Synthesis and Characterization Superabsorbent Hydrogels for Oral Drug Delivery Systems

Mohammad Sadeghi and Fatemeh Soleimani

***Abstract*—In this work, our purpose was to produce intelligent Starch-based superabsorbent polymers (SAP) to be used as pH carriers for the controlled delivery of metronidazoleloaded drug. A mechanism for hydrogel formation was proposed and the structure of the product was established using Fourier transform infrared spectroscopic (FT-IR) and scanning electron microscopy (SEM).the swelling behaviour of these polymers was investigated in various salt solutions. Finally, the effects of pH, and levels of loaded drug on drug release profile in various surrounding media were investigated. Release profiles of metronidazole, a water-soluble drug, from the hydrogels were studied under both simulated gastric and intestinal pH conditions.**

***Index Terms*—Starch; hydrogel; metronidazole; drug delivery; vinylic monomers.**

I. Introduction

Loosely cross linked hydrophilic polymers (hydrogels) being able to absorb and retain hundreds of their own weight of water are known as superabsorbents [1]. The swelling properties of these hydrogels have attracted the attention of researchers and technologists, and have found wide-spread applications in drug delivery systems, agriculture, separation processes and many other fields [2].

The modification of natural polymers is a promising method for the preparation of new materials. Graft copolymerization of vinyl monomers onto natural polymers is an efficient approach to achieve these materials. Superabsorbing resins were first developed with a view to utilizing agricultural materials, and are typed by the hydrolyzed corn starch-*g*-poly (acrylonitrile), H-SPAN [1]. Since then, starches from different resources as well as other polysaccharides, for example, cellulose, hydroxyethyl cellulose [2], agar [, sodium alginate [3] and guar gum were graft copolymerized to achieve water absorbing polymers. Polyacrylonitrile (PAN), polyacryamide, and poly (acrylic acid) have been frequently grafted, mostly onto starch, using different. initiators especially the ceric-saccharide redox system Radical polymerization, however, has several disadvantages. The reproducibility of this method is poor, and there is little control over the grafting process, so the molecular weight distribution is polydisperse. In addition, the necessity for inert gases (e.g., argon) to prepare an oxygen-free atmosphere and the need for initiators, toxic and/or expensive monomers, and crosslinkers are other disadvantages of free-radical polymerization reactions. These problems have been reviewed in detail. For the first time, Fanta et al., with a new method, tried to synthesize of HSPAN superabsorbent hydrogel. They indicated by a solubility test that crosslinks were formed during graft copolymerization, by coupling of the two growing PAN radicals, and during saponification, by the attack of starch alkoxide ions on the nitrile groups as the initioation reaction of nitrile polymerization in the early stages of saponification. The nitrile groups of PAN were converted to a mixture of hydrophilic carboxamide and carboxylate groups during alkaline hydrolysis followed by *in situ* crosslinking of the grafted PAN chains. The initially formed oxygen–carbon bonds between the starch hydroxyls and nitrile groups of the PAN chains remained crosslinking sites. Then, Fanta and Doane [19] attempted to extend this idea to the preparation of superabsorbent hydrogels by the saponification of PAN in the presence of polyhydroxy polymers. Finally, Yamaguchi et al.1 [20] reported the preparation of superabsorbing polymers from mixtures of PAN and various saccharides or alcohols.

In this investigation, we paid attention to the synthesis and investigation of a superabsorbent based on starch and PAA, PHEMA. The effect of pH,s reaction on the releasing drug was investigated in detail

