

Research Article

Development of a Gastroretentive Drug Delivery System based on Superporous Hydrogel

N Vishal Gupta* and HG Shivakumar

Dept. of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeswara Nagar, Mysore - 570 015, Karnataka, India.

Abstract

Purpose: The aim of this work was to synthesize superporous hydrogels of rosiglitazone using chitosan and to study its swelling behaviour for application as a gastroretentive drug delivery system.

Methods: Chitosan superporous hydrogels were synthesized using glyoxal as a crosslinking agent by gas blowing method. The effect of pH and ionic strength on the swelling ratio was determined. Swelling reversibility studies were also carried out. Fourier transform infrared (FTIR) analysis was undertaken to characterize the superporous hydrogels while dissolution studies were carried out to assess release characteristics.

Results: Swelling was highly dependent on the extent of crosslinking. The higher the amount of crosslinking agent, the lower the swelling ratio. Higher ionic strength in pH 1.2 solution led to a decrease in swelling ratio. The superporous hydrogels were highly sensitive to pH of swelling medium, and showed reversible swelling and de-swelling behaviour while still maintaining their mechanical stability. Apparent density was dependent on the volume of the superporous hydrogels and decreased with increasing crosslink density. Degradation kinetics showed that chitosan superporous hydrogels had good water retention capability. Drug release was inversely related to the amount of crosslinking agent and fitted best to the Korsmeyer-Peppas model.

Conclusion: The studies showed that chitosan-based superporous hydrogels can be used as a gastroretentive drug delivery system in view of their swelling characteristics in acidic pH.

Keywords: Gastroretentive, Porous hydrogels, Chitosan, Swelling, Rosiglitazone.

Received: 27 November 2009

Revised accepted: 27 April 2010

*Corresponding author: **E-mail:** vkguptajss@gmail.com; **Tel:** +91-821-2548353

INTRODUCTION

A problem frequently encountered with oral formulations is the inability to increase their residence time in the stomach and proximal portion of small intestine [1]. Retention of an oral formulation in the stomach prolongs the overall gastrointestinal (GI) transit time, thereby, resulting in an improved oral bioavailability of basic drugs that have poor solubility at higher pH, as well as drugs that are susceptible to circadian variations [2,3]. Under this condition, it becomes necessary to prolong the presence of the dosage form in the stomach or somewhere in the upper small intestine until all the drug is released over the desired period of time [4,5]. The retention of the dosage form in the stomach prolongs overall GI transit time, thus resulting in improved oral bioavailability of the drug.

Hydrogels are polymeric materials with open porous structures with the ability to take in large quantities of water and solutes. They have attracted much interest because of their potential to find different application. Biocompatible polymer hydrogels are being used in the biomedicine, agriculture, food-processing industry and immobilization of enzymes [6]. Stimuli-responsive hydrogels are one of the more promising types of polymeric materials. The water uptake of such hydrogels depends on environmental conditions (pH, ionic strength, temperature, and electrical or magnetic field). Superporous hydrogels are three-dimensional networks of hydrophilic polymers that contain many pores which are hundreds of micrometres in diameter [7]. Because these hydrogels absorb a large volume of environmental fluids, which expand their volume considerably over a very short time, their sheer bulk hinders their transport to the next organ via the narrow pylorus. This unique swelling property allows them to be used as gastric retention carriers, providing sustained release through long residence in the stomach [8].

Polyelectrolytes are ideally suited for the preparation of pH-sensitive hydrogels [9]. Chitosan is a polyelectrolyte and is obtained from renewable resources. It is a linear, semi-rigid polysaccharide and is biodegradable, biocompatible and of relatively low toxicity; it is a copolymer of N-acetyl D-glucosamine and D-glucosamine [10]. Because chitosan has abundant amine groups within its polymer chain, it dissolves in acidic solution and forms a gel with dialdehydes such as glutaraldehyde and glyoxal. In low pH solution, chitosan hydrogels swell due to the presence of positive charges in the network [11,12].

A gastric retention device is a type of drug delivery system designed to enhance drug release efficiency by prolonging drug retention in the stomach. Generally, drugs administered orally are not adequately absorbed in the stomach due to the pulsatory force of the latter in an acidic environment which easily breaks up carrier structures [13].

