, high electrolyte concentrations dramatically induced colloidal instability of aqueous nanoparticle suspensions eventually to form macroscopic precipitation.

Zeta-potential measurement of nanoparticles below 50 nm stabilized by cationic surfactants could not be determined. Electrophoretic mobility of nanoparticles below 50 nm stabilized by cetyltrimethylammonium chloride as a cationic surfactant could be measured above 3 mS/cm conductivity. However, the electrophoretic mobility was nearly zero above 3 mS/cm conductivity and the electrophoretic mobility for various conductivities did not show a linear relationship, indicating that extrapolation cannot be used.

In the present state, zeta-potential determination by the extrapolation of electrophoretic mobility at various conductivities

TABLE 1
Electrokinetic Radius and Conductivity According to Sodium Chloride Concentration

	NaCl [M]						
	0.025	0.03	0.035	0.04	0.05	0.07	0.10
κr (42 nm)	10.90	11.94	12.90	13.79	15.42	18.24	21.80
κr (150 nm)	38.94	42.65	46.07	49.25	55.06	65.15	77.87
Conductivity [mS/cm]	3.05	3.57	3.78	4.98	6.21	6.93	7.84

can be used for nanoparticles stabilized by highly negative surface charges.

SUMMARY

Extrapolation of electrophoretic mobilities at various conductivities was employed to determine the zeta potential of PMMA nanoparticles below 50 nm stabilized by SDS. A Doppler spectrum of nanoparticles below 50 nm could not be obtained with a He–Ne laser beam under an electric field in the absence of electrolyte, while a stable Doppler spectrum above critical conductivity was obtained by the addition of electrolyte and electrophoretic mobility was measured reproducibly. Throughout this study, the extrapolation of electrophoretic mobilities at various conductivities was revealed as an alternative method for the determination of zeta potentials of sub-50-nm polymeric nanoparticles.

APPENDIX: NOMENCLATURE

Symbols are defined as follows:

η: viscosity;
r: particle radius;
k_B: Boltzmann constant;
e: elementary electric charge;
μ: electrophoretic mobility;
ε: relative dielectric constant of medium;
ε_0: dielectric constant of vacuum;
T: temperature;
ζ: zeta potential;
κ: reciprocal of the electrical double layer thickness;
N_A: Avogadro constant;
Λ_0: limiting conductance.

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