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# Synthesis and Evaluation of pH and Salinity-Sensitive Superabsorbent Hydrogel Based on Starch-g-poly (MAA-co-HEMA) as Oral Drug Delivery Systems

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**ABSTRACT**

In this work, my purpose was to produce intelligent starch-based superabsorbent polymers to be used as carriers for the controlled delivery of cis-platin loaded drug. Mechanisms for hydrogel formation was proposed and the structure of the product was established using Fourier transform infrared (FTIR) spectroscopy and scanning electron microscopy (SEM). The effects of pH, ionic strength and levels of loaded drug on drug release profile in various surrounding media were investigated. The synthesized hydrogels were subjected to equilibrium swelling studies in simulated gastric and intestinal fluids (SGF and SIF). The loading drug yield was found to depend on both the impregnation time and the amount of encapsulated drug. In addition, the release of cis-platin from this kind of hydrogel was studied. In vitro drug-release studies in different buffer solutions showed that the most important parameter affecting the drug-release behavior of hydrogels is the pH of the solution. The release rate of cis-platin from hydrogel at pH 7.4 was faster than that at pH 1.2 due to the shrinkage of the hydrogel at pH 1.2.

**Key words:** Starch, Hydrogel, Cis-platin, Drug delivery, Vinylic monomers.

## INTRODUCTION

Loosely crosslinked 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[2-5].

Among this hydrogels, pH-sensitive hydrogels have been extensively investigated for potential use in site-specific delivery of drugs to specific regions of the gastrointestinal tract and have been prepared for delivery of low molecular weight drugs.

The principal requirement of any controlled release system is that the release profile and rate are controlled. Controlled or sustained release drugs

provide many advantages in comparison with conventional forms including reduced side effects; drug concentration kept at effective levels in plasma, improved utilization of drug and decreases the dosing times.

In the current study we investigated the synthesis and utility of an anionic hydrogel from graft copolymerization of methacrylic acid and 2-hydroxy ethyl methacrylate onto starch backbones, for the controlled release of an anti-cancer drug, cis-platin. The swelling properties as well as the salt and pH sensitivity of the hydrogels were investigated in detail. Finally, drug absorption and release capacities of hydrogel systems and influence of pH of the medium on the release properties were also examined.

## EXPERIMENTAL

### Materials

Starch (chemical grade, MW 50000) was purchased from Merck Chemical Co. (Germany). Methacrylic acid and 2-hydroxyethyl acrylate (Merck, Darmstadt, Germany) was used after vacuum distillation. N',N'-methylene bisacrylamide and ammonium persulfate (Fluka, Buchs, Switzerland) were of analytical grade and used without further purification. All other chemicals were also analytical grade. Double distilled water was used for the hydrogel preparation and swelling measurements. Cis-platin (Mw =300 g/mol and Half Life =30–100 hours, Figure 1) was purchased from Hakim Pharmaceutical Co. (Tehran, Iran).

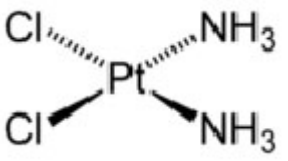



**Fig. 1: Chemical structure of drug cis-platin**

### Hydrogel Preparation

A pre-weighed amount of starch (2.0 g) was dissolved in 50 mL distilled water in a 200cc-reactor equipped with a mechanical stirrer (RZR 2021, a three-blade propeller type, Heidolph, Schwabach, Germany) and stirred (300 rpm) for 10 min. The reactor was placed in a thermostated water bath to control the reaction temperature at 65°C. Then, methacrylic acid, (0.5-4.0 g, completely neutralized with sodium hydroxide), 2-hydroxyethyl acrylate (4.0-0.5 g), ammonium persulfate (0.1 g, dissolved in 5 mL water) and methylene bisacrylamide (0.05-0.15 g, dissolved in 5 mL water) were added simultaneously to the reactor. The temperature was maintained at 65°C and the reaction mixture was stirred continuously (300 rpm) for 1 h. At the end of the propagation reaction, the gel product was poured into ethanol (500 mL) and was dewatered for 12 h. Then, the product was cut into small pieces, washed with 200 mL ethanol and filtered. The particles were dried in an oven at 55°C for 24 h. After grinding, the powdered superabsorbent composite was stored in absence of moisture, heat and light.

