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pH-sensitive superporous hydrogels composed of methacrylic acid and acrylamide: preparation and properties

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Abstract

In this investigation, superporous hydrogels containing poly(acrylamide-*co*-methacrylic acid) with interconnected pores were prepared using radical polymerization of methacrylic acid and acrylamide in the presence of N,N-methylene-bis-acrylamide as crosslinking agent. SPH composite polymers were made using Ac-Di-Sol as a stabilizer. Scanning electron microscopy (SEM), apparent density and swelling ratio studies were used to characterize these polymers. Characterization of the prepared polymers showed that SPH polymers have more pores and higher swelling ratio but less mechanical stability compared to SPH composite polymers, which have less pores and lower swelling ratio but a higher mechanical stability.

Keywords: Superporous hydrogels, Superporous hydrogel composites, Ac-Di-Sol, methacrylic acid, acrylamide.

Introduction

The drugs for oral delivery have its own convenience in being easy and economic administration, but the weakness is the loss of their functions due to their short residence time in the body. About 80% of the orally administrated drugs are reported to be excreted without being absorbed (Zhang et al. 2004, Chen et al. 2000). 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 (Qiu and Park 2001).

Stimuli responsive polymers, which can reversibly swell or shrink in response to external conditions, such as temperature, pH, solvent composition, electrical field and light are of great interest, especially in biomedical and pharmaceutical technology. Among them, pH-sensitive hydrogels that change properties by depending upon changes in pH have been extensively investigated for the development of new drug delivery systems (Peppas et al. 2000). These polymers can be prepared by the incorporation of one or more weakly acidic or basic monomers such as carboxylic acids (acrylic acid, methacrylic acid) and primary or substituted amines (N,N-dimethylaminoethyl methacrylate). Acidic gels are considered as good candidates for oral colon specific delivery of drugs that are susceptible to enzymatic degradation in the upper gastrointestinal tract. While these kinds of systems have slow equilibrium degree of swelling in acidic medium of stomach, their swelling degree increases as it passes down the gastrointestinal tract due to an increase in pH. Thus, the pH-sensitive drug delivery system protects the drug from the acid of stomach and releases the entire drug in the colon (Kost and Langer 2001).

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Hydrogels are crosslinked hydrophilic polymers with a network structure consisting of acidic, basic, or neutral monomers which are able to imbibe large amounts of water. Because of the hydrophilic nature of polymer chains, hydrogels absorb water to swell in the presence of abundant water. The swelling properties of hydrogels are mainly related to the elasticity of the network, the presence of hydrophilic functional groups (such as -OH, -COOH, $-CONH_2$, $-SO_3H$) in the polymer chains, the extent of cross-linking, and porosity of the polymer. A variety of stimuli sensitive hydrogels have been studied, but in many cases, slow response to environmental stimuli caused limitation to their effective use (Allan, 2002). Although such slow swelling is beneficial for many applications, there are many situations where a fast swelling of the polymer is more desirable. Therefore, a new generation of hydrogels, which swell and absorb water very rapidly, has been developed. Examples of this new generation are superporous hydrogels (SPH) and SPH composites (SPHC), which swell to equilibrium size in a short period of time (Chen et al. 1999).

A superporous hydrogel (SPH) 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. In this study, SPH and SPHC were synthesized in order to make these polymers appropriate for intestinal delivery of drugs. When these polymers are delivered into the intestine, they are able to mechanically stick for a certain period of time at the gut wall, sucking up deleterious luminal fluids and opening the tight junctions before finally releasing the drug. After having released the drug in a time controlled manner, the polymers become super hydrated and are easily broken down by the peristaltic force of the gut and subsequently excreted as fine particles. This action principle was verified in an study in pigs and octreotide as peptide drug, using various designs of SPH/SPHC delivery systems (Farid et al. 2002).

In this study, SPHs and SPHCs of poly(methacrylic acid-co-acrylamide) were prepared employing acrylamide and methacrylic acid as monomers and methylene-bis-acrylamide as crosslinking agent.

