International Journal of Pharmaceutics 372 (2009) 154–161

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Pharmaceutical Nanotechnology

The synthesis of novel pH-sensitive poly(vinyl alcohol) composite hydrogels using a freeze/thaw process for biomedical applications

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ARTICLE INFO

Article history:
Received 6 October 2008
Received in revised form 9 January 2009
Accepted 9 January 2009
Available online 20 January 2009

Keywords:
Hydrogel composite
Poly(vinyl alcohol)
Drug delivery
Aspirin

ABSTRACT

Physically cross-linked hydrogels composed of 75% poly(vinyl alcohol) PVA and 25% poly(acrylic acid) were prepared by a freeze/thaw treatment of aqueous solutions. Between 0.5 and 1 wt% of aspirin was incorporated into the systems. The purpose of the research was the development of a novel pH-sensitive hydrogel composite for the delivery of aspirin to wounds. Extensive research has being conducted on freeze/thaw poly(vinyl alcohol) hydrogels for use in active pharmaceutical ingredient (API) delivery. However very little research has been reported on the effects of an API on the overall properties of a freeze/thaw hydrogel. From the rheological analysis undertaken it was apparent that aspirin has a limiting effect on the formation of hydrogen bonding leading to hydrogels with reduced mechanical strength. To counteract this, a novel hydrogel system was developed encompassing a reinforcing film in the centre of the hydrogels. Freezing profiles were obtained to gain a better knowledge of the freezing behaviour of the hydrogels during the formation stage. Thermograms obtained from modulated differential scanning calorimetry (MDSC) indicated that the aspirin lowered the glass transition temperatures (T_g) of the constituent polymers. The pH-sensitive nature of the hydrogels was apparent from solvent uptake studies carried out. Increasing alkaline media led to a greater degree of swelling due to increased ionisation of PAA. The hydrogels exhibited non-Fickian release kinetics. The release rates were relatively slow with total release achieved at between 30 and 40 h. The quantity of drug incorporated was found to influence the release rates considerably.

1. Introduction

Hydrogels are cross-linked hydrophilic polymer networks which can absorb thousands of times their dry weight when submersed in suitable media (Hoffman, 2002). They can be either physically or chemically cross-linked and are rendered insoluble due to the presence of these chemical, covalent, ionic or physical cross-links. The latter can be entanglements, crystallites, or hydrogen-bonded structures (Peppas, 1987). Currently methods that do not use chemical cross-linking agents for producing hydrogels, have become very prevalent and necessary due to toxicity of many cross-linking agents (Hickey and Peppas, 1997; Hennink and Van Nostrum, 2002). One method for producing physically cross-linked hydrogels is the freeze/thaw method. This method produces stable gels that are cross-linked by the presence of crystalline regions (Hassan and Peppas, 2000a).

Hydrogels have become increasingly important materials for pharmaceutical and biomedical applications (Staudt-Bickel and Lichtenthaler, 1994). In particular the field of API delivery is advancing rapidly (Langer, 2001). By controlling the precise level and/or location of an API in the body, side effects are reduced, lower doses are often possible, as are new therapies (Langer, 1998). Some environmental variables, such as low pH and elevated temperatures, are found in the body. For this reason, either pH-sensitive and/or temperature-sensitive hydrogels can be used for site-specific controlled API delivery (Qiu and Park, 2001).

PVA is a unique material as even in atatic form, it is semi-crystalline despite the lack of stereo regularity (Huang et al., 2006). In aqueous solutions with a polymer concentration of more than 1%, entangled aggregates of hydrogen bonded PVA molecules are formed. This is the consequence of the formation of crystalline regions (Hernández et al., 2004). Freeze/thawed gels are formed by dissolving polymer in a suitable solvent and freezing the solution. Upon freezing the solvent, crystals grow until they meet the facets of other crystals. The effect of these crystals is the formation of a porous system upon thawing (Lozinsky et al., 2003). This porous structure allows diffusion of solutes of practically any size. PVA hydrogels prepared using freeze/thaw techniques have great potential for biomedical applications (Stauffer and Peppas, 1992; Peppas,

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doi:10.1016/j.ijpharm.2009.01.008

1975). This is due to a high swelling capability often coupled with relatively good mechanical properties and good biocompatibility (Hassan and Peppas, 2000b).

PAA is a biocompatible material that elicits little antigenic reaction *in vivo*. Hence, PAA has widely been used in the area of the site-specific API delivery to particular regions of the gastrointestinal tract (Huang et al., 2007). Polymer networks containing PAA can form polyelectrolyte or hydrogen bonded complexes that are strongly dependent on the environmental pH and ionic strength (Kim and Peppas, 2003). The pH-sensitive nature of these hydrogels is due to the presence of COOH within the hydrogel structure (Mahaveer and Aminabhavi, 2004). All the pH-sensitive polymers contain pendant acidic (e.g. carboxylic and sulfonic acids) or basic (e.g. ammonium salts) groups that either accept or release protons in response to changes in environmental pH, for instance PAA becomes ionised at high pH (Qiu and Park, 2001). This pH-sensitive nature of the hydrogel makes it ideal for use in API delivery due to localised swelling in target areas.

The main focus of this research was on creating a novel PVA/PAA hydrogel composite with aspirin incorporated into the gel. Research already conducted by Nugent and Higginbotham (2007) on hydrogel composites showed potential for use as drug delivery devices. In continuation of this research, solvent cast films are frozen into the centre of the hydrogel to act as reinforcing films creating a novel reinforced hydrogel system for use in the biomedical field. Hydrogel composites have the ability to possess numerous required properties in one system. They can be effective API delivery devices and have the ability to adhere to body parts, such as intestinal walls, bones, etc., for site-specific drug delivery (Wu et al., 2008). Hydrogel composites have also great potential as biosensors and electrically controlled artificial muscles (Brahim et al., 2002; Moschou et al., 2006).

