International Journal of Pharmaceutics 415 (2011) 95–101

Contents lists available at ScienceDirect

International Journal of Pharmaceutics

journal homepage: www.elsevier.com/locate/ijpharm

Characterisation of the interactive properties of microcrystalline cellulose–carboxymethyl cellulose hydrogels

G.H. Zhao[a], N. Kapur[b], B. Carlin[c], E. Selinger[c], J.T. Guthrie[a,*]

[a] *Department of Colour Science, School of Chemistry, University of Leeds, UK*
[b] *School of Mechanical Engineering, University of Leeds, UK*
[c] *FMC Biopolymer, Princeton, USA*

ARTICLE INFO

Article history:
Received 10 March 2011
Received in revised form 19 May 2011
Accepted 20 May 2011
Available online 27 May 2011

Keywords:
Hydrogel
Interaction
Composites
Rheology

ABSTRACT

Combinations of microcrystalline cellulose (MCC) and sodium carboxymethyl cellulose (Na-CMC) are commonly used as stabilising agents and suspending agents in pharmaceutical formulations. This paper is based on a study of the interactions that take place during the process of hydrogel formation, break down, and recovery. Also considered is the binding that occurs between the MCC and the Na-CMC.

Avicel RC 591, a processed mixture of MCC and Na-CMC, is one of the more commonly used commercial suspending agents for aqueous compositions. Avicel RC 591 is used as an effective, blended stabilising agent. In this study, the contributions made by each of the components of Avicel RC 591 have been rationalised by monitoring the behaviour of the individual components in Avicel RC 591 suspensions or solutions. The hydrogels that are formed by Avicel RC 591 and by their laboratory formulated equivalent, which is spray dried (MCC + Na-CMC), have been characterised by confocal microscopy scanning electron microscopy and by dynamic light scattering. A 3D network structure that is formed by the MCC, in Avicel RC 591 is visualised. This network is supported by hydrogen bonding and by ionic interactions among and between the MCC, the Na-CMC and water. The strength of the network determines the physical properties of the hydrogel system, as seen in the rheological behaviour.

1. Introduction

Microcrystalline cellulose (MCC) is used in the pharmaceutical industries because of its interactive behaviour nature and its biodegradability. Its crystalline nature and its involvements in hydrogen bonding processes make significant contributions to the physical properties and to the chemical properties of compositions, in a variety of environments (Kennedy, 1995). In its chemistry, cellulose can be viewed as behaving as an acid (when in the presence of a base), as a base (when in the presence of an acid) and as an ampholytic species, under appropriate circumstances. The appropriate chemical reactivity then follows. Physically, cellulose swells considerably in a number of fluid systems but does not dissolve in these (Hebeish and Guthrie, 1981). Exceptions are claimed to be the cellulose-NMMO system and solutions of cellulose in ionic liquids (Manning, 1985; Zhu et al., 2006).

Microcrystalline cellulose is a product of the wet granulation of cellulose that has been partially de-polymerised via hydrolysis in hydrochloric acid. The process helps to remove the disordered regions of the cellulose, only the highly ordered regions remaining (Biopolymer, 2008). The general compatibility of MCC changes during the granulation process. The reasons for such changes are not fully understood (Suzuki et al., 2001; Badawy et al., 2006). However, it is clear that microcrystalline cellulose has significantly different physical properties relative to those of the parent cellulose system. The mechanical disintegration of microcrystalline cellulose (MCC) in an aqueous dispersion, whereby at least 1% of the dispersed cellulose is broken down to sub-micron cellulose crystallites, gives thixotropic gels (Barrista, 1961). Drying these gels at elevated temperatures, at atmospheric pressure, gives a hornifiedproduct in which the gel-forming, sub-micron crystallites are hydrogen-bonded together and can no longer be liberated on subsequent redispersion in water, without the substantial input of energy. Such gels are also sensitive to flocculation by the addition of an electrolyte (Durand, 1970).

