

One-Step Microwave Preparation of Well-Defined and Functionalized Polymeric Nanoparticles

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Polymeric nanoparticles (NPs) represent an important class of materials that are critical in a wealth of advanced technologies, ranging from colloidal crystals,¹ microelectronics,² and drug delivery³ to immunoassays.⁴ Among various synthetic strategies for NP preparation (e.g., self-assembly of amphiphilic block copolymers⁵ and colloidal particles by emulsion polymerization⁶), surfactant-free emulsion polymerization (SFEP) has emerged as a simple, green process for NP production without addition and subsequent removal of the stabilizing surfactants.⁷ Even with this success, several challenges still exist that cannot be achieved using traditional SFEP, including the preparation of monodisperse, sub-100 nm NPs at high solids content and the synthesis of NPs incorporating functional groups and cross-links.⁸ The incorporation of cross-links is especially important as they maintain structural integrity, preventing the NPs from dissolution in good solvents or matrix materials, greatly expanding their utility.⁹

We report a facile microwave methodology that overcomes several major challenges associated with SFEP and allows the preparation of narrow dispersity, cross-linked poly(methyl methacrylate) (PMMA) NPs with hydroxy functional groups in the critical sub-50 nm range. As an alternative to using a two-stage approach to control the NP size,¹⁰ cross-linkers with enhanced reactivity are employed to effect cross-linking through a one-step process without detrimental effects on NP size or dispersity. This successful size control is realized by confining the cross-linking to *intraparticle cross-linking* rather than *interparticle cross-linking*. In addition to this novel one-step strategy, the increased efficiency and control associated with microwave chemistry is exploited to prepare stable 20 nm NPs with solids content up to 10%, which is in direct contrast to the 100+ nm NPs that can be prepared at only 5% solids content using traditional techniques.^{7b} By combining all of these features, a novel method for preparing well-defined nanoparticles is reported that offers significant advantages when compared to previous methods.¹¹

As shown in Figure 1, when methyl methacrylate (MMA) was polymerized with potassium persulfate (KPS) in water or in 25 wt.% acetone/water solution, the particles reached their final size (characterized by dynamic light scattering (DLS)) within 30 min under 23 ± 2 W microwave irradiation. Without cross-linker, the final size was reduced from 155 nm in water to 65 nm in 25 wt.% acetone/water. This size reduction in acetone/water solution was attributed to the greater number of nucleating seeds resulting from the increased solubility of the monomer in acetone/water solution. While adding cross-linker ethylene glycol dimethacrylate (EGDM) caused a small increase in NP size in water, 155 nm (0 mol % EGDM) versus 170 nm (0.5 mol % EGDM); a dramatic size increase was seen in acetone/water solution, 65 nm (0 mol %

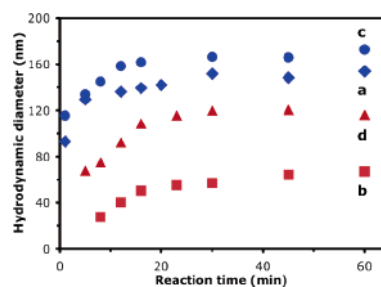


Figure 1. Particle size as a function of reaction time at 70 °C under microwave power of 23 ± 2 W (0.125 M MMA, 9.25 mM KPS): (a) 0 mol % EGDM in water; (b) 0 mol % EGDM in 25 wt % acetone/water; (c) 0.5 mol % EGDM in water; (d) 0.5 mol % EGDM in 25 wt % acetone/water.

EGDM) versus 120 nm (0.5 mol % EGDM), suggesting a different nucleation mechanism involved in acetone/water solution possibly owing to interparticle cross-linking, particularly when the number concentration of the nucleating seeds was significantly increased in acetone/water solution.

On the basis of the observed high sensitivity of the NP size to the reaction conditions in the presence of cross-linkers, we believe that two factors are critical in determining interparticle/intraparticle cross-linking and hence the NP size: the concentration of the NP seeds and the propagation rate coefficient k_p of the cross-linkers. To confirm our hypothesis, we performed the following experiments: (1) NP synthesis in water with cross-linkers of different k_p , representing conditions of low particle seed concentration and (2) NP synthesis in 25 wt.% acetone/water solution with cross-linkers of different k_p , representing conditions of high particle seed concentration. Two other cross-linkers, ethylene glycol diacrylate (EGDA) and *N,N'*-methylenebisacrylamide (MBA), were studied in addition to EGDM. The k_p values for the corresponding monomeric methacrylate, acrylate, and acrylamide are ~ 650 to 800 $M^{-1}s^{-1}$ (50 °C),^{12a} $\sim 11\,600$ to $16\,700$ $M^{-1}s^{-1}$ (20 °C),^{12a} and $\sim 20\,000$ to $30\,000$ $M^{-1}s^{-1}$ (20 °C),^{12b} respectively. Therefore, the k_p values for the corresponding cross-linkers should follow the order of $MBA > EGDA > EGDM$.

