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Investigation of a novel freeze-thaw process for the production of drug delivery hydrogels

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Poly(vinyl alcohol) (PVA) is a water-soluble, biocompatible and biodegradable polymer, which has been widely applied in biomedical fields. In this paper, novel physically cross-linked hydrogels composed of PVA and comprising a blend of poly(vinyl alcohol) (PVA) with different concentrations of HCl, NaOH and NaCl are prepared by a freezing/thawing treatment of aqueous solutions. The structure and complexation of the electrolytes were studied by Fourier transform infrared (FTIR) spectroscopy. The mechanical properties were investigated using rheometery and the thermal transitions of the hydrogels were examined by modulated differential scanning calorimetry (MDSC). Freeze/thawed PVA gels containing NaOH showed overall enhanced swelling with increased mechanical strength over traditional gels prepared by chemical or irradiative crosslinking techniques. These novel physically cross-linked hydrogels show promise for a variety of biomedical and drug delivery applications.

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 [1–4]. Hydrogels have important applications in the areas of controlled drug delivery, as coatings in gastrointestinal pharmaceutical applications and as dissolution and binding agents in tablets [5–7]. Hydrogels may be composed of homopolymers, copolymers or blends and are insoluble due to the presence of chemical cross links (covalent bonding) or physical cross links, such as entanglements or crystallites [8–10]. Aqueous poly(vinyl alcohol) (PVA) solution forms hydrogels by γ ray or electron-beam irradiation, freezing and thawing or mixing with a dye, such as Congo Red [11]. Hydrogels prepared by irradiation are categorized as chemical gels, and those prepared by freezing and thawing or mixing with a dye as physical gels [12–14].

PVA hydrogels prepared using freeze / thaw cycling have great potential for biomedical and drug delivery applications due to desirable mechanical and swelling properties [15–17]. These hydrogels are prepared by exposing aqueous PVA solutions to repeated cycles of freezing and thawing, which results in the formation of crystallites which render the material insoluble in water. The strength, stability and swelling ratio of the gels are a function of the solution concentration, freezing time and the number of freeze/thaw cycles.

Hassan *et al.* discussed cellular poly (vinyl alcohol) (PVA) hydrogels that were prepared by freezing and thawing techniques in the presence of NaCl [18]. These freeze/thawed, cellular PVA gels showed overall enhanced swelling with increased mechanical strength over traditional gels prepared by chemical or irradiative crosslinking techniques. Shaheen *et al.* discussed the use of PVA/NaCl/H_2O systems for the delivery of theophylline [19, 20]. The drug release behaviour showed an irregular Fickian diffusion.

It is generally agreed that the addition of electrolytes disrupts the extent of the structure of the hydrogen bonding, reduces the degree of hydrogen bonding in these systems, and causes a decrease of viscosity for aqueous polymer solutions [21]. Lewandowski *et al.* discusses the preparation of novel poly (vinyl alcohol) KOH-H_2O alkaline polymer electrolytes [22]. These films were prepared by solution casting as opposed to freeze thawing and the application was for solid batteries. The good electrochemical as well as mechanical properties of the electrolytes suggest that potential applications are in electrochemical devices. The addition of KOH to PVA, which is a polymeric alcohol, leads to the formation of alcoholates, probably responsible for the conductance of the solid electrolyte [22].

In this work, we investigated the addition of sodium chloride, sodium hydroxide and hydrochloric acid to produce freeze-thawed PVA gels with enhanced mechanical properties. Prepared gels were

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characterised by rotational rheometry, modulated differential scanning calorimetry and Fourier transform infrared spectroscopy. We hope that the introduction of these inorganic compounds into PVA hydrogels may improve properties such as enlarging the drug-loading amounts of small molecular drug and prolonging the drug release time.

2. Materials and methods

2.1. Preparation of samples

Poly (vinyl alcohol) used in this study was supplied by Aldrich and had a weight average molecular weight of 146,000–186,000 and a saponification value of 98–99%. Solutions were prepared by mixing polymer powder (1 g) with distilled water (40 mls) using the polymer feed percentages shown in Table I. The samples were prepared using either (i) HCl or (ii) NaOH or (iii) NaCl.

Dissolution was achieved by heating the mixture to 80 °C for 90 min, while slowly stirring. When the polymer was no longer apparent and the mixture was clear, the solution was cooled to 70 °C. To remove any bubbles the solution was placed in an ultra sonic water bath at 70 °C for five minutes. The solution was placed in an oven at 70 °C to further aid in the removal of bubbles. The remaining solution was removed from the oven and placed in a polystyrene beaker. The beaker was placed in a trough and approximately 500 mls of liquid nitrogen was added over a period of ten minutes. The solidified solution was allowed to stand for 24 h, removed and placed in a petri dish. Upon thawing, a gel was formed. The samples were characterised by MDSC, FTIR spectroscopy and rheometry. This analysis was performed on a given sample within a few days to minimise the effect of aging. Figs. (1)–(3) show pictures of a typical gel formed by this method.

2.2. Modulated differential scanning calorimetry

Modulated differential scanning calorimetry (MDSC) was carried out using a DSC 2920 Modulated DSC from TA instruments. A sample of between 10 and 11 mg was weighed out and the tests were carried out in sealed aluminium pans. The samples were cooled to −60 °C, the modulation was ±1.00 °C every 60 seconds and the temperature was ramped from −60 to 280 °C.

TABLE I Polymer feed ratios used in the preparation of the hydrogel complexes

NaOH	0.0625 M	0.05 M	0.0375 M	0.025 M	0.0125 M
HCl	0.0625 M	0.05 M	0.0375 M	0.025 M	0.0125 M
NaCl	0.0625 M	0.05 M	0.0375 M	0.025 M	0.0125 M

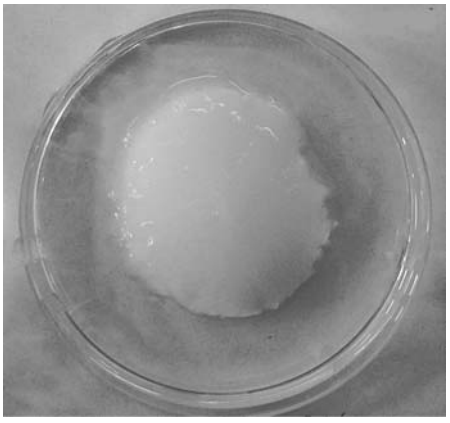

Figure 1 A picture of a PVA/NaOH/H_2O gel formed by the process described in the text.