### Method for swelling measurement in salt solutions

An accurately weighed sample of the powdered superabsorbent (0.2 ± 0.001 g) with average particle sizes between 40-60 mesh (250–350 $\mu m$) was immersed in saline solution (200 mL) and allowed to soak for 3 h at room temperature. The equilibrium swelling (ES) capacity was measured twice at room temperature according to a conventional tea bag method and using the following formula:

$$ES(g/g) = \frac{\text{Weight of swollen gel} - \text{Weight of dried gel}}{\text{Weight of dried gel}} \quad \ldots(1)$$

### Absorbency at various pHs

Individual solutions (50 mL) with acidic and basic pHs were prepared by dilution of NaOH (pH 10.0) and HCl (pH 1.0) solutions (0.1 M) to achieve pHe"6.0 and pH<6.0, respectively. The pH values were precisely checked by a pH-meter (Metrohm/ 620, accuracy ±0.1). Then, 0.5 (± 0.001) g of the dried hydrogel was used for the swelling measurements according to Eq. 1. Sensitivity of the hydrogel to pH was investigated in terms of swelling and deswelling of the final product at two basic (pH 7.0) and acidic (pH 2.0) solutions, respectively. Swelling capacity of the hydrogels at each pH was measured according to Eq. 1 at consecutive time intervals (15 min).

**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 dilute solution of cis-platin, 0.54 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 cis-platin 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 cis-platin concentration.

In vitro release was carried out by incubating 0.01±0.0001 g of cis-platin -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.

**Instrumental analysis**

Fourier transform infrared (FTIR) spectra of samples were taken in KBr pellets, using an ABB Bomem MB-100 FTIR spectrophotometer (Quebec, Canada), at room temperature. The surface morphology of the gel was examined using scanning electron microscopy (SEM). After Soxhlet extraction with methanol for 24 h and drying in an oven, superabsorbent powder was coated with a thin layer of gold and imaged in a SEM instrument (Leo, 1455 VP).

**Standard absorbance curve**

The standard calibration curve of the absorbance as a function of drug concentration was studied at 210 nm on the UV spectrophotometer.

**In vitro drug release**

The samples (0.1±0.0001 g) were immersed into 50 mL of the release medium (simulated gastric and intestinal fluids, SGF and SIF) with different pH values (pH 1.2 or 7.4) at 37°C with agitation. At given time intervals, 1 mL of the release medium was removed; using a syringe attached with a 0.45 $\mu m$ Millipore filter and after suitable dilution, the concentration of released drug was measured by UV spectrophotometer at 210 nm.

## RESULTS AND DISCUSSION

**Mechanism of Hydrogel Formation**

Scheme 1 shows a simple structural proposal of the graft copolymerization of MAANa and HEMA on the starch backbones and crosslinking of the graft copolymer. In the first step, the thermally dissociating initiator, i.e. APS, is decomposed under heating (65°C) to produce sulfate anion-radicals. Then the anion-radicals abstract hydrogen from the collagen backbones to form corresponding macroinitiators. These macroradicals initiate grafting of MAANa and HEMA onto starch backbones leading to a graft copolymer. Crosslinking reaction also occurred in the presence of the crosslinker, i.e. MBA.

FTIR spectroscopy was used for identification of the hydrogel. In the spectra of the hydrogel the characteristic band at 1564 $cm^{-1}$ was attributed to C=O asymmetric stretching in the carboxylate anion. This was confirmed by another peak at 1415 $cm^{-1}$ which is related to the symmetric stretching mode of the carboxylate groups. The main contribution to the absorption band in the 1725 $cm^{-1}$ is due to the ester group from the poly (2-hydroxyethyl acrylate).

