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SYNTHESIS AND CHARACTERIZATION OF POLY[N-VINYL-2-PYRROLIDONE-POLYETHYLENE GLYCOL DIACRYLATE] COPOLYMERIC HYDROGELS FOR DRUG DELIVERY

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ABSTRACT

Novel polymeric biodegradable and biocompatible copolymeric hydrogels based on N-vinyl-2-pyrrolidone (NVP) and polyethylene glycol diacrylate (PAC) were designed and synthesized. PAC macromonomer was synthesized by a modified procedure and characterized. Poly[N-vinyl-2-pyrrolidone-polyethylene glycol diacrylate] (Poly[NVP-PAC]) hydrogels were synthesized by varying the concentration of PAC. Azobisisobutyronitrile (AIBN) was used as the free radical initiator and N,N^1-methylene bis(acryl-amide) (BIS) was employed as the crosslinking agent. These hydrogels were characterized by various spectroscopic techniques. Fourier transform-infrared spectroscopy (FT-IR) confirms the formation of copolymer. Thermogravimetric analysis (TGA) curves obtained were continuous indicating the formation of copolymer. The glass transition temperature (T_g) of the copolymer was measured using differential scanning calorimetry (DSC). The equilibrium swelling measurements were carried out in simulated gastric and intestinal fluids (SGF & SIF). These swelling studies indicated that these gels had a higher sorption capacity in SIF when compared to that in SGF. 5-Fuorouracil (5-FU), an anti-cancer drug was entrapped in these hydrogels and the *in-vitro* release profiles were established in a sequential manner in SGF and SIF. About 50-56% of the drug entrapped was released in a period of 10 days.

INTRODUCTION

Hydrogels are three dimensional polymeric networks which can absorb biotechnolonology and medicine [3]. Hydrogels have been investigated for a wide variety of biomedical applications due to their physical similarity to the extra cellular matrix based on their high water content, soft and rubbery consistency and low interfacial tension [4, 5]. As a result, the development of biodegradable polymeric systems is currently being exploited for a variety of medical applications such as surgical sutures, orthopedic implants, scaffolds for cells in tissue engineering and controlled release depots for drugs [6-8].

The major advantage in biodegradable implants is that they do not require removal after delivering the drug. In addition, adverse tissue reactions from the implanted polymer are ameliorated as the polymer undergoes biodegradation [9]. Hence, in the current study we have undertaken the development of biodegradable and biocompatible poly[NVP-PAC] copolymeric hydrogels. PAC was synthesized by a modified procedure and characterized by FT-IR and nuclear magnetic resonance (NMR) spectroscopy. The hydrogels were prepared by varying the concentration of PAC. The free-radical initiator, AIBN and the crosslinking agent, BIS were employed for the hydrogel formation. These hydrogels were characterized by FT-IR, TGA and DSC. Equilibrium swelling measurements were carried out in SGF and SIF. 5-FU, an anti-cancer drug was entrapped in these hydrogels and the *in-vitro* release profiles were established in SGF and SIF in a sequential manner.

EXPERIMENTAL

Materials

N-vinyl-2-pyrrolidone was purchased from Fluka, Switzerland. Polyethylene glycol 6000 (SDS, India) and Acryloyl chloride (Aldrich, USA) were used as obtained. AIBN (Loba, India) was recrystallized from methanol before use. BIS (Sigma,USA) and 5-FU (SISCO Research Laboratory,India) were procured. All other chemicals used were of analytical reagent grade.

Methods

Preparation of PAC

Polyethylene glycol 6000 (0.002 moles) was taken along with 1 ml of triethylamine and 75 ml of toluene. To this mixture was added 1.448 moles of acryloyl chloride and refluxed for about 8 hours. At the end of this period , the reaction mixture was filtered and the filtrate was precipitated with *n*-hexane. The precipitate was dried and stored for further use.

Preparation of Poly[NVP-PAC] Hydrogels

The macromonomer PAC and NVP were taken in a ratio (w/w) of 1:8 (PP-I) and 1:4 (PP-II), respectively. About 3.5% (w/w) of AIBN and 2.5% (w/w) of BIS were added based on the weight of the monomer. The anti-cancer drug, 5-FU was added to this mixture and stirred thoroughly. The polymerization was allowed to proceed at 37°C for a period of 1 hour. Transparent, smooth and cylindrical gels were obtained . The hydrogels were extensively washed with distilled water to remove any residual monomer. The gels were air-dried and stored until further use.

