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RESEARCH ARTICLE

Application of in-line viscometer for in-process monitoring of microcrystalline cellulose-carboxymethylcellulose hydrogel formation during batch manufacturing

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Abstract

Physical stability and consistent dose delivery of pharmaceutical suspension formulations comprised of microcrystalline cellulose (MCC) and sodium carboxymethylcellulose (NaCMC) hydrogels is dependent on their rheological properties. To obtain the desired rheological characteristics, good control of the hydrogel dispersion in water is required. The goal of this study was to evaluate whether the XL7-100 Process Viscometer could be employed as a process analytical technology (PAT) tool to monitor the dispersion process in real time during batch manufacturing. Using this instrument, viscosity profiles were measured during the hydrogel processing for a range of operating conditions. It was confirmed that viscosity obtained by the XL7-100 Process Viscometer in the off-line mode, could be linearly correlated to that of the conventional Brookfield viscometer. In addition, the XL7-100 Process Viscometer was able to detect variations in the hydrogel concentrations as well as process conditions in real time. Under fixed operating conditions, the dynamic viscosity profile showed low variability and good inter-batch reproducibility for a properly dispersed hydrogel. For a well-validated mixing process, an off-trend in-line viscosity reading may be indicative of batch failure or poor dispersion homogeneity. Therefore, the in-line viscometer can be used in manufacturing to monitor the batch to batch consistency. However, it is not proven to be able to characterize the real-time structure formation of the hydrogel. It is recommended that the in-line viscometer be used as a complimentary tool along with the off-line rheometer for both efficient and effective in-process quality control of the MCC & NaCMC hydrogel dispersion.

Keywords

Hydrogel dispersion, in-line viscometer, microcrystalline cellulose and sodium carboxymethylcellulose, process analytical technology, suspension homogeneity

History

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Introduction

Microcrystalline cellulose (MCC) and sodium carboxymethylcellulose (NaCMC) NF is a colloid forming coattitred mixture, commonly used as a suspending agent and a viscosity modifier for aqueous based suspensions in the pharmaceutical and food industry. At a concentration above 1.0 wt%, it renders the formulation with a unique thixotropic property. Thixotropy is defined as a rheological property in which the microstructure of the material can change reversibly with time from a low viscosity fluid to a more structured gel matrix or vice versa upon the loading/unloading of shear forces. A thixotropic fluid is a shear-thinning material which exhibits a time-dependent change in viscosity at a constant shear rate. In the absence of shear stress, the microcrystals of microcrystalline cellulose (MCC) are weakly cross-linked by chains of water-soluble sodium carboxymethylcellulose (NaCMC), resulting in high apparent viscosity. When shear stress is applied, the polymer chains disentangle and the apparent viscosity is reduced over time. When the shear stress is

removed, the cross-linked matrix can reform, leading to an increase in the apparent viscosity as it recovers from the disturbance.

This unique thixotropic property is particularly important for aqueous based nasal suspensions. When the suspension is at rest, the gel structure allows the drug particles to disperse uniformly in the suspension without settling. When the suspension is subject to shear force upon actuation from the pump, it becomes a free-flowing fluid which is readily atomized through the nasal device. After dosing to the nasal cavity, the gel structure recovers rapidly so that the delivered drug can be retained in the target nasal cavity area with minimum dripping¹.

It is critical to properly disperse the suspending agent, i.e. the MCC and NaCMC NF powder, in water during manufacturing in order to obtain the functionality of the hydrogel. If it is flocculated or not completely dispersed, the quality of the final product may be jeopardized, resulting in an inconsistent viscosity and dose delivery. It is also important to have an appropriate analytical tool for evaluating this dispersion during processing. A visual confirmation that the suspension is free of lumps may not necessarily be predictive of the dispersion quality. Polarized microscopic imaging and viscosity/rheology measurements are often employed as off-line tools to characterize the hydrogel

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structure during the dispersion process^{2–5}. These off-line analytical methods are usually time consuming and cause a delay in the manufacturing process. Therefore, a rapid and accurate at-line measurement is desired for better in-process control.

The objective of this study was to determine if real time in-line viscosity measurements, obtained by the XL7-100 Process Viscometer, can be applied as a PAT tool during the hydrogel processing. To this end, the sensitivity of the XL7-100 Process Viscometer to variations in the hydrogel concentration as well as process conditions was evaluated.

