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Controlled Release of Methyl Salicylate in Chitosan-Poly(N-Isopropylacrylamide) Semi-Interpenetrating Networks

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A semi-interpenetrating network (semi-IPN) was produced by polymerizing N-isopropylacrylamide (NIPAAm) in the presence of chitosan and cross-linking agent, ethylene glycol dimethacrylate (EGDMA). The resulting material did not swell as much as poly(N-isopropylacrylamide) (pIPAAm), but still showed temperature- and pH-responsiveness. Swelling and differential scanning calorimetry (DSC) experiments showed that the lower critical solution temperature (LCST) of the material was at 31 °C. The semi-IPN was swollen below 30 °C but started to collapse at this temperature. This is in the same range as the LCST of carrageenan-pIPAAm semi-IPN. The chitosan-pIPAAm semi-IPN was in a collapsed state and reached maximum swelling at pH 9 whereas pure pIPAAm and pure chitosan both became swollen at a lower pH.

Methyl salicylate was absorbed by the semi-IPN. Its release was monitored with respect to temperature. The temperature-responsive release of methyl salicylate was more pronounced at the LCST of 31°C.

Keywords: chitosan, methyl salicylate,

INTRODUCTION

The chitosan- pIPAAm semi-interpenetrating network (semi-IPN) is a system that exhibits temperature-responsiveness, similar to κ-carrageenan-poly(N-isopropylacrylamide) semi-IPN. It also shows more pH sensitivity because of the presence of the amino group in chitosan.

Chitosan, a (partially) deacetylated derivative of chitin, is a biodegradable polymer present in the shell of oysters, shrimps and crabs. It consists of randomly repeating units of β-(1-4)-linked 2-amino-2-deoxy-D-glucopyranose (and 2-acetamido-2deoxy-D-glucopyranose, if only partially deacetylated [1], and acts as a polycation in 1% acetic acid (pH=2.8) [2].

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PIPAAm, on the other hand, is temperature-sensitive polymer that undergoes volume phase transition in water at lower critical solution temperature (LCST), which is about 32 °C. Below LCST, the polymer swells due to hydration, while above LCST the gel collapses because of greater hydrophobic interaction [3].

The chitosan- pIPAAm semi-IPN forms a hydrogel, a three dimensional polymeric network that retains a large quantity of water within its structure without dissolving in it. The objective of the study is to evaluate its use for potential drug delivery; in particular, the substrate will be methyl salicylate. The drugs loaded in the swollen hydrogel network through the crosslinked structure diffuse off during the dynamic collapse of the polymer [4].

METHODOLOGY

Synthesis of Semi-Interpenetrating Chitosan-(x)pIPAAm Network with Varying Amounts of Ethylene Glycol Dimethacrylate (EGDMA)

Free-radical solution polymerization was adapted from Brazel *et al.* [5] and Huang *et al.* [6] with few modifications. 10.27 g of NIPAAm (Aldrich) and 1.05 g of chitosan (Fluka) were dissolved in 100 mL of methanol:deionized water (50:50). The chitosan was completely dissolved in the monomer solution by adding 5 % HCl dropwise. The mixture was stirred at 60 °C for about 30 minutes while adding the crosslinker ethyleneglycol dimethacrylate (EGDMA) at different concentrations: 0, 1, 3, 5 and 10 mol%. The reaction mixture was sonicated for 10 minutes to remove the oxygen. About 0.10 g of 2,2'-azobis-isobutyronitrile (AIBN) (Chem Service) was added as initiator and was mixed by stirring for 2 minutes. The resulting solution was poured in a petri dish for polymerization in a preheated vacuum oven at 60 °C for 24 hrs to produce the crosslinked pIPAAm (x-pIPAAm) into the chitosan polymer. The resulting white gel was washed several times with 1% NaOH, then with water, until the pH of the supernatant liquid became neutral. The samples were air-dried on a Teflon sheet. Products were analyzed using Fourier transform infrared (FTIR) microscopy (Shimadzu AIM-8000R) using reflectance technique, thermogravimetric analysis (Shimadzu TGA-50) and differential scanning calorimetry (Shimadzu DSC-50).