To obtain additional evidence of grafting, a similar polymerization was conducted in the absence of the crosslinker. After extracting the homopolymers, PMAA or PHEA and unreacted monomers using a cellophane membrane dialysis bag (D9402, Sigma–Aldrich), an appreciable amount of grafted starch (88%) was observed. The graft copolymer spectrum was very similar to Figure 2b. Also according to preliminary measurements,

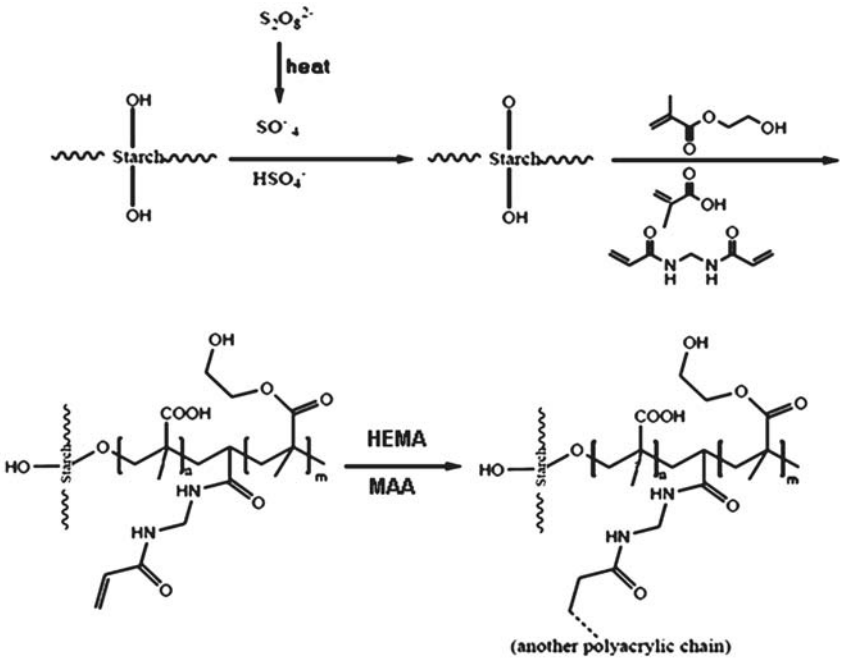
the sol (soluble) content of the hydrogel networks was as little as 1.3 %. This fact practically proves that all HEMA and MAA are involved in the polymer network. So, the monomers percent in the network will be very similar to that of the initial feed of reaction.

One of the most important properties that must be considered is hydrogel microstructure morphologies. The surface morphology of the samples was investigated by scanning electron microscopy (SEM). Figure 3 shows an SEM micrograph of the polymeric hydrogels obtained from the fracture surface. The hydrogel has a porous structure. It is supposed that these pores are the regions of water permeation and interaction sites of external stimuli with the hydrophilic groups of the graft copolymers.

**Investigation of swelling in various salt solutions**

The swelling ratio is mainly related to the characteristics of the external solution, i.e. the charge number and ionic strength, as well as the nature of polymer, i.e. the elasticity of the network, the presence of hydrophilic functional groups, and the extent of crosslinking density. For instance, swelling ability of "anionic" hydrogels in various salt solutions is appreciably decreased comparing to the swelling values in distilled water. This well-known undesired swelling-loss is often attributed to a "charge screening effect" of the additional cations causing a non-perfect anion-anion electrostatic repulsion[6]. Therefore, the osmotic pressure resulted from the mobile ion concentration difference between the gel and aqueous phases decreased and consequently the absorbency amounts diminished. In addition, in the case of salt solutions with multivalent cations, "ionic crosslinking" at surface of particles causing an appreciably decrease in swelling capacity.