Determination of the Amount of Drug Entrapped

The amount of drug entrapped in the poly[NVP-PAC] hydrogels was determined by an indirect method. After the gel preparation, the washings were collected, filtered with a .45u millipore filter and tested using UV/VIS spectroscopy. The difference between the amount of drug taken initially and the drug content in the washings is taken as the amount of drug entrapped.

Characterization

Infrared spectra of PAC and poly[NVP-PAC] hydrogels were obtained using Nicolet impact 400 FT-IR spectrophotometer. NMR spectra were recorded on Bruker MSL 300P (300 MHz) NMR spectrophotometer.TGA was carried out using Seiko SSC 5200 H TG/DSC in nitrogen atmosphere at a heating rate of 10°C min^{-1}. The DSC was carried out on Dupont 2000 in nitrogen atmosphere at a heating rate of 10°C min^{-1}.

Equilibrium Swelling Studies

The equilibrium swelling of the poly[NVP-PAC] hydrogels was determined by swelling the hydrogel pellets in SGF and SIF (specified in Japanese Pharmacopia XII). SGF (pH 1.2) was prepared by dissolving 2 g of sodium chloride and 7 ml of concentrated HCl in 1 liter of distilled water. SIF (pH 6.8) was prepared by taking 118 ml of 0.2 M sodium hydroxide and 250 ml. of 0.2 M potassium dihydrogen orthophosphate and making up to 1 liter with distilled water. The swelling study was carried out at room temperature until equilibrium was attained. The swollen weight of the pellet was determined by blotting off the pellet every hour until equilibrium was attained.

The percent swelling was calculated by the following equation:

$$\% \text{ swelling} = \frac{Wt - Wo}{Wo} \times 100$$

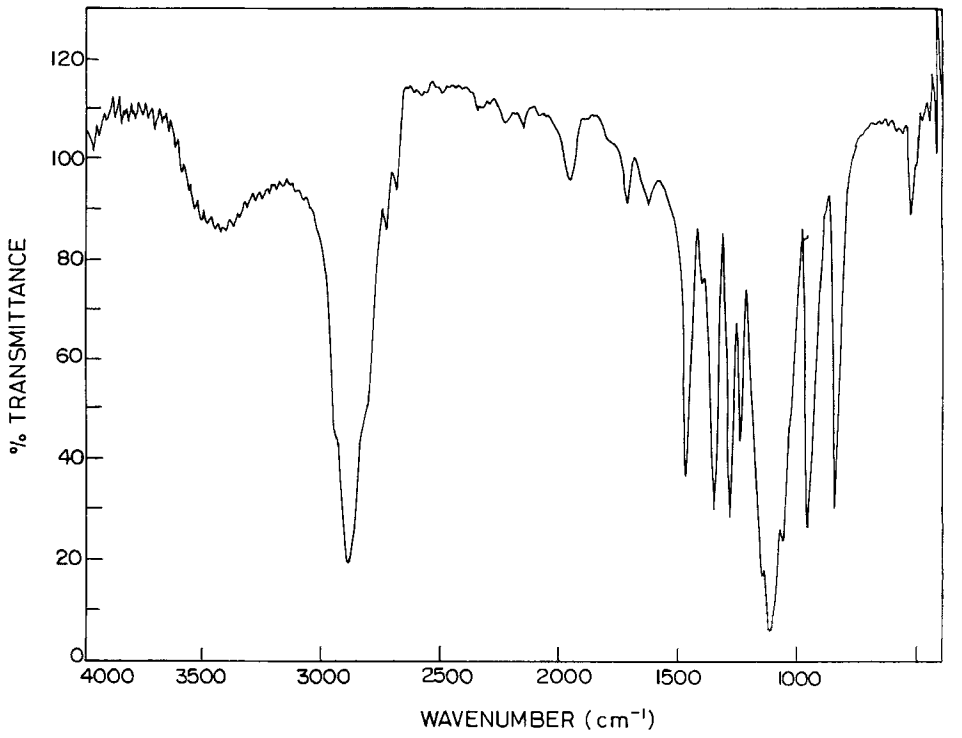

Figure 1. FT-IR spectrum of polyethyleneglycol diacrylate.

where Wo , being the initial weight and Wt the final weight of the pellet at time t.