Materials

Acrylamide (Loba Chemie, Mumbai, India), methacrylic acid (Aldrich, Steinheim, Germany), *N,N*-methylene-bis-acrylamide (Sigma, Steinheim, Germany), Pluronic-F127 (Sigma, Steinheim, Germany), tetramethyl ethylenediamine (Ranbaxy Fine Chemicals, Mumbai, India), ammonium persulphate (Ranbaxy Fine Chemicals, Mumbai, India) and sodium bicarbonate (Loba Chemie, Mumbai, India) were purchased from the source indicated. Methacrylic acid was distilled under vacuum at 70°C prior to use. All other reagents used were of analytical grade.

Methods

Preparation of Superporous Hydrogels and SPH Composites

All ingredients except for sodium bicarbonate and Ac-Di-Sol (cros-caramellose sodium) were used as solution in distilled water. For the synthesis of superporous hydrogels, the following substances were added subsequently into a test tube at ambient temperature: Acrylamide (50% w/v), methacrylic acid (50% w/v), *N,N*-methylene-bis-acrylamide (2.5% w/v), Pluronic-F127 (10% w/v), ammonium persulphate (20% w/v) and tetramethyl ethylenediamine (20% w/v). The pH was adjusted to 5.0 by adding 50% (w/v) sodium hydroxide solution. The mixture was vigorously shaken, and sodium bicarbonate was added very quickly to the solution and mixed. For the synthesis of superporous hydrogel composites, the procedure is same as that of superporous hydrogel; however, Ac-Di-Sol was added to the mixture after adding ammonium persulphate (APS) and before adding tetramethylethylenediamine (TMED). Polymerization was allowed to continue for approximately 10 min.

Effect of drying process on the swelling ratio of the polymers

The synthesized polymers were subjected to various drying procedures in order to study the effect of the drying process on the swelling ratio of the polymers. Different organic solvents were used to dehydrate the polymers quickly. The superporous hydrogels were taken from the reaction tubes and submerged three times for 10 min in one of the following organic solvents for 10 min: absolute ethanol, acetone and diethyl ether. Thereafter, the superporous hydrogels were put in an oven at 60 ^{0}C for 24 h for drying to complete (Farid et al. 2001).

Table 1. Formulations of superporous hydrogels and its composites

Ingredients	I	II	III	IV	V	VI	VII
Acrylamide	200 µl	200 µl	200 µl	200 µl	200 µl	200 µl	200 µl
Methacrylic Acid	50 µl	100 µl	150 µl	100 µl	100 µl	100 µl	100 µl
N,N-methylene-bis-acrylamide	25 µl	25 µl	25 µl	50 µl	75 µl	25 µl	25 µl
Pluronic-F127	20 µl	20 µl	20 µl	20 µl	20 µl	20 µl	20 µl
Ammonium Persulfate	25 µl	25 µl	25 µl	25 µl	25 µl	25 µl	25 µl
Tetramethylethylenediamine	25 µl	25 µl	25 µl	25 µl	25 µl	25 µl	25 µl
Ac-Di-Sol	--	--	--	--	--	100 mg	200 mg
Sodium Bicarbonate	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg	100 mg
Pantoprazole sodium	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg	20 mg

Swelling Studies

The dried SPHs and SPHCs were used to determine their swelling ratio in pH 1.2 hydrochloric acid buffer and pH 7.4 phosphate buffer. For calculation of the swelling ratio, the following equation was used:

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

where Q is the swelling ratio, M_s the mass in the swollen state and M_d the mass in the dried state. At the beginning of each experiment, the dried hydrogel was weighed to obtain M_d and then it was immersed in an excess buffer solution for swelling. At various time intervals, the hydrogel was removed from the water and weighed, when excessive water on the surface was blotted, to determine M_s (Tang et al. 2005).

