

INTERPENETRATING NETWORK SUPERPOROUS HYDROGELS FOR GASTRORETENTIVE APPLICATION-PREPARATION, SWELLING AND MECHANICAL PROPERTIES

Naresh Vishal GUPTA*, Hosakote Gurumallappa SHIVAKUMAR

JSS University, JSS College of Pharmacy, Department of Pharmaceutics,
Sri Shivarathreeshwara Nagar, Mysore - 570 015, Karnataka, INDIA

Abstract

Chitosan/poly(vinyl alcohol) interpenetrating polymer network type (IPN) superporous hydrogels were prepared using a gas foaming/freeze-drying method. A gas blowing method using bicarbonate as a foaming agent was applied to introduce the porous structure. Gelation kinetics was measured to determine the optimum introduction time for adding the blowing agent. Their swelling behaviors in acidic solution were studied to investigate their application as gastric retention device. The effect of the strengthener, poly(vinyl alcohol) (PVA), on the swelling and mechanical behavior of the superporous hydrogels was investigated. The introduction of a small amount of PVA significantly enhanced the mechanical strength but reduced the swelling capacity. The number of freezing/thawing (F/T) process had a significant effect on the physical properties of the chitosan/PVA superporous hydrogels, because of the formation of hydrogen bonds between the PVA molecules as a result of the number of F/T cycles. Swelling behaviors were significantly affected by crosslinking density. The increase in mechanical strength accompanied by the decrease in swelling kinetics was caused by the generation of smaller pores during the gelation process of the reactant systems associated with a higher solution viscosity. The prepared superporous hydrogels were highly sensitive to pH of swelling media and swelled only in acidic pH. Hence these superporous hydrogels could be used for gastric retention application.

Key words: Chitosan, PVA, Swelling, Superporous, Hydrogels, Gastric retention.

Midede Kalış Süresini Artırma Uygulaması İçin Birbiri İçine Geçişimli (İnterpenetre) Ağ Yapısında Süperporöz Hidrojeller: Hazırlanma, Şişme ve Mekanik Özellikleri

Kitozan/poli(vinil alkol) interpenetre polimerik (IPN) ağ tipi yüksek poroziteye sahip (süperporöz) hidrojeller, bir gaz köpük oluşturma/ dondurarak kurutma yöntemi kullanılarak hazırlanmıştır. Poröz yapıyı oluşturmak üzere köpük oluşturuucu madde olarak bikarbonatın kullanıldığı bir gaz oluşturma yöntemi uygulanmıştır. Gaz oluşturuucu maddenin ilave edilmesinde en uygun zamanı tayin etmek için jelleştirme kinetikleri ölçülmüştür. Midede kalacak bir sistem olarak uygulanmaları araştırıldığı için asidik çözelti içinde şişme davranışları çalışılmıştır. Süperporöz hidrojellerin şişme ve mekanik davranışı üzerine dayanıklılık verici poli(vinil alkol)'ün (PVA) etkisi araştırılmıştır. PVA'nun düşük miktarda ilave edilmesi, mekanik direnci önemli derecede artırırken şişme kapasitesini azaltmıştır. Dondurma/eritme (F/T) döngülerinin sayısının bir sonucu olarak PVA molekülleri arasında hidrojen bağlarının oluşumu nedeniyle F/T işleminin sayısı, kitozan/PVA süperporöz hidrojellerinin fiziksel özellikleri üzerinde önemli derecede etki göstermiştir. Şişme davranışları, çapraz bağ yoğunluğu ile önemli derecede etkilenmiştir. Şişme kinetiklerindeki azalma ile birlikte gerçekleşen mekanik dirençteki artış, daha yüksek bir çözelti viskozluğu ile ilişkili olarak reaksiyona giren madde jelleşme işlemi esnasında, daha küçük porların oluşumundan kaynaklanmıştır. Hazırlanan süperporöz hidrojeller, şişme ortamlarının pH'sına çok fazla duyarlıdır ve sadece asidik pH'da şişme göstermişlerdir. Bundan dolayı süperporöz hidrojeller, midede kalış süresini artırma uygulaması için kullanılabilir.

Anahtar kelimeler: Kitozan, PVA, Şişme, Süperporöz, Hidrojeller, Midede tutulma.

*Correspondence: E-mail: vkguptajss@gmail.com, Tel: +91-9242157508

INTRODUCTION

A number of controlled drug delivery systems have been developed for prolonging and controlling the release of drugs for a period of times for efficient medical treatment (1-4). The drugs for oral delivery have its own convenience in easy and economic administration, but the weakness is the loss of their functions due to the short residence in the body. About 80% of drugs administrated are reported to be wasted before it can perform its full function (5, 6). Many attempts have been proposed to prolong the residence time of drugs in the body for complete absorption, but not many systems have been successfully applied in practice.

Superporous hydrogels were recently developed for their potential applications in controlled drug delivery, especially for developing oral gastric retention devices. A superporous hydrogel is a three-dimensional network of a hydrophilic polymer that absorbs a large amount of water in a very short period of time due to the presence of interconnected microscopic pores. Gastric retention of superporous hydrogels is based on the fast swelling of dried hydrogels to a size larger than the pyloric sphincter. When applied as drug carriers, these highly swollen hydrogels remain in stomach for a long time, releasing almost all drugs loaded, as their volumes are too big to transport through the pylorus (7-11). Chitosan, a natural polysaccharide, is a biocompatible, biodegradable, and nontoxic material. Because of abundant amine groups within chitosan polymer chain, it dissolves in acidic solution and forms a gel with dialdehydes such as glutaraldehyde and glyoxal. Thus, in the low pH solution, chitosan hydrogels swell due to the presence of the positive charges in the network (12). Poly(vinyl alcohol) is a well known hydrophilic, biocompatible, and commercially available polymer.

