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Enhancement and restriction of chain motion in polymer networks

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ABSTRACT

Sevelamer carbonate, a polymeric drug, adsorbs phosphate ions from the gastro intestine of patients suffering from chronic kidney disease. Polymer chain mobility becomes critical during its manufacture and storage. How the polymer chain mobility in sevelamer carbonate is quantitatively controlled by small molecular species, in this case by water molecules and bicarbonate anions, is demonstrated here. Spin-lattice relaxation times of the protons in the hydrogel, detected by solid state NMR, are indicative of mobility within the polymer. They decreased with increasing water content but increased as the bicarbonate anion content increased. As the water content increased, the glass transition temperature decreased but increasing the bicarbonate anion content had the opposite effect. FTIR analysis indicated that the anions were involved in bonding while the water molecules were not. The stability and physicochemical properties of polymers during storage and formulation depend on the polymeric structure and the dynamic behaviour of the polymer chains.

1. Introduction

Polymers are prevalent in many of the drugs that people take daily to improve their quality of life. They are used as drug carriers (Hudson et al., 2010), storage networks (Moses et al., 2003), in solid dispersion formulations (Qian et al., 2010) and as the active ingredient (Dhal et al., 2009) in pharmaceutical formulations. Therefore, there is great interest in understanding the dynamics on a molecular level within polymeric networks. The physical properties of polymers are dependent on these molecular dynamics and they influence the final formulation, biological activity, manufacturing processes used and storage conditions chosen for pharmaceutical systems (Ergun et al., 2010; Geppi et al., 2010; Hancock and Zograf, 1997). Thus, the characterisation of polymer chain motion of existing and novel polymers in a quantifiable manner is necessary. Polymer chain movement depends on temperature, polymer chain interactions and the presence of plasticisers such as water molecules (Bershtein and Egorov, 1994; Freitas et al., 2009; Teng et al., 2010).

It has been shown in the literature that solid state nuclear magnetic resonance (NMR) can be used to measure the molecular dynamics of pharmaceutical and polymeric systems (Dastbaz et al., 1999; Geppi et al., 2010; Kakiage et al., 2008; Lubach et al., 2007; Mollica et al., 2011). Magnetically active nuclei, when placed in a magnetic field, can occupy a lower spin state (where their spin is aligned with the magnetic field) or a higher spin state (where their spin is opposed to the magnetic field). Radiation can be applied to excite these nuclei from the lower energy state to the higher energy state. The time it takes for the nuclei to relax back to their equilibrium state after excitation can be measured. The relaxation time measured here is called the proton spin-lattice relaxation time and is measured in the laboratory or longitudinal frame (T1) (Castelvetro et al., 2007; Kim et al., 2007; Lubach et al., 2007). The spin-lattice relaxation time depends on the degree of order and mobility, i.e. the dynamics, in the molecular system (Dastbaz et al., 1999; Geppi et al., 2008; Lam et al., 2002; Lubach et al., 2007; Suihko et al., 2005). Main chain segment reorientation, methyl group rotations or the reorientation of physisorbed water molecules can all act as proton T1 relaxation sinks, increasing molecular motion within the polymer network and decreasing T1 spin lattice relaxation times (Andrew, 1985; Geppi et al., 2010; Mollica et al., 2011). Proton spin lattice relaxation times in a biomacromolecule were found to decrease with increasing moisture contents (Geppi et al., 2010). Changes in proton relaxation times were indicative of the effect of mechanical stresses on molecular mobility in polyethylene melts (Kakiage et al., 2008). Similarly, processes such as compaction, lyophilization, spray drying, and cryogrinding were found to influence the relaxation times of protons in lactose (Lubach et al., 2007).

Thermal analysis (Allison, 2008; Chen et al., 2011; Luthra et al., 2008; Ren et al., 2003; Teng et al., 2010), phosphorescence (You and Ludescher, 2008, 2011), X-ray diffraction (Teng et al., 2010) and dielectric studies (Allison, 2008; Ren et al., 2003) have also been used to look at molecular mobility in pharmaceutical and polymeric networks. In this study, solid state NMR, thermal analysis and Fourier-transform infrared spectroscopy (FTIR) are the techniques used to determine the effect of anion and water content on polymer

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chain mobility. Thermal analysis allows the behaviour of polymers with changing temperature/influx of heat to be examined. The glass transition temperature (T_g) of a crosslinked polymer refers to the temperature at which the polymer moves from a glassy state to a rubbery state. In order for a glass transition step to be observed in a differential scanning calorimetry (DSC) profile, it requires the cooperative movement of large segments of the polymer chain which can be influenced by (i) the plasticising effect of water which will lower the T_g (Bershtein and Egorov, 1994; Castelvetro et al., 2007; Teng et al., 2010) and (ii) hydrogen bonding between the polymer chains which will raise the T_g (Lee et al., 2006). Shifts in the vibrational peaks in FTIR spectra are indicative of bonding between functional groups on the polymer back bone (Lee et al., 2006). Tempering, or aging at elevated temperatures, has also been shown to affect polymer chain dynamics in glassy or amorphous systems (Luthra et al., 2008). Thus it is expected that aging of polymer networks by treatment at elevated temperatures may cause some rearrangement of polymer chains in the polymer network, independent of the anion and water content. The main focus of this study was the effect of anion and water molecules on polymer chain mobility. Care was taken not to assign tempering effects to the restrictive or enhancing effects of small molecules on motion within the polymer network.

