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A thermorheological investigation into the gelation and phase separation of hydroxypropyl methylcellulose aqueous systems

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Abstract

The thermorheological properties of a range of hydroxypropyl methylcellulose (HPMC) solutions have been studied with a view to determining the concentration and substitution dependence of the gelation process. Solutions containing up to 20% w/v HPMC were prepared using three grades of material (METHOCEL[1] E4M, F4M, K4M). Rheological studies were performed using a TA AR1000-N Rheometer. Temperature sweeps were performed at a rate of 2 °C/min between 20 and 90 °C at 1.0 Hz and at 4.7 Pa, while frequency sweeps were performed at 4.7 Pa. A series of thermal transitions were observed for the E4M systems with a minimum seen at approximately 60 °C followed by an increase in moduli at approximately 70 °C, while on cooling an increase in moduli is seen over a wide range of temperatures, commencing at approximately 70 °C and plateauing at 50 °C. Comparison with frequency sweep data for the 2% E4M solutions indicated liquid-like behaviour at 25 and 55 °C with a lower frequency dependence and considerably higher moduli seen at 85 °C. Macroscopic examination of the 2% gels indicated that clouding was seen at ca. 42 °C, while phase separation was apparent at 55 °C. Comparison with F4M and K4M systems indicated a similar behaviour pattern, although the decrease in moduli and phase separation occurred at a higher temperature for the K4M systems. It is suggested that on heating HPMC solutions, the transitions indicated by the thermorheological studies relate to phase separation causing a decrease in moduli, followed by an increase in moduli which may correspond to gelation of the polymer rich phase. This process of phase separation has not been previously considered in the context of the rheology of HPMC thermogelation and may have implications for the behaviour of solutions of this material in a practical environment.

Keywords: Gelation; Hydroxypropyl methylcellulose; Rheology

1. Introduction

Thermoreversible gelation of aqueous solutions of macromolecules has been recognised as being a highly important phenomenon, with implications for several practical applications of these materials. Of particular interest is the behaviour of non-ionic water-soluble cellulose derivatives such as methylcellulose (MC) and hydroxypropyl methylcellulose (HPMC), whereby aqueous solutions have been shown to gel reversibly at elevated temperatures [1–3]. However, the study of this process is complicated by the possibility of a range of further phenomena occurring during the heating cycle. In particular, precipitation from aqueous solution may be apparent as a result of the inverse temperature–solubility relationship of these polymers. The onset of precipitation may be detected via light transmission measurements; as the temperature is increased the transmission remains unchanged until, at the initial precipitation temperature (IPT), a decrease is seen which becomes more marked with increasing temperature [4]. This is closely related to the cloud point of the solution, whereby the system becomes opaque over a narrow temperature range due to the presence of particulate matter. The interrelationship between gelation, clouding and precipitation remains relatively poorly understood and indeed the definitions used for these processes have not been assigned to universal agreement. Sarkar [5] has suggested that the IPT may be considered to be the point of 97.5% light transmission and the cloud point as the temperature of 50% transition, while the same author described the incipient gelation temperature (IGT) as the temperature of maximum viscosity. In practice, however, the terms are arguably used fairly loosely and indeed often interchangeably, further complicated by the fact that the

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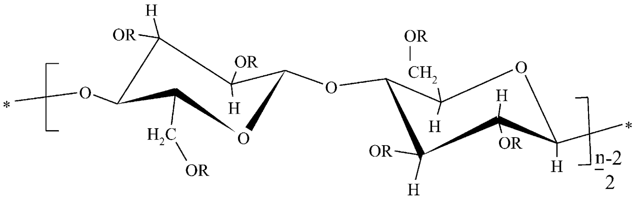
cloud point measurement, which is derived from the surfactant field, is only generally used for dilute solutions (usually $<1\%$ w/v) as a means of quality control. Similarly, the working definition of the temperature of gelation varies between groups, bearing in mind that gelation must be considered in terms of the viscoelastic properties of the system rather than the viscosity alone. Some workers consider the gelation concentration or temperature to be the point at which the elastic exceeds the viscous modulus (which may of course depend on the frequency of measurement), while others consider it to be the point at which a macroscopically discernible increase in 'stiffness' is apparent. All the above processes are further complicated by the possibility of heating rate dependence of the observed transitions due to their having a kinetic component to their onset.