In-line viscometers have been used in the mineral and food industries to measure the viscosity and rheology of non-Newtonian suspensions and slurries during processing^{6–8}. In a recent study the at-line measurement of the apparent viscosities of a hot-melt extruded matrix system has been used as an in-process control to detect the variations in the formulation and the process⁹. In another study it was demonstrated that the final product quality of tomato ketchup products can be predicted from in-line viscosity measurements of an intermediate product using magnetic resonance viscometer¹⁰. However, to the best of our knowledge, this is the first time that an in-line viscometer has been applied to the processing of pharmaceutical suspensions.

Experimental

Hydrogel dispersion processing

A series of hydrogel batches, designated as Trials I–VI, were manufactured to evaluate the performance of the XL7-100 Process Viscometer (Hydramotion Ltd., York, England). The hydrogel batches were composed of water and MCC and NaCMC NF powder (FMC Biopolymer, Philadelphia, PA). The batches varied in batch size, hydrogel concentration, method of addition, shear energy and mixing speed. The general composition and processing conditions of the individual batches are outlined in Table 1 and described in more detail in the following section.

Trial I: Five 1-kg batches (Table 1, Batches 1a–e) were prepared at hydrogel concentrations of 1.0%, 1.5%, 2.0%, 2.5% and 3.0%, respectively. The MCC and NaCMC NF powder was charged into purified water from the top of a stainless steel vessel. The mixture was then agitated at a constant speed of 500 rpm for 2 h. The viscosities of the corresponding hydrogel samples were measured off-line by both the Brookfield and XL7-100 viscometers after the samples had been stored at ambient conditions for 24 h.

Trial II: Five replicate 10-kg batches containing 2% hydrogel (Table 1, Batches 2a–e) were prepared. The MCC and NaCMC NF powder was added to purified water from the top of a stainless steel vessel. The mixture was then agitated at a constant speed of

350 rpm for 2 h. The in-line viscosity readings were taken using the XL7-100 viscometer which was vertically mounted in the mixing vessel with the sensor tip fully immersed in the liquid.

Trial III: The in-line viscosity measurements were obtained for four additional 10-kg batches that were prepared at a mixing speed of 700 rpm (Table 1, Batches 3a–d). For the first two batches (Table 1, Batches 3a and b), the hydrogel concentration was maintained at 2%. The other two batches were prepared with hydrogel concentrations of 1.5% and 3%, respectively (Table 1, Batches 3c and d). In-line and off-line viscosity testing as well as rheology testing was conducted for sample aliquots removed from the batch at 15, 30, 60, 90 and 120-min time points, respectively, after storage under ambient conditions for 24 h.

Trial IV: The in-line viscosity was measured for two 10-kg batches containing 2% hydrogel mixed at an agitation speed of 350 rpm with a re-circulated flow through in-line homogenizer (Ultra-Turrax T25 Basic, No.2, IKA Works, Inc., Wilmington, NC) at a flow rate of 1 L/min (Table 1, Batches 4a and b).

Trial V: In-line viscosity measurements were obtained for three replicate 40-kg batches containing 2% hydrogel (Table 1, Batches 5a–c). As in the previous batches, the powder was charged into water from the top of the mixing vessel. The mixture was processed at a constant agitation speed of 350 rpm as well as circulated at a constant pump speed of 700 rpm (DW1/007/7 positive pump, Invensys APV, London, UK) for 1 h. In-line viscosity readings were taken during processing by positioning the XL7-100 viscometer at the bend of the circulation pipe.

Trial VI: In the last series of experiments (Table 1, Batches 6a–d), the process was the same as in the fifth round of experiments except that the powder was charged from the bottom of the tank through a vacuum line.

Laboratory-based viscometer measurement

A laboratory-based viscometer (Brookfield DV-II+Pro, Brookfield Engineering Laboratories, Inc., Middleboro, MA) was used to measure the viscosity of the suspension samples off-line. A 10 ml sample was poured into the sample adapter and maintained undisturbed in a water bath for 30 min before the measurements were taken. The temperature was kept constant at 25 °C. The spindle was immersed in the sample and the adapter was covered by the solvent cap to avoid moisture loss during sample equilibration. When the motor was turned on, the spindle rotated at a constant speed of 30 rpm (shear rate = 8.4 s⁻¹). The viscosity value was recorded after 30 s of rotation. The simplified term “viscosity” was used to refer to the “apparent viscosity” of the suspension samples at ambient condition, if not stated otherwise.

Table 1. List of process variables for all the hydrogel dispersion batches.

