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The effect of hydration on the thermal behaviour of hydrophilic non-aqueous gels stabilised by Carbopol 974P[☆]

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Abstract

A thermal analysis of the effect of hydration of non-aqueous polymer-stabilised gels was investigated using differential scanning calorimetry (DSC). The interaction of water with the polymer and its distribution within the gel are critical to the physicochemical behaviour of the gel, and consequently affects the utility of the gel matrix as a drug delivery vehicle. Addition of water at levels up to and including 50% (w/w) did not result in an observable freezing event in the thermogram. However, at 60 and 80% (w/w) water, phase transitions were observed, the magnitude of which were found to be independent of the annealing time within the range used. The observed melting enthalpies increased as the water concentration increased for all formulations, but were always smaller than that of pure water. There was no evidence of multiple transitions that might be attributed to different populations of water molecules. However, the results demonstrate that DSC can be employed to differentiate between freezable and non-freezable water, in these particular formulations.

Keywords: Hydrogels; Carbopol; DSC

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1. Introduction

A number of bioadhesive polymers that bind to mucosal surfaces have been used to retain dosage forms at the site of application [1,2], with the aim of enhancing contact time and improving drug absorption. Bioadhesive polymers are typically hydrophilic, and swell on contact with water to form a gel [2]. On contact with a mucosal surface, bioadhesive polymers compete for the available water and as they hydrate, are drawn into closer proximity with the biological interface [3]. However, over-hydration leads to failure of the bonds formed between polymer chains or between polymer and tissue, resulting in either cohesive or adhesive failure, respectively [4]. Bioadhesive polymers are often used to formulate topical hydrogels, however improved adhesion of the formulation might be achieved if the bioadhesive polymer were not fully hydrated at the outset. This is easily achieved in tablet or powder formulations, but examples where such polymers are key components of low-water or non-aqueous gels are uncommon [5]. The characterisation of such systems, particularly in the presence of added water, is therefore of considerable interest.

Differential scanning calorimetry (DSC) has been employed to study the states of water in a number of polymer-stabilised hydrogel systems [6,7]. The interaction of water with such polymers and its distribution within the gel are critical to the physicochemical behaviour of the gel [4]. This important observation consequently affects the utility of the gel matrix as a drug delivery vehicle. On contacting a non-aqueous or low water gel stabilised by bioadhesive polymers with a mucosal surface, the initial diffusion of water into the matrix can result in the formation of a surface hydrogel layer. The rheology of this surface layer and diffusion through it may be very different from that of the bulk gel phase [8,9].

Most relevant DSC studies have argued that there are effectively three classes of water present in polymer-stabilised hydrogels. These are: (i) free water, i.e. unbound water with a

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transition temperature, enthalpy and peak shape comparable to that of bulk water, (ii) non-freezing water, which is tightly bound to the polymer and does not undergo a detectable phase transition and (iii) loosely bound water, which is characterised by a depressed freezing point attributable to weak interactions with the polymer chain, and/or increased ionic strength in the case of ionic polymers [10,11]. The peak in the DSC associated with a phase transition of loosely bound water is generally observed as a shoulder on the free water melting endotherm peak, and not as a discrete endotherm.

Contrastingly, however, Roorda et al. [12] and Bouwstra et al. [13] concluded that only a single state of water was present in poly(hydroxyethyl methacrylate) (p(HEMA)) hydrogels. Roorda et al. [12] have suggested that perturbations in the DSC profiles may not reflect the presence of different water states in the hydrogel. They argue that because the crystallisation of water in hydrogels is a gradual process, changes in the DSC profile reflect the formation of metastable non-equilibrium states. Bouwstra et al. [13] have suggested cooling of p(HEMA) hydrogels drives a transition from a rubbery state where the polymer network has high flexibility, to glassy state characterised by a polymer network with low flexibility.

The aim of the present study was to use DSC to study the progressive hydration of hydrophilic non-aqueous gel formulations stabilised by the bioadhesive polymer Carbopol 974P. The gel formulations have been developed for topical drug delivery, but for the purposes of the present study, the drug has been omitted.