Aspirin is a widely used mild analgesic. Long-term use of aspirin, which is finally metabolized to salicylic acid (SA), has been shown to reduce the risk of cancer of the colon, breast, prostate, lung, and skin (Pal and Banthia, 2006). Aspirin also possesses anti-coagulatory properties which make it ideal for use in limiting scar formation. The anti-coagulatory properties help reduce swelling around the wound which is essential in limiting scarring (Danielson and Walter, 2005).

2. Materials and methods

2.1. Preparation of samples

Gels were prepared by dissolving (PVA) supplied by Aldrich with an average molecular weight of 146,000–186,000 and a saponification degree of 98–99% and poly(acrylic acid) supplied by Aldrich with a weight average molecular weight of 3,000,000 in 40 ml of deionised water at 80 °C for 1 h under constant stirring. From previous research conducted by the authors, the optimum ratio for viable hydrogels was found to be 75% PVA and 25% PAA. All hydrogels in this current research were made in this ratio. The aqueous solutions were cast in polystyrene moulds and placed in a sonicator to remove any bubbles that may have been present. The solutions were then rapidly frozen using a Julabo F81-ME cryostat bath unit which circulates thermal oil at a constant temperature of −80 °C. The frozen solutions were then thawed at ambient temperature resulting in gelation. PVA/PAA gels were also produced without any aspirin present for comparative research. As in previous research undertaken by the authors, solvent cast films at a concentration of 66% PVA, 34% PAA were produced by casting an aqueous solution in polystyrene Petri dishes. These films were used as reinforcing films within the hydrogels. The reinforced hydrogels were prepared by freezing half a solution in a mould. The film was then placed on this frozen solution and the remaining solution was poured into the mould and frozen. Samples for drug dissolution were prepared by first dissolving the required quantity of aspirin, 0.5% or 1%, in 10 ml of deionised for 1 h at 80 °C and then adding this to the PVA/PAA solutions.

2.2. Freezing profile

A freezing profile was obtained using a Digitron ultra low temperature thermometer. Temperatures were recorded at 10 s intervals until the gels were completely frozen.

2.3. Solvent uptake studies

Solvent uptake studies were carried out on hydrogels comprised of 75% PVA, 25% PAA with 1 wt% aspirin incorporated. The gels were submerged in pH buffer solutions of 4, 7.2 and 9 at a temperature of 37 °C for 120 h. The samples were weighed at set intervals of 1, 2, 4, 8, 24, 48 and 72 h and the changes in weight were noted. Before samples were weighted they were blotted to remove any excess media from the surface. The solvent uptake was calculated using formula (1);

$$\text{solvent uptake} = \frac{W_t}{W_0} \times 100 \quad (1)$$

where W_t and W_0 are weight of gel at time interval and initial weight of gel respectively.

2.4. Modulated differential scanning calorimeter

MDSC scans were obtained from using a DSC 2920 MDSC from TA instruments. Scans were performed on pure PVA, PAA and aspirin respectively to obtain the values for each of their thermal transitions. All samples weighed between 10 and 11 mg. As hydrated gels did not comprise sufficient polymeric material to detect thermal transitions samples were dried in an oven at 37 °C for 48 h. All samples were encapsulated in sealed aluminium sample pans and ramped from a temperature of 20–260 °C at a rate of 3 °C/min and a modulation was ±1.00 °C every 60 s. The results were plotted as a function of heat flow (W/g) against temperature (°C).

2.5. Rheometry

Rheometry tests were carried out using an AR 1000 rheometer from TA instruments. The tests were carried out using the parallel plate method. A Peltier plate was used as the heating element. A 40 mm steel plate was used as the top geometry. The test comprised of a gel being heated from 20 to 60 °C at a rate of 2 °C/min while an oscillating stress was exerted on the gel. Three different oscillating frequencies were used in each test, 1, 5.5 and 10 Hz respectively.

2.6. Drug dissolutions studies

Drug dissolution profiles were obtained using a Sotax AT7 smart dissolution system from Carl Stuart Ltd. The hydrogels were loaded with 0.5 and 1 wt% of aspirin and cylindrical samples of 5 g in weight were tested in phosphate buffer solution of pH 7.2 at 37 °C. The stir rate was set to 50 rpm with 900 ml of dissolution media used per vessel. Six vessels were used for each scan. Samples were automatically taken at set intervals and analysed by ultraviolet (UV) light on a PerkinElmer lambda 2 spectrometer. Six samples of hydrogel with 0.5% aspirin incorporated were analysed and the software produced a plot of the average release from the six samples. The dissolution curve for the hydrogel samples with 1% aspirin was also obtained using this method.

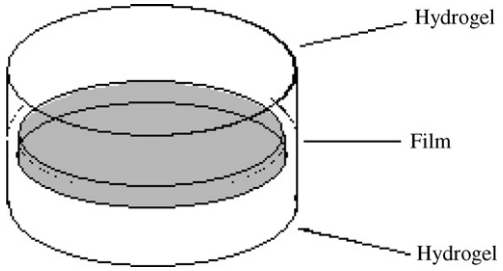

Fig. 1. Schematic of reinforcing film enclosed in a hydrogel.

3. Results and discussion

3.1. Visual inspection

As the PVA and PAA dissolved in the H_2O, the solution became very viscous with many bubbles present. These bubbles were eliminated using a sonicator. Upon addition of aspirin, the solution changed from a transparent solution to a white, opaque solution. Visual inspection of the gels after the freeze/thaw procedure showed that solutions without aspirin present formed translucent gels whereas the solutions with aspirin present formed white, opaque gels. This could indicate an increase in crystallinity which would lead to an increase in strength. However upon removal from the polystyrene moulds, the gels appeared weaker and did not hold their integrity as well as the gels without aspirin incorporated. This could indicate the colour change was due to the aspirin acting as a pigment.

