Swelling and Drug Release Properties of Starch Based Copolymer Hydrogel Prepared By Ionizing Radiation

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ABSTRACT

pH-sensitive hydrogels composed of starch /acrylic acid were prepared by means of \(\gamma\)-radiation induced graft copolymerization and crosslinking. The effects of the preparation conditions such as the feed solution concentration and composition and irradiation dose on the gelation process of the synthesized copolymer were investigated. The effects of pH and ionic strength on the equilibrium of swelling for the prepared hydrogels were studied. The swelling behavior of the starch/acrylic acid copolymer hydrogels was examined by studying the effect of the hydrogel composition on the time - and pH-dependent swelling. In order to estimate the ability of the prepared copolymer to be used as a colon-specific drug carrier, the release of ketoprofen was monitored as a function of time at pH 1 and pH 7.

Keywords: pH-sensitive / Starch / Acrylic acid / Copolymer / \(\gamma\)-Irradiation, Swelling / Drug release

1-INTRODUCTION

Starch is a well-known, versatile, and inexpensive agricultural material used for a variety of industrial applications. In addition to being a major food item, it is currently used industrially as coatings and sizing in paper, textiles and carpets, as binders and adhesives, as absorbants\(^1\), bone replacement implants\(^2\), bone cements\(^3\), drug delivery systems\(^4\) and tissue engineering scaffolds\(^5\).

During the last decades, the field of drug delivery and controlled release has seen a dramatic development. Ideal drug delivery system (DDS) should deliver a drug to a specific site, in a specific time and release pattern. In the early times, the basic deal was to get a constant (zero order kinetic) or sustained drug release in order to avoid the problems associated with a multiple conventional administration in chronic treatments. Nowadays, the challenges are much more ambitious. The current trends of new controlled release devices include the optimization on the targeting to specific sites and the fitting of the drug release to the circadian rhythm. Besides, drug delivery technology covers other specific needs such as: (1) to get a slow release of water soluble drugs; (2) to improve the bioavailability of low water soluble drugs; (3) to deliver two or more agents in the same formulation; (4) to develop carriers readily clearable; (5) to improve the biodistribution of drugs with a high rate of metabolism or rapid clearance; (6) to control the release of highly toxic drugs and; (7) to improve the targeting to the target tissues or cells.

Hydrogels are one of the upcoming classes of polymer-based controlled release drug delivery systems. Besides exhibiting swelling-controlled drug release, hydrogels also show stimuli-responsive changes in their structural network and hence, the drug release. Because of large variations in physiological pH at various body sites in normal as well as pathological conditions, pH sensitive hydrogels have been extensively investigated.

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PAAc and its lightly crosslinked commercial forms like Carbopol and Polycarbophil, usually exhibit strong pH-responsive property, and also appear to be biocompatible. However, PAAc highly swells in water and dissolves at high pH solutions. High water swelling property critically limits its use as a drug carrier, since the drug is fast delivered across the hydrogel.

The use of polymers from renewable resources is an environmentally advantageous alternative to synthetic polymers in some applications. The combination of the acrylic acid as pH-sensitive monomer with the biodegradable character of starch will lead to interesting hydrogels with potential applications as biomaterials exhibiting different properties depending on the hydrogel composition.

In this work, starch/acrylic acid copolymer hydrogels of different compositions were prepared using γ-rays as a clean source for polymerization and crosslinking. The preparation conditions will be optimized to produce hydrogel with the highest possible gel content. The prepared hydrogels will be characterized. The release profile of the prepared hydrogels will be studied using Ketoprofen as a model drug.

2-EXPERIMENTAL

1. Materials
Acrylic acid (AAc) of purity 98% (Spectrum chemical Mfg. Corp, USA) and water soluble potato starch (Himedia lab., India) were used as received. Ketoprofen, pharmaceutical grade, kindly provided by Alex. Co. Pharm. Chem. Ind. Alex., Egypt. Citric acid, Sodium citrate, Sodium dihydrogen phosphate, and Disodium hydrogen phosphate, analytical reagents, were analytical grade, purchased from El-Nasr Pharm. Chem. Co., Egypt.

