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Correlating rheological behavior with molecular weight of different pharmaceutical NaCMC grades

Abstract

Sodium carboxymethylcellulose (NaCMC) is used as excipient in several marketed products from the biopharmaceutical and food industries owing to its non-toxic biocompatible nature, thickening, and water retention properties. NaCMC is commercially available in different grades with varying molecular weight which in turn affects its viscoelastic properties. It is therefore imperative to properly characterize NaCMC prior to its incorporation in a product to assure optimal and consistent performance. This paper focuses on correlating observed viscoelastic properties of different NaCMC grades to their molecular weight distribution determined by the size-exclusion chromatographic characterization instrumentation, Advanced Polymer Chromatography™. NaCMC from two different vendors in two different viscosity grades, medium and high, were assessed. Significant differences in the rheological behavior were observed which corresponded well with the inter- and intra-grade molecular weight distribution variations of the investigated NaCMC grades.

Keywords: Sodium carboxymethyl cellulose, rheology, viscoelastic property, advanced polymer chromatography, molecular weight distribution

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Introduction

The biopolymer, cellulose, and its derivates, are incorporated into several industrial products and processes.[1] Since native cellulose is challenging to use, it is often modified to manipulate its physicochemical properties such as viscosity and solubility. One such modified cellulose is sodium carboxymethylcellulose (NaCMC). The cellulose base consists of a straight chain of polymerized glucose, linked together with β-1,4-glycosidic bonds. Each glucose unit can be chemically modified via the hydroxyl group on the C2, C3 or C6. Hence, up to three modification sites per glucose unit are possible for a mono sodium carboxymethyl substitution. Different modification processes provide varying substituent distribution and degree of substitution (DS) i.e., the average number of sodium carboxymethyl groups substituted per glucose unit.[2] From that perspective, NaCMC can be regarded as a complex copolymer composed of eight different monomer units, which differ by the position and number of the substituents on the glucose unit.[3]

NaCMC is increasingly used in many industrial sectors including foods, biopharmaceuticals, paints, ceramics, and oil.[4] Aqueous NaCMC solutions derived from the white, granular, odorless, and tasteless NaCMC powder can be highly viscous and find use for their thickening, suspending, and stabilizing properties in foods, biopharmaceutical, and cosmetics products.[5,6] Within the biopharmaceutical industry, NaCMC has a very wide application. For instance, it is used as enteric coating for tablets and capsules, to render them insoluble in the stomach acids but soluble in alkaline intestinal fluids. As a result, it either improves the drug uptake into the body from the intestine or it protects the drug from acidic stomach fluids.[7] NaCMC can also be found in nasal sprays, liquid suspensions, and ophthalmic solutions as thickening agent. Other areas of application include liquid-absorbing wound dressings that are saturated with NaCMC.[8]

NaCMC is often produced in a heterogeneous reaction of sodium hydroxide activated cellulose with monochloroacetic acid or its sodium salt,[9] where carboxymethyl groups are introduced along the cellulose backbone. Thus, NaCMC tends to have a heterogeneous chemical composition and a wide range of molecular weight (MW).[10] To determine the impact of the molecular structure of NaCMC on application properties, information regarding chemical composition and average MW is important.[3] For instance, understanding the effect of MW distribution (MWD) on the viscoelastic properties of NaCMC is key for successfully tailoring of the viscosity of parenteral pharmaceutical products.[11] The increasing industrial importance of NaCMC has created interest in different techniques and methods for its characterization. This cellulose-based polyelectrolyte, like many other polysaccharide derivatives, is very difficult to characterize due to their heterogeneity in molecular weight and chemical composition.[12] Low degree-substituted NaCMC types can be soluble in alkaline solution but not in water.[3] High degree-substituted NaCMC types are insoluble in alkali solution or water but can be dissolved in organic solvents.[6] To improve the functionality within existing applications, or to develop new applications, it is essential to determine the physicochemical characteristics, e.g., DS, MW, and rheological properties. Commonly used methods for DS determination are nuclear magnetic resonance spectroscopy (NMR) and conductimetric titration.[13]