To counter the apparently poor mechanical structure of the aspirin loaded gels a composite structure was formed by incorporating a film. Hydrogel composites loaded with aspirin appeared to have much better strength in comparison to the aspirin loaded gels without films. Fig. 1 shows a schematic of a film within the hydrogel.

3.2. Freezing profile

Fig. 2 shows the freezing profile of a hydrogel frozen in the cryostat bath and a hydrogel frozen liquid nitrogen. The linear curve obtained from the gel frozen in the cryostat bath indicates that the bath allows for total control over the freezing process in comparison to the erratic curve obtained from the freezing a gel in liquid nitrogen. This control allows for consistent gels to be continually produced. Hickey and Peppas (1995) reported that the freezing time and temperature can alter the properties of freeze/thaw technique. A cryostat bath enables the freezing temperature and conditions to be identical every time, ensuring consistent gels are produced.

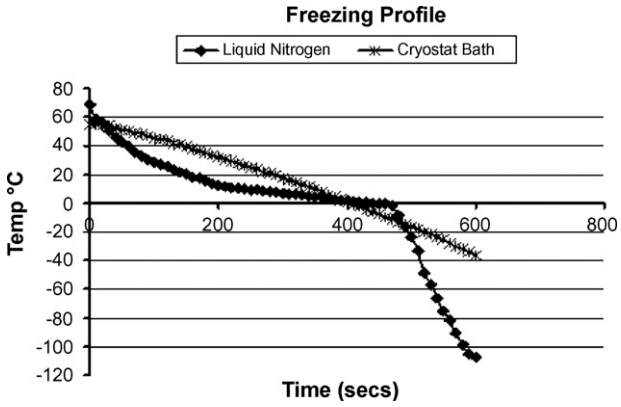

Fig. 2. Freezing profiles of hydrogel frozen in cryostat bath and liquid nitrogen.

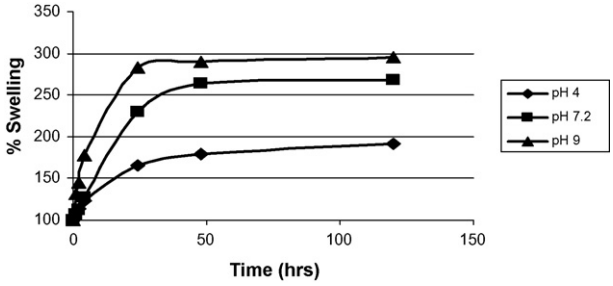

Fig. 3. Table showing % swelling versus time (h) for hydrogel.

3.3. Solvent uptake studies

As these hydrogels may have applications in wound care, a pH of 7.2, similar to the pH of blood was used. An acidic buffer solution of pH 4 and a basic buffer solution of pH 9 were used for comparative purposes. Fig. 3 shows solvent uptake studies carried out on hydrogels comprised of 75% PVA, 25% PAA with 1 wt% of aspirin incorporated. It was apparent that the degree of swelling of the gels in pH buffer of 7.2 was much greater than that of the gels in pH 4. This is due ionisation of the PAA in the polymer matrix. Due to the dissociation of carboxylic acid groups of the PAA and aspirin and the influx of counter ions, the concentration of ions in the hydrogel is higher than in the surrounding solution. This causes a difference in osmotic pressure and results in a solution flux into the hydrogel and, consequently, a swelling (Gerlach et al., 2005). This occurs to a greater extent in pH 7.2 than pH 4, as the pH of the media is closer to the pK_a value of PAA which is reported as 4.25 (Jin and Hseih, 2005). This results in reduced ionisation of PAA and less swelling. In the buffer solution of pH 9 the hydrogels swell to almost three times their initial weight.

3.4. MDSC characterization

Due to the high percentage of water content in the hydrogel samples, MDSC scans failed to detect any thermal transitions of the polymer present in the swollen polymers. Therefore all samples were dried at 37 °C for 48 h before testing.

Fig. 4 shows a thermogram obtained from pure aspirin in crystal form. The large peak at 135 °C represents the crystalline melting point (T_m) of aspirin. The peak at 241 °C is due to the degradation of the material at high temperatures. This corresponds to values reported by Pal and Banthia (2006).

Fig. 5 shows a thermogram of pure PVA in crystal form. The sharp peak at 219 °C represents the T_m of the PVA. The α relaxation which

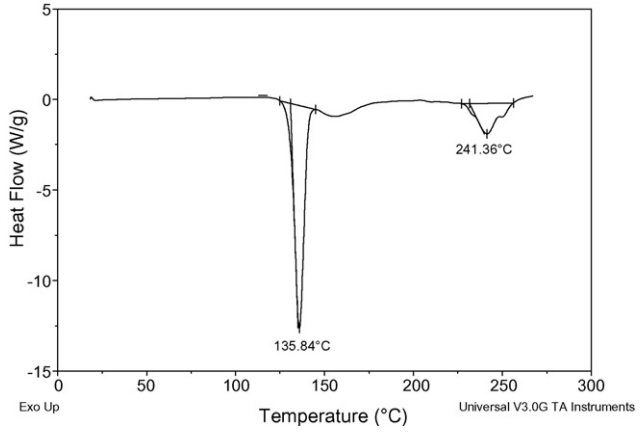

Fig. 4. DSC curve of aspirin in crystal form.

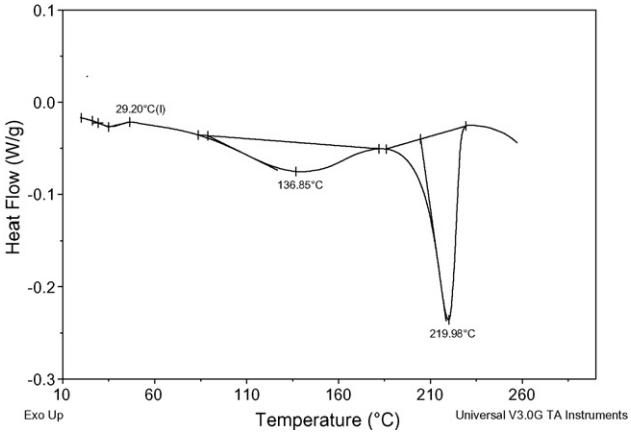

Fig. 5. DSC curve obtained from pure PVA in crystal form.

represents the T_g of PVA is represented by the step change at 29 °C. This is considerably lower than the value reported in literature (Maurer et al., 1987). This is due the presence of residual water and its plasticizing effect on the polymer (Hirankumar et al., 2005). The β relaxation which represents secondary crystalline relaxation can be seen at 137 °C. From literature these transitions are reported as being 85 and 143 °C respectively (Nugent and Higginbotham, 2007).

