# Rheology of Microcrystalline Cellulose and Sodiumcarboxymethyl Cellulose hydrogels using a controlled stress rheometer: part II

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## Abstract

Rheological properties of two different commercial grades of Microcrystalline Cellulose/Sodiumcarboxymethyl Cellulose (MCC/NaCMC) hydrogels were investigated. Viscoelastic characterization of the hydrogels using a controlled stress rheometer revealed that structure formation in the gels could be detected at a concentration as low as 1.0% w/w MCC/NaCMC in purified water. The elastic modulus ($G'$) and the linear viscoelastic region (LVR) increased with increase in hydrogel concentration. The frequency sweep study of the hydrogels exhibited a flat $G'$, indicating a stable structure at 1.5% w/w and 2.0% w/w concentrations. The oscillation time sweep study indicated that the rate of structure build up was dependent on the concentration of hydrogel. Structure buildup at various temperatures indicated that structure formation was rapid at higher temperature (40 °C), and the gel point was reached fairly quickly. Phase volume of the hydrogel significantly influenced structural recovery at different temperatures.
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## 1. Introduction

In the pharmaceutical industry, hydrogels are frequently used as suspending agents in liquid dosage forms, as adhesives in semisolid dosage forms and as modified release agents in solid dosage forms. Materials like carrageenan, gellan gum, xanthan gum and Mi-

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crocrystalline Cellulose/Sodiumcarboxymethyl Cellulose (MCC/NaCMC) are such hydrogels that are frequently used. Though MCC/NaCMC gels are extensively used in the drug development process, very little is known about their thixotropic behavior and its significance in drug development.

The Avicel® RC-591 (FMC) preparations are capable of forming highly stable thixotropic gels even at low concentrations (FMC). A study was done on the rheological behavior of the Microcrystalline Cellulose–Sodiumcarboxymethyl Cellulose gels at six different concentrations (Dolz-Planas et al., 1988). The resulting data showed an increase in gel viscosity with storage time. The thixotropic behavior of hydrogel containing 2.5% MCC/NaCMC, was studied as a function of NaCl concentration (Dolz-Planas et al., 1992). It was observed that the hysteresis area (measure of thixotropy) decreased with increase in electrolyte concentration and storage time. In another study, it was found that the MCC/NaCMC gels have higher thixotropy at lower temperature when compared to thixotropy at higher temperatures (Dolz et al., 1991).

Tamburic et al. (1996), in their study of creams using rheological techniques found that the addition of ionic ingredient (sodium lauryl sulfate) had a positive influence on structure formation when compared to the presence of a nonionic ingredient (Polysorbate 60).

All the above studies were conducted using a Brookfield viscometer where both the shear rate and time were changed simultaneously. The studies have established that the material under study is pseudoplastic and thixotropic but provided little insight into the evaluation of the thixotropy of these gels.

Suspensions, emulsions, dispersions, and polymer solutions or melts are generally non-Newtonian (Barnes, 2000). All liquids with microstructure can show thixotropy (Barnes, 1997), because thixotropy only reflects the finite time taken to move from any one state of microstructure to another and back again.

The rheological behavior of a thixotropic material is a function of time and a given shear rate or shear stress, and therefore cannot be properly accounted for with experiments where both these variables are changed simultaneously. There is a lack of fundamental understanding about the microstructure of hydrogels and the resulting thixotropic behavior. Therefore, the current study is part of a series of studies investigating the rhe-

ological behavior of MCC/NaCMC hdyrogels using a controlled stress rheometer. The theory and instrumental details about controlled stress rheometertry is presented elsewhere (Rudraraju and Wyandt, submitted for publication).

## 2. Materials and equipment

Two different grades of hydrogels: Avicel® RC-591 USPNF Lots D017N, D022N (Formula A) and Avicel® CL-611 USPNF Lot E042N (Formula B) were purchased from FMC in Newark, DE. Formulae A and B are combination products of Microcrystalline Cellulose and Sodiumcarboxymethyl Cellulose. The two different grades of Avicel differ in the type and concentration of Sodiumcarboxymethyl Cellulose present in the materials. AR 2000 Rheometer (TA Instruments) was used for performing the dynamic oscillatory testing and Silverson L4R mixer (Silverson Technologies) was used for preparation of hydrogels.

