Evaluation of dispersibility in liquid and AC magnetization properties of polion complex-coupled magnetic nanoparticles

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Medical applications such as those using magnetic nanoparticles (MNPs) for hyperthermia and magnetic particle imaging (MPI) require suitably designed particles with distinct characteristics. However, it is challenging to develop such particles with a high degree of biocompatibility. In this study, a cationic diblock copolymer (PMPC100-b-MMAPTAC100: P100M100) composed of poly(2-(methacryloyloxy)ethyl phosphorylcholine) (PMPC) and poly(3-(methacryloylamino)propyl trimethylammonium chloride) (PMAPTAC) was synthesized via a controlled radical polymerization technique to obtain particles with high biocompatibility and antithrombogenicity. Magnetic polion complex (PIC) aggregate (M-300/P100M100) is an aggregate of magnetic Fe3O4 nanoparticles (M-300), in which their anionic surface is electrostatically coated with cationic PMPC100-b-MMAPTAC100 (P100M100). We investigated the stability of the magnetic PIC aggregate in an ionic solution by evaluating the relationship between the particle diameter and salt concentration. We then estimated the intrinsic loss power (ILP) from the areas of the alternating τ−3 ητ T k B H B M N η τ τ       T k V B M N   ∑ 

Keywords: magnetic nanoparticles, hyperthermia, magnetic particle imaging (MPI), biocompatibility, polion complex (PIC), magnetic relaxation

1. Introduction

In recent years, several medical treatment applications have come to require magnetic nanoparticles with high biocompatibility. Research into magnetic nanoparticles (MNPs) coated with polion complex (PIC) organic materials is ongoing due to their wide clinical applicability1−8, and the sizes and characteristics of core-shell structures of PIC micelles have rendered them useful as carriers of oligonucleotides and plasmid DNA for human gene therapy9−10.

In the medical field, magnetic nanoparticles (MNPs) are employed in a variety of applications including magnetic hyperthermia5) and magnetic particle imaging (MPI)6,7). Magnetic relaxation loss is one of the heating mechanisms of MNPs used in the research of hyperthermia. In this regard, superparamagnetism in MNPs results from two distinct magnetic relaxation processes. The first occurs through a type of particle rotation called Brownian relaxation, whereas the other occurs through a magnetic moment rotation referred to as Néel relaxation. The Brownian (τB) and Néel (τN) relaxation times can be defined as follows8,9):

\[
\tau_B = \frac{3\eta V_H}{k_B T},
\]

\[
\tau_N = \tau_0 \exp \left( \frac{KV_M}{k_B T} \right)
\]

where \( \eta \) is the viscosity, \( \Omega \) is the hydrodynamic MNP volume, \( \tau_0 \) is the attempt time of \(~10^{-9} \text{ s}\) associated with gyromagnetic procession, \( K \) is the magnetic anisotropic constant, \( V_M \) is the core particle volume, \( k_B \) is Boltzmann's constant \((1.38\times10^{-23} \text{ J/K})\), and \( T \) is the temperature in Kelvin7). In theory, Brownian and Néel relaxations occur in parallel, and the effective relaxation time, \( \tau \), can be expressed as9):

\[
\frac{1}{\tau} = \frac{1}{\tau_B} + \frac{1}{\tau_N}
\]

The effective frequency for heat dissipation can be estimated from measuring the dependency of the intrinsic loss power (ILP) relative to the frequency. The ILP is the intrinsic heat dissipation independent of the applied field and is calculated from the specific loss power (SLP)10, which is defined as: 
Table 1. Concentration calculated from catalog data of M-300. Values in parentheses were used in calculations in this study.

| Composition (wt%) | H2O | Fe3O4 | RSO4Na | M-300 |
|------------------|-----|-------|--------|-------|
| Specific gravity (g/mL) | 0.998 (1) | 4.8–5.1 (5.1) | 1 | 1.3–1.4 (1.4) |
| CAS No.          | –   | 1309-38-2 | 1106-21-0 | – |
| M.W. (g/mol)     | –   | 231.53 | 298.42 | – |
| Concentration (g/L) | –   | 560 | 70.0 | – |

SLP = \frac{\Delta T}{\Delta t} \frac{c}{m_r}, \quad (4)

where \(\Delta T/\Delta t\) is the time rate of change of temperature, \(c\) is the heat capacity of the fluid per unit mass of fluid, and \(m_r\) is the iron mass in the fluid per unit mass of fluid. Then, the ILP is given as:

\[ \text{ILP} = \frac{\text{SLP}}{H^2 f}, \quad (5) \]

where \(H\) is the amplitude of the magnetic field.