Due to its extreme sensitivity to MW changes, rheological analysis is commonly used as quality assurance and quality control of polymers in many industries to monitor MW heterogeneity, especially in the case of semi-synthetic polymers like NaCMC.[14] However, rheological measurements do not detect the origin of the MW heterogeneity but only its impact on the polymer's viscoelastic behavior.[15] Therefore, combining rheological measurements with further analytical tools is essential to elucidate the origin of MW heterogeneity.[14,16] For NaCMC MW heterogeneity and MWD determination, size-based chromatography separation techniques have been mostly reported but without assessing consequential impact on the rheological properties.[17–19] The ultra-performance liquid chromatography (UPLC)-like size-exclusion chromatography separation instrumentation, Advanced Polymer Chromatography™ (APC™), has been utilized for characterization of bio-based and semi-synthetic polymers.[20–23] The APC™ system has short runtime, high resolution, and is very sensitivity to MW heterogeneity. In this work, small amplitude oscillatory shear (SAOS) testing for viscoelastic properties were performed on two set of commercially available NaCMC grades, namely medium and high viscosity grades, from two vendors to study inter and intra grade variability. We compared their viscoelastic behavior with their MW and MWD determined with APC™. Applying both analytical techniques improved the understanding of the underlying cause and impact of MW and MWD on the viscoelastic behavior of the studied NaCMC grades.

Material and methods

Chemicals, samples and standards

General chemicals used for the chromatography mobile phase comprised of liquid chromatography grade water, 0.1M sodium hydroxide and 1N hydrochloric acid purchased from Merck KGaA (Darmstadt, Germany), anhydrous sodium dihydrogen phosphate and sodium nitrate were purchased from PanReac AppliChem GmbH ITW Reagents (Darmstadt, Germany; Barcelona, Spain). Narrow molecular weight distribution pullulan standards utilized for calibration were purchased from PSS-Polymer (Mainz, Germany).

Five different NaCMC samples of two different viscosity grades, namely high and medium viscosity were obtained from Ashland (Hopewell, USA) and Amtex Chemicals (Lombard, USA). The DS of the polymers is 0.8-0.9 based on vendor information. The high viscosity grades are assigned NaCMC 1 and NaCMC 2, and the medium viscosity grades are assigned NaCMC 3, NaCMC 4, and NaCMC 5.

Characterization techniques

Rheology – instrumentation and method

A Discovery HR-2 rheometer (TA Instruments, New Castle, USA) equipped with a water-cooled Peltier heating element and a 60 mm 2° cone-plate geometry was utilized for the rheological experiments. All measurements were performed in small amplitude oscillatory shear (SAOS) mode at 25 °C with an amplitude of 0.5% which was verified by an amplitude sweep prior to characterization. The tested frequency range was 40 Hz to 0.1 Hz. For the rheological characterization, 750 mg polymer was added to 15 mL deionized water and homogenized using a smooth glass mortar and pestle. The samples were left overnight and degassed prior to measurement. Each sample was tested in triplicate.

Advanced polymer chromatography ™ – instrumentation and method

All samples and polymer standards were analyzed on an ACQUITY™ APC™ system (Waters, Milford, USA) equipped with a refractive index (RI) detector. The column bank comprised of ACQUITY™ BEH AQ 900Å + AQ 450Å + AQ 125Å (Waters, Milford, USA) in series. All columns had the dimensions 4.6 mm x 150 mm and a particle size of 2.5 µm. The columns and RI detector of the equipment were set to 40°C. Respective amounts of $NaNO_3$ and NaH_2PO_4 salt were dissolved in deionized water to make a 0.01M $NaNO_3$ + 0.2M NaH_2PO_4 buffer adjusted to pH 7 for the mobile phase (eluent). For sample preparation, 100 mg NaCMC was added to 10 mL deionized water and allowed to dissolve in a linear shaking water bath at 80 °C (70 rpm) for 1 h (GRANT LSB12 Aqua Pro, Grant Scientific; Cambridge, UK). The solutions were cooled to room temperature and diluted with eluent to make 100 mL of sample solution at 1 mg/mL. The solutions were filtered into 2 mL autosampler vials. The pullulan standards were dissolved in 1.5 mL of eluent in 2 mL autosampler vials. 10 µL of each sample was injected into the APC™ and measured at a flow rate of 0.5 mL/min. Measurements were performed in triplicates. Data acquisition and evaluation were performed using Empower™ 3 software with GPC module (Waters, Milford, USA). Relative calibration was conducted with narrow MWD pullulan standards.

Results and discussion

Rheological chracterization

The rheological behavior of the highly viscous NaCMC solutions was characterized by complex viscosity ($|\eta^*|$), storage (G’) and loss modulus (G’’). $|\eta^*|$ describes the total resistance against irreversible flow.[24–27] The storage modulus is a measure of the elastic part of a material, whereas the loss modulus describes the plastic part. Both parameters determine the viscoelastic property of materials. The relationship between G’ and G’’, is summarized in the phase shift angle, δ; $\delta=0°$ describes a completely elastic material, $\delta=90°$ represents an entirely plastic material, and $\delta=45°$ marks an ideal viscoelastic material. An increase in both $|\eta^*|$ and G’ at low constant angular frequency denotes an increase in polymeric chain length due to elevated friction and elastic recovery of the longer polymeric chains.