2. Experimental

2.1. Materials

Carbopol 974P was supplied by B.F. Goodrich, USA. Polyethylene glycol 400 was supplied by BASF, and glycerol by Croda International, Goole, East Yorkshire with US and European Pharmacopoeial grade purity, respectively.

2.2. Non-aqueous based drug delivery system preparation

A number of non-aqueous formulations (Table 1) with varying ratios of either polyethylene glycol 400 (P), Carbopol 974 (C) or glycerol (G) were prepared using a Silverson homogeniser (L4R Mixer). Initially, C was dispersed into P and mixed for 2 min at 4000 rpm using an ‘emulsor screen’ homogenising head. This was followed by addition of G (preheated to ca. 70 °C) with further mixing for a further 20 min at 4000 rpm using a general purpose ‘disintegrating’ head.

Table 1
Non-aqueous drug delivery formulations

Formulation	P400 (%, w/w)	C (%, w/w)	G (%, w/w)
G100	0	0	100
CG2	0	2	98
PCG2	5.5	2	92.5
PCG2,30	30	2	68

2.3. DSC of hydrated formulations

A series of hydrated samples were prepared in glass bottles from the non-aqueous formulations listed in Table 1 by addition of water to levels in the range 5–80% (w/w). Thus, an 80% (w/w) sample comprised a homogenous mixture of 2 g of the non-aqueous formulation and 8 g of water. The bottles were sealed and allowed to equilibrate for 12 h at room temperature before analysis. Thermoanalyses were performed using a TA Instruments 2920 Modulated DSC, with the samples contained in aluminium hermetically sealed pans. The instrument was calibrated using an indium standard (mp $= 156.6\,^{\circ}$C, enthalpy $= 28.2\,\mathrm{J\,g^{-1}}$). Experiments were carried out by accurately weighing samples (ca. 15 mg) into DSC pans, which were then sealed with the pan lid inverted. Typically, samples were cooled from $+20$ to $-55\,^{\circ}$C at a rate of $10\,^{\circ}\mathrm{C\,min^{-1}}$, held at this temperature for 30 min (the annealing time) and subsequently heated to 55 °C at the same rate. A series of studies were also conducted in which the annealing time was varied between 30 and 300 min. All pans were weighed before and after each run in order to confirm the integrity of the seals.

3. Results and discussion

3.1. Development of DSC protocol

The anhydrous formulations did not exhibit any peaks in the thermogram, reflecting an absence of phase transitions under the experimental conditions employed. Addition of water to PCG2 and PCG2,30 at levels up to and including 50% (w/w) did not result in an observable freezing event in the thermogram. However, at 60 and 80% (w/w) water, phase transitions were observed. At these water concentrations, the calculated enthalpy changes were independent of the annealing times employed (30–300 min), demonstrating that the systems had come to equilibrium.

The single exothermic peaks observed on cooling (Figs. 1 and 2, region ‘a’) occur at a temperature below that predicted for pure water. This phenomenon was attributed to supercooling in the DSC pan, which is characterised by the asymmetric peak shape. Similar behaviour has been previously reported in aqueous and liquid based systems [14–17]. However, these earlier studies report the formation of two discrete exothermic peaks, which are not seen in the present study). The first exothermic peak was described as a consequence of supercooling, however, the second peak was considered indicative of an increase in the proportion of freezing bound water.