Sevelamer is the active polymeric ingredient used to adsorb phosphate ions from the gastro intestine of patients suffering from chronic kidney disease. It is an insoluble, very hygroscopic, crosslinked polyallylamine polymer and is available in a hydrochloride or carbonate form. It functions by exchanging its anion (chloride or bicarbonate) for the phosphate ions in the patient's intestine. Sevelamer carbonate is formed by cross-linking (using epichlorohydrin) a partially neutralized solution of poly (allylamine hydrochloride) to give an insoluble gel (sevelamer hydrochloride). The gel contains protonated amine groups at low pH (<7) but by washing with a high pH wash (~7–10), the amine groups are deprotonated and the free base is formed and the chloride ions are removed. The free base suspension in water is then reacted with carbon dioxide and finally dried to give sevelamer carbonate (Dhal et al., 2009; Harland and Wrong, 2010), Fig. 1. As has been discussed in the literature, sevelamer carbonate contains the bicarbonate anion (HCO_3^-) as opposed to the carbonate (CO_3^{2-}) due to low pH conditions during the carbonation step and during its activity in the intestine of the patient (pH < 7) (Harland and Wrong, 2010). Note that at higher pH values (~10), where carbonate anions might be present, the free base would also exist and the gel would not be an effective anion exchange resin – thus its name is a slight misnomer (Harland and Wrong, 2010). The name sevelamer carbonate is used throughout this study but the anion will be referred to as the bicarbonate anion. This study examines the polymeric structure and dynamic behaviour of sevelamer carbonate and demonstrates how this behaviour is controlled by the percentage of bicarbonate anions and water molecules present in the hydrogel. The stability and physicochemical properties of polymers during storage and formulation depend on this behaviour. For the first time, the quantitative effect of ionic bonding due to the presence of a bicarbonate anion and the simultaneous plasticising and sink effect of water molecules on polymer chain motion in a crosslinked polyallylamine hydrogel have been demonstrated using solid state NMR, FTIR and thermal analysis.

2. Materials and methods

2.1. Materials

Sevelamer carbonate was received from Genzyme Waterford, Ireland.

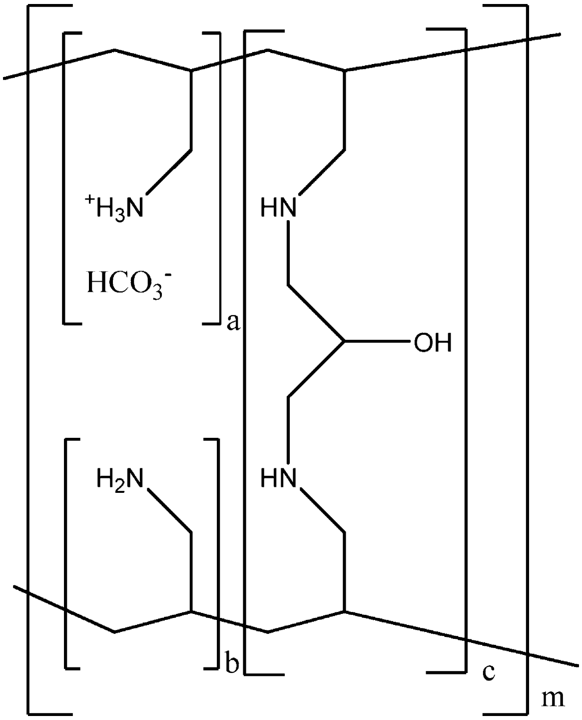

Fig. 1. Chemical structure of sevelamer carbonate.

2.2. Variation of water and bicarbonate anion content in sevelamer carbonate

Samples of sevelamer carbonate were held at 120 °C under vacuum for 10–72 h to obtain a particular anion content. The samples were then exposed to the atmosphere for 0–24 h to adsorb moisture. To reduce the water content of the 18% (as received) bicarbonate samples (not subjected to the thermal treatment at 120 °C under vacuum), samples were held at 60 °C under vacuum for 12–24 h. The water and bicarbonate anion contents were quantified using thermal gravimetric analysis. A control of sevelamer carbonate was treated at 120 °C, in a sealed Duran bottle to prevent loss of water molecules and bicarbonate anions, for 48 h to determine the effects of exposure to 120 °C for a prolonged duration of time. Sevelamer carbonate with different bicarbonate contents and 4% water content were stirred at room temperature in deionised water (0.6 g in 10 ml) and the pH of the solution was monitored over 48 h to determine any change in the pH of the hydrogel system.

2.3. FTIR analysis

FTIR analysis was conducted in attenuated total reflectance (ATR) mode on a Varian 660-IR FT-IR Spectrometer and Varian 610-IR FT-IR Microscope. Each spectrum was obtained through the averaging of 32 repetitive scans, at a resolution of 2 cm^{-1}.