Trial	Batch no.	Conc. (%)	Batch size (kg)	Method of addition	Method of dispersion	Mixing speed	Viscometer position
I	1a, 1b, 1c, 1d, 1e	1.0, 1.5, 2.0, 2.5, 3.0	1	Top addition	Marine impeller	500 rpm	Off-line, in the sample container
II	2a–e	2.0	10	Top addition	Marine impeller	350 rpm	In-line, in the tank
III	3a and b, 3c, 3d	2.0, 1.5, 3.0	10	Top addition	Marine impeller	700 rpm	In-line, in the tank
IV	4a and b	2.0	10	Top addition	Marine impeller with in-line homogenizer	350 rpm (circulation flow rate of 1 l/min)	In-line, in the tank
V	5a–c	2.0	40	Top addition	Marine impeller	350 rpm (circulation flow rate of 24.5 l/min)	In-line, in the bend of circulation line
VI	6a–d	2.0	40	Bottom (vacuum) addition	Marine impeller	350 rpm (circulation flow rate of 24.5 l/min)	In-line, in the bend of circulation line

Process viscometer measurement

A process viscometer was used to measure the viscosity of the suspension samples in both the off-line mode and the in-line mode. The XL7-100 viscometer operated with the sensing element at the end of the sensor shaft that twists backwards and forwards at high oscillatory frequency. In oscillation, the resonating parts of the sensor sheared through the fluid. As the shearing takes place, energy was lost to the drag forces on the sensor caused by the viscosity of the fluid, and this dampened the vibration. The loss of energy in each cycle of vibration was measured by the processor unit. By correlating the energy loss with viscosity, the actual viscosity of the fluid was determined. For the measurement of thixotropic fluids such as the hydrogels, the vibrational shear rate applied was much higher than that of the laboratory-based rotational viscometer. Since the shear rate varied cyclically with the sensor oscillation, there was no absolute value of shear rate to be reported for the XL7 viscometer.

In the off-line mode, the XL7-100 viscometer was held in place on top of the sample container, with the sensor tip fully immersed in the sample. The viscosity reading was recorded 30 s after the viscometer was turned on. For the in-line mode, the XL7-100 viscometer was installed vertically in the dispersion tank or within the re-circulation line so that the tip of the sensor was exposed to a representative flow of the mixture. The sensor measured the viscosity of the agitated material every 0.5 s. The transducer was connected to a computer so that each viscosity output was automatically recorded by the LabVIEW software (National Instruments, Austin, TX).

Laboratory-based rheology measurement

A laboratory-based rheometer (AR 2000, TA Instruments, New Castle, DE) was used to measure the rheology of the suspension samples off-line. The parallel plate geometry with a 60-mm acrylic top plate was selected for this measurement. About 2 ml of sample was loaded onto the lower plate. The upper plate was moved down to the position where the gap between the two plates was $1050 \pm 10 \mu\text{m}$. The extra sample beyond the gap area was removed with a spatula. The remaining sample was held between the two plates for 2 min in order to reach equilibrium. The oscillatory mapping (ramp range 0.1 to 50.0 Pa) was then applied at a constant frequency of 1.0 Hz under a continuous controlled stress mode. The elastic modulus (G') as a function of the oscillation stress was recorded.

Results

Off-line measurement of XL7-100 viscometer

The five 1-kg batch samples with different hydrogel concentrations (Table 1, Trial I, Batches 1a–e) were measured off-line by both the Brookfield viscometer and the XL7-100 process viscometer. As shown in Figure 1, the viscosity results measured by the two instruments increased as a function of the hydrogel concentration and followed similar trend lines, although the values measured by the Brookfield viscometer were two orders of magnitude higher than those from the XL7-100 viscometer. The lower XL7-100 viscometer readings were attributed to the intrinsic shear-thinning property of the hydrogel upon the high shear generated by the resonant vibrational oscillation of the transducer. In contrast, the Brookfield viscometer was operated at a relatively lower shear rate by means of rotational movements of the spindle and hence rendered a higher viscosity reading.

Despite the differences in the absolute values, the two readings showed a very good linear correlation within the investigated concentration range, as seen in Figure 2. These results indicated that the XL7-100 viscometer was able to characterize the

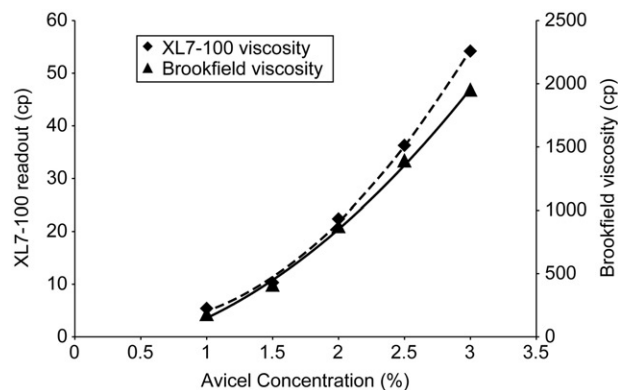


Figure 1. Off-line viscosity measured by both XL7-100 viscometer and Brookfield viscometer as a function of the hydrogel concentration (Batches 1a–e).