In this series of experiments, the swelling capacity was measured in various salt solutions (Figs. 4 and 5). It is obvious that swelling decrease is strongly depended on the "type" and "concentration" of salt added to the swelling medium. The effect of cation type (cations with different radius and charge) on swelling behavior is shown in Fig. 4. With increasing the charge of cation, degree of crosslinking is increased and swelling is consequently decreased. Therefore, the absorbency for the hydrogel in the studied salt solutions is in the order of monovalent > divalent cations. The effect




**Scheme 1: Proposed mechanism for crosslinking the starch-g-(MAA-co-HEMA) hydrogel**

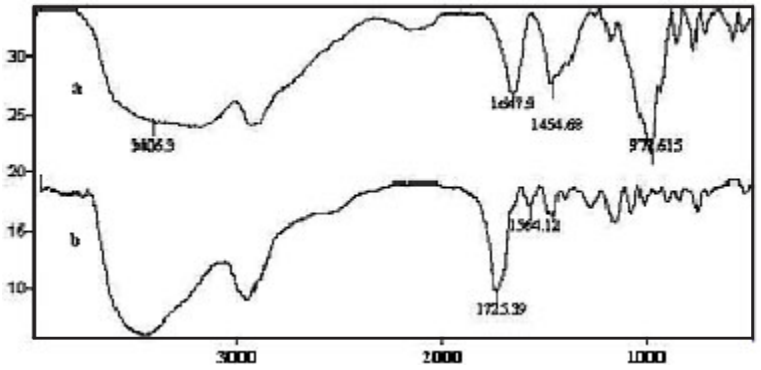



**Fig. 2: FTIR spectra of (a) pure starch and (b) starch-g-(MAA-co-HEMA) hydrogel**

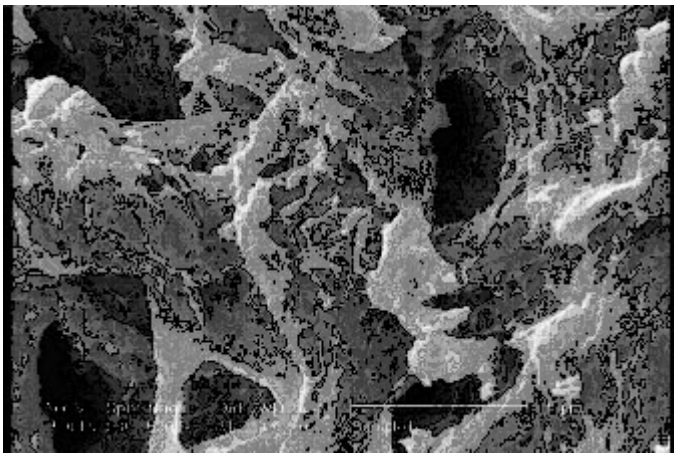


**Fig. 3: SEM micrograph of synthesized hydrogel**

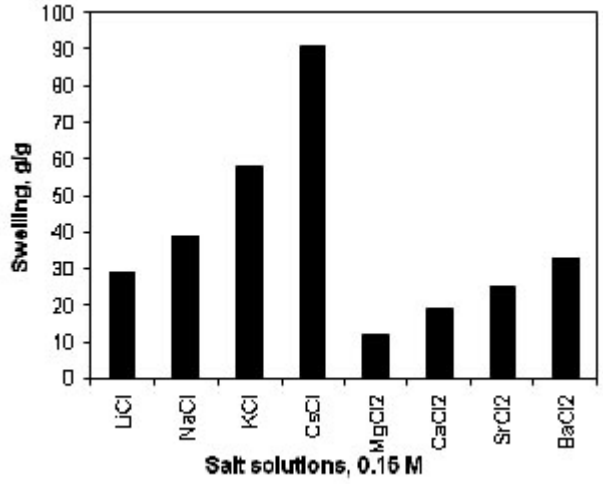



**Fig. 4: Swelling capacity of the hydrogel in different chloride salt solutions**

of cation radius on swelling may also been observed from Figure 4. As reported by Pass et al. (7), the carboxylate anion interacts with small cations, e.g. $Li^+$, stronger than with large cations, e.g. $K^+$. The stronger interactions of carboxylate-small cation have been observed using measurement of activating coefficients of various cations in several salt solutions. As a result, the absorbency in monovalent and divalent cation salt solutions is in the order of KCl>NaCl>LiCl>CsCl and $Ba^{2+}>Sr^{2+}>Ca^{2+}>Mg^{2+}$, respectively.