The objective of the study was to prepare chitosan/PVA superporous hydrogel and study its gastric retention properties. In this study, the interpenetrating polymer network of chitosan/PVA superporous hydrogel was prepared using a freeze drying/gas blowing technique. It was prepared using glyoxal as a crosslinking agent. The applications of the superporous hydrogels prepared as gastric retention devices were investigated by measuring their swelling and mechanical properties.

EXPERIMENTAL

Materials

Chitosan was purchased from Fluka (St. Gallen, Switzerland). Sodium bicarbonate (Loba Chemie, Mumbai), Glyoxal (40% water solution, Aldrich, Steinheim, Germany) and PVA (Mol. wt. 89,000-98,000) (Sigma, Steinheim, Germany) were procured from commercial sources. All other reagents used were of analytical grade.

Synthesis of superporous hydrogels

A 3 % w/w stock solution was prepared by dissolving chitosan in 0.1 M acetic acid. A 10 % w/w aqueous PVA solution was also prepared. The chitosan and PVA solutions were mixed together to have different compositions. Each chitosan/PVA mixture was placed in a test tube (inner diameter of 16 mm and height of 100 mm) and its pH value was adjusted to 5.0 by adding acetic acid. A glyoxal aqueous solution, 10 % w/w, was added to each chitosan/PVA mixture. 80 mg of sodium bicarbonate powder was added to the stock solution, and the mixture was stirred vigorously to induce the gelation and foaming reactions, simultaneously. The foamed hydrogels were left to stand overnight at room temperature. The hydrogels were frozen in a deep freeze-drier at -60°C for 12 h. After freeze-drying, the samples were removed from the freeze-drier and thawed to room temperature over a 4 h period. This freezing/thawing cycle was repeated up to 6 times. Seven formulations were prepared by changing the amount of the ingredients as shown in Table 1 (13).

Measurement of gelation kinetics

As the polymerization reaction proceeded, the viscosity continuously increased until the full network structure (gel structure) was formed. The gelation time (sol gel transition time) was defined as the duration time for gel formation after addition of glyoxal and pH adjustment. It was measured by a simple tilting method after adjustment of pH to 5.0. It was determined by the duration time until the reactant mixture was no longer descending in the tilted tube position. To measure this, the reaction

mixture was taken in a long cylindrical glass tube, tilted slightly downwards. The gelation time was determined by the measurement of time when the reaction mixture was no longer descending in the tilted tube as its movement was stopped as the mixture had become extremely viscous and converted into gel after the adjustment of pH. The time taken for conversion of solution to thick gel is the sol gel transition time.

Table 1. Formulations of chitosan-PVA superporous hydrogels.

Ingredients	I	II	III	IV	V	VI	VII
Chitosan (% w/w)	4	4	4	4	4	4	4
Poly Vinyl Alcohol (% w/w)	2	4	6	8	4	4	4
Glyoxal (% w/w)	4	4	4	4	2	6	8
Sodium Bicarbonate (mg)	80	80	80	80	80	80	80

Swelling studies

A completely dry, pre-weighed, disc-shaped superporous hydrogel was weighed and then immersed in excess of swelling medium. At various time intervals, the hydrogel was removed from the solution and weighed after excessive solution on the surface was blotted. Data presented in this experiment were the mean values of triplicate measurements. Results were calculated according to the following equation:

$$Q = (M_s - M_d) / M_d$$

where Q is the swelling ratio, M_s the mass in the swollen state and M_d the mass in the dried state (14). To study the pH sensitivity of the superporous hydrogels, HCl or NaOH solutions with defined pH of 1.0, 2.0, 3.0, 4.9, 6.2 and 7.4 were used as the swelling media.

Density measurement of the superporous hydrogels

Pieces of superporous hydrogels were taken and weighed in order to determine the mass of each piece. For measuring their volumes, the solvent replacement method was used. By this method the solvent penetrates into the pores of the superporous hydrogel; therefore, the volume can be related to the porosity of the superporous hydrogel, which results in the apparent density instead of actual density of the superporous hydrogel. For this purpose, a hydrophobic solvent such as hexane was used. By the use of forceps, a piece of the superporous hydrogel was immersed in a predetermined volume of hexane in a graduated cylinder, and the increase in the hexane volume was measured as the volume of the superporous hydrogel (15).

Viscosity measurements

The viscosity of the polymer solution (chitosan/PVA mixture) was measured using a Brookfield viscometer (LV DV-II+ Pro, Brookfield, MA). The Brookfield Viscometer measures viscosity by measuring the force required to rotate a spindle in a fluid. The samples were placed in the sample holder and the spindle was rotated. The temperature was maintained at $25 \pm 0.5^\circ\text{C}$. The viscosity was determined directly from the reading given by the viscometer and average of three measurements was taken.