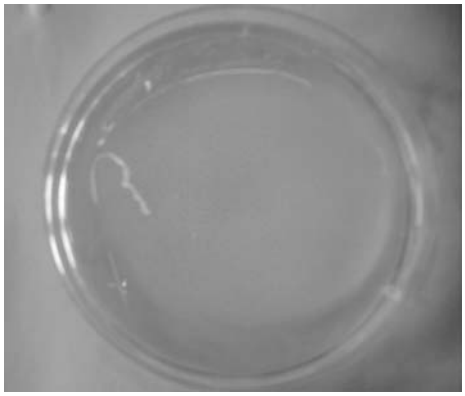

Figure 2 A picture of a PVA /NaCl/H_2O gel formed by the process described in the text.

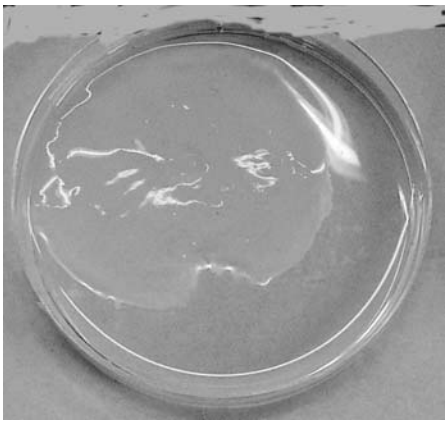

Figure 3 A picture of a PVA /HCl/H_2O gel formed by the process described in the text.

2.3. Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy was carried out on samples that had been 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. Rheometry

Rheological measurements were performed on a strain-controlled TA instrument AR1000. The geometry used was a 4 cm diameter parallel steel plate. The temperature was ramped from 20 to 80 °C with tests carried out at a two degree interval. The tests were in an oscillation form with a strain sweep of 1, 5.5 and 10 Hz with a constant strain, γ, of 10%. In all experiments, a weak normal force was applied to the surface of the sample discs in order to avoid the sweeping of the gel from the tool plates. This force resulted in a slight compression of the sample. All rheometry was carried out with disc shaped samples of diameter 40 mm and average thickness of 12 mm. Each measurement was performed, at least twice, on two different disc specimens from the same sample.

3. Results and discussion

3.1. Appearance of gels

PVA hydrogels exhibiting very different properties were obtained by varying the constituents of the initial solutions. The hydrogels ranged from being weak and soft to tough and rubbery. Gelation of the aqueous solutions containing either NaCl or HCl and PVA resulted in very weak and soft gels. On the contrary gelation of the aqueous solutions containing NaOH and PVA led to a tough and rubbery gel with enhanced swelling. The wide variations in physical and mechanical properties of PVA hydrogels are closely associated with differences in the microscopic structure. Hydrogel appearance also changed significantly from opaque and translucent to transparent. PVA/NaOH/H_2O gels were milky white, while PVA/NaCl/H_2O and PVA/HCl/H_2O gels were transparent. This is shown in Figs. (1)–(3). The opaque nature of the samples containing NaOH is, likely, due to phase separation and increased crystallinity of the material, a similar effect occurs in DMSO and PVA gels created by freeze thawing [23, 24]. The samples created using HCl and NaCl were transparent and this would imply less crystallinity. Increased crystallinity would lead to greater strength and toughness of the gels.

3.2. Modulated differential scanning calorimetry

MDSC was used instead of conventional DSC, due to the complex interaction of the polymers and additives. MDSC is more effective at determining the transitions from the different components of a blend [25]. In MDSC the total heat flow can be distinguished as the heat capacity component or reversing heat flow and the kinetic component or non-reversing heat flow. The use of reversible heat flow shows the underlying transitions and reduces the masking effect of solvents.

PVA gels are believed to consist of crystalline regions consisting of junction zones and amorphous regions consisting of long flexible chains [26]. Physical junctions in polymer gels may be classified into at least four types: crystallites for crystalline polymers, double helical structure for biological polymers, nodules for block copolymers and polymer—solvent complexes [27].

Park *et al.* found that PVA exhibits peaks at 85 and 143 °C, and a large peak above 210 °C. The peak at 85 °C, designated as the α relaxation, represents the glass transition temperature of PVA. The relaxation observed at 143 °C, designated as the β relaxation, is due to the relaxation in the PVA crystalline domains. The third relaxation, which occurs at a temperature between 200 and 260 °C, is caused by the melting of the crystalline domains of PVA [28]. Willcox *et al.* state that an endotherm present at 90 °C is indicative of secondary micro crystallite formation [13].

For aqueous PVA solutions containing salt the situation is more complicated, as NaCl primarily disrupts the inter and intra chain hydrogen bonding of the PVA chains [21]. Hirankumar *et al.* in their examination of PVA electrolytes suggested that the addition of salt reduces the Tg [29].

The influence of HCl and NaOH on freeze thawed PVA gels has not been reported previously. However Palacios *et al.* discussed the thermal characteristics of PVA/KOH/H_2O blends, which were solution cast, and also reports a lowering of the Tg. The thermal analysis seemed to be consistent with the interpretation of a two-phase mixture [30]. The two phases were: a polymeric one that reached a constant composition PVA/KOH/H_2O at low concentration of KOH and a separate second phase with composition KOH/H_2O [30]. It may be possible that phase separation would arise with PVA/NaOH and PVA/HCl aqueous gels.

