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Design a Biodegradable Hydrogel for Drug Delivery System

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***Abstract*—**In this article, we synthesize a novel chitosan -based superabsorbent hydrogel via graft copolymerization of mixtures acrylic acid (AA) and N-vinyl pyrollidon onto chitosan backbones. The polymerization reaction was carried out in an aqueous medium and in the presence of ammonium persulfate (APS) as an initiator and *N*,*N*′-methylene bisacrylamide (MBA) as a crosslinker.The hydrogel structures were confirmed by FTIR spectroscopy. The swelling behavior of these absorbent polymers was also investigated in various salt solutions. Results indicated that the swelling capacity decreased with an increase in the ionic strength of the swelling medium. Furthermore, the swelling of superabsorbing hydrogels was examined in solutions with pH values ranging between 1.0 and 13.0. It showed a reversible pH-responsive behavior at pHs 2.0 and 8.0. This on-off switching behavior makes the synthesized hydrogels as an excellent candidate for controlled delivery of bioactive agents.

***Keywords*—**chitosan; acrylic acid , N-vinyl pyrollidon; hydrogel; Ibuprofen´s drug delivery.

I. Introduction

CROSSLINKED hydrophilic polymers can form hydrogels that are able to absorb and retain hundreds of times their weight of water and are known as superabsorbents [1]. The properties of these hydrogels have attracted the attention of many researchers and technologists and have found wide-spread applications in many fields, such as drug delivery systems, agriculture, separation processes [1-2].

II. Experimental

A. Hydrogel Preparation

Chitosan solution was prepared in a one-liter reactor equipped with mechanical stirrer and gas inlet. chitosan was dissolved in degassed distillated water. In general, 0.50 g of chitosan was dissolved in 30.0 mL of distillated degassed water. The reactor was placed in a water bath preset at 60 ^{o}C. Then 0.10 g of KPS (dissolved in 5 mL water) as an initiator was added to chitosan solution and was allowed to stir for 10 min at 60 ^{o}C. After adding KPS, variable amounts of AA and NVP were added to the chitosan solution.

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MBA as a crosslinker (0.050 g in 2 mL water) was added to the reaction mixture after the addition of monomer and the mixture was continuously stirred for one hour under argon. The total volume of reaction was 40 mL. After 60 min., the reaction product was allowed to cool to ambient temperature and methanol (500 mL) was added to the gelled product. After complete dewatering for 24 h, the product was filtered, washed with fresh methanol (2×50 mL) and dried at 50 ^{o}C.

III. Results and Discussion

A. Synthesis and Characterization

PAA and PNVP was simultaneously grafted onto chitosan in a homogenous medium using KPS as a radical initiator and MBA as a crosslinking agent under an inert atmosphere[4].

The crosslinker, initiator and the monomer concentration, as well as the reaction temperature four important variables affected on swelling capacity of hydrogel, were investigated. The mechanism of co polymerization of AA and NVP onto chitosan in the presence of MBA is shown in Scheme 1. The persulfate initiator is decomposed under heating to generate sulfate anion-radical. The radical abstracts hydrogen from the hydroxyl group of the polysaccharide substrate to form alkoxy radicals on the substrate. So, this persulfate-saccharide redox system is resulted in active centers on the substrate to radically initiate polymerization of AA and NVP led to a graft copolymer. Since a crosslinking agent, e.g. MBA, is presented in the system, the copolymer comprises a crosslinked structure. The superabsorbency of this hydrogel in distilled water and various saline solutions were investigated[3]. For identification of the hydrogel, infrared spectroscopy was used. Figure 1 shows the IR spectroscopy of chitosan -g-PAA-PVNP hydrogel. The superabsorbent hydrogel product comprises a chitosan backbone with side chains that carry carboxamide functional groups that are evidenced by peaks at 1660 cm^{-1}. In fact, In the spectrum of the hydrogel (Fig. 1-b), new peaks are appeared at 3206 and 1660 cm^{-1} that may be attributed to amide NH stretching, asymmetric and symmetric amide NH bending, respectively.

