Synthesis and Characterization of a Temperature- and pH-responsive Sol-gel Hydrogel Suitable for Drug Delivery

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Statement of Purpose: Physical hydrogels that undergo a reversible, sol-to-gel phase transition in response to clinically-relevant stimuli have significant potential as drug delivery systems. In particular, polymers that are soluble at 37˚C and pH 7.4 but form gels under conditions of intermediate acidity (pH 6.0-7.0) at 37°C may be able to target regions of local acidosis, such as that found in ischemia, infection, or tumors. Dilute solutions of poly(N-isopropylacrylamide-co-propylacrylic acid) (p[NIPAAm-co-PAA]) have previously been shown to exhibit a cloud point that is highly sensitive to temperature and pH changes in this physiologically-relevant range.[1] In this study, we characterize the sol-gel behavior of higher concentrations of p(NIPAAm-co-PAA) as functions of temperature and pH.

Methods: P(NIPAAm-co-PAA) of varying NIPAAm:PAA molar feed ratios (0-20 mol% PAA) was synthesized by reversible addition fragmentation chain transfer (RAFT) free radical polymerization. Molecular weights and compositions were determined by gel permeation chromatography and proton NMR, respectively. Viscoelastic properties were quantified by rheometery under conditions of variable pH, temperature and concentration. Gelation temperature was identified when the storage modulus (G', Pa) showed a rapid increase in slope.

Results/Discussion: Varying compositions of P(NIPAAm-co-PAA) were successfully synthesized by RAFT. Figure 1 depicts the sol-gel behavior of a representative composition (15 mol% PAA in feed) in phosphate buffer at different pH values. Increasing pH led to an increase in the gelation temperature.

The sol-gel transition of p(NIPAAm-co-PAA) was highly sensitive to composition, pH, and temperature (Figure 2). Increasing compositions of PAA in the feed resulted in a lower gelation temperature for a given pH. In general, gels formed at lower pH values were more stable, as observed by the larger temperature range in which gels existed prior to syneresis. At lower pH, more carboxyl groups on PAA are protonated, rendering the polymer more hydrophobic and facilitating gelation.

Interestingly, no gels formed at pH values greater than or equal to 6.0 for the compositions studied. The pKa value of p(NIPAAm-co-PAA) was previously reported to be around 6.0, depending on the composition.[1] While the polymers do exhibit a cloud point at this pH, the hydrophobic interactions are not sufficient to form a gel at 37˚C.

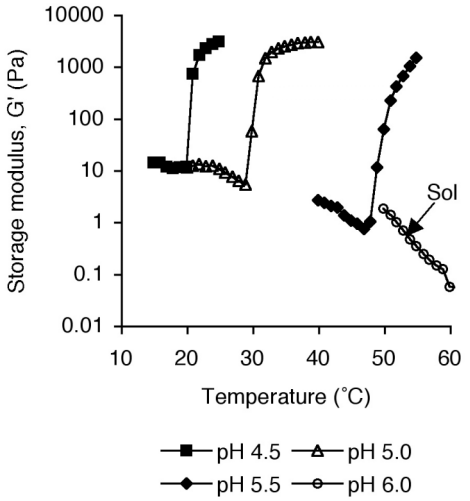

Figure 1. Sol-gel behavior of p(NIPAAm-co-PAA) (15 mol% PAA in feed, 26.5 kDa, 5 wt% in buffer) with pH values ranging from 4.5-6.0.

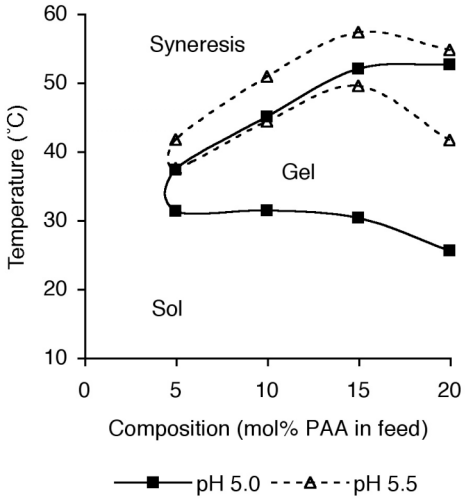

Figure 2. Gelation temperature of p(NIPAAm-co-PAA) (5 wt% in buffer, targeted degree of polymerization = 200) as a function of feed composition at pH 5.0 and 5.5.

Conclusions: P(NIPAAm-co-PAA) exhibits reversible sol-gel behavior that is highly sensitive to temperature and pH in a physiologically-relevant range. Future work may involve combinations of this polymer with other polymers or functional groups to further tune the sol-gel behavior within clinically-significant values.

Acknowledgement: This work was supported by NIH grant #EB002991.

Reference:

[1]Yin X. Biomacromolecules. 2006;7:1381-1385.