Synthesis and Evaluation of Sucrose-Containing Polymeric Hydrogels for Oral Drug Delivery

K. L. SHANTHA, D. R. K. HARDING

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

Received 16 January 2001; accepted 19 July 2001

ABSTRACT: Biodegradable and biocompatible copolymeric hydrogels based on sucrose acrylate, *N*-vinyl-2-pyrrolidinone, and acrylic acid were designed and synthesized. Because of the growing importance of sugar-based hydrogels as drug delivery systems, these new pH-responsive sucrose-containing copolymeric hydrogels were investigated for oral drug delivery. The sucrose acrylate monomer was synthesized and characterized. The copolymeric hydrogel was synthesized by free-radical polymerization. Azobisisobutyronitrile (AIBN) was the free-radical initiator employed and bismethyleneacrylamide (BIS) was the crosslinking agent used for hydrogel preparations. Homopolymeric vinyl pyrrolidone hydrogels were also prepared by the same technique. The hydrogels were characterized by differential scanning calorimetry, thermogravimetric analysis, and scanning electron microscopy. Equilibrium swelling studies were carried out in enzyme-free simulated gastric and intestinal fluids (SGF and SIF, respectively). These results indicate the pH-responsive nature of the hydrogels. The gels swelled more in SIF than in SGF. A model drug, propranolol hydrochloride (PPH), was entrapped in these gels and the *in vitro* release profiles were established separately in both enzyme-free SGF and enzyme-free SIF. The drug release was found to be faster in SIF. About 93 and 99% of the entrapped drug was released over a period of 24 h in SGF and SIF, respectively. © 2002 Wiley Periodicals, Inc. J Appl Polym Sci 84: 2597–2604, 2002

Key words: hydrogel; biodegradable; sucrose acrylate; pH-responsive; oral drug delivery

INTRODUCTION

Recent years have witnessed significant advances in controlled drug delivery using polymeric materials. Polymeric hydrogels are gaining more attention as drug delivery systems, especially for the controlled release of pharmaceutically active peptides and proteins.[1,2] Hydrogels have been widely used in many biomedical applications including contact lenses, wound dressings, artificial organs, and delivery carriers for bioactive agents because of their high degree of biocompatibility.[3,4] High water content and low interfacial tension with the surrounding biological environment impart biocompatibility to the hydrogels.[5] Stimuli-responsive polymers have the possibility to achieve a specific drug release in response to internal or external stimuli.[6] Stimuli such as changes in pH, temperature, and glucose concentrations help stimuli-responsive polymers achieve a desired function.[7] Biologically, adhesive delivery systems offer important advantages.[8,9] Hydrophilic polymers and hydrogels containing carboxyl groups have displayed bioadhesive properties.[10,11] These polymers maintain contact with

Correspondence to: D. R. K. Harding (D.R.Harding@massey.ac.nz).

Contract grant sponsor: Massey University Research Fund.

Journal of Applied Polymer Science, Vol. 84, 2597–2604 (2002)

the intestinal epithelium for extended periods of time and actually penetrate it through and between the cells. Synthetic polymers containing side-chain carbohydrates are considered high-value polymeric materials because of their potential as biocompatible materials with medical applications. These applications are generally based on the fact that cell–cell interactions between oligosaccharides and lipids play an important role in various life processes.[12] Polystyrene was studied, given both its pendent lactose residues and its application as substratum for liver cell cultures.[13]

In view of the potential advantages offered by sugar-based polymeric systems, we initiated the design and synthesis of new sucrose-containing biocompatible and biodegradable polymeric hydrogels for drug delivery/tissue engineering applications. Sucrose acrylate (SA) monomer was synthesized by modification of a synthetic route reported earlier.[14] SA was copolymerized with *N*-vinyl-2-pyrrolidinone (NVP) and acrylic acid (AA) by free-radical polymerization. Homopolymeric vinylpyrrolidinone (PVP) hydrogels were also prepared under the same conditions. The poly[sucrose acrylate-*N*-vinyl-2-pyrrolidinone-acrylic acid] (poly[SA–NVP–AA] or SVA) hydrogel was characterized by DSC, TGA, and SEM. The equilibrium swelling studies were carried out in enzyme-free samples of SGF and SIF. PPH was entrapped as the model drug and the *in vitro* release profiles were established separately in enzyme-free preparations of SGF and SIF.

