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The synthesis of a physically crosslinked NVP based hydrogel

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Abstract

Complexes of polyvinyl pyrrolidinone–polyacrylic acid (PVP–PAA) were prepared by photopolymerisation from a mixture of the monomers NVP and AA. The complexes were characterised by means of differential scanning calorimetry, Fourier transform infrared spectroscopy (Ftir), potentiometric titration, swelling studies and gel permeation chromatography. The Ftir spectra of PVP–PAA copolymer complexes indicates hydrogen bonding between the carbonyl group in the PVP and the carboxylic acid group in the PAA moiety. As the percentage of AA increases in the copolymer there is evidence of increased intermolecular hydrogen bonding between the carboxylic acid groups of the AA segments. Swelling of the PVP–PAA complex in a higher pH medium is significantly different from results in low pH solutions. The critical pH range was found to be between 4.07 and 4.49. Above a pH of 4.49, there is a progressive break up of the polymer chain due to a reduction in the amount of intermolecular hydrogen bonding. There is also a significant increase in the solubility of the copolymer complex at higher pHs. The low solubility of the copolymer at low pH may make the complex suitable for gastric drug delivery systems.

Keywords: Polymer; Polymer chemistry; Polymer synthesis

1. Introduction

The term hydrogel is used to describe materials that are three-dimensional, hydrophilic, polymeric networks capable of imbibing large amounts of water or biological fluids. These hydrogels exhibit a thermodynamic compatibility with water that allows them to swell in aqueous media. Hydrogels are best considered as polymeric materials, which are able to swell in water and retain a significant fraction of water within their structure, but do not completely dissolve in water [1–8]. Kunioka et al. [9], however, describes the thermal hydrolytic degradability of hydrogels prepared from microbial poly (γ-glutamic acid) (PGA) and poly (ε-lysine) (PL) by γ-irradiation. It was found that PGA and PL hydrogels were not degraded near ambient temperature but were hydro-degradable over 60 °C on heating.

Hydrogels are becoming increasingly important materials for pharmaceutical applications. They are used in a variety of applications including diagnostic, therapeutic, and implantable devices, for example, controlled release drug delivery systems which have being studied extensively [2,3,5,8,10–20] contact lenses [2,8,21–23] and tissue engineering [7]. Hydrogels have been widely used in such applications because of their biocompatibility with the human body and also because they resemble natural living tissue more than any other class of synthetic biomaterials. This is due to their high water content and soft consistency that is similar to natural tissue [2–7,24–25].

Hydrogels are prepared by synthetic chemical reactions from a range of speciality vinyl and acrylic monomers. Nguyen et al. [7] presented a review on UV curable hydrogels that may be used as biomaterials in medical applications including tissue engineering. The use of photopolymerisation of these hydrogels in situ is also discussed, and the possibility of their use in a minimally invasive manner where the liquid monomer can be injected and applications for these hydrogels such as barriers, localised drug delivery depots, cell encapsulation materials and scaffold materials are also noted. Hydrogels may be composed of homopolymers or copolymers, and are insoluble due to the presence of chemical crosslinks (covalent bonding) or physical crosslinks, such as entanglements or crystallites [1,2,4–5,26]. Anseth et al. [6] explored

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methods for analysing mechanical properties of hydrogels and their dependence on polymer structure, especially the crosslinking density and the degree of swelling. Methods for measuring the elastic and viscoelastic properties of hydrogels were examined along with mechanisms for controlling the properties; examples of these variables are variations in the polymer composition, the crosslinking density and the polymerisation conditions.

Chemical gels are three-dimensional molecular networks formed by the introduction of primary covalent crosslinks. Unless the covalent bonds can be broken, these types of gels do not dissolve in water or other organic solvents even upon heating; rather, they are observed to swell. Two common techniques used to produce chemically crosslinked hydrogels are the polymerisation of a water-soluble monomer in the presence of an appropriate crosslinking agent and crosslinking of an existing hydrophilic polymer, again with the use of a crosslinking agent. Both general methods obey common reaction mechanisms and can be implemented in a variety of ways. It is essential that monomeric species have functionality greater than two in order to form the characteristic three-dimensional structure of a gel [8].

Physical gels are hydrophilic networks comprised of an amorphous hydrophilic polymer phase held together by highly ordered aggregates of polymer chain segments arising from secondary molecular forces (van der Waals forces) in conjunction with other types of molecular interaction. Unlike chemical gels, these types of hydrogel systems eventually will dissolve in water or solvents and can be melted by applying heat to the systems. A novel approach to preparing physical crosslinks is the freeze/thawing technique [27–29]. Stauffer et al. [27] described a novel method of preparing a strong PVOH hydrogel without utilisation of chemical crosslinking or other reinforcing agents. This was achieved by freezing/thawing cycles of an aqueous solution containing 10–15 wt% PVOH. The process of reinforcement was a densification of the macro molecular structure. It was noted that the strength, stability and swelling ratio of the gels were a function of the solution concentration, freezing time and number of freezing/thawing cycles, and that freezing 15 wt% PVOH solution at −20 °C for 24 h followed by thawing at 23 °C for 24 h produced the strongest gels. Investigation of the swelling ratios indicated that denser structures were observed after five freezing/thawing cycles. Hassan et al. [29] further discussed the use of PVOH with particular interest for physically crosslinking hydrogels that were prepared by repeated cycles of freezing and thawing. This method of preparing hydrogels addresses the toxicity issues because it does not require the presence of a crosslinking agent. It was also noted that such physically crosslinked materials also exhibit improved properties, most notably higher mechanical strength than PVOH gels crosslinked by chemical or irradiative techniques because the mechanical load can be distributed along the crystallites of the three-dimensional structures. However, the long-term stability of such gels still remains an important issue.