Swelling Properties

The chitosan-PIPAAm semi-IPN hydrogel was allowed to swell in 10 mL deionized water at different temperatures (5, 10, 20, 25, 30, 40, 50 and 53°C) for 3 hours. At each temperature, the gels were removed from the swelling medium and were blotted to remove excess water, then weighed. The swelling ratio (Q) was calculated according to the following expression [6]:

$$Q = Ws / Wd \qquad (1)$$

where Ws was the weight of the swollen hydrogel and Wd was the weight of the dry hydrogel.

Chitosan-pIPAAm semi-IPN hydrogels were also allowed to swell in 10 mL buffered solutions with pH of 1.45, 3.88, 7.03, 9.00 and 12.5 for 3 hours at 10 °C. Calculation of the swelling ratio followed the same procedure as mentioned above.

Controlled Release Studies

The model drug used was methyl salicylate (UNILAB) in 70 % isopropyl alcohol (IsOH, JT Baker). The samples were equilibrated in 10 % methyl salicylate at 10 °C for 12 hours. After equilibration, the supernatant was separated from the gel sample through decantation. The gel sample was used further for controlled release studies. The supernatant was analyzed to determine the amount of methyl salicylate absorbed by the hydrogel.

Drug-containing chitosan-pIPAAm semi-IPN hydrogel was placed in 5 mL of 70 % 2-propanol and was observed for 24 hours at certain time intervals. At each sampling, a 20 μL-portion of liquid was taken from the mixture, diluted to 1 mL, and then injected into the HPLC (Perkin Elmer series 200 lc) using reverse-phase column (SUPELCO LC-18) and UV detection at 305 nm. This procedure was repeated for drug

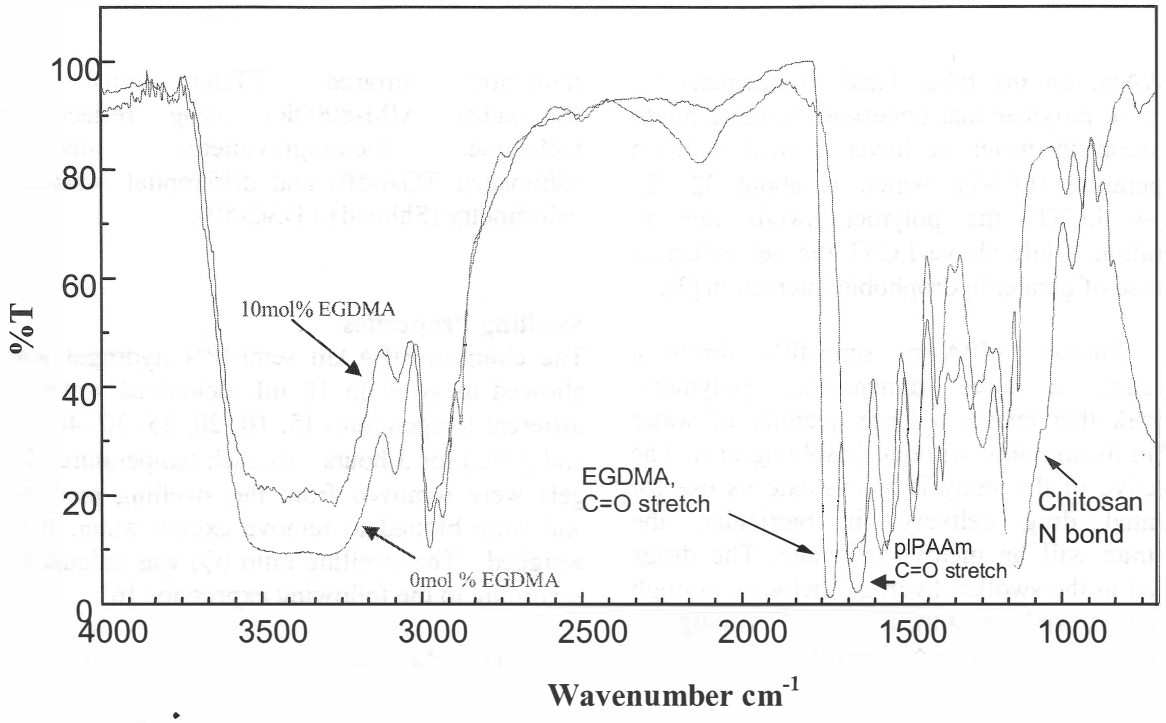

Fig 1. *Fourier transform infrared (FTIR) microscopy of Chitosan-pIPAAm Semi-IPN with Varying Amount of EGDMA*

release at different temperatures (10, 20, 25, 31, and 41°C).