Density measurement of the SPH and SPHC

The density (d) of the dried hydrogels was calculated by the following equation:

$$d = W_d/V_d$$

where W_d is the weight of a dried hydrogel and V_d is the volume of the dried hydrogel. Since SPH and SPHCs lost their regular shapes during the drying process, direct measurement of their volumes becomes difficult. Therefore, for measurement of their volumes, the solvent displacement method was applied. Briefly, a dried superporous hydrogel was submerged underneath the surface of hexane in a graduated cylinder and then quickly was removed from the hexane. The volume change read from the graduated cylinder before and after the removal was the volume of the dried superporous hydrogel. Hexane was used because it is very hydrophobic and superporous hydrogels do not absorb it (Assadang et al. 2004).

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 was defined as the duration time for gel formation after addition of initiator (APS). It was measured by a simple tilting method after adjustment of pH to 5.0 with sodium hydroxide solution. It was determined by the duration time until the reactant mixture was no longer descending in the tilted tube position (Park et al. 2006).

Scanning electron microscopy

The dried polymers 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, USA) was used after coating the samples with gold using a Technics Hummer Sputter Coater. Images were captured using a digital capture card and Digital Scan Generator 1 (Jeol USA Inc., Peabody, MA, USA).

Results and Discussion

Preparation of SPH and SPHC

In the synthesis procedure of superporous hydrogels, acrylamide and methacrylic acid are the monomers. *N,N*-methylene-bis-acrylamide was used as a cross-linker, and Pluronic-F127 was used as a foam stabilizer of the foam which is formed by carbon dioxide originating from sodium bicarbonate. After the foam formation has started, the foam should be stable for a few minutes in order to introduce the desired large number of pores during the synthesis of the superporous hydrogels. APS was used as a polymerization initiator and TMED as a catalyst. In the synthesis of superporous hydrogel composites all above mentioned compounds have the same role. However, in superporous hydrogel composites Ac-Di-Sol (a stabilizer) was used for introducing additional mechanical stability to the polymer by physical entanglement of the polymer chains with Ac-Di-Sol fibres. The combination of APS and TMED will initiate the radical polymerization. The radicals formed will then attack the double bonds of acrylamide and methacrylic acid, and also to a less extent to the double bond of *N,N*-methylene-bis-acrylamide. Subsequently, the double bonds will be opened and the monomers will covalently bind to each other and form a long aliphatic chain. These chains are subsequently cross-linked by the added cross-linker. The frequency of cross-linking between the polymer backbone chains is related to the concentration of the cross-linker used during polymerization.

Effect of drying process on the swelling ratio of the polymers

The SPH polymers dried by different organic solvents were subjected for the swelling ratio studies. When polymers are placed in organic solvents, the water will be deprived from the polymers very quickly and some of the pores of the polymer may be closed. As shown in Figure 1, when the polymers were dried with organic solvents and subsequently dried, there was no difference between drying with acetone and absolute ethanol. With diethyl ether, however, the swelling ratio was less, probably due to its fast evaporation and reduced water miscibility that resulted in closing of some of the pores in the polymer.