In-vitro Release Studies

The *in-vitro* release of the entrapped anticancer drug, 5-FU was carried out by placing the hydrogel pellets loaded with 5-FU in SGF and SIF in a sequential manner at 37°C in a GFL-1086 water bath shaker incubator with reciprocating motion (100 rpm). At periodic intervals aliquots were withdrawn and tested using Shimadzu UV-2100S, UV-VIS spectrophotometer. The release media were replaced periodically with equal volume of fresh SGF/SIF to create infinite sink conditions. These studies were carried out in triplicate.

RESULTS AND DISCUSSION

Biodegradable and biocompatible hydrogels based on NVP and PAC were developed for the controlled drug delivery of 5-FU. PAC macromonomer was

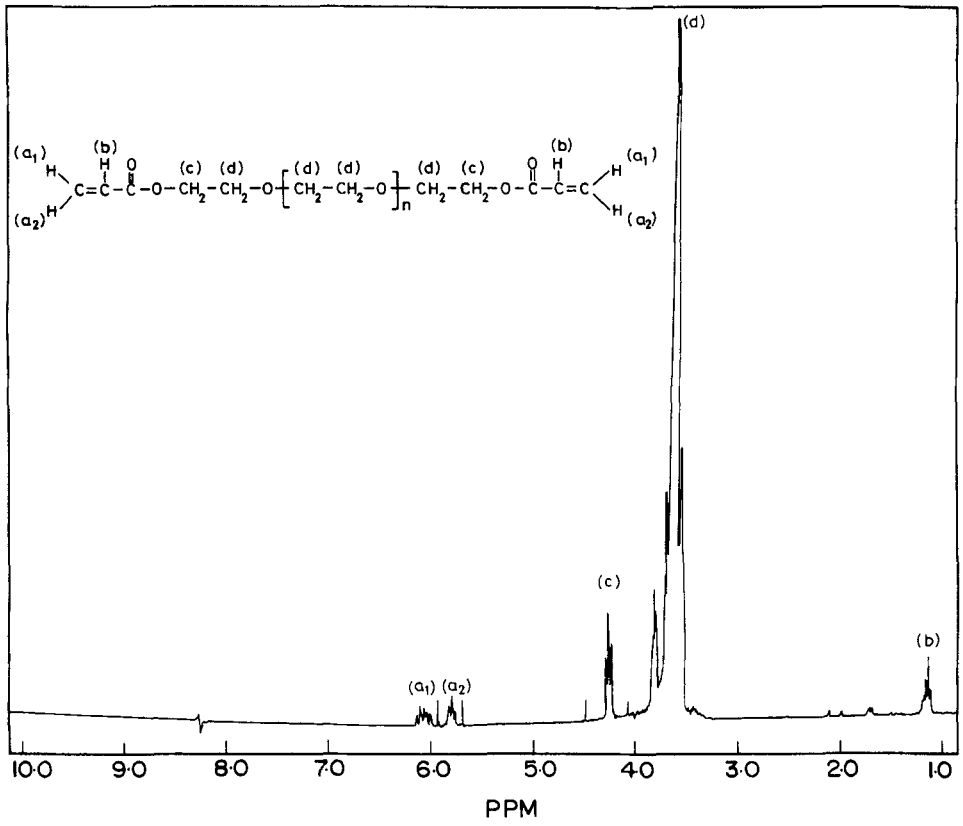

Figure 2. ^1H NMR spectrum of polyethyleneglycol diacrylate.

synthesized and characterized by FT-IR and NMR spectroscopy. FT-IR of PAC (Figure 1) shows the presence of vinylic unsaturation at 1640 cm^{-1} and the ester carbonyl group at 1740 cm^{-1} . The disappearance of hydroxyl group absorption at 3400 cm^{-1} was also significant.The ^1H NMR spectrum (Figure 2) of PAC indicates the presence of vinylic protons (a_1 and a_2)as non-identical multiplets in the regions 6.2 and 5.4, respectively. The methine (b) protons appear as quartet due to *cis* and *trans* allylic coupling with vinyl group at 1.1. The methylene protons (c) appear as triplet at 3.78 and the methylene protons (d) also appear as triplet at 3.51. The intensity of the peak at 3.51 increased with increase in the chain-length.