2.4. Solid state nuclear magnetic resonance (SSNMR)

Samples were analysed using a JEOL 400 MHz spectrometer with a broad band solid state probe. The samples were packed into 3.2 mm silicon nitride rotors. The spectrometer was set up by optimising the probe factors using a mixture of adamantane, KBr and glycine, Table 1. The ^{13}C CPMAS spectrum of this standard was taken between each sample to ensure the magnetic field or magic angle had not drifted. Magic angle spinning was applied using 3.2 mm silicon nitride rotors at a frequency of 10 kHz. ^{1}H inversion experiments were run to obtain the T1 spin lattice relaxation

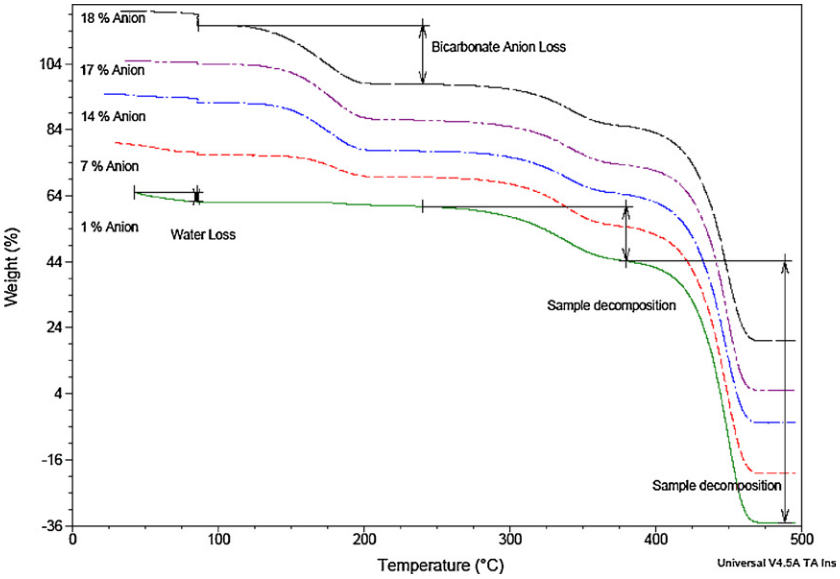

Fig. 2. TGA profiles of sevelamer carbonate with 1%, 7%, 14%, 17% and 18% bicarbonate anion content.

value for each sample with a relaxation delay of 15 s. A minimum of two T1 measurements for sevelamer carbonate were taken for each bicarbonate anion concentration (at each water content).

^{13}C CPMAS experiments with arrays to optimise contact times for cross polarisation were also run. Finally, a ^{13}C CPMAS spectrum was collected with 400 scans using the optimised contact times (0.5 ms) and relaxation delays (1.4*T1) for each sample. All samples were spun at room temperature (25 °C), which at a spinning speed of 10 kHz, will cause the sample to experience a temperature of ~31 °C in the probe.

2.5. Thermal analysis

Thermal gravimetric analysis (TGA) was conducted to determine the water content (loss on drying (%LOD)) and bicarbonate anion content (% bicarbonate anion) of each sample. Sevelamer carbonate (10–15 mg) was placed on an open aluminium pan in a platinum basket on a TA TGA Q50 instrument. The water content and bicarbonate anion content were determined by heating from room temperature to 85 °C at a heating rate of 10 °C/min, holding the pan at 85 °C for 60 min and then heating to 300 °C at 10 °C/min. The water content was calculated from the first weight loss (heating from room temperature and holding at 85 °C for 60 min) while the bicarbonate anion content was determined by weight loss during heating from 85 °C to 240 °C.

Differential scanning calorimetry (DSC) was conducted on a TA DSC Q2000 to determine glass transition temperatures. Samples (6–15 mg) were weighed into Tzero hermetic aluminum pans and crimped with a Tzero aluminum lid with and without a pinhole. Conventional DSC heating profiles were used at (i) a rate of 10 °C/min on a 3 cycle heating program, heating from 0 °C to 240 °C, cooling to 0 °C and lastly heating back up to 240 °C for pans with a pinhole to determine the glass transition of the dry crosslinked polymer backbone and (ii) a rate of 3 °C/min heating from −50 °C to 120 °C for sealed pans to determine the glass transition temperature with particular water and bicarbonate anion contents.

Table 1
Optimised probe parameters.

^{1}H pulse width	1.99 μs
^{13}C pulse width	3.4 μs
Spinning rate	10 kHz
CP conditions	^{1}H 40%, ^{13}C 76%
Ramp cross polarisation	10%
TPPM decoupling	100%

3. Results and discussion

Sevelamer carbonate is an extremely hygroscopic polymer and absorbs water from the atmosphere easily. Thus, samples were stored in sealed plastic containers and their water content was continuously monitored by thermogravimetric analysis (TGA) for a maximum of 1–2 days before or after FTIR, DSC or solid state NMR analysis. The water and bicarbonate anion contents were determined by TGA as described in Section 2. An assumption was made that when the samples were held at 85 °C for 1 h under a flow of nitrogen, all water would be removed and further heating up to 240 °C would result in loss of the bicarbonate anion. The anion contents shown in Table 2 are an average of at least 10 TGA runs in total with water contents varying from 2 to 14% for all 5 samples. The standard deviations of the bicarbonate anion contents are all ≤0.5, indicating that the above assumption is acceptable. TGA decomposition profiles from room temperature up to 500 °C indicated that the crosslinked polymer backbone was unchanged as the bicarbonate anion content was progressively reduced from 18% to 1% or when the polymer was treated at 120 °C in a sealed container (the 17% sample), Fig. 2. The 18% bicarbonate sample is the as received material and contained ~3.5–4% water and 17.7 ± 0.5% bicarbonate (w/w) upon receipt. This sample was exposed to temperatures of less than 60 °C to reduce moisture content when necessary but no loss in bicarbonate anion content was observed during this drying step. The small shifts in temperature of the main decomposition

Table 2
Anion content of sevelamer samples.