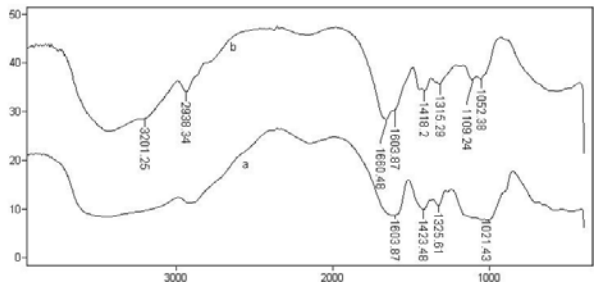
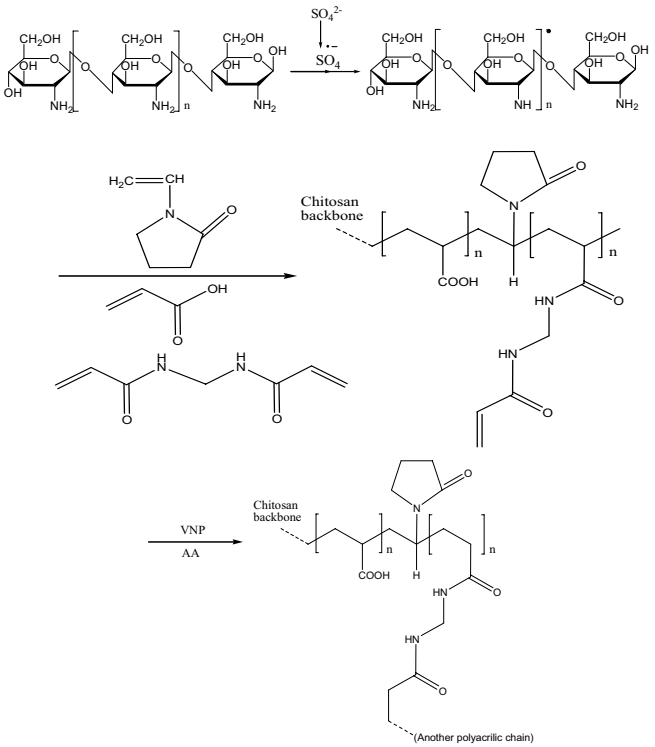


Fig. 1 FTIR spectra of CMC (a) and chitosan -*g*-poly(AA-*co*-NVP) hydrogel (b)

B. Mechanism of Hydrogel Formation

The mixture of monomers, NVP and acrylic acid, was simultaneously grafted onto chitosan backbones in a homogeneous medium using APS as a radical initiator and MBA as a crosslinking agent. A general reaction mechanism for chitosan -*g*-poly(NaAA-co-NVP) hydrogel formation is shown in Scheme 1.At the first step, the thermally dissociating initiator, i.e. APS, is decomposed under heating to produce sulfate anion-radical. Then, the anion-radical abstracts hydrogen from one of the functional groups in side chains (i.e. COOH, SH, OH, and NH_2) of the substrate to form corresponding radical. So, these macroradicals initiate monomers grafting onto chitosan backbones led to a graft copolymer.



Scheme 1**.** Proposed mechanistic pathway for synthesis of the partially chitosan -*g*- poly(NaAA-co-NVP)

C. Drug Loading Efficiency and In vitro Drug Release

Powdered samples (1 g ± 0.0001), with average particle sizes between 40-60 mesh (250-420 μm), were accurately weighted and immersed in an alkaline solution of ibuprofen (IBU, 0.54 g dissolved in 50 mL distilled water) at 0°C for 25 h. The swollen hydrogels loaded with drug were placed in a vacuum oven and dried under vacuum at 37°C. The loading amount of drug in the hydrogels was calculated from the decrease in the concentration of the IBU solution which was determined using a UV spectrophotometer (UV-1201, Shimadzu, Kyoto, Japan). The loading efficiency of the chitosan -based hydrogels was calculated as the ratio of the final to the initial IBU concentration.

In vitro release was carried out in duplicate by incubating 0.01±0.0001 g of the IBU-loaded hydrogels into a cellophane membrane dialysis bag ($D_{9402,}$ Sigma-Aldrich) in 50 mL of buffer solution (either pH 1.2 or 7.4) at 37°C. At specific time intervals, 1 mL aliquots of sample was withdrawn and after suitable dilution the concentration of drug released was measured by UV spectrophotometer. The drug release percent was calculated twice using the following equation[14]:

$$\text{Released drug (\%)} = R_t/L \times 100 \quad (2)$$

where L and R_t represent the initial amount of drug loaded and the final amount of drug released at time t.

In addition, crosslinking reaction was occurred in the presence of a crosslinker, i.e., MBA, so that a three dimensional network was obtained.