The addition of sodium carboxymethylcellulose (Na-CMC) during the mechanical disintegration of MCC reduces hornification. Hence, the pharmacopoeial description of the co-processed product concerns a "co-attrited, colloid-forming mixture" (USP-NF, 2008a). The co-processed product is also known as Dispersible Cellulose (BP) and Cellulose Gum (European Pharmacopoeia, 2008b), in addition to the National Formulary titles of microcrystalline

---

* Corresponding author. Tel.: +44 113 343 2934; fax: +44 113 343 2947.
E-mail addresses: Cp06gz@leeds.ac.uk (G.H. Zhao), N.Kapur@leeds.ac.uk (N. Kapur), Brian.Carlin@fmc.com (B. Carlin), Edward.Selinger@fmc.com (E. Selinger), ccdjtguthrie@leeds.ac.uk (J.T. Guthrie).

0378-5173/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ijpharm.2011.05.054

cellulose and sodium carboxymethylcellulose (USP-NF, 2008a). Pharmacopoeial grades of MCC/Na-CMC are marketed by FMC BioPolymer under the trade names Avicel® RC and Avicel® CL. The primary pharmaceutical application of MCC/Na-CMC is to provide structured media for the suspension of active pharmaceutical ingredients. The stabilising system is a mixture containing 8–13% of Na-CMC within the commercial Avicel RC 591 (1995).

Hydrogels formed from MCC/Na-CMC are commonly used in formulations of orally taken products and nasally dosed products (Sharpe et al., 2003; Zietsman et al., 2007). This type of hydrogel gives the required rheological characteristics because it forms a thixotropic system at a low loading, in aqueous media. The yield stress of the gel is relatively high, providing good stability with respect to maintaining the suspension of suspended particles. For applications such as in intranasal spray delivery, the viscosity needs to be low at high shear rates due to the requirements of the spraying action. The rheological properties of compositions that contain hydrogels of MCC and Na-CMC have been studied (Walkling and Shangraw, 1968; Rowe and Sadeghnejad, 1987). However, characterisation studies have not been extensive because of limitations in the sensitivity of the available instrumentation. Recently, the rheological properties of the hydrogels have been evaluated using controlled stress rheometry (Rudraraju and Wyandt, 2005a,b; Mihranyan et al., 2007). However, interpretation of the data relating to the microstructure of hydrogels, with respect to the influence of intermolecular forces, has not been undertaken to any great extent.

2. Experimental

2.1. Materials

The microcrystalline cellulose (MCC), sodium carboxylmethyl cellulose (Na-CMC), and Avicel RC 591 were supplied by FMC Biopolymer, Cork, Ireland. MCC and Na-CMC are the components of commercial Avicel RC 591. Deionised water was used to make up the appropriate solutions and dispersions.

2.2. Sample preparation

Following a detailed study, Rudraraju concluded the optimal gel formation loading for Avicel RC 591 to be around 1.5% (Rudraraju and Wyandt, 2005a). Thus, for the current work, three appropriate loadings of Avicel RC 591 were chosen, 1%, 1.5% and 2% respectively. Solutions of Na-CMC and suspensions of MCC were prepared in a study of the individual characteristics of solutions of Na-CMC and of MCC. The ratio of Na-CMC and MCC in Avicel RC 591 is 1–9. Therefore, the loadings of Na-CMC and MCC were chosen as 0.1%, 0.15%, 0.2%, and those of MCC were at 0.85%, 1.35%, 1.8% (Avicel RC/CL, 1995). These solutions and suspensions were used to provide comparisons with the results of three corresponding dispersions of Avicel RC 591. In addition, a 4% Na-CMC solution and a 5% MCC dispersion were also prepared to give comparisons for the lower loadings. The spray-dry blend of MCC and Na-CMC, identified as SD (MCC + Na-CMC), is a laboratory prepared suspending agent that was formulated by spray drying an aqueous suspension of Na-CMC and MCC, present in a ratio 1–9. Dispersions of SD (MCC + Na-CMC) at loadings 1.5% and 2% were assembled. As a comparison to the spray dried sample, mixtures of a Na-CMC solution and a MCC dispersion, containing 0.15% of Na-CMC solution and 1.35% of MCC dispersion were prepared. Typically, 200 g of sample were prepared for each fixed dispersion time. Each sample was dispersed, using a high speed mixing system, at 8000 rpm for 10 min (Silverson, Silverson Machines Ltd., Chesham Bucks, UK). The Na-CMC solutions were assembled by dissolving the Na-CMC in deionised water, without mixing.