The curve progression of $|\eta^*|$ was similar for all the tested NaCMC samples but differed in level as depicted in Figure 1a. As expected, the high viscosity grades NaCMC 1 and NaCMC 2 obviously yielded higher $|\eta^*|$ values (214.29 Pa·s and 43.51 Pa·s, respectively at 1 Hz) than NaCMC 3 – 5 (10.02 - 21.94 Pa·s at 1 Hz). Interestingly, the $|\eta^*|$ of NaCMC 1 at low angular frequency was about a decade higher than that of NaCMC 2, suggesting higher fraction of long polymeric chains in NaCMC 1 compared to NaCMC 2. NaCMC 1 also shows a very low δ value (Table 1), much lower than 45° which implies a highly elastic behavior. Furthermore, the slope of the NaCMC 1 G’ curve is less steep than NaCMC 2 G’ curve as depicted in Figure 1b and 1c, respectively, suggesting a broader MWD for NaCMC 1 than for NaCMC 2.[28–30] For the medium grade samples, $|\eta^*|$ decreased in the order NaCMC 5 (21.91 Pa·s) > NaCMC 3 (13.94 Pa·s) > NaCMC 4 (10.02 Pa·s).

Table 1 Rheological data of all NaCMC samples

Sample	**G’/G” - Crossover**		**Rheological properties at 1 Hz**	
	Angular frequency [rad/s]	**G’ and G” at Crossover [Pa]**	**Complex viscosity $|\eta^*|$ [Pa s]**	**Phase shift angle, δ [°]**
NaCMC 1 (high viscosity)	Out of range (<0.63)	-	214.29 (±8.45)	19.35 (± 0.27)
NaCMC 2 (high viscosity)	7.54	213.8	42.51 (±3.81)	45.53 (± 0.32)
NaCMC 3 (medium viscosity)	45.19	186	13.94 (± 1.78)	53.22 (± 0.47)
NaCMC 4 (medium viscosity)	138.15	309.9	10.02 (± 0.41)	62.64 (± 0.22)
NaCMC 5 (medium viscosity)	10.49	128.2	21.91 (± 0.44)	45.62 (± 0.48)

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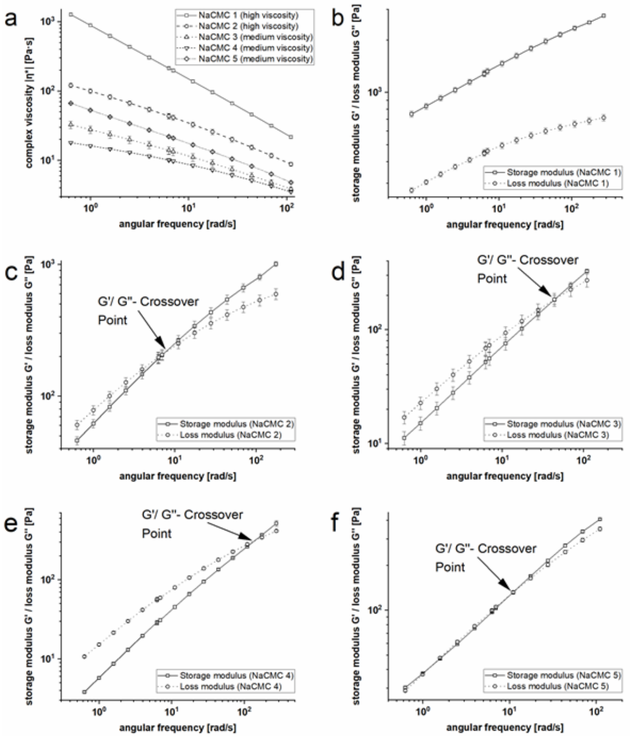

Figure 1 (a) Overlaid complex viscosity, |η*| of all NaCMC samples, storage G' and loss G" modulus plots of (b) NaCMC 1, (c) NaCMC 2, (d) NaCMC 3, (e) NaCMC 4, and (f) NaCMC 5.

