Controlled release of ophthalmic therapeutics from injectable, resorbable copolymer scaffolds

Graeme Prosperi-Porta, Ben Muirhead, and Heather Sheardown
McMaster University

Introduction: The delivery of ophthalmic therapeutics to the back of the eye is a significant challenge in the treatment of posterior segment ocular conditions. Back of the eye drug delivery is particularly difficult due to the segmented structure of the eye, separation from systemic circulation by blood-ocular barriers, and effective clearance mechanisms that eliminate pharmaceuticals before they reach the posterior segment (Del Amo EM. Drug Discov Today 2008;13:135-43).

We hypothesize that poly(N-isopropylacrylamide) (NIPAAm), a thermoresponsive polymer that undergoes a reversible phase transformation from liquid to gel when heated above the lower critical solution temperature (LCST) of ~32°C can serve as an injectable drug delivery scaffold. By synthesizing copolymers based on NIPAAm, dimethyl-γ-butyrolactone acrylate (DBA), N-acryloxy succinimide (NAS), and acrylamide (AAm) using reversible addition-fragmentation chain-transfer (RAFT) polymerization we are able to control the copolymer's physical properties, resorption, and drug release profile.

Methods: Copolymers were synthesized using varying amounts of 2-(dodecylthiocarbonothioylthio)-2-methylpropionic acid as the chain transfer agent, NIPAAm, NAS, DBA, and AAm, and AIBN in 1,4-dioxane. Copolymer compositions were assessed using ^{1}H nuclear magnetic resonance (NMR) and Fourier transform infrared spectroscopy (FTIR). Molecular weights were determined using ^{1}H NMR and gel permeation chromatography (GPC) in DMF. LCST was determined using differential scanning calorimetry (DSC). Equilibrium water content was determined at 37°C. Degradation was assessed by copolymer weight loss, and FTIR and NMR were used to elucidate the degradation mechanism in NaOH. Dexamethasone drug release was assessed by high performance liquid chromatography (HPLC). All applicable measurements were conducted using 20 wt.% copolymer solutions in PBS.

Results: Table 1 shows the copolymer scaffold compositions. The final compositions correspond closely to the initial feed compositions.

Table 1. Copolymer compositions determined by ^{1}H NMR (Naming: PNAND-AAm/DBA-target MW NAS = 5mol%)

Copolymer	Composition (^{1}H NMR) NIPAAm:NAS:DBA:AAm
PNAND-13/8-5kDa	76.6:4.1:8.5:12.0
PNAND-17/6-5kDa	75.3:4.1:6.6:16.4
PNAND-21/4-5kDa	73.0:4.0:4.4:22.8
PNAND-13/8-30kDa	76.4:2.8:8.5:14.2
PNAND-17/6-30kDa	75.0:3.3:6.1:18.4
PNAND-21/4-30kDa	75.1:3.0:4.9:20.5

Copolymer molecular weight and phase change characteristics are shown in Table 2. NMR and GPC results show good control over MW and polydispersity, which is characteristic of RAFT polymerization.

Table 2. Copolymer physical properties (TBD = to be determined).

Copolymer	LCST, DSC	Mn,NMR (g/mol)	Mw,GPC (g/mol)	PDI, GPC
PNAND-13/8-5kDa	20.5	5484	3964	1.1
PNAND-17/6-5kDa	26.0	5387	3869	1.1
PNAND-21/4-5kDa	32.1	5600	3861	1.1
PNAND-13/8-30kDa	27.2	28926	17624	1.4
PNAND-17/6-30kDa	32.5	27388	17685	1.5
PNAND-21/4-30kDa	38.4	28475	18962	1.5

Water contents, shown in Figure 2, illustrate that both increasing the AAm/DBA ratio and the molecular weight increases the equilibrium water content of the copolymer.

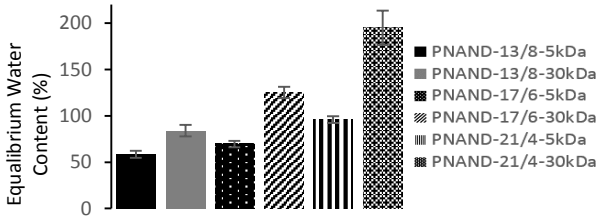

Figure 2.Copolymer equilibrium water content

Degradation results show approximate weight losses of 5-10% over 60 days in PBS for the 5kDa copolymers. The 30kDa copolymer degradation is in progress. Based on NMR and FTIR data (not shown), the degradation mechanism is suggested to be hydrolytic opening of the DBA ring, which raises the copolymer's LCST above body temperature allowing it to re-dissolve.

Drug release for the 5kDa copolymers is shown in Figure 3. Copolymers with lower AAm/DBA ratios have lower initial burst and slower drug release.

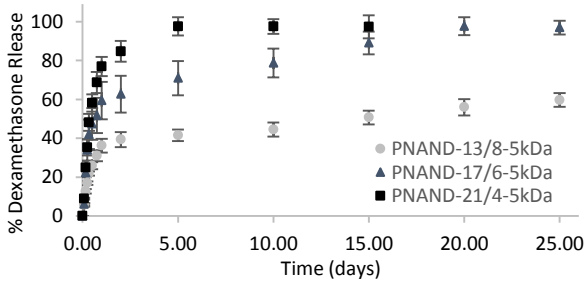

Figure 3. Dexamethasone release profile from copolymer scaffolds

Conclusions: This work has shown that the AAm/DBA ratio can affect the physical properties, drug release, and degradation of these NIPAAm based copolymers. Higher MW has also shown to cause changes in copolymer physical properties. Current work is aimed at studying the degradation and drug release of the higher MW copolymers. Future work is aimed at quantifying the injectability of these copolymers as well as testing in vitro and in vivo biocompatibility.