## 3. Methods

### 3.1. Hydrogel preparation

The hydrogels were manufactured using the Silverson L4R homogenizer equipped with a general-purpose screen. The homogenizer is a high shear rotor/stator laboratory mixer which provides multi-stage mixing/shearing action as materials are drawn through the specially designed workhead and mixed. Purified water was used as the vehicle for all the suspensions used in the study. Hydrogels were prepared at 1.0% w/w, 1.5% w/w and 2.0% w/w concentrations. The suspensions were then transferred to 1 L high-density polyethylene bottles and were allowed to equilibrate for 1 week for complete structure formation (Rudraraju and Wyandt, submitted for publication).

### 3.2. Rheological studies

The gel sample was gently loaded onto the rheometer peltier plate using a tablespoon. Care was taken to minimize shearing during sample removal and sample loading. All rheology studies were done at 20 °C unless specified otherwise.
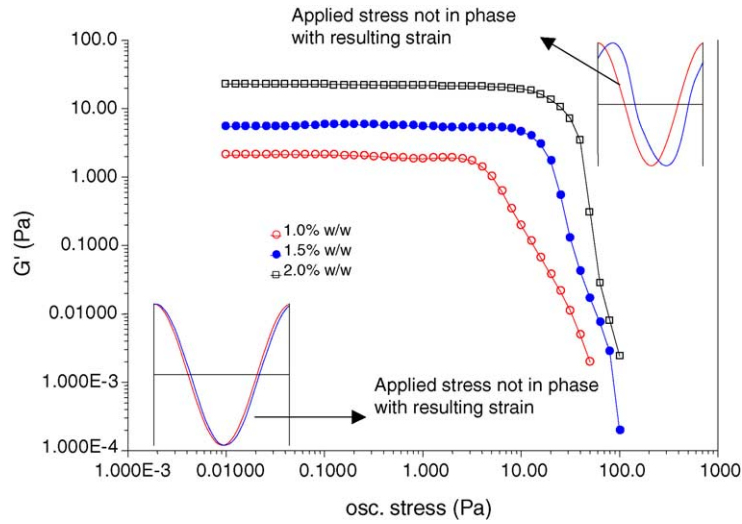
Fig. 1. Effect of oscillation shear stress on the elastic modulus ($G'$) of MCC/NaCMC hydrogels (Formula A) at varying concentrations.

The suspensions were analyzed on the rheometer using a 6.0 cm acrylic parallel plate, plate gap of 1000 μm and a frequency of 1 Hz. The operating parameters were established based on preliminary evaluation (Rudraraju and Wyandt, submitted for publication).

### 3.3. Oscillatory stress sweep

The oscillation stress sweep studies to scan the material under study were conducted over the range of 0.01–100 Pa (log mode), and at a frequency of 1 Hz unless specified otherwise. The resulting viscoelastic parameters were monitored.

### 3.4. Structure buildup—oscillation time sweep

Upon loading of the sample onto the peltier plate, the sample was equilibrated at the specified temperature for 1 min. Sample was pre-sheared at a shear rate of 2500 L/s for 1 min to completely break down the struc-
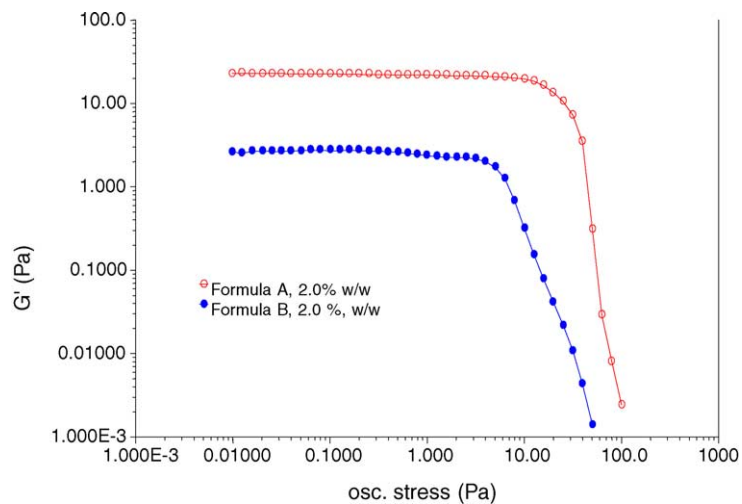


Fig. 2. Effect of oscillatory shear stress on elastic modulus ($G'$) of different grades of MCC/NaCMC hydrogels.

ture, and the structure buildup was monitored at 1 Hz frequency and an oscillatory stress of 0.25 Pa (linear viscoelastic region) unless otherwise specified.