Additionally, the crossover point of G' and G" was determined for all the samples (Table 1). Crossover is the point at which the material changes its viscoelastic behavior from a more elastic to a more plastic behavior.[24–28] For a given polymeric material, the crossover point is very sensitive to variations in the MW and MWD as schematically depicted in Figure 2.[15]

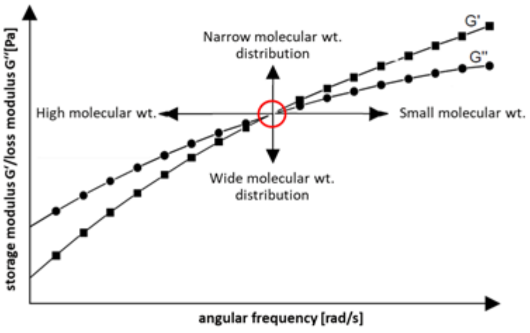

Figure 2 Impact of molecular weight on crossover point.

Reduction in the G' and G" magnitude, and angular frequency at which the crossover occurs, correlate with increasing MWD and MW, respectively as schematically depicted in Figure 2. In the case of the high viscosity grade NaCMC 1, the crossover point was out of range of the minimum angular frequency applied in the measurements (<0.63 rad/s) (Table 1). Interestingly, the crossover point of the other high viscosity grade sample, NaCMC 2 in Figure 1c, was 7.1 rad/s and within the range of the measurement.

Examining the three medium grade samples, the order of the angular frequency at crossover was NaCMC 5 (10.41 rad/s) < NaCMC 3 (47.99 rad/s) < NaCMC 4 (135.72 rad/s) indicating that NaCMC 5 would act more elastic to shear than NaCMC 3 and 4 (Table 1). Thus, NaCMC 5 is expected to have a high fraction of long polymer chains (high MW) compared to NaCMC 3 and NaCMC 4. Amongst the three medium viscosity grades, NaCMC 4 exhibited the highest angular frequency and modulus at the crossover point (135.72 rad/s, 309.9 Pa), suggesting it may have the lowest MW and narrowest MWD, respectively.

Molecular weight characterization

To ascertain the observed differences in the inter- and intra-grade rheological behavior of the NaCMCs, APC™ characterization of the samples was performed to investigate the MW, MWD, and polydispersity (Đ). As documented in literature, the best practice when analyzing NaCMC by size-exclusion chromatography is to add salts to the mobile phase to prevent coil repulsion or expansion effects of the polymer chains and minimize ion exclusion.[31] In our case $NaH_2PO_4/NaNO_3$ buffer at pH 7 was used as mobile phase.

The determined molecular weights along with Đ of all the samples are listed in Table 2. The calculated standard deviation (RSD) of the samples is extremely low attesting to the high reproducibility of the measurements. As expected, the high viscosity grade samples NaCMC 1 and NaCMC 2 exhibited the highest weight-average molecular weight (M_w) in the range of 900-1000 kDa while the medium viscosity grades exhibited M_w in the range 700-750 kDa. However, a more careful examination of the MWD characteristics, which are reflected in the Đ, reveals significant intra-grade differences. For instance, the MWD of NaCMC 1 is more polydisperse with Đ of 5.23 compared with Đ of 4.76 for NaCMC 2 which agrees with the observed rheological behavior that the slope of of NaCMC 1 G' curve is less steep than NaCMC 2 G' curve (Figure 1 b-c). Amongst the medium viscosity grade NaCMC 4 is the least polydispersed with Đ of 4.09 which correlates well with the fact that it has the highest modulus at the crossover point.

Table 2 Molecular weights and polydispersity of all NaCMC samples

Sample	Mn, kDa	%RDS	Mw, kDa	%RDS	Đ
NaCMC 1 (high viscosity)	201.5	3.2	1051.9	1.8	5.23
NaCMC 2 (high viscosity)	190.2	1.2	905.6	3.3	4.76
NaCMC 3 (medium viscosity)	151.6	2.8	698.2	3.1	4.61
NaCMC 4 (medium viscosity)	175.7	4.4	718.1	4.5	4.09
NaCMC 5 (medium viscosity)	154	0.6	750	2.6	4.87

