Preparation of Uniform Nanospheres with a Hydrophilic Core and a Hydrophobic Corona by the Macromonomer Method

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Uniform polymeric nanospheres comprised of hydrophilic cores and hydrophobic coronas were prepared by dispersion free radical copolymerization of acrylamide with poly(*tert*-butyl methacrylate) macromonomer (PtBMA) in ethanol/water mixed solvents, and the effects of cross-linker addition on the nanosphere size were investigated. Chemical analysis by electron spectroscopy confirmed that hydrophobic PtBMA chains grafted to the nanosphere surfaces. Changes in concentrations of the monomers and the cross-linker controlled the hydrodynamic diameter of the nanospheres (140–540 nm).

In recent years, the preparation and characterization of polymeric nanoparticles have been widely studied because these particles have an extremely large specific surface area which is useful in various technological systems[1] and biomedical fields.[2,3] In these studies of polymeric nanoparticles, the formation mechanism,[4] surface functionality,[5] synthetic methods,[6,7] and morphology control[8,9] have been reported.

In our previous work, polymeric nanospheres with various kinds of functional groups on their surfaces and nanospheres comprised of a hydrophobic core and a hydrophilic corona were prepared by dispersion copolymerization of hydrophobic monomers such as styrene or methyl methacrylate with hydrophilic macromonomers in polar solvents (macromonomer method).[9–11] The core-corona nanospheres have a monodispersed diameter and surface functionality which can be easily controlled by the molecular design of the macromonomers. If the polymeric nanospheres have a hydrophilic core and a hydrophobic functional surface, they can be expected to have applications as novel drug carrier devices. However, no hydrophilic nanospheres having a reverse core-corona structure have been reported.

In this paper, we extended the macromonomer method to prepare nanospheres having a hydrophilic polyacrylamide (PAAm) core and a hydrophobic corona of poly(*tert*-butyl methacrylate) (PtBMA). The core could be chemically cross-linked or not cross-linked.

Radical copolymerization was carried out as follows. The monomer *tert*-butyl methacrylate (tBMA, Wako) was purified by distillation under reduced pressure prior to use. Hydroxyl-terminated tBMA oligomer was synthesized by the free radical polymerization of tBMA monomer using 2,2′-azobis(isobutyronitrile) as an initiator in the presence of 2-mercaptoethanol as a chain transfer agent in tetrahydrofuran at 60 °C. The PtBMA macromonomers (number-average molecular weight M_n = 5400 and 6400) were then obtained by using the capping reaction of *p*-vinylbenzyl chloride with purified tBMA oligomer in the presence of tetrabutylphosphonium bromide as a phase transfer catalyst in dimethylformamide at 30 °C. PAAm nanospheres were prepared by dispersion copolymerization of PtBMA macromonomer with acrylamide in the presence of 2,2′-azobis[2-(2-imidazolin-2-yl)propane] (VA-061, Wako) as an initiator and the presence/absence of *N*,*N*′-methylenebis(acrylamide) (Bis-A, Wako) as a cross-linker in ethanol/water mixed solvents at 60 °C for 24 h. The resulting products were purified by centrifugation and redispersion in ethanol a total of three times to remove unreacted monomers. The hydrodynamic diameter, D_h, of the nanospheres in ethanol was measured by laser light scattering (LLS; ALV 230) and nanosphere morphologies in the dry state were directly observed using a transmission electron microscope (TEM; Hitachi 7000A). The surface composition was evaluated by electron spectroscopy for chemical analysis (ESCA; Shimazu ESCA 1000).

Figure 1 shows the relationship between the D_h of the PAAm nanospheres measured by LLS and the molar composition of Bis-A to total monomers in the feed. The D_h of uncross-linked nanospheres was 140 nm, but D_h was increased up to 480 nm when the composition of Bis-A was increased up to 2.0 mol %. It was also found that the D_h of the nanospheres was dependent on the water content in the solvent, and the water content of the nanospheres changed from 0 to 12 vol % meaning the change in diameter from 0 to 2.3% which was negligibly low. As a consequence, the nanospheres were obtained by dispersion copolymerization in either the presence or absence of cross-linker and in either ethanol or ethanol/water solvents. LLS measure-

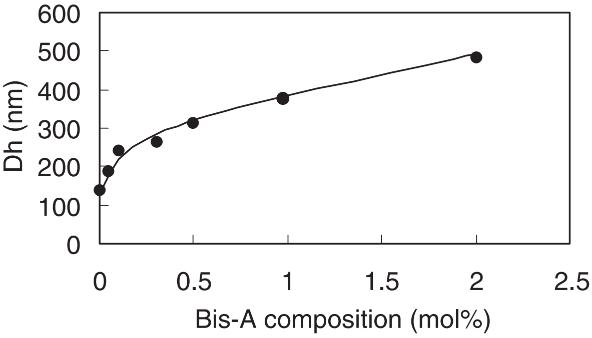

Figure 1. The effects of Bis-A composition on the Dh of the nanospheres, which were obtained by dispersion copolymerization of AAm (6 mmol; AAm/PtBMA=600) with PtBMA macromonomer (M_n=5400) in the presence of VA-061 (2 mol % to total monomers) in mixed ethanol/water (10 ml, vol/vol= 9/1) solvents.