RESULTS AND DISCUSSION

Chitosan-pIPAAm Semi-IPN with Varying Amount of EGDMA

The resulting polymer blends as well as the standard samples were analyzed using FT-IR microscope in reflectance mode (Fig. 1). The characteristic absorption band (C-N) at 1230-1030 cm^{-1} is present due to chitosan in the semi-IPN. The characteristic C=O band at 1650 cm^{-1} due to pIPAAm is masked by other bands in the region; however, cross-linking with EGDMA resulted in a strong stretching carbonyl band at 1725 cm^{-1} which is due to the ester carbonyl present in the cross-linker EDGMA. This result implies cross-linking reaction has occurred.

Thermal Analysis

Thermogravimetric results showed slight increase in thermal resistance of the pIPAAm-chitosan blends at 0 to 10 mol% EGDMA, compared to plain chitosan, with degradation temperatures ranging from 290 °C to an average of 340 °C. The material with 3 mol % EGDMA displayed slightly higher thermal tolerance at 363 °C relative to the other hydrogels, though this may not be significant considering lack of homogeneity of the sample.

The DSC transition can be linked to the lower critical solution temperature (LCST) of a hydrogel. In the case of pIPAAm, it collapses at temperatures higher than the LCST of 32°C and swells at temperatures below it. This phenomenon is the direct consequence of the hydrogen bonding between solvent and polymer.

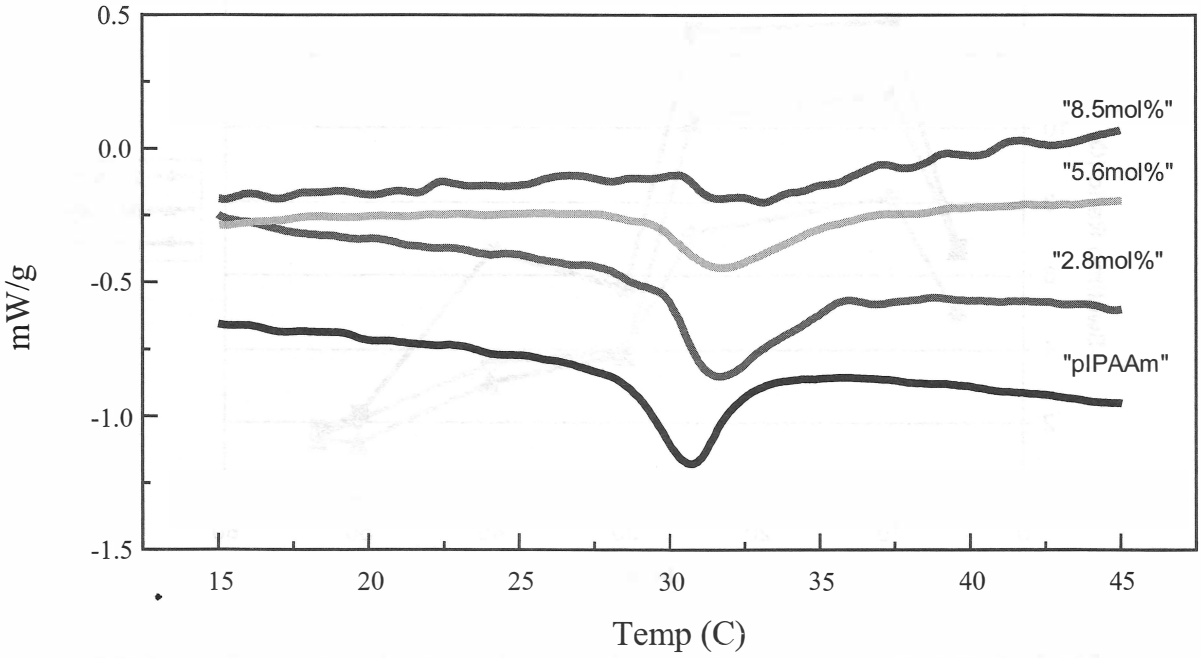

Fig 2. *Differential Scanning Calorimetry (DSC) of Chitosan-pIPAAm Semi-IPN; the mol% refers to the amount of chitosan*

Temperature- and pH-Sensitive Swelling of Chitosan-(x)pIPAAm semi-IPN

The trend in LCST obtained from DSC agrees with the observations from swelling studies at different temperatures, although the latter is not as precise. All the samples started to collapse at about 30 °C.