Hatakeyema *et al.* studied the gel-sol transition of PVA and found that it occurred for physically cross linked hydrogels in the region of 55 to 70 °C. Brisoe *et al.* found for PVA/ H_2O /NaCl solutions that the extent of hydrogen bonding was disrupted at temperatures between 54 and 67 °C [21]. It is not possible to view these transitions using DSC as the gel-sol transition was completely masked by vaporization [11]. Sol gel transitions can be detected using viscosity measurements [21].

DSC graphs of 100% PVA polymer produced in water and hydrogels containing HCl, NaOH and NaCl are presented in Figs. (4)–(6) respectively. The Tg of the 100% PVA samples was at 30 °C. This low value is due to the presence of water in the samples which has had a plasticising effect and, therefore, reduces the Tg. The thermal transition in the region of 84 °C for the PVA samples could be due to micro crystallites or possibly due to the onset of vaporisation of water.

Fig. 4 shows the effect of HCl on the thermal transitions of PVA. The Tg appears to remain constant with the addition of HCl and the transitions picked up in the region of 78 to 91 °C for the PVA/HCl/H_2O samples could be micro crystallites or possibly due to the onset of vaporisation of water. The addition of HCl has reduced the melting point of PVA from 200 °C to between 164 and 170 °C and the melting endotherm has become broader which indicates less crystallinity.

Fig. 5 shows the effect of the addition of NaOH on the thermal transitions of PVA. The Tg has increased to between 57 and 61 °C for the various concentrations. An increase in Tg implies less chain mobility and therefore more inter- and intra-molecular hydrogen bonding. The interesting phenomenon is the melting of the crystalline segments. PVA exhibited a relatively large and sharp endothermic curve, with a peak at 203 °C. Upon addition of NaOH, the endothermic curve of PVA became sharper and its peak shifted to a higher temperature. In Fig. 5 it can be clearly seen that the peaks in the crystalline melting region, for the PVA/NaOH/H_2O samples are sharper, implying more ordered structure. This indicates that the addition of the NaOH has increased the crystallinity of the samples. The thermal transitions in the 0.025 M NaOH/ PVA/H_2O hydrogel show clearly separable multi peak endotherms which could be related to a multi phase structure, such as coexistent polymer-rich and polymer-poor phases [21, 31]. The transition visible for 0.0625 M NaOH/ PVA/H_2O hydrogel at 133 °C could be secondary crystallisation.

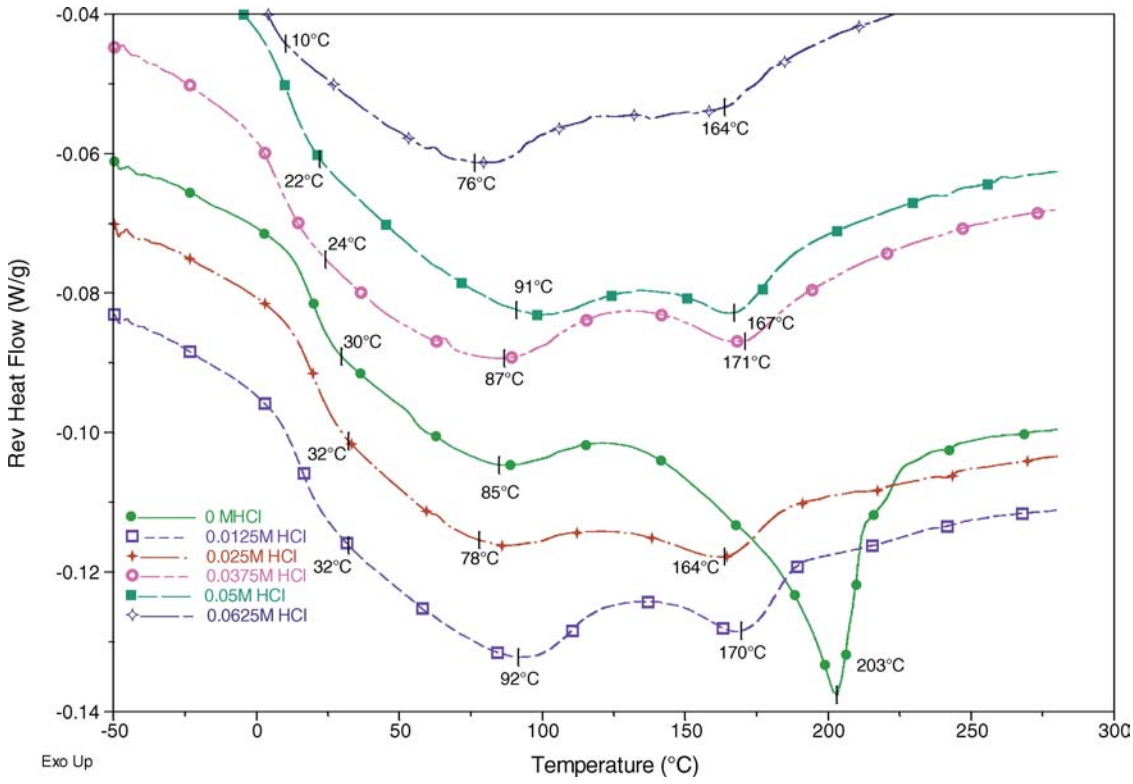

Figure 4 Reversible thermal transitions in PVA/H_2O/HCl.

