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Research Article

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Investigation of hydroxypropyl methyl cellulose swelling in binary and ternary organic/water mixtures using solution calorimetry

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ABSTRACT

The swelling behavior of hydroxypropyl methyl cellulose (HMPC) in organic-aqueous mixtures is investigated via solution calorimetry. The polymer is stirred in a mixture of acetone:isopropyl acetate, water is injected into the system, and the heat released due to the polymer swelling is recorded by the calorimeter. A systematic study of the heat outputs at various acetone:isopropyl acetate:water compositions indicates that the swelling of the polymer is highly influenced by the solution composition. The increased swelling noted in isopropyl acetate rich compositions is attributed to the enhanced availability of water to interact with the polymer; the converse is true for the acetone rich systems. Calculations of the water activity in these different solvent systems substantiate this understanding, as the water activity is greater in isopropyl acetate rich compositions. Increased swelling was also noted at elevated temperatures. The understanding of HPMC behavior elucidated here allows for control over the polymer swelling in binary organic-water systems, and can be used to design non-aqueous granulation processes incorporating HPMC.

Keywords: hydroxypropyl methyl cellulose, swelling, solvent based granulation, solution calorimetry

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INTRODUCTION

Hydroxypropyl methyl cellulose (HPMC) is a commonly used polymeric excipient in the pharmaceutical industry due to its low toxicity, availability of a variety of viscosities and substitution levels, and compatibility with various drugs.[1] It is frequently employed in controlled release formulations, wherein an active pharmaceutical ingredient (API) is granulated together with HPMC. Upon exposure to aqueous media, the polymer forms a gel layer, and the API is released over an extended period of time as the drug diffuses out of the polymer matrix and as the polymer matrix erodes.[2] The behavior of HPMC in water has been widely studied in order to understand the mechanism and kinetics of drug release from HPMC matrices,[3] as well as to understand the performance of the polymer during processes such as wet granulation.[2]

Upon contact with water, water molecules enter the solid HPMC phase and insert themselves between the inter-chain hydrogen bonds, giving the chains more rotational freedom and mobility, and eventually forcing the chains apart. This water-polymer interaction is termed “swelling”, as it results in the polymer occupying more physical volume, and is a composite phenomenon encompassing hydration and gelation of the polymer.[4] Effectively, water lowers the glass transition temperature of the polymer, causing the polymer to transition from glassy state to rubbery state. As the polymer continues to interact with water, the polymer chains are forced further apart, and water can then penetrate deeper into the polymer matrix, allowing for increased transport of the drug out of the matrix via diffusion. Physical entanglement of the polymer with neighboring chains hinders immediate dissolution of the HPMC into the water.[5] Following prolonged exposure, the polymer matrix ultimately erodes in aqueous media.[4]

Experimental methods to measure polymer behavior in water include imaging via optical microscopy, [4,6,7] magnetic resonance imaging, [8,9] or nuclear magnetic resonance [10-12] to monitor polymer matrix size and morphology, testing of drug concentration in the dissolution media to monitor drug release kinetics, [4] and measuring the heat release associated with polymer swelling via solution calorimetry.[13] As a result of the numerous in-depth studies of this system, the behavior of HPMC in water is well characterized.

Little work, however, has been conducted on the behavior of HPMC in organic-water systems. Understanding the behavior of HPMC in mixed solvent systems would allow for the design of granulation processes involving organic solvents together with water, which has advantages over pure aqueous systems. A study of the physical properties and release characteristics of HPMC-acetaminophen granules and tablets generated with various granulation solvents demonstrated that granules and tablets prepared from a mixture of ethanol and water had better flow, less bridging, and more desirable extended release profiles than those prepared from water alone.[14] An investigation of the properties of HPMC-propranolol hydrochloride granules prepared from various granulation fluids found that granules prepared from an isopropanol-water mixture were less friable, less porous, and denser than granules prepared from pure water.[15] Additionally, for API that can undergo polymorphic transformations in aqueous environments, a granulation process involving solvent and water can be used to mitigate form change risks. For example, it has been demonstrated that the dissociation of an API hydrochloride salt of an amine, which occurred during wet granulation when the binder fluid was aqueous, was prevented by granulation with a 90/10 ethanol/water mixture.[16]