Nomenclature	Exposure to 120 °C (h)	Bicarbonate anion content (%)
1%	72	1.4 ± 0.3
7%	28	6.6 ± 0.5
14%	10	14.2 ± 0.3
17%[a]	48[a]	17.0 ± 0.2[a]
18%	0	17.7 ± 0.5

[a] No vacuum, sealed container.

$$2HCO_3^- \Leftrightarrow 2CO_2 + 2OH^-$$

Fig. 3. Chemical equilibrium of bicarbonate anions decomposing to carbon dioxide gas and hydroxide ions.

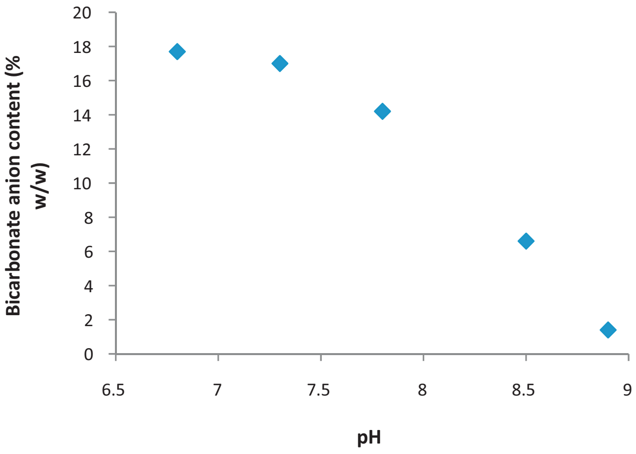

Fig. 4. The variation in pH with bicarbonate anion content of sevelamer carbonate samples upon suspension in deionized water.

steps were not significantly different when the average values of three TGA profiles per sample were examined.

Upon removal of the bicarbonate anions in the form of carbon dioxide from the polymer matrix, hydroxide anions replace them to maintain charge neutrality of the system, Fig. 3. However, this causes in an increase in the pH of the system, as shown in Fig. 4. As previously reported (Holmes-Farley et al., 1999), the cationic amines on the polymer chains are deprotonated at higher pH and thus are unable to engage in ionic bonding, decreasing the rigidity of the hydrogel matrix.

The aliphatic carbon peaks of sevelamer carbonate in the ^{13}C CPMAS spectra, Fig. 5, did not show any changes in chemical shift as the bicarbonate anion content was reduced by heating in the vacuum oven at 120 °C. This showed that the chemical structure of the hydrogel, shown in Fig. 1, as the bicarbonate anion content was reduced remained the same, apart from the reduction in intensity of the carbonyl peak of the anion (~164 ppm). Note that the peaks of the aliphatic carbon atoms (~20–75 ppm) became sharper as the level of anion was reduced – this is explained further in the next section on polymer chain mobility. These spectra were not used to quantify the amount of bicarbonate anion present due to the dependence of peak intensity on contact times during the cross polarisation stage of the CPMAS experiment. Due to the insolubility of sevelamer carbonate, it was not possible to quantify the bicarbonate and water content by ion chromatography. Gases desorbed from the hydrogel were analysed by gas chromatography but while the low molecular weight of the carbon dioxide and water molecules were qualitatively detected, quantitative measurements were inconclusive (data not shown). Thus thermogravimetric analysis alone was used to quantify bicarbonate anion content.

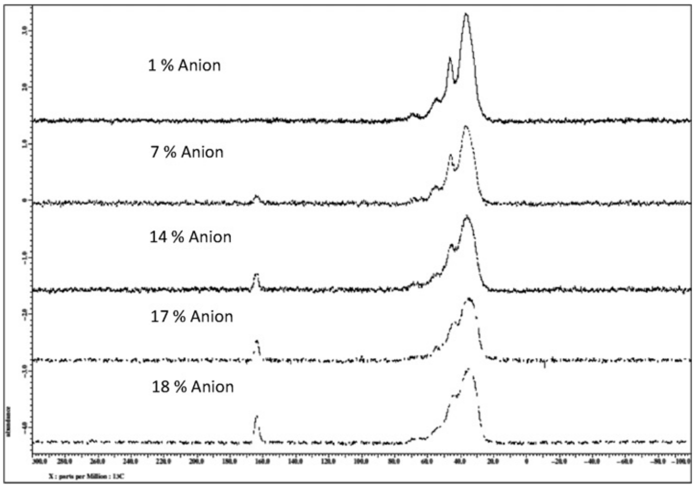

Fig. 5. ^{13}C CPMAS spectra of sevelamer carbonate containing 2% water and 1%, 7%, 14%, 17% and 18% bicarbonate anion content.

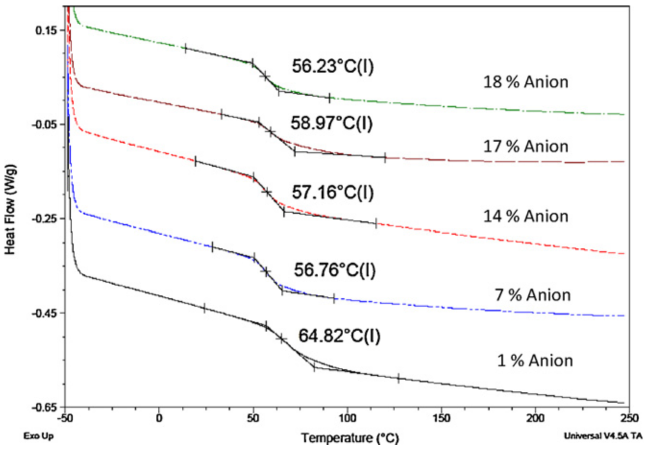

Fig. 6. Dry glass transition temperatures of sevelamer carbonate with 1%, 7%, 14%, 17% and 18% bicarbonate anion content when heated for a second time from 0 °C to 250 °C.