Fig. 6 shows the thermogram of pure PAA in powder form. The α relaxation peak of the PAA is represented by the step change at 58 °C. This is lower than reported values which is again due to the plasticizing effect of residual moisture on the polymer (Park et al., 2001; Maurer et al., 1987). PAA is an amorphous material hence no crystalline melting peak is present.

Fig. 7 shows thermograms obtained from hydrogels comprised of PVA/PAA in the ratio of 75:25. One hydrogel has 1% aspirin incorporated. The T_m of both hydrogels is 204 °C. This is a decrease of 14 °C in comparison to that of pure PVA seen in Fig. 5. This decrease in melt temperature is possibly due to morphological changes within the polymer matrix. These may involve changes in the size of the crystallites and the degree of crystallinity (Devine et al., 2006). The hydrogel without aspirin incorporated exhibits a T_g of 103 °C. This is a significant increase from that of pure PVA in Fig. 5. This increase is possibly due to hydrogen bonding between the O–H group of the PVA and the carboxylic acid group of the PAA. These hydrogen bonds act as physical cross-links and induces an increase in the molecular chain stiffness of PVA in the crystalline regions. The hydrogel with aspirin incorporated exhibits a T_g at 75 °C represented by the step change in the curve shown in Fig. 8. This is a significant increase from that obtained from pure PVA as can be

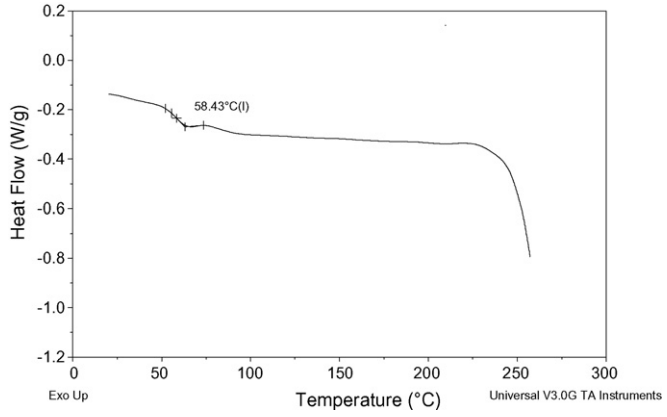

Fig. 6. DSC curve obtained from pure PAA in powder form.

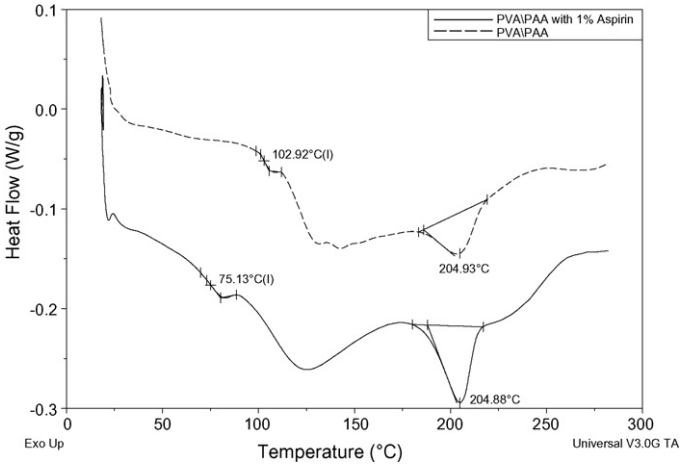

Fig. 7. DSC thermogram of a PVA/PAA hydrogel in the ratio of 75:25 with 1 wt% aspirin incorporated.

seen in Fig. 5. Again this is due to hydrogen bonding between the PVA and PAA. However there is a distinct decrease of the T_g of this hydrogel from that observed in the thermogram of the PVA/PAA hydrogel without aspirin incorporated as seen in Fig. 9. This is possibly due to the carboxylic acid group of the aspirin interacting with the carboxylic acid group of the PAA which results in a decrease in hydrogen bonds being formed between the PVA and PAA (Hassan et al., 2000).

3.5. Rheology analysis

Fig. 8 shows the storage modulus (G') and loss modulus (G'') as a function of temperature obtained from a swollen hydrogel composed of PVA/PAA in the ratio of 75:25. Focusing on the storage modulus, the gel has reasonable strength ranging from 260 to 350 Pa over the range of frequencies with the curve marked 1 being 1 Hz, the curve marked 2 being 5.5 Hz and the curve marked 3 being 10 Hz. A decrease in strength is observed between 35 and 45 °C. This decrease is possibly due to the uncoiling of crystalline regions within the polymer matrix (Huang et al., 2006). This happens at such low temperatures due to the high quantity of water and its plasticising effect on the polymer. At 55 °C a much sharper decrease in strength is observed. This decrease is due to breaking of the hydrogen bonds acting as physical cross-links. This was determined by initially creating a hydrogel of 100% PVA. The result was a gel with extremely poor viability.

However with the addition of PAA a much more viable gel was produced. This indicates that crystalline regions in the PVA act as physical cross-links but only to a small degree. This phenomenon has already being reported by Sinclair and Peppas (1984). The predominant factor in the gelation of these hydrogels is hydrogen bonds acting as physical cross-links. These hydrogen bonds are formed between the carboxylic acid groups of the PAA and the O–H group of PVA.