The configuration of the aforementioned ordered domains varies with the type of secondary forces involved in their formation, as well as the general molecular structure and configuration of the hydrophilic polymers that comprise them. Some of the intermolecular forces responsible for giving rise to these physical bonds include London dispersion forces, permanent dipoles, hydrogen bonding and ionic attraction. These forces are cumulative in nature and contribute greatly to the ordered structure exhibited by the physical bonds. The so-called ‘bonds’ that hold these types of gels together are actually sections of the polymer chain, which are in the crystalline state. Segments of the molecule arrange themselves into a tightly packed repeating structure. To achieve this, the polymer must exhibit a certain degree of structural regularity along the main chain [8] (Fig. 1).

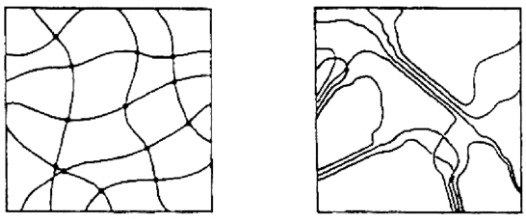

Fig. 1. Schematic representation of general structure of (a) chemical and (b) physical gels [8].

2. Experimental

2.1. Preparation of samples

The hydrogels investigated in this work were prepared by free-radical polymerisation. The monomers used were 1-vinyl-2-pyrrolidinone (NVP, Lancaster synthesis) and acrylic acid (AA, Merck-Schuchardt, Germany). Both monomers were used as received. To initiate the reactions, 1-hydroxycyclohexylphenylketone (Irgacure® 184, Ciba speciality chemicals) was used as a UV-light sensitive initiator at 3 wt% of the total monomer weight. This was added to the NVP/AA monomeric mixture and stirred continuously until completely dissolved. The solution was then pipetted into a silicone mould (W.P. Notcutt, Middlesex) that contained disk impressions and rectangular impressions for use in Fourier transform infrared spectroscopy (Ftir). The mould was then positioned horizontally to the gravity direction under two UVA 340 UV lamps (Q-panel products) and the solution was cured for 1–2 h in an enclosed environment. The films were then dried in a vacuum oven at 40 °C, 500 mm Hg for 24 h prior to use.

2.2. Differential scanning calorimetry

Differential scanning calorimetry (DSC) was carried out using a Perkin–Elmer, Pyris 6 DSC. Firstly, a sample of between 10–12.5 mg was weighed out using a Sartorius scales capable of being read to five decimal places. The tests were carried out in pierced lid pans by heating the samples from 20 to 200 °C at 30 °C per minute, the samples were then held isothermally at that temperature for 10 min, the samples were then cooled back to 20 °C at 30 °C per minute and were again held isothermally for 10 min. This was carried out in order to remove any thermal history. The samples were then reheated to 200 °C at 10 °C per minute. All DSC tests were carried out under a 20 mL per minute flow of nitrogen to prevent oxidation.

2.3. Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy was carried out on the rectangular samples that had being exposed to atmospheric conditions for a minimum of 7 days, using a Nicolet Avator 360 Ftir, with a 32 scan per sample cycle.

2.4. Potentiometric titration

The potentiometric titrations of the UV cured PVP–PAA copolymers were executed by firstly grinding the sample that had being vacuum dried as described previously. The sample was placed into a 200 mL bottle, into which 25 mL of 0.05N HCl containing 0.1 M NaCl. A lid was placed on the bottle to prevent evaporation. The sample was stirred continuously for 24 h prior to use. A burette that could be read to ±0.1 mL was used to titrate 0.05N NaOH containing 0.05 M NaCl with the HCl solution. An Orion 420A + pH meter capable of reading pH changes of 0.01 was used to monitor the progress of the titration.

2.5. Swelling studies

Swelling experiments were preformed in buffered solutions (buffered tablets, BDH Ltd., Poole, England) in triplicate at pH values of pH 4.0, pH 7.0 and pH 9.2 at ambient temperature. Samples of the cured polymer with a mass of 1.38 ± 0.42 g were placed into a petri dish; the petri dish was then filled with the appropriate buffered solution. Periodically excess-buffered solution was removed by pouring the solution through a Buchner funnel, the samples were then pat-dried with filter paper and weighed. The