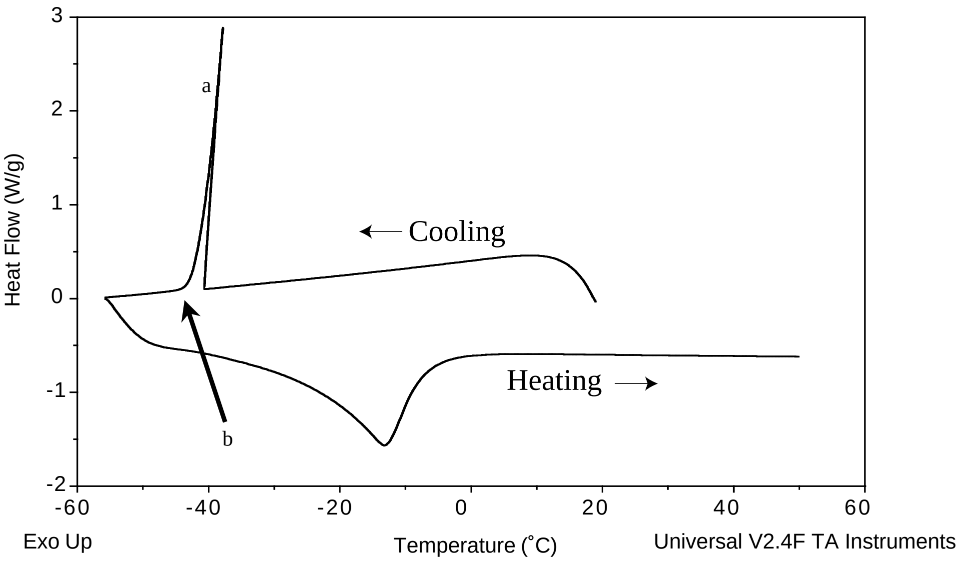

Fig. 1. DSC curve of PCG2 containing 60% (w/w) water. Annealing time at −55 °C = 30 min, ramp rate = 10 °C min^{-1}. Region 'b' represents the base line of the cooling profile.

A typical thermogram for a formulation based on PCG2 but containing 60% (w/w) water is shown in Fig. 1. The freezing process, as indicated by the return to the base-line of the signal (region 'b'), is complete at the temperatures below −45 °C, confirming that an equilibrium state has been reached.

3.2. Characterisation of hydrated formulations—melting enthalpies

When 60 and 80% (w/w) water was added to the PCG2,30 formulations, the thermograms exhibited clear exothermic and endothermic peaks, illustrated by regions 'a' and 'c' respectively in Fig. 2. As the water content of these two samples increases, the temperatures associated with the endothermic and exothermic peaks shift toward those for bulk water.

The heating curves, derived from samples containing either 60 or 80% (w/w) water, contain single broad endothermic peaks, with lower temperatures than that expected for the melting of pure water. Once again the position of these peaks is shifted towards bulk water values as the water content is increased. The enthalpies calculated for the formulations investigated in this study are presented in Table 2 and show the trend of increasing enthalpy with increasing water content. A degree of difficulty was encountered in estimating the enthalpy values in the case of the 60% (w/w) water formulations, due to the broadness of the endothermic peak.

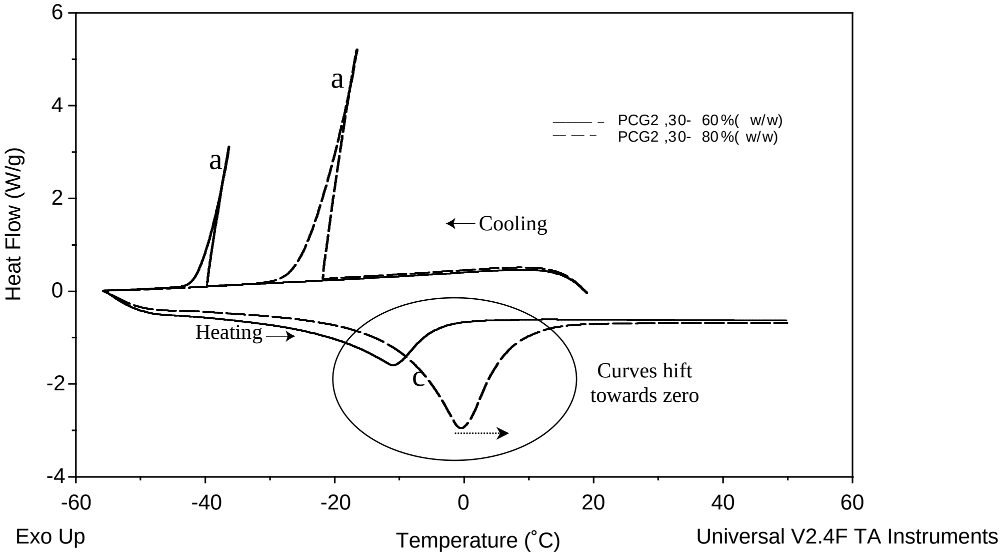

Fig. 2. DSC curves of PCG2,30 containing 60% and 80% (w/w) water, respectively. Annealing time at −55 °C = 30 min, ramp rate = 10 °C min^{-1}.