In Figure 3, the weight-normalized chromatogram peak area and cumulative amount are plotted against M_w to illustrate the contributions of the different MW fractions to the overall MWD of the samples. It becomes obvious from these plots that within each viscosity grade set no two lots were identical, especially the high viscosity grade set (NaCMC 1 and NaCMC 2). According to Figure 1a, NaCMC 1 is predominately composed of high MW population (long polymeric chains) compared to NaCMC 2 (Figure 1b) which has a very significant amount of low MW population (short polymeric chains) in addition to the high MW population. This explains and agrees with the fact that the measured complex viscosity, |η*| of NaCMC 1 was about a decade order of magnitude higher than NaCMC 2, as the former is predominantly composed of long polymeric chains which contributes to its markedly different elastic behavior. Comparing the medium viscosity grade in Figures 3, all three lots show bimodal distribution of high and low MW populations. Amongst the three lots, NaCMC 4 and NaCMC 5 have higher MW value (log 5.75) for the high MW population, however, NaCMC 5 additionally has a prominent shoulder peak in the much higher MW region (log 6.5). The presence of the shoulder peak indicates that NaCMC 5 has a minor population of very high MW polymeric chains. Hence, NaCMC 5 exhibited the highest M_w as given in Table 2 and correspondingly showed the highest $|\eta^*|$ amongst the three lots as seen in Table 2. Interestingly, NaCMC 3 which recorded the lowest M_w amongst the three lots unexpectedly showed a higher $|\eta^*|$ than NaCMC 4 as noted in Table 2 and Table 1, respectively. By closely examining Figure 3c and d, it can be noted that NaCMC 3 has the lowest MW value (log 5.5) for its high MW population but, it also has a prominent shoulder peak in the much higher MW region (log 6.5). It therefore appears that the amount of these very high MW polymeric chains is not enough to considerably change the overall M_w but nonetheless significant enough to increase the $|\eta^*|$ due to their very long chain length.

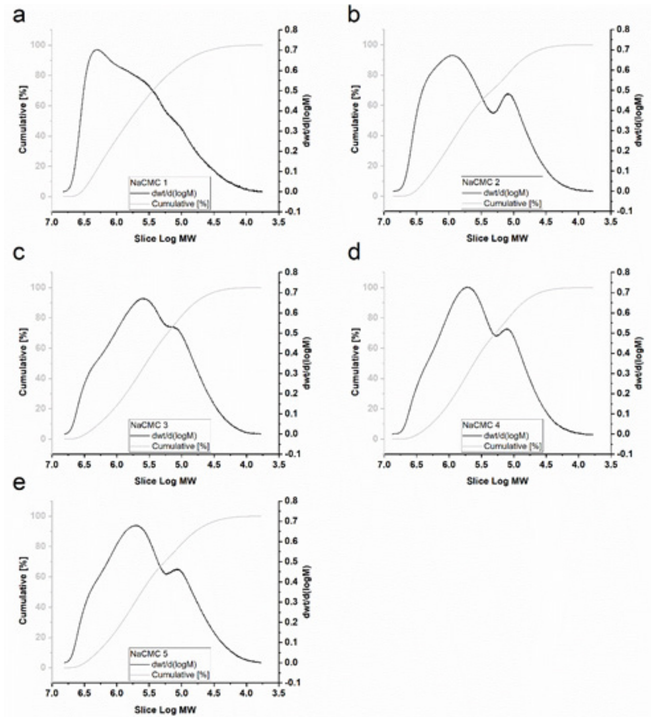

Figure 3 Molecular weight distribution plots of (a) NaCMC 1, (b) NaCMC 2, (c) NaCMC 3, (d) NaCMC 4, and (e) NaCMC 5.

Conclusion

The rheological properties of two different grades namely, high and medium viscosity grades, of commercially available pharmaceutical NaCMC from two vendors were studied and their molecular weight characterized by the Advanced Polymer Chromatography (APC™) system. Overall, the high viscosity grade lots exhibited higher viscosity as expected. However, a marked difference in viscosity was observed amongst the high viscosity grade lots, which could be explained by the observed large difference in their molecular weight distributions. Although the medium viscosity grade lots did not show large intra-lot viscosity variation, they exhibited subtle differences in viscosity and other viscoelastic properties which could be traced and explained by their respective molecular weight distribution. Thus, the combined application of rheological testing and APC™ provides an investigative means to ascertain inter- and intra-grade variability of NaCMC which can applied in the industrial setting to ensure the right excipient is being selected to meet target product quality and performance.

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Conflicts of interest

Disclosure

Ekaterina Sobich, Esther S. Bochmann, Matthias Degenhardt and Samuel O. Kyeremateng are employees of AbbVie and may own AbbVie stock. Claudia A. Lohmann is an employee of Waters Corporation and has no additional conflicts of interest to disclose. AbbVie sponsored and funded the study; contributed to the design; participated in the collection, analysis, and interpretation of data, and in writing, reviewing, and approval of the final publication.

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