The FT-IR spectrum of poly[NVP-PAC] clearly indicates (Figure 3) the disappearance of the vinylic unsaturation at 1640 cm^{-1}. The absorption ranging from 1740-1660 cm^{-1} indicates the overlapping of the ester carbonyl and C-N strectching vibration. The absorption due to C-O-C linkage appeared at 1040 -1100 cm^{-1}. This clearly indicates the formation of the copolymer. The TGA curves of poly[NVP-

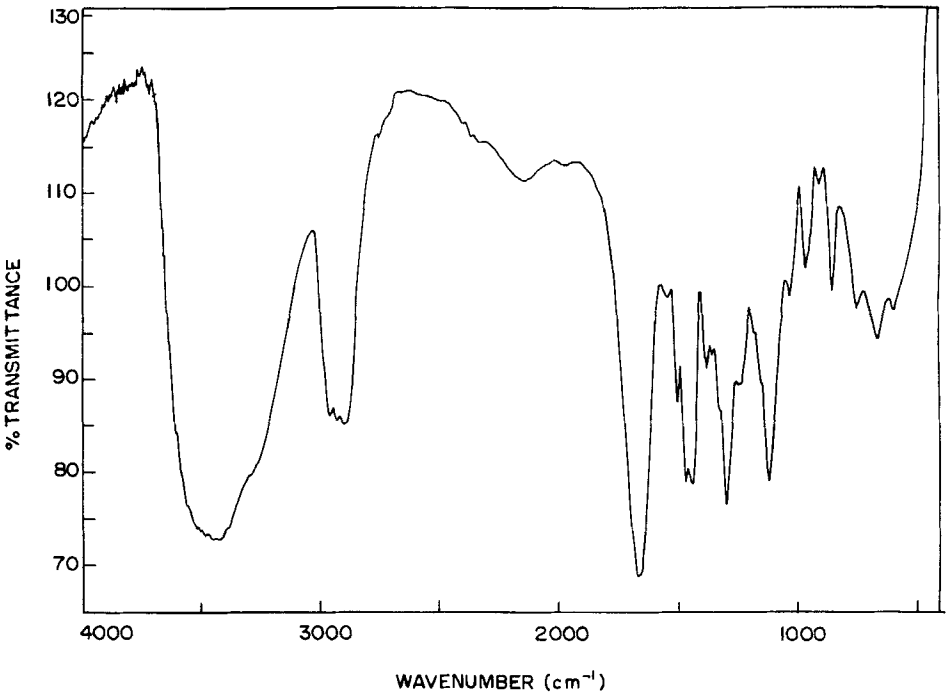

Figure 3. FT-IR spectrum of poly[NVP-PAC] copolymeric hydrogel.

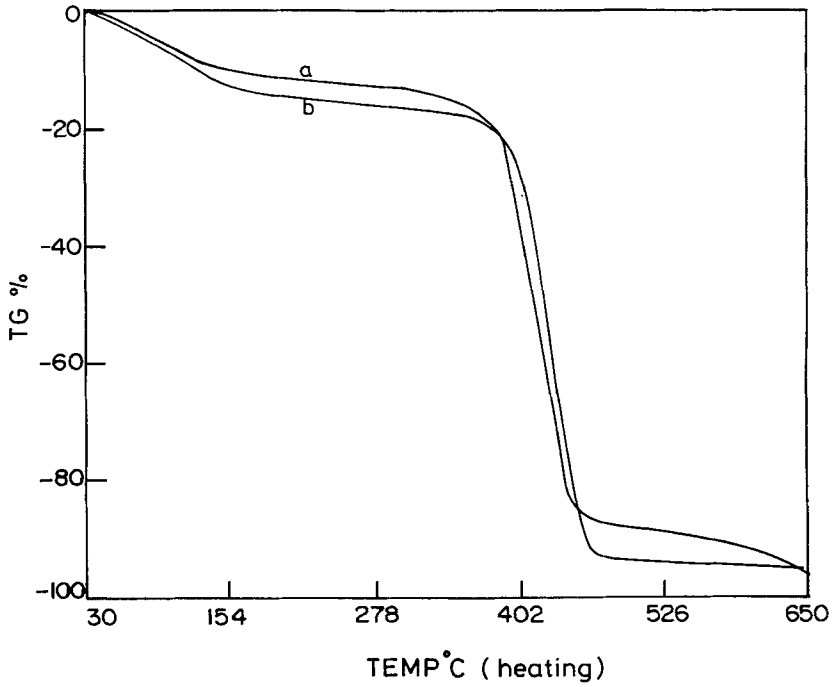

Figure 4. TGA of poly[NVP-PAC] copolymeric hydrogel.