D. In vitro Ibuprofen Release in the Simulated Human Gastrointestinal System

To determine the potential application of chitosan-based superabsorbent containing a pharmaceutically active compound, we have investigated the drug release behavior Ibuprofen form this system under physiological conditions. The percent of released drug from the polymeric carriers as a function of time is shown in Figure2**.**

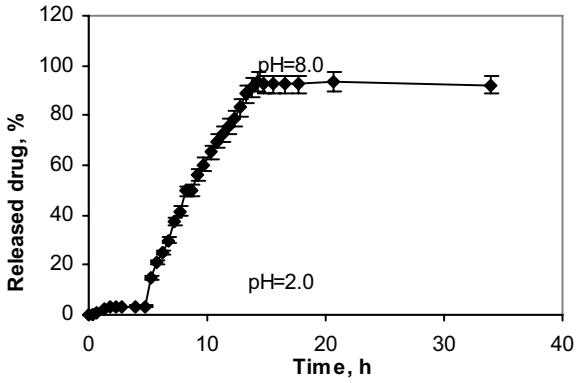


Fig. 2 Release of Ibuprofen from hydrogel carrier as a function of time and pH at 37ºC

The concentration of Ibuprofen released at selected time intervals was determined by UV spectrophotometer. The Ibuprofen -loaded hydrogels with high degrees of drug loading (>83%) were prepared by the swelling-diffusion method. The amount of Ibuprofen released in a specified time from the Pectin-based hydrogel decreased as the pH of the dissolution medium was lowered, indicating better release in a medium with a pH much higher than that of the stomach.

At low pH values, electrostatic repulsion between the carboxylic acid groups of backbone is low, thus decreases gel swelling and minimizes release of Ibuprofen via diffusion. However, in alkaline media the presence of OH^- increases the electrostatic repulsion between carboxylate groups, thus increases the gels swelling degree and so the release of metronidozule was increased [3]. The amounts of the loaded drug in superabsorbent hydrogels was significantly affected by the loading time (Figure3). With increasing loading time, the amount of drug loaded is initially increased and then begins to level off.

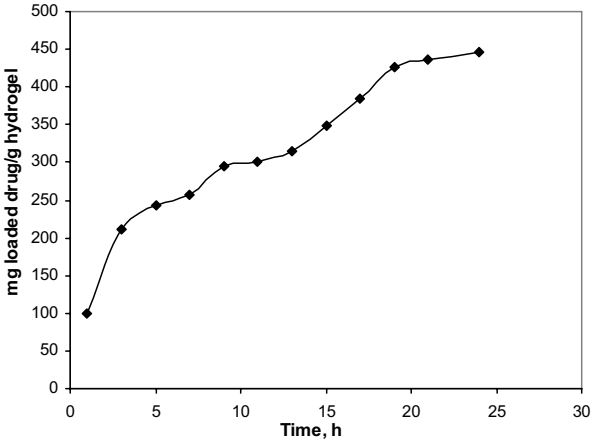


Fig. 3 The dependency of the drug loading amount to the loading time

IV. Conclusion

The grafting of acrylic acid and N-vinyl pyrollidon onto chitosan was carried out using APS as an efficient initiator in the presence of methylenebisacrylamide (MBA) as a crosslinking agent. The characteristic absorbing peaks in the FTIR spectra have proven That chitosan participates in graft copolymerization with AA and NVP. The superabsorbent hydrogels exhibited high sensitivity to pH, so that, the reversible swelling-deswelling behavior in solutions with acidic and basic pH, contributes to the suitability of these hydrogels as candidates for controlled drug delivery systems.

References

[1] L. P. Krul, E. I. Narciko, Y. I. Matusevich, L. B. Yakimtsova, V. Matusevich, and W. Seeber, Polym. Bull., 45, 159(2000)
[2] F. A. Dorkoosh, J. Brussee, J. C. Verhoef, G. Borchard, M. Rafeiee-Tehrani, and. Rahman, J. Appl. Polym. Sci. 76, 516(2000)
[3] Pourjavadi, A., Sadeghi, M. and Hosseinzadeh, H. (2004). Polym. Adv. Technol., 15: 645–653.
[4] Lowman, A. M. and Peppas, N. A. (1999). Hydrogels, In: Mathiowitz, E. Encyclopedia of Controlled Drug Delivery, p. 139, Wiley, New York.

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