EXPERIMENTAL

Materials

Sucrose and BIS were obtained from Serva (Heidelberg, Germany). Acryloyl chloride and acrylic acid were obtained from Acros Organics (NJ). NVP was obtained from Fluka Chemie (Buchs, Switzerland). AIBN was a gift sample from Flex Carpets (Wellington, New Zealand) and used after recrystallization from methanol. PPH was obtained from Sigma (St. Louis, MO). All other chemicals were of reagent grade and used as obtained.

Methods

Preparation of Sucrose Acrylate

A solution of sucrose (25 g) in water (75 mL) was pH maintained at 10.5 with sodium hydroxide (6*M*). To this solution acryloyl chloride (3 mL) was added dropwise. This mixture was stirred at 20°C for 36 h then neutralized with hydrochloric acid. The resulting solution was extracted with methyl ethyl ketone (3 × 20 mL), then with butane-2-ol (8 × 25 mL), and finally evaporated to give sucrose acrylate. The proton nuclear magnetic resonance shows the presence of the vinylic protons at 5.8 and 6.2 ppm.

Preparation of Hydrogel

In a typical hydrogel preparation, SA (30% aqueous solution w/v) was taken for all the gels prepared. SA solution was added to NVP monomer taken in different weight ratios. AIBN (1% w/w) and BIS (1% w/w) were added based on the total monomer concentration. Acrylic acid was added to the reaction mixture(1.5×10^{-3} *M*) and polymerized. The polymerization was allowed to proceed for 24 h at 50°C. The resulting gels were washed thoroughly with distilled water to remove any residual monomers and dried at 50°C for 24 h. Hydrogels with three weight ratios of SA : NVP, SVA-1 (1 : 1), SVA-2 (1 : 2), and SVA-3 (1 : 3), were prepared. PVP hydrogels were also prepared by the same technique without the acrylic acid and SA monomers. PPH-loaded hydrogels were prepared by a similar procedure. A known amount of drug was added to the SA solution and dissolved before addition to the NVP. Figure 1 shows the monomer synthesis and the hydrogel preparation.

Determination of Amount of Drug Entrapped

The amount of drug entrapped in the SVA hydrogels was determined by an indirect method. After the gel preparation, the washings were collected, filtered, and tested using UV–Vis spectroscopy. 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.

Characterization

DSC spectra were obtained on a Perkin–Elmer PC Series DSC7 thermal analyzer (Perkin Elmer Cetus Instruments, Norwalk, CT) in nitrogen atmosphere at a heating rate of 5°C min^{-1}. The TGA spectra were obtained on a Perkin–Elmer 7 in nitrogen atmosphere at a heating rate of 10°C min^{-1}. The SEM was carried out on a Cambridge Stereoscan (Cambridge Biotech, Worcester, MA) electron microscope. The gel samples were