Mechanical Properties

The compressive strengths of various superporous hydrogel formulations were determined using a bench comparator (Ames, Waltham, MA, USA). Briefly, after the fully swollen hydrogel was put longitudinally under the lower touch of a bench comparator, different scale loads were successively

applied on the upper touch until a point was reached when the hydrogel could not support any more weight and completely fractured.

The pressure at that point was defined as penetration pressure (PP) and could be calculated based on the following equation:

$$PP = F_u/S$$

where F_u is the ultimate compressive force at complete breakage of polymer and S is the contact area of the lower touch (16).

FT-IR spectroscopy

FT-IR spectroscopy used to investigate the chemical structure of the synthesized hydrogels. The FTIR spectrum was recorded over the range of 400 - 4000 cm^{-1} by KBr pellet method using Fourier-Transform Infrared (FT-IR) spectrophotometer, (Shimadzu, FT-IR 8400S, Japan).

Differential scanning calorimetry (DSC)

Differential scanning calorimetry was performed on the formulations using DSC-Q200 (TA instruments) apparatus. DSC thermograms were recorded at a heating rate of 5 $^{\circ}$ /min in an open aluminum pan.

Scanning electron microscopy

The dried superporous hydrogels were used for scanning electron microscopy (SEM) studies. Scanning electron microscopy was used to determine the morphology of the dried samples. A JEOL JSM-840 scanning electron microscope (Jeol USA, Inc., Peabody, MA) was used after coating the samples with gold using a Hummer Sputter Coater (Technics, Ltd.). Images were captured using a digital capture card and Digital Scan Generator 1 (JEOL).

RESULTS AND DISCUSSION

Synthesis of superporous hydrogels

In the above procedure, chitosan and PVA are the polymers used. Glyoxal was used as crosslinking agent. Sodium bicarbonate was used as a porogen or foam generator. Chitosan is crosslinked by glyoxal by condensation reaction (Schiff base reaction). PVA is crosslinked by physical method employing freezing/thawing. Interpenetrating polymer network is formed when both chitosan and PVA are crosslinked. PVA was crosslinked by physical method employing freezing/thawing. The freezing and thawing cycle led to the crosslinking of PVA by formation of physical cross-linking (i.e. weak bonding through a nonpermanent "association" of the polymer chains). Physical crosslinking that occurs during the freeze-thaw cycle was due to direct hydrogen bonding, direct crystallite formation and liquid-liquid phase separation followed by a gelation mechanism.

Gelation kinetics

The rate of gelation is very important to determine the time to introduce a blowing agent. Too early introduction of a blowing agent during gelation results in formation of foams that may not last long enough until the completion of the gelation process. Introducing a blowing agent too late may not even generate foam due to completion of the cross-linking reaction. The gelation kinetics gives good information determining the introduction time of blowing agent (sodium bicarbonate). For making homogeneous superporous hydrogels, the timing of foam formation and polymerization processes was very important. Foaming and gelation reactions should take place simultaneously to obtain well-established porous structures. The gelation reaction took place only at the pHs higher than 6, and the fastest reaction was observed at pH 7. When gelation times are not short enough, bubbles are not stabilized during gelation reaction. On the other hand, the foaming reaction took place only at the acidic conditions (pH lower than 6). As NaHCO_3 is decomposed to release CO_2 gas in acidic conditions and this decomposition reaction neutralizes the medium (increases the pH), the addition of certain amount of NaHCO_3 eventually induced the gelation reactions at medium pH. Therefore, the

gelation process and foam formation are of significant importance for making superporous hydrogels. The gelation kinetics provided valuable information to determine the proper time to introduce a gas blowing agent into the reaction mixture. The optimal pH for the gelation was around 7–8. At this pH, the polymerization proceeds rapidly and the gelling usually started within 0.5-1.0 min. The Sol-gel transition time for various formulations as shown in Figure 1 was between 20-26 seconds. This clearly indicated that the blowing agent must be introduced immediately after the adjustment of pH to 5.0 (17).

