Thermosensitive, Injectable, Biodegradable Polymers for Ocular Drug Delivery

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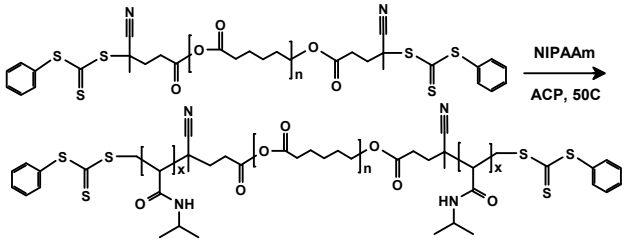
Introduction: Irreversible blinding conditions related to the posterior eye segment, such as age-related macular degeneration and diabetic retinopathy, afflict more than 13 million people in the United States today, and are expected to increase significantly in coming years as the population ages [1]. The treatment of these diseases includes drug administrated directly to the posterior of the eye, through repeated periocular or intravitreal injections [2,3].

Poly(N-isopropyl acrylamide) (pNIPAAm) is a well-known thermosensitive polymer displaying a phase transition from liquid solution to solid polymer above the lower critical solution temperature of 32°C [4].

The purpose of this study was to synthesize an innovative polymer composition using advanced techniques of controlled radical polymerization (CRP) integrating pNIPAAm with predefined molecular weight and a biodegradable polyester as a thermosensitive biodegradable polymeric platform for sustained drug release within an eye [5].

Methods: Polymer samples of molecular weight (Mw) ranging from 10 to 40 kDa were synthesized as block copolymers having a central degradable polyester block. Carboxy functional trithiocarbonates (CTC) was first synthesized and used then as a specific reversible addition-fragmentation chain transfer (RAFT) agent. It ultimately was conjugated to the polyester oligomers of polycaprolactone (PCL) with Mw 530 and 1250 Da, using carbodiimide to form a macroinitiator. The macroinitiator structure was confirmed with ^{1}H-NMR. Then, an adequate molar ratio of NIPAAm monomer was added, resulting in polymers with controlled Mw.



Scheme 1. The macroinitiator structure with PCL central block and trithiocarbonates at both ends, and RAFT polymerization of NIPAAm.

Various analytical tools were used to assure structure and Mw of polymers made, including ^{1}H-NMR, GPC and water solution rheometry. Norfloxacin antibiotic (1% wt/wt) was then incorporated into the pNIPAAm (20% wt/wt) solution at room temperature. Drug release was measured in a shaker-incubator at 37°C and release rate was measured spectrophotometrically using a UV/Vis microplate reader. Cytotoxicity assays of polymers were conducted *in vitro* using 3T3 NIH fibroblasts cells to confirm biocompatibility. For the *in vivo* pilot study, pNIPAAm-Norfloxacin solutions were injected into the anterior eye chamber of New Zealand white rabbit followed by monitoring of both drug release and eye inflammation.

Results: The ^{1}H-NMR measurement has showed 86-89% yield of the PCL-di-CTC macroinitiator. The controlled Mw of polymers with low polydispersity (PDI<1.4) synthesized by the RAFT polymerization was confirmed by GPC. Rheological experiment indicated the sharp phase change at 32.0±1.8°C for water solutions of all polymers, whereas elasticity modulus for the PCL_{530}-di-CTC macroinitiator was higher compared to PCL_{1250}-di-CTC.

Polymer samples were successfully loaded with drug and injected into the eye at room temperature followed by solidification at 39°C (rabbit body temperature). This transition from solution to the solid polymer matrix was fast, and reversible as temperature was lowered. The *in vitro* drug release studies demonstrated an initial burst release within the first 48 hours, followed by continued release of drug at levels above the MIC (1μg/ml) over the period of three weeks, with extended and more stable release profile for the polymers with Mw of 15 and 20 kDa. The *in vitro* cytotoxicity showed good tolerance of the cells (91-96% cell viability) growing on a preheated polymeric matrix.

In vivo, the polymer drug depots caused an initial moderate inflammation that afterwards was completely resolved. The drug release levels were above the MIC, with some burst release at the first four hours and tapering levels over the subsequent two weeks.

Conclusions: The delivery platform developed here holds promise for sustained drug release to the posterior segment of the eye. Biodegradable thermosensitive well-defined polymers were synthesized and shown to be capable of both entrapping and releasing a drug over an extended period. The optimal rheological behavior and drug release profile were noted for the polymer using a macroinitiator based on PCL_{530}-di-CTC with total pNIPAAm Mw of 15 and 20 kDa. Future directions include modification of the current composition to slow the phase transition time from 10 seconds to about one minute, offering better handling characteristics for the surgeon (e.g., improved injectability, and extended release time of medication *in vivo*.)

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