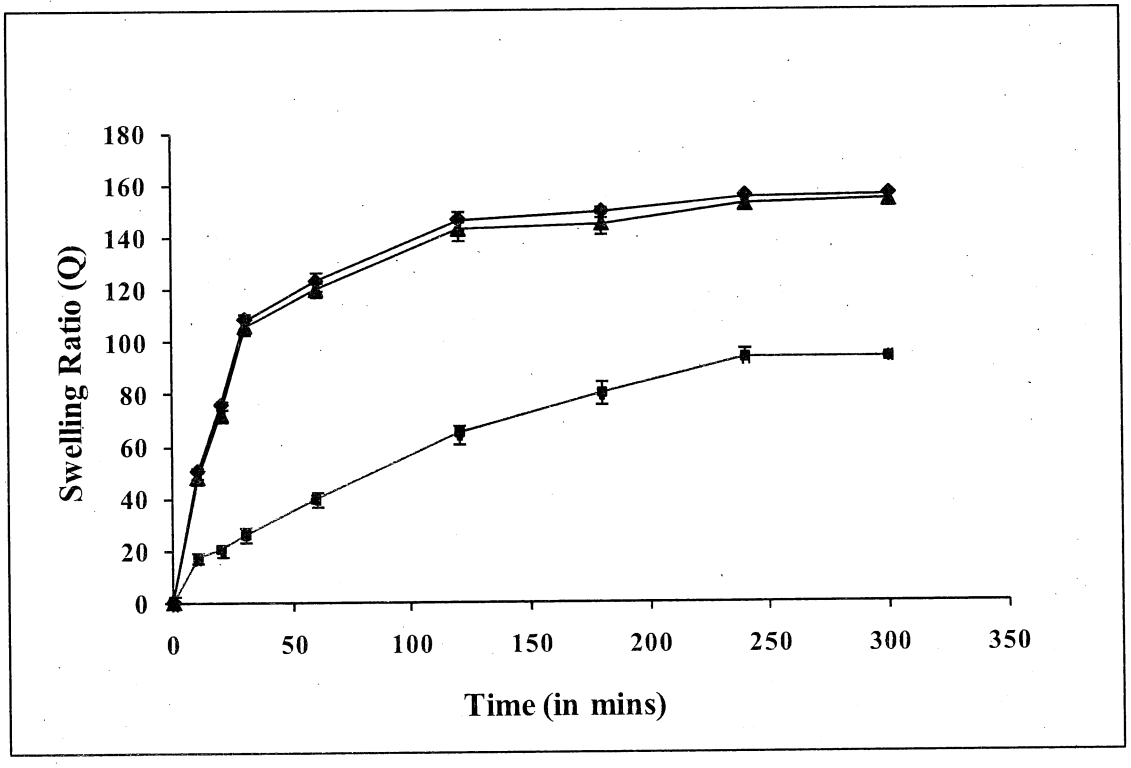

Figure 1. Swelling ratio curves for SPH polymers dried with various solvents: (♦) drying with absolute ethanol; (▲) drying with acetone; (■) drying with diethyl ether. Data are depicted as the mean ± SD of three experiments.

Swelling Studies

The swelling ratio of the prepared formulations in pH 1.2 hydrochloric acid buffer was minimal (< 5). As shown in Figure 2, the swelling ratio of the prepared formulations in pH 7.4 phosphate buffer was found to increase with time. The swelling studies for SPH and SPHC were carried out in both acidic pH and basic pH media to check its pH sensitivity.