Table 2
Observed enthalpy ($\mathrm{J\,g^{-1}}$, of final hydrated sample) values for samples containing 60 and 80% (w/w) water, respectively (±S.D., $n = 6$)

Formulation	Observed enthalpy ($\mathrm{J\,g^{-1}}$)	
	60% (w/w)	80% (w/w)
G100	87 ± 2	198 ± 3
CG2	100 ± 2	197 ± 4
PCG2	104 ± 3	199 ± 6
PCG2,30	105 ± 2	199 ± 4

Annealing time at $-55\,^{\circ}\mathrm{C} = 30\,\mathrm{min}$, ramp rate $= 10\,^{\circ}\mathrm{C\,min^{-1}}$.

Nonetheless, formulations containing C and/or P, exhibited significantly higher enthalpies compared to the formulation comprising G alone when the formulations were hydrated to 60% (w/w) water content ($P < 0.05$). The reason for these differences is not clear at the present time; there were no significant differences when the water content of the formulations was increased to 80% (w/w).

Roorda and Biomater [18] reported a single melting peak when studying aqueous based p(HEMA) hydrogels as did McCrystal et al. [10] when characterising hydroxypropyl methylcellulose (HPMC) gels, however, the endotherms were noticeably sharper than those obtained in the present study. In our case, the peak broadening can be attributed to the interaction of the hydrophilic liquid components of the non-aqueous formulations with the water. Both G and P serve to depress and broaden the freezing point of the hydrated formulation, which at these compositions is dominated by the aqueous component. It is believed, although not conclusively shown, that the observed phase transition is associated with complete freezing of the liquid phase, rather than phase transition, separation, and freezing at the microscopic level. As previously indicated, a number of workers have reported the presence of ‘double’ endothermic peaks, which were attributed to different states of water present in the hydrogel. Ford and Mitchell [19], investigating HPMC aqueous gels, suggested super-cooling may occur in the gel on ‘rapid’ cooling (e.g. $-50\,^{\circ}\mathrm{C\,min^{-1}}$), leading to polymer coiling and formation of an unnatural tertiary structure. The authors argued that water could have been trapped within the high-energy structure on cooling, but was released as the temperature was raised, and the polymer chains regained their mobility. In contrast, the authors argue that when the gel is cooled ‘slowly’ (e.g. $-5\,^{\circ}\mathrm{C\,min^{-1}}$) or moderately (e.g. $-10\,^{\circ}\mathrm{C\,min^{-1}}$), a low energy organised structure forms and a single peak endotherm is produced. Extending the arguments of Ford and Mitchell [19] to the presently studied systems, it seems likely that a low energy single-phase system is formed at the moderate heating rate employed.

Apparent melting enthalpies of water were calculated from the observed melting enthalpies by reference to the total water content of each formulation. All these calculated values were substantially lower than the melting enthalpy of pure water ($334\,\mathrm{J\,g^{-1}}$). This result provides further evidence for the argument that the gel-solid transition does not occur via a number of separated microphases. Rather, it is more likely that the gel–solid transition occurs as a single step in which the admixture of G, P and water freezes as a separate amorphous entity. Similar findings have been reported by other workers [13,20].

4. Conclusions

Unlike their hydrogel counterparts, obvious phase transitions were not apparent in the thermograms of the non-aqueous formulations. Even on addition of comparatively large amounts of water to the original non-aqueous formulations, phase transitions were not observed until the concentration of added water exceeded 50% (w/w). This is despite the fact that those containing G and/or P might have been expected to solidify at temperatures close to zero degrees centigrade. At higher water contents, the endotherms were broad, and no evidence of multiple transitions, which might be attributed to different populations of water molecules was discernible. The apparent enthalpy values calculated for water in the various formulations were markedly reduced in comparison to that of pure water. This is further evidence that the water component does not freeze as a separate discrete phase. The results show a single-phase transition with a lower melting point and enthalpy than would be expected for water. This suggests a single phase, with both the water and gel components interacting. In the present study DSC has proven useful in identifying interactions between the non-aqueous based formulations and water, however, the precise nature of these interactions require further study.

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