### 3.5. Frequency sweep

Samples were subjected to a frequency ranging from 0.01 to 10 Hz at a controlled variable of 5% strain (linear viscoelastic region).

### 3.6. Temperature ramping study

The influence of temperature on sample structure was investigated over a temperature range of 5–40 °C at ramp rate of 5 °C/min. An oscillatory stress of 0.25 Pa (linear viscoelastic region) and a frequency of 1 Hz were used.

## 4. Results and discussion

Dispersions with varying concentrations of hydrogel were subjected to dynamic oscillation stress ramping. The results are presented in Fig. 1. Oscillation stress ramping data for different grades (Formulae A and B) is presented in Fig. 2. The stress range over which $G'$ is independent of the applied stress is called the linear viscoelastic (LVR) region. Over the LVR the

material structure was not broken as indicated by the graph in the subset where the applied stress is in phase with the resulting strain ($\delta = 0$). The end of linear region is called the critical stress, $\sigma_C$. Beyond the critical stress, the structure of the material was disturbed as evidenced by the data (Fig. 1) in the subset where applied stress is not in phase with the responding strain ($\delta > 0$). As noted from the graph, the 2.0% w/w gel exhibits significantly high $G'$ values and longer linear viscoelastic regions compared to the 1.5% w/w and 1.0% w/w dispersions. The dispersion exhibits structure albeit a weak one even at 1.0% w/w.

It is well established in the literature that the quantitative composition of Formula B is different from Formula A. To understand the difference in composition on hydrogel rheology, Formula B was investigated using identical experimental parameters.

Formula B hydrogel exhibited a significantly weaker structure ($\downarrow G'$), a shortened LVR and a lower critical stress (Fig. 2). This is attributed to the change in MCC particle concentration and the use of a different grade of NaCMC in Formula B when compared to Formula A. At stresses below the critical stress, the sample behaves like a viscoelastic solid. At higher stresses, the material starts to flow as its yield value is exceeded (Kutschmann). To maintain consistency, the critical stress values (Table 1) were obtained from the cross over point of the phase angle ($\delta$) values with the
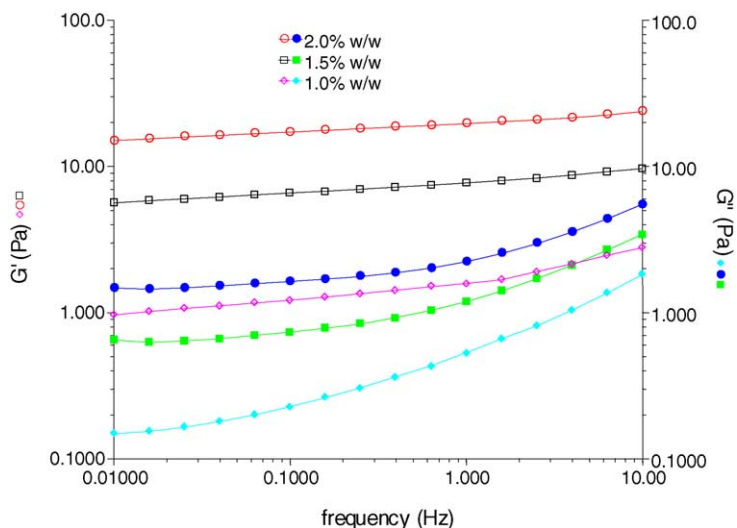


Fig. 3. Influence of frequency on the elastic modulus ($G'$) and viscous modulus ($G'$) of MCC/NaCMC hydrogels (Formula A) at varying concentration.
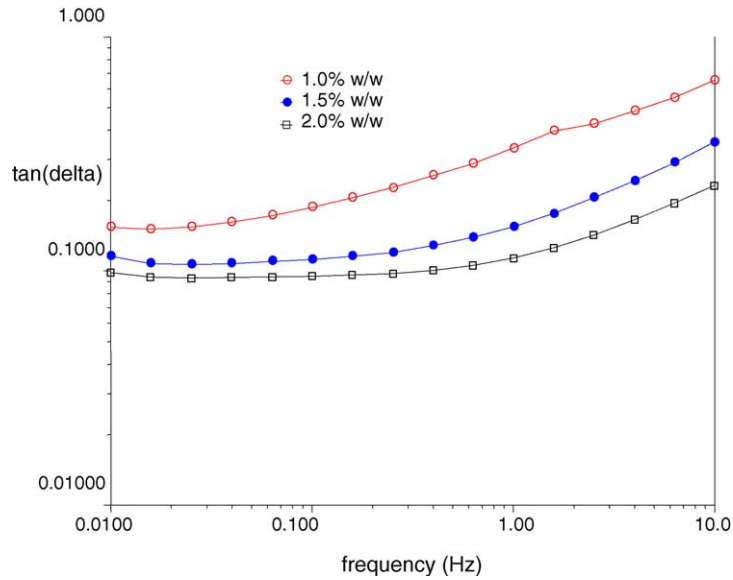
Fig. 4. Influence of frequency on tan δ of MCC/NaCMC hydrogels (Formula A) at varying concentration.