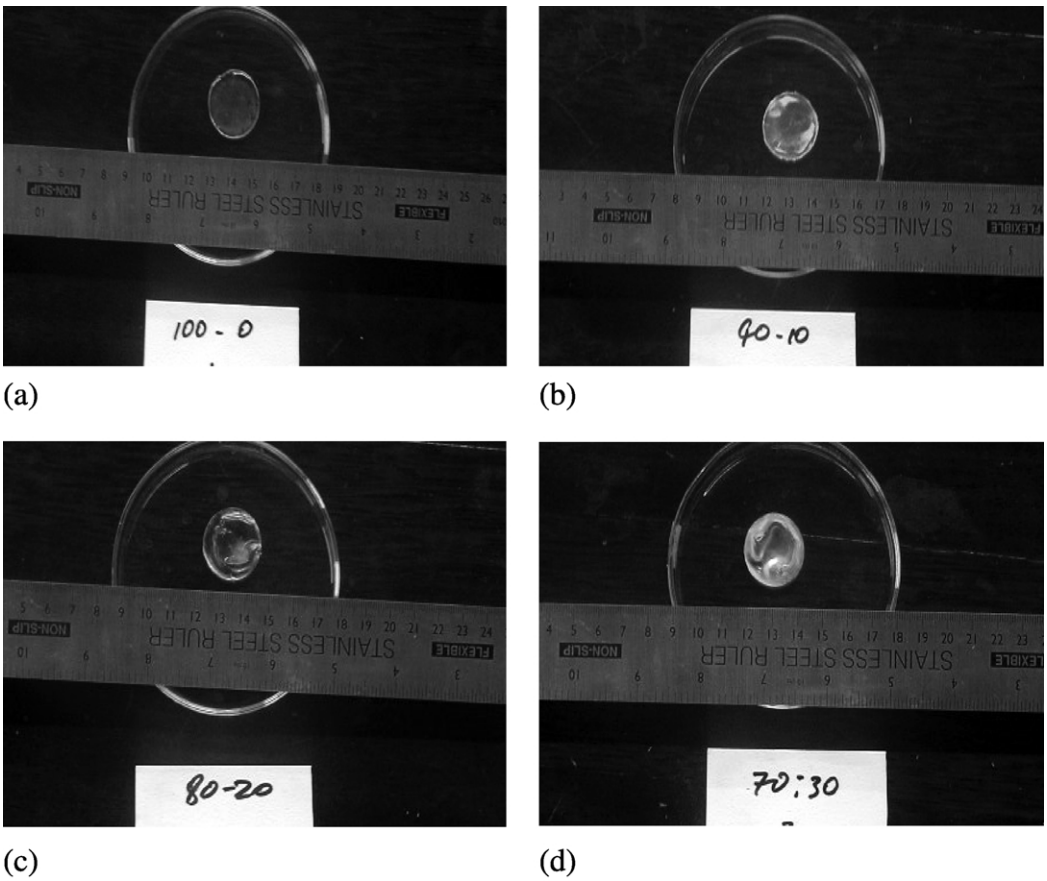

Fig. 2. Cured samples of PVP–PAA complexes. The initial composition of these were (a) 100 wt% NVP, (b) 90 wt% NVP–10 wt% AA, (c) 80 wt% NVP–20 wt% AA and (d) 70 wt% NVP–30 wt% AA.

samples were re-submerged in fresh-buffered solution. The percentage that the hydrogels swelled was calculated using the formula:

$$\text{Swelling (\%)} = W_t/W_0 \times 100$$

Where W_t is the weight of the hydrogel at a predetermined time, and W_0 is the weight of the hydrogel before swelling experiments took place. Pictures of the swollen samples were also taken of the samples before the removal of the buffered solution for comparative reasons. This process was continued until the sample appeared to have dissolved.

2.6. Gel permeation chromatography

Gel permeation chromatography was carried out using a polymer labs aquagel-OH 30 8 μm mixed column (using a suitable guard column), with a mobile phase of water: methanol in the ratio of 10:1. This solution was filtered and degassed using a Millipore filtration system under vacuum using 50 μm PTFE filter paper. The solution was then further degassed by passing helium through it.

The detector used for these tests was a polymer labs evaporative light scattering (PL ELS 1000) detector, which had an evaporator temperature set to 100 °C, nebuliser temperature set to 85 °C and a nitrogen flow rate set to 1.5 mL min^{-1}. Polyethylene glycol (PEG) calibration standards were used as reference standards. However, results dictated that a wider range was necessary, therefore, high molecular weight polyethylene oxide's (up to eight million) were also used. These standards were prepared by weighing 25–25.5 mg of PEG into 28 mL bottles, 25 mL of high purity water was then pipetted into the bottle. The samples were allowed to dissolve for 24 h before use. All tests were carried out using a flow rate of 1 mL min^{-1}.

The samples tested were collected by swelling the hydrogels in deionised water for defined periods of time, removing a sample of water, and then replacing the water with fresh water.

3. Results and discussion

3.1. Preparation of samples

Samples of both NVP and NVP/AA were photopolymerised using Irgacure® 184 as a photoinitiator. These samples were cured on a silicone moulding, and prior to use dried for 24 h in a vacuum oven. Cured samples are shown in Fig. 2. The sample containing 100 wt% NVP cured with a uniform smooth surface, which would indicate that it could have potential in coating applications. With the addition of AA, the uniformity of the surface of the samples deteriorated. This deterioration increased with an increase in AA concentration; in the samples whose initial composition was 100 wt% NVP all the samples were transparent in appearance and yellowish in colour after photopolymerisation. However, the addition of AA caused the formation of some white solids [30] being formed as is shown in Fig. 2. These white solids would suggest a degree of phase separation in the cured copolymer.