In this investigation, the swelling of various molecular weights of HPMC is explored in binary and ternary organic-water systems at different solvent ratios by modifying the solution calorimetry method previously developed by Conti et al.[13] The activity of water in the various solvent compositions is calculated to substantiate the understanding of the role of solvent composition in swelling the polymer. To demonstrate the broader applicability of the methodology to a range of polymers, not just HPMC, the swelling of sodium carboxymethylcellulose (NaCMC) was also measured. Acetone and isopropyl acetate, both FDA Class 3 solvents (low toxicity), were used as the organic solvents for polymer swelling measurements due to considerations regarding the particular API to which we desired to apply this data for process design purposes, but the methodology and findings are relevant across a variety of solvents. The aim of this study is to demonstrate a method by which polymers, such as HPMC, can be characterized in organic-water environments.

EXPERIMENTAL SECTION

HPMC grades E15, K4M & K100M, and sodium carboxymethylcellulose (NaCMC) grade 7HXFPH were purchased from Dow Colorcon (Harleysville, PA) and used as received. HPMC E15 has a higher degree of methoxyl content than K4M and K100M (28-30% for E15 vs. 19-24% for K polymers), and the viscosity of each HPMC grade is different: 3,000-5,600 cP for a 2 wt % solution of K4M in water, 11,250-21,000 cP for a 2 wt % solution of E15 in water, and 80,000-120,000 cP for a 2 wt % solution of K100M in water. Acetone and isopropyl acetate (IPAc), reagent grade, were purchased from Sigma Aldrich (St. Louis, MO) and used as received. Heat release was measured with an Insight Parallel Reaction Calorimeter (Omnical, USA).

In a typical experiment, 215 mg polymer was weighed into a 6 dram vial (Kimble Chase, Vineland, NJ) equipped with a magnetic stir bar and screw cap with PTFE faced silicone rubber septa. A known volume of organic non-solvent (acetone or isopropyl acetate) or mixture of non-solvents was added to the vial. The vials were placed into the calorimeter and allowed to come to thermal equilibrium, which was indicated by a variation of 0.07 mW or less on the calorimeter. A reference vial containing a stir bar, organic non-solvent, and no polymer was also equilibrated in the instrument to account for solvent heat of mixing. Following thermal equilibration, 1 mL of water was rapidly injected into the vials via a syringe (Henke Sass Wolfe, Germany) with 1.5 inch 18 gauge needles (Becton Dickinson, Franklin Lakes, NJ). Unless otherwise noted, the temperature was held constant at 25^{o}C. Experiments were performed in triplicate to determine experimental error. Following the end of each experiment, vials were removed from the calorimeter and visual observations regarding the physical appearance of the polymer were noted.

Heat associated with swelling was calculated by the Insight software from the area under the heat output curve recorded by the instrument.

Water activity, defined as the vapor pressure of water in a substance divided by the vapor pressure of pure water at the same temperature, was modeled using the NRTL model within the ProPhyPlus software from PROSIM.[17] The binary interaction parameters between water/acetone were available within the software. The missing NRTL interaction parameters for water/isopropyl acetate and acetone/ isopropyl acetate were estimated using the UNIFAC modified (Dortmund) model [18] within the ProPhyPlus software. The resulting binary interaction parameters between all the components are listed in the table below. The terms for use within the NRTL model are derived using the following expressions along with the tabulated values below.

gij-gjj = Cij0 + CijT * (T-273.15)
gji-gii = Cji0 + CjiT * (T-273.15)

where gij is the binary interaction parameter between components i and j, Cij0 is the coefficient of interaction, and CijT is the temperature coefficient.