2. Preparation of Starch/AAc Gels
Starch/AAc gels were obtained by radiation-induced homo/copolymerization of mixtures of different compositions using 60Co gamma rays at irradiation dose of 20 and 40 kGy and dose rate of 10.28 kGy/h. All samples were washed in excess water to remove the unreacted component then air dried at room temperature.

3. Preparation of Buffer Solutions of Different pH’s
(Citric acid/trisodium citrate) and (Sodium dihydrogen phosphate/ disodium hydrogen phosphate) were used to prepare buffer solutions of pH values ranged from 3-5 and 6-7, respectively. HCl was used to prepare solutions of pH 1.

4. Swelling Study
The prepared gels were cutted into disks and then swollen in buffer solution of different pH’s ranged from 1 to 7 at 37°C. The swelling ratio (S %) was determined from the following equation:

\[ S\% = \frac{W_s - W_o}{W_o} \times 100 \]

Where Ws and Wo are the weights of the swollen and the dry hydrogel, respectively.

5. Ultraviolet (UV) Measurements
Determination of the released amount of Ketoprofen as a model drug was carried out using Perkin Elmer, Lmbda1 Uv-Vis spectrophotometer in the range from 190-900.

6. Preparation of Ketoprofen-loaded Hydrogel
Starch/AAc gels dry gels were immersed in saturated aqueous solution of Ketoprofen at room temperature until equilibrium and the drug loaded gels were dried at room temperature.
7. Release of Ketoprofen

Starch/AAc gels loaded with Ketoprofen were allowed to swell in buffer solution of pH 3 and 7. At first, the loaded gel were put in 25 ml citrate buffer (pH 3) for 3.5 h, and then transferred to 100 ml phosphate buffer (pH 7). One-ml sample was withdrawn on time intervals to follow the release process.

3-RESULTS AND DISCUSSION

Polysaccharides are, in general, non-toxic, biocompatible, biodegradable, and abundant \(^{(12)}\). However, as polysaccharides dissolve easily in water, cannot form stable hydrogel. An effective method to produce a natural polymer based hydrogels is to make them into a synthesized polymer gel networks to form natural and synthesized polymer blend hydrogels, which is becoming a subject of academic as well as of industrial interest.

1. Effect of Preparation Conditions on the Swelling Behavior of Starch/AAc Hydrogels

Potato starch was copolymerized with acrylic acid using gamma radiations. Fig (1) shows the effect of starch content on both conversion and gelation degrees of the produced hydrogels. It is well known that gamma irradiation of starch leads to the breakdown of glycoside bonds and decomposition of macromolecules accompanied by the creation of macromolecules with smaller chains i.e. chain scission \(^{(13-15)}\).

![Graph showing conversion and gelation vs Starch content](image)

Fig (1): Effect of starch content (wt%) on conversion and gelation process of Starch/AAc hydrogels prepared at total concentration 20 wt% and irradiation dose 20 kGy

In accordance, the results can be explained in the light of chain scission/crosslinking balance. At low Starch concentration, even though AAc has high ability of copolymerization and crosslinking, the main chain scission is the predominant reaction due to low probability of the recombination of the degraded starch chains and/or the grafted PAAc onto starch segments. Consequently, loose network of low crosslinking density is obtained. Meanwhile, the increase in the starch content within the reaction medium to be 10 wt% increases the probability of the recombination of the degraded starch chains as well as crosslinking and self bridging of the PAAc. Consequently, much perfect network of higher crosslinking density is obtained. On the other hand, the further increase in the starch concentration reallocate scission/crosslinking to be scission predominates due to the lowering in the AAc content.
Figure (2) shows the time dependent swelling of Starch/AAc copolymer hydrogels of different starch content, different concentrations and irradiations doses. It is obvious that the preparation conditions can remarkably control the swelling behavior of the prepared hydrogels. The Starch/AAc hydrogel that prepared at lower concentration and irradiation dose possessed the highest swelling rate and water capacity. The swelling rate and capacity of the prepared hydrogels decreases by increase either the concentration or irradiation dose. The increase in the concentration remarkably decreased the swelling rate and the capacity of the Starch/AAc hydrogels.