3.2. Differential scanning calorimetry

DSC were carried out by heating the sample to 200 °C, and then cooling it back to 20 °C to remove all thermal history. The samples were then reheated back to 200 °C at 10 °C per minute.

DSC scans were performed in order to determine the effect that the addition of PAA had on the properties of PVP. Yaung et al. [1] also performed DSC scans on PVP–PAA complexes and found, that for the three formulations tested the T_g of the samples were 134, 142 and 146 °C. In this work the T_g of the samples tested were found to be 146.1, 146.5, 140.4 and 141.3 °C for samples whose initial composition was 100 wt% NVP, 90 wt% NVP–10 wt% AA, 80 wt% NVP–20 wt% AA and 70 wt% NVP–30 wt% AA, respectively. These results correlate to those presented by Yaung and would give evidence to a slight reduction in stiffness with an increase in AA content.

3.3. Fourier transform infrared spectroscopy

The formation of hydrogen bonding is exhibited on the IR spectrum as a negative shift of the stretching vibration of the functional group involved in the hydrogen bond, which is typically a carbonyl group. Bures et al. [31] states that the carboxylic acid groups can exist in both free and dimeric form depending upon their environment. Lee et al. [32,33] describes how the stretching frequency of the carbonyl moiety in the carboxylic acid group as is defined by absorption at 1750 cm^{-1}, whereas the dimer stretching frequency was reported as been 1700 cm^{-1} by both Lee and Bures et al. [31] this was also reported by Yaung et al. [1] as 1717 cm^{-1}. In this work, the dimer was identified by the clear formation of a shoulder on the PVP carboxyl group absorption peak. This shoulder is visible in both samples 90–10 and 80–20. This shoulder develops into a peak in the 70–30 sample, which appears at 1719 cm^{-1} and corresponds to values reported in literature.

Yaung et al. [1] describes how the frequency of the PVP carbonyl group shifts from 1670 to 1680 cm^{-1} to 1630 to 1640 cm^{-1} when it forms hydrogen bonds to the carboxyl group of the AA. In this work, the PVP carboxyl group for PVP was found to be at 1650 cm^{-1}, and shifted to 1639 cm^{-1} with the inclusion of AA thus giving evidence of hydrogen bonding in the copolymer complex.

3.4. Potentiometric titration

Potentiometric titrations were carried out on pre-dried samples that were firstly ground and then dissolved in a 0.05N HCl solution. Into this solution, a 0.05N solution of

NaOH was titrated using a burette capable of being read to ± 0.1 mL. All titrations were repeated to confirm reproducibility.

From the resultant graphs two neutralisation transitions could clearly be seen. The latter transition is merely the neutralisation of the HCl. The first neutralisation transition can be attributed to the neutralisation of the carboxylic acid group associated with PAA/AA. From this neutralisation transition, the $pK_{initial}$ can be defined. The $pK_{initial}$ was taken as the first point of pH drop from equilibrium. The range of $pK_{initial}$ values obtained in this work was 4.07–4.49. These values compare favourably to values obtained by Yaung et al. [1] who recorded a $pK_{initial}$ range of 4.39–4.22.

Yaung also described $pK_{initial}$ for a weak polyelectrolyte such as PAA. The number of ionic charges on the backbone depends upon the pH of the solution. When the pH value of the solution is above $pK_{initial}$, which is the lowest pH at which the carboxylic acid can be neutralised, a fraction of the carboxylic acid groups dissociate to form carboxylate ions. Therefore, under pH4 swelling conditions the carboxylic acid groups will not be fully dissociated. Therefore, the bonds between PVP and PAA are expected to remain intact.

3.5. Swelling studies

Swelling experiments were performed in solutions of various pH values. The swelling experiments were carried out by placing a circular disc of photopolymerised polymer into a petri dish. The polymer was then immersed in the appropriate buffered solution, and allowed to swell. Periodically removing the buffered solution, pat-drying the sample, and weighing the sample, obtained the amount that the hydrogel swelled. Pictures were taken of each of these samples to correlate the weight changes recorded.