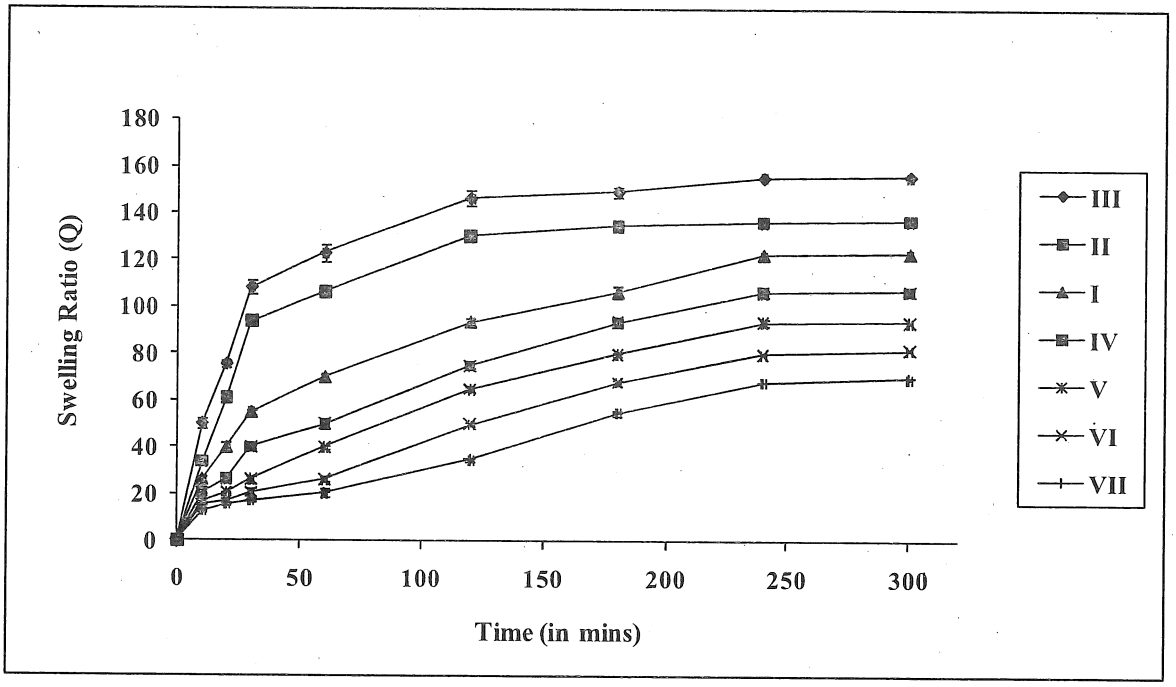

Figure 2. Swelling studies of prepared formulations in pH 7.4 phosphate buffer. Data are depicted as the mean ± SD of three experiments.

The results indicate that with an increase in pH from acidic to basic, a considerable increase in swelling was observed for all the formulations. The presence of methacrylic acid increases the swelling of the superporous hydrogel in basic solutions and collapses in acidic solutions. This increase in swelling ratio was due to the dissociation of the carboxyl groups of methacrylic acid, thereby increasing the osmotic pressure inside the hydrogels resulting in increased swelling. At high pH values, the carboxylate side chains are repelled by the ions in the solution and minimize the charge concentration by expanding. Swelling mainly depends upon the extent of crosslinking. With increasing amounts of cross-linker, the two polymer chains will attach to each other more strongly and the size of pores during the foam formation will be smaller. On the other hand, when the amount of cross-linker is high, the flexibility of the chains will be less, resulting in a reduced swelling capacity of the superporous hydrogel. SPHC contain Ac-Di-Sol to increase the mechanical stability of these polymers. The cellulosic fibres of Ac-Di-Sol will occupy some space of the pores inside the superporous hydrogel, and will reduce the flexibility of the polymer chain. Therefore, at the start of the swelling, superporous hydrogel composites cannot absorb water very quickly, but after initial swelling, the pores are opened enough to absorb additional water.

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 Superporous hydrogel composite is higher in comparison to the superporous hydrogels due to the presence of the cellulosic fibres within the polymer structure.

Table 2. Density measurements of formulations of SPH and SPHC. Data are depicted as the mean ± SD of three experiments.

Formulation	Apparent Density(g/cm^3)
I	0.59 ± 0.077
II	0.52 ± 0.028
III	0.48 ± 0.038
IV	0.65 ± 0.020
V	0.72 ± 0.032
VI	0.79 ± 0.014
VII	0.87 ± 0.024

Measurement of gelation kinetics

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. 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 shapes by completion of reaction when blowing agent is introduced too early, and they cannot even be formed when introduced too late. The Sol-gel transition time for various formulations was between 18-22 seconds. This clearly indicated that the blowing agent must be introduced immediately after the adjustment of pH to 5.0 with sodium hydroxide solution.