2.3. Determination of the average molar mass and polydispersity of the sodium carboxymethyl cellulose

The CMC was analysed by size extrusion chromatography using a Suprema Linear-M, Mixture Bed column, S/N: 7041112. To support the determination of the average molecular mass and polydispersity, an Optiab DSP interferometric refractomer (Wyatt Technology Corporation, USA) was used. The GPC was characterised using mono-dispersed poly(ethylene oxide) in water, and had a delay volume of 0.225 mL. The eluent contained 0.1 M sodium nitrate and 0.001 M sodium azide, in distilled water. The reasons for adding the sodium nitrate and sodium azide were to screen the charge of electrolyte and to prevent bacterial growth. The specific refractive index increment (γ) obtained using an Optiab DSP interferometric refractomer (Wyatt Technology Corporation, USA) was 0.137 cm^3/g at 25 °C. This is in close agreement with the value obtained by Pramanik (Pramanik and Chowdhur, 1969).

2.4. Rheological evaluation of hydrogel dispersions

The rheological properties of the assembled hydrogel dispersions were assessed using a AR1500ex Rheometer (TA Instruments, Crawley, UK). This unit gives either a controlled shear rate or a controlled shear stress, in a cone and plate rheometry format. A 60 mm cone (1° angle geometry) was used for all of the measurements, to provide uniform shearing to the sample. Samples were transferred to the plate with the minimum of shearing. The equilibration time before measurement was 2 min. The temperature was kept at 25 ± 0.1 °C for each measurement. As part of the study, comparisons were made between the rheological behaviour of "fresh" samples (measured 1 h after the preparation) and the rheological behaviour of samples that had been "stored", at 25 °C, in sealed vessels, in darkness for two weeks. Each measurement was repeated and the mean value calculated.

2.5. Assessment of dispersed particles by confocal laser scanning microscopy, scanning electron microscopy, and dynamic laser light scattering techniques

A LSM 510 META microscope (Carl Zeisis Ltd., Hertfordshire, UK) was used to visualise the microstructures of the dispersions. In addition, scanning electron microscopy (FEI Quanta 200F Scanning Electron Microscope) was used to provide information concerning the structure of the resulting dried dispersions. The solid samples were coated with a thin layer of platinum (approximately 3 nm) at 80 mA, using a Cressington 208 HR Sputter Coater.

Dynamic light scattering (Brook Haven Instruments Corporation, Holtsville, New York) was used to analyse the particle size distribution. The 150° angle detector was used in the study to reduce the excessive scattering caused by any particularly large particles. The dispersion was diluted (10× dilution) and centrifuged for 15 min at room temperature, prior to analysis.

3. Results and discussion

3.1. Molecular mass determination

The weight average molar mass and the polydispersity of Na-CMC used in the experiments were 4.5×10^5 g/mol and 3.55, respectively. The relatively high weight average molecular mass provides the Na-CMC with the physical properties that are needed to ensure structure in the aqueous fluids that contain the Na-CMC. This structure provides a basis for the controlled flow behaviour that is so important to the delivery of the fluid in a specific application: that of dispensation onto nasal cavities, the intended target.