Rosiglitazone, an anti-diabetic agent, improves glycaemic control by improving insulin sensitivity. It is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR γ). In humans, PPAR receptors are found in key target tissues for insulin action such as adipose tissue, skeletal muscle and liver. Activation of PPAR γ nuclear receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, PPAR γ -responsive genes also participate in the regulation of fatty acid metabolism [14].

EXPERIMENTAL

Materials

Chitosan was procured from Vishu Aquatech, Madras. Glyoxal (40 % aqueous solution) was obtained from Aldrich. Sodium bicarbonate and acetic acid were purchased

from Loba Chemie, India. All other reagents used were of analytical grade.

Preparation of superporous hydrogels

To prepare chitosan stock solution, 2 g of chitosan was dissolved in 100 ml of 0.1M acetic acid. An amount of the stock solution (3 ml) was placed in a test tube, and then 10 % glyoxal aqueous solution (0.06, 0.12, 0.18 or 0.24 ml) was added to induce network structures. The pH of the solution was adjusted to 5 by adding 0.1M acetic acid. Sodium bicarbonate (50 mg) was added to the mixture and vigorously stirred for 10 to 30 s. Foaming ensued immediately after the addition of sodium bicarbonate and gelation was complete in 30 to 60 s. The foamed hydrogels were kept at room temperature overnight and then dried using a freeze dryer (LD 53, Millrock, USA) [15].

Drug loading

The drug selected for the study was rosiglitazone. The method of soaking or equilibration was employed for drug loading. In this method, the amount of buffer necessary for complete swelling of superporous hydrogel was first determined. Thereafter, 15 ml of the drug solution (0.13 %w/v in buffer) was prepared. The superporous hydrogel (100 mg) was placed in the drug solution and left until all the drug solution was sucked up. Finally, the completely swollen superporous hydrogel loaded with the drug was dried in an oven at 30 °C overnight.

Swelling studies

The dried superporous hydrogel (100 mg) was immersed in excess of the swelling medium (20 ml) at 37 °C. At various time intervals, the hydrogel was removed from the solution and weighed after excess solution on the surface was blotted. The experiment was performed in triplicate and the swelling ratio (Q) was calculated by Eq 1.

$$Q = (M_s - M_d) / M_d \dots\dots\dots (1)$$

where M_s and M_d are the weight of the hydrogel in the swollen and dried states, respectively. Five NaCl solutions (pH = 1.2) with different ionic strengths (0.0001 – 1M) were used to evaluate the effect of salt on the swelling properties of the hydrogels.

To study the pH sensitivity of the superporous hydrogels, HCl or NaOH solution with defined pH of 1.0 (ionic strength: 0.1M), 2.0 (ionic strength of 0.01M), 3.0 (ionic strength: 0.001M), 6.2 (ionic strength: 0.0001M) and 7.4 (ionic strength: 0.0001M) were used. The molar concentrations were adjusted with NaCl. Pulsatile pH-dependent swelling of the superporous hydrogels was evaluated at 37 °C with alteration of the swelling medium between the HCl solution (pH 1.2) and phosphate buffered solution (PBS, pH 7.4) every 30 min and weighing the hydrogel on each occasion [16].

Measurement of density of superporous hydrogel

The density (d) of the dried hydrogels was calculated by Eq 2.

$$d = W_d / V_d \dots\dots\dots (2)$$

where W_d is the weight of dried hydrogel and V_d is its volume. The volume of the hydrogel was determined by the solvent displacement method using hexane as the displacement fluid. Hexane was used because it is very hydrophobic and superporous hydrogels do not absorb it [17].

Determination of gelation kinetics

As gelation (polymerization reaction) proceeded, the viscosity of the mixture continuously increased until the full network (gel) structure was formed. Gelation time was defined as the duration of gel formation and was measured by a simple tilting method after adjustment of pH to 5.0 with acetic acid. This parameter was taken as the time taken

until the reactant mixture was no longer descending in the tilted tube position [18].

Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of the superporous hydrogels and chitosan were recorded over the range of 400 - 4000 cm^{-1} by KBr pellet method using FTIR spectrophotometer, (model FT-IR 8400S, Shimadzu, Japan).

Evaluation of degradation kinetics

The degradation kinetics of the hydrogels was examined by measuring the swelling ratio as a function of water retention. The hydrogels were placed in pH 1.2 (0.1 M HCl) medium at 37° C for 12 h, and the samples were periodically weighed at 6 h interval [18]. Water retention capacity (WR_t) as a function of time was assessed as in Eq 3.

$$WR_t = (W_p - W_d) / (W_s - W_d) \dots\dots\dots (3)$$

where W_d is the weight of the dried hydrogel, W_s the weight of the fully swollen hydrogel, and W_p the weight of the hydrogel at various exposure times.