At a glance it would appear the samples whose original composition was 100 wt% NVP appeared to swell less as the pH increased. However on re-evaluation of these

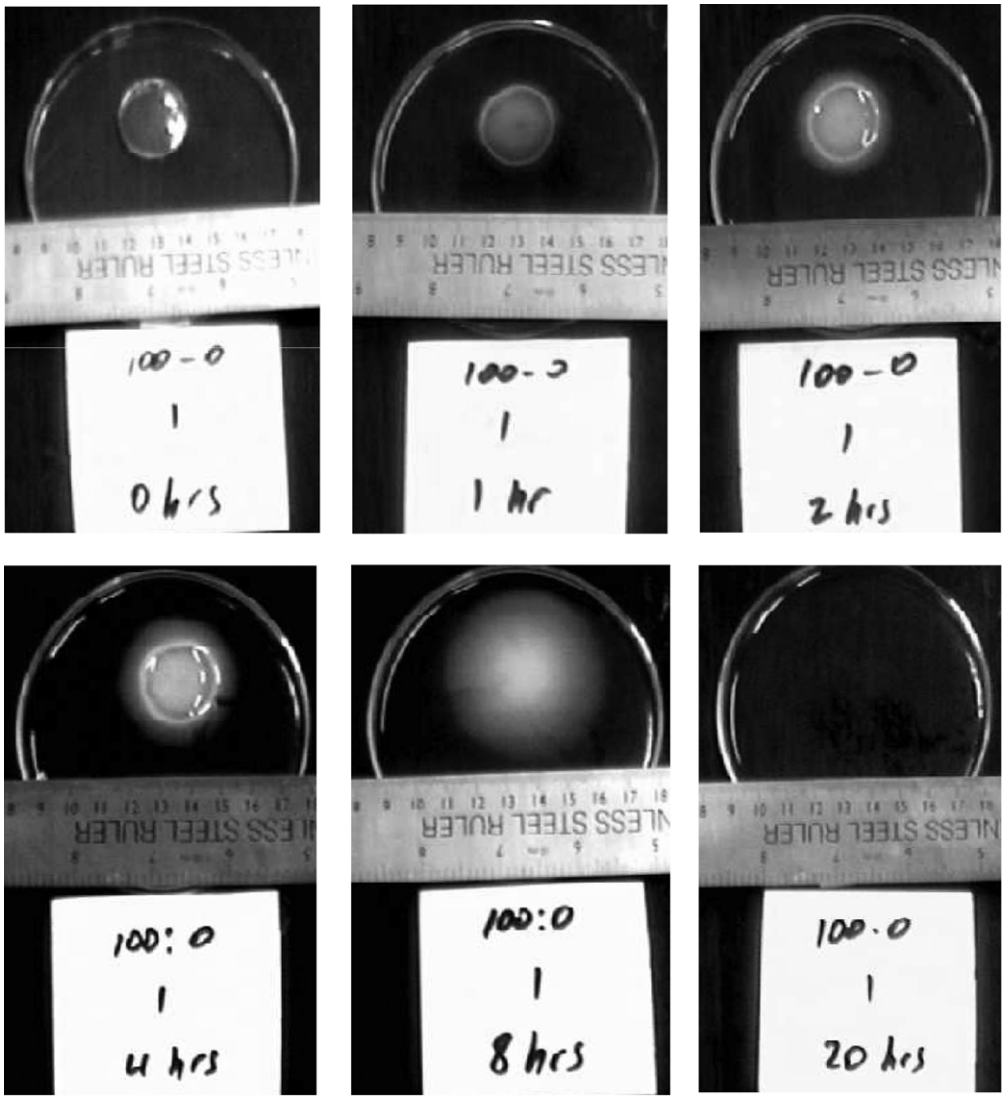

Fig. 3. Typical swelling characteristics of hydrogel with initial composition 100 wt% NVP. This sample was swollen in pH7 buffered solution.

samples with reference to the pictures taken it would appear that the samples swelled more as the pH increased. As no crosslinking could occur the rapid swelling of this polymer led to rapid dissolution of the samples in all pHs used (within 24 h). All samples reached their maximum swollen weight from 0 to 2 h, which would also indicate rapid dissolution.

When the pH value of the solution is above $pK_{initial}$, which is the lowest pH at which the carboxylic acid can be neutralised, a fraction of the carboxylic acid groups dissociate to form carboxylate ions [1]. From examination of samples that originally contained 90 wt% NVP and 10 wt% AA, it can be seen that the samples swollen in pH4