Fig. 9 shows the storage and loss modulus for a swollen hydrogel with the same composition as Fig. 11 but with 0.5% aspirin incorporated. The strength of this gel is observed as being between 100 and 145 Pa over the three frequencies. This is a sharp decrease in comparison to the gel without aspirin. This decrease is most likely due to the aspirin preventing hydrogen bonds forming between the PVA and PAA due to interactions between the carboxylic acid groups of the PAA and aspirin. This corroborates the findings from the MDSC scans which also indicated that the addition of aspirin led to a decrease in the degree of hydrogen bonding. The curves on this graph follow the same trend as the curves in Fig. 8. There is a

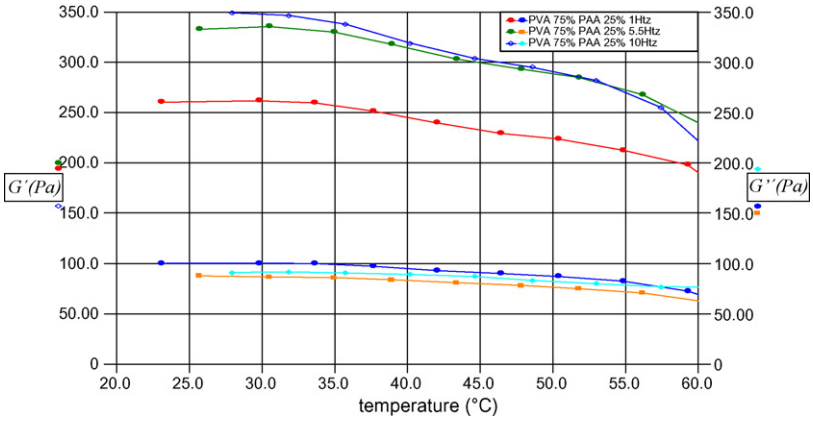

Fig. 8. Curve of storage {G' (Pa)} and loss {G'' (Pa)} versus temperature for a PVA/PAA gel.

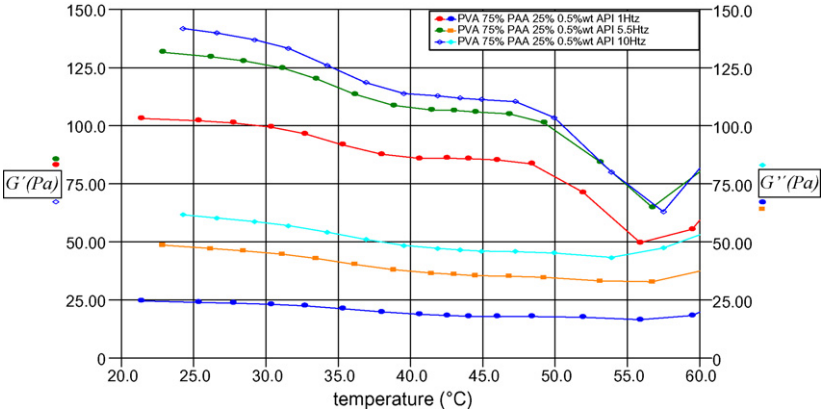

Fig. 9. Curve of storage {G' (Pa)} and loss {G'' (Pa)} versus temperature for a PVA/PAA gel with 0.5 wt% of aspirin incorporated.

visible decrease in the strength of the gel between 30 and 40 °C. The strength of the gel then remains constant until 47 °C at which point the strength of the gel sharply decreases. As stated already the small decrease in strength at 30 °C is due to the uncoiling of crystalline regions acting as physical cross-links (Huang et al., 2006). The sharp decrease in 47 °C is due to the breaking for hydrogen bonds acting as physical cross-links.

Fig. 10 shows the storage and loss modulus for a swollen gel of the same composition as above but with 1% aspirin incorporated into the matrix. The strength of this gel is approximately 60–75 Pa across the frequencies, again showing a further decrease in the strength with the addition of aspirin.

The results obtained show that the addition of aspirin into the polymer network inhibits hydrogen bonding between the PVA and PAA. It is also apparent that the strength of the gels is proportional to the amount of aspirin incorporated.

Fig. 11 shows the storage and loss modulus obtained for a hydrogel composite with 1 wt% of aspirin incorporated and also a novel reinforcing film incorporated in the centre of the gel. The film is a solvent cast film of PVA and PAA in the ratio of 66:34. The strength of the gel ranges from 175 to 260 Pa across the frequencies. This is a considerable increase from that of the gel in Fig. 10. The film effectively accomplishes its objective and acts as a reinforcing film leading to a more viable gel with much improved mechani-

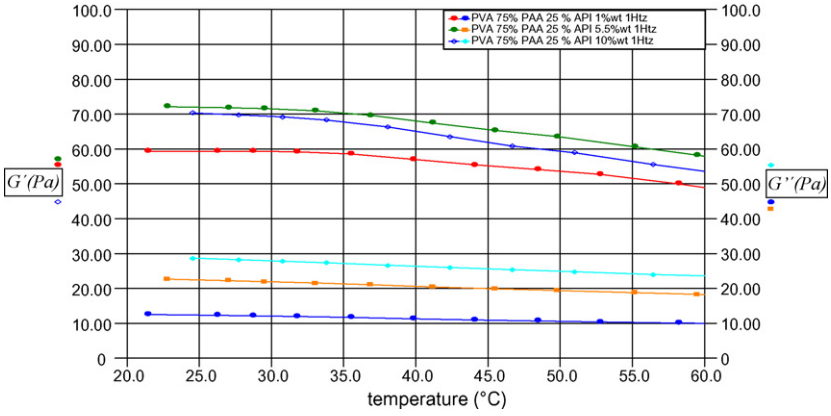

Fig. 10. Curve of storage {G' (Pa)} and loss {G'' (Pa)} versus temperature for a PVA/PAA gel with 1 wt% of aspirin incorporated.

