Temperature Controlled Grafted Polymer Network Incorporated With Magnetic Nano Particles To Control Drug Release Induced By An External Magnetothermal Trigger

Induvadana Ankareddi, Mary L. Hampel, Mary Kathryn Sewell, Dong-Hyun Kim, Christopher S. Brazel[1]

Department of Chemical and Biological Engineering
The University of Alabama
Tuscaloosa, AL 35487-0203 USA

ABSTRACT

A thermosensitive grafted polymeric system which can be triggered to release the loaded drug with an increase in temperature, induced by a magnetic thermal heating event was developed. The desirable carrier will have minimal release at 37 °C so that the system can be localized (e.g., to cancer cells) prior to activation of the delivery of medication. The grafted hydrogel system is shown to exhibit a desirable positive thermal response with an increased drug diffusion coefficient for temperatures higher than physiological temperature.

Keywords: thermosensitive, grafted, hydrogel

1 INTRODUCTION

Research in the field of biopolymers and drug delivery has led to the development of intelligent therapeutic systems which have the advantage of maximizing drug effectiveness, avoiding side effects, decreasing the frequency of administration thus improving patient compliance [1-4]. Various controlled drug release strategies have been developed to maintain drug concentrations within a therapeutic range, localize the drug activity and make optimal usage of the drug. The purpose of this research is to design a thermosensitive polymeric system which can be triggered to release the loaded drug with an increase in temperature, and shut off release with a decrease in temperature. Drug diffusivities at these on/off temperatures have been experimentally calculated.

Cancer can be treated with surgery, radiation therapy, chemotherapy or other methods. The probability of cancers to invade adjacent tissue or to spread to distant sites by metastasis often limits the effectiveness of surgery. The effectiveness of chemotherapy and radiation therapy is limited by toxicity or damage to other tissues in the body. Hyperthermia is expected to be a promising treatment of cancer. Hyperthermia combined with magnetothermal heating to trigger a T-spike of 45-50 °C has the potential to address targeting, tissue heating and toxic limitations of other forms of therapy. By judicial selection of magnetic materials such as NiPd or FePt, magnetic nanoparticles with self limiting ability that can stop heating at their curie temperature of about 50-60 °C can be synthesized. The overall goal is to develop a system that combines radiation therapy and chemotherapy in a localized manner to reduce side effects while treating metastatic cancers.

It is well known that crosslinked poly(N-isopropylacrylamide), PNIPAAm, exhibits an abrupt volume change at its lower critical solution temperature (LCST) of 32 °C which can be tuned by the addition of hydrophilic or hydrophobic comonomers [5]. Based on PNIPAAm's sharp transition and negative thermo responsiveness, short polymeric chains or oligomers based on NIPAAm were synthesized, characterized and grafted to a poly(hydroxyethyl methacrylate) HEMA hydrogel [6-7]. This switches the thermosensitivity to a positive response, as the expanded grafts at low temperatures block diffusion, while the collapsed oligomers open mesh space for drug release as the grafted hydrogel is heated (Fig. 1).