Differential scanning calorimetry was used to check that the basic polymer chain structure of the crosslinked polymeric network (molecular weight and degree of crosslinking) was not altered during reduction of the bicarbonate anion concentration. The dry glass transition temperature of sevelamer carbonate depends on the molecular weight of the polymer chains and the degree of crosslinking of the polymer network. The higher the molecular weight and crosslink density of the polymer network, the higher the temperature at which the polymer will undergo a transition from the glassy to the rubbery state. The sample was placed into a pan with a pinhole in the lid such that the water and anions can escape from the polymer during the first heating cycle. On the second heating cycle of this analysis (10 °C/min), the glass transition temperature of the dry crosslinked polymer backbone was found to be 56.3 ± 0.6 °C for sevelamer carbonate for anion contents of 7%, 14% and 18% and all water contents, Fig. 6. However, the dry glass transition temperature of sevelamer carbonate containing 1% anion had increased to 68 ± 3 °C. This, coupled with the slight yellowish discolouration of the polymer after 3 days at 120 °C under vacuum, indicates that there may be some changes in the polymer structure of the 1% sample when exposed to 120 °C for long periods of time. To test this, sevelamer carbonate of 18% bicarbonate anion content was placed in a sealed Duran bottle and heated at 120 °C for 48 h and again, a slight discolouration was observed. The dry glass transition temperature of this sample (17% bicarbonate anion content) was found to be 59 ± 1 °C. Thus, there appears to be a slight increase in the dry glass transition temperature when the polymer is held at 120 °C for prolonged periods of time. This may be due to an aging or tempering effect on the polymer chains at the elevated temperatures, resulting in a realignment of the polymer chains and more energy being required to undergo a glass transition. Differences in chemical composition between any of the sevelamer carbonate samples from Table 2 were below the detection limit of the analysis techniques used throughout this study, namely TGA, Fig. 2, ^{13}C CPMAS NMR, Fig. 5 or FTIR, shown later. As mentioned above, use

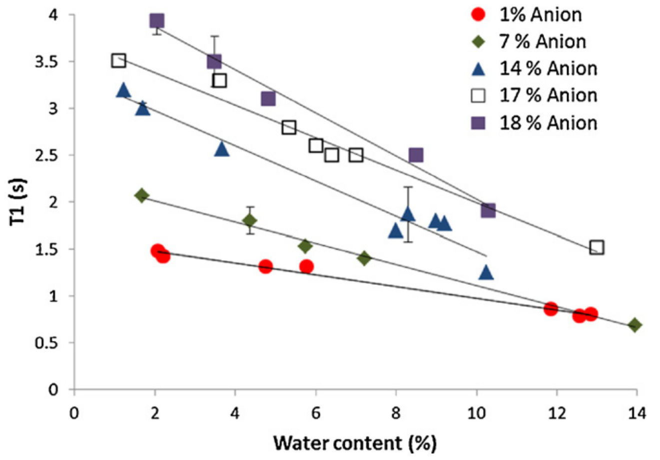

Fig. 7. Proton spin-lattice relaxation times in the laboratory frame for sevelamer carbonate batches with different water contents and approximately 1%, 7%, 14%, 17% or 18% bicarbonate anion content.

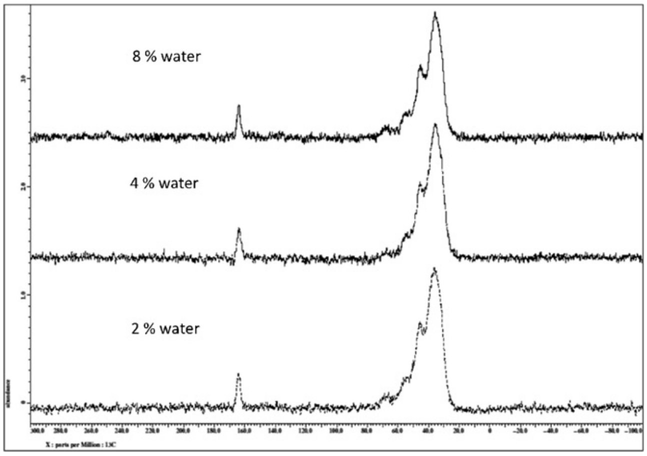

Fig. 9. ^{13}C CPMAS spectra of sevelamer carbonate with 14% bicarbonate anion content and 2%, 4% and 8% water content.

of other chromatographic techniques were not possible due to the insolubility of sevelamer.

It was found that upon varying the water content of sevelamer, the T1 spin-lattice relaxation times decreased with increasing water content, at fixed bicarbonate anion contents, Fig. 7. This is expected, firstly, as water acts as a plasticiser reducing rigidity and increasing the mobility in the polymer network at a local molecular level (Suihko et al., 2005), and secondly, because reorientation of the physisorbed water molecules can act as a T1 relaxation sink (Andrew, 1985; Geppi et al., 2010). When the concentration of bicarbonate anion in the polymer network was increased, the spin-lattice relaxation time also increased, at a given moisture level over the range of 2–14% water content. This implies that the bicarbonate anions lent a degree of rigidity to the polymer network, most likely through ionic bonding between protonated amines on the polymer chain and bicarbonate anions. As the bicarbonate anions are removed, the pH of the system increases (due to the production of OH^- ions, Fig. 4), reducing the number of protonated amines on the polymer chains and thus reducing the level of ionic bonding between chains and the overall rigidity of the system. Fig. 8(a) shows the dependence of the T1 relaxation times for sevelamer carbonate on the bicarbonate anion content with 0% water present, as extrapolated from the *y*-intercepts of the plots in Fig. 7. Note the more rigid the polymer networks, the greater the effect of the water molecules on polymer mobility, i.e. the slope of the lines in Fig. 7 decreased in magnitude with decreasing bicarbonate anion content, Fig. 8(b). This implies that the reduction in T1 relaxation times with increasing water content was dependent on the chain segment mobility as well as the reorientation of physisorbed water molecules.