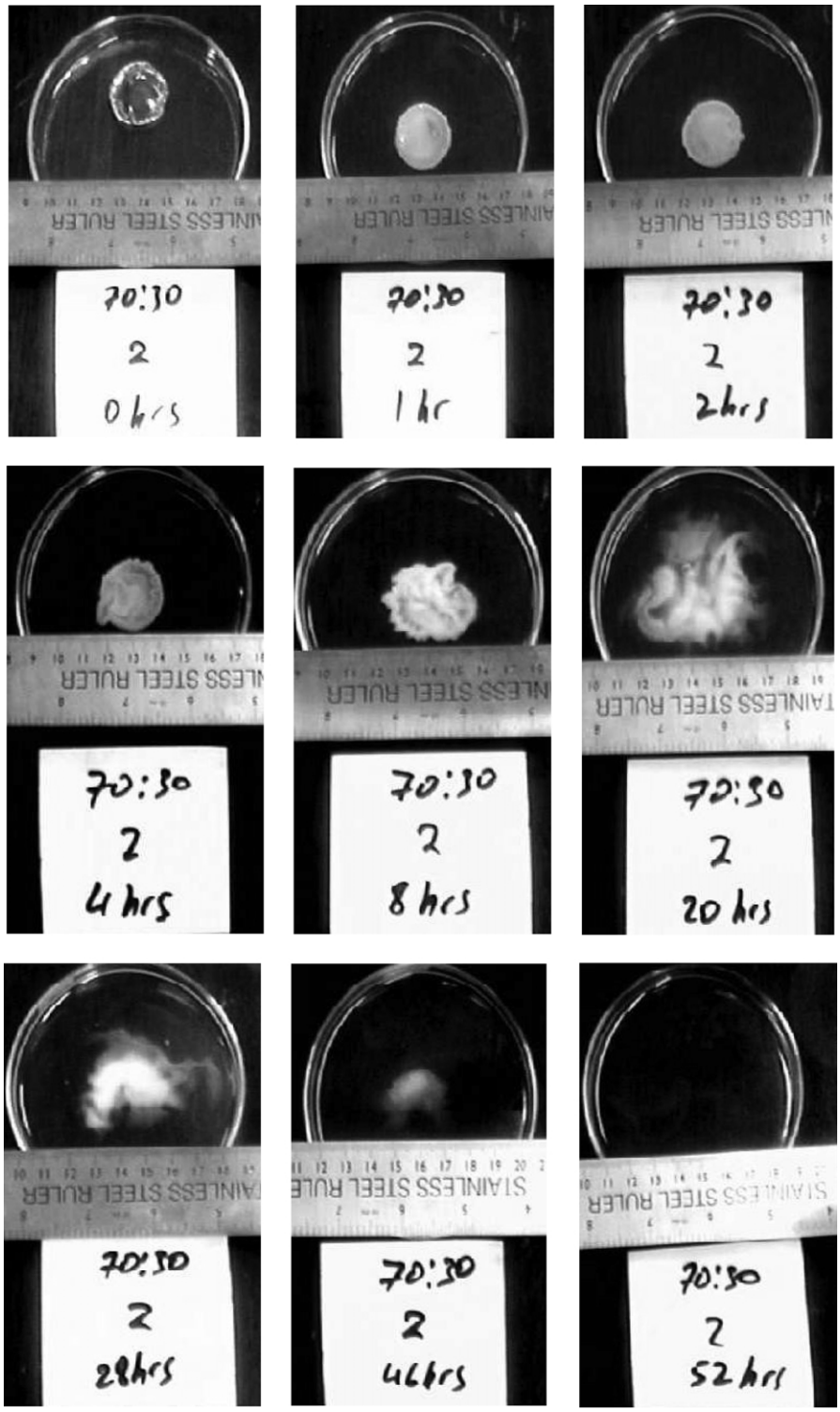

Fig. 4. Typical swelling characteristics of hydrogel with initial composition 70 wt% NVP–30 wt% AA. This sample was swollen in pH7 buffered solution.

tended to swell less than samples swollen in a higher pH. However, if all three swelling medias are compared at 30 h it can be seen that samples swelled in higher pHs had dissolved while the samples swollen at pH4 were still approximately 20% of original weight. However, samples that were swollen in pH9 did not appear to swell as much as samples swollen in pH7. In pH7 and pH9 buffered solutions the $pK_{initial}$ values (between 4.07 and 4.49) are exceeded, and the progressive break up of the polymer chains liberates more and more free polymer. The number of carboxylate ions also increases in the process. This leads to an increase in solubility of the complex as the pH increases and this may give rise to an apparent decrease in swelling at pH9. Similar trends are seen for samples whose original composition was 80 wt% NVP–20 wt% AA and 70 wt% NVP–30 wt% AA.

As the AA content was increased the hydrogels were capable of swelling more and did not dissolve as quickly. This is due to the increase in intermolecular bonding caused by the addition of AA. Figs. 3 and 4 show typical dissolution processes observed.

3.6. Gel permeation chromatography

GPC experiments were carried out using a mobile—phase of water/methanol in the ratio of 10:1 at a flow rate of 1 mL min^{-1}, using an aquagel-OH 30 8 μm mixed column. The calibration used in this experiment had a range between 400 and 8,000,000. It was possible to calculate molecular weights outside this range, however, as these results would be estimates at best they will not be presented in this work. The calibration curve used was a polynomial of the 4th order. This curve was used as each calibration point had a 'fit ratio' within ±0.029. The molecular weight values quoted are Mp or peak average molecular weight, where [34]:

$$M_p \sim (M_w \times M_n)^{0.5}$$

From the analysis of the samples whose original composition was 100 wt% NVP (Fig. 5) it can be seen that as the sample dissolved an increase in M_p was recorded up to a time of 8 h. The M_p value of the polymer eluted after 24 h showed a reduction in molecular weight. However, the molecular weight distribution was broader after 24 h as the sample had completely dissolved. This could cause a reduction in the M_p value as up to this point only surface polymer was released, but at 24 h the bulk material had completely dissolved, reducing the M_p value (Fig. 6).

From analysis of the samples whose original composition was 90 wt% NVP–10 wt% AA, 80 wt% NVP–20 wt% AA and 70 wt% NVP–30 wt% AA, respectively, there is a large number of molecular weight points outside of calibration. The M_p values eluted prior to 6.25 min are all in excess of a molecular weight of eight million. As the polymerisation process was identical to that which provided a molecular weight in the region of 290,000 for polymerised NVP it is reasonable to assume that a polymer of this size should not be possible using this polymerisation method. Thus, it must be assumed that these ultra high molecular weights achieved were caused by a physically crosslinked polymer rapidly passing through the GPC column (Fig. 7).