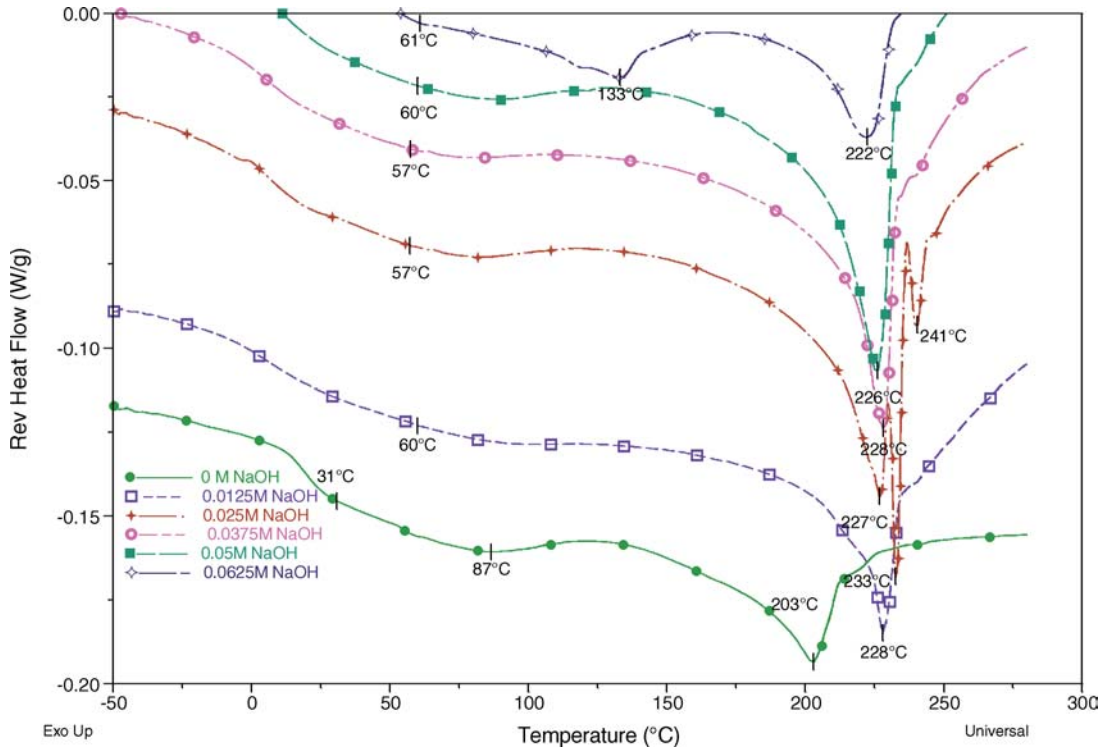

Figure 5 Reversible thermal transitions in PVA/H_2O/NaOH.

Fig. 6 shows the effect of NaCl on the thermal transitions of PVA. The transitions of 66 and 89 °C are likely due to micro crystallites or the vaporisation of water. The transitions of 111, 113 and 118 °C are not due to water and are indicative of secondary crystallisation. The melting temperature has increased with the addition of NaCl from 203 °C to between 215 °C to 216 °C.

For both the PVA/NaCl/H_2O and the PVA/HCl/H_2O blends, the crystalline endothermic peak of PVA became less prominent. The peak broadening indicates that the ordered association of the PVA molecules was decreased by the presence of HCl and NaCl. For PVA/HCl/H_2O there are even less visible crystalline peaks and there is a depression of the melting points, which indicates that the presence of the HCl

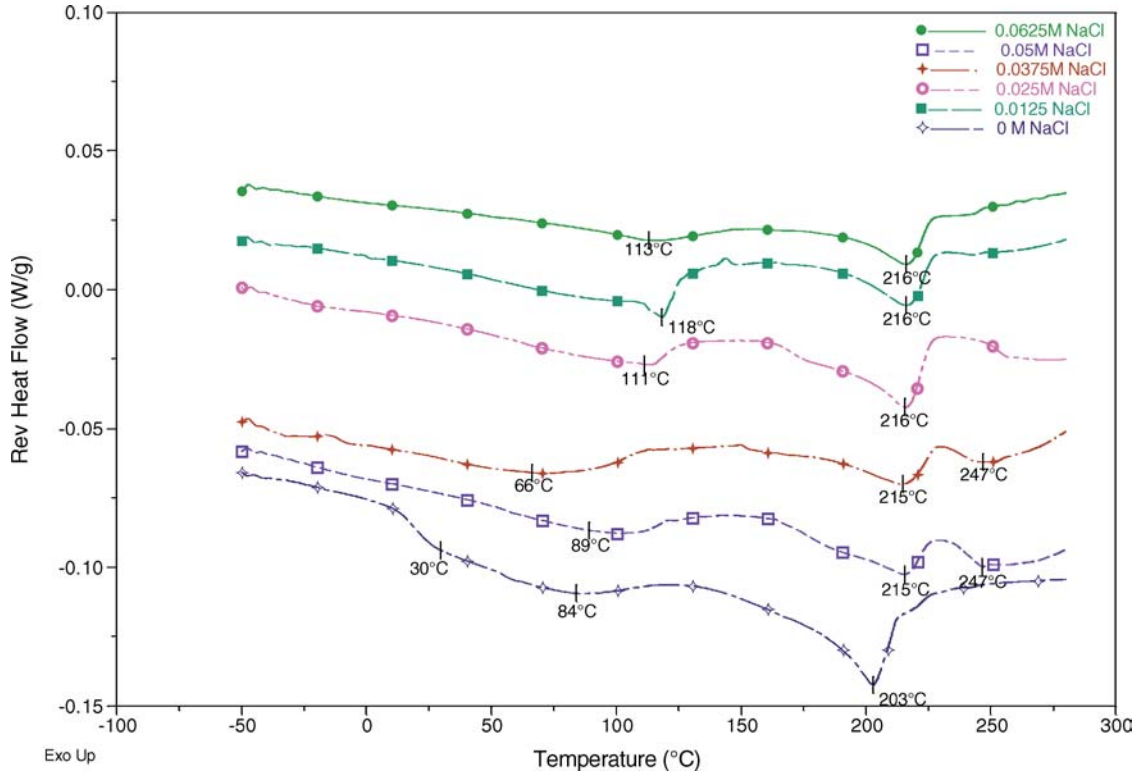

Figure 6 Reversible thermal transitions in PVA/H_2O/NaCl.

interferes with the crystallisation of the gels. For the PVA/NaCl/H_2O gels the melting point has increased slightly, but not to the same extent as with the addition of NaOH.

The overall conclusion is that the extent of crystallinity and the melting temperature increases with the addition of NaOH. On the other hand, even though the melting temperature increases with the addition of NaCl the extent of crystallinity is reduced. The addition of HCl reduces the melting point and the extent of crystallinity.