Table 1. Binary interaction parameters for solvent pairs for NRTL model input to calculate water activity; aij is the empirical constant

Solvent1	Solvent2	Cij0	Cji0	aij	CijT	CjiT
Water	Isopropyl acetate	2484.859	1023.331	0.3	10.23097	-5.39567
Water	Acetone	1197.41	631.046	0.5343	0	0
Isopropyl acetate	Acetone	-229.433	351.1399	0.3	-0.66985	0.643273

RESULTS AND DISCUSSION

In order to ensure that the heat output detected by the calorimeter is indeed a result of the exothermic event of polymer swelling upon contact with water, initial experiments were performed wherein a known weight of polymer and triple the weight were charged into vials containing a known volume of isopropyl acetate (a non-solvent for the polymer), and equilibrated in the calorimeter. A known volume of water was then injected into the vials, and the heat output recorded. The heat output was 3.15 J and 9.1 J for 300 mg and 900 mg polymer, respectively (Fig. 1). When the amount of injected water was increased and the polymer weight was held constant, the heat output was not significantly different. As the heat of mixing is accounted for by subtraction of the signal from the reference vial containing isopropyl acetate, water, and no polymer, the heat output detected by the calorimeter from the test vials is due to the interaction of the polymer with the water. Therefore, tripling the amount of polymer resulted in approximately triple the heat output. No additional heat was generated when a larger volume of water was injected, indicating that the water was already in excess relative to the polymer, therefore additional water did not result in further polymer swelling. Based on the length of the experiments (~20 min), and visual observations of the vials post experiment, it is unlikely that dissolution is contributing significantly to the measured heat output.

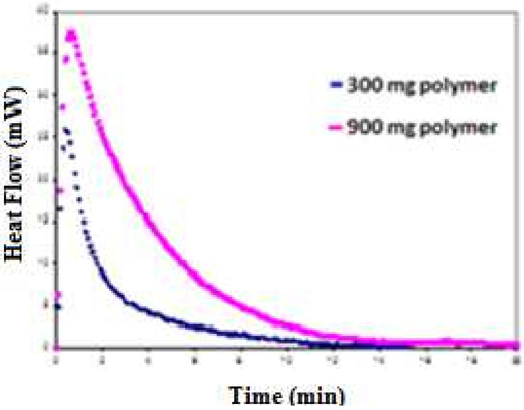
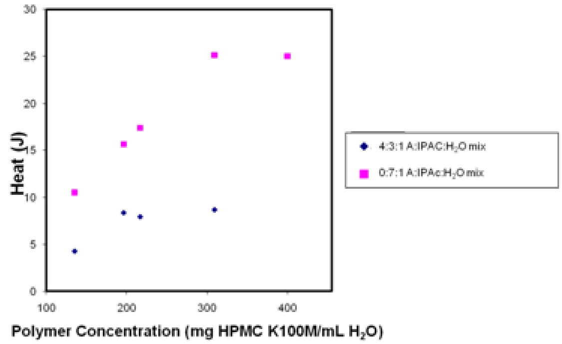


Figure 1. Heat flow vs. time as recorded by the calorimeter for a given volume of water injected into a vial containing a 300 mg of polymer (lower curve), and 900 mg (upper curve). The area under the lower curve is 3.15 J and the area under the higher curve is 9.1 J. Time was offset to have time=0 as the time of water injection

Following confirmation of the suitability of the instrumentation and methodology to detect the heat associated with polymer swelling, the polymer behavior in organic/water mixtures of varying ratios was investigated. Varying weights of polymer were stirred in a mixture of acetone and isopropyl acetate and equilibrated in the calorimeter. A constant volume of water was injected, and heat outputs were recorded and graphed according to solvent composition and polymer weight, as shown in Fig. 2.