In the ^{13}C CPMAS spectra shown in Fig. 5, it was clear that the sharpness of the aliphatic carbon peaks increased with decreasing bicarbonate anion content. With higher anion contents, the carbon atoms in the polymer network were held in fixed orientations with little mobility. This rigidity is due to ionic bonding between polymer segments via the bicarbonate anions and protonated amines. As sevelamer is an amorphous hydrogel, each carbon atom exists in a varied chemical environment. Thus, a broader peak was observed for the aliphatic carbons at the higher anion content as the carbon atoms do not have the freedom to move and average out their orientation/position, as they could at lower anion contents. Increasing the water content did not affect the chemical environment of the carbon atoms of the polymer backbone or crosslinker – there was no narrowing of peaks in the ^{13}C CPMAS spectra of sevelamer carbonate with increasing water content, Fig. 9. Sevelamer carbonate with different moisture levels appeared chemically identical, by ^{13}C CPMAS NMR analysis. This implies that the plasticising effect of the water molecules on main chain segment motion was not large enough to average out the rigidity introduced by the bicarbonate anions over the ranges of anion and water contents studied here.

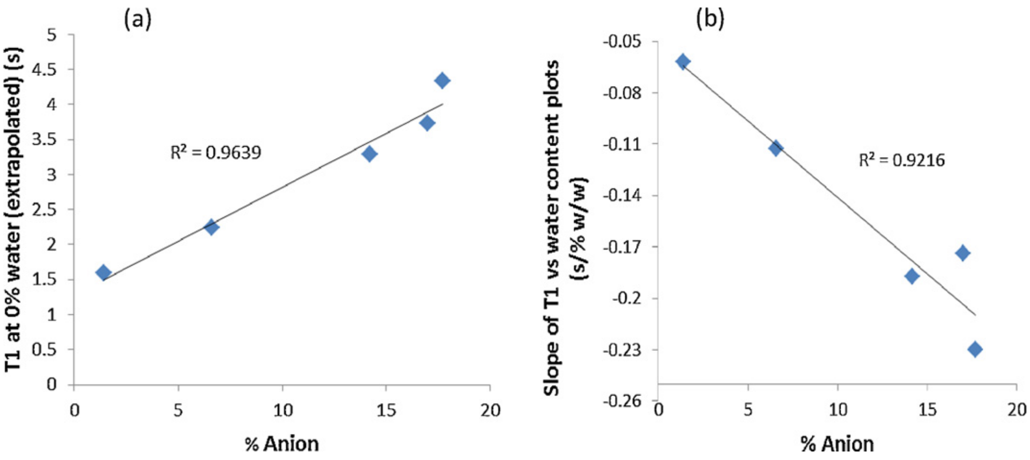

Fig. 8. (a) Extrapolated T1 spin-lattice relaxation times for dry sevelamer carbonate with varied bicarbonate anion content. (b) Effect of water on T1 spin lattice relaxation times with varied bicarbonate anion content.