On the other hand polymers eluted after 9.78 min had a molecular weight of less than 400. From the sample whose original composition was 90 wt% NVP–10 wt% AA, there is evidence of a peak in this region after 24 h. From the 80 wt% NVP–20 wt% AA, there is even more evidence of peaks in this region after 24 h, 48 and 72 h. However, the sample containing 70 wt% NVP–30 wt% AA there is a clear peak obtained after 24 h with further evidence of peaks

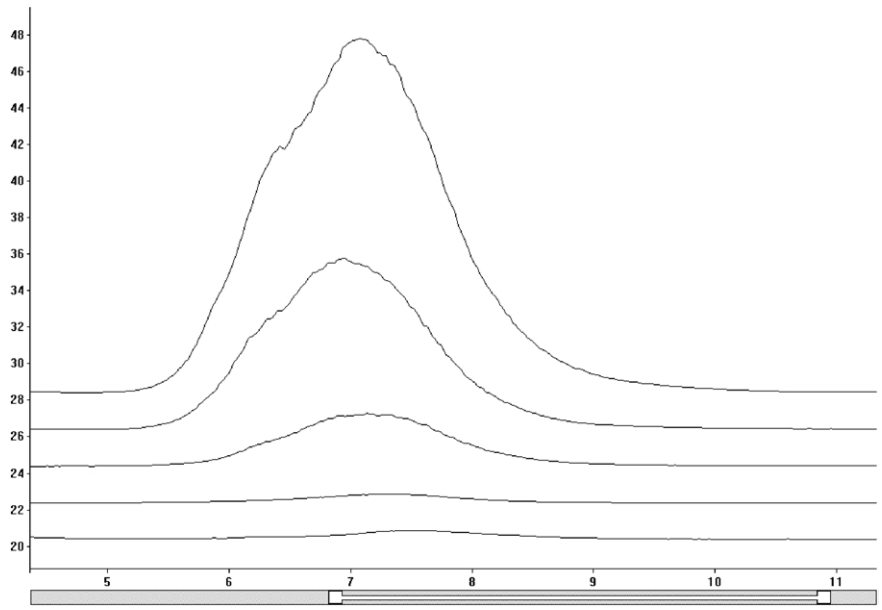

Fig. 5. GPC curves obtained for samples whose original composition was 100% NVP. From bottom to top, sample taken after 1, 2, 4, 8 and 24 h, respectively.

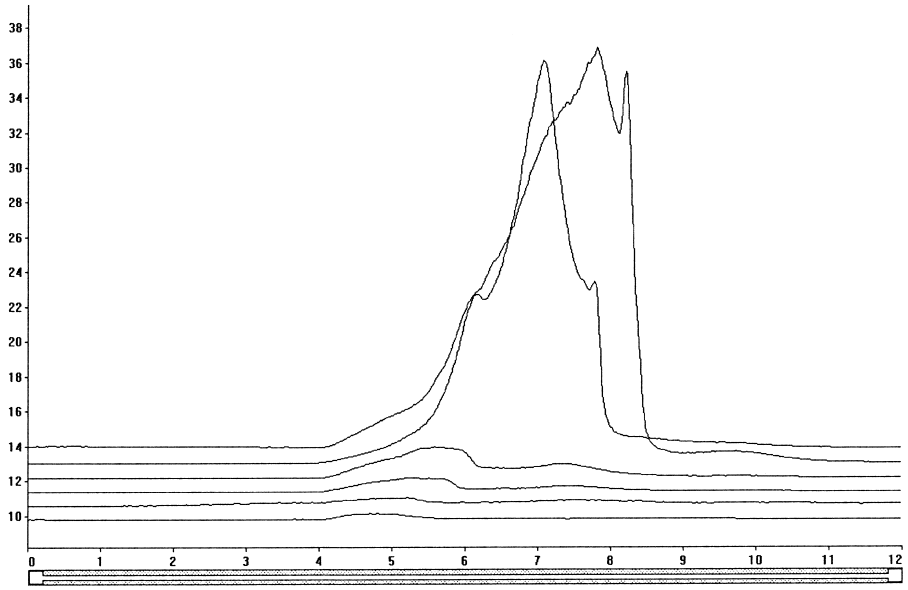

Fig. 6. GPC curves obtained for samples whose original composition was 90% NVP/10% AA. From bottom to top, sample taken after 1, 2, 4, 8, 24 and 48 h, respectively.

in several samples tested. As the evidence for a peak in this region increased with increasing AA content, coupled with the visual inspection performed after sample preparation that showed phase separation due to the AA content, it can be surmised that this peak is caused by phase separated AA oligomers, the molecular weight of which was below 400 (Fig. 8).

