Iron Oxide Nanocomposite Sol-Gel Systems for Remote Controlled Drug Release

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Statement of Purpose: Remote controlled degradation and drug release have previously been demonstrated using magnetic nanoparticles incorporated into a biodegradable polymer matrix. The remote heating of the nanoparticles was used to modulate the rate of degradation. This ability to remotely heat magnetic nanoparticles can also be used to cause other temperature-based transitions, such as the solution to gel to solution behavior (sol-gel) exhibited by some block copolymers. In this work, we used the heating of magnetic nanoparticles in an alternating magnetic field (AMF) to control the phase behavior of a sol-gel block copolymer system and, subsequently, the release of a drug from the polymer depot. Pluronic® F-127, a poly(ethylene oxide) – poly(propylene oxide) – poly(ethylene oxide) triblock copolymer system was used as the matrix material into which iron oxide magnetic nanoparticles and a model drug were loaded. The goal of this work is to demonstrate remote actuation of drug release through the manipulation of the phase behavior in the polymer composites.

Methods: Pluronic® systems were synthesized using the cold method in which polymer particles are dissolved in phosphate-buffered saline (PBS) solution at 4°C. Systems were made in the range of 16% to 25% by weight of Pluronic® in PBS. For drug loaded systems, the drug particles were dissolved in the PBS prior to the polymer addition. Iron oxide nanoparticles were dispersed into the polymer using a sonication probe. Phase transitions were determined through test tube inversion, and the heating studies were carried out using a Luxtron FOT temperature probe on samples exposed to a Taylor-Winfield AMF. Drug release studies were carried out by measuring the drug movement into either a PBS sink or a synthetic tissue model. In the PBS method, the PBS supernatant was exchanged for fresh PBS at pre-determined time intervals and the collected PBS was analyzed. To assess release into a model tissue environment, highly swollen PEG gels were polymerized in test tubes. Sol-gel samples were pipette onto the top, and the movement of the diffusion front was measured.

Results: Pluronic® F-127 systems were successfully prepared with both iron oxide nanoparticles and several model drugs. It was observed that the iron oxide nanoparticle presence altered the transition temperatures of the sol-gel system, effectively decreasing the temperature range in which the system is a gel. When loaded with iron oxide, the systems heated substantially when exposed to the AMF. The representative heating plot in Figure 1 shows the temperature changes measured in a pure (0% loading) and loaded (2.5% iron oxide loaded) 16% F-127 system. The gel was kept at 37°C prior to heating and exposed to the AMF for 60s. A 20°C temperature change was observed, which would allow the system to reach the upper gel to sol transition.

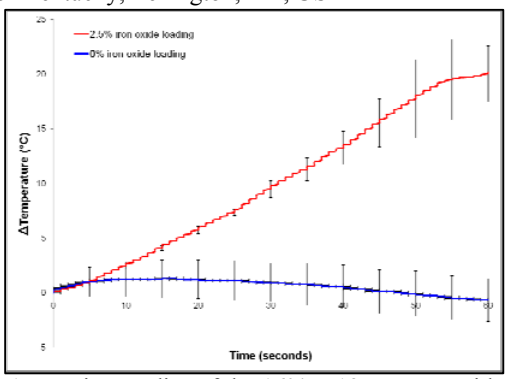

Figure 1: Heating studies of the 16% F-127 system with either 2.5% iron oxide loading or 0% iron oxide loading. N = 3 ± 1 STDV

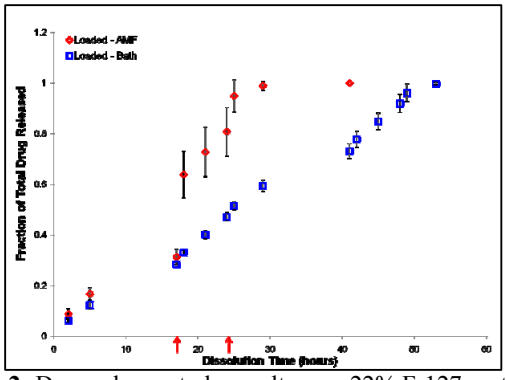

Figure 2: Drug release study results on a 22% F-127 system with 2.5% iron oxide nanoparticles and 1% vitamin B12. AMF exposure is indicated by red arrows. N = 3 ± 1 STDV

Several drug release studies were carried out using Pluronic® loadings ranging from 15% to 25%. The higher polymer loadings resulted in slower dissolution and drug release rates in PBS. The higher loading of polymer also had larger temperatures ranges of gelation and higher upper transition temperatures.

The results of a release study are shown in Figure 2. In this study, a 22% F-127 polymer with 2.5 wt% iron oxide and 1% vitamin B12 was allowed to dissolve into a PBS sink. The test study exposed the system to the AMF for 5 minute doses at 17 and 24 hours. A significant shift in the fraction of drug released curve was observed as compared to the control samples stored in the 37°C bath.

Conclusions: We have demonstrated that iron oxide loaded sol-gel polymer systems heat significantly when exposed to an alternating magnetic field. Preliminary studies also show that AMF exposure can cause a phase change in the system thereby allowing a significant increase in the rate of drug release. Future studies are working to better tune the drug release characteristics and approach on-off control.

Acknowledgement: This work was supported in part by NSF-IGERT.