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Preparation, swelling characteristics and evaluation of hydrogels for stomach specific drug delivery

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Abstract

The development of pH sensitive, biocompatible and biodegradable hydrogels as novel drug delivery systems was carried out to achieve localized drug delivery. Poly[*N*-vinyl pyrrolidone-acrylic acid]-polyethylene glycol (Poly[NVP-AA]-PEG) interpolymer type systems were prepared by free radical polymerization. Azobisisobutyronitrile (AIBN) was used for initiating the polymerization and *N*,*N*″-methylene bisacrylamide was employed as a crosslinking agent. The concentration of initiator and crosslinking agent were varied and the reaction parameters were optimized. The obtained poly[NVP-AA]-PEG hydrogels were fully characterized by fourier transform infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and optical microscopy (OPM). The equilibrium swelling studies were carried out in simulated gastric fluid (SGF) of pH 1.2 and simulated intestinal fluid (SIF) of pH 6.8. The gels were swollen extensively in SIF when compared to SGF. The influence of pH on the swelling of the hydrogel was also studied in buffers of varying pH. 5-Fluorouracil (5-FU) was loaded and the in vitro release studies were carried out in SGF. The results of this study suggest that poly [NVP-AA]-PEG hydrogels could be useful for localized delivery of drugs in the stomach. © 1997 Elsevier Science B.V.

Keywords: Hydrogels; Biodegradable; pH Sensitive; Equilibrium swelling; Stomach; Drug delivery; 5-Fluorouracil

1. Introduction

Recent research efforts throughout the world have resulted in significant development of controlled drug delivery systems (Hutchinson and Furr, 1990; Maa and Heller, 1990). Of which hydrogels have been extensively exploited for biomedical applications due to their high water content which imparts excellent biocompatibility (Kost and Langer, 1986; Pitt, 1990). Hydrogels and their properties have been studied by several authors (Zentner et al., 1978; Gander et al., 1989). Drug delivery systems developed for many different purposes have been based on hydrogels, mostly the neutral hydrogels.

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Site specific drug delivery has become a major research endeavor for the pharmaceutical scientists. pH Sensitive hydrogels usually contain pendent acidic or basic groups such as carboxylic acids and primary amines, or strong acid and bases, such as sulfonic acids and ammonium salts which change ionization in response to changes in pH, thus changing the properties of the gel (Heller et al., 1990; Siegal and Firestone, 1988).

In the current investigation, we have attempted to develop a pH sensitive, biodegradable and biocompatible hydrogel to achieve site specific drug delivery. Poly [NVP-AA]-PEG interpolymeric hydrogels were prepared by free radical polymerization. Azobisisobutyronitrile (AIBN) was used as an initiator and *N*,*N*″-methylene bisacrylamide (BIS) was employed as crosslinking agent. These hydrogels were characterized by FT-IR, DSC, TGA and OPM. Equilibrium swelling studies were also carried out in SGF and SIF. The influence of pH on the swelling capacity of the hydrogels was also investigated. 5-fluorouracil, an anticancer drug was entrapped into the hydrogels and the in vitro release profiles in SGF were established.

2. Experimental

2.1. Materials

Poly(ethyleneglycol) 4000 (SDS, India) and *N*-vinyl-2-pyrrolidone (Fluka, Switzerland) were used as obtained. *N*,*N*″-Methylene bisacrylamide was procured from Sigma, USA. Azobisisobutyronitrile (LOBA, India) was recrystallised from methanol before use. All other chemicals used were of analytical reagent grade. The anticancer drug, 5-FU was obtained from SISCO research laboratory, India.

2.2. Methods

2.2.1. Preparation of poly[NVP-AA]-PEG hydrogels

Appropriate quantities of AA and NVP were taken in a mole ratio of 1:2.6 into a gel tube and an aqueous solution of PEG-4000 was added. To this AIBN and BIS were added. The concentration of PEG, AIBN and BIS were varied systematically with respect to the concentration of the monomers. The reaction parameters for the hydrogel formation were optimized to achieve the best results. The reaction contents were thoroughly mixed and the polymerization was allowed to proceed at 37°C for 1 h. The resulting hydrogels were smooth, cylindrical and opaque in the dry state. The hydrogels were extensively washed with distilled water to remove any residual monomer. The gels were air-dried and stored until further use.

2.2.2. Entrapment of anticancer drug

5-FU was entrapped by adding the drug to the PEG solution before the addition of NVP and mixed thoroughly. The monomers and other reagents were added subsequently just as in the case of placebo hydrogel and incubated at 37°C for 1 h. The resulting hydrogels were washed with distilled water, dried and stored until further use.