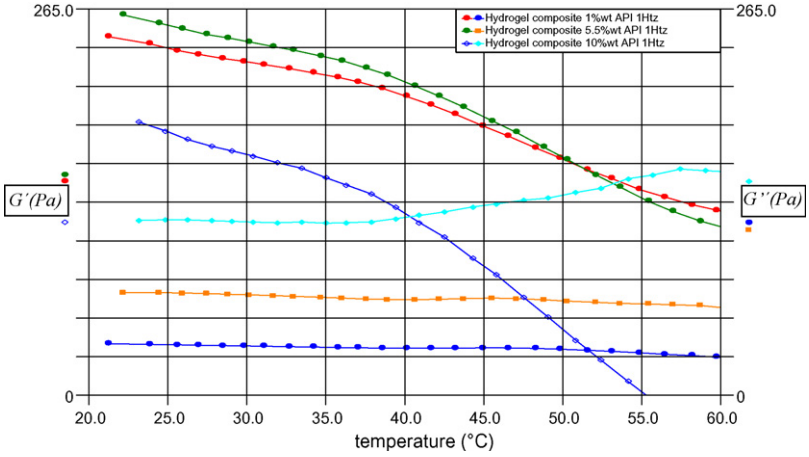

Fig. 11. Curve of storage {G' (Pa)} and loss {G'' (Pa)} versus temperature for a PVA/PAA gel with 1 wt% of aspirin incorporated and a reinforcing film in the centre of the gel.

cal properties. However at 45 °C the hydrogen bonds break and the composite reverts back to a viscous solution.

The decrease in the strength of the gels can be possibly explained by the formation of carboxylic acid dimers between the PAA and aspirin. These dimers form readily at elevated temperatures and are essentially hydrogen bonding between the PAA and the aspirin. A diagram of this reaction can be seen in Fig. 12. As the aspirin is bonded to the reactive groups of the PAA chains, little hydrogen bonding can occur between the PVA and PAA. This would also explain why an increase of aspirin incorporated into the gels leads to a decrease in the mechanical strength of the gel. A higher quantity of aspirin in the hydrogel would lead to a greater the degree of bonding between the aspirin and the carboxylic acid groups of the PAA. This leaves less reactive groups of PAA to bond with the PVA. Consequently the degree of hydrogen bonding between the PVA and PAA would be further diminished. This would also explain the changes in the T_g values observed in Fig. 7.

3.6. Drug dissolution studies

Fig. 13 shows the results obtained from drug dissolution studies carried out on PVA/PAA hydrogels with 0.5% and 1% aspirin incorporated. The media used for these analyses was buffer solution with pH 7.2.

The drug release mechanisms in swellable hydrogels have been widely reported (Mahaveer and Aminabhavi, 2004; Qiu and Park, 2001). Before swelling occurs the drug molecules are entrapped within the polymer matrix. As the hydrogel swells, the molecular weight between cross-links increases. This essentially means that the mesh size becomes larger. With a greater mesh size, the drug molecules are free to diffuse out of the gel.

The gels in this research are partially swollen initially. Research conducted by Nugent and Higginbotham (2007) showed that the API molecules are free to diffuse out of these hydrogels without the occurrence of swelling. The driving mechanism for molecule transport in this previous research was diffusion. However as there is a different API used in this research the properties of the hydrogels have been altered. The hydrogels characterised in this research exhibit significant degrees of swelling in media of pH 7.2.

Diffusion coefficients were calculated based on fitting the first 60% of the release to the equation (Peppas and Scott, 1992):

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

where M_t/M_∞ is the fractional release, k is the kinetic constant and n is the diffusion exponent. When $\log M_t/M_\infty$ is plotted against $\log t$, the value of the diffusion exponent n was obtained. The diffusion exponent (n) for the samples loaded with 0.5% and 1% aspirin was found to be 0.65 and 0.71 respectively. Peppas has reported that for cylindrical devices a diffusion exponent less that 0.45 indicates diffusion-controlled transport. A diffusion exponent of between 0.45 and 1 indicates non-Fickian or anomalous transport and a value above 1 indicates Case Π transport (Ritger and Peppas, 1987). Therefore the driving mechanism in the API release of these hydrogels is non-Fickian transport. This was expected as Case Π transport only occurs when a hydrogel swells from a dry glassy phase to a wet rubbery phase upon contact with media (Ritger and Peppas, 1987). The gels in this research are partially swollen upon synthesis and therefore API molecules are free to diffuse out without further swelling. However in the basic media of pH 7.2 the gels swell to a greater extent allowing more ease for solute diffusion. Therefore drug release occurs due to a combination of macromolecular relaxations due to swelling and Fickian diffusion.

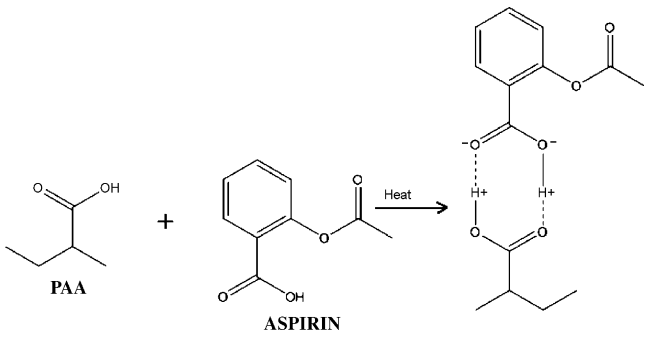

Fig. 12. Diagram of interaction between PAA and aspirin.