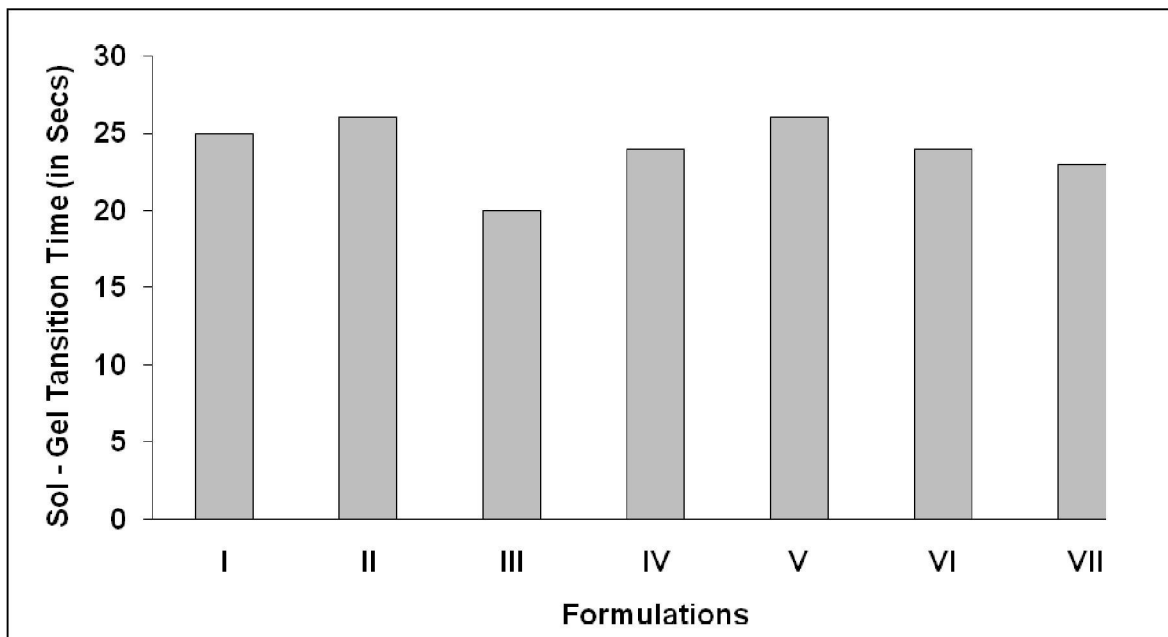


Figure 1. Sol-gel transition time during the synthesis of superporous hydrogels after pH was adjusted to 5.0.

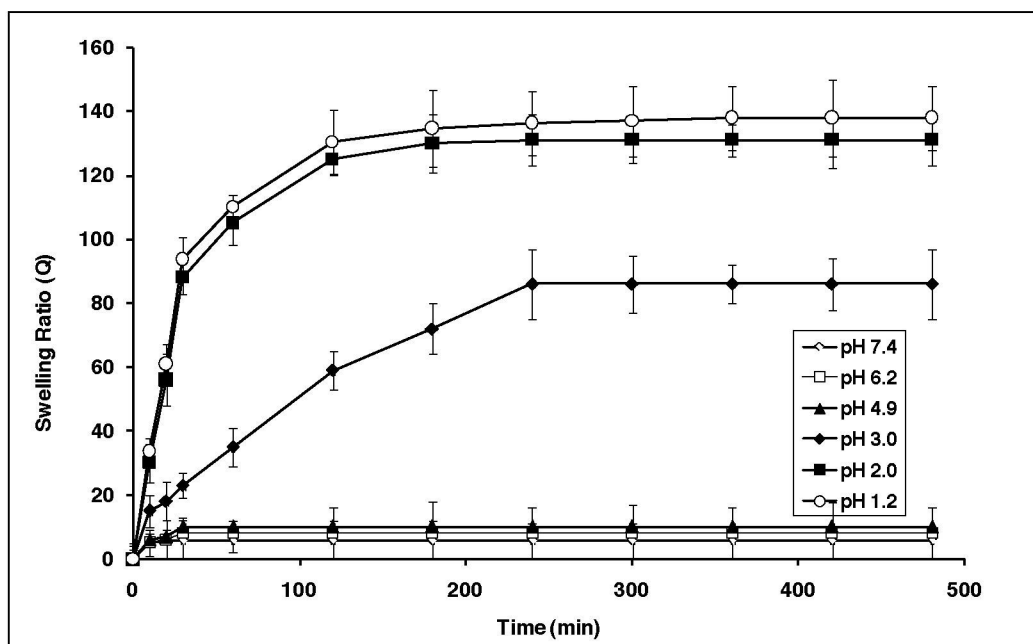


Figure 2. Effect of the pH of swelling medium on the swelling kinetics of the superporous hydrogel formulation V (n = 3, mean ± standard deviation).

Effect of the pH on the swelling capacity

Figure 2 shows the dynamic uptake of water of formulation V in the solutions with pH 1.2, 2.0, 3.0, 4.9, 6.2, and 7.4. Swelling of the superporous hydrogels reduced as the pH increased. In acidic environment, chitosan superporous hydrogels showed higher swelling ratio than in basic environment. It was because the amine groups in the chitosan molecules are 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. Moreover, the ionization also caused an increase in ion osmotic pressure. These two factors and the capillary wetting of interconnected open pores of superporous hydrogel were thus responsible for a higher degree of swelling in the acidic pH. At higher pH values protonation of the amine groups lead to decreased swelling ratios.

Effect of crosslinking density and PVA on swelling capacity

The swelling ratios of all the formulations in pH 1.2 HCl buffer solution is represented in Figure 3. The swelling ratio of the prepared formulations in pH 1.2 HCl buffer solution was found to increase with time. The swelling ratios of superporous hydrogels decreased with increasing crosslinking density, as much tighter networks were formed at higher concentration of crosslinking agents. The amount of crosslinking agent influenced 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. As the concentration of PVA increased, there was a decrease in the swelling ratio. This was due to high viscosity during gelation leading to smaller pores. Furthermore, chain flexibility decreases, resulting in reduced swelling capacity of the polymer (18).