It is generally agreed that the addition of electrolytes disrupts the extent of hydrogen bonding. For aqueous PVA solutions the situation is rather more complicated than for many other aqueous polymer solutions due to the existence of hydrogen bonding not only between the PVA chains and water molecules but also with the PVA chains themselves. NaCl, NaOH and HCl might disrupt both inter and intra molecular hydrogen bonding of the PVA in solution, but different interactions occur upon freeze/thawing.

According to the modern theory of gelation polymer segments are allowed to interact with each other in two ways, one is by van der Waals interaction, the other by a directional interaction which leads to the tie point in the gel [20]. When an infinite network is formed by a directional interaction, the system is a gel and is assumed to be hydrogen bonded. The inclusion of NaCl and NaOH might contribute to high polar interactions, however during thawing the hydrogels, might absorb free energy as heat for aggregation. In this case it can serve as inter and intra molecular space conductor for heat transfer. NaCl and NaOH also caused high polar interactions in the macromolecular network system of the hydrogel and all these helped form an infinite network of directional interactions or tie points that caused hydrogen bonding. These van der Waals interactions of NaCl and NaOH and hydrogen bonding of inter and intra molecular hydroxyl groups of PVA contributed to the high melting temperature and higher crystallinity. This effect was greater with NaOH than with NaCl. Conversely the addition of HCl disrupted the inter and intra molecular bonding in solution but did not contribute to polar interaction upon freeze thawing.

3.3. Fourier transform infrared spectroscopy

The FTIR analysis indicated that the NaOH, NaCl and HCl were successfully introduced into the formed hydrogels, possibly via hydrogen bonds among hydroxyl groups, in the process of the freezing-thawing cycle. Figs. (7)–(9) show the FTIR spectrum of pure PVA/H_2O and a blend of PVA/H_2O/HCl, PVA/H_2O/NaOH and PVA/H_2O/NaCl respectively (0.025 M solutions).

Rajendran *et al.* have studied the effect of salt concentration on PVA [32]. The O─H stretching band in the IR spectrum is by far the most characteristic feature of alcohols and appears at 3555 cm^{-1} in pure PVA. This is indeed present in the samples. The peak at 1726 cm^{-1} is assigned to C═O stretching in the acetate group of PVA, and is shifted to 1731 cm^{-1} in the samples containing PVA/NaOH/$H_2$0, 1724 cm^{-1} in the samples containing PVA/HCl/H_2O and 1724 cm^{-1} in the samples containing PVA/NaCl/H_2O. This is due to the presence of intermolecular hydrogen bonding in PVA. This effect is most apparent in the presence of NaOH which would indicate that hydrogen bonding is strongest in these gels.

Figure 7 FTIR spectrum of pure PVA/H_2O and, a blend of PVA/HCl/H_2O (0.025 M HCl solution).

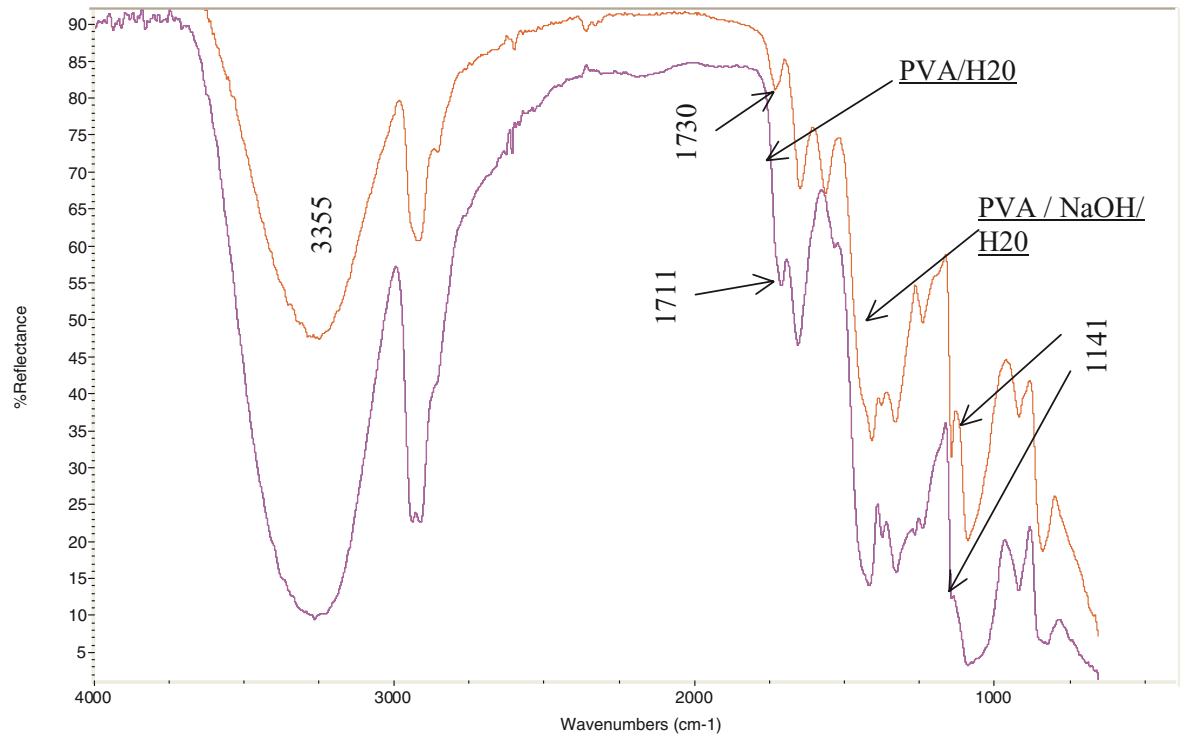

Figure 8 FTIR spectrum of pure PVA/ H_2O and, a blend of PVA/NaOH/H_2O (0.025 M NaOH solution).

