ELSEVIER

International Journal of Pharmaceutics 207 (2000) 65–70

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Preparation and in-vitro evaluation of poly[*N*-vinyl-2-pyrrolidone-polyethylene glycol diacrylate]-chitosan interpolymeric pH-responsive hydrogels for oral drug delivery

K.L. Shantha, D.R.K. Harding *

Chemistry, Institute of Fundamental Sciences, Massey University, Palmerston North, New Zealand

Received 26 May 2000; received in revised form 20 July 2000; accepted 21 July 2000

Abstract

Biocompatible and biodegradable pH-responsive hydrogels based on *N*-vinyl pyrrolidone (NVP), polyethylene glycol diacrylate (PAC) and chitosan were prepared for controlled drug delivery. These interpolymeric hydrogels were synthesized by a free radical polymerization technique using azobisisobutyronitrile (AIBN) as initiator and *N*,*N*′-methylenebisacrylamide (BIS) as crosslinker. These hydrogels were subjected to equilibrium swelling studies in enzyme-free simulated gastric and intestinal fluids (SGF and SIF). These swelling studies clearly indicated that these hydrogels were swollen more in SGF when compared to SIF. Theophylline and 5-fluorouracil (5-FU) were entrapped into these hydrogels and equilibrium-swelling studies were carried out for the drug-entrapped gels in enzyme-free SGF and SIF. The in-vitro release profiles of the drugs were established in enzyme-free SGF. More than 50% of the entrapped drugs were released in the first 2 h at gastric pH and the rest of the drug release was slower.

Keywords: pH-responsive; Interpolymeric hydrogel; Equilibrium swelling; Drug-delivery

1. Introduction

Recent years have witnessed significant advances made in the controlled drug delivery technology using polymeric hydrogels. Stimuli-responsive polymeric hydrogels, which swell or shrink in response to changes in the environmental conditions, have been extensively studied and used as smart materials for various biomedical applications (Peppas, 1997; Kurisawa et al., 1998; Langer, 1998). These polymeric hydrogels are being prepared from a limited number of synthetic polymers and their derivatives such as copolymers of methacrylic acid, acrylamide and *N*-isopropylacrylamide (Kopecek et al., 1971; Suzuki and Tanaka, 1990; Kokufuta et al., 1991;

* Corresponding author. Tel.: +64-6-3505016; fax: +64-6-3542140.

E-mail address: d.r.harding@massey.ac.nz (D.R.K. Harding).

0378-5173/00/$ - see front matter
PII: S0378-5173(00)00533-0

Kwon et al., 1991; Osada et al., 1992; Chen and Hoffman, 1995; Yoshida et al., 1995; Holtz and Asher, 1997). The design of a new biodegradable and biocompatible stimuli-sensitive polymeric systems play a key role in the development of multi-stimuli responsive biomaterials (Kurisawa and Yui, 1998).

Chitosan, a natural polysaccharide exhibits favorable biological properties such as biocompatibility, biodegradability and non-toxicity (Muzzarelli, 1977; Akbuga, 1995). For several years, chitosan has been largely evaluated as a potential vehicle for drugs administered orally. The development of hydrogel matrices incorporated with chitosan for oral drug delivery is still a virgin area of study. Hence the current investigation deals with the development of a new chitosan based hydrogel system for oral drug delivery to the stomach region.

2. Materials and methods

2.1. Materials

NVP (Fluka, Buchs, Switzerland) was used as obtained. PAC was synthesized in the laboratory as reported earlier (Yamini et al., 1997). AIBN was a gift sample from Flex Carpets, Wellington, New Zealand and used after recrystallization from methanol. BIS (SERVA, Hiedelberg 1-Carl-Benz-Stra be 7, Germany), theophylline and 5-FU were from SIGMA, St. Loius, USA. Chitosan (catalogue number: 44,887-7, medium mol. wt.) was obtained from ALDRICH, Milwaukee, WI, USA and used without further purification. All other chemicals were reagent grade and used as obtained.