$G'$ curves. Different lots of Formula A with varying viscosity values (data from vendor generated by conventional viscometry) exhibited comparable critical stress values when probed using oscillation rheometry.

The critical stress or the yield stress has a significant value in pharmaceutical formulations. Depending on the yield stress, different filling and packing machines are used and the final products are sold in bottles, tins, boxes, tubes or other special containers. The critical stress also has a significant use in developing stable products, and this aspect was investigated further in other studies (Kutschmann).
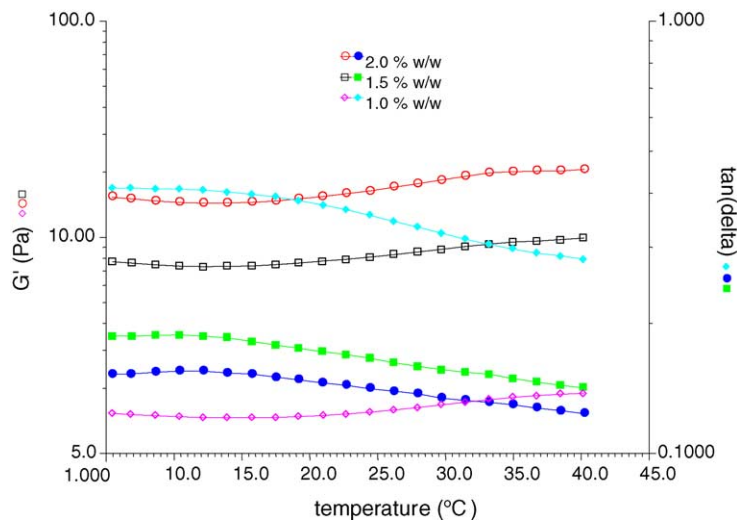


Fig. 5. Influence of temperature on $G'$ and tan δ of MCC/NaCMC hydrogels (Formula A) at varying concentration.

Table 1
Critical stress values of MCC/NaCMC hydrogels—oscillatory rheometry

| MCC/NaCMC | Critical stress (Pa) | $G'$ at LVR |
|---|---|---|
| Formula A (1.0% w/w) | 5.3 | 2.0 |
| Formula A (1.5% w/w) | 17.6 | 8.8 |
| Formula A (2.0% w/w) | 29 | 22.8 |
| Formula B (2.0% w/w) | 5.8 | 2.6 |
| Formula A (1.5% w/w)—low viscosity | 19.0 | 9.1 |
| Formula A (1.5% w/w)—high viscosity | 20.4 | 11.4 |

### 4.1. Frequency sweep of MCC/NaCMC hydrogels

The interpretation of data from oscillatory studies on viscoelastic materials can be conveniently visualized by considering a number of elastic elements or springs coupled in series with a number of viscous dashpots or pistons (Eidam and Kulicke, 1995; David and Khanderia, 1981; Barry and Meyer, 1990).

At very low frequencies the springs can elongate and dashpots have time to move to extensions which significantly exceed those of the springs. The deformation of the springs will not continue indefinitely and will reach an equilibrium, at which point no further deformation will take place. Whereas the dashpots will deform continuously under the imposed oscillatory shear. During this phase, energy is dissipated and the sample behaves as a liquid ($\eta'$ will be high and $G'$ will be low).