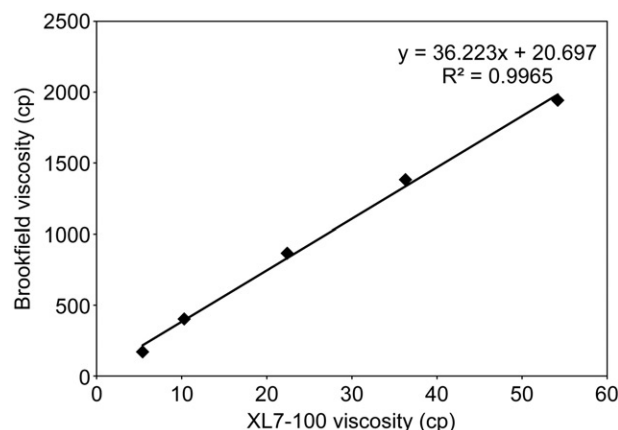


Figure 2. Off-line viscosity readings of Brookfield viscometer in correlation with XL7-100 viscosity readings (Batches 1a–e).

viscosity changes of the hydrogels as a function of the hydrogel concentration and that the process viscometer readings were proportional to those obtained by the laboratory-based viscometer for the same sample.

In-line measurement of XL7-100 viscometer in the mixing vessel

Repeatability of the in-line viscometer

The dispersion study was carried out at the same mixing condition for five replicate batches (Table 1, Trial II, Batches 2a–e) to test the repeatability and the robustness of the process viscometer. The difference between Batch 2a and Batches 2b–e was that, only the impeller was used to disperse the powder for Batch 2a, while for Batches 2b–e, a spatula was used to move the lumps of the hydrogel from the ‘‘dead spots’’ to the vortex of the tank and thereby facilitate the dispersion process.

The viscosity change during mixing was recorded in real time for each individual batch. As shown in Figure 3, Batch 2a could be easily distinguished from Batches 2b–e in that the viscosity profile of Batch 2a appeared in a relatively low viscosity region and did not show any substantial increase over time. In contrast, the viscosity profiles of Batches 2b–e increased dramatically from the initial value of 0.8 cp (the viscosity of pure water at 25 °C) to a maximum value (22–25 cps) upon the charging and dispersing of the powder in water, and subsequently decreased gradually towards a plateau stage. A slightly lower viscosity was obtained for Batch 2b compared to that of Batches 2c and d. A plausible reason for this disparity is due to a reduction in the use of the

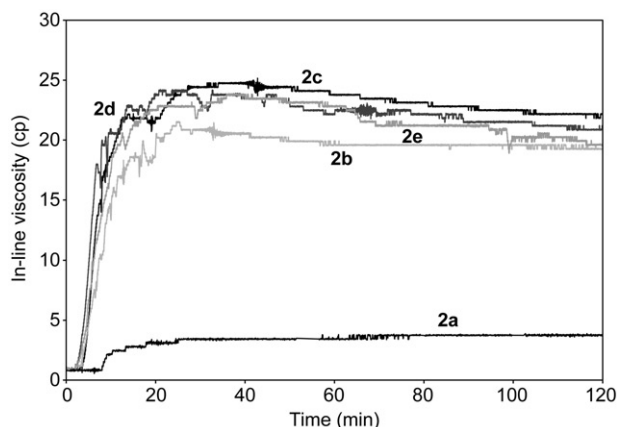


Figure 3. In-line viscosity profiles of Batches 2a–e (10 kg, 350 rpm, 2% hydrogel).

spatula to facilitate the hydrogel dispersion during the manufacturing of Batch 2b.

The viscosity differences among the batches were reflected in corresponding differences in their physical appearance. In Batch 2a, which had the lowest viscosity, a significant amount of water was separated out after overnight storage, indicating that the hydrogel had not been adequately dispersed in the batch. In Batch 2b, which had a viscosity that was lower than Batches 2c and d, a few lumps were observed after mixing and a very thin layer of water appeared on the top of the bulk sample after overnight storage, also suggesting that the hydrogel was not completely dispersed in the batch. Batches 2c–e, which had the highest viscosity, appeared to be a homogeneous gel-like structure with no water separation.

These results showed that the poorly dispersed hydrogel exhibited a distinct in-line viscosity profile from the properly dispersed hydrogel, as demonstrated in Batch 2a. It implied that for batches of the same composition and the same process condition, an off-trend viscosity profile may be indicative of a batch failure or inconsistent product quality.