In vitro release studies

In vitro drug release of rosiglitazone from the superporous hydrogels was evaluated in triplicate at $37 \pm 0.5^\circ \text{C}$ using a United States Pharmacopoeia (USP) Dissolution Test Apparatus Type 2 (paddle method) at a rotation speed of 50 rpm in 900 ml of 0.1M HCl (pH 1.2 buffer) for 6 h [14]. At regular time intervals, 10 ml sample of the dissolution medium were withdrawn, replaced with an equivalent volume of fresh dissolution fluid and analyzed for the drug using a UV-Vis spectrophotometer (UV-1700, Shimadzu, Japan) at 228 nm. The release data obtained were fitted into various release models. To determine release mechanism, the parameters n and k of the Korsmeyer-Peppas equation were computed.

Statistical analysis

Data were assessed for statistical significance by Student t-test at 95 % level of confidence using Microsoft Office Excel 2007.

RESULTS

Swelling properties

The effect of ionic strength on the swelling of the hydrogels is illustrated in Figure 1(a). It ranged between 11 and 156%. Maximum swelling was seen in the solution with an ionic strength of 0.0001 M and lowest at ionic strength of 1.0 M.

The results of pH sensitivity studies are shown in Figure 1(b). Maximum swelling (156 %) was seen in pH 1.2 medium and least in pH 7.4 buffer. Thus, swelling decreased with increase in pH.

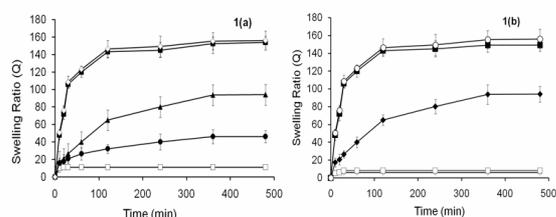


Figure 1: (1a) Effect of ionic strength of the swelling medium on the swelling properties of chitosan superporous hydrogel (formed with 4 % crosslinking agent) in pH 1.2 buffer solution. (**Key:** 1M (□); 0.1 M (●); 0.01 M (▲); 0.001 M (■); 0.0001 M (◇); (n = 3, error bar = standard deviation). **(1b)** Effect of pH of swelling medium on the swelling kinetics of chitosan superporous hydrogel (formed with 4 % crosslinking agent); (**Key:** pH 1.2 (○); 2.0 (■); 3.0 (◆); 6.2 (□); 7.4 (◇). (n = 3, error bar = standard deviation).

The results of the effect of pulsatile pH on swelling are shown in Figure 2. The superporous hydrogels swelled at a fast rate in pH 1.2 medium but contracted when transferred to pH 7.4 medium. Swelling

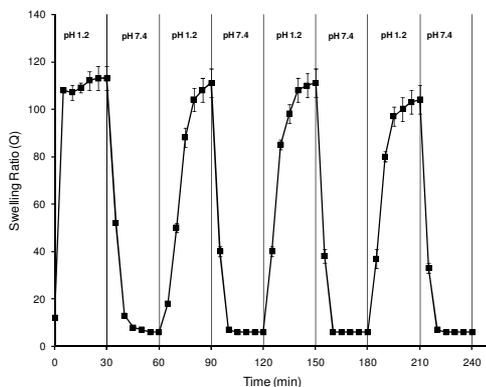


Figure 2: Pulsatile pH-dependent swelling behaviour of chitosan superporous hydrogel (formed with 4 % crosslinking agent) in alternating HCl (pH 1.2) and PBS (pH 7.4) media; (n = 3, error bar = standard deviation).

reversibility/contraction occurred repeatedly each time the medium was interchanged.

Density of the superporous hydrogels

The apparent density of the various superporous hydrogels was between 0.32 and 0.71 g/cm³. Density increased with increasing amount of crosslinking agent.