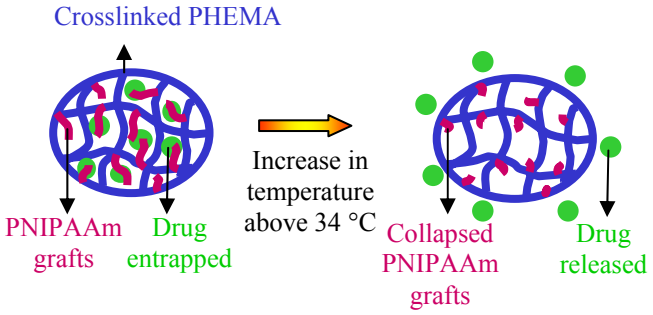

Figure 1: Schematic of the proposed grafted drug delivery system

[1] Corresponding Author; e-mail: CBrazel@eng.ua.edu

2 MATERIALS

The monomers used were N-isopropylacrylamide (NIPAAm), 2-hydroxyethyl methacrylate (HEMA) and Acrylamide (AAm) (Acros Organics, Fair Lawn, NJ). Redox initiators ammonium persulfate (AmPS) and sodium metabisulfite (NaMBS), thermal initiator azobisisobutyrolnitrile (AIBN), crosslinking agent methylenebisacrylamide (MBAAm) and chain transfer agent 2-aminoethanethiol hydrochloride (AESH) were obtained from Acros Organics, (Fair Lawn, NJ). Activating agent acryloyl chloride was obtained from Aldrich Chemical Company Inc., (Milwaukee, WI) and solvents tetrahydrofuran (THF), toluene and methanol were obtained from Fisher Scientific, (Fair Lawn, NJ). Inhibitors were removed from HEMA by passing the liquid through a De-hibit® column (Aldrich Chemical Company Inc., Milwaukee, WI), all other chemicals were used as received.

3 POLYMER SYNTHESIS

Crosslinked PNIPAAm copolymer samples were prepared by free radical polymerization of varying compositions of NIPAAm and a comonomer in 50% aqueous methanol using 1 mol% MBAAm as crosslinker and 1 wt% each of AmPS and NaMBS as initiators. The mixture was poured between two siliconized glass plates separated by 8 mm thick Teflon® spacers to obtain samples of uniform thickness. The reaction was carried out at room temperature (25 °C) for 24 hours. The gels were then cut into discs (25 mm in diameter and 8 mm in thickness). These discs were rinsed thoroughly in distilled water for a week to leach out excess solvent and unreacted monomers.

Oligomers of NIPAAm-co-AAm were synthesized by free radical polymerization of NIPAAm using toluene as the solvent. Monomer was dissolved at 5 wt% in this solvent, nitrogen gas was purged through the mixture, and AIBN and AESH were each added at 5 mol% of the monomer content. After 24 hours of polymerization at room temperature (25 °C), oligomer samples precipitated during the reaction were recovered by decanting the solvent and drying in a vacuum desiccator and then characterized for their average molecular weight by gel permeation chromatography (GPC). These oligomers were then functionalized or activated by adding 5 mol% acryloyl chloride. The reaction was carried out while purging nitrogen gas through the mixture in an ice bath at a temperature of 4°C for one hour. In a subsequent step, the oligomers containing a polymerizable double bond were incorporated into a hydrogel network by free radical copolymerization of the acrylated oligomers with HEMA monomer using 1 mol% of crosslinking agent MBAAm and 1 wt% each of redox initiators AmPS and NaMBS in pH 8 buffer.

4 CHARACTERIZATION

NIPAAm oligomers were characterized for their molecular weight distribution using gel permeation chromatography (Shimadzu, System controller SCL-10A VP and Liquid controller LC-10AT VP). Transition temperature measurements were confirmed using differential scanning calorimetry (TA Instruments, Model 2920MDSC). P(NIPAAm) copolymer hydrogel discs were equilibrated in deionized water at temperatures ranging between 5 °C and 40 °C and their respective weights (W_s) noted at each temperature. After immersion in water at a desired temperature, each polymer gel was removed from the water and blotted with Kimwipes® to remove excess water on the surface of the gel. Each gel was repeatedly weighed over a course of days and reimmersed in water at a fixed temperature until the hydrated weight reached a constant value. It was then reequilibrated at another temperature. The gels were then dried in a desiccator under vacuum until reading a constant dry weight (W_d). The equilibrium weight swelling ratios (q) were calculated as W_s/W_d and the equilibrium polymer weight fractions were found as 1/q.

In vitro drug release experiments were performed in a 6 chambered thermostatted USP type II dissolution cell system (Distek, Model 2100C) connected to a six-line cassette pump and a UV spectrophotometer (Model UV-2401 PC).