Hassan *et al.* in the discussion of PVA gels referred to an absorption peak at 1141 cm^{-1}, which is indicative of PVA crystallinity, which arises from a C–C stretching mode and increases with an increase in the degree of crystallinity [14]. A peak at 1141 cm^{-1} is present in the hydrogels, indicating that a crystalline effect is occurring, this is most visible in the spectrum of PVA/NaOH/H_2O which would indicate that this hydrogel is the most crystalline.

3.4. Rheometry

Data reported in the literature on the mechanical properties of hydrogels are mostly obtained in tension/compression or using dynamic mechanical analysis. Dynamic mechanical methods have been successfully used to characterize the thermo/rheological properties of gel systems for polymeric films, for solid dosage coatings and as wound dressings [33]. To examine the stress strain relationship for the hydrogels, they

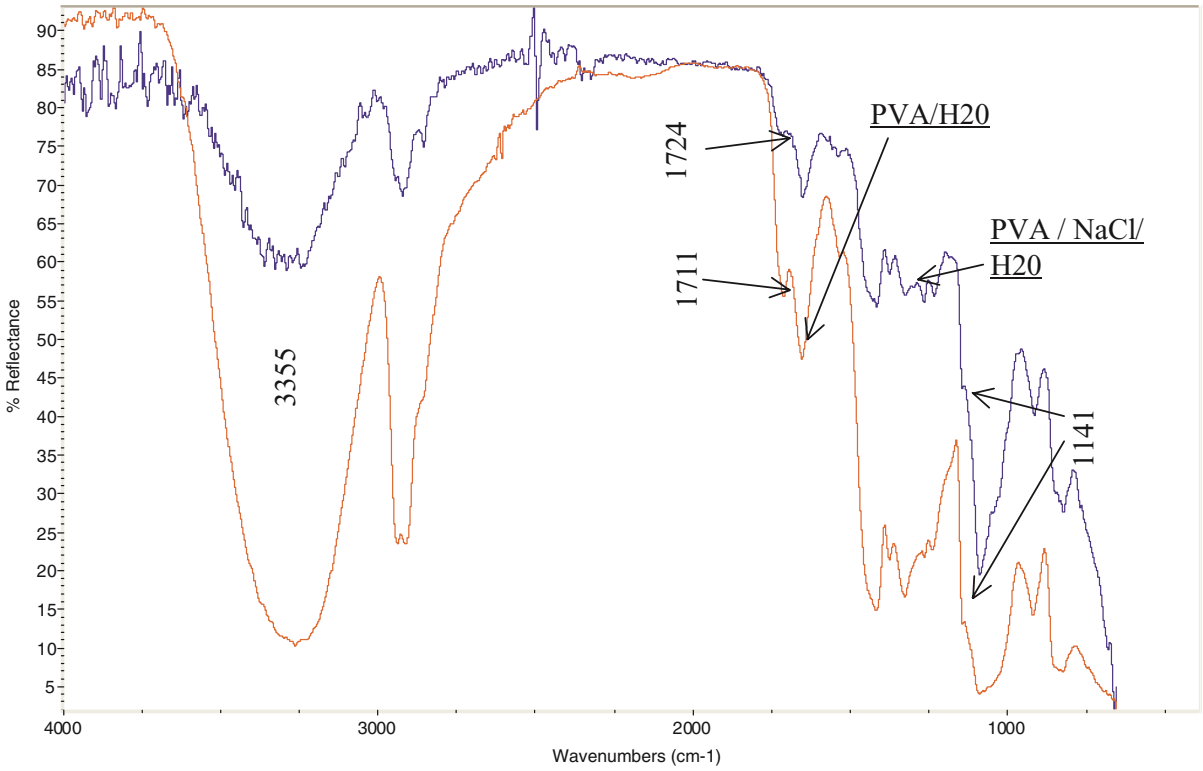

Figure 9 FTIR spectrum of pure PVA/H_2O and, a blend of PVA/NaCl/H_20 (0.025 M NaCl solution).

were subjected to an alternating strain, while simultaneously measuring the stress. For viscoelastic behaviour, when equilibrium is reached, the stress and strain will both vary sinusoidally, but the strain lags behind the stress. These relationships are shown in Equation 1 and 2 [34].

$$\text{Strain } e = e_o \sin\omega t \quad (1)$$

$$\text{Stress } \sigma = \sigma_o \sin(\omega t + \delta) \quad (2)$$

where ω is angular frequency and δ is the phase lag. The stress strain relationship can be defined by quantities G′ and G″ [42] which are 90° out of phase with the strain. These are described in Equation 3 and 4.

$$G' = (\sigma_o/e_o)\cos\delta \quad (3)$$

$$G'' = (\sigma_o/e_o)\cos\delta \quad (4)$$

G′ is in phase with the solid and is called the storage modulus because it defines the energy stored in