For MC, both opacity and gelation effects have been attributed to the temperature-dependent predominance of hydrophobic interactions between adjacent polymer molecules. At low temperature water is believed to form an ice-like structure around the hydrophobic methyl groups, which on heating breaks down allowing the hydrophobic structure to interact causing gelation and precipitation [6]. Furthermore, there is some evidence that the gelation of MC may be coupled to phase separation [7]. There is conflicting evidence regarding the exact nature of the phase separation and gelation processes. It has been suggested that phase separation caused by precipitation leads to the formation of dense aggregates which reduce the mobility of the system leading to gelation [8]. Desbrieres et al. suggested that a clear gel was formed at temperatures between 35 and 50 °C depending on the polymer concentration followed by phase separation above 60 °C leading to an increase in viscosity [9], while Kobayashi et al. [10] showed gelation of MC to proceed in two stages with both the phase separation and gelation occurring above 60 °C. They suggested that the first stage comprises hydrophobic associations leading to 'cluster' formation due to interactions in the regions of heavy methyl substitution and the second, to phase separation accompanied by gelation of the polymer-rich phase. However in general terms, there is a paucity of information available regarding the role of phase separation in gelation and indeed, it is usually not discussed in the majority of studies.



For MC **R = -H, -CH_3**
For HPMC **R = -H, -CH_3, -Ch_2-C(OH)H-CH_3**

Fig. 1. Chemical structure of a section of two anhydroglucose units in MC and HPMC.

HPMC (Fig. 1) is the most widely used cellulose ether and, like MC, is characterised by the degree of substitution, i.e. the average number of substituted hydroxyl groups, the maximum being 3. In addition, the number of hydroxypropyl groups attached is given by the degree of reaction, also known as molar substitution (MS), i.e. the average number of molecules of reagent (propylene oxide) reacted with each anhydroglucose unit, which can exceed 3 [11]. Typical values of MS range from 0.1 to 1.0 [12]. This material is used for a number of applications, including film coats, pharmaceutical controlled release matrices, adhesives, ceramic processing, agricultural chemicals and construction products. As many of these applications involve the application of heat to aqueous solutions of this polymer, an understanding of the temperature-dependent behaviour of HPMC solutions is essential. Like MC, the methoxy residues of HPMC are responsible for gelation, the presence of the hydroxypropyl residues have been reported to significantly alter the gelation characteristics in a temperature-dependent manner [3,4]. At low concentrations, HPMC systems with the same methoxy content show an increase in IGT with increasing hydroxypropyl content, while at higher concentrations the hydroxypropyl content has little effect. Haque and Morris have studied the gelation process of both MC and HPMC extensively and have proposed a model for the gelation process [3, 14]. They suggested that structures present in the solution of MC at low temperatures are disrupted in the initial stages of heating and reaggregate so as to allow the development of a distinct structure at higher temperatures, similar to the thermogelation of a globular protein in which the unfolding of the original structure is necessary for network formation. The initial melting exposes the methoxy residues for the formation of hydrophobic associations. Incorporation of small proportions of hydroxypropyl groups to the MC inhibited the intermolecular association causing the gelation to occur at a higher temperature. The inhibition of thermogelation was explained by the more polar nature of hydroxypropyl derivatives in comparison with methoxy residues and the larger size of the residues hindering association of chains [14].

In this investigation, we describe the use of thermorheology as a means of studying the thermal transitions of a range of HPMC solutions, with a particular view to studying the effects of temperature on concentrated systems (up to 20% w/w). Such systems have not been widely studied but are of considerable practical importance, not least because such concentrated solutions will inevitably be formed either during drying processes, as used for film coating and spray drying, or during hydration of dry HPMC systems, as is the case for controlled release pharmaceutical tablet formulations. In this manner, it is intended that insights be gained into both the behaviour of these concentrated

Table 1
Substitution of METHOCEL brand of cellulose ethers (information supplied by Dow Chemical Company)

METHOCEL	Methoxy (%)	Hydroxypropyl (%)
E4M	28–30	7–12
K4M	19–24	7–12
F4M	27–30	4–7.5

systems and the mechanisms underpinning the thermal transitions observed.

2. Experimental section

HPMC was supplied by The Dow Chemical Company and used as received. Three grades of non-ionic HPMC were utilised (METHOCEL E4M, F4M, K4M) as indicated. Table 1 gives the methoxy and hydroxypropyl content of various grades used.