5 RESULTS AND DISCUSSION

Figure 2 shows the equilibrium polymer weight fraction as a function of temperature for PNIPAAm based gels and illustrates their LCST behavior. The polymer weight fractions of PNIPAAm based hydrogels which are less than 0.1 at low temperatures suddenly rise up to as much as 0.6 at higher temperatures. At a certain temperature which is the LCST of the particular PNIPAAm copolymer, the curve bends sharply depicting a sharp transition. Equilibrium swelling data can therefore be used to predict the approximate LCST of the polymer. It can be observed from the figure that with the increase in hydrophilic content, the LCST of the polymer increased. These results thus confirm the earlier observations of modifying the LCST of PNIPAAm by the addition of hydrophilic and hydrophobic comonomers [8].

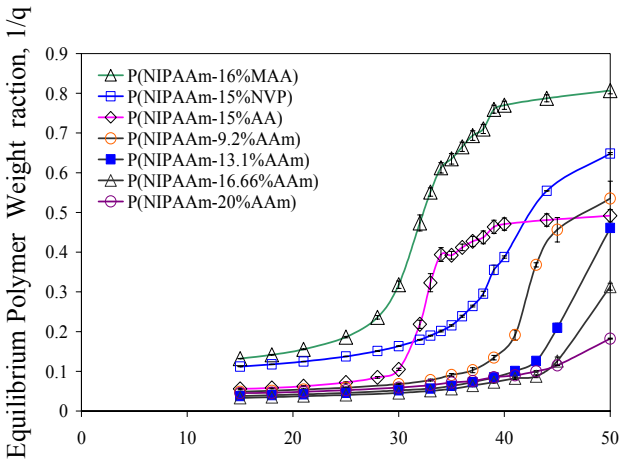

Figure 2: Equilibrium polymer weight fractions for PNIPAAm copolymer hydrogels in water measured at different temperatures. Error bars indicate standard deviation for three samples. Where not shown, error bars are smaller than the data symbols.

Hydrogels synthesized from 80 mol% NIPAAm and 20 mol% AAm, hereafter referred to as P(NIPAAm-co-20%AAm) gels were found to have an LCST of about 45 °C, so oligomers of this composition were synthesized and characterized by GPC to obtain an average molecular weight of 2166. These oligomers were then grafted onto a PHEMA network with varying graft densities and the grafted matrix was characterized for drug diffusivity as a function of temperature. The effect of polymer structure and composition on the release behavior of model drugs was observed at temperatures above and below the LCST of P(NIPAAm-co-20%AAm). Drug release profiles for P(HEMA-g-NIPAAm), with varying graft densities, loaded with theophylline provide proof of the designed grafted system's positive thermosensitivity (Figure 3).

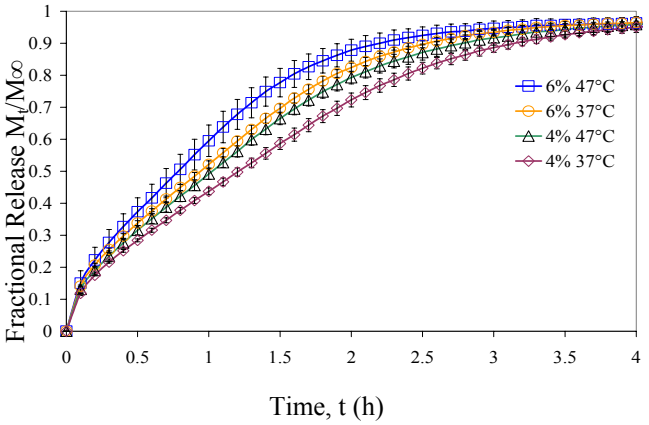

Figure 3: Theophylline Release Profiles from P(HEMA-g-NIPAAm-co-20%AAm) hydrogels with varying graft densities at two temperatures . DI water was used as the release medium. Error bars indicate the standard deviation for three samples.

