



Synthesis of pH Sensitive Hydrogels Based on Poly Vinyl Alcohol and Poly Acrylic Acid

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Abstract

In this research, hydrogels based on poly vinyl alcohol and poly acrylic acid blend were prepared which were cross-linked by applied thermal conditions. Afterward, effects of time and heating on water uptake were investigated. The highest water uptake value exhibited by the sample that was heated for 20 min. at 110 °C was about 2129% after 4 days at equilibrium state. Hydrogels exhibited pH-sensitive behaviors in a way that decreasing pH values down to 4.8 did not have any effect on the hydrogels size, whereas with increasing pH upto 8, the hydrogels were expanded. These synthetic hydrogels were evaluated as a controlled drug delivery systems and theophylline released concentration was measured by UV-spectrophotometric method at different pH values. *In vitro* biocompatibility experiments were undertaken using L-929 mouse fibroblast cell lines where the results showed appropriate cell attachment and cell spreading with spindle like morphologies.

Keywords: Biocompatibility; Controlled drug release system; pH-Sensitive hydrogels; Poly acrylic acid; Poly vinyl alcohol.

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1. Introduction

Hydrogel is a network of water-insoluble polymer chains which can absorb a large amount of water. Ionic polymers contain an ionic side-chain and gel is immersed in an electrolyte fluid. These polymers are known as active because they expand (swell) or contract (shrink) in response to environmental stimuli [1-3]. Such stimuli include changes in temperature [4], electric voltage [5, 6], pH [7-13] and surrounding fluid [14-19]. The ability of active polymer gels to expand and

contract has fostered great interest in the use of these materials for a variety of applications [17, 18]. Polymer gels are also being used in drug delivery systems [19] and other medical applications [20]. The swelling ability of pH-sensitive hydrogels depends on the functional acidic or basic groups at the polymer backbone. Due to the dissociation of these groups and the influx of counterions, the concentration of ions in the hydrogel is higher than in the surrounding solution. This causes a difference in osmotic pressure and results in a solution flux into the hydrogel and, consequently, a swelling. The interaction and repulsion of charges along the polymer chain also leads to an increased swelling. In

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hydrogels containing acidic groups, the gel is ionized when pH is higher than pKa of the acidic group, and this leads to pH-sensitivity.

Poly vinyl alcohol (PVA) and poly acrylic acid (PAA) are hydrophilic polymers used in many biomedical researches, previously [21]. There are several ways for cross-linking PVA, such as gamma radiation, chemical crosslinking agents and heat treatment [21-28]. PAA can be trapped in PVA network by these methods [29]. Preparing polymer blends is a useful method for controlling hydrogel behavior by changing components. Cross-linking PVA/PAA blends by heat treatment may produce a pH-sensitive hydrogel that can be used for release of drugs. Such drugs like insulin may denature in acidic media of stomach [22].

In this work, PVA/PAA pH sensitive hydrogels were prepared and the release of theophylline at different pH values was evaluated.

2. Materials and methods

2.1. Materials

PVA (MW=72,000, 98% hydrolysed), hydrochloric acid, sodium hydroxide and sodium hydrogen carbonate were purchased from Merck. PAA (MW=240,000) was supplied by Aldrich.

2.2. Synthesis method

PVA (1 g) was dissolved in 40 ml deionized water for 2 h at 98 °C. PAA (1 g) was also separately dissolved in 40 ml of deionized water and solutions were thoroughly mixed. The combined solution was then poured into a glass pan where it remained for 3 days. A thin transparent film of PVA/PAA was then easily peeled off the glass pan and cross-linked by applied heat

condition. Table 1 gives the data of the thermal treatment. Properties of gels strongly depend on time and temperature of heating.

2.3. Preparation of pH-sensitive hydrogels

To study the effect of the water incorporated into the hydrogel on the activity of Na⁺ groups, one sample was immersed in deionized water until it reached its equilibrium state at 25 °C. Then, it was boiled in NaOH solution.

Two other samples were boiled in 1 M and 2 M NaOH solution to discover the effect of NaOH concentration on the swelling behavior. Samples were prepared as mentioned in Table 2.

2.4. Drug loading in prepared samples

The selected gel was placed in theophylline solution for 3 days to load drug into the polymeric network via diffusion phenomena. The weight ratio of hydrogel to drug was 5:1. Gel was then completely washed in distilled water to remove any remaining drug on the surface of the gel.

