Surfactant Effect on Gelation in an *In Situ* Forming Reverse Emulsion Polymeric System for Tissue Reconstruction

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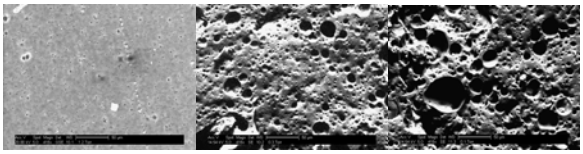
Statement of Purpose: *In situ*-forming gels are of medical interest for clinical embolization and tissue reconstruction. Controlling the gel time and viscosity of these systems is of utmost importance during injection to prevent down-stream stroke in clinical applications. This work analyzes a reverse emulsion polymer formed by the Michael Type Addition reaction of water insoluble but water dispersible multi-thiols and multi-acrylates, initiated by basic water droplets emulsified in the bulk polymeric material. Our experiments encorporate results obtained in previous work(McLemore, R.,Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2006; 79(2):398-410.) showing the dependence of Michael type addition reaction rates upon the pKa(Lutolf, M., et al., Bioconjugate Chem, 2001; 12(6): 1051-1056.) of the mercaptan and pH(McLemore, R.,Journal of Biomedical Materials Research Part B: Applied Biomaterials, 2006; 79(2): 398-410.) of the initiating solution. Detailed experimentation in this work examines the effect of surfactant incorporation upon that gelation rate to improve upon injection variability and biocompatibility of these reverse emulsion materials.

Methods: Materials employed include poly(ethylene glycol) diacrylate (PPG), pentaerythritol tetrakis 3-mercaptopropionate (QT), phosphate buffered saline, sodium hydroxide. Surfactants tested include polyoxyethylene (20) sorbitan monolaurate (TWEEN 20), sodium dodecosulfate (SDS), and a Poly(propylene glycol)-poly(ethylene glycol)-poly(propylene glycol) block copolymer with an Mn of 3300. Initial sample preparation involved combining PPODA and QT at functionally equivalent concentrations. The organic materials were combined with water to provide an initiator. Samples were mixed with either no surfactant, or with 2 wt% SDS , Tween 20, or the PPG-PEG-PPG copolymer. Samples were analyzed on the rheometer at 10 Pa and .1 Hz to determine the effect of surfactant on the gelation rate, and imaged on an Environmental Scanning Electron Microscope to determine the material microstructure.

Results/Discussion: Initial SEM images showed a distribution of pore sizes in the reverse emulsion materials which was seen to grow as a function of the time materials took to reach gel point. These pores contain water, and provide a large concentration of OH^- ions which act as initiators in the Michael Type Addition Reaction used to form the overall polymeric structure. As thiolate forms in the bulk phase, the resulting hydrogen ions are though to diffuse short distances into the disperse phase, where they are quenched to form H_2O.

After witnessing the effect of rate of gelation on the material, it was asked what effect stabilizing the pores shown below, which contain the pH sink which serves to activate the system, might have on the gelation rate of the material.



A B C

Figure 1. ESEM showing the gradual coarsening of the material as the time to gelation increases, as a function of both mixing and pH. A indicates the most quickly gelling material, whereas C indicates the slowest.

Rheological analysis showed that combining the system with TWEEN 20, or with the PPG-PEG-PPG block copolymer significantly shortened the measured time to gel, while combination of the material with SDS produced little to no effect upon material gelation. A sample comparative trace is produced below as Figure 2.

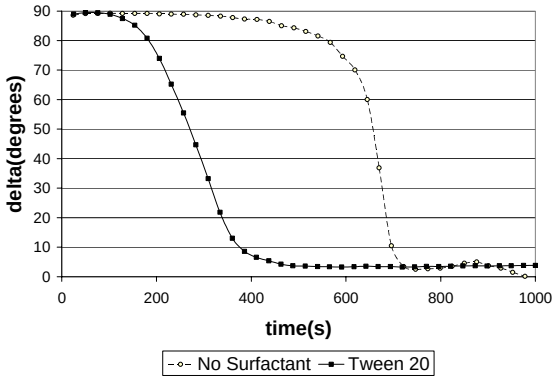


Figure 2: Rheological trace showing effect of TWEEN 20 on gelation time. The first line from the left shows the δ vs. time for the material with 2wt% TWEEN, the second line shows δ for the standard material.

Effect of the surfactants has been related to the size of the hydrophilic portion of the molecule, and the overall molecular weight of the construct. Decrease in gelation time has been attributed to increased flux of hydrogen ions resulting from stabilization of the dispersed phase in smaller spheres for a longer period of time. Surfactants need to be selected for chemical stability in a high pH environment, but intelligent selection of surfactants can allow for reduction of the pH necessary to initiate the reaction at a given rate, thereby rendering all of the components more biocompatible.

Conclusions: These results suggest that incorporation of surfactants into gels intended for the clinic will allow their initiation at lower pH, and will help to reduce variability in gelation rates due to separation of the emulsion over time. Future work will explore the comparative biocompatibility of these constructs.