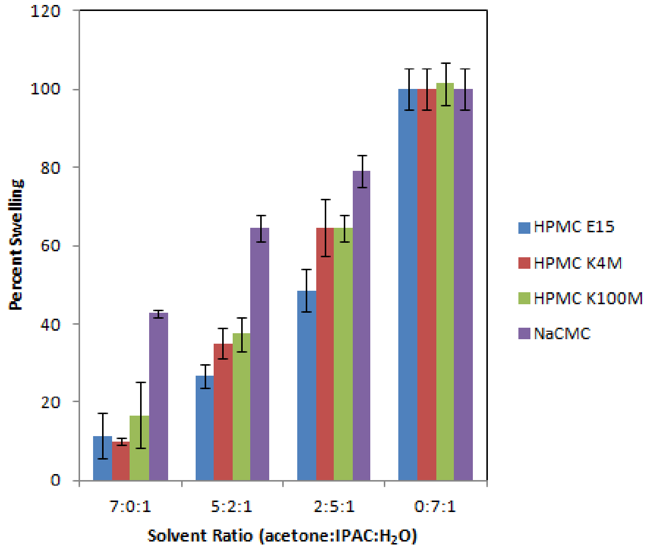


(a)

Polymer conc. (mg/mL H_2O)	Heat Output (J) in 4:3:1 acetone:IPAc:water	Heat Output (J) in 0:7:1 acetone:IPAc:water
135	4.2	10.8
170	8	16
216	7.5	18
308	8.6	25.1
420	NA	25

(b)

Figure 2. Heat output obtained from solution calorimetry vs. polymer concentration with respect to water: (a) graphical representation, wherein 4:3:1 Acetone:isopropyl acetate:water mixture values are denoted with diamonds and 0:7:1 acetone:isopropyl acetate:water mixture values are denoted with squares, and (b) tabulated values



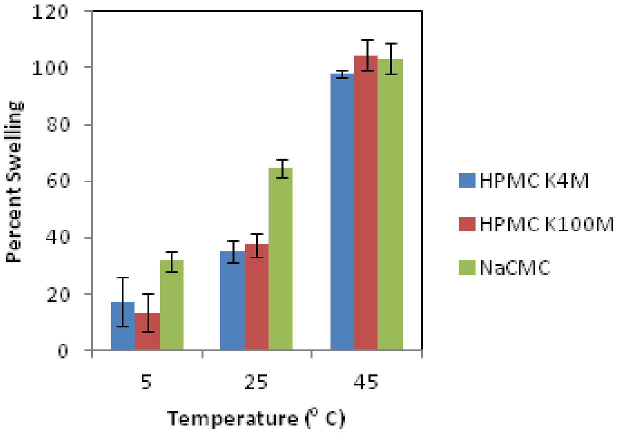
(a)

Solvent Ratio (acetone:IPAC:water)	Polymer	% Swelling
7:0:1	HPMC E15	11
	HPMC K4M	10
	HPMC K100M	17
	NaCMC	43
5:2:1	HPMC E15	27
	HPMC K4M	35
	HPMC K100M	37
	NaCMC	65
2:5:1	HPMC E15	49
	HPMC K4M	65
	HPMC K100M	64
	NaCMC	79
0:7:1	HPMC E15	100
	HPMC K4M	100
	HPMC K100M	100
	NaCMC	100

(b)

Figure 3. The degree of polymer swelling *vs.* solvent composition for various molecular weights of HPMC and NaCMC across a range of solvents. The heat output detected by the calorimeter in the isopropyl acetate/water system was established as the heat associated with complete swelling, and the heat output in other systems was normalized relative to that value: (a) graphical representation, and (b) tabulated values

