Controlled Delivery of Paclitaxel and Heat from Poly(ß-amino ester)-Based Magnetic Hydrogel Nanocomposites for the Treatment of Cancer

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Statement of Purpose: This research investigates using poly(ß-amino ester) (PBAE) and iron oxide-based hydrogel nanocomposites (NCs) for combined chemotherapy and heat delivery for the synergistic treatment of cancer. Hyperthermia, the heating of cancerous tissue from 42 to 45°C, has been shown to increase the efficacy of conventional cancer therapies such as irradiation and chemotherapy (Issels 2008). The NCs in this work provide a drug delivery vehicle (via the degradable PBAE polymer network) the ability to be heated remotely upon exposure to an alternating magnetic field (via iron oxide nanoparticles) to be used for this application. PBAE degradable polymers are finding a broad range of applications as drug delivery vehicles, tissue-engineering scaffolds, and in the fabrication of microdevices (Brey 2007). These polymers consist of acrylate-terminated poly(ß-amino ester)s that are synthesized via a condensation reaction that combines primary or secondary amines with diacrylates. The hydrogel networks degrade over time via hydrolysis of ester groups in the polymer backbone. One significant advantage of PBAE hydrogel NCs is that they can potentially be polymerized *in situ* without unnecessary harmful solvents which may allow them to be used as injectable materials in areas where surgical resection of tumors is not possible. Another advantage of these systems is the tailorability of the degradation and mechanical properties of the PBAE polymers through the chemistry and molecular weight of the macromer(s).

Methods: Diethylene glycol diacrylate and poly(ethylene glycol) (n=9) diacrylate were each heated at 85°C with isobutylamine to form the PBAE macromers (2EG-IBA and 9EG-IBA, respectively). The hydrogel NCs were fabricated by mixing various ratios of the macromers with 5 wt% iron oxide nanoparticles, 5 mg/g paclitaxel to macromer, and 1.5 wt% ammonium persulfate before placing them in 1.5mm thick templates. Degradation was characterized by placing gels in PBS at 37°C and 100rpm and measuring their mass over time. The compressive modulus of the gels was measured with a BOSE Electroforce 3300 in displacement mode at various times throughout the degradation of the gels. The gels were heated at various states of degradation in a Taylor Winfield alternating magnetic field at 294 kHz and 17.4 kA/m for 5 minutes and the surface temperature was recorded with an infrared camera. Paclitaxel release was done under sink conditions in a modified PBS release medium (2.4 wt% Tween and 4 wt% Cremophor EL) and the amount of drug in these solutions was analyzed via reversed-phase HPLC in a C_{18} column (5µm, 4.6 x 150mm) with a 50:50 (v/v) acetonitrile to water mobile phase at 1 ml/min, 20µL injection volume, and the paclitaxel was detected at 227nm with UV detector.

Results: The degradation profile of the hydrogels was found to be tailorable by the amount macromer in the gel which corresponded to the amount of ethylene glycol (EG) present. Pure 9EG-IBA gels completely degraded in 12 hours were as pure 2EG-IBA gels degraded in 70 days as seen in Figure 1 which shows that degradation increases with increasing EG content.

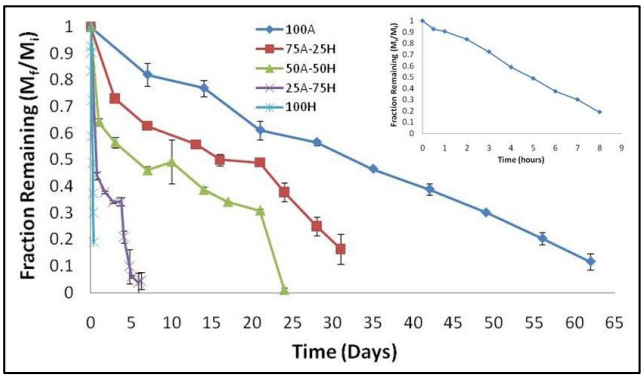

Figure 1. Degradation profile of PBAE hydrogel NCs. A=2EG-IBA, H=9EG-IBA and the preceding number refers to the wt% of macromer present in the gel.

The compressive modulus of the gels increased with increasing EG content (0.10 and 1.01 MPa for 100% 9EG-IBA and 25% 9EG-IBA, respectively), and it also decreased as degradation occurred due to higher water and less polymer content in the gel. Paclitaxel release from 9EG-IBA gels was shown to be controlled by degradation with a zero-order release profile for up to 10 hours as seen in Figure 2a.

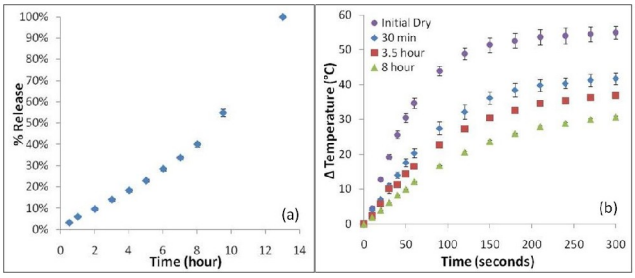

Figure 2. Paclitaxel release profile (a) and pure 9EG-IBA hydrogel NC heating profile over 5 minutes (b).

The hydrogel nanocomposites were shown to heat upon exposure to an alternating magnetic field (Figure 2b) and the change in temperature for pure 9EG-IBA decreased with degradation over time but heated well above the necessary hyperthermia temperature values.

Conclusions: PBAE hydrogels exhibit controlled release of paclitaxel and the ability to heat above hyperthermia temperatures showing the potential to be used in synergistic cancer therapy. The degradation, release, and mechanical profiles of the NCs can be tailored with the type and amount of macromer present in the gel.

References:

Issels RD. Euro J Canc. 2008;44:2546-2554
Brey DM. JBMRA. 2007;85A:731-741