Supporting Information

Injectable and Self-Healing Nanocomposite Hydrogels with Ultrasensitive pH-Responsiveness and Tunable Mechanical Properties: Implications for Controlled Drug Delivery

Meng Wu[†], Jingsi Chen[†], Weijuan Huang[‡], Bin Yan[§], Qiongyao Peng[†], Jifang Liu[†,#], Lingyun Chen[‡], Hongbo Zeng[,†]*

[†] *Department of Chemical and Materials Engineering, University of Alberta, Edmonton, Alberta T6G 1H9, Canada*

[‡] *Department of Agricultural, Food and Nutritional Science, University of Alberta, Edmonton, Alberta T6G 2P5, Canada*

[#] *The Fifth Affiliated Hospital, Guangzhou Medical University, Guangzhou, Guangdong, 510700, China*

[§] *College of Biomass Science and Engineering, Sichuan University, Chengdu, Sichuan, China*

**Corresponding Author. E-mail: hongbo.zeng@ualberta.ca (H.Zeng), Phone: +1-780-492-1044*

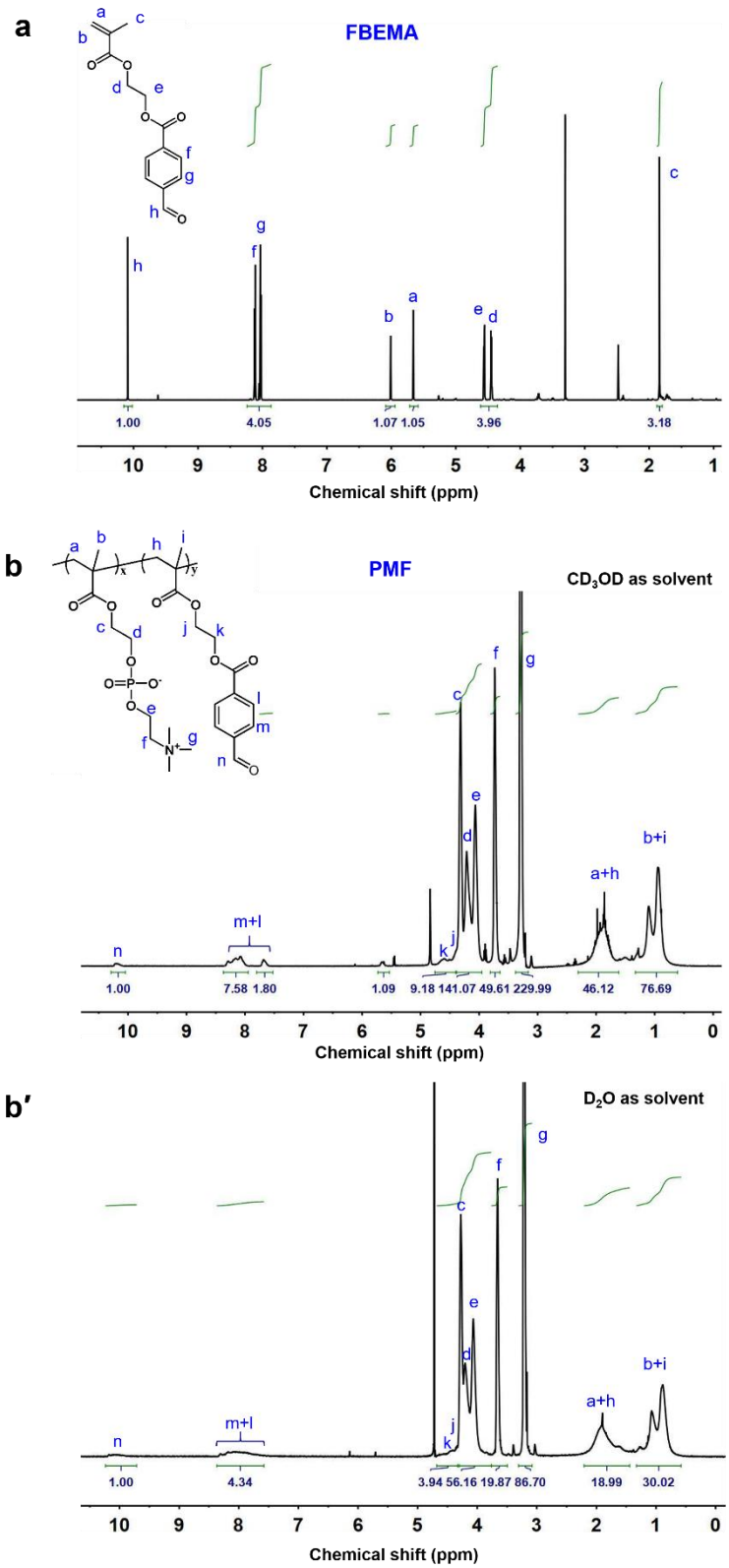

Figure S1. ^{1}H NMR spectra of (**a**) FBEMA, (**b**) PMF10 with CD_3OD as solvent and (**b′**) PMF10 with D_2O as solvent.

In Figure S1b, when CD_3OD was used as the NMR solvent for PMF copolymer, the integration ratio of the peak for formyl proton (n) to aromatic ring signals (m+l) is less than the theoretical value, while the ratio shows good consistency with the