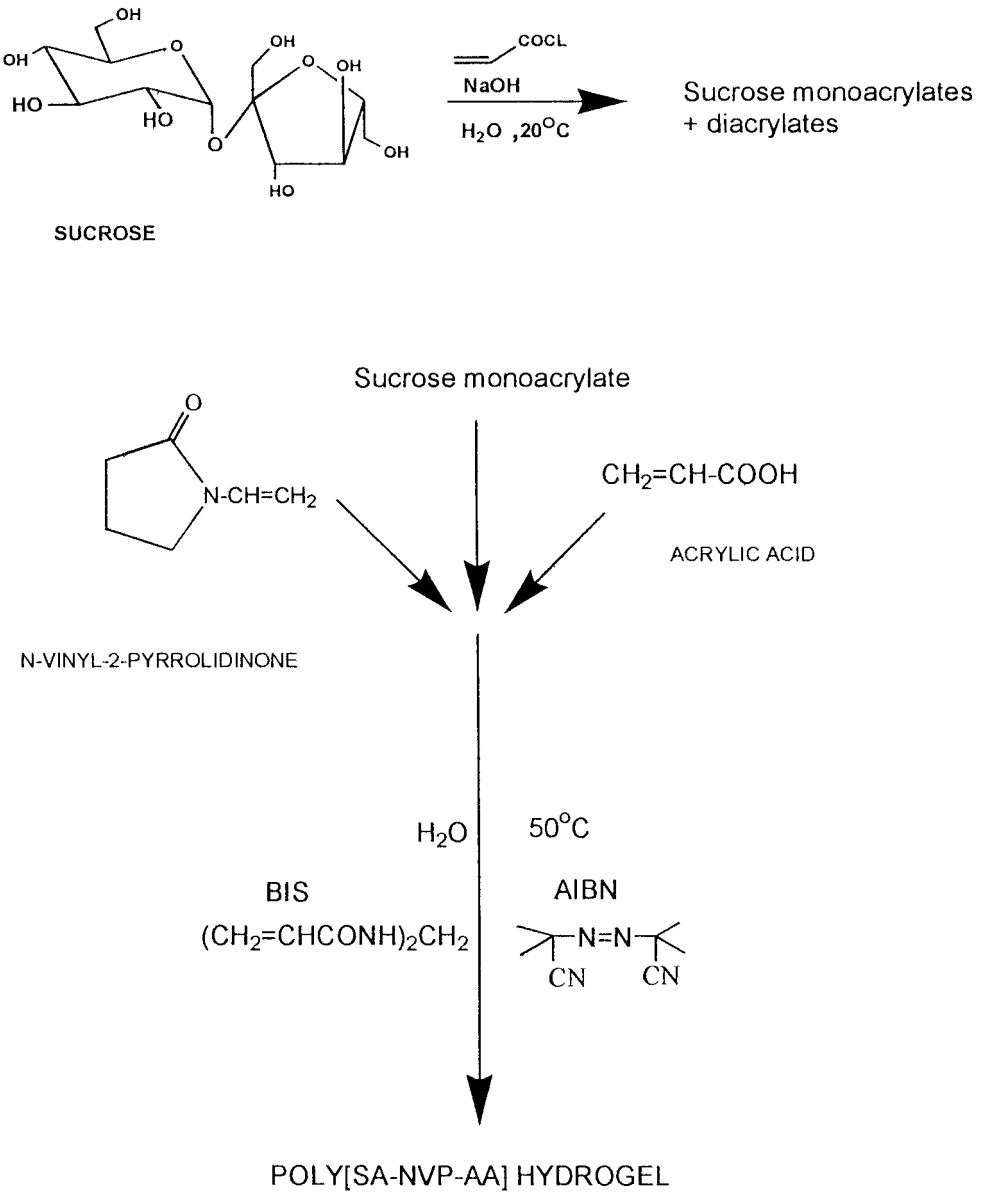


Figure 1 Preparation of SVA hydrogels.

mounted on a stub and coated with gold using a Bal-tec scd.050 sputter coater.

Equilibrium Swelling Studies

The equilibrium swelling of the SVA and PVP hydrogels was determined by swelling the gel pellets in SGF and SIF at 37°C. Enzyme-free SGF and SIF were prepared according to the procedure described in the U.S. Pharmacopeia.[15] The swelling of the pellet was determined gravimetrically after the gel attained equilibrium swelling. The data represent means ± SD from three independent experiments.

The percentage 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 is the final weight of the pellet.

In Vitro Release Studies

The *in vitro* release of the entrapped drug PPH was carried out by placing the hydrogel pellets

loaded with the drug in enzyme-free SGF and SIF at 37°C. The study was carried out in Julabo SW 20C shaking water-bath incubator with reciprocating motion (100 rpm). At periodic intervals, the release medium was replaced with fresh SGF and SIF after each estimation. These studies were carried out in triplicate. The data represent the means ± SD from three independent experiments.