Figure 5 illustrates a reverse and power law relationship between concentration of salt solutions (NaCl, $CaCl_2$, and $AlCl_3$) and swelling capacity of the hydrogel. Again, charge screening effect and ionic crosslinking are the main explanations for the intense loss of swelling

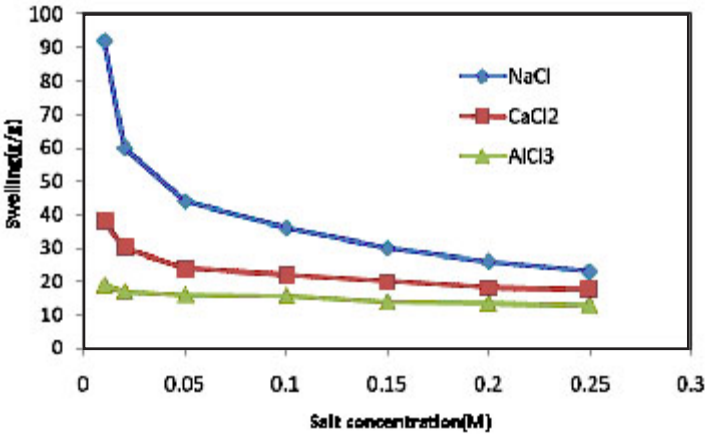



**Fig. 5: Swelling capacity variation of the hydrogel in saline solutions with various concentrations**

**Investigation of pH-responsiveness behavior of the hydrogel**

In this series of experiments, swelling reversibility for the synthesized hydrogels was measured in the solutions with two different pHs 1.2 and 7.4 (Figure 6). Since the swelling capacity of all "anionic" hydrogels is appreciably decreased by the addition of counter ions (cations) to the swelling medium, no buffer solutions were used. Therefore, stock NaOH (pH 10.0) and HCl (pH 1.0) solutions were diluted with distilled water to reach desired basic (7.4) and acidic (1.2) pHs, respectively

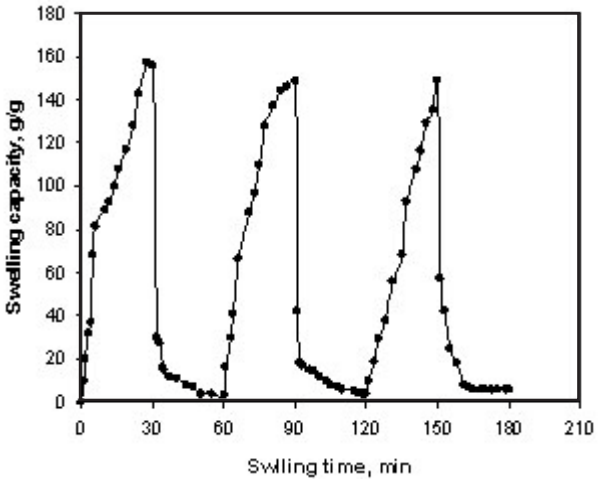



**Fig. 6: On-off switching behavior as reversible pulsatile swelling (pH 7.4) and deswelling (pH 1.2) of starch-g-(MAA-co-HEMA) hydrogel**

**Table 1: The percent of released cis-platin from the polymeric carriers as a function of pH**

| pH | 1.2 | 2 | 3 | 4 | 5 | 6 | 7 | 7.4 | 9 | 10 | 11 | 12 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Concentration (mol/L $10^{-4}$) | 2.15 | 2.25 | 2.49 | 2.73 | 2.8 | 3.74 | 4.43 | 5.12 | 4.65 | 4.60 | 4.03 | 3.52 |
| Percent released | 33% | 39% | 48% | 47% | 48% | 72% | 83% | 97% | 81% | 80% | 70% | 61% |

The figure shows a stepwise reproducible swelling change of the hydrogel at 25°C with alternating pH between 1.2 and 7.4. At pH 7.4, the hydrogel swells up to 158 g/g due to anion–anion repulsive electrostatic forces, while, at pH 1.2, it shrinks within a few minutes due to protonation of carboxylate groups. This sharp swelling-deswelling behavior of the hydrogels makes them suitable candidates for controlled drug delivery systems.