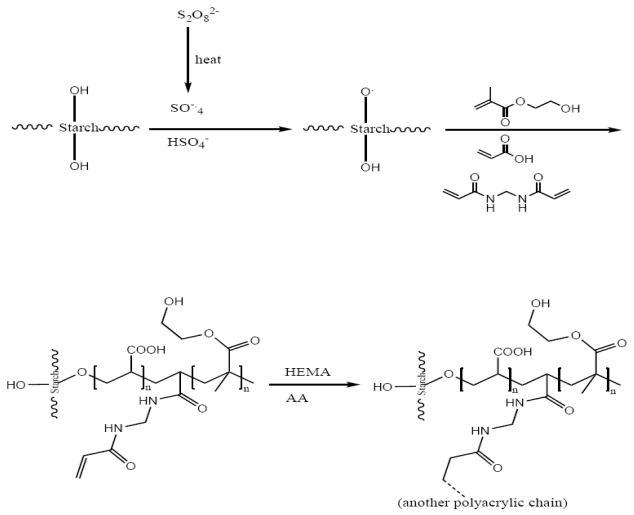
II. Experimental

A. Procedure to Graft Copolymerization

A one step preparative method was used for synthesis of Starch-g-poly (sodiumacrylate-co-HEMA) hydrogel.Starch (1.33 g) was added to 35 mL of doubly distilled water in a three-neck reactor equipped with a mechanical stirrer (Heidolph RZR 2021, three blade propeller type). The reactor was immersed in a thermostated water bath. After complete dissolution of the Starch, sodium hydroxide (10.0 wt%) was added to the Starch solution at desired temperature (alkalization temperature, 80^{o}C). The mixture was allowed to stir for certain times (alkalization times, 120 min). The various amount of polyacrylic acid (1.0 g) and HEMA (1.0 g) were dispersed in the reaction mixture. The pasty mixture was allowed to cool to room temperature and neutralized to pH 8.0 by addition of 10 wt % aqueous acetic acid solution. Then the gelled product was scissored to small pieces and poured in ethanol (200 mL) to dewater for 5 h. The hardened particles were filtered and dried in oven (50^{o}C, 10 h). After grinding, the powdered superabsorbent hydrogel was stored away from moisture, heat and light. Infrared spectroscopy(fig1) and SEM (fig2) were carried out to confirm the chemical structure of the materials obtained. Crosslinking graft copolymerization of vinyl monomers (AA and HEMA) onto starch was shown in Scheme 1.

Manuscript received June 13, 2011; revised September 22, 2011.

The authors are with the Department of Chemistry, Science Faculty, Islamic Azad University, Arak Branch Arak,,Iran (Email; m-sadeghi@iau-arak.ac.ir)



Scheme 1 A proposed mechanism for synthesis of Starch -poly (NaAA-co-HEMA) hydrogel

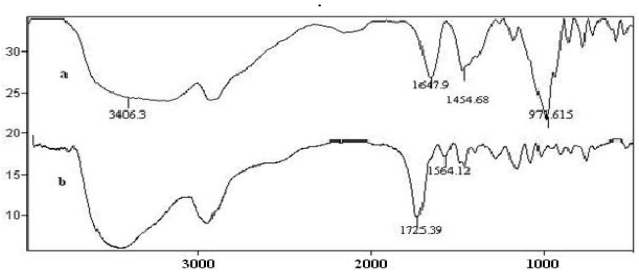


Fig. 1 FTIR spectra of (a) the physical mixture of Starch and (b) the crosslinked Starch -poly (NaAA-co-HEMA) hydrogel

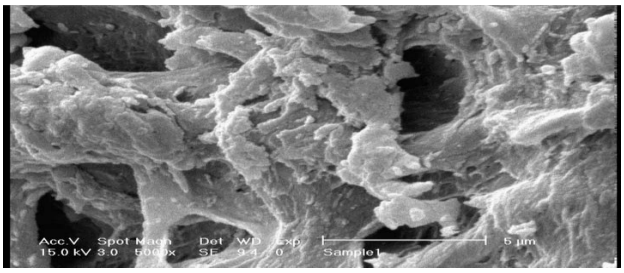


Fig.2 SEM micrograph of synthesized hydrogel.

B. Drug Loading Efficiency and in vitro Drug Release

An accurately weight powdered sample (optimized sample, 1 ± 0.0001g) with average particle sizes between 40-60 mesh (250-420 µm) was immersed entirely in alkaline solution of metronidazole (0.5 gram drug dissolved in 50 mL distilled water), and were incubated at 0°C for 25 h in refrigerator, later the completely swollen hydrogels loaded with drug were placed in vacuum oven and dried under vacuum at 37°C. The loading amount of drug in the hydrogel was calculated from the decrease in the concentration of metronidazole solution which was determined using UV spectrophotometer (UV-1201, Shimadzu, Kyoto, Japan). The loading efficiency of the starch-based hydrogel was calculated as the ratio of the final to the initial metronidazole concentration.

In vitro release was carried out by incubating 0.01±0.0001 g of metronidazole-loaded hydrogel using 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 specified 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:

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

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

III. Results and Discussion

A. Swelling Behavior in Salt Solutions

Changing of environmental ionic strength affects significantly the swelling capacity of superabsorbents. Figure 3 shows the effect of the various salt solutions with various concentrations on the water absorbency of Starch-poly (NaAA-co-HEMA) hydrogel. The decrease of the swelling capacity of the both hydrogels is due to the screening effect and a loss of the osmotic pressure difference between the hydrogels and the fluids. The superabsorbents comprise carboxylate groups in their structures. In salt solutions, the perfect anion-anion repulsion of the carboxylate groups is prevented by the M^{n+} cations that shield the carboxylate groups, so the swelling capacity is decreased [1, 2, 4]. In addition, the swelling of the superabsorbents depends on the valency of the cations. Multivalent cations decrease drastically the swelling capacity. The decrease is attributed to the complexing ability of carboxylate groups inducing interchain complexes formation and consequent enhancing of the network crosslink density [4]. The hydrogel comprises carboxylate anions ($-COO^-$). The water absorbency of the hydrogel in the presence of the Ca^{2+} and Al^{3+} cations is lower than that of NaCl solution. This phenomenon is arisen from ionic crosslinking of these cations with carboxylate anions that causes low water absorbency.