theoretical value when using D_2O as the solvent as shown in Figure S1b′. This difference is due to the reaction between the PMF copolymer and d-methanol, leading to the formation of hemiacetal, which was evidenced by the broad peak assigned to hemiacetal α-proton at chemical shift of 5.6 ppm in Figure S1b.[1-4] The integration ratio of the sum of formyl proton peak and hemiacetal α-proton peak to aromatic ring signals (m+l) is around 1/4, which is in good agreement with the theoretical value. Since CD_3OD gives sharper NMR peaks and more detailed information of the functional aldehyde group while the peaks are broad with D_2O because of the limited solubility of the benzaldehyde moiety in D_2O, the actual aldehyde contents in the copolymers were calculated from the integral values of the characteristic aromatic ring signals (m+l) of FBEMA and characteristic peaks of MPC (c+d+e). It worth noting that although hemiacetals between aldehyde groups and the solvent might form when ethanol was used as the solvent for copolymer synthesis, the unstable hemiacetals would decompose to aldehydes when the polymer was purified with the removal of ethanol[2].

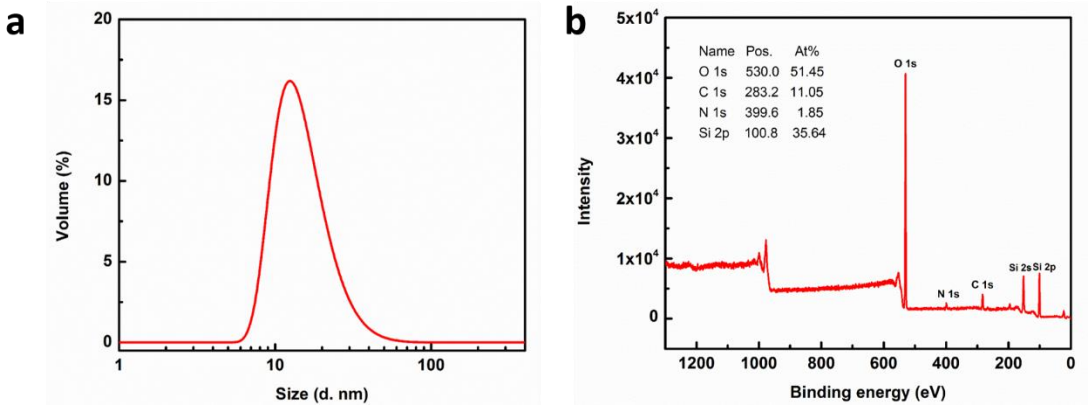

Figure S2. (**a**) DLS and (**b**) XPS results of ASNP.