For a given concentration of polymer, the heat output was approximately two and a half times greater in the 0:7:1 acetone:IPAc:water system than in the 4:3:1 acetone:IPAc:water system. Additionally, in the 0:7:1 acetone:IPAc:water composition, the heat output reached a plateau at approximately 308 mg/mL water, and further addition of polymer did not result in additional heat output. The same leveling off of heat output occurred at lower polymer concentrations (approximately 170 mg/mL water) in the 4:3:1 acetone:IPAc:water system. It is hypothesized that the availability of the water to interact with the polymer is dictated by the organic-water interactions. In poorly water miscible solvents, such as isopropyl acetate, most of the injected water was available to interact with the polymer, whereas in acetone/IPAc mixture, some of the water was associated with the acetone, and therefore was not available to interact with the polymer. This is reflected in the overall higher heat output for the IPAc/water system as compared to the acetone/IPAc/water system. As the amount of polymer increases for a given solvent-water system, greater heat output is detected, until the point is reached where polymer is in excess relative to the water, and no further swelling is generated by the addition of more polymer. Since water is more readily available in the IPAc:water system, this point of "polymer saturation" does not occur until higher polymer amounts relative to the acetone/ IPAc/water system. Visual observations of the polymers in the different solvents corroborate this, as the IPAc/water samples appeared transparent and gel-like, whereas the acetone/IPAc/water samples appeared opaque and white.



(a)

Temp (°C)	Polymer	%Swelling
5	HPMC K4M	17
	HPMC K100M	14
	NaCMC	32
25	HPMC K4M	35
	HPMC K100M	37
	NaCMC	65
45	HPMC K4M	98

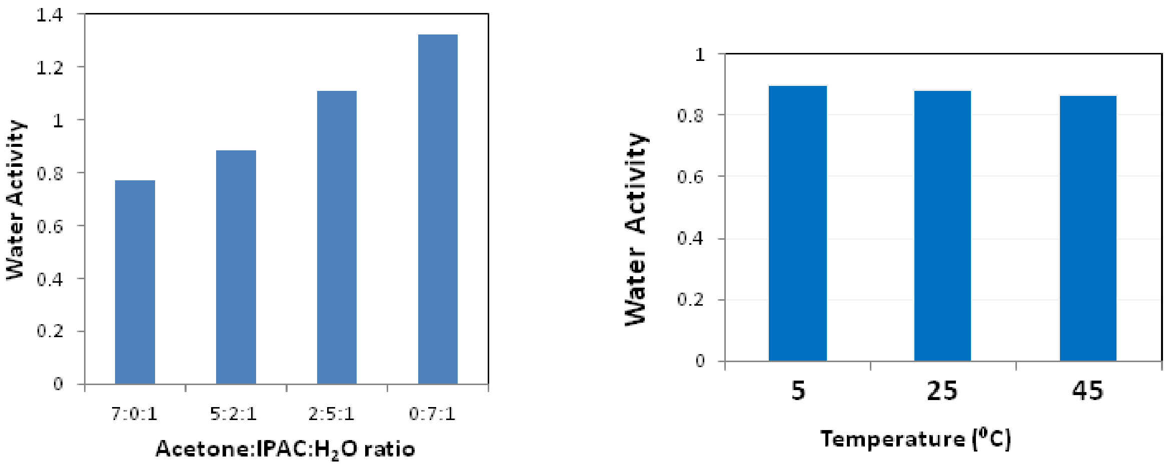
(b)

Figure 4. Percent swelling of different polymers in the 5:2:1 acetone:isopropyl acetate:water solvent system vs. temperature. At elevated temperatures, all polymers swelled more than at cool or room temperature: (a) graphical representation and (b) tabulated values

The heat outputs of the various HPMC grades, as well as NaCMC, were then measured across a range of organic-water compositions. The values were normalized to the heat output in the 0:7:1 acetone:IPAc:water system, which was the benchmark for heat associated with complete swelling (Figure 3). Thus, percent swelling was determined by dividing the average heat output of the polymer in a given solvent composition by the average heat output of the polymer in the 0:7:1 acetone: IPAc:water system and multiplying by 100 to convert to percent.