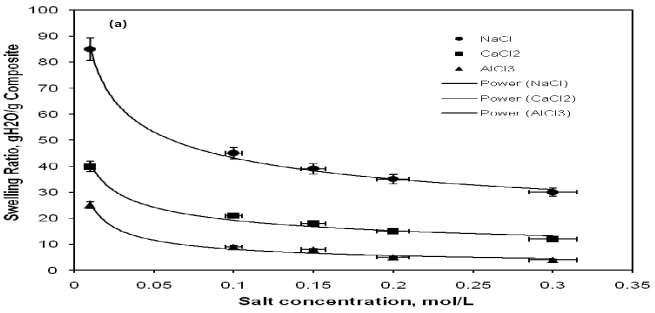


Fig.3 Swelling capacity variation of superabsorbent hydrogel in different saline solutions with various concentrations

B. Release in the Simulated Human Gastrointestinal System

To determine the potential application of starch-based superabsorbent containing a pharmaceutically active compound, we have investigated the drug release behavior metronidazole form this system under physiological conditions. The percent of released drug from the polymeric carriers as a function of time is shown in Figure 4. The concentration of metronidazole released at selected time

intervals was determined by UV spectrophotometer. The metronidazole -loaded hydrogels with high degrees of drug loading (>80%) were prepared by the swelling-diffusion method. The amount of metronidazole released in a specified time from the starch-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[5]

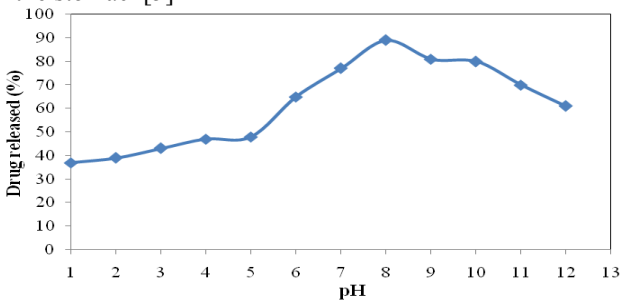


Fig. 4 Diagram investigation drug released in various pHs

At low pH values, electrostatic repulsion between the carboxylic acid groups of backbone is low, thus decreases gel swelling and minimizes release of metronidazole 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 metronidazole was increased [2,3]. The amounts of the loaded drug in superabsorbent hydrogels was significantly affected by the loading time . With increasing loading time, the amount of drug loaded is initially increased and then begins to level off.

IV. Conclusions

The superabsorbent hydrogel, starch-g—poly (NaAA-co-HEMA), was synthesized through graft copolymerization mixture. the maximum water absorbency superabsorbent was 355 g/g. Also the superabsorbent hydrogels exhibited high sensitivity to pH, so that, several swelling changes of the hydrogel or drug releasing percent were observed in lieu of pH variations in a wide range (1-13). Furthermore, the reversible swelling-deswelling behavior in solutions with acidic and basic pH, makes the hydrogels as a suitable candidate for controlled drug delivery systems. This was demonstrated via metronidazole loading and releasing from the synthesized pH-sensitive hydrogels. Also swelling measurement of the synthesized composites in different salt solutions showed appreciable swelling capacity, especially in NaCl solution, due to an anti-salt characteristic originated mainly from the starch part and carboxylic groups of the superabsorbing network

V. Acknowledgements

The authors thank the Research centre of Islamic Azad University of Arak.

References

[1] Buchholz, F.L. and Graham, A.T. (1997). *Modern Superabsorbent Polymer* Technology; Wiley, New York.

[2] Po, R. (1994). Water-absorbent Polymers, A Patent Survey, *J. Macromol. Sci., Rev. Macromol. Chem. Phys.*, **C34**: 607–661.

[3] Kost, J. (1999). *Encyclopedia of Controlled Drug Delivery*. E. Mathiowitz (Ed.), Vol. 1, p. 445. Wiley, New York.

[4] Hoffman, A. S. (1996). *Polymeric Materials Encyclopedia*; vol. 5, p. 3282, Salamone, J. C.; Ed.; CRC Press, Boca Raton, FL.

[5] Peppas, N.A. and Mikes, A.G. (1986). *Hydrogels in Medicine and Pharmacy*, vol. 1, p. 27, CRC Press Inc., Boca Raton, Florida.