In this study, we synthesized a diblock copolymer (PMPC100-PMAPTAC100:P100M100) composed of biocompatible poly(2-(methacryloyloxy)ethyl phosphorylcholine) (PMPC) and cationic poly(3-(methacryloylamino)propyl trimethylammonium chloride) (PMAPTAC) via a controlled radical polymerization technique. PMPC shows excellent biocompatibility and antithrombotic properties because it has hydrophilic pendant phosphorylcholine groups, which are structurally identical to the hydrophilic surfaces of biological membranes. In our study, we characterized the chemical structure of the diblock copolymer and evaluated the dependence of particle size on salt concentration to confirm its stability in an ionic solution. We then measured the AC magnetiztion properties of a magnetic PIC aggregate (M-300/P100M100) comprising anionic Fe3O4 nanoparticles (M-300) electrostatically coated with cationic P100M100. Finally, we calculated the ILP and MPI signals from the AC hysteresis loops and compared the results with those of unmodified M-300.

2. Materials and Methods

2.1 Materials

The characteristics of M-300 used for particle synthesis in this study, along with its catalog data, are shown Table 1. As calculated from the catalog data, the concentrations of Fe3O4 and RSO4Na in M-300 were 560 and 70.0 g/L, respectively. M-300 was subjected to dynamic light scattering (DLS), and the zeta potential of the solution diluted 100 times in pure water was measured (Fig. 1). After dilution, the concentrations of Fe3O4 (Cy) and RSO4Na (Cs) were 5.60 and 0.700 g/L, respectively. In this case, the hydrodynamic radius (Rθ) obtained from the DLS measurement was 21.2 nm and the zeta potential was -52.0 mV. M-300 had a very low scattering light intensity (SI) when diluted 1,000,000 times; although Rθ was not calculated at this dilution level, it remained constant to 100,000 times dilution (C0 = 0.00560 g/L). In contrast, the zeta potential of the 10,000-fold diluted solution (C0 = 0.00700 g/L) was -47.4 mV. Overall, it is clear that M-300 exhibited high stability as evidenced by constant value of Rθ versus dilution in pure water.

PMPC100-CTA (Mθ = 29800, Mw/Mn = 1.08 (acetate buffer as the eluent), 1.50 g, 0.0503 mmol), MAPTAC (1.11 g, 5.03 mmol), and V-501 (4.59 mg, 0.0201 mmol) were dissolved in 5.03 mL of pure water, and the mixture was degassed by purging with Ar gas for 30 min. Polymerization was performed at 343.15 K for 5 h, and the diblock copolymer (PMPC100-block-PMAPTAC, P100M100, 2.36 g, 90.4%) was recovered by freeze-drying after the reaction mixture was dialyzed against pure water for 2 days. The M-300/P100M100 complex was prepared by adding a P100M100 aqueous solution to an M-300 aqueous solution so that the mixing ratio (R = P100M100/M-300, v/v) was 0.0739. The concentration of Fe3O4 was 5.31 g/L (3.84 mg·Fe/mL) in the M-
300/P100M100 complex. For comparison, we also diluted water-based Fe3O4-containing sodium α-olefin sulfonate-coated nanoparticles, which are commercially distributed as M-300 by Sigma Hi-Chemical Inc. (Chigasaki, Kanagawa, Japan), 100 times in pure water to give a concentration of 5.31 g/L. The core diameter was 11 ± 3 nm, which is identical to that of M-300/P100M100.

2.2 Methods

The physical properties of M-300/P100M100 were evaluated with nuclear magnetic resonance spectroscopy (NMR: Bruker, DRX500), dynamic light scattering (DLS), zeta potential measurements (Malvern, Zetasizer nanoZS), and transmission electron microscopy (TEM: Jeol, JEM-2100). During this process, we also evaluated the NaCl concentration dependence of M-300/P100M100.

The AC hysteresis loops were measured in the frequency range of 100 Hz–100 kHz at a field intensity of 4 kA/m, and the DC hysteresis loops were measured using a vibrating sample magnetometer (VSM: Toei Kogyo, TEM-WFR7) at 298.15 K. For these measurements, 0.2 mL of the sample encapsulated in cylindrical tubes with a diameter of 10 mm were used. MNPs dispersed in water were used as the liquid sample, and MNPs fixed with epoxy bonds were used as the solid sample. The ILP and MPI values of the samples were calculated, and the results were compared with those of M-300.