RESULTS AND DISCUSSION

Synthesis of Poly[SA–NVP–AA] Copolymeric Hydrogel

Design and synthesis of new biodegradable and biocompatible polymeric hydrogel systems based on sugar-containing monomers was the primary objective in our study. These polymeric hydrogels containing hydrophilic constituents are expected to serve not only as drug delivery matrices for oral drug delivery but also as tissue engineering scaffolds. The bioadhesive character of both the sugar monomer and the acrylic acid serve the purpose of prolonged attachment to the mucous membrane in the gastrointestinal (GI) tract for controlled drug delivery. Three copolymeric hydrogels were prepared by varying the ratio of SA and NVP. Acrylic acid was incorporated at a constant concentration for all three gel preparations. Acrylic acid was incorporated into the gels to improve the pH sensitivity of the polymeric matrix. Acrylic acid in the gel matrix would provide a basis for tissue engineering applications of these materials in the future. Poly[SA–NVP] hydrogels were also prepared and the pH sensitivity of these gels was studied.[16] Equilibrium swelling studies of these gels in SGF and SIF indicate that these gels by themselves exhibit pH sensitivity, even in the absence of acrylic acid.

Differential Scanning Calorimetry

Figure 2 shows the DSC thermograms of the SVA-1, SVA-2, SVA-3, and PVP gels. The SVA-1 [Fig. 2(a)] gel shows broad exothermic transition around 182°C and a second smaller exothermic transition at 272°C. The first transition may be attributed to the decomposition of sucrose in the gel. The decomposition of sucrose acrylate would have resulted in the second thermal transition. The DSC of SVA-2 [Fig. 2(b)] shows a sharp peak at 187°C. This may be attributed to the glass transition (T_g) of the PVP moiety in the hydrogel.

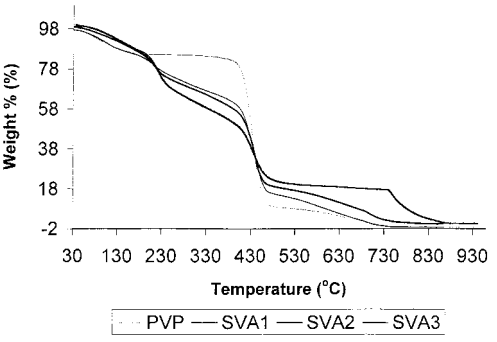


Figure 3 TGA of PVP and SVA hydrogels.

There is a broad exothermic transition at around 278°C, which may result from the decomposition of sucrose acrylate. The SVA-3 hydrogel [Fig. 2(c)] also shows a sharp transition at 195°C and a broad exotherm around 305°C, which may be attributed to the T_g of PVP and the decomposition of sucrose acrylate, respectively. In the case of PVP [Fig. 2(d)], a sharp glass transition at 160°C was observed. There is a clear indication of shift of T_g of the PVP moiety in the case of SVA-2 and SVA-3 gel samples. The T_g of PVP could not be observed for the SVA-1 gel, which may be the result of the higher concentration of sucrose acrylate in the gel preparation. The sucrose in the sucrose acrylate combined with the bound and loose water in the sample would have resulted in the broad transition at 182°C. With increasing concentration of NVP in the SVA-2 and SVA-3 gels, the T_g of the PVP moiety appeared with a shift in transition temperatures.

Thermogravimetric Analysis

The effect of copolymerization on the thermal stability of the hydrogels was studied by thermogravimetric analysis. Typical thermograms obtained by plotting the percentage of residual weight against temperature for PVP and SVA hydrogels are shown in Figure 3. TGA of PVP shows weight loss in three stages. The first stage of weight loss may result from the loss of loose and bound water in the hydrogel; in the second stage there is a major weight loss resulting from the degradation of the polymer; and the third stage of weight loss may be attributable to the decomposition of the remaining organics in the sample. TGA of SVA-1 and SVA-3 gels showed weight loss in four stages, whereas SVA-2 recorded three stages of weight loss. Table I shows the comparative TGA data for all the hydrogels. The two main stages of weight loss can be attrib-