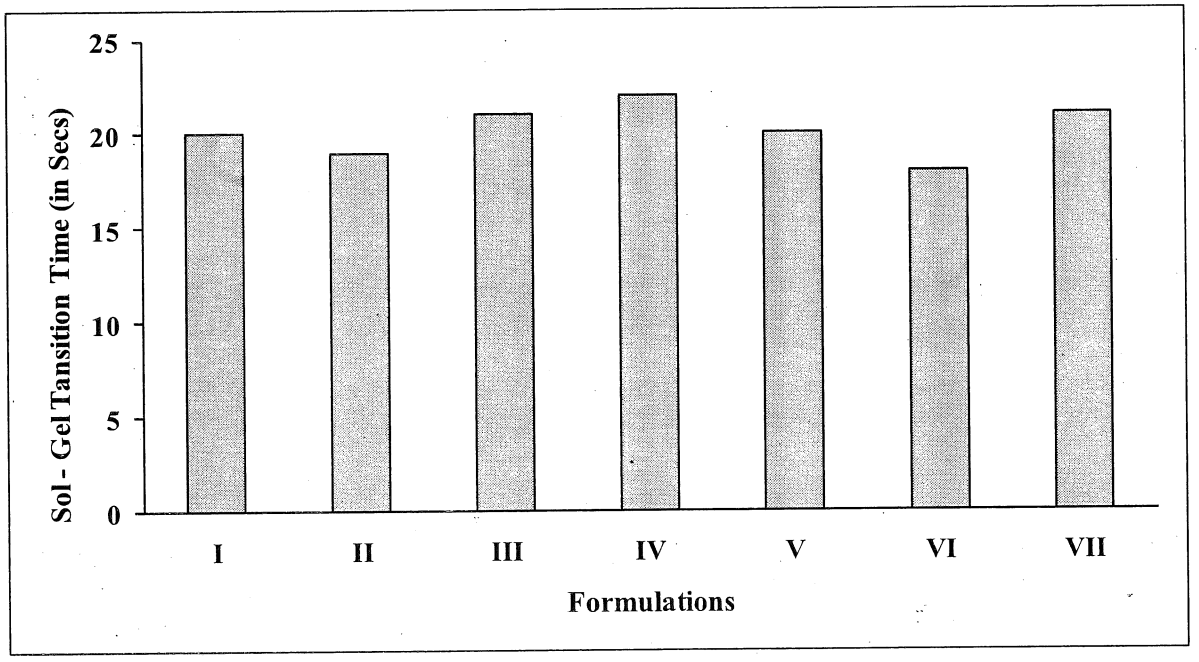

Figure 3. Sol-gel transition time during the synthesis of SPH and SPHC after pH was adjusted to 5.0

In the beginning of polymerization, all the ingredients except sodium bicarbonate were mixed. The presence of acid reduced the pH to an acidic level (pH 2.0-3.0). At such low pH, gelation and foaming do not occur. The gelation reaction took place only at pH 6.0-7.0. On the other hand, the foaming reaction took place only at the acidic condition (pH 5.0-5.5). Hence the pH was adjusted to 5.0 by addition of sodium hydroxide solution. The amount of sodium hydroxide required for various formulations is shown

in Figure 4. At this pH, the TMED catalyzed free radical generation from APS was inhibited because TMED was protonated. This resulted in a very slow polymerization.