FTIR

The FTIR spectra of chitosan and superporous hydrogel are represented in Figure 3. Chitosan exhibited the main characteristic bands of carbonyl (C=O-NHR) and amine group (-NH₂) at 1653 cm⁻¹ and 1560 cm⁻¹, respectively. The broad band due to the stretching vibration of -NH₂ and -OH group was observed at 3400 – 3500 cm⁻¹. The bands at 1000 – 1200 cm⁻¹ are attributed to the saccharide structure of chitosan. The peak at 1381 cm⁻¹ represents the -C=O stretch of primary alcoholic group (CH₂-OH). These peaks, with minor shifts, are clearly seen in the IR spectra of superporous hydrogel indicating the presence of chitosan in the structure of the hydrogel. There was no interaction between the drug and chitosan in the hydrogel.

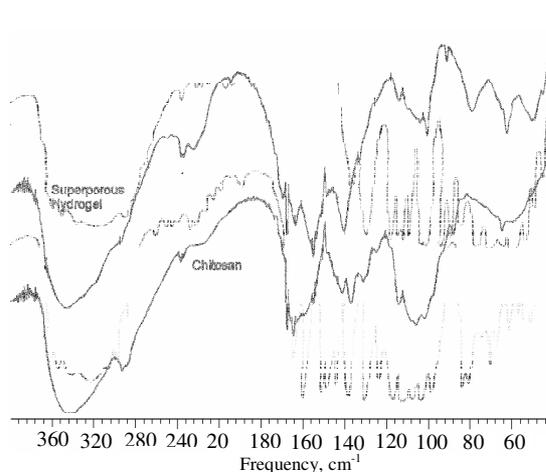


Figure 3: FTIR spectra of pure chitosan and superporous hydrogel.

Degradation kinetics

Figure 4 shows the degradation kinetics of superporous hydrogels after complete swelling in pH 1.2 buffer solution for 12 h. The hydrogels physically degraded by losing water, and water loss was a function of time, losing most of their water after 60 h. The lower the concentration of crosslinking agent in the hydrogel the faster and greater the water loss (p < 0.05).

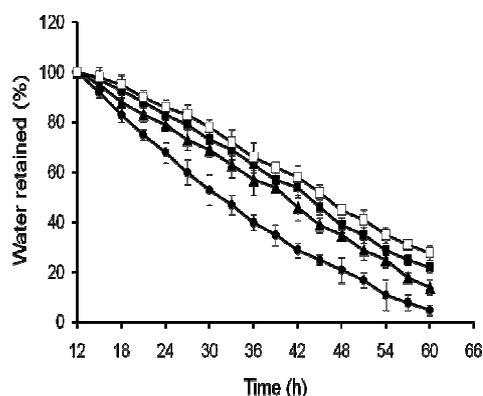


Figure 4: Water retention capacity of superporous hydrogels with 2 % (●), 4 % (▲), 6 % (■) and 8 % (□) crosslinking agent (n = 3, error bar = standard deviation). **Note:** Water retention (WR_t), expressed as a percentage of water retained in the polymer at any time, t, is a measure of hydrogel stability.

In vitro release studies

The drug release profiles of the hydrogels are shown in Figure 5. Drug release was inversely related to the amount of crosslinking agent used. The best-fit model was Korsmeyer-Peppas.

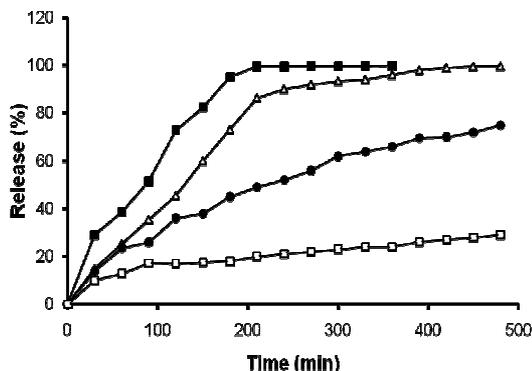


Figure 5: *In vitro* release of rosiglitazone from superporous hydrogels prepared with 2 % (■), 4 % (Δ), 6 % (●) and 8 % (□) crosslinking agent (n = 3, error bar = standard deviation)

DISCUSSION

In the synthesis of superporous hydrogels, chitosan was the monomer. while glyoxal and sodium bicarbonate were used as crosslinking and blowing agents, respectively. The amount of cross-linking agent influences the swelling ratio of the polymer because as its concentration increases, polymer chains attach to each other more strongly and the size of pores during foam formation is smaller. Furthermore, chain flexibility decreases, resulting in reduced swelling capacity of the polymer.