These results have also shown that for a process in which the hydrogel is properly dispersed as in the case of Batches 2c–e, the in-line viscosity measurements have good repeatability between multiple runs.

Effect of the mixing speed on the in-line viscosity measurement

To investigate the effect of the mixing speed on the performance of the in-line viscometer, Batches 3a and b (Trial III, Table 1) were prepared in a similar way as Batches 2a–e except that the mixing speed was increased from 350 rpm to 700 rpm. Batches 3a and b appeared homogeneous and showed no water separation. The real-time viscosity profiles of Batches 3a and b presented in Figure 4, exhibited similar viscosity trends as well-dispersed Batches 2c–e. However, due to the higher mixing speed of Batches 3a and b relative to Batches 2c–e, the maximum viscosity value was reached sooner for Batches 3a and b, at 16 ± 2 min, compared to Batches 2c–e, at 30 ± 5 min.

It was also observed that, for Batches 3a and b, the viscosity dropped sharply and then remained stable at a lower value when the agitation was stopped after the 2-h mixing period (Figure 4). It was speculated that the viscosity change upon cessation of agitation is attributed to the intrinsic boundary effect of the viscometer. Because the shear wave generated by the oscillatory movement of the probe only penetrates a very small distance into the fluid, the sensor only measures the localized viscosity of the fluid in its immediate vicinity. When agitation was applied,

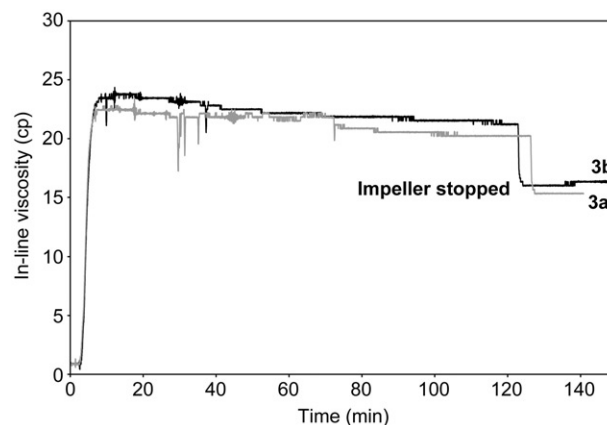


Figure 4. In-line viscosity profiles of Batches 3a and b (10 kg, 700 rpm, 2% hydrogel).

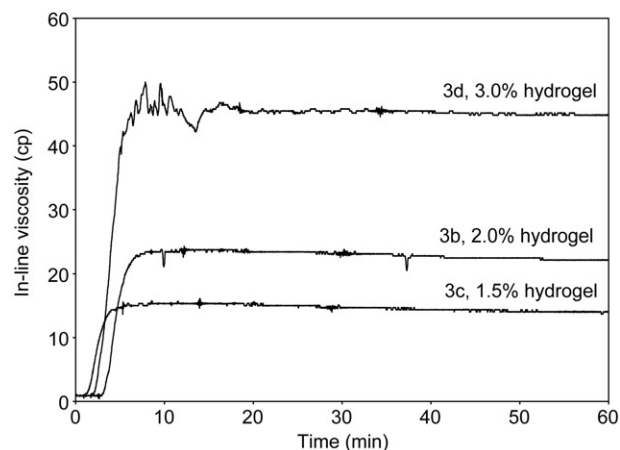


Figure 5. In-line viscosity profiles of Batches 3b–d (10 kg, 700 rpm).

the sensor was measuring a flowing fluid in the tank. When the agitation was removed, the sensor was surrounded by a stagnant and non-homogeneous fluid instead. Given the high shear rate of the vibrating sensor, a separation of water and suspended solids may take place within a small-scale boundary layer just around the sensor, resulting in a slight decrease in apparent viscosity. Therefore, it is essential to have the viscometer probe exposed to a consistent and representative flow of the fluid in the process.

Effect of hydrogel concentration on the in-line viscosity measurement

The real time viscosity profiles of Batches 3b–d (Trial III, Table 1), presented in Figure 5, illustrate the sensitivity of the in-line measurement to the hydrogel concentration. It is evident that the in-line viscosity profile shifted upward with the increase of the hydrogel concentration. The time shifts between the three profiles were mainly due to variations in the material charging time, which were 1, 1.5 and 2 min, respectively. These findings confirm that the in-line viscometer is sensitive to changes in the hydrogel concentration in both the off-line and in-line modes.