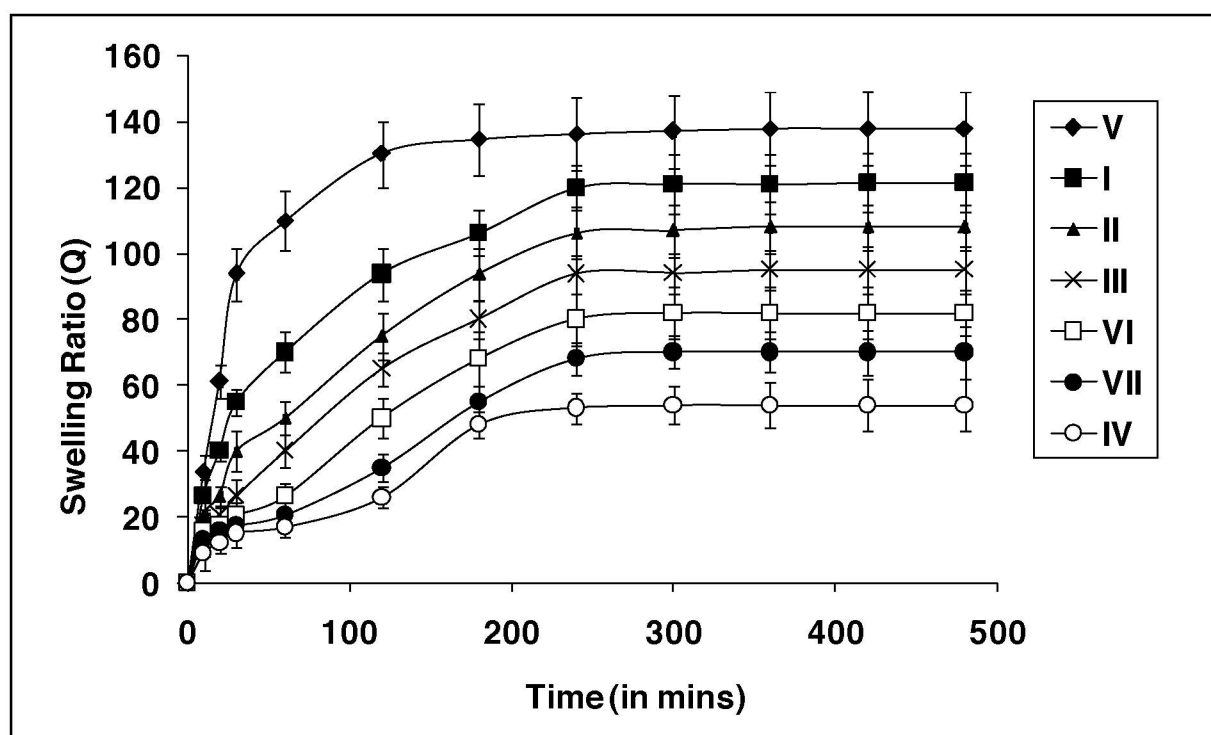


Figure 3. Swelling studies of superporous hydrogel formulations in pH 1.2 buffer solution ($n=3$, mean \pm standard deviation).

Effect of freezing/thawing repetition number

The physical properties of PVA are considerably affected by the repetitive process of freezing/thawing because the gelation of PVA molecules occurs via the development of hydrogen

bonds. In this study, the effect of the number of F/T cycles on the dynamic and equilibrium swelling behaviors were examined. Figure 4 shows the equilibrium swelling ratio of the superporous hydrogels as a function of the number of F/T cycles. The swelling ratios decreased with increase in the number of F/T cycles. The increases in the crystallinity and entanglement were the main reasons for the decreased swelling ratio as a result of the increase in the number of F/T repetitions (13).

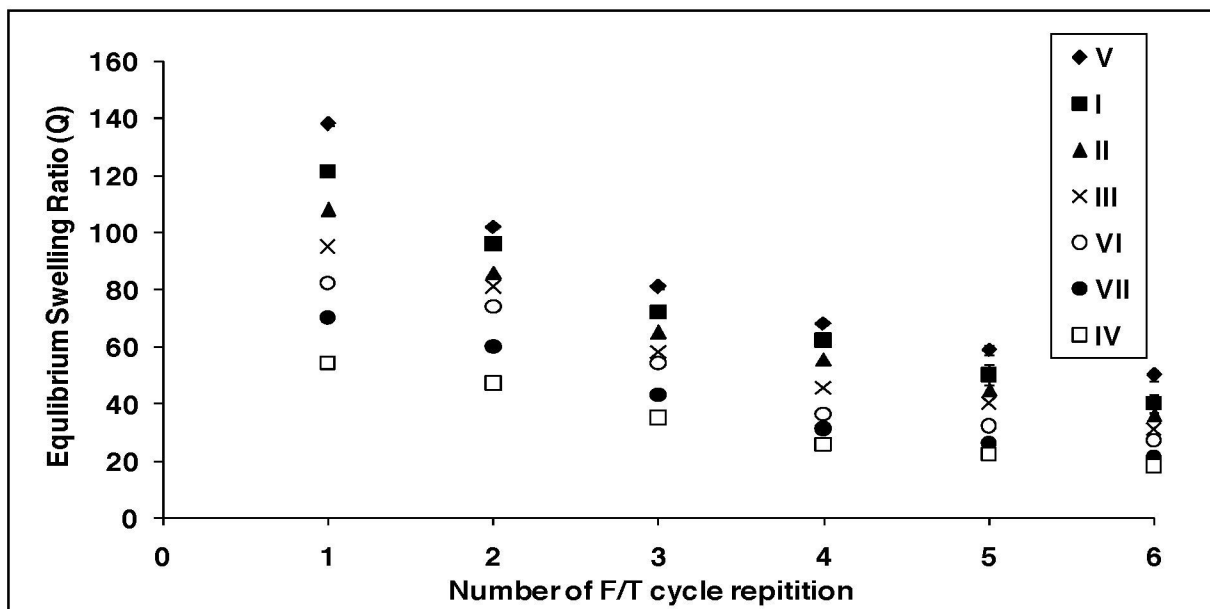


Figure 4. Equilibrium swelling ratios of various formulations as a function of the number of F/T cycles.