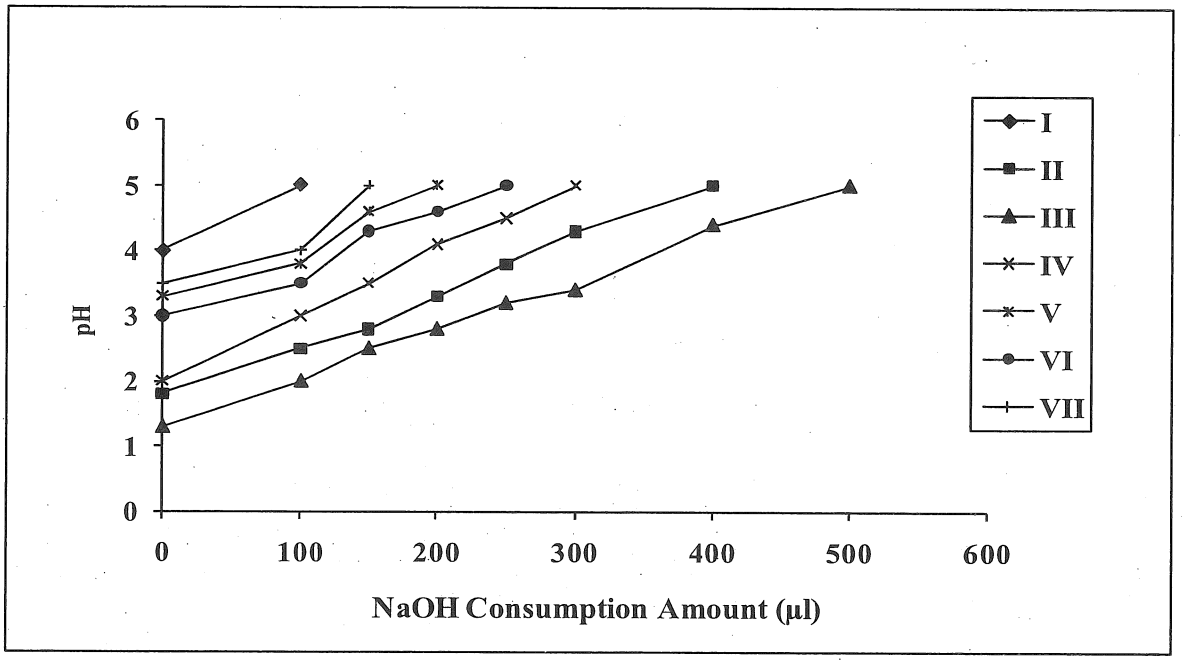

Figure 4: The amount of NaOH solution (50% w/v) necessary to adjust the pH of the monomer solution to 5.0 for the synthesis of poly(acrylamide-co-methacrylic acid) SPH and SPHC.

When sodium bicarbonate was added to the monomer solution, it reacted with acid to start the foaming process. In the meantime, the pH of the solution increased to 7–8 because an excess amount of sodium bicarbonate had been used. At this pH, TMED (in it's free-base form) could catalyze the free radical generation from APS and start the accelerated polymerization. Consequently, the polymerization proceeded rapidly and the solution gelled. This resulted in the inclusion of gas bubbles and gas channels in the polymer matrix. The foam stayed at its maximum height in the presence of foam stabilizer.

The scanning electron microscopy photograph of superporous hydrogel (Figure 5) clearly shows the presence of pores on the surface. The superporous hydrogel has high porosity, which is responsible for faster swelling of superporous hydrogels when compared to conventional hydrogels.

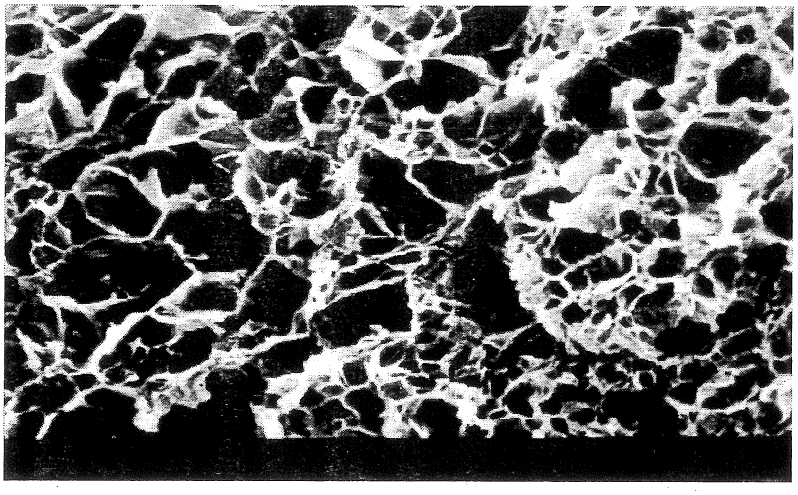

Figure 5. Scanning electron microscopy photograph of SPH recorded at 800X magnification showing porous surface.

Conclusions

Novel SPH and SPHC as candidates for drug delivery were prepared from free radical copolymerization using APS and TEMED as an initiator system using various amounts of acrylamide and methacrylic acid. 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. The high polar internal surface of these pores within the superporous hydrogels is responsible for the very fast swelling rate and resulting high swelling ratio of the superporous hydrogels. The superporous structure is additionally stabilized by cellulosic fibres (Ac-Di-Sol) which are responsible for a delayed but also complete swelling of these SPH composites. The unique characteristics of these superporous hydrogels open a new field of application in controlled drug delivery. Because the swelling properties of both SPH and SPHC are pH dependent, these polymers can be used as drug delivery systems for drug release in the intestine. SPH and SPHC can quickly adhere to the intestinal mucosa owing to the carboxylic groups in the structure and fast swelling, thus suggesting their potential use for mucosal drug delivery, especially for effective peroral delivery of peptide and protein drugs.

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