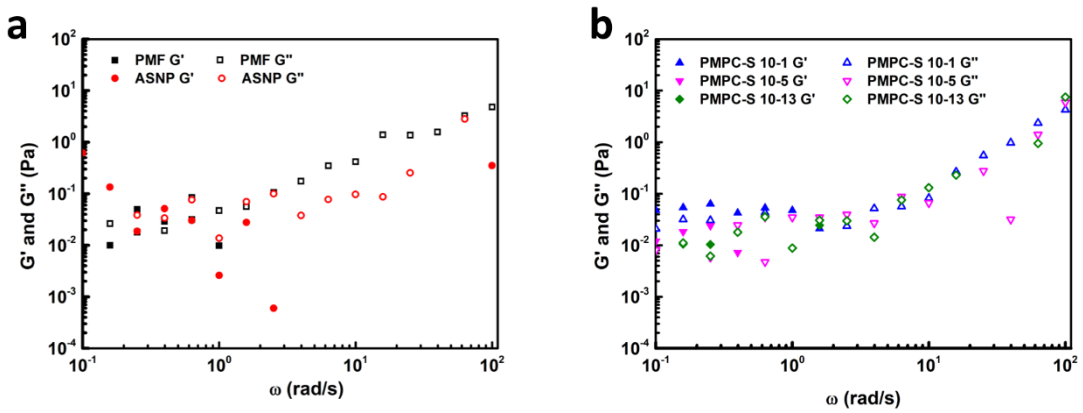

Figure S3. Rheological frequency sweeps (1% strain and 37 °C) of (**a**) PMF10 (20 wt%) and ASNP (26 wt%) solutions, and (**b**) mixtures of pure polymer of 2-methacryloyloxyethyl phosphorylcholine (PMPC) and different concentrations of amine-modified silica nanoparticle (ASNP). The mixtures were denoted as PMPC-S x-y, where S represents ASNP, x and y are the weight percent of polymer and nanoparticles in the mixture, respectively. It is noted that the fluctuation of some of the data points in Figure S3 was due to the very low viscosities of the related samples and the measured torques were close to the detection limits (in the cone-plate geometry) of the instrument.

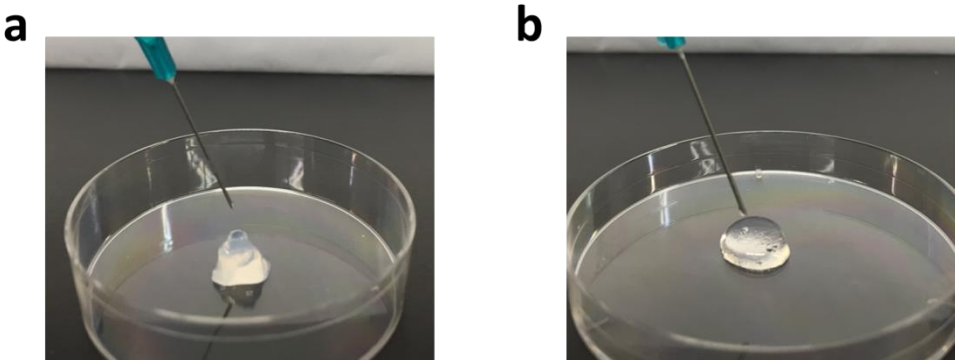

Figure S4. Injected bulk hydrogels of (**a**) PMF10-S 10-13, and (**b**) PMF5-S 10-13 through 23-gauge needles.