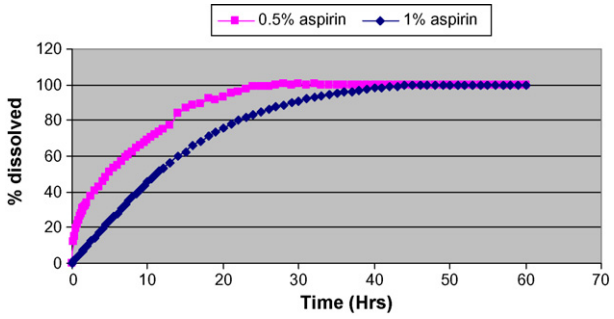

Fig. 13. Drug dissolution studies carried out on a PVA/PAA hydrogel with 0.5% and 1% aspirin incorporated.

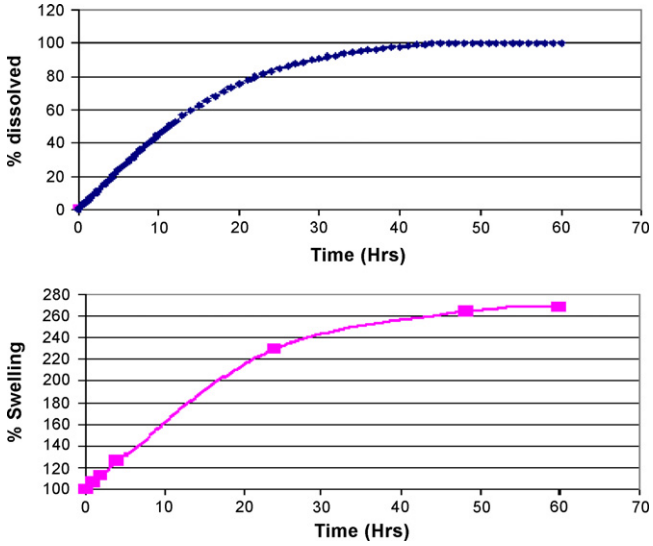

Fig. 14. Comparison between drug release and swelling ratio for hydrogel with 1% aspirin incorporated in pH 7.2 media.

Langer and Kost (2001) proposed that the release from swellable hydrogels is mediated by a moving front mechanism. This moving front is the swelling of the hydrogel from its outer surface to its centre. The API molecules are assumed to be somewhat free to diffuse out of the partially swollen hydrogel in its initial state. From the solvent uptake studies carried out in this research, it is evident that the gels swell further in basic pH media. As the swelling front passes a given API molecule, the latter finds itself in a more swollen polymer phase, through which it may diffuse to the outer solution with greater ease (Peppas et al., 1999). Assuming the API molecules diffuse much faster than the polymer swells, drug release should follow almost precisely the swelling front (Siegel and Kost, 1990). For true swelling-controlled release systems, the diffusional exponent, n, is 1 (Lowman and Peppas, 1999).

Comparing the swelling results for a hydrogel with 1% aspirin incorporated in media of pH 7.2 with drug release results of the same gel and media it is evident that the release follows the same trend as swelling (Fig. 14). Samples loaded with 1 wt% of aspirin were found to have 100% release after 40 h. There is an initial burst release after which the release slowed. As the swelling reaches equilibrium the release rate slows. This indicates that the swelling of the hydrogel has a significant effect on the transport of the aspirin from the gel to the surrounding media.

The quicker release for the gel with 0.5% aspirin incorporated is simply due to the fact that there is less API to be released and so it takes less time. 100% release is achieved after 25 h.

4. Conclusion

In this work we have evaluated the potential for novel poly(vinyl alcohol)–poly(acrylic acid) freeze thaw composite hydrogels for use as a wound dressing with the capability of delivering aspirin to the wound. The research showed that the incorporation of APIs, in this case aspirin, can have a significant effect on the overall mechanical properties of freeze/thaw PVA/PAA hydrogels. The effect of incorporating aspirin within the hydrogel led to a decrease in the mechanical properties of the overall structure. To compensate for this loss in mechanical strength, a novel hydrogel-film composite was produced. The film acted as a reinforcing film within the hydrogel.

From DSC analysis carried out it was evident that aspirin had a plasticizing effect effectively lowering the T_g of the PVA within the gels by more than 25 °C. From solvent uptake studies carried out it was observed that less swelling occurred in media of pH 4 than in pH 9. This is due to the pH-sensitive nature of the hydrogel caused by the addition of PAA and aspirin which contain reactive groups. Anomalous or non-Fickian transport was the predominant release mechanism for these hydrogels. The novel composites produced in this study have particular potential in wound care, specifically scar limitation.

