METOPROLOL TARTRATE RELEASE STUDIES OF POLY(ACRYLAMIDE-CO-ITACONIC ACID) HYDROGELS

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Hydrogels are hydrophilic, three–dimensional, polymeric networks, capable of imbibing significant amounts of water or biological fluids. The networks are usually composed of homo– or copolymers which are insoluble due to the presence of chemical or physical crosslinks. Thus, hydrogels have found widespread applications in biomedical and pharmaceutical fields. Hydrophilic hydrogels swell in water and the swelling is influenced by the chemical structure and the crosslinking ratio.

Besides exhibiting the swelling–controlled drug release, some hydrogels also show stimuli–responsive volume changes. In the case of stimuli–sensitive hydrogels the swelling behavior can be determined by pH, temperature, ionic strength, etc. [1,2]. The pH–responsive polymeric networks have been extensively studied owing to the large variations in physiological pH values, as well as the pH values in pathological conditions.

The aim of this study was to investigate the swelling properties of hydrogels based on AAm and IA with respect to itaconic acid content and the pH values of the media. The potential use of these hydrogels as drug delivery systems was considered.

MATERIAL AND METHODS

Materials: Acrylamide (AAm), itaconic acid (IA) were obtained from Fluka, potassium persulfate (PPS), potassium pyrosulfate (PyPS) and N, N'–Methylenebicacrylamide (MBA) were obtained from Merck. All reagents were used without further purification.

Preparation of hydrogels: The copolymer hydrogels of acrylamide (AAm) and itaconic acid (IA) were obtained by radical crosslinking copolymerization at 60°C during 24 h (N_2 atmosphere). The monomers (AAm/IA: 90/10, 95/5 and 99/1 wt%) were dissolved in water with the redox couple PPS/PyPS (1.0 wt%) and MBA (2.0 wt%) with respect to the monomers. The reaction mixture was placed between two glass plates sealed with a rubber spacer. After completion of reaction, the gels were cut into discs and immersed in water to remove unreacted monomers. The discs were dried at room temperature to xerogels (1 mm thick and 5 mm in diameter).

Equilibrium swelling studies: The xerogels discs were immersed in buffer solutions (pH 2.2; 4.5 and 6.8) to obtain equilibrium swelling at 30°C. The progress of the swelling process was monitored gravimetrically and the degree of swelling was calculated using the equation:

$$q = W_t/W_o,$$

where W_o is the weight of xerogel at time 0 and W_t is the weight of swollen hydrogel at time t.

Loading of drug: Dry hydrogel discs were loaded with metoprolol tartrate (pKa 9.5) by immersion in an aqueous solution of the drug (14 mg/ml) at room temperature for two days. The with drug loaded hydrogels were removed from the solution and left to dry to constant weight.

Release experiments: The release studies were performed using the testing apparatus 1 of USP 23 (Erweka DT 70 dissolution apparatus), at 50 r.p.m. at 37°C [3]. Three buffer solutions (pH 2.2; 4.5 and 6.8) were used as the dissolution media. At predetermined times 3 ml samples were removed and assayed for metoprolol tartrate at 275 nm using a Varian Cary UV–VIS spectrophotometer. The cumulative amount of the metoprolol tartrate released from the hydrogel was determined from the calibration curve. Every data point is the average value of three independent experiments.

RESULTS AND DISCUSSION

The swelling degree is strongly dependent on the buffer pH value: at low pH values, the itaconic acid

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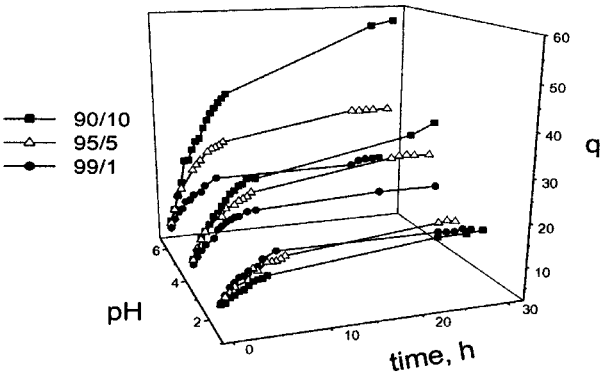

Figure 1. The swelling degree of PAAm/IA hydrogels vs. pH vs. time

COOH groups are not ionized, so the swelling ratio is low. In addition, intermolecular complexation due to hydrogen bonding between functional groups occurs, acting as physical crosslinks. Above the nominal pK_a values of IA (3.85; 5.44) [4], the swelling ratio increases with increasing pH due to the progressive ionization of the COOH groups (Figure 1).

Water transport in polymer networks can be analyzed according to the Peppas equation: $M_t/M_\infty = k \cdot t^n$ [1]. The results obtained ($n \geq 0.5$), indicate that the water transport mechanism is non–Fickian in the pH range investigated. As gel ionization occurs the osmotic swelling pressure increases as well as macromolecular relaxation caused by electrostatic repulsion of the COO^- groups.