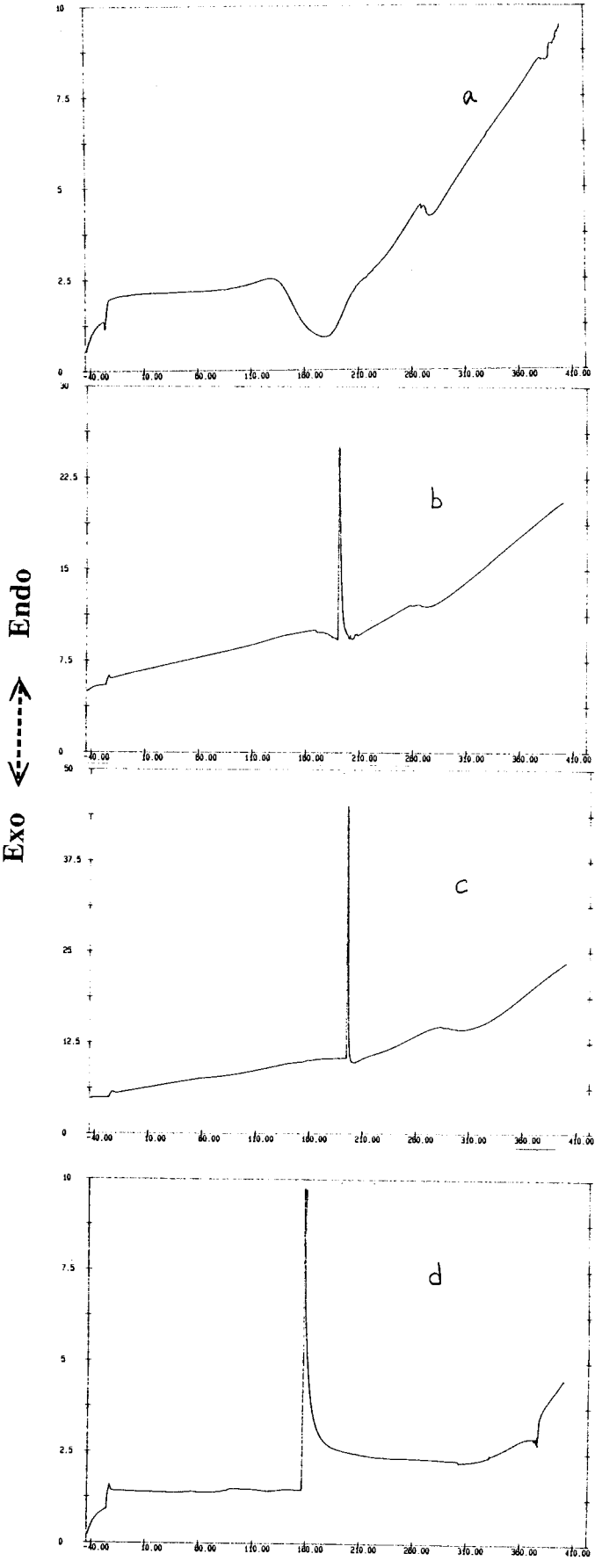


Figure 2 DSC of (a) SVA-1, (b) SVA-2, (c) SVA-3, and (d) PVP hydrogels.

Table I Thermogravimetric Analysis of PVP and SVA Hydrogels

	T_r[a] (°C)			
Sample	T_1	T_2	T_3	T_4
PVP	36–300 (14.8)	300–500 (76)	500–900 (9.9)	
SVA-1	35–180 (12.8)	180–350 (30.5)	350–700 (38.5)	700–900 (17.3)
SVA-2	30–300 (31.1)	300–500 (49.6)	500–860 (18.1)	
SVA-3	30–165 (11.9)	165–350 (20.2)	350–500 (50.9)	500–740 (15.7)

[a] T_r, temperature range of weight loss. Weight loss (%) in parentheses. T_1, first stage of weight loss; T_2, second stage of weight loss; T_3, third stage of weight loss; and T_4, fourth stage of weight loss.