METHOCEL gels of concentrations ranging from 2 to 20% were prepared. Deionised water (50 ml) was heated to 80–85 °C while stirring. HPMC was added slowly and the mixture stirred for further 30 min. The gel formed was allowed to cool to room temperature before the rest of the water was added. The gels were then refrigerated for at least 2 weeks to allow the hydration process to reach equilibrium.

Temperature ramps were performed out using the TA AR1000-N Rheometer at a rate of 2 °C/min between 20 and 90 °C at 1.0 Hz and at 4.7 Pa. The frequency sweeps were carried out at 4.7 Pa at various temperatures. For concentrations ranging from 2 to 5% w/v, a 6 cm cone and plate geometry with truncation of 70 μm was used, whereas a 2 cm parallel plate with a gap set at 500 μm was used for the 20% solution. Low viscosity silicone oil was used to seal round the sample to avoid evaporation. All studies were performed within the viscoelastic limit of the samples.

The 2% w/v E4M and K4M solutions were used for the visual inspection. The changes in the colour and opacity during heating a sample in a beaker on a hot plate from 20 to 90 °C were visually observed and photographed.

3. Results

Fig. 2(a) shows the thermorheogram of a 2% (w/v) E4M gel. At 20 °C G'' is greater than G', indicating a viscoelastic system dominated by the liquid (viscous) component. As the temperature is increased G' decreases gradually, until the temperature reaches 55 °C where a minimum is observed. This minimum persists until approximately 70 °C at which point an increase is seen. G'' follows a similar trend on heating with a sharp decrease at 55 °C and an increase at 75 °C. On cooling a two step increase is observed for both G'' and G', but is more prominent for the latter. The two steps are observed at 65 and 50 °C.

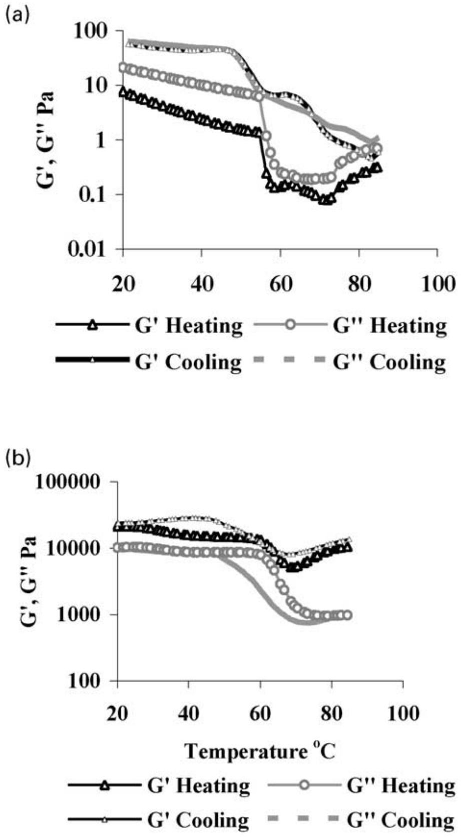


Fig. 2. Thermorheogram of a (a) 2% (w/v) and (b) 20% w/v HPMC E4M system.

The behaviour pattern of a minimum followed by recovery on heating with an increase in moduli with one or more steps on cooling was seen at all concentrations, albeit with different proportionalities in response. For example, Fig. 2(b) shows the thermorheogram of a 20% (w/v) HPMC E4M. On heating G' falls sharply at 60 °C and rises at 65 °C, while G'' falls sharply at 55 °C and levels off at 65 °C. On cooling G' increases below 65 °C and levels off to the original value at 50 °C. G'' rises sharply below 70 °C and levels off below 50 °C. Obviously, the absolute values of the moduli are considerably greater for the more concentrated systems, but it is interesting to note that the general temperature dependence remains similar.

The aforementioned similarity is exemplified by Fig. 3(a) and (b), showing the G' and G'' thermorheograms for various different concentrations of E4M studied on heating. The sharp decrease in G' is observed at 55–60 °C in all cases. However, it was noted that changes in both G' and G'' varied from a two-step to a single step increase on cooling at increased concentrations.