The release profiles obtained under different experimental conditions are presented in Figure 2. Certain differences between the obtained release profiles were observed indicating the influence of the itaconic acid content as a hydrogel property and pH as an environmental variable on the drug release. It can be seen that for all the investigated buffer solutions, increasing the content of itaconic acid leads to an increase of the time of drug release, as well as increase of the rate of drug release from low to neutral pH values.

A pH sensitive hydrogels are interesting for the colon–specific delivery of drugs. For that purpose the swelling in the stomach, where the pH is low, should be negligible, while at the neutral pH, which is the case in the colon, high swelling degree is nedeed in order to release the drug to that specific site. This was not completely achieved using PAAm/IA system, because the swelling was high in acidic buffers used. Further studies should be focused on the replace AAm with N–isopropylacrylamide (NIPAM) in order to achieve desired drug release profiles and to obtain a better understanding of the influence of the hydrogel synthesis variables on the mechanism of drug release.

At 37°C NIPAM is above its phase transition temperature and in the collapsed state, so the swelling

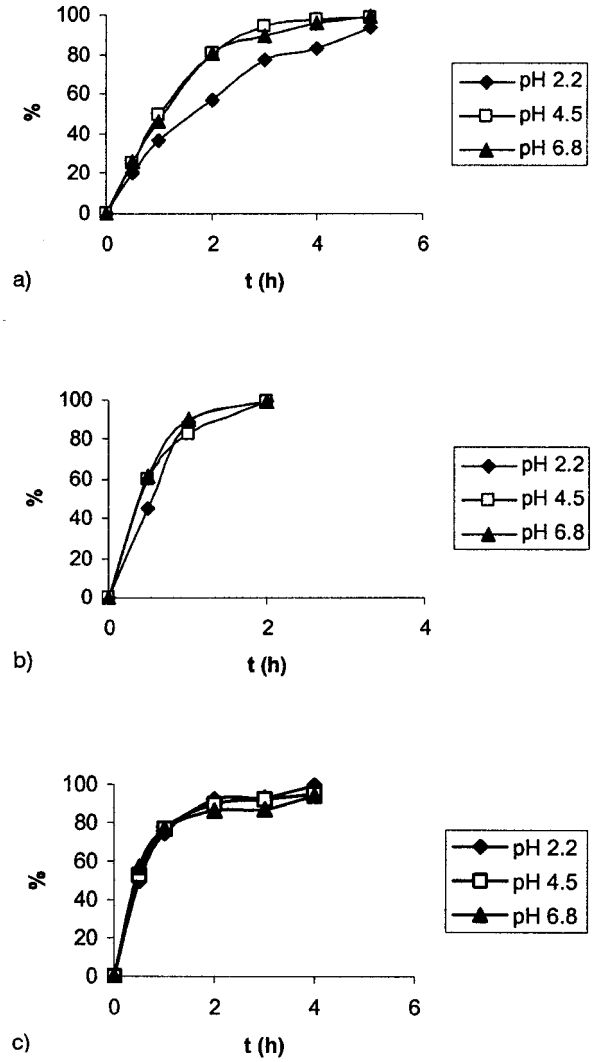

Figure 2. The effect of itaconic acid content on the release of metoprolol tartrate from PAAm/IA hydrogels in different buffer solutions: 90/10 (a); 95/5 (b) and 99/1 (c)

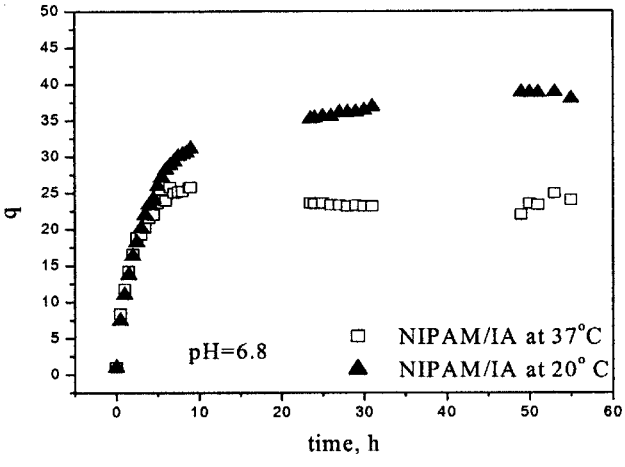

Figure 3. Degree of swelling vs. time for NIPAM/IA gels at 20 and 37°C at pH=6.8

degree is low at pH=2.2, while at pH=6.8 it is higher, owing to the itaconic acid ionization (Figure 3). For that reason, hydrogel, which is practically not swelling at body temperature in acidic solutions and swollen at pH neutral media (pH=6.8), was desined for the possible use in the colon–specific drug delivery applications.

CONCLUSION

The release studies indicate that the hydrogel composition is one of the main factors affecting the swelling of hydrogels and, hence, drug release.The PAAm/IA system with different IA content was not sucessful for the metoprolol tartrate release. Therefore, PAAm is replaced with NIPAM, so the temperature and pH sensitive system was obtained. According to the swelling profile of the new system more favourable drug release can be expected, which is important for the potential application of the investigated hydrogels as controlled release drug delivery systems.

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