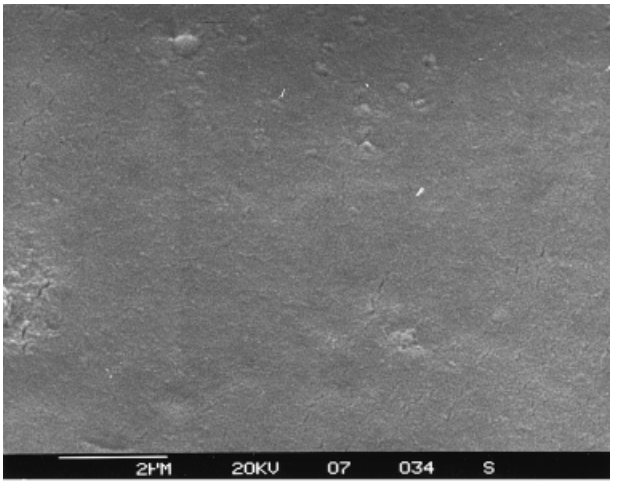
uted to the degradation of the sucrose acrylate and PVP moieties in the copolymer. In SVA-2 there was almost 30% of weight loss, which continued up to 300°C. The first and the second stages of weight loss in other SVA gels would have combined into one single stage in this case. The first stage in SVA-1 and SVA-3 may be attributed to loss of water and the final stage may be attributed to the decomposition of residual organics. The temperature range of decomposition of the sucrose acrylate moiety in the SVA gels is lower than that in the PVP. In the case of SVA-1 gel, the PVP moiety was found to have undergone weight loss in a much broader range of temperature compared to that of the homopolymeric PVP hydrogel. This clearly demonstrates the increased thermal stability of the SVA hydrogels with the copolymer formation.

Scanning Electron Microscopy

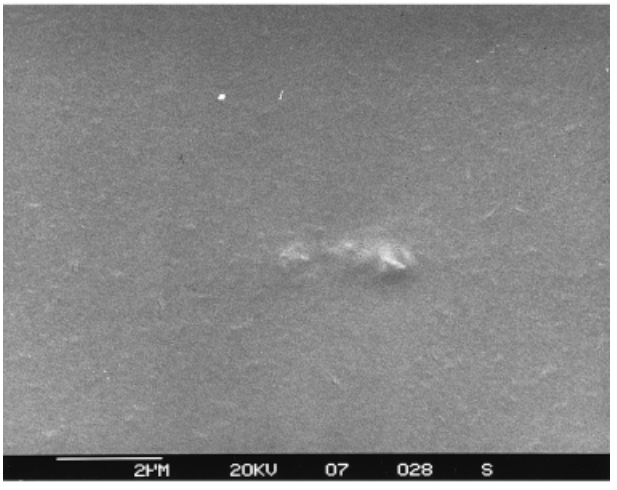
Figure 4 shows the scanning electron micrographs of the SVA-2 [Fig. 4(a)] and PVP [Fig. 4(b)] gels. The surface morphology of the SVA-2 hydrogels appeared to be rough and porous. The surface of the PVP hydrogels was found to be smooth and nonporous. The pore size of the swollen copolymeric hydrogels may also depend on the hydrodynamic properties of the polymeric chains involved in the copolymer formation. In the case of PVP, the uniform homopolymeric gel matrix may result in the smooth surface morphology, which in turn leads to a nonporous surface. The heterogeneous nature of the gel matrix of the SVA-2 hydrogel is expected to contribute to the rough surface morphology.

