

Development of Injectable Polymers that Cross-Link by Click Chemistry

M. Brett Runge & Michael J. Yaszemski

Mayo Clinic, Rochester MN

Statement of Purpose: Injectable bone substitutes such as the non-degradable polymethylmethacrylate bone cement, or degradable polypropylene fumarate (PPF) use free radical polymerization to cross-link in situ. Both resins for injectable applications contain a mixture of polymer, comonomer, initiator, and accelerator. The use of small molecules as comonomers, initiators, and accelerators creates toxicity issues because they can total more than 40% of the resin weight^{1,2}, and are not always 100% consumed during curing. To remove these toxic small molecules from injectable resin formulations a new approach to cross-linking polymers in situ (Figure 1) using thiol-ene click chemistry is being developed. The approach utilizes thiol functionalized polymers (termed PPST) synthesized from PPF. A blend of PPST and PPF is mixed with <1% photo-initiator and cross-links upon exposure to UV, thereby avoiding the additional toxic small molecules.

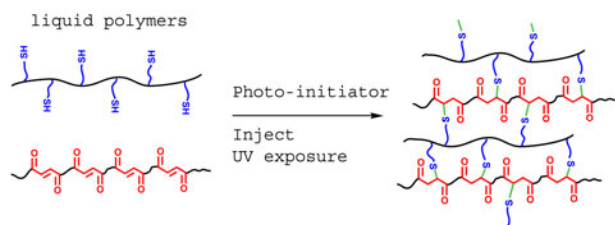


Figure 1. General approach for using click chemistry with injectable polymeric resins.

Methods: *Synthesis of polypropylene succinate thiol (PPST).* 1,6-dithiol hexane (9.71 g, 0.065 mol) was dissolved in 300 mL THF with triethylamine (10.1 g, 0.065 mol). Trimethylsilylchloride (7.03 g, 0.065 mol) was added dropwise to the reaction and allowed to stir for 4 h. Five addition molar equivalents of triethylamine were added followed by polypropylene fumarate (10.1 g) dissolved in 150 mL THF and stirred for 4 h. Acidic water was added to the reaction vessel and the polymer. The polymer was extracted with methylene chloride and precipitated in petroleum ether to remove impurities.

Cross-linking of PPST-PPF. PPST of M_n 3122 (1.04 g) and PPF of M_n 900 (1.16 g) were mixed together. BAPO (.1 g) (Irgacure 819, Ciba) was dissolved in 2mL ethanol. 300uL of the BAPO solution was added to the PPST and PPF mixture and thoroughly mixed. The solution was irradiated with UV at λ of 315-380 nm for 30 min.

Mechanical Testing. The compressive modulus of cross-linked PPST-PPF scaffolds was determined on a dynamic mechanical analyzer (DMA-2980, TA Instruments) at load rate of 4 N/min. The compressive modulus was determined from the slope of the stress versus strain curve in its linear region. Samples were performed in triplicate and are reported as mean \pm standard deviation.

Results: Polypropylene succinate thiol (PPST) was synthesized by the Michael's addition of mono silane protected dithiols to polypropylene fumarate in the presence of triethylamine (Figure 2.) The reaction was

quantitative, as the complete consumption of the olefin in PPF was observed by ¹H NMR. The TMS protecting group was easily removed from the thiol during aqueous work up following the Michael addition. This approach gives dramatic control over the design of the cross-linking polymeric system by varying the R group of the dithiol.

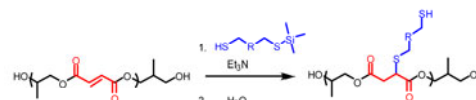


Figure 2. Synthetic approach to PPST.

PPST polymers were characterized by GPC, DSC, TGA, and FTIR. GPC analysis shows a significant increase in molecular weight from PPF as expected with the significant addition of molecular weight to the polymer.

PPF		PPST	
M_n	PDI	M_n	PDI
980	3.05	3122	3.2

Table 1. Polymer characterization of PPF and PPST.

The compressive modulus of two cross-linked blends of PPST and PPF are shown in Table 2. These were initially used to investigate whether this approach to cross-linking polymeric materials in situ would work. PPST and PPF were cross-linked with less than 1% photo-initiator under UV for 30 min and have a compressive modulus of 1.7 and 2.4 MPa. This approach to injectable polymeric materials removes the addition of toxic small molecule additives such as N-vinyl pyrrolidinone, dimethyl toluidine, and benzoyl peroxide that are typically used when cross-linking PPF.

PPST (% wgt)	PPF (% wgt)	E_c (MPa)
50	50	2.4 \pm .2
20	80	1.7 \pm .2

Table 2. Mechanical strength of cross-linked PPST-PPF.

Conclusions: PPF was functionalized with thiol groups resulting in a PPST. PPST shows an increase in molecular weight and small increase in PDI from the starting PPF. PPST can be cross-linked with PPF in the presence of < 1 wgt % BAPO photo-initiator. The two examples of cross-linked PPST-PPF materials reported here have a compressive modulus of 2.4 or 1.7 MPa. This approach to cross-linking polymeric materials avoids the major drawbacks associated with injectable materials that utilize free radical polymerization, mainly the use of substantial amounts of small molecules as comonomers, accelerators, and initiators.

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References:

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