2.2. Preparation of interpolymeric hydrogels

The macromonomer PAC and NVP were taken in a ratio of 1:4 (w/w) as reported earlier (Yamini et al., 1997). To this 2.5% (w/v) of a 5% aqueous acetic acid solution of chitosan was added. About 3.5% (w/w) of AIBN and 2% (w/w) of BIS were added based on the weight of the monomer. The polymerization was allowed to proceed at 37°C for a period of 3 h. Smooth cylindrical gels were obtained. The hydrogels were extensively washed with distilled water to remove any residual monomer. The placebo gels (GCP) were air-dried and stored until further use. Fig. 1 shows the schematic preparation of the hydrogels. Hydrogels loaded with theophylline (GCT) and 5-FU (GCF) were also prepared in the same manner as placebo gels. Known amounts of drugs were added to the reaction mixture, stirred thoroughly and the polymerization carried out.

2.3. Determination of the amount of drug entrapped

The amount of drug entrapped in the poly[NVP-PAC]-chitosan hydrogels was determined by an indirect method. After the gel preparation, the washings were collected, filtered with a 0.45 μm Millipore filter and tested at λ_{max} 273 and 267 for theophylline and 5-FU respectively using UV/VIS spectroscopy. The drugs entrapped exhibited the same λ_{max} as the free drug. This clearly indicates that the drugs entrapped have not undergone any possible chemical reaction during the matrix formation. The difference between the amount of drug initially employed and the drug content in the washings is taken as an indication of the amount of drug entrapped.

2.4. Equilibrium swelling studies

The equilibrium swelling of the poly[NVP-PAC]-chitosan hydrogels was determined by swelling of the gel pellets in enzyme-free SGF and SIF (see Japanese Pharmacopoeia XII). SGF (pH 1.2) was prepared by dissolving 2 g of sodium chloride and 7 ml of concentrated HCl in 1 L of distilled water. SIF (pH 6.8) was prepared by mixing 250 ml of 0.2 M KH_2PO_4 and 118 ml of 0.2 N NaOH. The swelling study was carried out at room temperature until equilibrium was attained. The swollen weight of the pellet was determined by blotting the pellet every hour until equilibrium was attained. The data represents mean $\pm$ S.D. from three independent experiments.

The percent swelling was calculated by the following equation:

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

where W_0 is the initial weight and W_t, the final weight of the pellet at time t.

2.5. In-vitro release studies

The in-vitro release of the entrapped drugs, theophylline and 5-FU were carried out by placing the hydrogel pellets loaded with the drug into 500 ml of SGF at 37°C in a Julabo SW.20C shaking water bath incubator with reciprocating motion (100 rpm). At periodic intervals 3 ml of aliquots were withdrawn and tested at λ_{max} 273 and 267 for theophylline and 5-FU respectively using Hewlett Packard 8452A UV-VIS spectrophotometer. The release media were replaced periodically with an equal volume of fresh SGF to create infinite sink conditions. The data represents mean ± S.D. from three independent experiments.

3. Results and discussion

Chitosan, a natural polymer which exhibits pH sensitivity (Patel and Amiji, 1996) was chosen to develop interpolymeric hydrogels for oral controlled drug delivery to the stomach region in combination with NVP and PAC. Interpolymeric hydrogels are formed when two monomers are copolymerized in the presence of a polymer (Ravichandran et al., 1997). We expected a kind of intermixing of the polymeric systems to take place when these polymers are crosslinked to form polymeric networks. A totally new biodegradable and biocompatible system was developed to achieve stimuli responsive drug delivery. The choice of the ratio of the comonomers NVP and PAC was based on the swelling results of our previous investigation (Yamini et al., 1997). The gels prepared with PAC:NVP in a weight ratio of 1:4 exhibited higher swelling in physiological