ments showed the coefficients of variation for nanosphere size to be very low at 14–16%, indicating that the nanospheres have a monodispersed size-distribution. In the previous case of nanospheres with a hydrophobic core and a hydrophilic corona, the nanospheres were formed through the growth of nuclei stabilized by hydrophilic chains at the early formation stage, and the size was predominantly determined by the number of stabilized nuclei. In the present case, since the early-formed nuclei should be interconnected by cross-linkage to give the secondary nuclei, the number of stabilized nuclei might be reduced to yield the increased D_h of the nanospheres. CV values in the present case were a bit higher than the previously-reported nanospheres (lower than 10%), which may be associated with the interconnection of the nuclei.

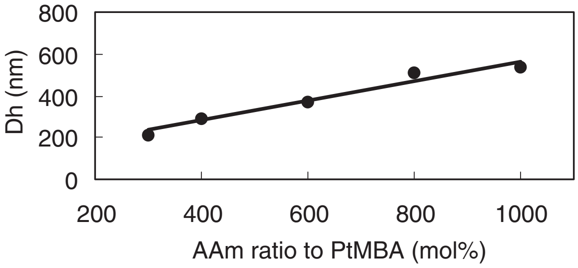

Figure 2. The effects of the ratio of AAm to PtBMA (0.01 mmol; M_n=5400) on the D_h of nanospheres obtained by dispersion copolymerization in the presence of Bis-A (1 mol% to total monomer) in mixed ethanol/water (9/1 vol/vol) solvents.

The effects of the AAm to PtBMA ratio on the Dh of the nanospheres were investigated (Figure 2). The Dh of the nanospheres increased from 220 to 540 nm with an increase in AAm composition from 300 to 1000 mol %. In the system producing nanospheres having a hydrophobic core and a hydrophilic corona, the D_h could also be increased by increasing the ratio of hydrophobic monomer i.e. decreasing the ratio of the hydrophilic macromonomer which stabilized the water-dispersion of the nanosphere by attaching to the surface.[10,11] In the present system, we speculate that the PtBMA macromonomer acts not only as a comonomer but also as a dispersion stabilizer in ethanol or ethanol/water mixed solvents, as similarly reported with a previous case.

If the nanosphere has a hydrophilic PAAm ($\text{–}CH_2CH(CONH_2)\text{–}$) on the surface, the amount of nitrogen should be equal to that of oxygen. The surface composition of the freeze-dried nanospheres (AAm/PtBMA = 600, Bis-A: 1 mol %) was investigated by ESCA. It was found that the peak area of the oxygen component was greater than that of the nitrogen component. The N_{1s}/O_{1s} value was 0.39 for the nanospheres. Other nanospheres also showed N_{1s}/O_{1s} values less than 1.00. The low nitrogen composition may be attributed to the presence of the PtBMA corona ($\text{–}CH_2C(CH_3)(COOC(CH_3)_3)\text{–}$) having two oxygen atoms and no nitrogen ($N_{1s}/O_{1s} = 0$). This observation is direct evidence for a nanosphere structure comprised of a PAAm core and PtBMA corona.

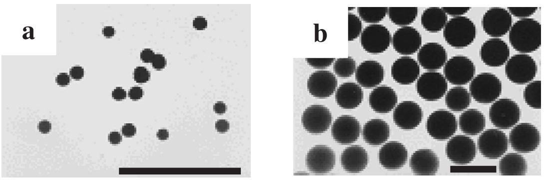

Figure 3. TEM images of PAAm nanospheres obtained by dispersion copolymerization (PtBMA M_n=6400; AAm/PtBMA=600) in the absence of Bis-A (a); Bis-A composition was 1 mol% to total monomers (b) in mixed ethanol/water (9/1 vol/vol) solvents. (Bar: 500 nm).

The TEM images are shown in Figure 3 where one can clearly see nanospheres with excellent sphericity. The number-average diameter (D_h) of the nanospheres in the absence of Bis-A is estimated as ca. 54 nm, which is smaller than the D_n of the nanospheres with the cross-linked core (300 nm) (b). Cross-linking has the same effect on D_h as it does on D_n (Figure 1). The application of these nanospheres with their novel structure as a drug carrier will be subsequently reported.

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