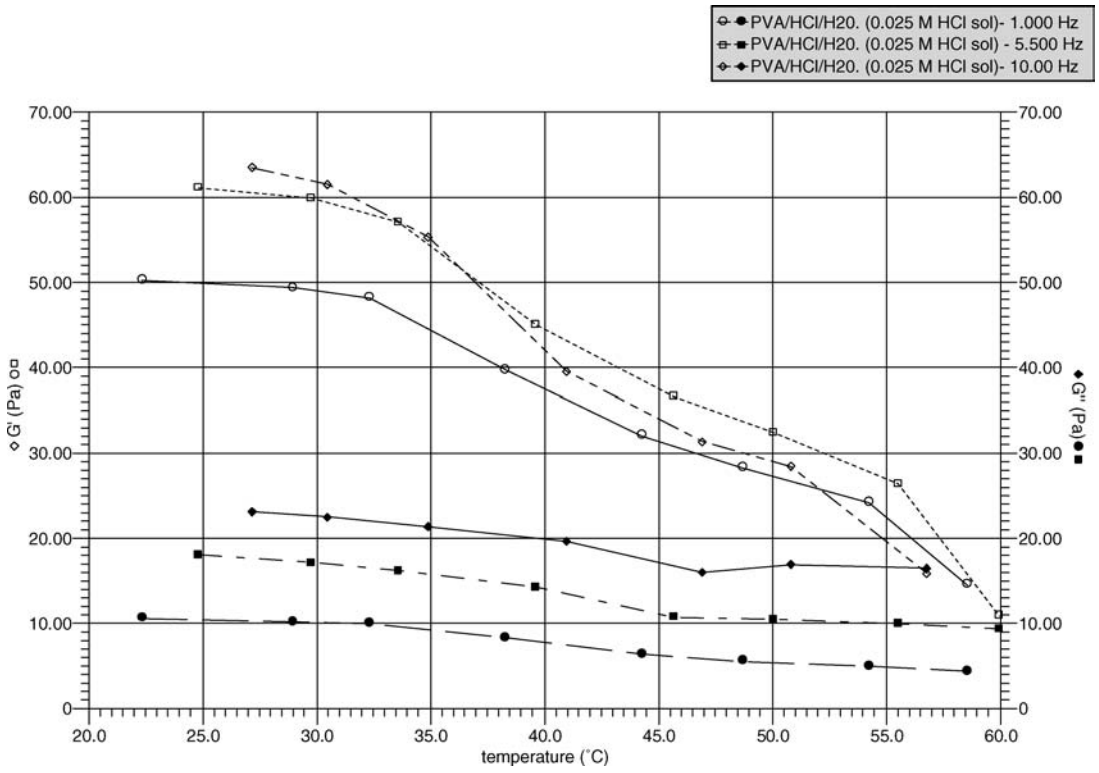

Figure 10 PVA/HCl/H_2O (0.025 M HCl solution).

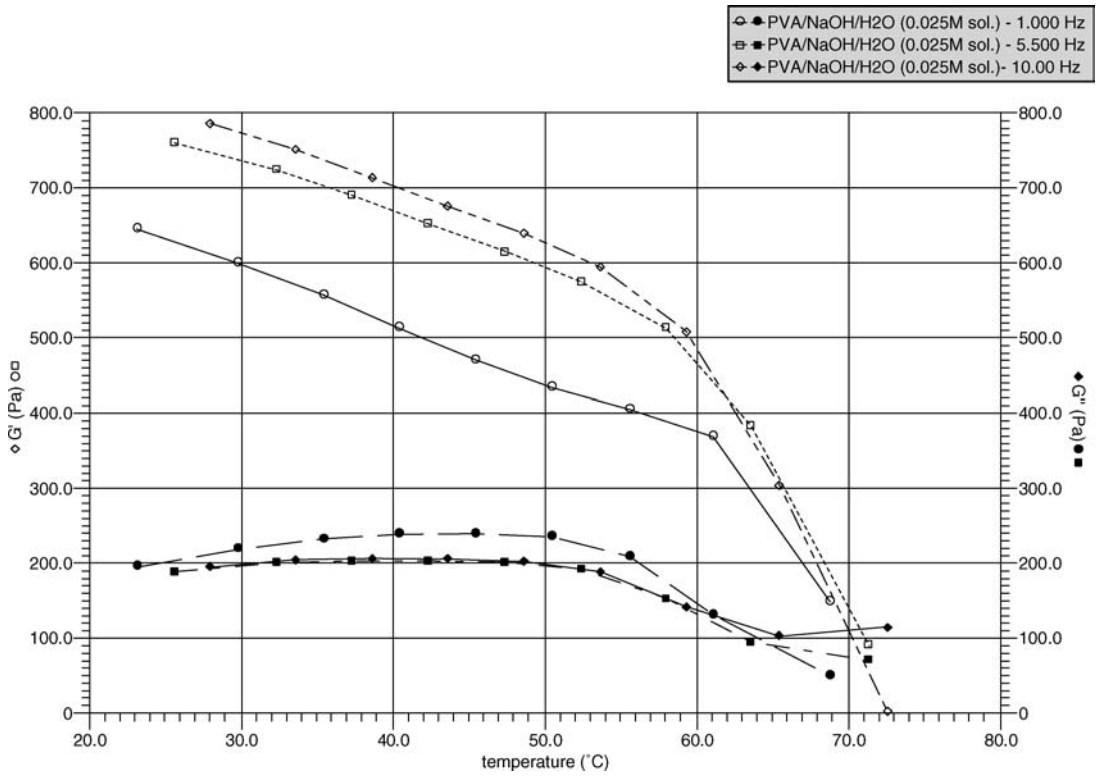

Figure 11 PVA/NaOH/H_2O (0.025 M NaOH solution).

the specimen due to the applied strain and G″ which is $\pi/2$ out of phase with the strain defines the dissipation of energy and is called the loss modulus [34]. It should be noted that for small strain amplitudes G′ is independent of the strain amplitude. In the following all the experiments were performed at the low strain amplitude which is the constant regime for G′.

The rheological properties of aqueous PVA solutions are mainly determined by the hydrogen bonding within