At high frequencies, the springs can elongate and contract under the imposed oscillatory shear, but the
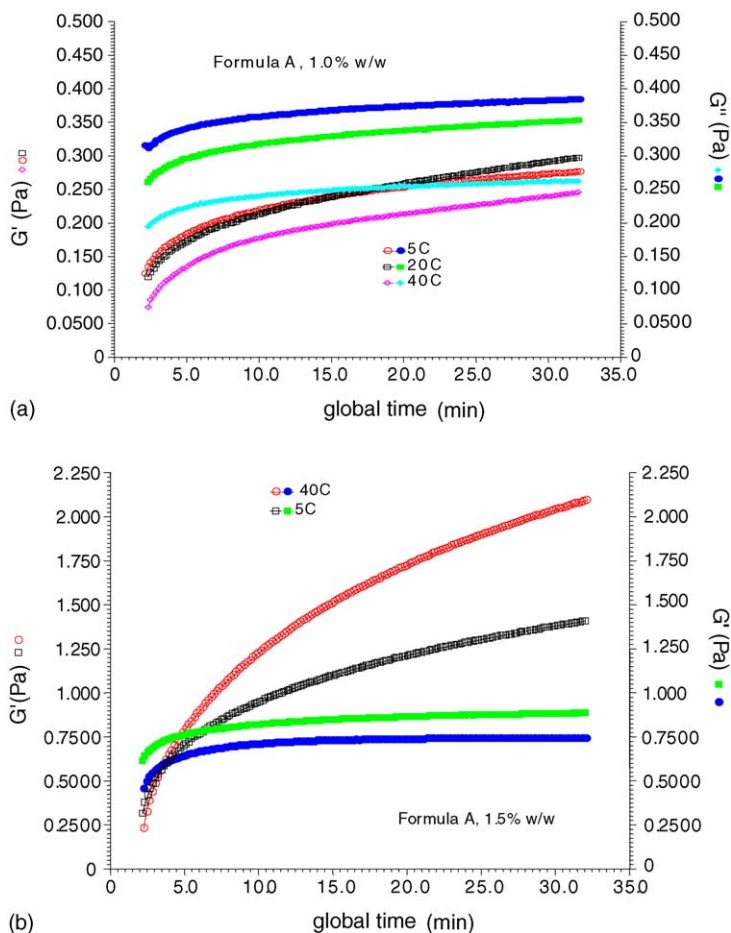


Fig. 6. Influence of temperature on $G'$ and $G'$ on MCC/NaCMC hydrogels—oscillatory testing/structure buildup: (a) 1.0% w/w and (b) 1.5% w/w.

dashpots have little time to react to the high frequencies. Energy is stored in each cycle of deformation and the material will behave as an elastic solid ($G'$ will be high and $\eta'$ will be low). At intermediate frequencies both springs and dashpots will provide contribution and viscoelastic behavior is observed.

The variation of $G'$ and $G''$ (viscous modulus) with frequency for the hydrogels is presented in Fig. 3. The plot of $G'$ versus frequency for all Formula A dispersions with varying concentrations were similar in pattern, and the magnitude of $G'$ was directly proportional to hydrogel concentration. Frequency versus $G'$ plots show a very small but gradual increase in $G'$ with an

increase in frequency. This indicates a largely elastic behavior with a comparatively small dissipation in energy. Consequently, the $G''$ plots in the measured frequency range were lower than the $G'$ plots. However, $G''$ for Formula A (1.0% w/w) hydrogel shows a considerable increase with increase in frequency indicating the material could be predominantly viscous in nature.