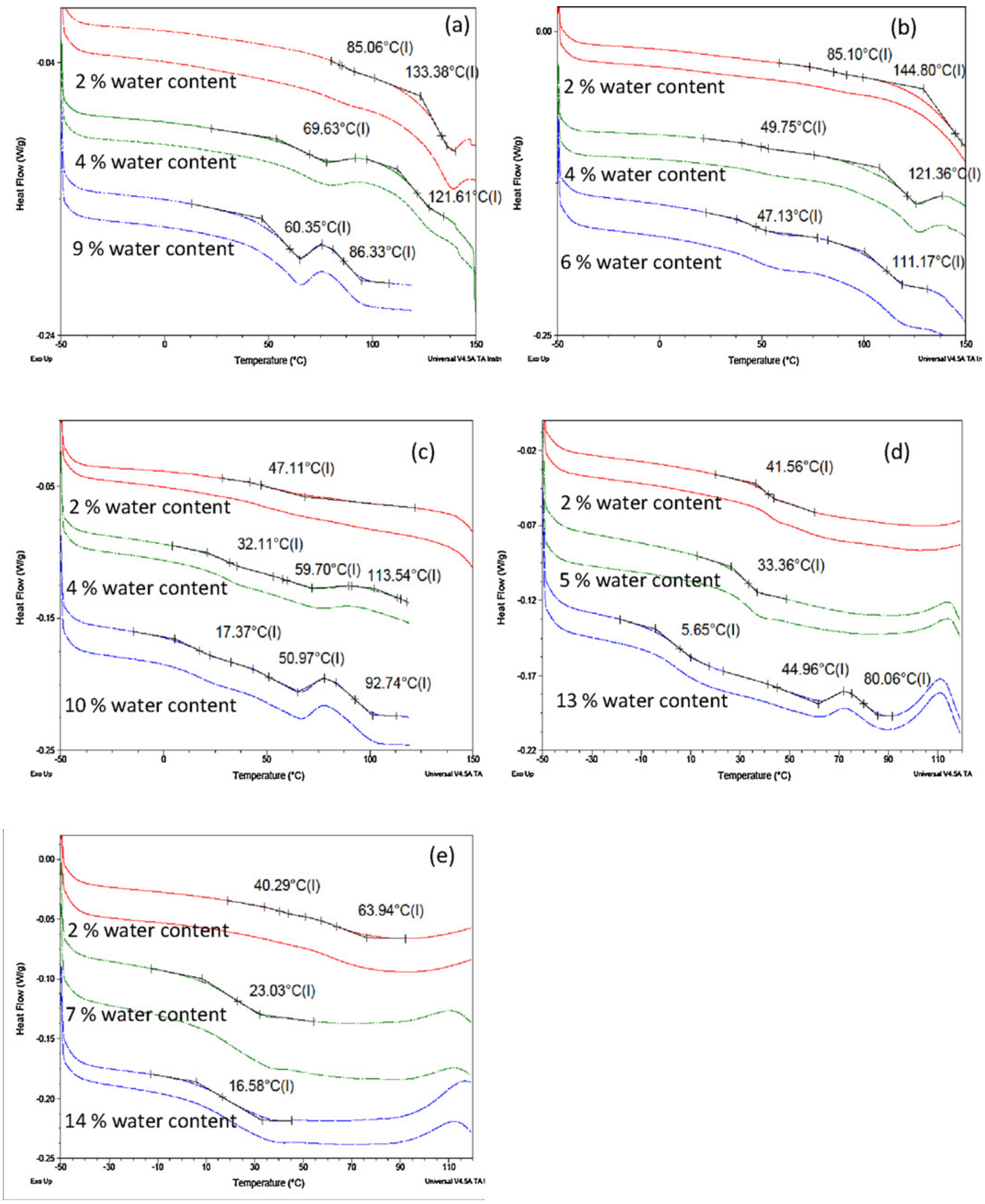

Fig. 10. DSC profiles of sevelamer carbonate with (a) 18%, (b) 17%, (c) 14%, (d) 7% and (e) 1% bicarbonate anion content with varied water content (shown in duplicate).

DSC analysis was also used to examine polymer chain mobility in sevelamer carbonate with varying water and bicarbonate anion content. The temperature at which sevelamer carbonate undergoes a transition from its glassy state to a rubbery state was examined. In sevelamer carbonate before any heat treatment (18% bicarbonate content, as received material), when heated at 3 °C/min in a sealed pan, the glass transition was reduced from ~85 °C at 2% water content to ~60 °C at 9% water content, Fig. 10(a). Thus water molecules have a plasticising effect on the glass transition event. As the water content increased, all of the glass transitions observed in Fig. 10(a)–(e) shifted to lower temperatures, at a given anion content. Glass transitions involve the cooperative movement of large segments of the polymer chain, unlike the spin lattice relaxation events which can involve the movement of single segments of the main chains and reorientation of water molecules. The removal of anions, increase in pH, water sorption and treatment at elevated temperatures appear to have created a heterogeneous polymer network, with micro domains of glassy states that relax and move at different temperatures, Fig. 10. If the first glass transition observed in all samples at 2% water content is considered, the general trend demonstrated that the glass transition temperature increased with increasing bicarbonate anion content in a non-linear fashion at constant water content, Fig. 11. This was due to increased ionic bonding between the protonated amine groups of the polyallylamine polymer chains and the bicarbonate anions. While the glass transition temperatures and spin-lattice relaxation times are both indicative of molecular mobility, they are not describing the same type of motion and thus the level of influence of bicarbonate anion content on each type of motion is different, Fig. 8(a) versus Fig. 11.

FTIR analysis indicated that the bicarbonate anion is involved in bonding with the protonated amine groups in the crosslinked polyallylamine hydrogel. FTIR spectra were obtained for sevelamer

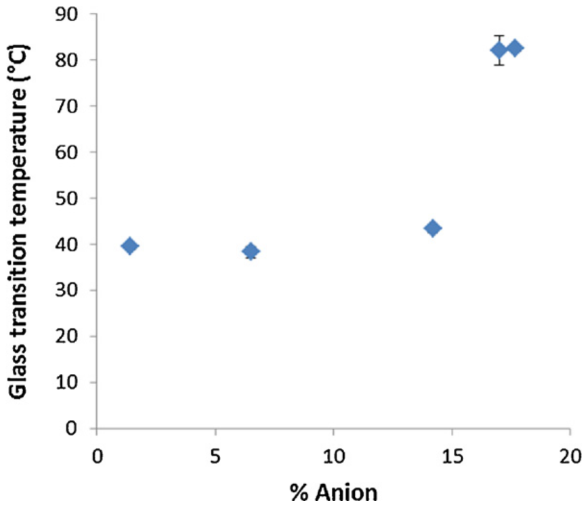

Fig. 11. Variation of glass transition temperature of sevelamer carbonate with bicarbonate anion content at 2% water content.

Table 3
N—H vibrational band shifts with bicarbonate anion content.