2.5. Characterization methods

A pH/Ion meter (Metrohm 692, Switzerland) and a UV spectrophotometer (Milton Roy 601, United States) were used for evaluating hydrogel behavior.

In vitro cytotoxicity of the samples was assessed as per ISO-10993-5. The mouse L929 fibroblast cells were used as a test model in this study. The cells were maintained in Roswell Park Memorial Institute ORPMI-1640 culture medium, supplemented with 100 IU/ml penicillin, 100 µg/ml streptomycin, and 10% fetal calf serum. A routine subculture was used to maintain the cell line. The cells were incubated in a humidified atmosphere of

Table 1. Thermal treatment of hydrogel.

Temperature (°C)	Time (min.)
110	20,30,45,60,120,180,240
120	20,30,45,60,120,180,240
130	20,30,45,60,120,180,240

Table 2. Preparing pH-sensitive samples.

Sample	Preparation condition
Sample 1	Swelled in water and boiled in 1 M NaOH solution
Sample 2	boiled in 1M NaOH solution
Sample 3	boiled in 2M NaOH solution

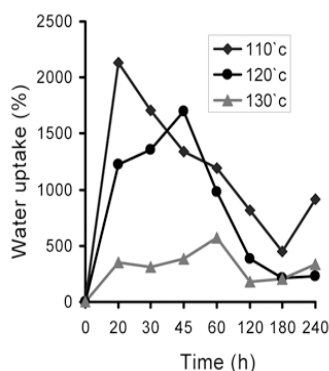


Figure 1. Water uptake percentage for samples prepared as described in Table 1.

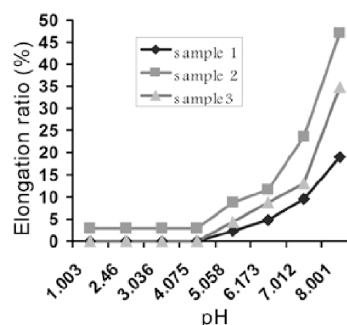


Figure 2. Swelling elongation ratio at different pH values.

5% CO₂ at 37 °C. After 1-week incubation, the monolayer was harvested by trypsinization. The cell suspension of 4×10⁵ cells/ml was prepared before seeding. The samples were washed with PBS and rinsed with distilled water and then sterilized in an autoclave at 120 °C and placed in a multiwell tissue culture polystyrene plate (Nunc, Denmark) with 5 ml cell suspension, with one well kept as a negative control, and then maintained in the incubator for one week. After incubation, the samples were examined by optical microscopic examinations.

3. Results and discussion

3.1. Water uptake

Swelling behavior of PVA/PAA films was studied by measuring the amount of water incorporated into the samples. Hydrogels were immersed in deionized water at 25 °C to reach their equilibrium state, which occurred

after 2-4 days. Water uptake of hydrogels was calculated as follows:

$$\text{Water uptake (\%)} = [(W_t - W_d) / W_d] \times 100$$

where W_t is the weight of swollen gel and W_d is the weight of dry gel. Figure 1 shows the percentage of water uptake in synthesized samples. As shown in Figure 1, water uptake percentage increased as the heating temperature decreased but there is no general rule for the time of heating. Water uptake increased to a maximum value at 120 °C and 130 °C. After that, growth of crystalline regions in polymeric gel causes a decrease in water uptake by increasing the time of thermal treatment. Additionally, gel becomes rigid and brittle by decreasing the elasticity of polymer network. Gel behavior at 110 °C is totally different, because this temperature is

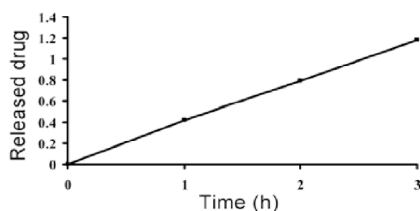


Figure 3. Theophylline released in acidic solution (pH=2).

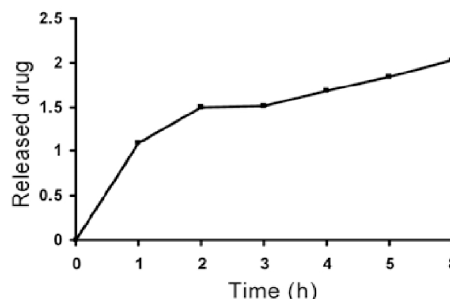


Figure 4. Theophylline released in buffer solution (pH=7.4).

not enough for crosslinking polymer blend.