![Figure (2): Time dependent swelling of Starch/AAc copolymer hydrogels prepared at different conditions; ( ) total concentration 10wt% and 20 kGy, ( ) total concentration 20wt% and 20 kGy, ( ) total concentration 20wt% and 40 kGy.](image)

Further decrement in the swellability observed as the irradiation dose increases. These results could be explained in the light of crosslinking density of the prepared hydrogels. At low feed solution concentration, a loose network of low crosslinking density was formed. Such network possesses wider pore size and larger free space to retain water which facilitates the diffusion of water and maximize the amount of water retained. The increase in the feed solution concentration and/or irradiation dose would hold the network perfectly by increasing the network density which as a result narrows the pore size and reduces the free spaces available for water retention.

2. **pH-dependent Swelling of Starch/AAc Hydrogels**

The response of the polymeric hydrogel to the change in the pH value of the surrounding environment is the most important and evaluating character for a polymeric hydrogel to serve as a carrier for site specific drug delivery. Figure (3) shows the pH dependent swelling behavior of starch/AAc hydrogels of different starch content. It is clear that all starch/AAc hydrogels show pH dependent phase transition i.e. they possessed higher swelling degrees at buffer solution of high pH values (pH > 4) much higher than that possessed at low pH values (pH < 4). This behavior can be explained as follow At pH values lower than pH 4, the contained PAAc chains are associated and forming inter- and intra-molecular hydrogen bonding which acquire its chains and consequently all the sample a relative hydrophobic character and minimum free spaces for...
water retention resulting in very low swelling rate and capacity. On the other hand, at pH values higher than pH 4, the dissociation of the carboxylic groups of the AAc into carboxylate is the major driving force for the swelling.

![Swelling vs pH](image)

**Figure (3): pH dependent swelling of Starch/AAc copolymer hydrogels prepared at total concentration 20 wt%, irradiation dose 20 kGy and different starch content (wt%). (5), (10), (15) and (20).**

The ionized pendant carboxylic groups develop fixed charges on the polymer network not only possess high degree of hydration but also the electrostatic repulsive forces leads to maximize the free spaces within the sample which consequently enlarge the amount of retained water. On the other hand, the data also show that the position and magnitude of such phase transition is directly related to the starch content within the hydrogels. In other words, the increase in starch content within the hydrogel shifts the position of the pH threshold to a lower values as well as it reduces the magnitude of the phase transition. The effect of the increase of starch content on position and magnitude of such phase transition might be attributed to the hydrophilic character of the starch.

3. In-vitro release of Ketoprofen from starch/AAc hydrogels

The release experiments were conducted at buffer solution of pH 1 which is almost similar to that of stomach medium for 3.5 hours and at buffer solution of pH 7 which is similar to that of the intestine medium for 21.5 hours. Figure (4) shows the effect of the preparation conditions and hydrogel composition drug release profile of starch/AAc copolymer hydrogels, respectively, as a function of time at pH 1 and pH 7. The figures generally show that there is no significant drug release at pH 1 whereas the drug release occurs as soon as the copolymer transferred to buffer solution of pH 7 which nominate such hydrogel as a suitable materials for colon specific drug carrier. The Figure also shows the possibility of controlling the drug dosing rate by controlling the preparation conditions and the internal chemical composition of the prepared hydrogels. It is clear that the degree of crosslinking as well as the AAc concentration is key factors for controlling the drug release rate. The increment in the crosslinking density resulted from either the increase in the total concentration or the increase in the irradiation dose, decreases the drug release rate. Meanwhile the increment in the AAc content in the hydrogel composition increases the drug release rate.
4-CONCLUSION

A series of Starch/AAc copolymer hydrogels were synthesized by means of gamma radiation induced copolymerization and crosslinking. The preparation condition such as feed solution composition and concentration and irradiation dose was studied to achieve the highest gelation degree. The prepared hydrogel possessed good pH-sensitivity which recommends them as carriers for colon specific drug delivery systems. The in-vitro drug release experiment show a promising ability for the prepared hydrogels not only to control the release site but also to control the release rate.

5-REFERENCES