In acidic environment, chitosan superporous hydrogels showed a higher swelling ratio than in basic environment probably because the amine groups in the chitosan molecules were ionized to ammonium ion (NH_3^+) in acidic aqueous media and these cationic charges in gel phase act as cationic repulsive forces between polymer molecules. The superporous hydrogels crosslinked with low

concentrations of glyoxal were mechanically so weak that the samples cracked during the swelling process. For this reason, only concentrations of crosslinking agent higher than 2 % were suitable for hydrogel formation. When crosslinking concentration exceeded 2 %, the swelling ratio of the superporous hydrogels decreased with increased crosslinking density, as much tighter networks were formed at higher concentration of crosslinking agent.

When ionic strength was lesser than 0.001 M, the swelling behaviour of the hydrogels was not affected. The sensitivity of hydrogel swelling to ionic strength may be attributed to change in charge distribution on the surface of the gel network. As the concentration of cations in the swelling medium increases, a stronger “charge screening effect” of the additional cations is achieved, causing imperfect anion-anion electrostatic repulsion and a decreased osmotic pressure difference between the polymer network and the external solution. The structure of the polymers with large numbers of pores connected to one another to form capillary channels was favourable for easy diffusion of the swelling medium into the polymeric matrix, thus contributing to its quick response toward pH change. The time for swelling was longer than that for de-swelling of the hydrogels. This may be due to the restricted chain mobility of crosslinked chitosan [20,21]. Since the hydrogels are very porous, the measured density is related to the porosity of the polymer and can be defined as apparent density. The actual density of the polymer is the same but when the polymer has fewer pores, the occupied volume will be less, thus resulting in high apparent density. Therefore, the higher the concentration of the crosslinking agent, the greater is the apparent density. The results, in this respect, correlate with swelling ratio data.

In order to produce large and uniform pores, the blowing agent must be introduced when the reactant system has appropriate viscosity. Bubbles cannot maintain their

shape up to the completion of the reaction when blowing agent is introduced too early, and cannot be formed if introduced too late. Gelation kinetics gives good information that aids in determining the most suitable time to introduce the blowing agent. Foaming and gelation reactions should take place simultaneously in order to obtain well-established porous structures [22]. The gelation reaction took place only at pH higher than 6, and the fastest reaction was observed at pH 7. The gelation time should be very short or else bubbles would collapse leading to formation of non-porous hydrogels. On the other hand, foaming reaction took place only at acidic conditions. As sodium bicarbonate is decomposed to release CO₂ gas in acidic conditions and this decomposition reaction neutralizes the medium (increases the pH), the addition of a certain amount of sodium bicarbonate eventually induced gelation reactions at medium pH [22].

The interconnected pores allowed the polymer to hold more water by capillary force and the hydrogel structure which appears as a net-like distribution brought about decreased polymer rigidity, thus improving the resilience of the polymer in response to compression and effectively preventing water loss. The lower the concentration of the crosslinking agent, the faster was the loss of water from the superporous hydrogel.

At high crosslink density, the openings (pores) of the hydrogel are less in size and number, and hence drug release is also lower. Since the value of *n*, the time exponent calculated from the Korsmeyer-Peppas equation, was found to be greater than 1 in all the drug release profiles, the release mechanism is assumed to be super case-II transport, wherein multiple release mechanisms exist.

CONCLUSION

Suitable chitosan superporous hydrogels, which swelled and de-swelled reversibly depending on the pH of media, were

successfully formulated. Swelling of the hydrogels was affected by ionic strength. This study also demonstrates that superporous hydrogels of chitosan may be suitable for use as a gastroretentive drug delivery system.

ACKNOWLEDGEMENT

The authors wish to thank JSS Mahavidyaapeetha, Mysore, and JSS University, Mysore, India for their valuable support for this research.