The cumulative release data were analyzed according to the the early time approximation of the Fickian equation [9]:

$$\left(\frac{M_t}{M_\infty}\right) = 4\left(\frac{Dt}{\pi\delta^2}\right)^{1/2} \qquad 0 \le \left(\frac{M_t}{M_\infty}\right) \le 0.6 \tag{1}$$

Using the above equation, diffusion coefficients for theophylline release from P(HEMA-g-NIPAAm-co-20%AAm) gels were calculated to show the difference in diffusivity of the grafted system at temperatures below and above the LCST of the graft copolymers (Figure 4).

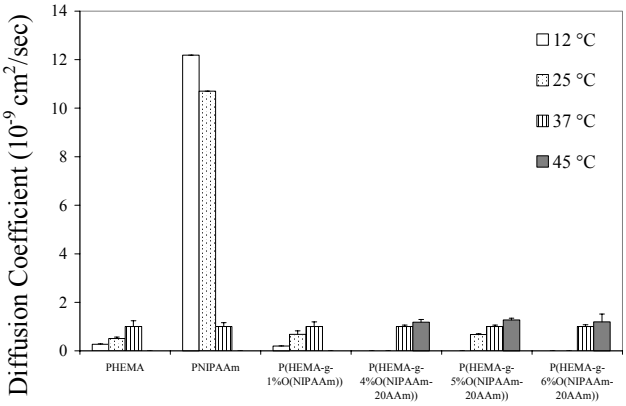

Figure 4: Diffusion Coefficients for Drug Release from Hydrogels with varying graft densities and at temperatures 12, 25, 37 and 45°C. Error bars indicate standard deviation for three samples. Where not shown, error bars are smaller than the data symbols.

6 CONCLUSIONS

This report illustrates the successful synthesis of a grafted polymeric drug delivery system exhibiting a positive thermal responsiveness to temperature. The release profile for the release of model drugs from the newly grafted hydrogel system, P(HEMA-g-NIPAAm-co-AAm), showed the expected positive thermoresponsive release trend of a higher release rate at 47 °C. Although, the oligomer synthesis and grafting techniques are still being optimized, initial success has been found in obtaining desired high release rates at temperatures higher than the human body temperature. Current work in our lab has shown that FePt and magnetite nanoparticles can be incorporated into hydrogels and forthcoming experiments will identify parameters important for AC-magnetic field induced heating. This, in combination with the thermosensitive polymers that can be triggered to release the loaded drug by a heating event will yield an important novel tool for localized treatment of cancer.

REFERENCES

[1] Kost, J., and Langer, R., 2001. Responsive polymeric delivery systems. Adv.Drug Delivery Rev. 46, 125-148.

[2] Kikuchi, A., and Okano, T., 2002. Pulsatile drug release control using hydrogels. Adv Drug Delivery Rev. 54, 53–77.

[3] Brazel, C.S. and Peppas, N.A., 1999. Mechanisms of solute and drug transport in relaxing swellable hydrophilic glassy polymers. Polymer. 40, 3383-3398.

[4] Brannon-Peppas L., 1997. Polymers in controlled drug delivery, Medical Plastic and Biomaterials Magazine. November, 34.

[5] Feil, H., Bae, Y.H., Feijen, J., Kim, S.W., 1993. Effect of comonomer hydrophilicity and ionization on the lower critical solution temperature of N-isopropylacrylamide copolymers. Macromolecules. 26, 2496-2500.

[6] Ankareddi, I. and C.S. Brazel, *Int. J. Pharm*., accepted in press.

[7] Brazel, C.S., I. Ankareddi, M.L. Hampel, H. Bagaria, D.T. Johnson, and D.E. Nikles, *Control. Rel. Soc. Trans.*, **33** (2006), #762.

[8] Bae, Y.A., Okano, T., Kim, S.W., 1989. Insulin permeation through thermo-sensitive hydrogels. J. Controlled Release. 9, 271-279.

[9] Brazel, C.S. and Peppas, N.A., 2000. Modelling of drug release from swellable polymers. Eur. J. Pharm. and Biopharm. 49, 47-58.