Compared to pure pIPAAm the addition of chitosan decreased the swelling ratio of the material. This indicates that chitosan formed an interpenetrating network with pIPAAm. However, if we look at the trend with respect to amount of chitosan, it shows that swelling ratio increases as the amount of chitosan increases (Figure 3). This corroborates the DSC results.

To obtain maximum swelling for pH-sensitivity all experiments were performed at 10 °C, since the polymer system has the highest swelling ratio between 10 and 20 °C. The materials also showed stability at pH ranging from 4 – 7, in comparison with the pure chitosan or pIPAAm, which began to swell above pH 4 to about four times. The semi-IPN started to swell above pH 7, with the swelling ratio of about double.

Controlled Release Behavior

All the release experiments were done using 70% isopropyl alcohol. The temperature response of the material loaded with the model drug was tested. Methyl salicylate began to be released steadily as temperature increased. For 8.5 mol % of chitosan in the semi-IPN, there was a significant release at 20 °C and in the region of LCST, i.e. 31°C (Figure 3). However, for lower amounts of chitosan in the semi-IPN the pattern of release is not too dependent on the LCST, indicating that other physical processes such as dissolution and diffusion are probably more significant in the presence of solvent.

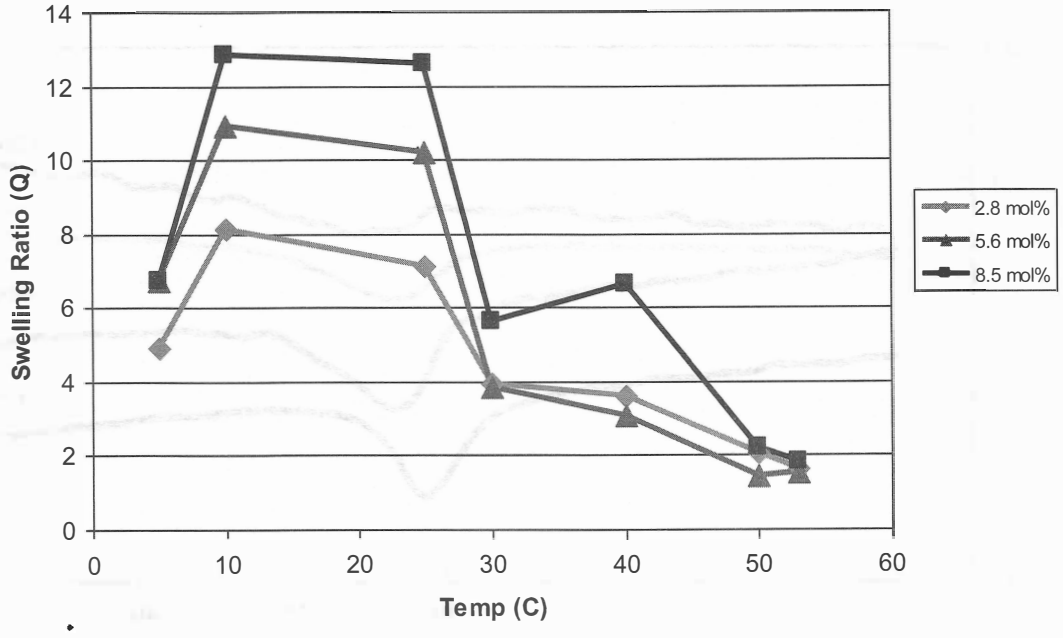

Fig 3. *Swelling of Chitosan-(x)pIPAAm semi-IPN as a function of Temperature*

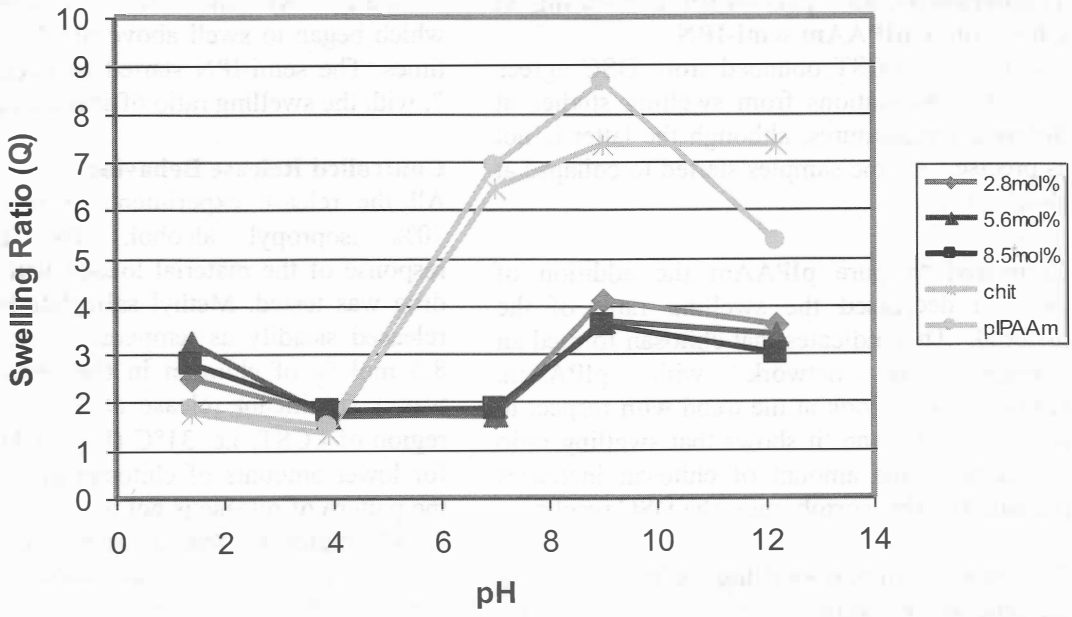