The loss tangent ($\tan \delta$) is a dimensionless parameter which is a measure of the ratio of energy lost to the energy stored in a cyclic deformation. Data for the $\tan \delta$ versus frequency (Fig. 4) provides a comparative measure of both the elastic and viscous contributions, and the plots of $\tan \delta$ versus frequency sweeps are also
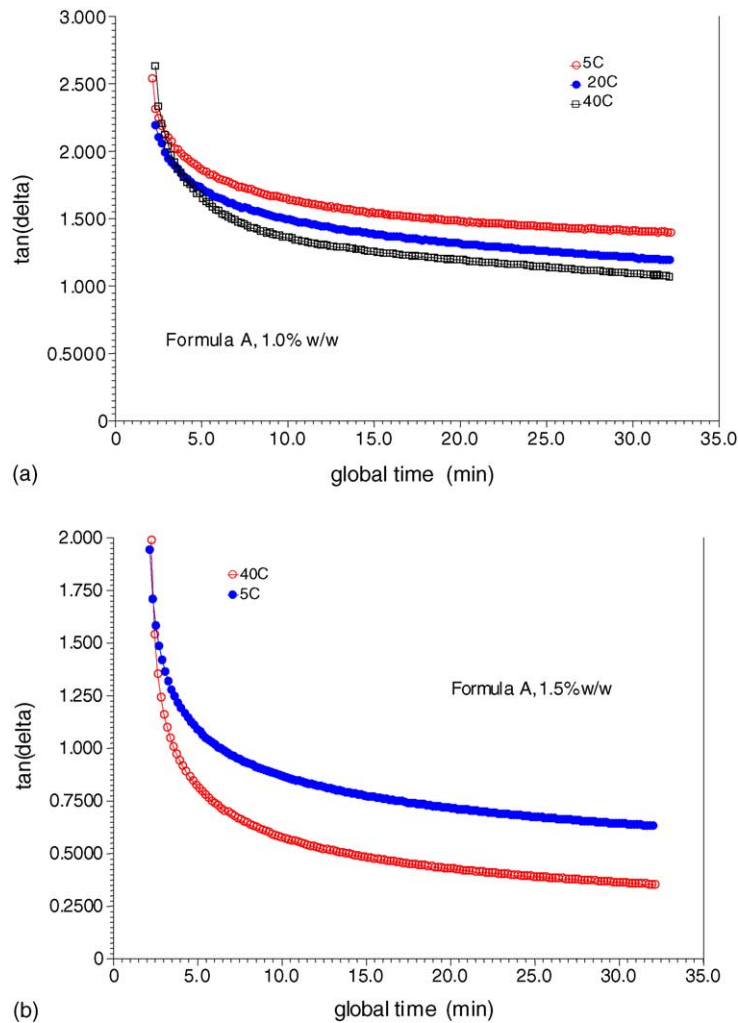


Fig. 7. Influence of temperature on $\tan \delta$ of MCC/NaCMC hydrogels—oscillatory testing/structure buildup: (a) 1.0% w/w and (b) 1.5% w/w.

termed as 'consistency spectra'. The derived values of tan δ were all less than 0.5 for the 2.0% w/w and 1.5% w/w gel indicating that the hydrogel at these concentrations is predominantly elastic.

The hydrogel with the lowest concentration of MCC particles showed the biggest shift in tan δ over the frequency range tested. This could be indicative of the predominantly viscous nature of the material, and a lesser degree of particle association (Rohn, 1987).

### 4.2. Influence of temperature on MCC/NaCMC hydrogel rheology

To understand the behavior of hydrogels at different energy states, the Formula A hydrogels were subjected to a temperature ramping study. The lower temperature (5 °C) was chosen because of its close proximity to the refrigeration temperature. The resulting data (Fig. 5) with varying concentration of hydrogel indicates that $G'$ for all the three hydrogels was directly proportional to the hydrogel concentration. All the hydrogels displayed a small shift to the upside in $G'$ beyond the 20 °C. This was further evidenced by the decrease in tan δ indicating the shift of the material towards increased elasticity as temperature increased.

To further probe this phenomenon, the hydrogels were characterized for structural formation after shearing at 5 and 40 °C. The pre-shear data indicates that the viscosity of the gels was inversely proportional to

temperature (Barnes, 2000). Viscosity of the gels during preshear studies decreased with increase in temperature because of the increasing Brownian motion of their constituent molecules, and generally the higher the viscosity, the greater was the rate of decrease.

The structural recovery studies of the 1.0% w/w hydrogel, show that $G''$ is predominant initially with a significant increase in $G'$ as time elapsed. The viscous modulus which is indicative of the material's ability to dissipate energy, decreased with increase in temperature. The gel formation was quicker at 40 °C when compared to gel formation at 5 °C (Fig. 6a).

A similar phenomenon was observed for the 1.5% w/w hydrogel (Fig. 6b). The structural recovery was quick and the gel point was significantly lower at 40 °C when compared to 5 °C data. The $G'$ was significantly high at 40 °C indicating improved elasticity for the gel at higher temperatures. This was further supported by the change in tan δ values. At 40 °C, the tan δ values were significantly lower than the values observed at 5 °C, indicating increased degree of elasticity being built into the structure at higher temperatures. $G''$ behavior at different temperatures followed the same trend as was observed with the 1.0% w/w hydrogel (Fig. 7a and b).