Equilibrium Swelling Studies

Figure 5 shows the equilibrium swelling degree of the hydrogels in SGF and SIF. The degrees of equilibrium swelling of SVA-1 hydrogels were 164 and 1040% in SGF and SIF, respectively. The SVA-2 gels were swollen to 205 and 702% at equilibrium and the SVA-3 gels showed 233 and 569% equilibrium swelling. The equilibrium swelling for PVP hydrogels was 1307 and 1308% in SGF and SIF, respectively. These swelling studies demonstrate the difference in swelling at equilibrium for gels prepared with varying amounts of SA and NVP. The difference in swelling in SGF and SIF was very distinct in SVA-1 gels compared to that of the SVA-2 and SVA-3 gels. The difference in swelling at equilibrium for SVA-2 and SVA-3 hydrogels has gradually reduced. This can be ascribed to the higher concentration of PVP in the hydrogels. The equilibrium swelling values for PVP gels in SGF and SIF were similar, which clearly shows that PVP is not pH responsive. The addition of a small constant quantity of AA did not dramatically improve the pH sensitivity of the SVA hydrogels, which in turn would improve the bioadhesion. This further confirms that SA is responsible for the pH sensitivity of these hydrogels. The poly[SA–NVP] hydrogels prepared in a similar study also revealed pH sensitivity of the SA incorporated gels compared to that of PVP homopolymeric hydrogels.[16] The extent of crosslinking agent concentration in the case of SVA hydrogels was varied and the gels were prepared. Hydrogels with the higher BIS concentrations were found to show very low swelling at equilibrium and the gels were rigid when dried. The gel integrity was lost when the gels were fully swollen, thus making them more difficult to handle. On the other hand, the SVA-2 gels were found to have optimum levels of swelling at equilibrium in both SGF and SIF. Hence further studies of drug entrapment were continued with the SVA-2 gels.



(a)



(b)

Figure 4 SEM of (a) SVA-2 and (b) PVP hydrogels.

In Vitro Release Studies

The *in vitro* release profiles of PPH entrapped in the SVA-2 hydrogels are shown in Figure 6. The

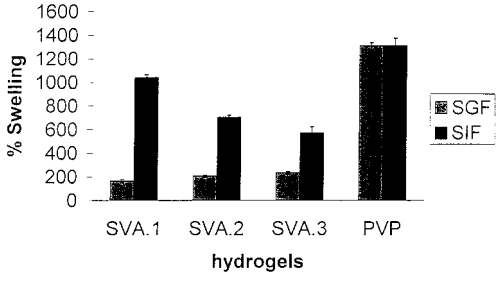


Figure 5 Equilibrium swelling studies of hydrogels in enzyme-free SGF and SIF.

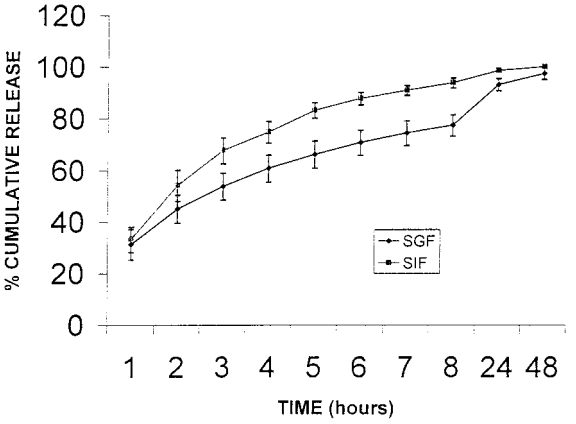


Figure 6 *In vitro* release studies of PPH from SVA-2 hydrogels in enzyme-free SGF and SIF.

release in SGF and SIF displayed pH sensitivity of these hydrogels. In SGF, the release of drug in the first 2 h was found to be about 44% compared to the release of 53% in SIF. There was not much difference between the amounts of drug released in the first hour. This may be attributed to the drug adsorbed toward the surface of the gel matrix. This surface-adsorbed drug may cause the boost release in the first hour in both SGF and SIF. The drug release thereafter was very uniform in both SGF and SIF. At the end of 8 h, there was about 93% drug release in SIF, whereas it was only 77% in the case of SGF. After 24 h the amounts of drug released in SGF and SIF were 93 and 99%, respectively. At the end of 48 h nearly 100% of the entrapped drug was released from the gels in SIF. In SGF, there was about 97% release at the end of 48 h. The drug release seems to have followed a near zero-order pattern in both SGF and SIF. The mechanism of drug release after the initial boost can be mainly attributed to the diffusion of drug from the bulk of the gel matrix. This is clearly evident from the uniform drug release leading to near zero-order kinetics. The drug entrapped in the gel matrix is expected to release in a controlled fashion because of diffusion of the drug from these highly swelling hydrogels. The hydrogel in SIF was found to undergo slight degradation, which may result from the higher swelling level. This loss in gel integrity did not result in any burst drug release in SIF. This can also be attributed to the diffusion of drug from the bulk of the gel matrix. These results indicate that the SVA hydrogels can be exploited for oral drug delivery in both stomach and intestinal regions of the GI tract. By appropriate modification of the surface crosslinking densities, the drug re-

lease in the stomach region can be limited, in case preferential release in the intestinal region is required. Given the bioadhesive nature of the sugar-based hydrogel, this polymeric system may suit the requirement for a bioadhesive, pH-sensitive oral drug delivery system.