Fig 4. *Swelling of Chitosan-(x)pIPAAm semi-IPN as a function of pH*

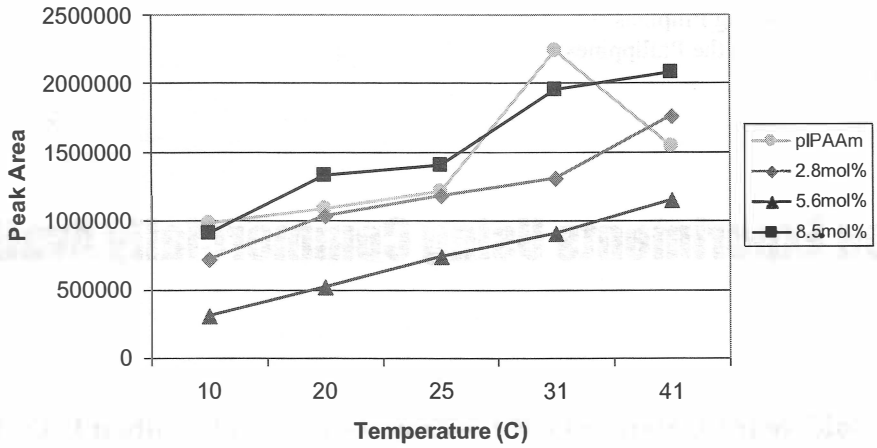

Fig 5. *Release of Methyl Salicylate from Chitosan-(x)pIPAAm semi-IPN as a function of Temperature*

CONCLUSION

Free radical solution polymerization was used to prepare modified hydrogel from cross-linked pIPAAm-chitosan. Results of FTIR, thermal analysis and swelling experiments, support the semi-IPN of the material. DSC and TGA showed increase in thermal stability of material due to presence of chitosan.

Addition of chitosan to pIPAAm decreased the swelling ratio of the material, and the collapse of the hydrogel was more pronounced in the 30 °C-region.

Swelling and DSC results gave similar value of LCST at 30-31°C. Both experiments showed that as the amount of chitosan increased the amount of water liberated by the hydrogel decreased.

The material also exhibited pH-sensitivity. The modified hydrogel had lower swelling ratio compared with pure pIPAAm. At pH 7, the pure samples were swollen while the modified hydrogels were still in the collapsed state. Only when the solution turned basic would the modified material swell.

Chitosan-(x)pIPAAm exhibited controlled release but the trend with respect to composition appeared to prefer an optimum % chitosan. The material exhibited minimal temperature sensitivity in a different environment, *i.e.* 70% isopropyl alcohol. Methyl salicylate was slowly released with increasing temperature at LCST (~ 31°C) of the gel.

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