The overall trend noted is that as the solvent composition becomes richer in isopropyl acetate and contains a lower volume fraction of acetone, the polymers swell more, supporting the hypothesis that the polymers swell more in solvent environments where water is more available to interact with the polymer chains. Without polymer present, 2:5:1 acetone: IPAc:water composition and 0:7:1 acetone:IPAc:water compositions phase separate. The swelling of NaCMC is significantly more than the swelling of various grades of HPMC in all compositions except 0:7:1 acetone:IPAc:water. In the 0:7:1 acetone:IPAc:water composition, NaCMC swells approximately four times as much as HPMC E15 and HPMC K4M, and two and a half times as much as HPMC K100M. In the 5:2:1 acetone:IPAC:water composition, NaCMC swells approximately two and a half times as much as HPMC E15, and one and a half times as much as HPMC K100M. In the 2:5:1 acetone:IPAc:water composition, NaCMC swells approximately one and a half times more than HPMC E15, and one and a quarter times more than HPMC K4M and HPMC K100M. This difference in swelling can be attributed to the higher affinity of NaCMC for water due to the carboxylic side chains.[13] When water is limited due to solvent competition, NaCMC is a stronger attractor than HPMC, thus it can swell more. When water is not limited, as in the isopropyl acetate/water systems, all polymers are fully swollen.

Differences in degree of swelling between HPMC K4M and HPMC K100M in any given solvent system could not be detected, whereas HPMC E15 swells less than the K grades for solvent compositions 5:2:1 and 2:5:1 acetone:IPAc:water. HPMC E15 has a higher degree of methoxy substitution (~30%) on the cellulose ether backbone as compared to K grade (~23%), rendering it more hydrophobic in nature than the K grade, and accounting for the lower degree of swelling relative to the K grades. The viscosity difference (viscosity being directly related to molecular weight) between K4M (~4,000 mPa·s) and K100M (~100,000 mPa·s) did not render any differences in the degree of swelling. This finding is not surprising, considering that the equilibrium moisture uptake curves of K4M and K100M have been measured and found to be very similar.[19] Future work will investigate the impact of more drastic differences in viscosity, as well as other variations in chemistry substitution, on polymer swelling.



(a) (b)

Figure 5. Calculated activities of water in: (a) acetone:IPAc:water mixtures at 25°C. The activity of water is greatest in the 0:7:1 acetone:IPAC:water system, and lowest in the 7:0:1 system, reflecting the trend observed with the heat outputs from the polymer in various solvent compositions, and (b) 5:2:1 acetone:IPAc:water mixture at 5°C, 25°C, and 45°C. Water activity is similar across the temperature range, indicating that increased polymer swelling at elevated temperatures is due to a different mechanism

The effect of temperature on polymer swelling was investigated in the 5:2:1 acetone:IPAc:water system by measuring polymer swelling at 5°C and 45°C. A concentration of 215 mg polymer/mL water was used, and heat outputs were normalized to the same values associated with maximum swelling as the room temperature experiments. At elevated temperatures, all polymers swell more than at room temperature and low temperature. As the temperature increases, the diffusivity of water increases, and thus water is more available to penetrating the polymer chains and cause swelling.[20] This phenomenon has been noted in epoxy resins, where increased swelling and increased weight gain from water uptake was seen at elevated temperatures.[20] Temperature modulation is therefore an alternative option to controlling polymer swelling when there may be process constraints on solvent composition adjustments.