3. Results and Discussion

3.1 Synthesis, structure, and characterization

NMR spectroscopy was used to identify the chemical structure of P100M100 synthesized by the above method, and it was confirmed that the peaks of PMPC and PMAPTAC P100M100 were present (Fig. 2). On the basis of the consumption of the vinyl group before and after polymerization, the degree of polymerization (DP (theo)) of the monomer MAPTAC was determined to be 99. In addition, we determined that the degree of polymerization (DP (NMR)) from the integrated intensity ratio of the PMPC and PMAPTAC peaks in the NMR spectrum of P100M100 after recovery was 100. The molecular weight distribution (Mw/Mn) obtained from gel permeation chromatography (GPC) was as narrow as 1.10, and a structure-controlled polymer was obtained (Table 2). We therefore concluded that P100M100 was synthesized by the cationic monomer MAPTAC and the betaine monomer MPC, as observed from the 1H NMR spectrum. We also confirmed the mixing ratio

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Table 2. Degree of polymerization (DP), number-average molecular weight (Mn), and molecular weight distribution (Mw/Mn) of P100M100.

| DP(theo) | Mw(theo) | DP(NMR) | Mn(NMR) | Mw/Mn |
|---------|----------|----------|----------|--------|
| 99      | 51,700   | 100      | 51,900   | 1.10   |

Notes: Theoretical values estimated from the feed ratio and conversion. Estimated from 1H NMR. Estimated from GPC.
dependence of the M-300/P₁₀₀M₁₀₀ complex. The concentration of M-300 anions was identical to the concentration of the anionic surfactant sodium α-olefin sulfonate in solution, although the exact concentration of the anions is unknown. Therefore, in order to confirm the neutralization point of the complex, we investigated the changes in \( R_h \) and the zeta potential of the aggregate with respect to the mixing ratio of M-300 and P₁₀₀M₁₀₀ in the complex. Figure 3 plots the \( R_h \) values obtained by DLS measurement versus the mixing ratio \( R = P₁₀₀M₁₀₀ / M-300, \text{v/v} \) of M-300 and P₁₀₀M₁₀₀ in pure water after 72 h. When P₁₀₀M₁₀₀ was mixed with M-300, \( R_h \) increased as the value of \( R \) increased until it reached a maximum at \( R = 0.0474 \). Increasing \( R \) beyond this point decreased both \( R_h \) and SI. In addition, in M-300/P₁₀₀M₁₀₀ with \( R = 0.0474 \), the SI decreased sharply after 72 h, suggesting that precipitation had occurred.

By comparison, we concluded that the aggregates were stable since M-300/P₁₀₀M₁₀₀, other than that for \( R = 0.0474 \), neither precipitated nor demonstrated a change in \( R_h \) over the course of 72 h. Figure 4 shows the zeta potential versus the mixing ratio of the synthesized M-300/P₁₀₀M₁₀₀ after 96 h. The M-300/P₁₀₀M₁₀₀ with \( R = 0.0474 \) precipitated; thus, the zeta potential of the supernatant was measured. As the \( R \) value of M-300/P₁₀₀M₁₀₀ increased, the zeta potential also increased as the solution concentration of P₁₀₀M₁₀₀ increased. Previously, it was thought that the charge would neutralize with a zeta potential of zero for M-300/P₁₀₀M₁₀₀ with \( R = 0.0739 \). It was also thought that larger absolute values of the zeta potential indicated stronger repulsive forces between the particles and hence higher particle stability. However, the results of this study indicate that the surface charges were neutralized to completion, and they were stably dispersed due to steric hindrance by the polymer material outside the particles. In this case, the Na⁺ cations from sodium tetradecane sulfonate and the Cl⁻ anions from P₁₀₀M₁₀₀ were ionically bonded in water, while the Na⁺ cations from P₁₀₀M₁₀₀ and the O⁻ anions from tetradecane sulfonate were electrostatically bonded. In this way, the magnetic PIC aggregate was synthesized as shown in Fig. 5.