REFERENCES

1. El-Gibaly I. Development and in vitro evaluation of novel floating chitosan microcapsules for oral use: Comparison with non-floating chitosan microspheres. *Int J Pharm* 2002; 249: 7-21.
2. Sun Y, Peng Y, Chen Y, Shukla AJ. Application of artificial neural networks in the design of controlled release drug delivery systems. *Adv Drug Deliv Rev* 2003; 55: 1201–1215.
3. Risbud MV, Hardikar AA, Bhat SV, Bhonde RR. pH-sensitive freeze-dried chitosan-polyvinyl pyrrolidone hydrogels as controlled release system for antibiotic delivery. *J Control Release* 2000; 68: 23-30.
4. Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. *Adv Drug Delivery Rev* 2001; 53: 321–339.
5. Karadag E, Uzum OB, Saraydin D. Swelling equilibria and dye absorption studies of chemically crosslinked superabsorbent acrylamide/maleic acid hydrogels. *Eur Polym J* 2002; 38: 2133-2141.
6. Allan SH. Hydrogels for biomedical applications. *Adv Drug Deliver Rev* 2002; 43: 3-12.
7. Chen J, Park H, Park K. Synthesis of superporous hydrogels: Hydrogels with fast swelling and superabsorbent properties. *J Biomed Mater Res* 1999; 44: 53–62.
8. Klausner EA, Lavy E, Friedman M, Hoffman A. Expandable gastroretentive dosage forms. *J Control Release* 2003; 90: 143-162.
9. Chen L, Tian Z, Du Y. Synthesis and pH sensitivity of carboxymethyl chitosan-based polyampholyte hydrogels for protein carrier matrices. *Biomaterials* 2004; 25: 3725-3732.
10. Wenming X, Peixin X, Wei W, Qing L. Preparation and antibacterial activity of a water soluble chitosan derivative. *Carbohydrate Polym* 2002; 50: 35-40.
11. Mi FL, Kuan CY, Shyu SS, Lee ST, Chang SF. The study of gelation kinetics and chain-relaxation properties of glutaraldehyde-cross-linked chitosan gel and their effects on microspheres

- preparation and drug release. *Carbohydrate Polym* 2000; 41: 389-396.
12. Lee M, Clire GW, Fariba K, Laureuce T, Alexander IG, Sevda S, Ijeoma FU. The release of model macromolecules may be controlled by the hydrophobicity of palmitoyl glycol chitosan hydrogels. *J Control Release* 2002; 80: 87-100.
 13. Chen J, Blevins WE, Park H, Park K. Gastric retention properties of superporous hydrogel composites. *J Control Release* 2000; 64: 39-51.
 14. Shiva SK, Subhabrata Ray, Thakur RS. Formulation and evaluation of mucoadhesive dosage form containing rosiglitazone maleate. *Pak J Pharm Sci* 2006; 19(3): 208-213.
 15. Dorkoosh FA, Brussee J, Verhoef JC, Borchard G, Rafiee-Tehrani M, Junginger HE. Preparation and NMR characterization of superporous hydrogels (SPH) and SPH composites. *Polymer* 2000; 41: 8213-8220.
 16. Gemeinhart RA, Chen J, Park H, Park K. pH-sensitivity of fast responsive superporous hydrogels. *J Biomater Sci Polymer Edn* 2000; 11: 1371-1380.
 17. Assadang P, Verhoef JC, Borchard G, Sarisuta N, Hans EJ. In vitro evaluation of intestinal absorption of desmopressin using drug-delivery systems based on superporous hydrogels. *Int J Pharm* 2004; 269: 303-310.
 18. Farid AD, Verhoef JC, Borchard G, Rafiee-Tehrani M, Hans EJ. Development and characterization of a novel peroral peptide drug delivery system. *J Control Release* 2001; 71: 307-318.
 19. Zhang JP, Lil A, Wang AQ. Study on superabsorbent composite. V. Synthesis, swelling behaviors and application of poly(acrylic acid-co-acrylamide)/sodium humate/attapulgite superabsorbent composite. *Polym Adv Technol* 2005; 16: 813-820.
 20. Yin L, Fei L, Cui F, Tang C, Yin C. Superporous hydrogels containing poly(acrylic acid-co-acrylamide)/O-carboxymethyl chitosan interpenetrating polymer networks. *Biomaterials* 2007; 28: 1258-1266.
 21. Abd El-Rehim HA, Hegazy EA, Abd El-Mohdy HL. Effect of various environmental conditions on the swelling property of PAAm/PAAcK superabsorbent hydrogel prepared by ionizing radiation. *J Appl Polym Sci* 2006; 101: 3955-3962.
 22. Tang C, Yin L, Pei Y, Zhang M, Wu L. New superporous hydrogels composites based on aqueous carbopol solution (SPHCcs): synthesis, characterization and in vitro bioadhesive force studies. *Eur Polym J* 2005; 41: 557-562.