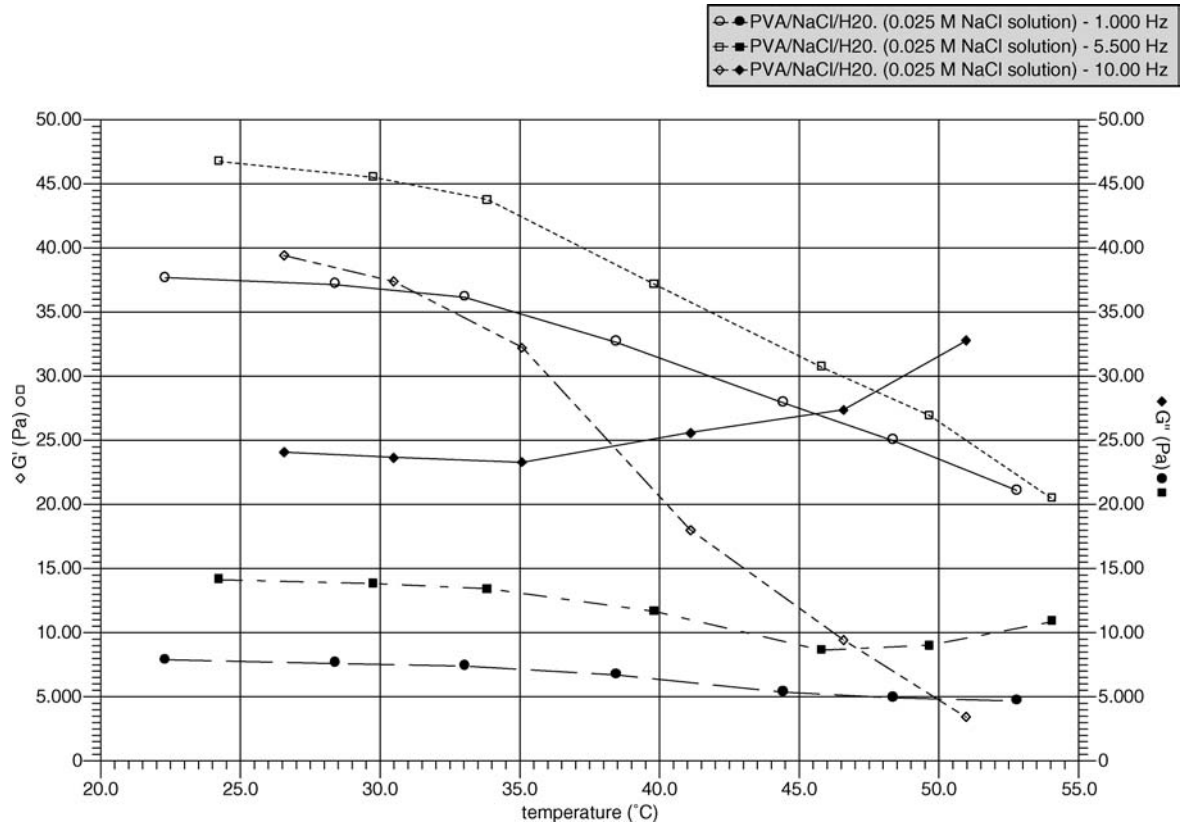

Figure 12 PVA/NaCl/H_2O (0.025 M NaCl solution).

the polymer chains and between the polymer chains and water molecules. This equilibrium can be varied by changing the degree of hydrolysis of the polymer, adding an electrolyte into the solution, and by varying temperature and pressure in a limited range [21]. Watase and Nishinari have shown that gels with a high concentration of PVA show rubber elastic behaviour up to 45 °C and after this point a transition to liquid-like behaviour occurs [35]. Hatekeyema *et al.* studied freeze thawed gels, and found that when the physical gels are heated at a temperature of between 55 and 70 °C, clear sols are obtained [11]. However, distinct gel-sol transition has not previously been observed by thermal analysis, since the transition caused by the dissociation of hydrogen bonding cannot be detected when the amount of hydrogen bonding is small [11].

It can be seen in Figs. (10)–(12) that G′ is much larger than G″ from 20 to 40 °C. This suggests that the elastic response dominates, which is typical for gels and solid-like materials. The G′ values obtained for PVA/NaOH/H_2O gels, at temperatures between 20 and 40 °C are in the region of 500 to 1000 Pa. This is in the useful range for biomedical applications [36]. The major difference arises when comparing PVA/H_2O/NaOH to PVA containing NaCl and HCl. The PVA/H_2O/HCl and PVA/H_2O/NaCl gels are significantly weaker than the PVA/H_2O/NaOH gels. The increased strength of the PVA/H_2O/NaOH is probably due to increased crystallinity and stronger hydrogen bonding. This was detected by the MDSC and FTIR analysis. The rheometry was carried out using a frequency sweep of 1 to 10 Hz and resulted in a negligible increase in G′ and G″.

The hydrogels are viscoelastic solids with both the storage modulus (G′) and loss modulus (G″) being temperature dependent. A significant drop in G′ at a temperature of 40 °C is observed for all the gels and at 70 °C all the gels have become liquid. This effect is the gel-sol transition which was studied by Hatekeyema [11]. These results indicates the feasibility of producing gels of high mechanical strength, which are temperature sensitive.

4. Conclusion

PVA is a biocompatible polymer which forms a hydrogel by strong non-covalent cross-linking. PVA gels prepared by freezing and thawing techniques show increased mechanical strength over most hydrogels due to the presence of crystalline regions that serve as the physical crosslinks. The potential applications are limited by the weak mechanical properties of the gels. To increase the mechanical strength repeated freeze/thaw cycles are performed, which is not commercially attractive. The novel gel created using PVA in the presence of NaOH by freeze thawing has significantly increased mechanical strength and is created with only one cycle of freeze thawing. A comparison of the mechanical and thermal properties of physically cross linked PVA containing HCl, NaCl and NaOH was undertaken to elucidate the mechanism of this increased strength. The physical and mechanical properties of the gels, are determined by entanglement, hydrogen bonding, primary and secondary crystallization and phase separation. The hydrogels prepared using a PVA/H_2O/NaOH were significantly stronger than those that contained HCl and NaOH, especially at temperatures of 20 to 40 °C. The thermal analysis shows distinct endotherms which showed increased crystallization for the PVA/H_2O/NaOH gels, which was further confirmed by the FTIR analysis. The significant feature of the research is that gels with different properties are created by varying the additives. In addition the work has indicated that the thermal transitions that are present are in the region of interest to drug delivery systems and may be modified by careful blending. These characteristics were demonstrated using rheometry which demonstrated the transition from a gel to a sol with increasing temperature. This could have potential in thermo responsive sytems These novel physically cross-linked PVA/$H_2$0/NaOH hydrogels are expected to show potential in drug delivery, including increasing drug-loading amounts and prolonging release time. By also varying such parameters as the initial aqueous concentration of PVA, molecular weight of PVA, and freezing and thawing conditions, we can likely further enhance the swelling of freeze/ thawed PVA hydrogels. Such gels with enhanced swelling and mechanical strength show promise for a variety of applications in the biomedical and pharmaceutical areas. The investigation of the influence of these additives on the drug release behavior from PVA hydrogels is in progress in our lab.

Acknowledgments

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