In Situ-Gelling Polymer System for Vascular Embolization: Effect of Radio-opaque Agent on Gelation

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Statement of Purpose: The introduction of endovascular embolization techniques to treat vascular conditions, such as aneurysms, has spurred the development of numerous embolic materials in recent years. However, there is still much room for improvement of these materials. The most commonly used endovascular technique for aneurysm treatment is coil embolization. One drawback to this technique is the relatively high failure rate of aneurysm flow obliteration and recanalization associated with the procedure, likely resulting from the significant volume that remains unfilled by coils (1). Other emerging techniques include liquid copolymer systems where polymers are deposited into an aneurysm as they precipitate out of solution on contact with blood. Most of these copolymers must be delivered in organic solvents, which pose a threat to blood vessels due to their propensity for angiotoxicity (2). Water-based *in situ* gelling polymeric materials for use in endovascular embolization have the potential to bypass some of the problems with current embolization materials (3). We examined an *in situ* gelling polymer system formulated with two different types of radio-opaque agents in order to determine how each of these agents affect the gelation process. Identifying differences is critical for optimizing this material, since the gelation process can affect clinically relevant parameters such as deliverability and the material lifetime *in vivo*.

Methods: This study is aimed at characterizing differences in the gelation process of reverse emulsion materials formulated with two different radio-opaque contrast agents. The organic polymer phase consists of a mixture of poly(propylene glycol) diacrylate (PPODA) and pentaerythritol tetrakis(3-mercaptopropionate) (QT), to make up 75% (wt.) of the final composition. These monomers undergo Michael-type addition upon initiation by a basic, aqueous solution. The 25% (wt.) dispersed aqueous phase consists of a commercially available injectable contrast agent, either Conray™ (Mallinckrodt St. Louis, MO) or Omnipaque™ 300 (GE Healthcare Princeton, NJ). These liquid radio-opaque agents were pH-adjusted to basic conditions and incorporated into the system through mixing with the organic phase. Mix times of 0.5 minutes and 1.5 minutes were examined with each formulation. Material gelation characteristics were identified through rheology, while scanning electron microscopy (SEM) provided information about the dispersed aqueous droplets after the material solidified.

Results: Gels formulated with Conray show faster polymerization kinetics, given that during rheological testing they reach the gel point ($\delta=45^{o}$) faster than Omnipaque materials. However, Conray-formulated gels also show a more gradual increase in viscosity over the course of the reaction than Omnipaque gels, indicating there is a difference in reaction kinetics not only up to the point of gelation, but that persists throughout the entire process of gelation.

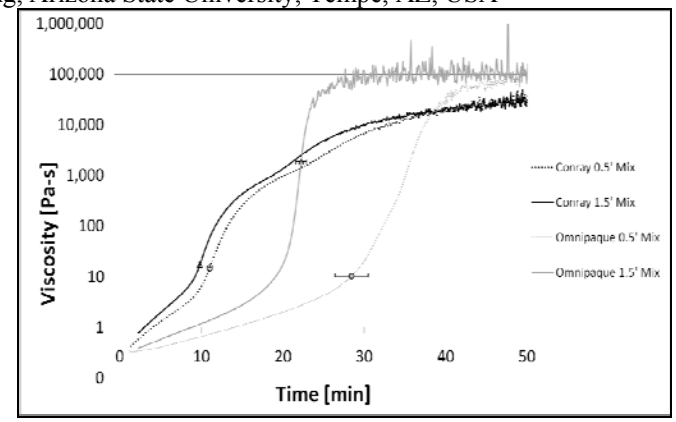

Figure 1: Viscosity profile of gels mixed for 0.5 and 1.5 minutes. Average gel times ± stdev are also shown.

SEM analysis shows that Conray gels contain dispersed droplets in greater quantity and of smaller average size than in Omnipaque-formulated gels, but the combined total area of droplets in Conray gels is less than the total droplet area in Omnipaque gels (Figure 2).

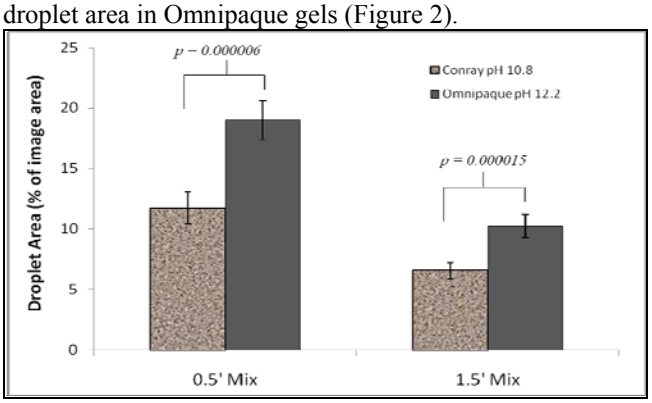

Figure 2: Combined droplet area per image, reported as the percent of total image area for each gel formulation.

Conclusions: Conray gels undergo network formation sooner than Omnipaque gels, and thus have smaller and a greater number of droplets because there is less available time for unstable droplets to fuse together and grow. Slower gelling Omnipaque materials allow more droplet coalescence to occur, given the extended time of initial slow viscosity growth (Figure 1). Differences in the gelation process between formulations occur because dispersed radio-opaque agents interact differently with the continuous PPODA-QT organic phase. We propose that Conray is more soluble in the organic phase, leading to more widespread distribution of reaction initiation sites throughout the organic phase. This results in faster reaction kinetics for Conray gels, as well as significantly less Conray present in droplet form when compared to Omnipaque gels. Data analysis from rheology and SEM is ongoing to further support or refute this hypothesis.

References:

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