2.2.3. Determination of percentage of drug entrapped

The amount of drug entrapped in the poly[NVP-AA]-PEG interpolymeric hydrogels was determined by an indirect method. After the gel preparation the washings were collected, filtered with a 0.45-μm millipore filter and assayed using UV/VIS spectroscopy. The difference between the amount of drug taken initially and the drug content in the washings is the amount of drug entrapped.

2.2.4. Characterization

Infrared spectra of poly[NVP-AA]-PEG hydrogel was obtained using Nicolet impact 400 FTIR spectrometer. TGA and DSC were carried out on Seiko SSC 5200 H TG/DSC in nitrogen atmosphere at a heating rate of 20°C/min. The morphological characteristics of the hydrogels were studied using Richert polyvar 2 MET-optical microscope.

2.2.5. Equilibrium swelling studies

The equilibrium swelling of the poly[NVP-AA]-PEG hydrogels was determined by swelling the

hydrogel pellets in SGF and SIF (specified in Japanese Pharmacopia XII) at room temperature until equilibrium was attained. The influence of pH on the swelling behavior of the hydrogels was determined by placing the hydrogel pellets in buffers of different pH ranging from 2–9 at 37°C until they attained equilibrium. The swollen weight of the pellet was determined by blotting of the pellet every hour until equilibrium was attained.

The percent swelling was calculated by the following equation.

$$\% \text{ Swelling} = \frac{W_t - W_0}{W_0} \times 100$$

where W_o, being the initial weight and W_t the final weight of the pellet at time t.

The swelling of all the hydrogels prepared using various concentrations of initiator, crosslinking agent and PEG were analyzed.

2.2.6. 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 at 37°C in a GFL-1086 water bath shaker incubator with reciprocating motion (100 rpm). At periodic intervals, aliquots were withdrawn and assayed using Shimadzu UV-2100S, UV-VIS spectrophotometer. After each sampling an equal volume of fresh SGF was taken as release medium. All the release determinations were carried out in triplicate.

3. Results and discussion

To achieve long-term oral site specific drug delivery, it is desirable to develop devices that could be selectively retained at the site of action. The use of bioadhesives, floating systems and size exclusion devices has shown little success in achieving gastrointestinal residence times near the 24-h time range (Davis et al., 1987; Grubber et al., 1987). For such hydrogels to be used as gastric retention devices, they are required to undergo considerable size expansion to prevent premature gastric emptying and biodegradation to control residence time and removal (Waleed Shalaby et al., 1990). Highly swellable biodegradable hydrogels may suit this requirement. In the present study we have prepared poly[NVP-AA]-PEG interpolymeric type hydrogels and investigated their efficacy for localized drug delivery in the stomach.

3.1. Preparation of poly[NVP-AA]-PEG hydrogel

The interpolymeric hydrogel system consists of polyvinylpyrrolidone which is slowly degradable and has a high glass transition temperature and PEG, a highly biocompatible and hydrophilic polymer with low T_g. This combination provides the required resiliency to the biocompatible and biodegradable polymeric matrix for the controlled drug delivery. Polyacrylic acid was also included in the system which imparts pH sensitivity. This pendent acidic moiety changes ionization in response to the changes in pH. The poly[NVP-AA]-PEG hydrogel also displays pH sensitive nature which can be exploited for site specific controlled drug delivery.

The poly [NVP-AA]-PEG hydrogels were characterized by FT-IR spectroscopy. IR (Fig. 1) shows the disappearance of the vinyl unsaturation at 1640 cm^{-1} due to the formation of the polymer. The acid carbonyl peak at 1652 cm^{-1} and the peak at 3400 cm^{-1} due to the hydroxyl group are observed. This clearly indicates the formation of inter polymer type system. The thermal analysis of the poly[NVP-AA]-PEG gel by TGA (Fig. 2) demonstrates the stability of the polymeric matrix up to 320°C. There was initial weight loss due to loss of moisture in the gel from 60–120°C. The gel undergoes weight loss around 322°C and continues up to 441°C. The continuous TGA curve also indicates the formation of interpolymeric matrix. The DSC (Fig. 3) of poly[NVP-AA]-PEG indicates an endothermic transition at about 125°C which can be attributed to the loss of loose and bound water in the hydrogel. The gel appeared to be thermally stable up to 320°C. The DSC results corroborates with that of the TGA. The optical micrographs of the dry gel clearly shows that the gel surface appears to be somewhat compact in dry condition. The gel swells extensively in water and the morphology appears