Effect of shear energy on the in-line viscosity measurement

To evaluate the impact of shear energy on the in-line viscosity measurement, the MCC and NaCMC NF powder was dispersed in Batches 4a and b (Trial 4, Table 1) with an impeller as well as with a high shear in-line homogenizer. The real-time viscosity

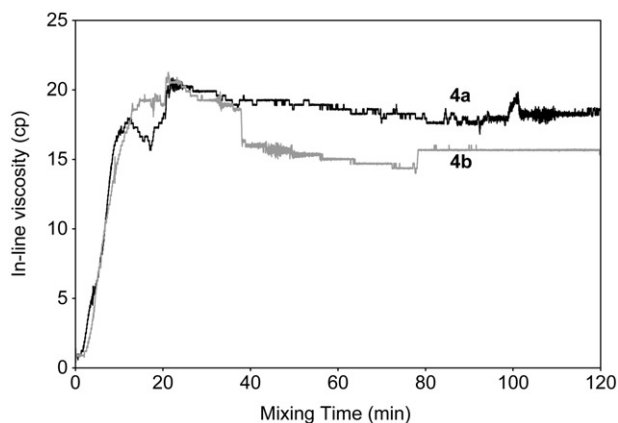


Figure 6. In-line viscosity profiles of Batches 4a and b (10 kg, 700 rpm with homogenizer, 2% hydrogel).

profiles of Batches 4a and b are shown in Figure 6. Batch 4a was well dispersed and had a similar viscosity trend as observed in the corresponding low shear batches (Batches 2c–e). However, the apparent viscosity value at the plateau stage of Batch 4a (18 cp) were slightly lower than that of the low-shear Batches 2c–e (21 ± 1 cp). A plausible reason is the intrinsic shear-thinning of the hydrogel under the high shear condition, which is a property of thixotropic materials and can lead to lower dynamic viscosity readings.

The two steep changes in the viscosity profile of Batch 4b (Figure 6) occurred in response to two adjustments in the impeller position during mixing. It is plausible that when the fluid is not a homogeneous phase, the impeller agitation has impact on the composition of the localized fluid surrounding the sensor. As a result, the viscosity reading was varied with the change of the position of the impeller relative to the viscometer.

In-line Measurement of XL7-100 Viscometer in the circulation line

When the in-line viscometer was used in a 40-kg batch, it was installed in the bend of the circulation line so that the sensor was in contact with the circulation flow at all times. The real-time viscosity profiles of three top-addition batches (Trial V, Batches 5a–c) are shown in Figure 7. The viscosity plateau values of Batches 5a–c were similar to that of the corresponding 10-kg batches (Batches 2a–e). The only difference is that the viscosity increase in the beginning of the mixing was steeper in Batches 5a–c. It is likely that the recirculation flow facilitated the dispersion of the powder into water more quickly.

Batch 5a had a time lag due to the delay in the addition of the material after the data acquisition started. Therefore, initially, the viscosity reading remained at 0.8 cp (viscosity of water).

In Batches 5b and c, it was also observed that the viscosity dropped sharply with the cessation of recirculation and returned to the original value with the reoccurrence of the recirculation. This demonstrated the sensitivity of the viscometer to the temporary change in the process flow, consistent with the observations from previous batches.

One disadvantage of the top addition is that lumps of the hydrogel could potentially adhere to the tank wall which would make it difficult to disperse later on in the process. In Batch 5c, the tank had to be reopened during the course of batch manufacture to remove the lumps of the hydrogel from the wall surface and add to the bulk using a spatula. Therefore, the viscosity reading could not be obtained during this short period of time. This again illustrates the sensitivity of the viscometer to the process variability, and this should not be misinterpreted as a variation of the homogeneity of the bulk material.

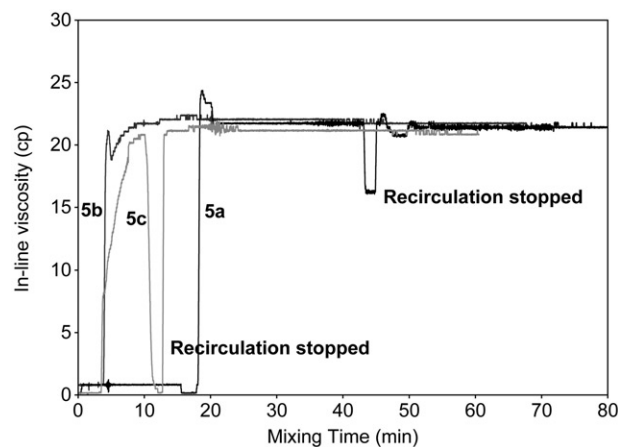


Figure 7. In-line viscosity profiles of Batches 5a–c (40 kg, 350 rpm, 2% hydrogel, top addition).