Density measurement of SPH and SPHC

Since the superporous hydrogels are very porous, the measured density is related to the porosity of superporous hydrogels and can be defined as apparent density. The apparent densities of the formulations are shown in Table 2. These results are in accordance with the swelling ratio studies. The apparent density of the formulations increased with an increase in amount of PVA due to the presence of the cellulosic fibres within the polymer structure. The density of superporous hydrogels increased with the increase in amount of glyoxal. This is due to the incorporation of the higher crosslink density within the polymer structure leading to the decrease in the occupied volume (19).

Table 2. Density, penetration pressures and viscosity of superporous hydrogel formulations (n = 3, mean ± standard deviation).

Formulations	Apparent Density(g/cm ³)	Penetration pressure (g/cm ²)	Viscosity (cP)
I	0.48 ± 0.037	68 ± 5	31.8 ± 2.1
II	0.54 ± 0.018	82 ± 8	52.6 ± 2.2
III	0.61 ± 0.032	108 ± 9	98.5 ± 3.6
IV	0.82 ± 0.025	205 ± 10	201.2 ± 5.1
V	0.43 ± 0.036	56 ± 4	20.5 ± 1.6
VI	0.71 ± 0.056	138 ± 13	131.3 ± 4.1
VII	0.76 ± 0.029	156 ± 15	182.3 ± 4.2

Effect of viscosity of polymer solution

The time to reach the equilibrium uptake was quite different for different formulations. This difference in the time to reach equilibrium was caused by the difference in pore size and the entanglement degree associated with the polymer and PVA solution viscosity. At high viscosity, the evolution of CO₂ gas bubbles was not as easily detectable as that at a low viscosity, leading to smaller pore sizes and slower swelling. Table 2 shows the viscosities of various formulations.

Mechanical Properties

Appropriate mechanical strength should be provided to superporous hydrogels in order for their effective application. Table 2 shows the penetration pressures of the formulations. The results indicate that increase in amount of crosslinking agent increased the penetration pressure values thus increasing the mechanical stability. The presence of PVA increased the overall cross-linking density of the superporous hydrogels by the polymer chains with PVA fibers. This entanglement significantly improved the structural integrity of the hydrogel and decreased stress relaxation, which helped enhance its ability to withstand pressure (20, 21).

Chemical identification

The chemical structure of the synthesized superporous hydrogel was identified by FTIR. The amino peak of the chitosan was observed at 1402 cm⁻¹, as shown in Figure 5. The imine bond (C=N) produced from the crosslinking between the chitosan amino group and the glyoxal aldehyde group via a Schiff base reaction was observed at 1572 cm⁻¹ (22).

