Synthesis and Characterization of 'Smart' Microgels that Respond to pH and Temperature Changes

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Statement of Purpose: We report here the synthesis and characterization of temperature- and pH-responsive microgels for drug delivery applications. Microgel particles have many advantages as a drug carrier because of their hydrophilicity (stealth) and stability. Microgels composed of *N*-isopropylacrylamide (NIPAAm) and propylacrylic acid (PAA) were synthesized via precipitation polymerization. This copolymer has a higher p*K*a value than those of conventional monomers (*e.g.*, acrylic acid; pKa <5) and is capable of responding to physiologically relevant pH values between 5.0 and 7.4.[1] The NIPAAm-PAA microgels are designed to exist in the slightly swollen, inert state at 37˚C and pH 7.4 but to shrink and release drug at 37 °C and below pH 6.0, which is a representative pH for tumor tissues. In this study, we investigated how microgel size is influenced by changes in temperature and pH.

Methods: NIPAAm-PAA microgels were synthesized via free-radical precipitation polymerization in aqueous solution.[2] Briefly, NIPAAm and PAA monomers (6.3 mM), *N,N'*-methylene(bisacrylamide) (BIS; 0.32 mM) as a crosslinker, and sodium dodecyl sulfate (SDS; 0.1 mM) as a surfactant were dissolved in distilled water (DI water) and purged with N_2. Polymerization was initiated by adding ammonium persulfate (APS; 0.17 mM) at 70 °C and the reaction proceeded for 6 h with stirring. The prepared particles were characterized by a dynamic light scattering (DLS) particle sizer at different temperatures and pH values. All measurements were carried out in both DI water and phosphate buffer (pH 5-7.4 and 0.15 M ionic strength).

Results/Discussion: Figure 1 shows the temperature-dependent size changes for NIPAAm-PAA microgels with different PAA compositions in DI water (pH 5.5). The sizes of microgels at 20 °C were identical (around 240 nm) regardless of their composition of PAA, while they are larger than that of NIPAAm homopolymer gel (130 nm). The size of the NIPAAm-PAA microgel decreased as temperature increased (around 110 nm at 40 °C). However, the gel containing 20 mol% of PAA did not shrink significantly due to the increased number of carboxyl groups in the gel.

The NIPAAm-PAA microgels also demonstrated pH-responsive size changes in buffer solutions at 37°C as seen in Figure 2. Although all microgels aggregated at lower pH (*e.g.*, pH 5), the gels with more than 10 mol% of PAA did not aggregate above pH 6 and their particle sizes increased as pH increased. This is because the carboxyl groups in the microgels continue to ionize with increasing pH, which opposes the tendency to collapse due to the PNIPAAm component.

Conclusions: The dual stimuli-responsive NIPAAm-PAA microgels were synthesized via precipitation polymerization and characterized in this study. The smart gels demonstrated sharp phase transition behavior in response to pH and temperature changes at physiological conditions. The gels also displayed tunable properties that could make them useful in a variety of drug delivery applications where responses to small pH changes are relevant.

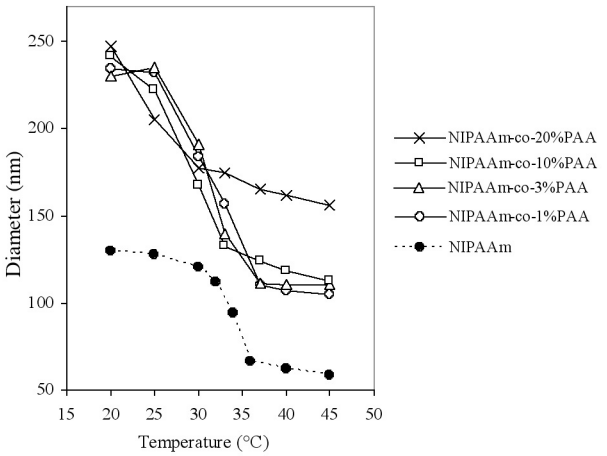

Figure 1. Temperature dependent changes in hydrodynamic diameters of NIPAAm-PAA microgels in DI water measured by DLS.

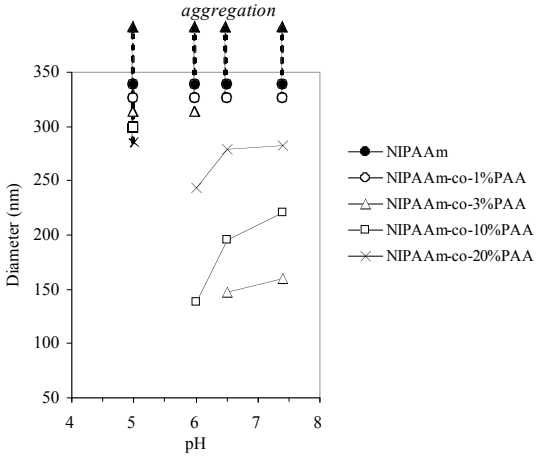

Figure 2. pH dependent changes in hydrodynamic diameters of NIPAAm-PAA microgels at 37 °C in buffers (0.15 M) measured by DLS.

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References:

[1]Yin X. Biomacromol. 2006;7:1381-1385.
[2]Jones CD. Macromol. 2000;33:8301-8306.