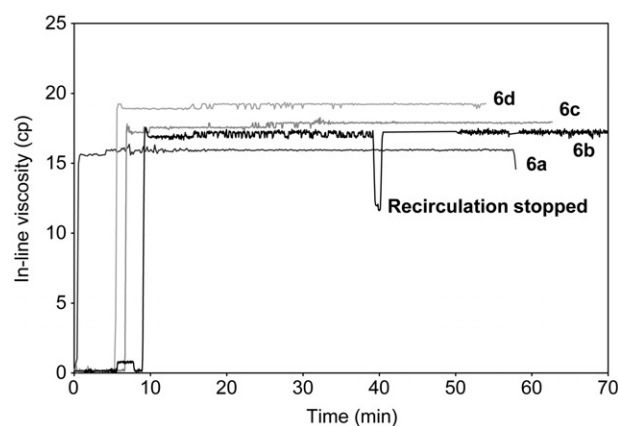


Figure 8. In-line viscosity profiles of Batches 6a–d (40 kg, 350 rpm, 2% hydrogel, bottom addition).

To better represent the scale-up of the powder addition and dispersion process, four additional 40-kg batches (Trial 6, Batches 6a–d) were prepared with 2% hydrogel charged from the bottom of the tank through a vacuum line. As shown in Figure 8, a lower viscosity was seen for Batch 6a relative to Batches 6b–d which was attributed to the entrapment of a few lumps in the vacuum line. Batches 6b–d were free of lumps and produced final viscosities in the range of 17.5–19 cps.

Batches 6b–d (Figure 8) showed consistently lower viscosity readings than those of the corresponding top-addition batches (Batches 5a–c). Given that the same amount of hydrogel was well dispersed under the same mixing condition, the final viscosity values of all the batches were expected to be independent of the method of addition. It was hypothesized that the lower viscosity reading was resulted from the loss of the material during the bottom addition as the hang-up of a small amount of powders was observed in the vacuum line and the tubing at the bottom of the tank. The in-line viscometer is sensitive enough to capture the decrease of the hydrogel concentration in those bottom-addition batches. Future studies to investigate the factors that contribute to viscosity differences between different processes, e.g. different routes of the powder addition, are recommended.

Discussion

The results show that using the XL7-100 Process Viscometer in-line, variations in the hydrogel concentrations as well as process conditions could be detected. The in-line viscosity profile,

Table 2. Viscosities of Batch 3a samples at different mixing time points measured off-line by Brookfield viscometer.

Mixing time (min)	15	30	60	90	120
Viscosity (cps @ shear rate of 8.4 s^{-1})	527.9	577.9	685.9	777.8	881.8

i.e. the viscosity plateau value and the time to reach the plateau stage, was affected by both the formulation and the process conditions. The viscosity plateau value is mainly determined by the hydrogel composition as well as the shear energy regardless of the batch scale or method of addition. The time to reach the plateau is affected by the mixing speed and the recirculation flow. Temporary change in the process flow may introduce fluctuations in the viscosity reading but will not affect the profile by large unless it causes changes in formulation composition of the localized fluid around the sensor surface, e.g. separation of water from solids in a suspension, or lumps of material adhering on the sensor surface, etc. Under fixed operating conditions, the viscosity profile showed low variability and good inter-batch reproducibility for properly dispersed suspension. Therefore, the in-line viscosity data can be used in the manufacturing process to monitor the batch to batch consistency.

It should be pointed out, however, that an important characteristic of the hydrogel dispersion that is not reflected in the in-line viscosity profile is the structure strength of the final product. This is illustrated with the 700-rpm mixing batch (Batch 3a). For samples taken from Batch 3a at different mixing time points and stored overnight, the viscosity readings obtained by the Brookfield viscometer increased as a function of mixing time, as shown in Table 2. The same trend was observed when the same samples were measured by the rheometer which also showed that the longer the mixing time, the stronger the gel structure of the sample appeared, as shown in Figure 9. In Figure 9, this structure is characterized by the maximum elastic modulus value (G'_{\max}) and the critical stress point (σ_c) where the linear viscoelastic region ends. At the mixing time of 15 min, the powder was not homogeneously dispersed. As a result, the sample showed more solid-like rigidity (higher G'_{\max}) but weaker structure (lower σ_c) (Figure 9). With the increase of time, the sample became more homogeneous in the liquid phase (reduced G'_{\max}) and developed a stronger cross-linking matrix structure (increased σ_c). After 90 min, the gel structure was almost fully developed with the enhanced gel strength (higher G' and higher σ_c).