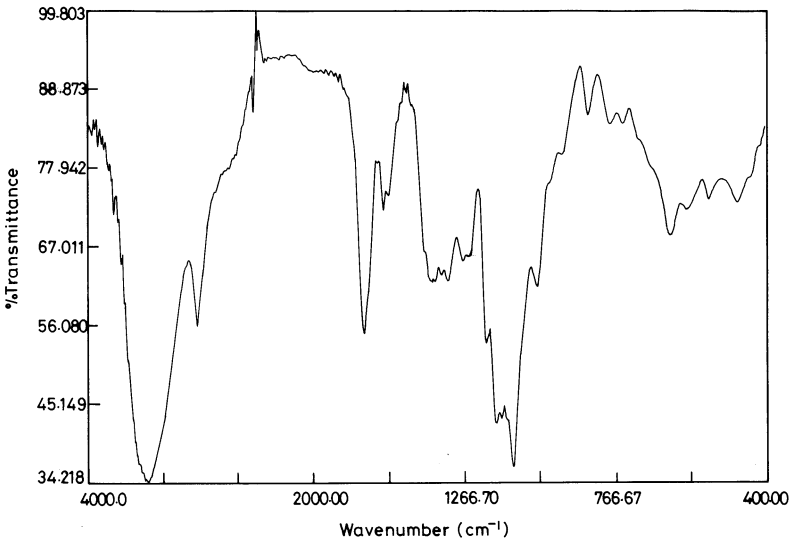

Fig. 1. Fourier transform infrared spectrum of Poly[NVP-AA]-PEG hydrogel.

that the gel network gets loosened and expands. The optical micrographs of the gel after release indicates the large voids in the loosened hydrogel network due to the release of the incorporated drug.

3.2. Equilibrium swelling studies

The equilibrium swelling capacities of the poly[NVP-AA]-PEG hydrogels prepared by variation of the concentration of initiator in SGF and SIF are shown Table 1. The swelling capacity increased tremendously in SIF and lost gel integrity. Table 1 shows the swelling capacities of the gels prepared by variation of the crosslinking

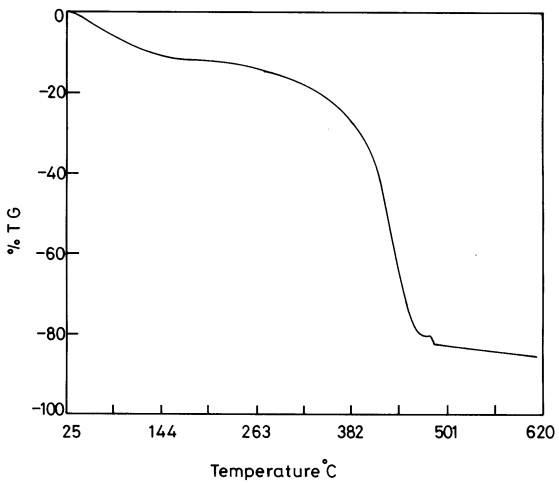

Fig. 2. Thermogravimetric analysis of Poly[NVP-AA]-PEG hydrogel.

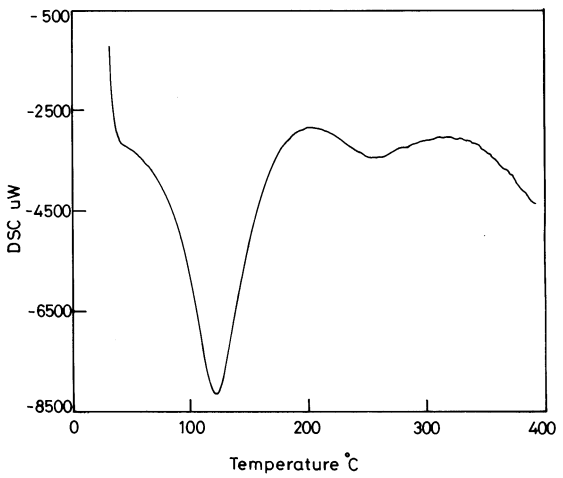

Fig. 3. Differential scanning calorimetric thermogram of Poly[NVP-AA]-PEG hydrogel.

Table 1
Equilibrium swelling studies of poly[NVP-AA]-PEG hydrogels

Poly[NVP-AA]-PEG hydrogels prepared with variation of:	Percent swelling at equilibrium	
	SGF	SIF
Initiator concentration		
G-I (2.75%)	93	222
G-II (3.25%)	190	440
G-III (3.75%)	75	345
Crosslinker concentration		
G-IV (1.75%)	74	381
G-V (2.0%)	190	440
G-VI (2.25%)	60	608
PEG concentration		
G-VII (4.0%)	81	207
G-VIII (5.25%)	190	440
G-IX (6.5%)	88	275

agent. This study also indicates that at optimum levels of crosslinker concentration, the swelling capacities were high. The gels prepared with variation of PEG concentration also displayed similarity in the sorption capacities of SGF and SIF (Table 1). Overall the equilibrium swelling of the gels prepared at optimum concentrations of initiator, crosslinking agent and PEG were swollen more in SGF when compared to the other gels. The swelling was much higher in SIF for all the gels and the gel integrity was lost. Hence G-II, the gel prepared with optimum levels of initiator, crosslinker and PEG were chosen to carry out in-vitro release profiles. Further G-II was also stable in SGF for longer periods. The influence of pH on the swelling capacity of the gels was also analyzed (Fig. 4). This swelling curve clearly indicates that these gels are pH sensitive with an upward rise in the sorption capacities with increasing pH of the medium.