% Bicarbonate anion content	N—H band stretch (cm^{-1})
1	1593
7	1587
14	1579
17	1562
18	1550

carbonate at constant water content but with varying bicarbonate anion content, Fig. 12. The absorption at ~800 cm^{-1} is due to C—O vibrational stretches from the bicarbonate anion (Ritter et al., 2010) and is a sharp absorption peak at 18% and 17% anion contents, indicating that the bicarbonate anions present were all in similar chemical environments. Upon reduction of the level of anion content to 14%, that sharp peak was still observed but there was also a broader peak at ~860 cm^{-1}, indicating a greater variation in the environment of the anions, perhaps due to a more mobile polymer network. This broad peak was also observed at ~7% and ~1% anion content. While an increase in signal intensity was observed at ~860 cm^{-1} for the C—O stretch, a reduction in the intensity of the C—O stretch at ~1295 cm^{-1} is also observed, as the anion content was reduced from 18% to 1%. The N—H absorption band shifts, Table 3, were independent of water content. With bonding between the protonated amine groups and the bicarbonate anion, the N—H bond became weaker and thus less energy was required to make this bond stretch. Thus, as is seen in Fig. 12, the higher the bicarbonate anion content, the lower the wavenumber at which the N—H stretch appeared. When the bicarbonate anion content was kept constant and the water content was varied, the FTIR spectra showed no significant differences in absorption peak positions and/or shapes indicating that the water molecules were not involved with hydrogen bonding with the free alcohol or protonated amine groups on the polymer backbone or the bicarbonate anion (supplementary information). While water molecules decreased the spin-lattice relaxation time and glass transition temperatures, they did not alter the average chemical environment of the aliphatic carbons of sevelamer carbonate, shown by the ^{13}C CPMAS spectra (Fig. 9) and the FTIR spectra (supplementary information). The bicarbonate anions, on the other hand, decreased mobility both on the glass transition scale and the spin-lattice relaxation scale but also created significant variation in the average chemical environment experienced by the aliphatic carbons, broadening their peaks in the ^{13}C CPMAS spectrum (Fig. 5) and shifting the N—H stretch in the FTIR spectra (Fig. 12).

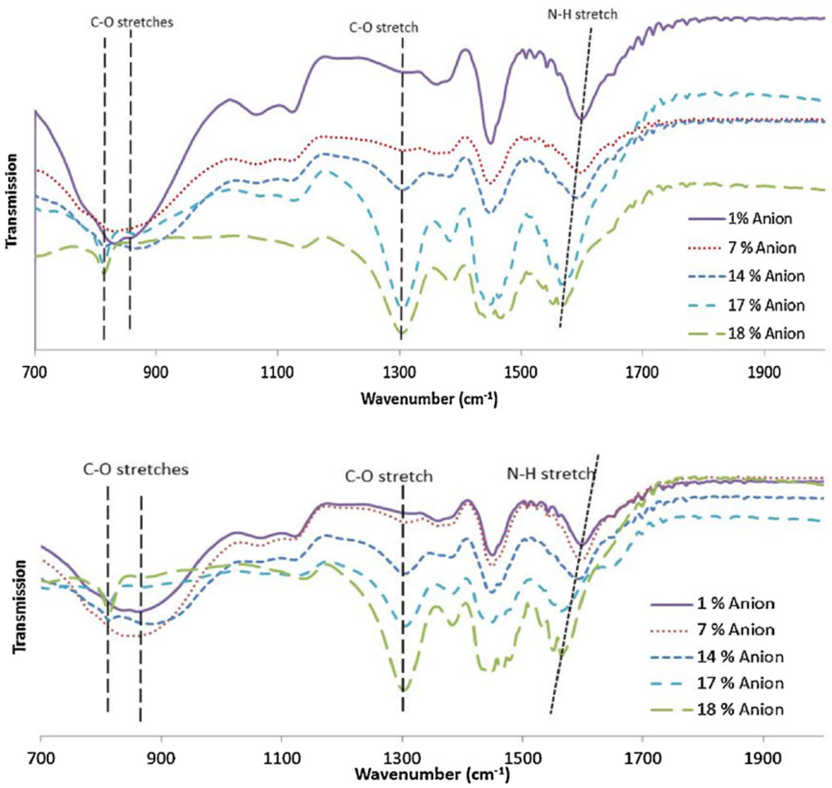

Fig. 12. Comparison of FTIR spectra of sevelamer carbonate with 1%, 7%, 14%, 17% and 18% bicarbonate anion content at fixed water contents of 2% (top) and 4% (bottom).

4. Conclusions

Solid state NMR, thermal analysis and FTIR analysis showed how bicarbonate anions promoted bonding in the sevelamer carbonate polymer network and decreased the mobility of the polyallylamine chains. This was demonstrated by shifts in the N—H vibrational band to lower wavenumbers and increases in spin-lattice relaxation times and glass transition temperatures with increasing bicarbonate anion content (over the range of 1–18%). Upon reduction of bicarbonate anion content, the pH of the hydrogel increases, reducing the number of protonated amines on the polymer chain and increasing the mobility of the polymer segments. When considering the motion of segments of the polyallylamine polymer chains, water molecules acted as plasticisers and T1 relaxation sinks, increasing molecular motion, decreasing spin-lattice relaxation times and allowing the polymer network to undergo glass transitions at lower temperatures. Tempering at 120 °C did not have an effect on the spin-lattice relaxation times or the chemical properties of sevelamer. For the first time, it has been shown how polymer chain mobility in a crosslinked polyallylamine, sevelamer carbonate, was quantitatively controlled by the water and bicarbonate anion content, using solid state NMR and thermal analysis. The more mobile the polymer chains, the higher the probability of structural changes occurring during storage, formulation and manufacturing processes of polymeric products.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijpharm.2012.03.045.

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