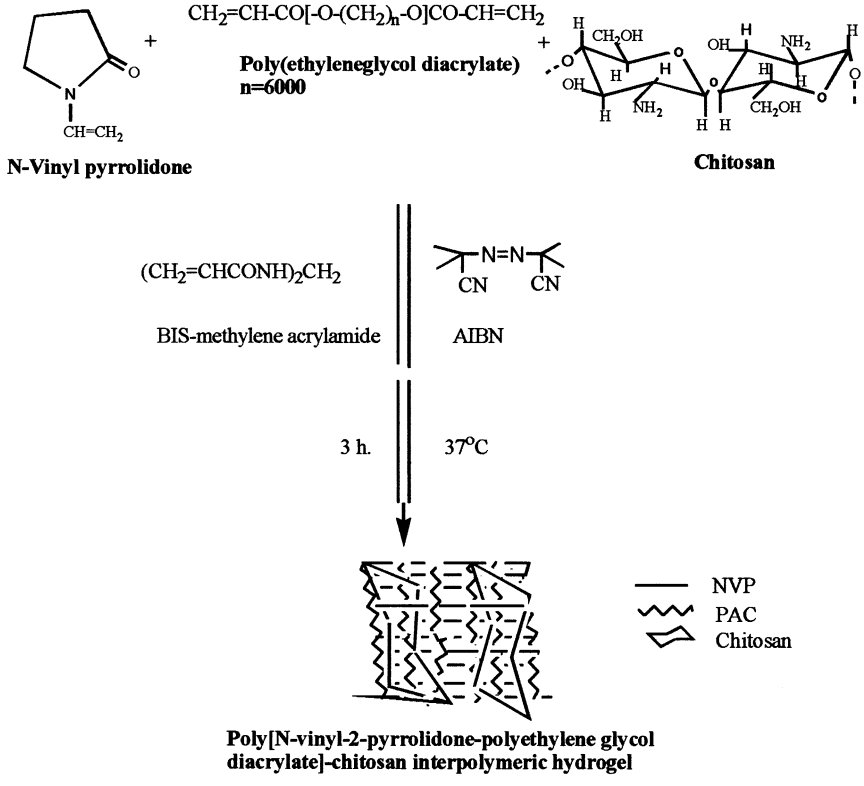

Fig. 1. Schematic preparation of poly[NVP-PAC]-chitosan hydrogels.

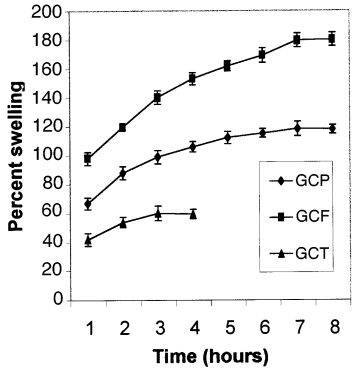

Fig. 2. Equilibrium swelling measurements of poly[NVP-PAC]-chitosan hydrogels in SGF. Placebo (GCP), theophylline loaded gel (GCT) and 5-FU loaded gel (GCF).

fluids when compared to the gels prepared with a weight ratio of 1:8. The presence of a chitosan in a small amount has imparted pH sensitivity to the polymeric matrix. The concentration of chitosan was limited to 2.5% after repeated trials with higher concentrations of chitosan in the gel preparation. Gels formed beyond this limit were not stable. This interpolymeric hydrogel was characterized for equilibrium swelling and drug release kinetics.

