STUDY ON RELATION BETWEEN SPATIAL DISTRIBUTION AND RELEASE RATE OF HYDROPHOBIC COMPOUNDS INCORPORATED IN POLYMER MICELLES WITH ANOMALOUS SMALL ANGLE X-RAY SCATTERING

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Amphiphilic block copolymers in aqueous solution undergo self-assembly into polymer micelles composed of hydrophobic core and hydrophilic shell. The polymer micelles can solubilize hydrophobic compounds in aqueous solution by incorporating them in the hydrophobic core. Therefore, they have been expected to be a drug career in drug delivery system (DDS). In DDS, controlling of the drug release behavior and retention stability are critical issues. However, tuning release rate and stability of retention of drug molecules is significantly difficult. Since the hydrophobic molecules must pass through the hydrophobic cores and hydrated corona layers to go out the polymer micelles, their release properties should strongly depend on spatial distribution of drug molecules in polymer micelles. Therefore, to elucidate the relation between spatial distribution of drug molecules and release properties of drug molecules is of significant importance to design a novel DDS. Thus, the aim of this study is to clarify the relation between spatial distribution of hydrophobic compounds in polymer micelles and their release and retention property. Poly(methyl methacrylate)-block-poly(N,N-(dimethylamino)ethyl methacrylate) (Poly-1) as amphiphilic block copolymer was synthesized by reversible addition-fragmentation radical polymerization. The weight- and number-average molecular weights of the resulting Poly-1 were 1.6104 g mol-1 and 1.9104 g mol-1, respectively. Three kinds of compounds (9-bromofluorene (BrF), 4-bromobenzyl alcohol (BrBzOH), 4-bromophenol (BrPh)) were employed as bromine-labeled hydrophobic compounds. Poly-1 and a hydrophobic compound were mixed at 10 wt% of a hydrophobic compound against Poly-1. The mixture was micellized by solvent substitution. Finally, concentration of the micelle solution was toned to 1.0 mg/mL. For the resulting solutions of Poly-1 micelles containing hydrophobic compounds, small angle X-ray scattering (SAXS) and anomalous small angle X-ray scattering (ASAXS) near the K-edge of bromine were carried out at BL-40B2 of SPring-8, Japan. A micelle solution was packed in dialysis tube, and then soaked in a large amount of water. The amount of hydrophobic compounds released from micelles to water was measured by UV-Vis spectra. Figure 1 (a) shows spatial distributions of hydrophobic compounds incorporated in Poly-1 micelles obtained by ASAXS analyses. It was revealed by ASAXS that BrF formed micro domain in the core, BrBzOH was homogeneously dispersed in the core, and BrPh was spread out to shell of the micelles. Such differences of spatial distributions should be dominated by molecular characteristics of hydrophobic compounds because BrF is highly hydrophobic, and the others have hydroxyl groups. The differences of spatial distributions should strongly effect on release or retention properties. Figure 1 (b) shows the comparison of changes of the amount of hydrophobic compounds retained in Poly-1 micelles against elapsed time. The order of retention stability in Poly-1 micelles is BrF, BrBzOH, and BrPh. This order agrees with the order of hydrophobicity that dominantly effects on spatial distributions of hydrophobic compounds in polymer micelles. Hence, it is suggested that the spatial distribution of hydrophobic compounds had significant effect on their retention stability in polymer micelles

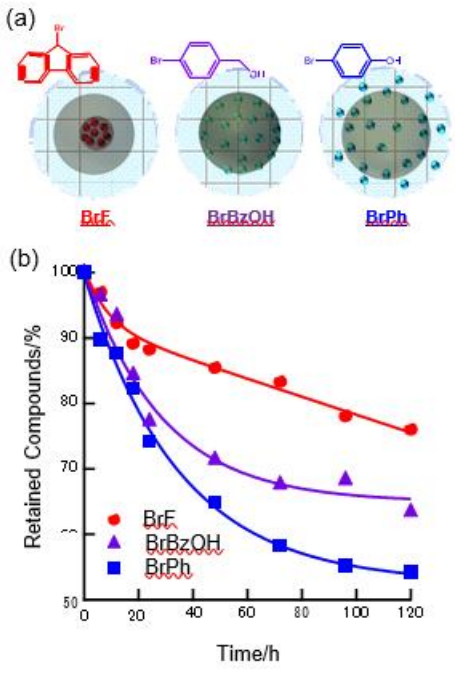

Figure 1 - Schematic diagrams of three kinds of compounds in Poly-1 micelles (a) and retention property of each compounds in Poly-1 micelles (b).