3.2. pH-sensitivity

After evaluating water uptake results, the gel sample which was heated for 60 min. at 130 °C was chosen for pH-sensitivity measurements. This sample keeps its mechanical strength after 45 days immersing in deionized water.

To increase pH-sensitivity of gels, samples were boiled in NaOH solution whereby Na⁺ causes COOH group dissociation and so COO⁻ pendent groups remain in hydrogel network [30].

For pH-sensitivity measurements, samples were immersed in hydrochloric acidic solution, and sodium hydrogen carbonate gradually added to increase the pH value.

Hydrochloric acid is the most similar one to stomach acidic mucus. It should be mentioned that different acidic solutions by similar pH value, have different effects on gel behavior. For example, immersing PVA/PAA blends in acetic acid solution causes gel expansion while gel remains constant at hydrochloric acid solution by the same pH value.

Figure 2 shows swelling elongation ratio (%) for sample 1, sample 2 and sample 3. These values were measured by the following expression:

$$\text{Swelling elongation ratio (\%)} = [(L_t - L_0) / L_0] \times 100$$

where L_0 is the initial length of the samples and L_t is their length in desirable pH values at equilibrium state.

The pKa of PAA is 4.8. When the pH is less than the pKa, the H⁺ ionic strength is very high. This effectively suppresses the ionization of the carboxylic groups and, therefore, the gel is neutral and the flexibility of the polymeric chain is rather low. Carboxylic groups within the network ionize and attract cations into the gel to replace the H⁺ ions, as the pH of the environmental solution rises above its pKa. This effectively raises the concentration of free ions inside the gel. Thus, the ionic swelling pressure will increase and so does the swelling. Additionally, the gel tends to expand to minimize the repulsion between the ionized carboxylic groups. With increasing pH the polymeric network becomes more hydrophilic as the degree of ionization increases. However, as the pH increases still further, the ionic strength also increases. The osmotic pressure difference of free ions between the internal and external solution decreases and the gel tends to shrink [31].

3.3. Release of theophylline

Swelling properties of gels and their pH-sensitivity confirms their ability to release incorporated drug. Because of physical crosslinking, these hydrogels contain no toxic materials and so can be used as drug release systems. Gel was placed in acidic solution by pH=2 and release of thophylline was measured for 3 h in acidic solution which is

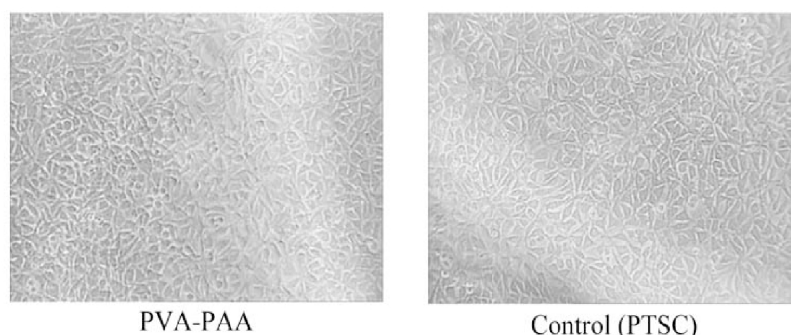


Figure 5. L929 cell culture and their morphology in PVA-PAA sample and control sample after 1 week.

the time of digestion in the stomach.

Release of theophylline in acidic solution was approximately constant as shown in Figure 3, and this approves the gel stability in acidic solutions. After that, gel was immersed in a solution by pH=7.4, and the release of theophylline was measured. As shown in Figure 4, slope of theophylline release curve increases by increasing time, and drug releases in a regular rate.

3.4. Cytotoxicity

Cytotoxicity evaluation of hydrogels is shown in Figure 5. Cellular morphology of cultured cells on PVA/PAA hydrogels is like their morphology on control sample. All samples exhibit cell attachment, spindle like cells formation and pseudo pods development.

4. Conclusion

In this work, biocompatible hydrogels were prepared and release of theophylline as a model drug was investigated various pH values. Synthesized hydrogels show considerable sensitivity to alternative pH values and because of their constancy and resistance in acidic solution, they can be promising candidates to transfer drugs - such as insulin and peptides - into intestine (oral) or blood, where they can be released. It should be mentioned that the structure of insulin and its molecular weight is totally different and so other ways of loading drug into synthesized hydrogels is under investigation.

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