3.1. Equilibrium swelling studies

The percent equilibrium swelling of poly[NVP-PAC]-chitosan hydrogels in SGF and SIF are shown in Fig. 2 and Fig. 3. The placebo gel exhibits 118% equilibrium swelling in SGF in 7 h and 80% swelling in SIF obtained in 5 h. Theophylline entrapped gels showed about 60% swelling in SGF and 42% swelling in SIF and attained equilibrium in 3 and 2 h respectively. The 5-FU entrapped hydrogels exhibited much higher swelling at equilibrium. These gels were swollen to 180% in SGF and 160% in SIF at equilibrium respectively. The swelling of all the gels was higher in SGF when compared to SIF. These hydrogels exhibit pH sensitive swelling due to the presence of very small amounts of chitosan in the interpolymeric gel matrix. This can be explained due to the ionic interaction of the amino group of chitosan in stomach pH conditions. Theophylline entrapped gels exhibited much lower swelling than the placebo gels at equilibrium. This may be attributed to the hydrophobic drug-polymer interactions, which limit the diffusion of the fluids into the partially swollen hydrogels. This may further retard the equilibrium swelling of these hydrogels. In the case of 5-FU loaded hydrogels, the swelling at equilibrium is higher than the placebo gels indicating the hydrophilic nature of the entrapped drug. The presence of homogenously dissolved or dispersed drug in poly(hydroxyethyl methacrylate) beads was found to generate an additional osmotic driving force which alters both the swelling osmotic pressure and the associated time-dependent relaxation of hydrogel network during the simultaneous sorption of water and desorption of drug (Lee and Kim, 1991). These chitosan-based hydrogels are able to retain gel integrity for nearly 24 h after attaining equilibrium swelling in SGF and later they degrade very slowly.

3.2. In-vitro release studies

The in-vitro release profiles of the theophylline and 5-FU in SGF are shown in Fig. 4. As the gels exhibited higher swelling at equilibrium in SGF, the in-vitro release studies were carried out further in SGF to achieve localized oral drug delivery to the stomach region. About 41% of theophylline entrapped was released in the first 1

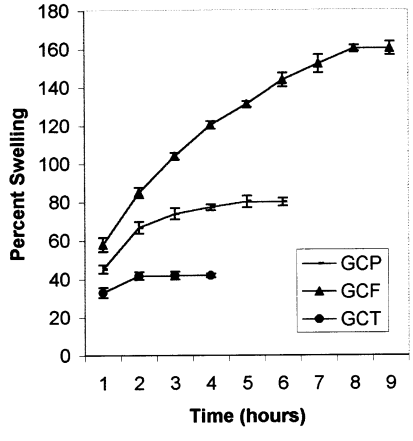

Fig. 3. Equilibrium swelling measurements of poly[NVP-PAC]-chitosan hydrogels in SIF. Placebo (GCP), theophylline loaded gel (GCT) and 5-FU loaded gel (GCF).

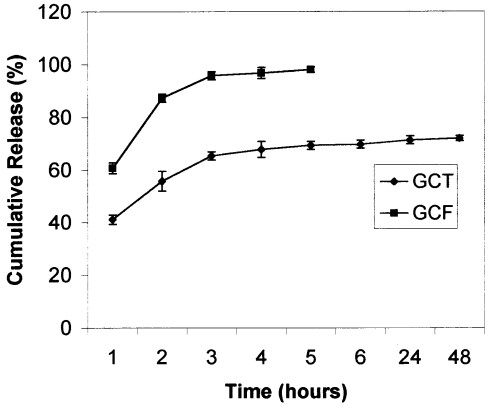

Fig. 4. In-vitro release profiles of theophylline (GCT) and 5-FU (GCF) loaded poly[NVP-PAC]-chitosan hydrogels.

h in SGF. This initial burst effect may be attributed to the diffusion of the drug caused by rapid gel swelling and also the release of drug adsorbed towards the surface of the gel matrix. After 2 h, 62% of the drug had been released. This may be due to the diffusion of the drug entrapped in the bulk of the matrix. Thereafter the drug release had slowed down probably due to reduced swelling in SGF in addition to the lower concentration of drug in the gel matrix. The remaining drug in the matrix may be released in a very slow fashion due to the slow rate of degradation of the gel matrix. In total about 72% of theophylline was released at the end of 48 h. The release of 5-FU from these hydrogels was much faster in SGF. This result corroborates with the greater swelling of the drug-entrapped gel in SGF. About 61% of the entrapped drug were released in the first hour. By the end of 5 h, about 98% of the drug entrapped was released. The release profiles of the theophylline and 5-FU entrapped hydrogels indicate that these pH responsive hydrogels can be exploited for oral drug delivery. By appropriate chemical modification of cross-linking densities of these gels, the rate of drug release can be modulated. These chitosan based interpolymeric hydrogels exhibit a strong potential for successful exploitation for the localized delivery of drugs to the gastric environment.