For the 2.0% w/w hydrogel prepared using Formula A polymer, the gel point was independent of temperature (Fig. 8). The effect of temperature on $G'$ was less pronounced when compared to gels with lower con-
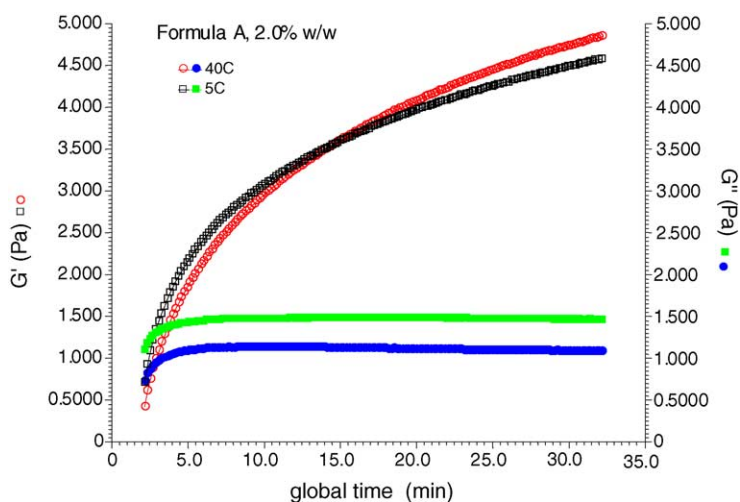


Fig. 8. Influence of temperature on $G'$ and $G''$ of MCC/NaCMC hydrogels—oscillatory testing/structure buildup.

centration of MCC/NaCMC. This could be attributed to the increased phase volume occupied by the colloidal particles in the dispersion. However, $G''$ declined with increase in temperature, and followed the same pattern observed with 1.0% w/w and 1.5% w/w hydrogels.

The structure of gels, previously described, is the result of particle–particle interactions or molecular entanglement. With MCC/NaCMC hydrogels, the former is the primary contributing factor for structure. The particle–particle interactions may be from the colloidal origin, due to Brownian motion and the viscous forces

acting on particles (Winter, 1987). For particles of all shapes, constant randomization by the Brownian randomizing force influences the form of random distribution function, whereas, for non-spherical particles, spatial orientation is being randomized.

At elevated temperatures, the additional energy put into the system coupled with the reduced gel viscosity may be responsible for the rapid randomization of the particles, thus rapid structure buildup. Flocculation processes are perikinetic (Kissa, 1999), originating from Brownian translation (diffusion controlled),
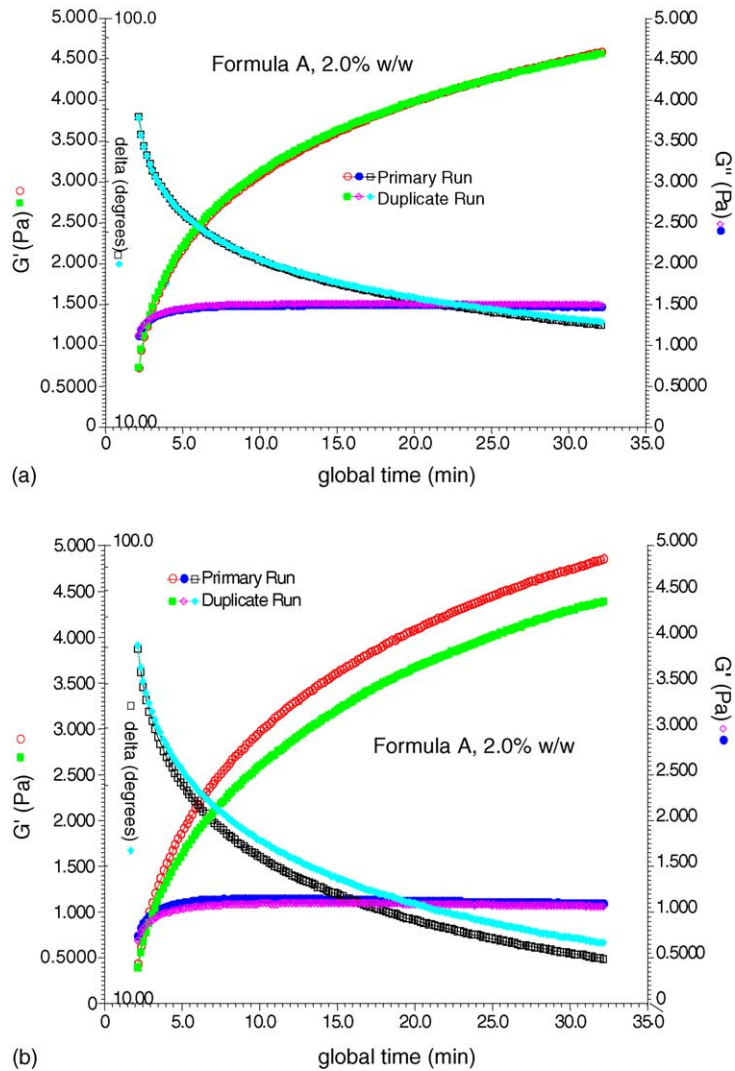