References

Brahim, S., Narinesingh, D., Guiseppi-Elie, A., 2002. Polypyrrole-hydrogel composites for the construction of clinically important biosensors. Biosens. Bioelectron. 17, 53–59.
Danielson, J.R., Walter, R.J., 2005. Case studies: use of salicylic acid (Avosil®) and hydrogel (Avogel®) in limiting scar formation. J. Burns Wounds 4, 119–127.
Devine, D.M., Devery, S.M., Lyons, J.G., Geever, L.M., Kennedy, J.E., Higginbotham, C.L., 2006. Multifunctional polyvinylpyrrolidinone-polyacrylic acid copolymer hydrogels for biomedical applications. Int. J. Pharm. 326, 50–59.
Gerlach, G., Guenther, M., Sorber, J., Suchaneck, G., Arndt, K.F., Richter, A., 2005. Chemical and pH sensors based on the swelling behavior of Hydrogels. Sens. Actuators B 111–112, 555–561.
Hassan, C.M., Peppas, N.A., 2000a. Structure and morphology of freeze/thaw hydrogels. Macromolecules 33, 2472–2479.
Hassan, C.M., Peppas, N.A., 2000b. Structure and applications of poly(vinyl alcohol) hydrogels produced by conventional crosslinking or by freezing/thawing methods. J. Adv. Polym. Sci., 37–65.
Hassan, C.M., Ward, J.H., Peppas, N.A., 2000. Modeling of crystal dissolution of poly(vinyl alcohol) gels produced by freezing/thawing processes. Polymer 41, 6729–6739.
Hennink, W.E., Van Nostrum, C.F., 2002. Novel crosslinking methods to design hydrogels. Adv. Drug Deliv. Rev. 54, 13–36.
Hernández, R., Sarafian, A., López, D., Mijangos, C., 2004. Viscoelastic properties of poly(vinyl alcohol) hydrogels and ferrogels obtained through freezing–thawing cycles. Polymer 46, 5543–5549.
Hickey, A.S., Peppas, N.A., 1995. Mesh size and diffusive characteristics of semicrystalline poly(vinyl alcohol) membranes prepared by freezing/thawing techniques. J. Membr. Sci. 107, 229–237.
Hickey, A.S., Peppas, N.A., 1997. Solute diffusion in poly(vinyl alcohol)/poly(acrylic acid) composite films using freezing/thawing techniques. Polymer 38, 5931–5936.
Hirankumar, G., Selvasekarapandian, S., Kuwata, N., Kawamura, J., Hattori, T., 2005. Thermal, electrical and optical studies on the poly(vinyl alcohol) based polymer electrolytes. J. Power Sources 144, 262–267.
Hoffman, A.S., 2002. Hydrogels for biomedical applications. Adv. Drug Deliv. Rev. 43, 3–12.
Huang, H., Gu, L., Ozaki, Y., 2006. Non-isothermal crystallization and thermal transitions of a biodegradable, partially hydrolyzed poly(vinyl alcohol). Polymer 47, 3935–3945.
Huang, Y.H., Lu, J., Xiao, C.B., 2007. Thermal and mechanical properties of cationic guar gum/poly(acrylic acid) hydrogel films. Polym. Degrad. Stab. 92, 1072–1081.
Jin, X., Hsieh, Y.-L., 2005. pH-responsive swelling behavior of poly(vinyl alcohol)/poly(acrylic acid) bi-component fibrous hydrogel films. Polymer 46, 5149–5160.
Kim, B., Peppas, N.A., 2003. Analysis of molecular interactions in poly(methacrylic acid-g-ethylene glycol) hydrogels. Polymer 44, 3701–3707.
Langer, R., 1998. Drugs delivery and targeting. Nature 392, 5.
Langer, R., 2001. Drugs on target. Science 293, 58.
Langer, R., Kost, J., 2001. Responsive polymeric delivery systems. Adv. Drug Deliv. Rev. 46, 125–148.
Lowman, A.M., Peppas, N.A., 1999. Hydrogels. In: Mathiowitz, E. (Ed.), Encyclopedia of Controlled Drug Delivery. Wiley, New York, pp. 397–418.
Lozinsky, V.I., Galaev, I.Y., Plieva, F.M., Savina, I.N., Jungvid, H., Mattiasson, B., 2003. Polymeric cryogels as promising materials of biotechnological interest. Trends Biotechnol. 21, 445–451.
Mahaveer, D.K., Aminabhavi, T.M., 2004. Poly(vinyl alcohol) and poly(acrylic acid) sequential interpenetrating network pH-sensitive microspheres for the delivery of diclofenac sodium to the intestine. J. Control. Release 96, 9–20.
Maurer, J.J., Eustace, D.J., Ratcliffet, C.T., 1987. Thermal characterization of poly(acrylic acid). Macromolecules 20, 196–202.
Moschou, E.A., Madou, M.J., Bachas, L.G., Daunert, S., 2006. Voltage-switchable artificial muscles actuating at near neutral pH. Sens. Actuators B 115, 379–383.
Nugent, M.J.D., Higginbotham, C.L., 2007. Preparation of novel freeze thawed for poly(vinyl alcohol) composite hydrogel for drug delivery applications. Eur. J. Pharm. Biopharm. 67, 377–386.
Pal, K., Banthia, A.K., 2006. Polyvinyl alcohol—gelatin patches of salicylic acid: preparation, characterization and drug release studies. J. Biomater. Appl., 75–91.
Park, J.S., Park, J.W., Ruckenstein, E., 2001. Thermal and dynamic mechanical analysis of PVA/MC blend hydrogels. Polymer 42, 4271–4280.
Peppas, N.A., 1975. Turbidimetric studies of aqueous poly(vinyl alcohol) solutions. Macromol. Chem. Phys. 176, 3433–3440.
Peppas, N.A., 1987. Hydrogels of poly(vinyl alcohol) and its copolymers. Hydrogels Med. Pharm. 2, 1–48.

Peppas, N.A., Scott, J.E., 1992. Controlled release from poly(vinyl alcohol) gels prepared by freezing–thawing processes. J. Control. Release 18, 95–100.
Peppas, N.A., Keys, K.B., Torres-Lugo, M., Lowman, A.M., 1999. Poly(ethylene glycol)-containing hydrogels in drug delivery. J. Control. Release 62, 81–87.
Qiu, Y., Park, K., 2001. Environment-sensitive hydrogels for drug delivery. Adv. Drug Deliv. Rev. 53, 321–339.
Ritger, P.L., Peppas, N.A., 1987. A simple equation for description of solute release. I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J. Control. Release 5, 23–26.
Siegel, R.A., Kost, J., 1990. pH-sensitive gels: swelling equilibria, kinetics and applications for drug delivery. Pulsed Self-regulated Drug Deliv., 129–157.
Sinclair, G.W., Peppas, N.A., 1984. Analysis of Fickian transport in polymers using simplified exponential expressions. J. Membr. Sci. 17, 329–331.
Staudt-Bickel, C., Lichtenthaler, R.N., 1994. Pervaporation thermodynamic properties and selection of film polymers. Polym. Sci. 36, 1628–1640.
Stauffer, S.R., Peppas, N.A., 1992. Poly(vinyl alcohol) hydrogels prepared by freezing thawing cyclic processing. Polymer 33, 3932–3936.
Wu, G., Su, B., Zhang, W., Wang, C., 2008. *In vitro* behaviors of hydroxyapatite reinforced polyvinyl alcohol hydrogel composite. Mater. Chem. Phys. 107, 364–369.