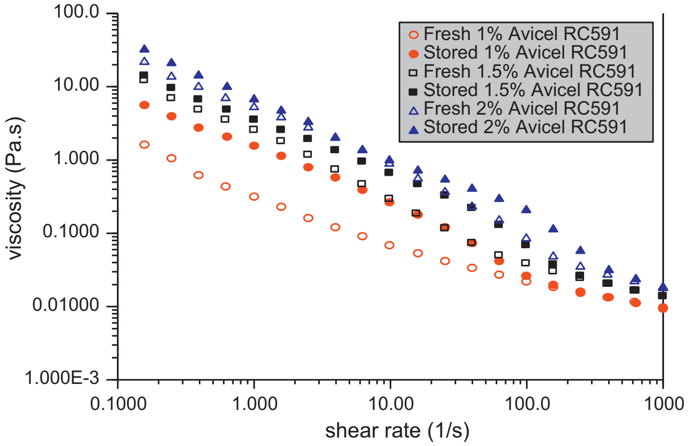

Fig. 1. The shear thinning behaviour of "fresh" Avicel RC591 and of "stored" Avicel RC591 suspensions at loadings of 1%, 1.5%, and 2%.

The broad molar mass distribution provided the hydrogel with elements of compatibility and flexibility, governed by the lower molar mass components in the formulation.

3.2. *Rheological characterisation of the interactions in the formulated hydrogel*

Rheometry was used to characterise the micro-structures that arose through polymer–polymer chain interactions that occurred in the hydrogel systems. In this study, the shear thinning behaviour and storage modulus (G') of "fresh" samples and of "stored" dispersions of Avicel RC 591 (loadings 1%, 1.5% and 2%), in deionised water, were measured. The results (Figs. 1 and 2) show that the viscosity increased as the loading of the suspending agent increased. In addition, G' increased and the linear viscoelastic region (LVR) expanded as the loading of suspending agent increased, indicating that polymer–polymer chain interactions had increased with increase in the loading of the suspending agent.

During the shear thinning process, the hydrogel dispersion experiences several changes to its physical form and to the strength of the various interactions that are inherent in such dispersions. At the lower shear rate (around 0.1 s^{-1}), the applied force would be less than the interaction forces that operate between the polymer chains. Such interactions are dominated by hydrogen bonding, by ionic interactions, and by Van der Waal's forces (Watanabe et al., 2006d,a,b,c). At relatively higher shear rates (around 10 s^{-1}), the applied force becomes greater than the forces of interaction between the polymer chains. The material therefore flows. As the shear rate is increased, the applied force is significantly greater than the forces of interaction between the polymer chains. The complex matrix now begins to collapse and chain orientation dominates. The magnitude of the strain or stress, at the point at which the hydrogel system starts to flow, is important with respect to the physical stability of the suspended particles within the hydrogel matrix. Therefore, the strength of the physical interactions among the hydrogels is critical to the physical stability of the hydrogel matrix under the prevailing conditions (temperature, shearing) under which it exists.