***In vitro* Cis-platin 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 Cis-platin form this system under physiological conditions. The percent of released drug from the polymeric carriers as a function of pH is shown in Table 1. The concentration of cis-platin released at selected pH intervals was determined by UV spectrophotometer. The cis-platin-loaded hydrogels with high degrees of drug loading (>80%) were prepared by the swelling-diffusion method. The amount of cis-platin 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.

At low pH values, electrostatic repulsion between the carboxylic acid groups of backbone is low, thus decreases gel swelling and minimizes release of cis-platin 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 cis-platin was increased[8,9].

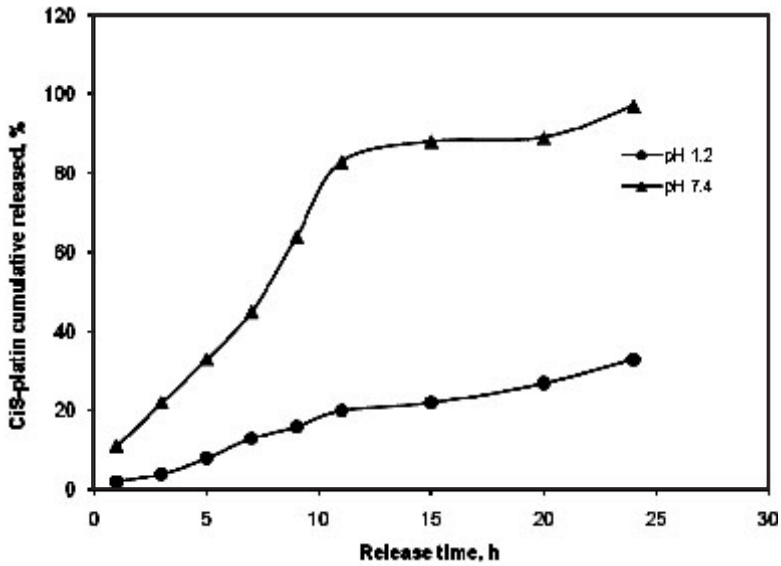



**Fig. 7: Release of Cis-platin from hydrogel carrier as a function of time and pH at 37°C**

The release rate experiments were also performed in SFG (pH 1.2) and SIF (pH 7.4) solutions at 37 $^{o}$C (Figure 7). As can be seen from Table 1, when pH of the medium is 1.2, the cumulative release ratio of cis-platin from the test hydrogels is below 35% at the end of the experiment (24 h), whereas almost 88% of the loaded drug is released within 15 h in pH 7.4 medium. Again, these results indicate that the higher swelling ratios of the hydrogel create larger surface areas to diffuse the drug. In basic solutions (pH 7.4), the electrostatic repulsion between $COO^-$ anions of grafted poly (sodium methacrylate) on the hydrogel accelerates the release of Cis-platin from the hydrogel.

## CONCLUSION

A novel biopolymer-based superabsorbent hydrogel, starch-*g*-poly(MAA-*co*-HEMA), was synthesized through simultaneous crosslinking and graft polymerization of methacrylic acid/2-hydroxy ethyl methacrylate mixtures onto starch. The superabsorbent hydrogels exhibited high sensitivity to pH, so that, several swelling changes of the hydrogel were observed in pH variations of a wide range (1-13). Ionic repulsion between charged groups incorporated in the gel matrix by an external pH modulation could be assumed as the main driving force responsible for such abrupt swelling changes. Furthermore, the reversible swelling-deswelling behavior in solutions with acidic and basic pH makes the hydrogels a suitable candidate for controlled drug delivery systems.

The release value of cis-platin from hydrogels at pH 7.4 was higher than that at pH 1.2 due to the electrostatic repulsion between carboxylate groups. Overall, the hydrogels presented in this study may serve as a platform for a wide range of pharmaceutical uses to improve the bioavailability of non-steroidal anti inflammatory drugs.

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