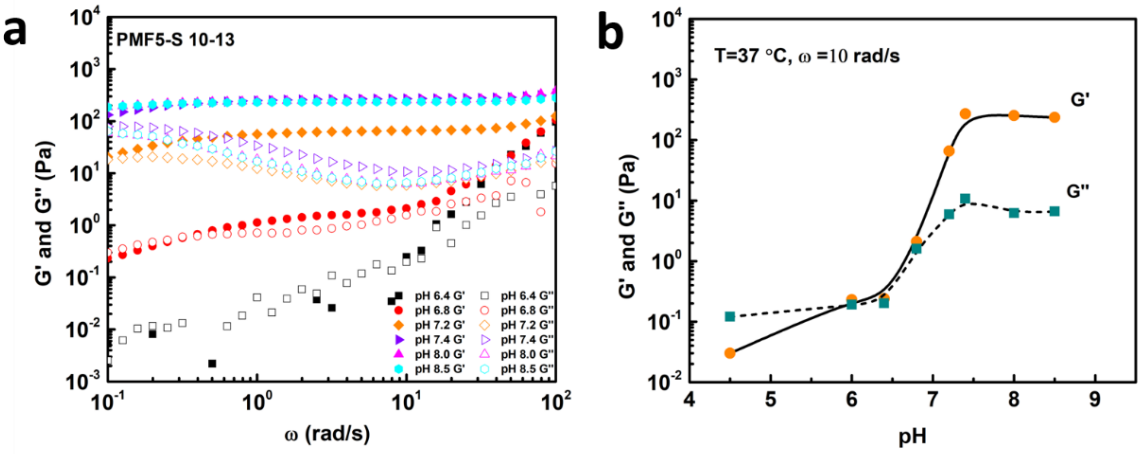

Figure S5. Rheological characterization of the pH dependent behavior of PMF5-S 10-13 hydrogel at 37 °C and strain of 1%. (**a**) Oscillatory frequency sweeps, and (**b**) G′ and G″ versus pH at 10 rad/s.

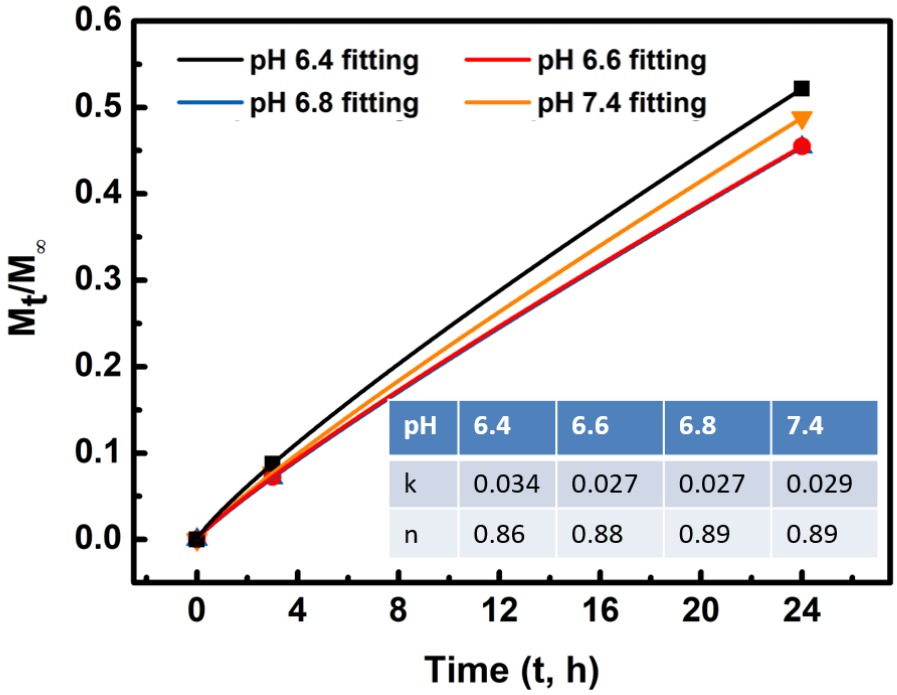

Figure S6. Fitting of BSA-FITC release data of first 24 hours according to Korsmeyer-Peppas equation. Inset table shows the fitting parameters.

References

(1) Guthrie, J. P. Carbonyl Addition Reactions: Factors Affecting the Hydrate–Hemiacetal and Hemiacetal–Acetal Equilibrium Constants. *Can. J. Chem.* **1975**, *53*, 898-906.

(2) Clayden, J.; Greeves, N.; Warren, S.; Wothers, P. Chapter 14: Nucleophilic Substitution at C=O with Loss of Carbonyl Oxygen. Organic Chemistry, 1st Edition; ISBN: 0198503466; Oxford University Press Inc., New York, **2001**; page 339-360.

(3) Ashley, D. L.; Orti, D. L.; Hill Jr, R. H. Proton Nuclear Magnetic Resonance Evidence for Two Configurations of the Hemiacetals of Aflatoxin B1 and Sterigmatocystin. *J. Agric. Food. Chem.* **1987**, *35*, 782-785.

(4) Evans, D. A.; Gauchet-Prunet, J. A. Diastereoselective Synthesis of Protected Syn 1, 3-Diols by Base-Catalyzed Intramolecular Conjugate Addition of Hemiacetal-Derived Alkoxide Nucleophiles. *J. Org. Chem.* **1993**, *58*, 2446-2453.