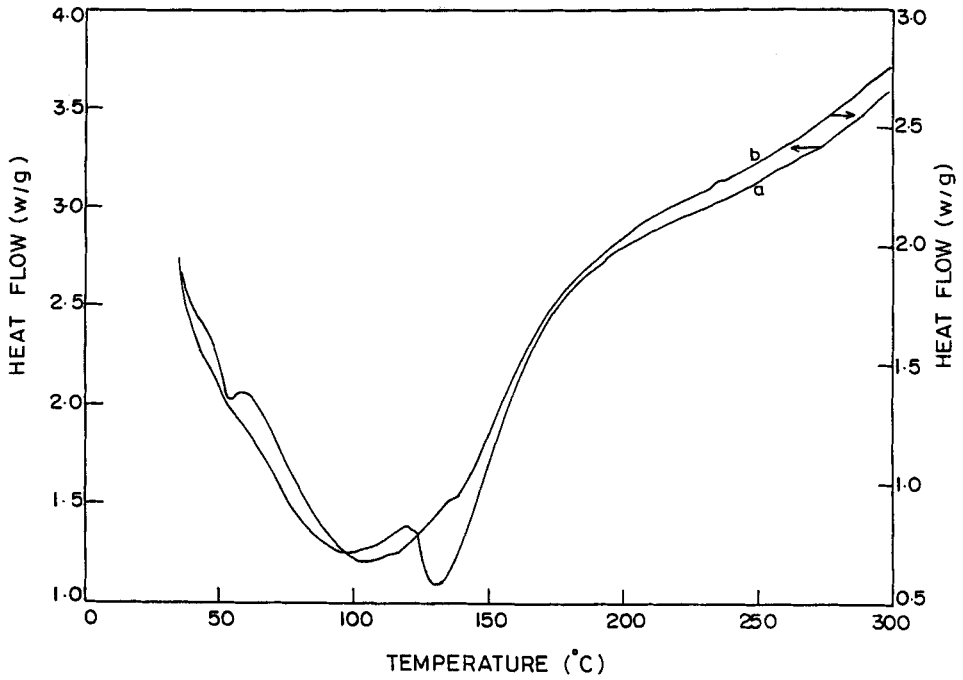

Figure 5. DSC of poly[NVP-PAC] copolymeric hydrogel.

PAC] hydrogels are shown in Figure 4. The TGA curve of PP-I shows the initial weight loss from around 50°-102°C which may be attributed to the loss of loose and bound water in the gel. The maximum weight loss due to the degradation of the polymer starts from 390°C and extends up to 475°C. The TGA curve of PP-II also indicates an initial weight loss at temperatures ranging from 61°C to 120°C which may be attributed to the loss of moisture content of the gel. The polymer degradation ranges between 396 and 464°C. Both the hydrogels appeared to be thermally stable and the continuous TGA curves indicate the formation of the copolymer.

Figure 5 shows the DSC of the poly[NVP-PAC] hydrogels. The DSC of PP-I indicates the presence of a broad endotherm at about 90-100°C which may be due to the presence of moisture. The second endothermic transition at 131 °C may be attributed to the melting of the polymer. The glass transition temperature (T_g) could not be recorded. The DSC of PP-II shows a broad endothermic tramsition ranging from 90-125°C which may be due to water loss and also due to the melting of the copolymer. The T_g of this copolymer was at 53°C. The exothermic transition peaks could not be recorded in both the cases.

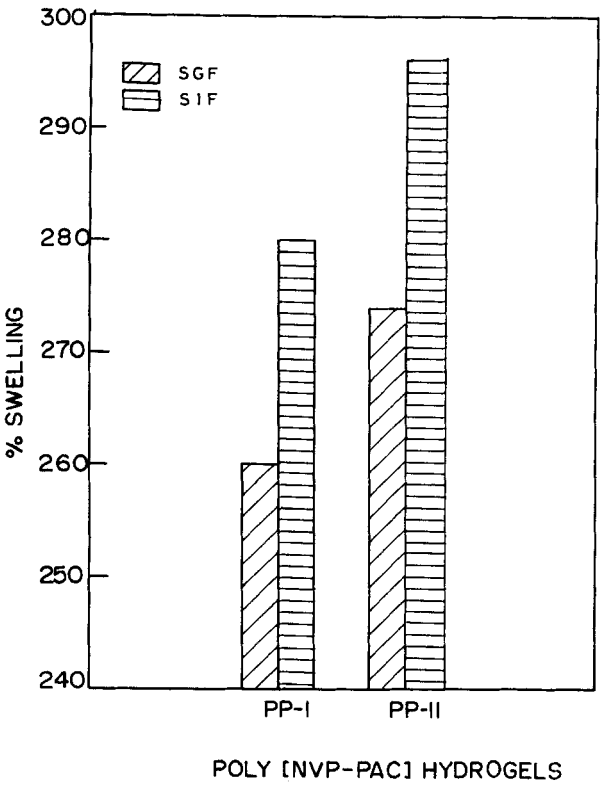

Figure 6. Equilibrium swelling studies of poly[NVP-PAC] copolymeric hydrogel.