The thermorheological behaviour of METHOCEL F4M and K4M solutions were similar, although the temperatures at which the events occurred differed for K4M. To

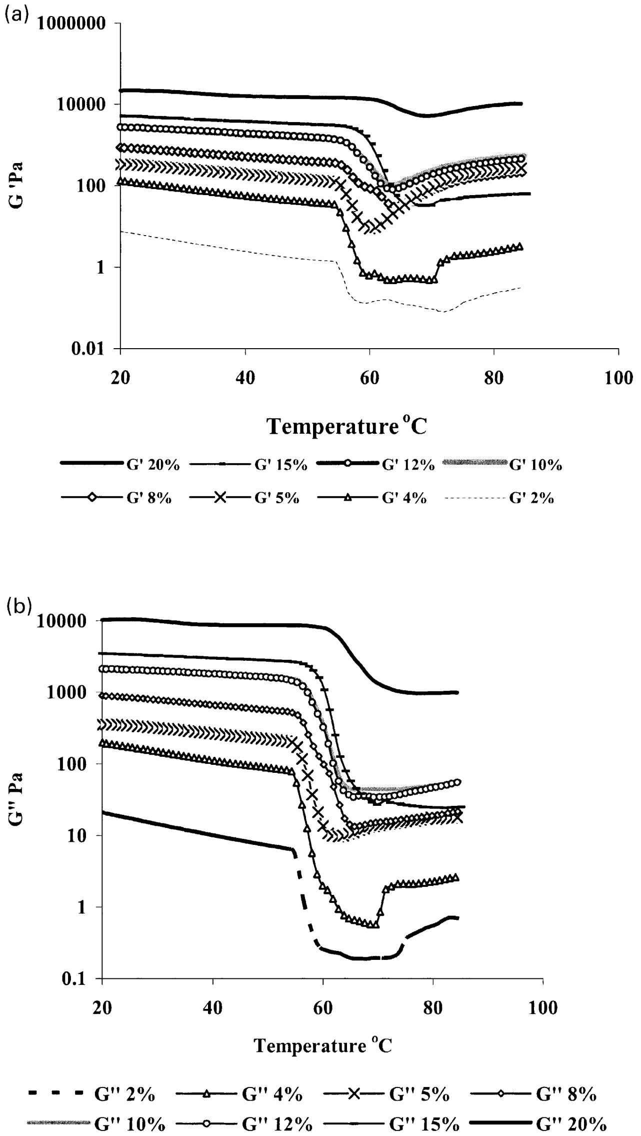


Fig. 3. Thermorheogram showing the change in the (a) storage modulus G' and (b) loss modulus G'' for different concentrations of E4M solutions.

exemplify this, Fig. 4(a) and (b) shows the thermorheograms of 2 and 5% (w/v) K4M gels. The low temperature event observed for E4M is seen at a higher temperature of 67 °C in this case, with an increase in moduli seen at ca. 89 °C. Similarly, on cooling an increase in moduli is seen commencing at ca. 79 °C. The 5% K4M follows a similar trend for both the heating and cooling processes.

In addition to thermorheological temperature ramp studies, frequency sweeps were also performed at a range of temperatures. Fig. 5 shows a frequency scan for a 12% solution of E4M. In particular, it is interesting to note the differences in frequency dependence of the gels. At 25 °C, both G' and G'' show a marked increase with frequency, with $G' \propto \omega^{0.49}$ and $G'' \propto \omega^{0.29}$. Such frequency dependence is typical of an entangled polysaccharide solution [3]. As the temperature is increased to 55 °C, which is prior to the transition seen on the temperature sweep, the frequency dependence is reduced, with $G' \propto \omega^{0.27}$ and $G'' \propto \omega^{0.25}$. Increasing the temperature to 85 °C reduces the frequency dependence further with $G' \propto \omega^{0.05}$, while $G'' \propto \omega^{0.10}$. This low frequency dependence is characteristic of a polymer gel [13]. Similar results have been previously reported for low concentration solutions of both MC and HPMC [3,14], although less information is available with regard to higher concentration systems. In this respect, the values of the power law indices are given in Table 2 for a range of concentrations. It is interesting to note that the same trend is