Moreover, we confirmed that the surface of the M-300/P₁₀₀M₁₀₀ complex \( (R = 0.0739) \) was covered by a PMPC shell based on the dispersion stability (i.e., the \( R_h \) and SI) versus the NaCl concentration in solution (Fig. 6). The \( R_h \) and SI values of M-300/P₁₀₀M₁₀₀ were independent of the NaCl concentration \([\text{NaCl}]\); however, the \( R_h \) and SI values of M-300 increased when \([\text{NaCl}]\) was increased to 0.2 M (mol/L). These results indicate that M-300/P₁₀₀M₁₀₀ was covered by a PMPC shell since the dispersion stability improved upon complexation, which was synthesized with P₁₀₀M₁₀₀. Further, aggregates appeared in M-300 for \([\text{NaCl}] = 0.2 \text{ M} \) when left overnight. In contrast, M-300/P₁₀₀M₁₀₀ did not precipitate but was maintained as a stable dispersion. For a NaCl concentration of 0.2 M, specific quantities of M-300/P₁₀₀M₁₀₀ and M-300 aqueous solutions were

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**Fig. 4** Zeta potential for mixing ratio \( (R = P₁₀₀M₁₀₀/M-300, \text{v/v}) \) of water-based M-300/P₁₀₀M₁₀₀.

**Fig. 5** Schematic representation of M-300/P₁₀₀M₁₀₀ preparation.

**Fig. 6** Change in \( R_h \) and SI with respect to NaCl concentration of M-300 (open squares) and M-300/P₁₀₀M₁₀₀ (open circles).
allowed to stand still for one week to confirm the changes over time. The $R_h$ value of M-300/P$_{100}$M$_{100}$ was 63.2 nm and remained unchanged over time, whereas that of M-300 increased to 144 nm. Furthermore, since M-300 precipitated by salting-out, we concluded that the PMPC shell of the complex inhibited this process. Based on these results, we inferred that as the sodium concentration in the solvent increased, the sodium ions on the M-300 surface ionically bonded with the chlorine ions, resulting in aggregation. However, the magnetic PIC aggregate surface was not affected by the salt concentration since it was charge-neutralized. From this property, we conclude that magnetic PIC aggregates can be stably dispersed in biological bodies.

Figure 7 shows the TEM images of M-300 and M-300/P$_{100}$M$_{100}$. On this basis, we confirmed that M-300 was an aggregate of Fe$_3$O$_4$ (Fig. 7 (a)) and that M-300/P$_{100}$M$_{100}$ was the same aggregate as M-300 (Fig. 7 (b, c)). Therefore, we concluded that M-300/P$_{100}$M$_{100}$ was packed with anionic M-300 by the cationic diblock copolymer P$_{100}$M$_{100}$, and the estimated radius of M-300/P$_{100}$M$_{100}$ was ~50 nm. Moreover, the hydrodynamic radii of M-300 and M-300/P$_{100}$M$_{100}$ were 20.2 nm and 47.8 nm, respectively, as determined by DLS measurements (Fig. 8). The characteristics of M-300 and M-300/P$_{100}$M$_{100}$ are listed in Table 3.

### Table 3. Characterization of M-300 and M-300/P$_{100}$M$_{100}$

|          | $R_h$ (nm) | SI (kcps) | PDI  |
|----------|------------|-----------|------|
| M-300    | 20.2       | $4.21 \times 10^5$ | 0.120 |
| M-300/P$_{100}$M$_{100}$ | 47.8       | $1.70 \times 10^6$ | 0.119 |

Figure 9 shows the DC hysteresis loops of M-300 and M-300/P$_{100}$M$_{100}$ for the fixed and liquid samples at field intensities of 0–800 kA/m. We also measured the DC...
hysteresis loops for field intensities of 0–4 kA/m to better understand the magnetization process (Fig. 10). As observed from the results of DC measurements, the MNPs exhibited superparamagnetic characteristics because the coercive force and remanence magnetization could not be confirmed from the hysteresis loops. In this case, the fixed samples had the same magnetization because only the Néel relaxation from the magnetic moment rotation of the core particles operated in the fixed state. However, the magnetization of M-300 was higher than that of M-300/P100M100 in the liquid state. We concluded that the spin of Brownian relaxation caused by particle rotation was very weak in M-300/P100M100 because their $R_C$ value was larger than that of M-300.

Figure 11 shows the dependence of the AC hysteresis loops on frequency at 3.84 mg-Fe/mL for the fixed and liquid samples. As seen, the magnetization decreased as the frequency increased because the particle rotation and magnetic moments gradually became delayed. We also confirmed that the magnetization of M-300/P100M100 was lower than that of M-300 in the liquid samples under an AC magnetic field of 10 kHz (Fig. 12). Based on these results, we concluded that the influence of Brownian relaxation was small in the liquid state of the magnetic PIC aggregate due to the difference in the hydrodynamic particle size in M-300. The increase of the hydrodynamic particle size in M-300/P100M100 decreased the degree of particle rotation because of dipole interactions$^{13}$.