4. Conclusion

A new pH responsive drug delivery system based on interpolymeric hydrogel, poly[NVP-PAC]-chitosan was developed for oral drug delivery. The preparation of these copolymeric hydrogels was carried out using a free-radical initiation technique. The equilibrium swelling measurements of these hydrogels carried out in simulated fluids clearly indicated the pH responsive nature of these hydrogels. The in-vitro release profiles of theophylline and 5-FU were established in SGF. This preliminary investigation of chitosan based interpolymeric pH responsive hydrogels indicates that further modification of these hydrogels can lead to the successful application for the localized oral drug delivery to the gastric environment.

References

Akbuga, J., 1995. A biopolymer: Chitosan. Int. J. Pharm. Adv. 1, 3–18.

Chen, G., Hoffman, A.S., 1995. Graft copolymers that exhibit temperature-induced phase transitions over a wide range of pH. Nature 373, 49–52.

Holtz, J.H., Asher, S.A., 1997. Polymerized colloidal crystal hydrogel films as intelligent chemical sensing materials. Nature 389, 829–832.

Kokufuta, E., Zhang, Y.Q., Tanaka, T., 1991. Saccharide-sensitive phase transition of a lectin-loaded gel. Nature 351, 302–304.

Kopecek, J., Vacik, J., Lim, D., 1971. Permeability of membranes containing ionogenic group. J. Polym. Sci. A-1 (9), 2801–2815.

Kurisawa, M., Matsuo, Y., Yui, N., 1998. Modulated degradation of hydrogels with thermo-responsive network in relation to their swelling behaviour. Macromol. Chem. Phys. 199, 705–709.

Kurisawa, M., Yui, N., 1998. Modulated degradation of dextran hydrogels grafted with poly(*N*-isopropylacrylamide-co-*N*,*N*′-dimethylacrylamide) in response to temperature. Macromol. Chem. Phys. 199, 2613–2618.

Kwon, I.C., Bae, Y.H., Kim, S.W., 1991. Electrically erodible polymer gel for controlled release of drugs. Nature 354, 291–293.

Langer, R., 1998. Drug delivery and targeting. Nature 392 (suppl.), 5–10.

Lee, P.I., Kim, C.-J., 1991. Probing the mechanisms of drug release from hydrogels. J. Cont. Rel. 16, 229–236.

Muzzarelli, R.A.A., 1977. Chitin. Pergamon Press, Oxford.

Osada, Y., Okuzaki, H., Hori, H., 1992. A polymer gel with electrically driven motility. Nature 355, 242–244.

Patel, V.R., Amiji, M.M., 1996. Preparation and characterization of freeze-dried chitosan-poly(ethylene oxide) hydrogels for site-specific antibiotic delivery in the stomach. Pharm. Res. 13, 588–593.

Peppas, N.A., 1997. Hydrogels and drug delivery. Curr. Opin. Coll. Inter. Sci. 2, 531–537.

Ravichandran, P., Shantha, K.L., Panduranga Rao, K., 1997. Preparation, swelling characteristics and evaluation of hydrogels for stomach specific drug delivery. Int. J. Pharm. 154, 89–94.

Suzuki, A., Tanaka, T., 1990. Phase transition in polymer gels induced by visible light. Nature 346, 345–347.

Yamini, C., Shantha, K.L., Panduranga Rao, K., 1997. Synthesis and characterization of poly{*N*-vinyl-2-pyrrolidone-polyethylene glycol diacrylate} copolymeric hydrogels for drug delivery. J. M. S.-Pure Appl. Chem. A34, 2461–2470.

Yoshida, R., Ucida, K., Kaneko, Y., Sakai, K., Kikuchi, A., Sakurai, Y., Okano, T., 1995. Comb-type grafted hydrogels with rapid de-swelling response to temperature changes. Nature 374, 240–242.