CONCLUSIONS

Design and synthesis of new polymeric biodegradable, pH-responsive, and bioadhesive hydrogels containing sucrose acrylate, *N*-vinyl-2-pyrrolidinone, and acrylic acid were carried out. Sucrose acrylate monomer was synthesized and characterized. The copolymeric hydrogels were prepared by free-radical polymerization. These hydrogels and a PVP hydrogel were prepared under the same conditions and characterized. Equilibrium swelling data in enzyme-free SGF and SIF confirmed the pH-responsive nature of the SVA hydrogels. PPH was entrapped as a model drug and *in vitro* release studies were carried out in enzyme-free SGF and SIF. These studies indicated that the drug entrapped in SVA hydrogels released faster in SIF than in SGF as a result of the pH sensitivity. These preliminary investigations also revealed that SVA hydrogels can be applied for the oral drug delivery by virtue of both the bioadhesive and pH-sensitive nature of the sugar-based polymeric systems. This study also envisages the potential of these matrices for tissue engineering applications.

The authors acknowledge Prof. Robert Shanks of the Department of Polymer Science at RMIT, Melbourne, Australia, for the TGA analysis and D. Hopcroft in the electron microscopy facility at Hort Research, Palmerston North, New Zealand, for the SEM analysis. The Massey University Research Fund support for this study is also acknowledged.

REFERENCES

1. Bell, C. L.; Peppas, N. A. Biomaterials 1996, 17, 1203.
2. Wang, C.; Stewart, R. J.; Kopecek, J. Nature 1999, 397, 417.
3. Yoshida, R.; Sakai, K.; Okano, T.; Sakurai, Y. Adv Drug Delivery Rev 1993, 11, 85.
4. Cheng, J.; Jo, S.; Park, K. Carbohydr Polym 1995, 28, 69.
5. Dong, L. C.; Yan, Q.; Hoffman, A. S. J Controlled Release 1992, 19, 171.
6. Kost, J. Pulsed and Self-Regulated Drug Delivery; CRC Press: Boca Raton, FL, 1990.
7. Okano, T.; Yui, N.; Yokoyama, M.; Yoshida, R. Advances in Polymeric Systems for Drug Delivery; Gordon & Breach: New York, 1994.
8. Davis, S. S.; Illum, L. Biomaterials 1988, 9, 111.
9. Frisbie, C. D.; Lawrence, F.; Rozsnyai, A. N.; Wrighton, M. S.; Charles, M. L. Science 1994, 265, 2071.
10. Peppas, N. A. Hydrogels in Medicine and Pharmacy; CRC Press: Boca Raton, FL, 1987.
11. Lenaerts, V.; Couvreur, P.; Grislain, L.; Maincent, P. in Bioadhesive Drug Delivery Systems; Lenaerts, V.; Gurny, R., Eds.; CRC Press: Boca Raton, FL, 1990; pp 93–104.
12. Zhou, W. J.; Wilson, M. E.; Kurth, M. J.; Hsieh, Y. L.; Krochta, J. M.; Shoemaker, C. F. Macromolecules 1997, 30, 7063.
13. Kobayashi, A.; Akaike, T.; Kobayashi, K.; Sumitomo, H. Makromol Chem Rapid Commun 1986, 7, 645.
14. Jhurry, D.; Doffieux, A.; Fontanille, M. Makromol Chem 1992, 193, 2997.
15. The United States Pharmacopeia/National Formulatory; The United States Pharmacopeial Convention: Rockville, MD, 1990; Vol. XXII, pp 1786–1792.
16. Shantha, K. L.; Harding, D. R. K. Unpublished results.