In contrast, the in-line viscosity profile showed that the peak viscosity was reached after 14 min of mixing; then the dynamic viscosity was gradually reduced until the end of the mixing due to the intrinsic shear-thinning property of the material (Figure 4).

The discrepancy between the in-line measurement and the off-line measurement suggests that the in-line viscosity measurement is not able to reveal the formation of the hydrogel structure during the dispersion. The structure characterization requires a certain equilibrium time prior to the measurement to diminish the effect of shear history on the sample, which cannot be achieved by an in-line viscosity measurement.

In addition, the in-line viscosity data is not predictive of the end point of the hydrogel dispersion. This point is illustrated for the three batches (Batches 2c, 3a and 4a) made at different mixing conditions, i.e. 350-rpm mixing, 700-rpm mixing and in-line homogenization. For each batch, the relative standard deviation (RSD) of the viscosity, calculated for every 60 consecutive data points (time frame = 30 s), was plotted as a function of the mixing time (Figure 10). It was found that the RSD curves of all three batches had no significant differences and dropped below 5% within 10 min. This is inconsistent with our practical experience,

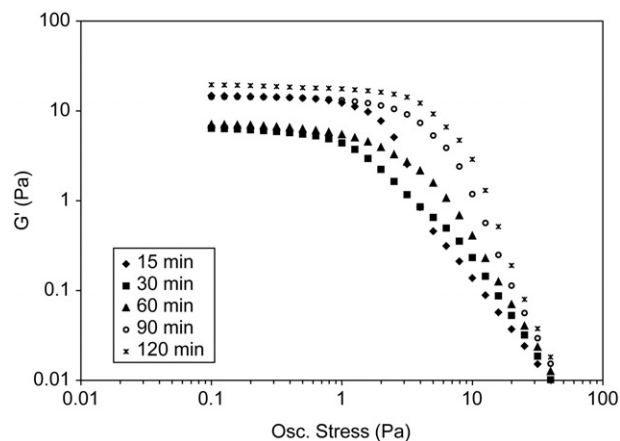


Figure 9. Elastic modulus profiles as a function of the oscillatory stress of Batch 3a samples taken at different mixing time points.

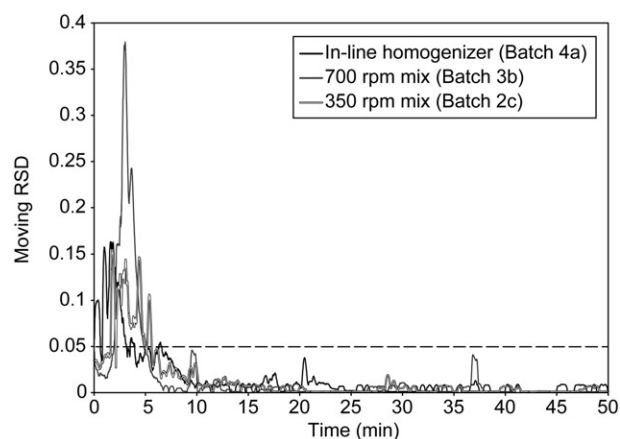


Figure 10. Moving relative standard deviation (RSD) of in-line viscosity as a function of time at different mixing conditions.

in which the end point is always seen to be reached in a shorter time when higher speed or higher shear energy is applied. Thus, the end-point should be determined by an off-line rheology measurement.

Conclusions

The XL7-100 in-line viscometer was implemented in the MCC and NaCMC hydrogel dispersion process to monitor the viscosity change of the suspension in real time. It was found that the in-line viscometer was able to characterize the hydrogel concentration variation, and its off-line reading was proportional to the Brookfield viscosity data. The in-line dynamic viscosity profile was affected by the mixing speed, the hydrogel concentration, the shear energy, the batch scale and other operating parameters which may alter the process flow exposed to the sensor. The result was consistent and reproducible for a proper dispersion process at a given mixing condition. For a well-validated mixing process, an off-trend in-line viscosity reading in contrast to the established reference profile may be indicative of batch failure or poor dispersion homogeneity. Therefore the in-line viscometer can be used as an in-process control of the batch to batch consistency. However, it cannot be used as a PAT tool to monitor the final product quality of the hydrogel, i.e. the structure strength and integrity of the hydrogel. Neither can it be used to determine the optimum mixing time required to achieve the target product quality, since it was not able to characterize the dynamics of the structure formation of the hydrogel in real time.

It is recommended that the in-line viscometer be used as a complimentary tool along with the off-line rheometer for both efficient and effective in-process quality control of the MCC & NaCMC hydrogel dispersion.

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Declaration of interest

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