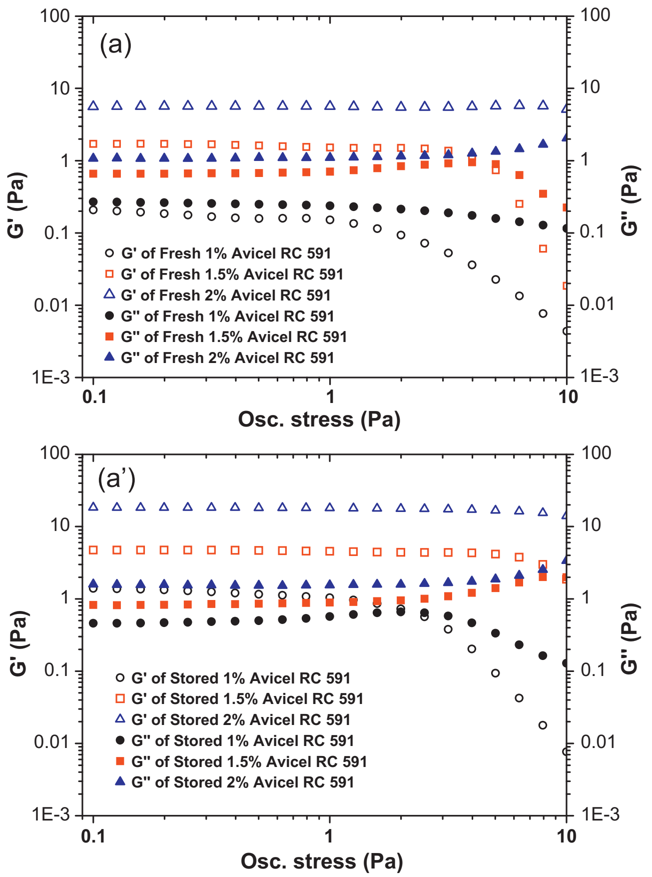

Fig. 2. (a) Measurements from the linear viscoelastic region of "fresh" Avicel RC591 suspensions at loadings 1%, 1.5%, and 2%; (a′) measurements from the linear viscoelastic region of "stored" Avicel RC591 suspensions at loadings 1%, 1.5%, and 2%.

The recovery, however, is not instantaneous. The consequence of this is shown in Fig. 3. A three step approach was used in measurements of the thixotropy of the dispersions. Initially, the dispersion was sheared at the lower shear rate for 2 min (step 1). The dispersion was then sheared at a greater shear rate for 2 min (step 2). Finally, the dispersion was sheared at the low shear rate for 10 min (step 3). The ability to recover structure was used as a route to qualifying the behaviour of these samples. This recovery is defined as:

$$\text{“Structure recovering” ability} = \left[\frac{\text{End viscosity at step 3}}{\text{End viscosity at step 1}}\right] \times 100$$

The recovery abilities of fresh Avicel RC 591 suspensions at 1%, 1.5% and 2% were 74%, 77% and 72%, respectively. After two weeks of storage, the corresponding recovery abilities of the Avicel RC 591 at 1%, 1.5% and 2% were 64%, 74% and 78%, respectively. The results show that the extent of recovery is largely unchanged. This applies to both the "fresh" samples and the "stored" samples.

Changes in the intermolecular arrangement among the polymer chains occur during the storage process. An increase in the viscosity and in the shear thinning behaviour was observed in samples that were "stored" for two weeks, compared with the "fresh" sample (Fig. 1). This change is influenced by the swelling behaviour of the Na-CMC and MCC in water, due to the hydrogen bonding and other interactions. This swelling process is relatively slow in terms of the time used in the preparation of the suspension. After the swelling process, the system becomes more structured (elastic) than the fresh sample. Therefore, an increased G' occurs in the "stored" samples at all three loadings, compared with the values from the fresh samples, Fig. 2(a) and (a′). Rudraraju in his study of the equilibrium time for structure development in assemblies of Avicel RC 591 hydrogels, observed that there were no rheological changes one week after manufacture (Rudraraju and Wyandt, 2005a,b). In the current study, slight changes were observed one week after formulation. Thus, two weeks of the storage time was chosen as the