Equilibrium Swelling Studies

The percent equilibrium swelling of the poly[NVP-PAC] hydrogels are shown in Figure 6. The gel PP-I swells to about 260% in SGF and 280% in SIF, respectively at equilibrium. The equilibrium swelling of gel PP-II was about 274% in SGF and 296% in SIF, respectively. These gels were found to swell more in SIF when compared to that in SGF in general. This may be expected due to the alkaline hydrolysis of the polyester in SIF. With increasing concentration of the PAC in the copolymer as in gel PP-II, the swelling at equlibrium in SIF was significantly greater. The difference in the sorption capacities of these gels in SGF or SIF alone was relatively insignificant with variation in the concentration of PAC in the copolymeric system. Both the copolymeric hydrogels displayed good stability in SGF. In SIF, the gel pellet swells tremendously concomitant with the very slow hydrolytic degradation of the ester linkages.

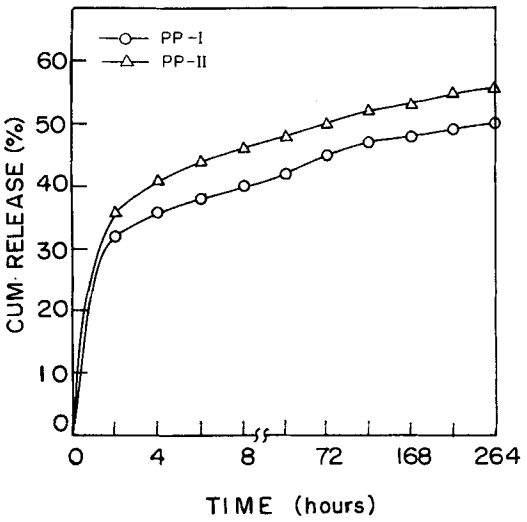

Figure 7. *In-vitro* release profiles of 5-FU from poly[NVP-PAC] copolymeric hydrogel.

In-vitro Release Studies

The *in-vitro* release studies of 5-FU entrapped in poly[NVP-PAC] hydrogels was carried out in SGF and SIF in a sequential manner (Figure 7). There was about 23% drug release in the first one hour from PP-I gels and the release was 25% in case of PP-II gels. There was about 42% release from PP-I and 48% from PP-II gels at the end of 24 hours. The release gradually slowed down after 24 hours. About 50% of the entrapped drug released in a period of 10 days from PP-I whereas in case of PP-II the release was 56% at the end of 10 days. The release study was suspended at the end of 10 days after achieving 50% and 56% of drug release from PP-I and PP-II, respectively. After the initial burst effect the release slowed down releasing in a near zero-order fashion for a period of 10 days. The initial burst effect may be due to the drug entrapped towards the surface of the gel matrix. The maximum amount of drug released in the first 24 hours may be attributed to the gel matrix attaining equilibrium swelling during that period. Later the drug may be released by the slow diffusion through the matrix. Finally, the very slow hydrolytic degradation of the gel matrix could be the reason for the extreme slowing down of the release, releasing the drug entrapped in the bulk of the gel matrix. The drug release kinetics from these poly[NVP-PAC] hydrogels may be appropriately altered by chemical modification of the gel surface which may drastically reduce the initial burst effect.

CONCLUSION

Novel biocompatible and biodegradable copolymeric hydrogels, poly[NVP-PAC] matrices were designed and successfully developed for controlled drug delivery. The macromonomer PAC was prepared by a modified procedure and characterized by FT-IR and ^1H NMR spectroscopy. The poly[NVP-PAC] hydrogels were developed by varying the concentration of PAC in the copolymer. These copolymeric matrices were fully characterized by FT-IR, TGA and DSC. Equilibrium swelling measurements of these hydrogels carried out in SGF and SIF, indicated that these gels had higher sorption capacities in SIF. The *in-vitro* release studies of 5-FU from the poly[NVP-PAC] hydrogels revealed that about 50-56% of the drug entrapped could be released in a period of 10 days. These intial interesting results on the development of biodegradable copolymeric matrices can be further exploited for their potential as the future oral drug delivery systems.

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