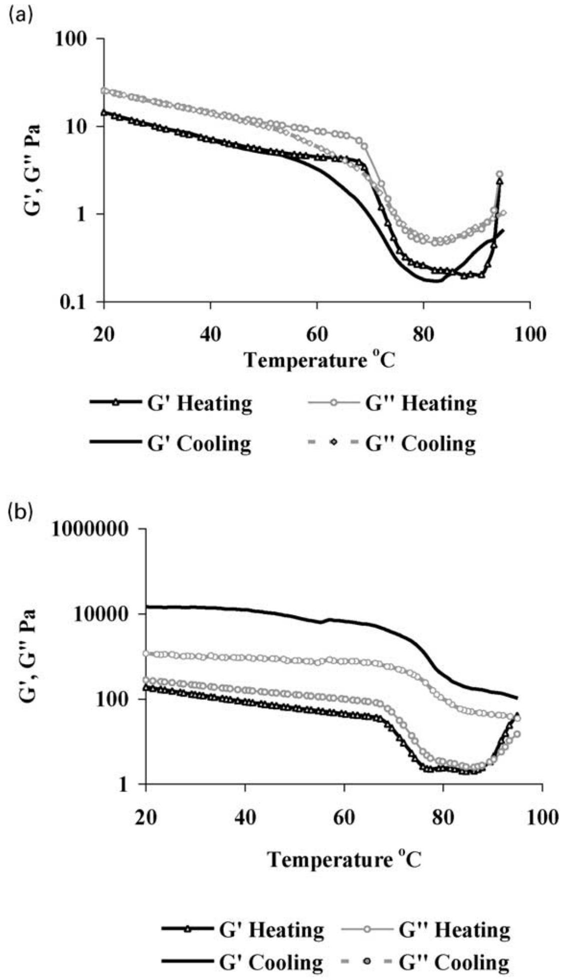


Fig. 4. Thermorheogram of (a) 2% (w/v) and (b) 5% K4M gels.

Table 2
Frequency dependence of various concentrations of E4M (G' and $G'' \propto \omega^x$ the values of x are shown)

Concentration	25 °C		55 °C		85 °C	
	G'	G''	G'	G''	G'	G''
2%	1.16	0.74	0.32		0.06	0.10
4%	0.85	0.58	0.59	0.53	0.05	0.10
5%	0.84	0.53	0.57	0.55	0.05	0.09
10%	0.58	0.35	0.23	0.33	0.05	0.10
12%	0.49	0.29	0.27	0.25	0.05	0.11

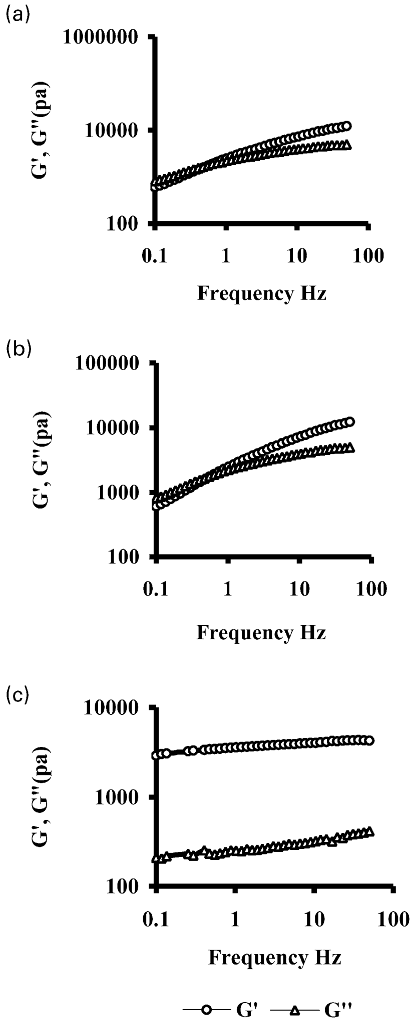


Fig. 5. Frequency sweeps of 2% E4M solution at (a) 25, (b) 55 and (c) 85 °C.

seen in each case, namely that at low temperatures the indices are relatively high (indicative of an essentially viscous system), while at higher temperatures the frequency dependence is considerably reduced, reflecting the more elastic nature of the gelled systems. The difference between the high and low temperature indices were greater for the low concentration systems than for the 12% system, presumably because of the more fluid-like nature of the former at low temperatures.

In order to correlate the observed transitions with visual clouding, corresponding solutions were heated and the behaviour observed visually (Fig. 6). It was interesting to note that clouding was apparent for the 2% E4M systems, commencing at ca. 42 °C which is lower than the temperature at which the thermal transition (i.e. the decrease in G' and G'') was observed. As the temperature was increased the system started to phase separate into two layers at approximately 51 °C, which is close to the transition temperature seen during the temperature sweeps. It was noted that on further increasing the temperature, the polymer rich (cloudy) layer appeared to increase in stiffness at approximately 75 °C. On stirring the solution, the watery phase acted as a lubricant for the polymer rich phase making it easy to move around the beaker. This lubrication effect was also observed on the rheometer plate. On cooling the phase separation process reversed giving a clear single phase below 50 °C.