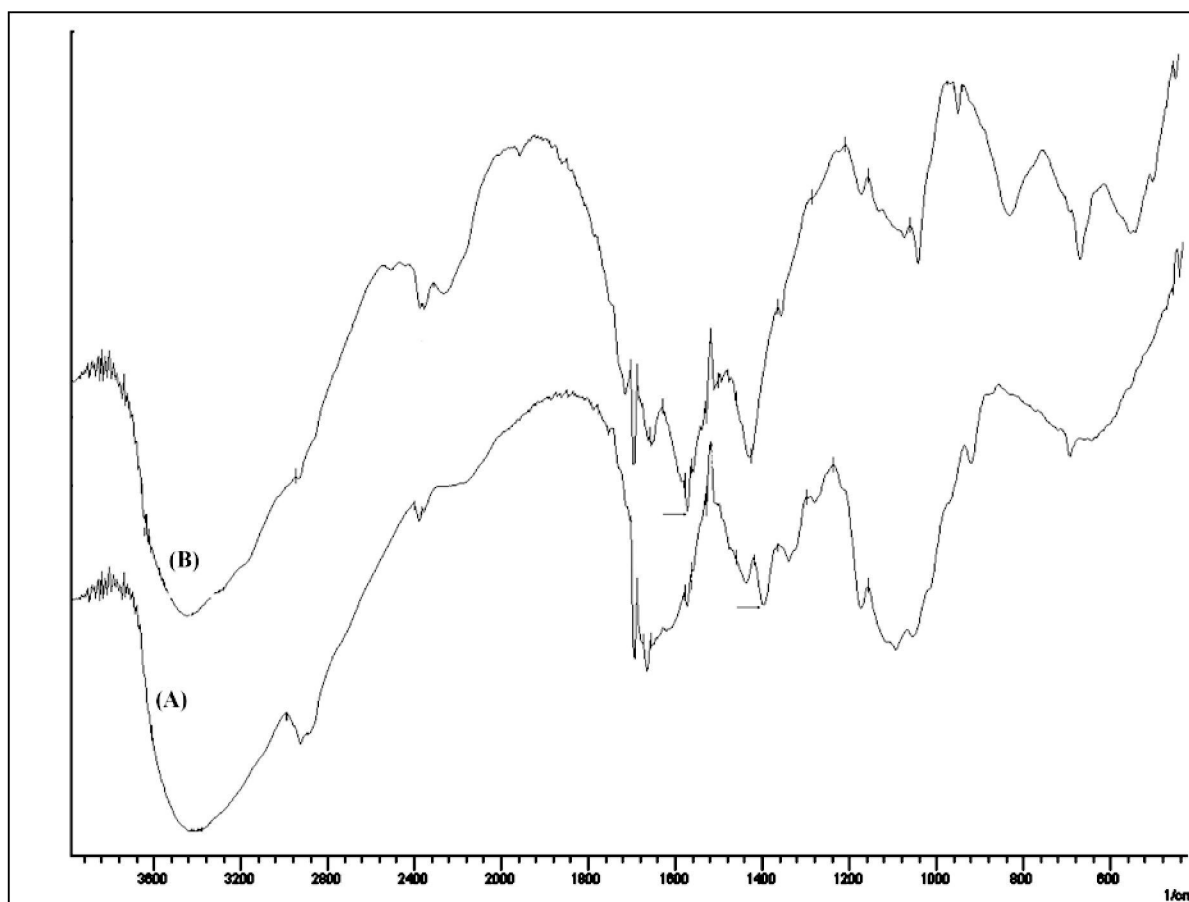


Figure 5. FTIR spectra of chitosan (A) before and (B) after gelation (crosslinking).

Differential scanning calorimetry

The gastroretentive formulations V, VI and VII were subjected DSC studies. Figure 6 shows the thermal transition behaviors of the gastroretentive formulations as a function of varying amounts of crosslinking agent. The thermal behaviors of these superporous hydrogels were investigated using DSC because the increase in the mechanical strength was presumably due to increased crosslinking density. If a polymer is mechanically strong higher energy would be required to melt or induce rubbery state in a polymer. Hence the glass transition temperature and melting point of the polymers would give an idea about its mechanical strength. In our mechanical strength studies, we found that an increase in the amount of glyoxal (crosslinker) increased the mechanical strength. From the figure 6, it is clear that there is a shift in the glass transition temperature to a higher temperature with increase in the amount of glyoxal. An increase in the amount of crosslinker led to the development of a tighter and rigid network in the superporous hydrogel structure. There were no freely mobile polymeric chains as most of them would have been cross linked with an increment in the amount of crosslinker. Hence a higher amount of heat energy is required to break the crosslinked chains when compared to a loose network.

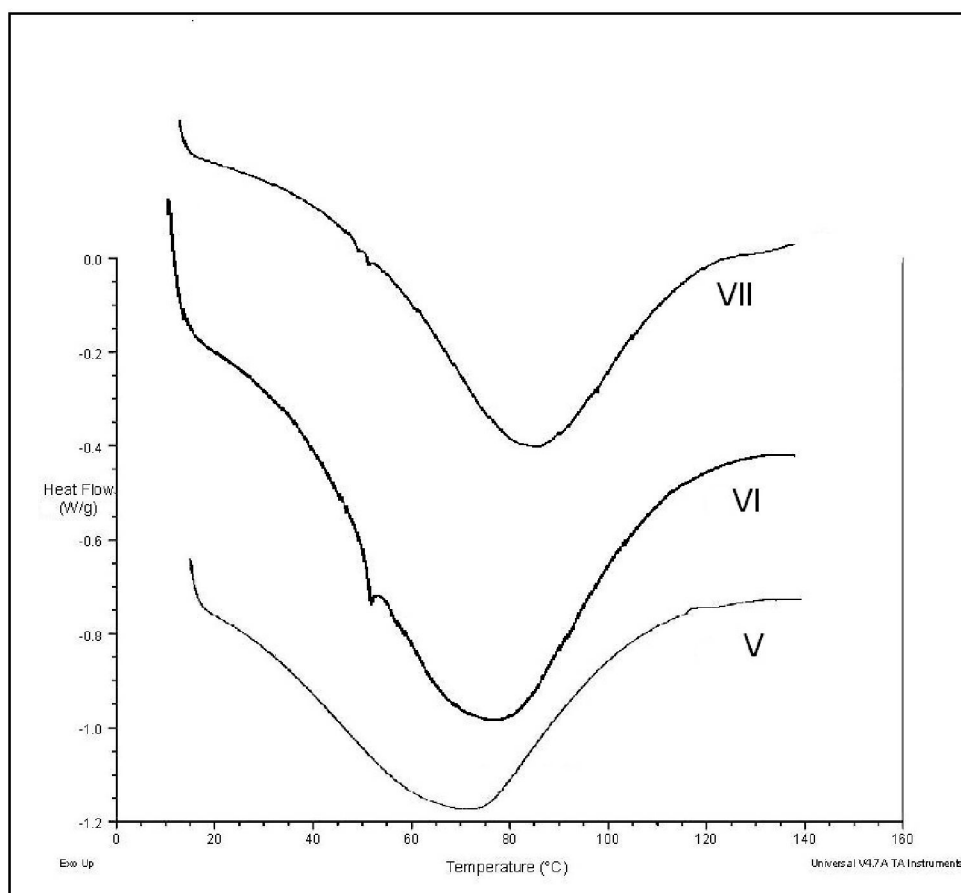


Figure 6. DSC thermograms of gastroretentive formulations.