To support the hypothesis that the solvent-water interactions dictate the availability of water to interact with the polymer, and hence control the polymer swelling, the initial water activity in the various organic-water compositions was calculated, without accounting for the polymer (Fig. 5a). Water activity is a thermodynamic measurement of the energy status of water in the system, and provides an indication of the intensity with which water associates with a given component - lower water activity values reflect stronger association of water with that component. Water activity values above 1 indicate that water and the component are immiscible (i.e. no association of water with the component). Although for the 2:5:1 and 0:7:1 acetone:IPAc:water systems the calculated water activity (>1) indicates immiscibility, when polymer is present in the system, a single liquid phase is observed, due to the imbibing of water by the polymer. While the calculations presented here do not account for the presence of polymer, and are therefore not calculations of the actual equilibrium water activity of the system, they can be used to make relative comparisons from one solvent system to another. The trend observed in the calculated water activities matches that observed with the heat outputs, i.e. the highest water activity and swelling is in the 0:7:1 acetone:IPAc :water system, followed by 2:5:1, 5:2:1, and 7:0:1 acetone:IPAc:water systems. Calculations of the water activity in 5:2:1 acetone:IPAc:water at 5°C, 25°C, and 45°C (Fig. 5b) indicate that the water activity is similar across the temperature range, substantiating that the difference in swelling observed at different temperatures is not due to the availability of water in this case, but from a different mechanism likely involving the increase in water diffusivity at higher temperatures. Further investigation is required to fully elucidate the mechanism of increased swelling at elevated temperatures.

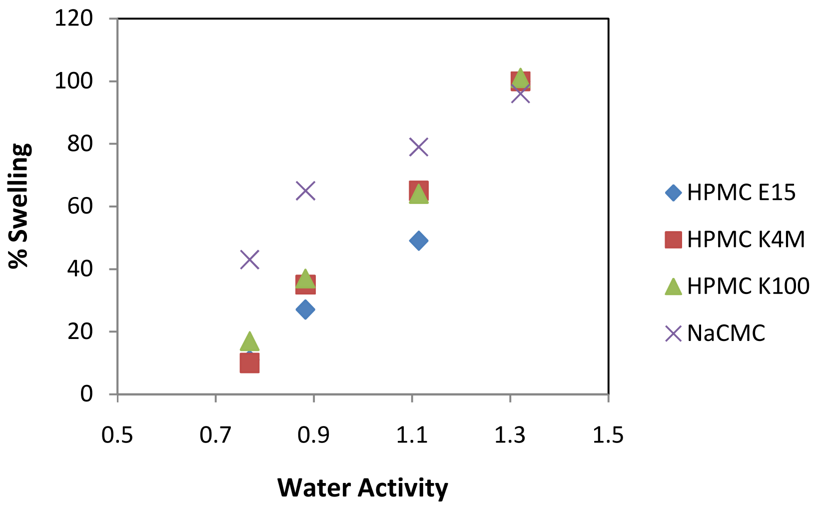


Figure 6. Percent swelling for various grades of HPMC and NaCMC *vs.* water activity. As the water activity increases, percent swelling for all polymers increases

In order to apply the findings in this study to a broad range of organic-water systems, such as hydro-alcoholic systems that are more commonly used in solvent based granulation, the percent of polymer swelling can be correlated directly to the water activity (Fig. 6). This master plot can be used to predict or control polymer swelling based on water activity and not specific solvent composition. As seen from the plot, the higher the water activity, the greater the polymer swelling. Thus, if less swelling of the polymer is desirable for processing or performance considerations, solvents which have a high affinity for water (providing low water activity) should be employed. If more swelling of the polymer is desirable, solvents with less affinity or poorer water miscibility should be incorporated.

CONCLUSION

Solution calorimetry was effectively employed to measure the heat released as a result of HPMC swelling. The degree of swelling is strongly affected by the composition of the solution, where the affinity of the organic solvent for water is found to be the key factor; this finding is substantiated by water activity calculations. When the solvent system has high affinity for water, less water is available to penetrate the polymer chains and interact with the polymer, hence less swelling occurred. When the solvent system has low affinity for water, water is readily available to interact with the polymer, and more swelling occurs. The varying availability of water is reflected in calculations of water activity in the different solvent compositions. At elevated temperatures, HPMC swells more than at room temperature or cool temperatures, due to the increased ability of water to diffuse into the polymer network. This understanding of the swelling behavior of HPMC in organic-water systems allows for predicting and modulating the polymer swelling in such systems, which can facilitate the incorporation of HPMC into formulation processes involving organic solvents and water.

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