[6] M. Sadeghi and H. Hosseinzadeh, Synthesis and super-swelling behavior of a novel low salt-sensitive protein-based superabsorbent hydrogel: collagen-*g*-poly(AMPS)*Turk. J. Chem.* 34 ,739-752(2010).

[7] Chen J, Zhao Y. Relationship Between Water Absorbency and Reaction Conditions in Aqueous Solution Polymerization of Polyacrylate Superabsorbents.*J Appl Polym Sci*;75:808(2000).

[8] Flory PJ. Principles *of Polymer Chemistry*, Ithaca, Cornell University Press, New York, (1953).

[9] Hsu S.C, Don T.M, Chiu W.Y. Free Radical Degradation of Chitosan with Potassium Persulfate. *Polym Degrad Stab*;75:73(2002).

[10] Lim DW, Whang HS, Yoon KJ. Synthesis and Absorbency of a Superabsorbent from Sodium Starch Sulfate-g-Polyacrylonitrile. *J. Appl. Polym. Sci.*; 79:1423(2001).

[11] Barbucci R, Maganani A, Consumi M. Swelling Behavior of Carboxymethylcellulose Hydrogels in Relation to Cross-linking, pH, and Charge Density. *Macromolecules*; 33:7475(2000).

[12] Omidian H, Hashemi SA, Sammes PG, Meldrum I. A Model for the Swelling of Superabsorbent Polymers. *Polymer*; 39:6697(1998).

[13] Omidian H, Hashemi SA, Sammes PG, Meldrum I. Modified Acrylic-based Superabsorbent Polymers (Dependence on Particle Size and Salinity). *Polymer*; 40:1753(1999).

Khorramabad, Lorestan, Iran on15/06/1973.Educational backgroungs are: High School Diploma (GPA 15.5/ out of 20), Shahid taleghani High School, khorramabad, lorestan, 1992.B.Sc. In Pure Chemistry (GPA 14.50/ out of 20), Lorestan University, khorramabad, 1996.M.Sc. In Organic Chemistry -Polymer(GPA 15.95/ out of 20), Sharif University of Technology, Tehran, 2000.Ph.D. in Organic Chemistry (Polymer Chemistry), Sharif University of Technology, 2004 .

He is associate professor at Islamic Azad University ,Arak Branch. his works are:

1. Synthesis and super-swelling behavior of a novel low salt-sensitive protein-based superabsorbent hydrogel: collagen-g-poly(AMPS), Turk J Chem , 2010, 34, 739-752
2. Studies on graft copolymerization of 2-hydroxyethylmethacrylate onto kappa-carrageenan initiated by ceric ammonium nitrate, Journal of The Chilean Chemical Society,55N 4(2010)
3. Swelling Behaviour of a Novel Protein-Based Super Absorbent Hydrogel Composed of Poly(methacrylic Acid) and Collagen, Asian Journal of Chemistry,2010,22,6734-6746

His Major Research Interests are:

1.Hydrogel Synthesis and Properties. Hydrophilic polymer networks especially superabsorbent polymers (SAPs) are of his main interests. SAPs are hydrogels having ability to absorb huge amounts of water or aqueous fluids, as high as 10-1000 times their own weight. Their application includes mainly healthcare products (baby napkins, female pads) as well as the resins using in agriculture. They have revolutionized the arid-area agriculture and soil conditioning. These gluttonous hydrogels have been one of his main research interests. Interpenetrating polymer network (IPN) hydrogels are also interested.

2.Modification of Natural Polymers. Natural polymers from renewable resources such as carbohydrate polymers (starch, cellulose, carrageenans, chitin, natural gums) are interested to be chemically modified (e.g., monomer grafting, or IPN formation) to achieve water soluble/swellable materials. The products may be used in a wide range of applications, e.g., medicine, pharmacy (biocompatible devices, drug delivery systems), water treatment (flocculants), water-borne surface coatings, cosmetics and food industries (thickeners), enhanced oil recovery (shear stabilized drilling mud), and drug reducing agents.

And His Current Research Interests are:

1. Synthesis of novel superabsorbent hydrogels with high pH and low salt sensitivity
2. Synthesis of intelligent hydrogels as excellent candidate in cotrolled release drug delivery systems.
3. Synthesis of composite hydrogels for preparing of new superabsorbents with high mechanical stability.
4. Modification of natural polymers via free radical graft copolymerization of vinylic monomers.

Dr.Sadeghi is associate Professor at Islamic Azad University, Arak Branch.He is member of Iranian Polymer Association, member of Iranian Chemistry Association, member of American Plastic Association, The fifth person in Chemistry Olymiad in Iran, the best researcher in the Province, district, and also university for several years.