Scanning electron microscopy

The scanning electron microscopic photograph of superporous hydrogel shown in Figure 7 clearly shows the presence of pores on the surface. The superporous hydrogel has high porosity and is responsible for faster swelling of superporous hydrogels.

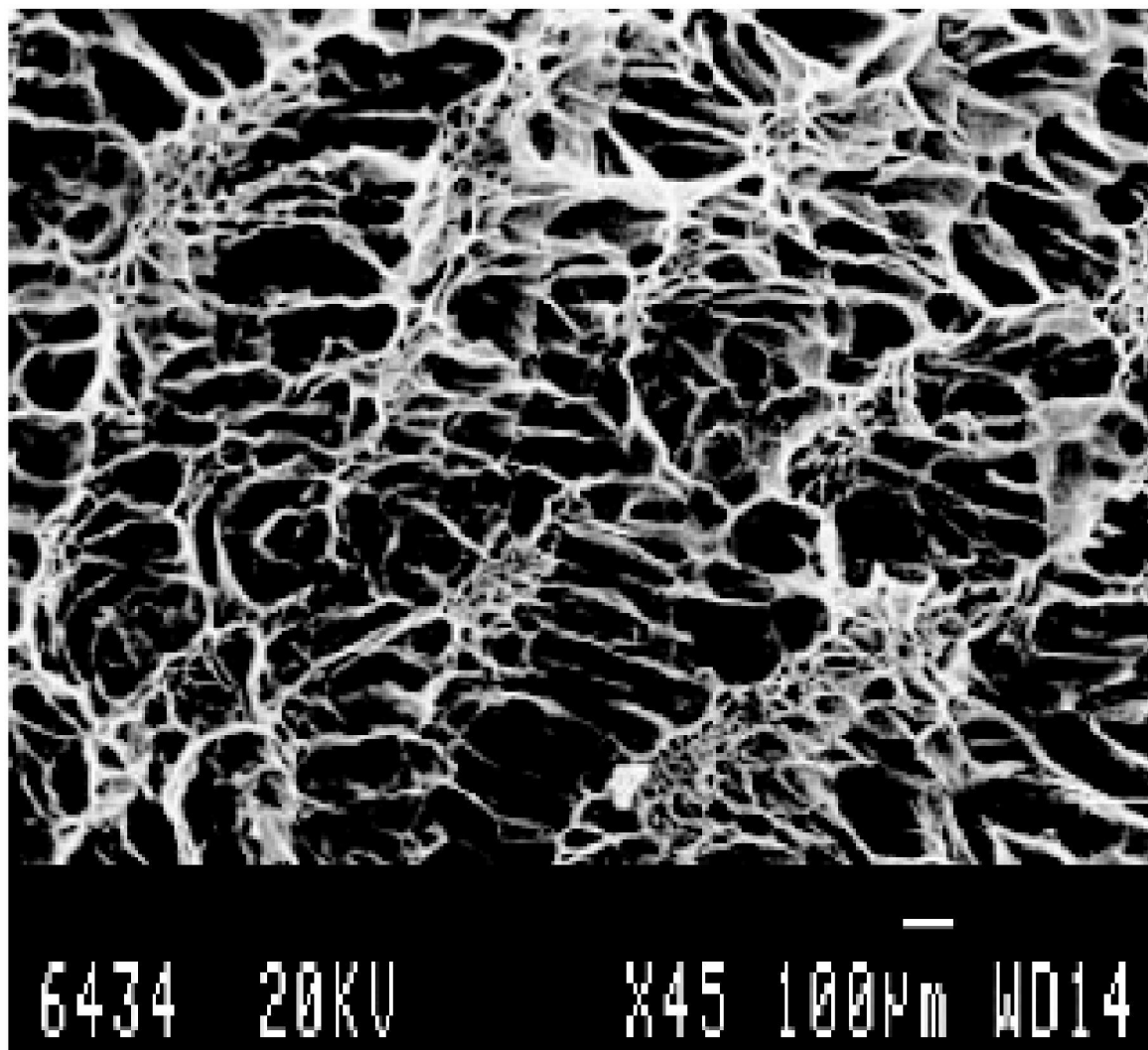


Figure 7. Scanning electron microscopic photograph of formulation IV recorded at 45X Magnification.

CONCLUSION

Suitable chitosan superporous hydrogels which swelled depending on the pH of media were successfully formulated. The high porosity of the superporous hydrogel is achieved by the carbon dioxide formation during the polymerization process, resulting in a capillary structure of interconnecting pores. In the preparation of superporous hydrogels, the introduction time of a blowing agent was determined from the gelation kinetics. In acidic environment, superporous hydrogels showed higher swelling ratio because of the cationization of amine groups in acidic condition. The swelling ratios of superporous hydrogels decreased with increasing crosslinking density, as tighter networks were formed at higher concentration of crosslinking agents. The mechanical strength of the superporous hydrogels increased with the amount of crosslinking agent and PVA. The effect of the number of freezing/thawing repetitions was clearly observed. As the number of repetitions increased, there was a relatively slight decrease in the swelling ratio. The increase in the mechanical properties was confirmed by DSC studies. This study demonstrates that IPN superporous hydrogels of chitosan/PVA may be suitable for use as a gastroretentive drug delivery system.

ACKNOWLEDGEMENTS

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

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Received: 21.04.2011

Accepted: 26.05.2011