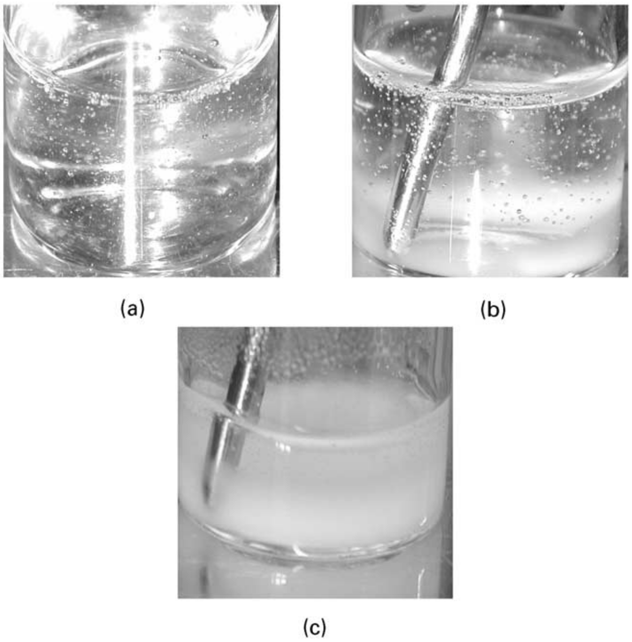


Fig. 6. Photographs of 2% w/v E4M solutions at (a) 25 °C showing an isotropic solution, (b) 42 °C showing the onset of clouding and (c) 51 °C showing phase separation.

These observations were correlated to the behaviour of the system within the rheometer by repeating the aforementioned studies by stopping the experiment following the main transition and observing the solution within the instrument. It was clear that phase separation had indeed occurred during the measurement at equivalent temperatures to those noted above.

4. Discussion

The study has focussed on the temperature-dependent behaviour of HPMC solutions, with a particular view to investigating the effect of concentration on that behaviour. It is clear that there remains a need to unequivocally define the terms used with respect to gelation, clouding and IPT. However, perhaps more importantly, it is essential to consider the macroscopic behaviour of these systems as well as considering the molecular mechanisms involved in the interaction between the polymer chains and water. It is clear that all the solutions undergo two main transitions on heating, involving a decrease followed by an increase in moduli. Previous studies have attributed these to some form of thermal softening followed by gelation at a higher temperature, while Sarkar [4] reported a sharp fall in the storage and loss moduli (G' and G'') at about 55–60 °C, ascribed the precipitation of high molecular weight fractions, and an increase in the solid component, G' at 65–70 °C, ascribed to the gelation temperature. The present study has suggested the further possibility that the first transition corresponds to phase separation and the second to the gelation of the polymer-rich phase. The mechanisms associated with these processes remain obscure, with only a small number of papers having addressed this issue in the past. Takahashi et al. [15] reported a concurrence of phase separation and gelation for aqueous solutions of MC with the possibility of the formation of two separate gels with differing polymer concentrations at high temperatures. However, the visual inspection of heating the HPMC solutions in this study showed only one phase to be gel-like, whereas the other phase appeared very dilute with more solution-like properties.

5. Conclusion

There may be several implications associated with the phase separation process outlined in the present study. In the first instance, it does indicate that the absolute values of the real and imaginary rheological moduli at high temperatures must be viewed with some scepticism, as the models underpinning these measurements assume a high degree of homogeneity. In the present case, the distribution of the two phases within the rheometer are unknown and almost certainly non-uniform. Furthermore, the proportions of the two phases and their polymer contents may well be changing with temperature, rendering detailed rheological analysis even more difficult. On a broader basis, however, the possibility of phase separation has interesting implications for the practical utility of these systems, notably in terms of understanding the drying process. The presence of two phases, one of which contains a higher content of water that is, presumably, proportionately less associated with the hydrophilic polymer, may mean that the phase separation process has a profound effect on drying rates which in turn influences processes such as film coating and capsule manufacture. Clearly, more work is required in order to clarify the precise mechanisms involved, but it is nevertheless of use to highlight the possibility of this process occurring in a practical environment.

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