From these results it can also be seen that a molecular weight was also recorded in the region that was achieved by polymerising 100 wt% NVP. This would signify that a portion of the copolymer complex was a PVP homopolymer. The concentration of this homopolymer reduced as expected with the increase of AA, giving way to a combination of physically crosslinked copolymer, PVP homopolymer and AA oligomers.

4. Conclusion

We have synthesised a series of random copolymers, by photopolymerisation containing different monomeric concentrations of NVP and AA. The Ftir spectra of PVP–PAA copolymer complexes indicates hydrogen bonding between the carbonyl group in the PVP and the carboxylic acid group in the PAA moiety. As the percentage of AA increases in the copolymer there is evidence of increased intermolecular

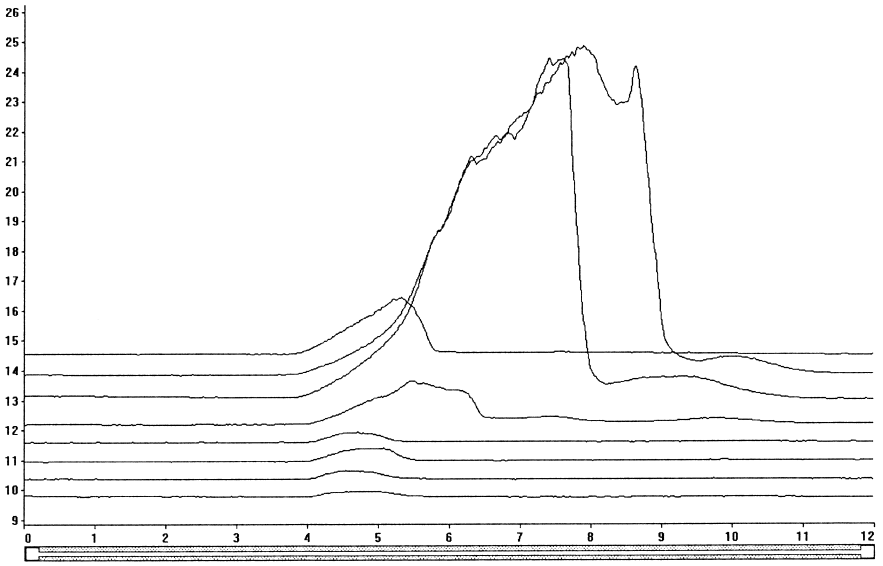

Fig. 7. GPC curves obtained for samples whose original composition was 80% NVP/20% AA. From bottom to top, sample taken after 1, 2, 4, 8, 24, 48, 72 and 98 h, respectively.

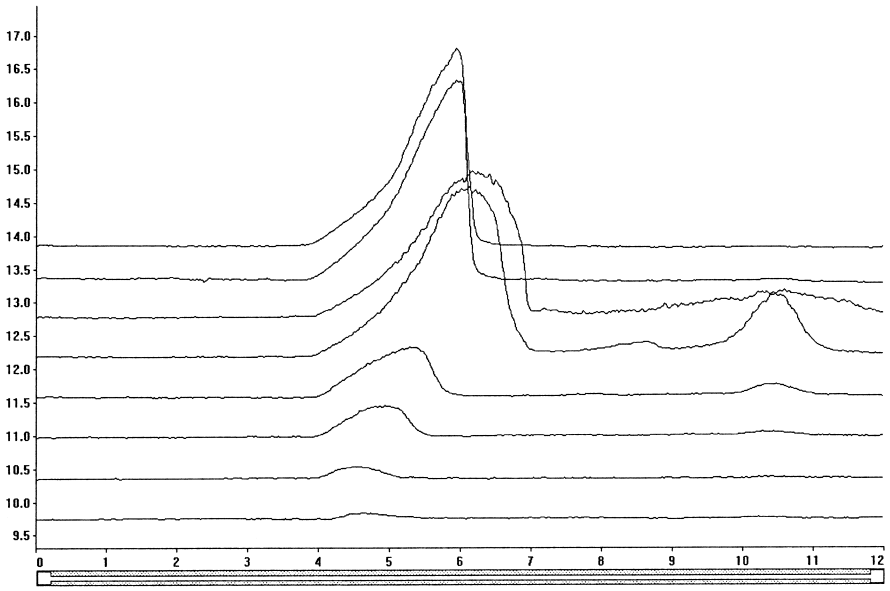

Fig. 8. GPC curves obtained for samples whose original composition was 70% NVP/30% AA. From bottom to top, sample taken after 1, 2, 4, 8, 24, 48, 72 and 98 h, respectively.

hydrogen bonding between the carboxylic acid groups of the AA segments. Swelling of the PVP–PAA complex in a higher pH medium is significantly different from results in low pH solutions. The critical pH range was found to be between 4.07 and 4.49. Above a pH of 4.49 there is a progressive break up of the polymer chain due to a reduction in the amount of intermolecular hydrogen bonding. This is caused by an increase in the amount of carboxylate ions as the pH increases. There is also a significant increase in the solubility of the copolymer complex at higher pHs. The low solubility of the copolymer at low pH may make the complex suitable for gastric drug delivery systems. Finally, some of the copolymers produced seemed to have extraordinary high molecular weights and this needs to be investigated further.

Acknowledgements

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