As shown in Figure 2A,B, when prepared in water, the particle size (~ 155 nm) was not affected by the type and amount of cross-linkers, indicating that interparticle cross-linking was negligible owing to the low particle concentration ($\sim 4.9 \times 10^{12}$ mL^{-1}). However, in 25 wt.% acetone/water, the particle concentration increased by ~ 25 times,¹³ resulting in significantly enhanced interparticle cross-linking for cross-linkers with lower k_p (Figure 2C,D). In 25 wt.% acetone/water, for 1 mol % cross-linker, EGDM with the lowest k_p led to larger particle size (~ 115 nm) than NPs without cross-linker and with 1 mol % EGDA/MBA (~ 55 nm), whereas for 3 mol % cross-linker, particles with EGDA started to increase (~ 100 nm) and particles with EGDM displayed a further enlargement (~ 230 nm), consistent with the corresponding k_p order

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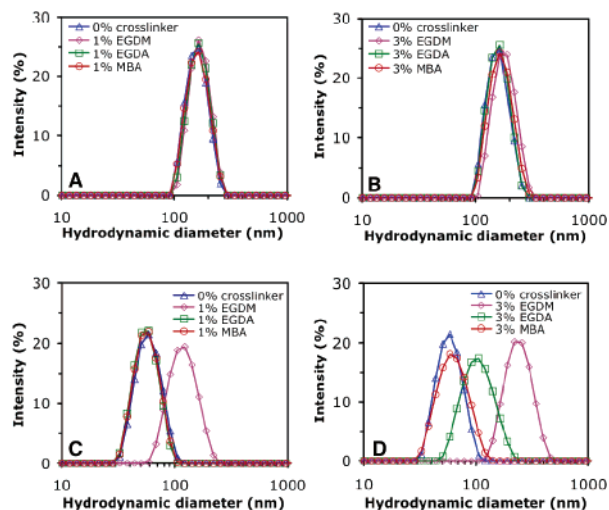


Figure 2. DLS size of NPs prepared in water with 1 mol % (A) and 3 mol % (B) of cross-linkers and in 25 wt % acetone/water with 1 mol % (C) and 3 mol % (D) of cross-linkers. Reaction conditions are 70 °C, 28 ± 2 W, 1 h, 0.125 M MMA, and 9.25 mM KPS.

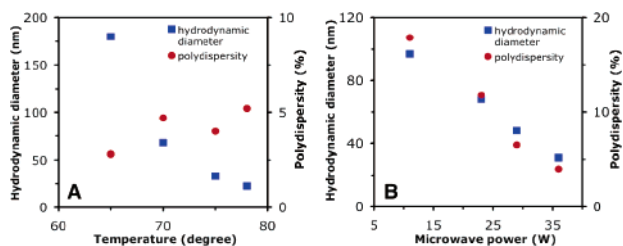


Figure 3. (A) Particle size as a function of temperature under microwave power of 23 ± 2 W in 25 wt % acetone/water (0.125 M MMA, 9.25 mM KPS); (B) particle size as a function of microwave power at 70 °C in 25 wt % acetone/water (0.125 M MMA, 1.5 mol % MBA, 9.25 mM KPS).

of the cross-linkers. In all cases, the NP size (55–60 nm) was well controlled with MBA, the cross-linker with the highest k_p , and this is attributed to the decreased occurrence of interparticle cross-linking. The cross-linked NPs showed narrow polydispersity and maintained their integrity in *N,N*-dimethylformamide (DMF). In addition, NPs prepared under thermal heating conditions displayed no control for cross-linked NPs, resulting in poorly defined systems.

In contrast to thermal heating reactions, one of the advantages of microwave systems is the ability to control other facets of the reactions. In this respect, microwave polymerization was examined in the superheated state of the solution by increasing the temperature from 65 °C to 78 °C (azeotropic point of 25 wt % acetone/water is 68 °C) which showed a significant reduction in NP size from 180 nm at 65 °C to 23 nm at 78 °C (Figure 3A). In addition, for polymerizations performed at the same temperature (i.e., 70 °C), an impressively wide range of diameters (100 to 30 nm) could be obtained by varying the microwave power (11 to 36 W) (Figure 3B). Control reactions without KPS did not produce any colloidal NPs or polymers, indicating that polymerization was not initiated by microwave irradiation. The dramatic reduction in NP size suggests enhanced radical influx in the solution, which further implies that microwave can dielectrically couple with the persulfate anions to accelerate the decomposition of the initiator.

Having demonstrated the ability to prepare cross-linked NPs with diameters less than 50 nm, the versatility of this technique was further established by increasing the solids content and by the inclusion of functionalized monomers, such as 2-hydroxyethyl methacrylate (HEMA) into the polymerization system. After a high-throughput analysis of various reaction parameters (Supporting Information), it was found that decreasing the solvent polarity to 40 wt % acetone/water while increasing the reaction temperature (80 °C) and microwave power (50 ± 2 W) allowed the preparation of cross-linked, HEMA functionalized NPs at unprecedented solids content, from 14 nm at 5.6 wt % to 41 nm at 12.6 wt % solids (molar ratio of MBA/HEMA/MMA/KPS = 1.0:1.6:30.7:1.6). In each case, the monomer conversion was essentially quantitative (96–100%), and stable colloidal solutions without any agglomeration were obtained.

In conclusion, a novel strategy for controlled preparation of cross-linked polymeric NPs is reported. Key to this development is the use of cross-linkers with enhanced reactivity and controlled microwave reaction procedures. This combination proved to be a powerful tool for the synthesis of cross-linked, functionalized NPs under high solids content and surfactant-free conditions. In addition, these findings based on PMMA can be easily extended to other polymers and other emulsion polymerization techniques.

Acknowledgment. Financial support from MC-CAM and the central facilities of the UCSB Materials Research Laboratory (NSF Grant DMR05-20415) is gratefully acknowledged. Drs. Kim van Berkel and Nanfeng Zheng are thanked for helpful discussions and Chia-Kuang Tsung is thanked for help on TOC art.

Supporting Information Available: Experimental details, NP characterizations, optimization of reaction parameters on NP size. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (13) Particle concentration was calculated from the mass of the monomer and the particle diameter, assuming spherical NP and 100% monomer conversion.

JA065250F