After swelling to the equilibrium state these swollen hydrogels undergo degradation in a phased manner. PEG being a highly water soluble polymer starts undergoing dissolution which is manifested as surface erosion of the interpolymeric matrix. Polyacrlic acid also being water soluble will slowly dissolve and undergo degradation in the system. Finally the polyvinylpyrrolidone which constitutes the bulk of the gel

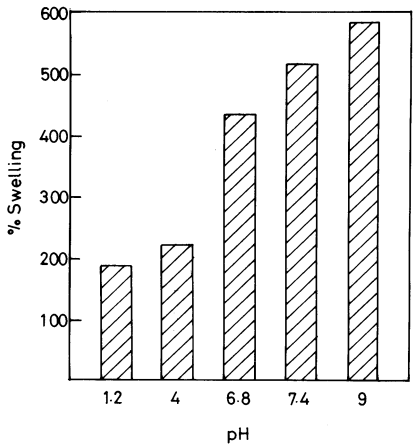

Fig. 4. Influence of pH on the equilibrium swelling of the Poly[NVP-AA]-PEG hydrogels.

matrix undergoes very slow hydrolytic degradation in the physiological environment to yield non-toxic normal metabolites. This process of degradation being very slow may take from several weeks to months depending on the molecular weight of the PVP in the hydrogel.

3.3. In vitro release studies

The in vitro release profiles of the entrapped anti-cancer drug 5-FU in the poly[NVP-AA]-PEG hydrogels were established in SGF (Fig. 5). There was an initial burst release of the drug to an

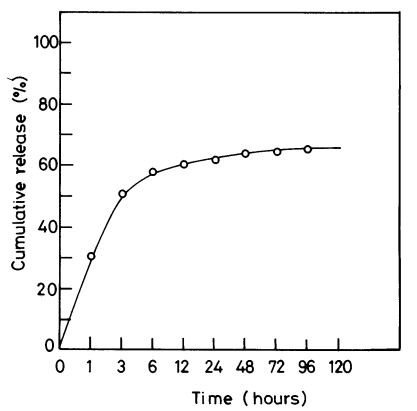

Fig. 5. In vitro release profile of 5-FU from Poly[NVP-AA]-PEG gels in SGF. Each datum point represents the average of three determinations.

extent of about 30% and thereafter the release followed almost zero-order fashion. There was about 43% release in the first 2 h. of the release study. The release slowed down later. By 24 h there was 62% release of the entrapped drug. Thereafter the release was very slow and released about 65% in a period of 4 days. The drug release profile of 5-FU from poly[NVP-AA]-PEG hydrogels follows a characteristic pattern. The initial burst effect may be attributed to the release of drug entrapped towards the surface of the gel matrix. The drug releases by diffusion which is correlated to the high degree of swelling of the gel and the equilibrium swollen state being achieved in 2 h in SGF. The release slowed down after 2 h. The drug release mechanism at this stage can be understood by correlating the release data with the expected degradation pattern of the gel matrix. The drug released after two hours may be attributed to the erosion of the PEG component in the matrix. After 6 h the drug continued but was very slow. This slow release may be attributed to the very slow hydrolytic degradation of the polymeric matrix. With appropriate modification of the crosslinking density of the polymeric matrix, the desired drug release rates may be achieved. The release profiles obtained indicate that these polymeric matrices can be utilized for localized drug delivery in the acidic environment of the stomach.

4. Conclusion

Biocompatible and biodegradable pH sensitive hydrogel matrices are developed for the controlled drug delivery in the gastric environment of stomach. Poly[NVP-AA]-PEG interpolymeric hydrogels were synthesized by free radical polymerization using AIBN as initiator and BIS as crosslinking agent. The conditions for the hydrogel formation were systematically optimized by varying the concentration of the initiator, crosslinking agent and PEG. These hydrogels were characterized by FT-IR, TGA, DSC and optical microscopy. Equilibrium swelling measurements were carried out in SGF and SIF. The influence of pH on the swelling was also studied in various buffers. 5-FU, an anti-cancer drug, was entrapped into these gels and the in vitro drug release profiles were established in SGF. These highly swellable polymeric matrices may be utilized for gastric retention owing to the large expansion which prevents gastric emptying. These novel drug delivery matrices hold a great promise for localized drug delivery in the acidic environment.

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