Figure 13 (a) shows the dependence of ILP on frequency in the liquid sample, as estimated from the areas of the AC hysteresis loops. Note that the observed ILP peaks derived from Brownian relaxation did not appear for the fixed sample (Fig. 13(b))$^{12}$. Furthermore, we calculated the theoretical Brownian relaxation time using Eq. (1), and determined the viscosities of M-300 and M-300/P100M100 at 297.15 K as 1.081 mPa·s and 1.037 mPa·s, respectively. The experimental Brownian relaxation times were 0.909 and 0.872 mPa·s, respectively.

**Fig. 10** DC hysteresis loops of (a) fixed sample and (b) liquid sample in magnetic field amplitudes ranging from 0–4 kA/m. Concentration of Fe was 3.84 mg/mL.

**Fig. 11** AC hysteresis loops at 1, 10, and 100 kHz for M-300 and M-300/P100M100.

**Fig. 12** AC hysteresis loops of liquid samples in applied magnetic field with amplitude of 4 kA/m. Frequency was 10 kHz.
The measured frequency of the Brownian relaxation peaks was in good agreement with the calculated frequency. The frequency of the Brownian relaxation peak in M-300 was significantly higher than that in M-300/P100M100. Thus, particle rotation derived from Brownian relaxation, which increases the degree of the magnetization rotation, clearly occurred in M-300 relative to M-300/P100M100. A higher ILP was obtained for M-300 in the liquid state, whereas a comparable ILP was obtained in the fixed state. The frequency of the Néel relaxation peak, fN, was not observed in the range of 0.1–100 kHz for the fixed samples. Note that the theoretical Néel relaxation peak was higher than 450 kHz (K ≤ 41 kJ/m³)\(^{15}\).

Finally, we assessed the suitability of the magnetic PIC aggregate for applications in MPI. Figures 14 and 15 show the third-harmonic intensities of M-300 and M-300/P100M100. The third harmonic signal intensity of M-300 decreased with increasing frequency. We concluded that this was due to a decrease in magnetization caused by magnetic relaxation\(^{16}\). In contrast, the magnetic PIC aggregate changed very little under the same conditions. However, it was confirmed that M-300 and M-

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**Fig. 13** Dependence of ILP on frequency for the liquid and fixed samples. Dotted lines indicate theoretical Brownian relaxation frequencies of fB = 5.8 kHz (M-300) and fB = 460 Hz (M-300/P100M100). Solid lines indicate experimental Brownian relaxation frequencies of fB = 9.0 kHz (M-300) and fB = 250 Hz (M-300/P100M100). No Néel relaxation peaks were observed.

**Fig. 14** Dependence of the third-harmonic signal on frequency in liquid and fixed samples.

**Fig. 15** Dependence of ratio of the third-harmonic signal to fundamental signal on frequency in liquid and fixed samples.
300/P100M100 had comparable MPI signal intensities in the fixed state, whereas stronger signal intensities were obtained for M-300 in the liquid state. The harmonic signal used for MPI is normally concerned with the nonlinear component of magnetization property. The difference in this nonlinear component of magnetization with and without an applied DC bias field is significant for spatial resolution of the constructed image. As shown in Figs. 10 and 11, the nonlinear component of the magnetization loops is not very large. Although the surface modification using P100M100 was successfully achieved, optimization of the magnetic core is inevitable to lead to a higher ILP and harmonic signal.

4. Conclusion

In this study, we successfully fabricated P100M100 with a biological membrane structure and evaluated the salt concentration dependence of M-300/P100M100 when coated with P100M100. When the mixing ratio was 0.0739, the surface of the synthesized particles was neutralized by the charge, and the magnetic PIC aggregate was stable and dispersible in pure water and ionic solutions. Based on this result, we infer that the magnetic PIC aggregates can be stably dispersed in a biological body. The results of magnetization measurements allowed us to characterize the influence of different hydrodynamic radii on the magnetization. As the hydrodynamic particle size of the magnetic PIC aggregate increased, the influence of Brownian relaxation decreased due to magnetic interactions. Further, the ILP was measured to investigate the applicability of M-300 and M-300/P100M100 to hyperthermia. The particles had comparable ILP values in the fixed state, but that of M-300 was higher in the liquid state. In addition, comparable MPI signal intensities were confirmed in the fixed state by evaluating the third harmonic.

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