Fig. 9. Reproducibility of structural recovery analysis of MCC/NaCMC hydrogels: (a) at 5 °C and (b) 40 °C.
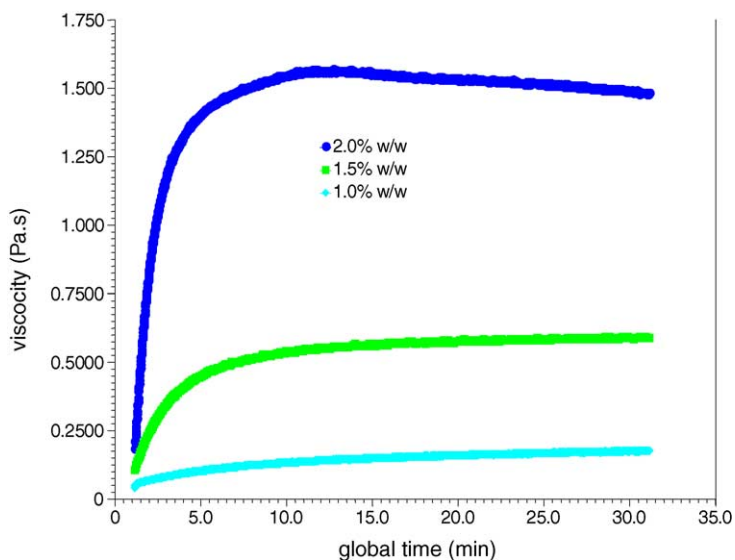
Fig. 10.  Viscosity vs. time relationship of MCC/NaCMC hydrogels at varying concentration—continuous shear method.

or orthokinetic, induced by a flow of liquid bringing the particles together and increasing the collision rate (agitation induced). The flocculation rate depends on the number and efficiency of collisions. It is hypothesized that an energy barrier exists in the gels that may hinder the contact of particles so that only a fraction of collisions result in floc formation. At elevated temperatures, the energy barrier is overcome more frequently resulting in high efficiency collisions. The influence of temperature on flocculation kinetics (Kissa, 1999; Liebermann et al., 1988) is given below:

$$\frac{J}{I} = \eta R^3 \frac{(\mathrm{d}u/\mathrm{d}z)}{2kT} \tag{1}$$

where $J$ is the probability (agitation induced flocculation) of a central particle with another adjacent particle, $I$ is the probability of diffusion controlled (Brownian) collisions, $\eta$ is the gel viscosity, $k$ is the Boltzman constant, $T$ is the temperature, $R$ is the collision radius and $\mathrm{d}u/\mathrm{d}z$ is the velocity gradient.

At elevated temperatures, the apparent reduction in viscosity and velocity gradient may result in a lower $J/I$ ratio resulting in diffusion controlled coagulation and improved flocculation efficiency. Also, at elevated temperatures, the force with which the particles interact with each other may lead to stronger floc formation

thereby increasing the elasticity of the resulting product.

The structural recovery studies were highly reproducible (Fig. 9a and b). The conventional continuous flow method (Fig. 10) simply revealed that the gels had higher viscosity with increase in MCC/NaCMC concentration. The elastic and viscous elements inherent to the gel structure, and particle–particle interaction information could not be extracted from conventional flow studies.

## 5. Conclusions

Viscoelastic characterization of the hydrogels revealed that structure formation in the gels could be detected at a concentration as low as 1.0% w/w MCC/NaCMC in water. The gel structure was dependent on the concentration of the hydrogel as evidenced by the increase in $G'$ and the extension of the linear viscoelastic region with concentration.

The frequency sweeps of the hydrogels exhibited a flat $G'$, indicating a fairly rigid structure at 1.5% w/w and 2.0% w/w concentrations. The oscillation time sweeps also indicated that the rate of structure build up was dependent on the concentration of hydrogel. Struc-

ture buildup at various temperatures indicated that at higher temperature (40 °C), the structure builds up fast and the gel point was reached fairly quickly. Phase volume or concentration of the hydrogel also influenced structural recovery at different temperatures.

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