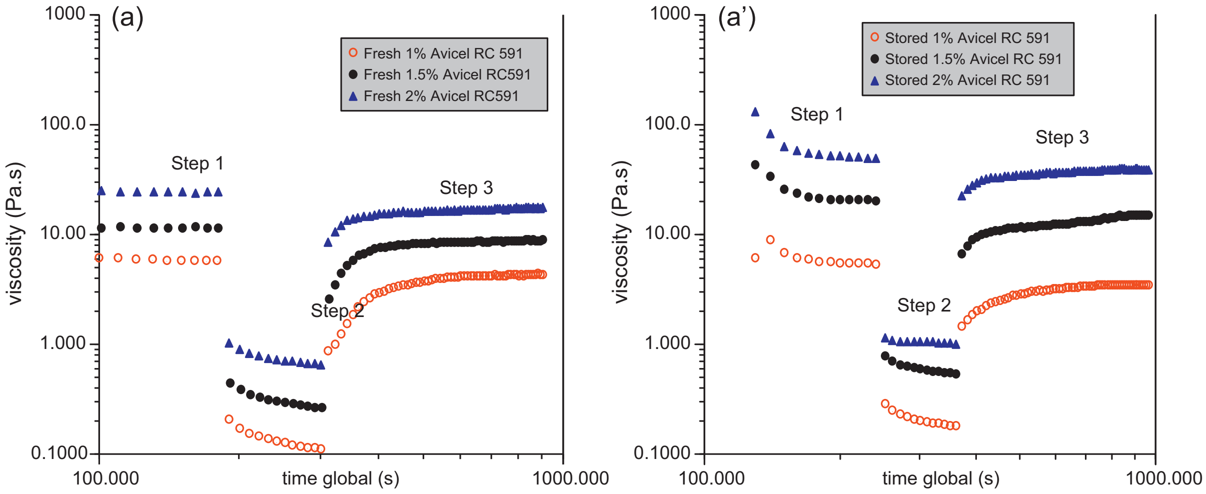

Fig. 3. (a) The three step measurements of the recovery ability of "fresh" Avicel RC 591 dispersions at 1%, 1.5% and 2% loadings; (a′) the three step measurements of the recovery ability of "stored" Avicel RC 591 dispersions at 1%, 1.5%, and 2% loadings.

time to be allowed for samples to reach the equilibrium stage in their hydrogel structure development.

3.3. Interactions between MCC and Na-CMC in mixed compositions in water

The shear thinning behaviour of the dispersions and solutions, at various loadings of MCC and Na-CMC, over a range of 0.1–1000s^{-1}, was monitored. All of the measurements were taken after two weeks of storage to enable the system to achieve equilibrium. Fig. 4(a) shows that there is a relatively independent relationship between the shear rate and the viscosity, when the loading of the Na-CMC is at 0.1% or 0.15%. These solutions can be considered to be Newtonian in type over the shear rate range that was covered. The situation changes if the loading of the polymer in solution is increased to 0.2%. This increased loading brings about shear thinning behaviour to the solution, indicating that the polymer chains were initially somewhat entangled. The critical range in the loading of the Na-CMC, with respect to changes in the interactions, is between the 0.15% and 0.2%. In this instance, this critical loading is the loading that leads to gel forming in the Na-CMC/water system. This point is important when considering hydrogel formation involving Avicel RC 591. This is because the stabilising component of the Avicel RC 591 is Na-CMC.

Fig. 4(b) gives the results of a study of the viscosity of formulations containing different amounts (0.85–5%) of MCC, in aqueous suspensions. In the range from 0.85% to 1.8%, the viscosities of the suspensions, at 1000s^{-1}, are similar to that of water. The shear viscosity increased as the loading increased. The shear thinning profile of 5% MCC showed a similar trend to that obtained with Avicel RC 591 (1.5%), Fig. 4(c). However, the dispersion of Avicel RC 591 (1.5%) only contained 1.35% of MCC. In addition, a significant difference in the flow behaviour was observed within the dispersion of Avicel RC 591 (1.5%), the solution of CMC (0.15%) and the dispersion of MCC (1.35%), Fig. 4(c). The solution of CMC (0.15%) and the dispersion of MCC (1.35%) are typical the loadings of the individual components in Avicel RC 591 (1.5%). This synergy in behaviour between the Na-CMC and the MCC is significant because it helps promote the networking structure of the MCC in stabilising the system.

However, at similar loadings, not all the combinations of Na-CMC and MCC give significant changes in rheological properties. Fig. 4(d) provides a comparison of the behaviour arising from the three compositions of mixtures of MCC and Na-CMC, at a total loading of 1.5%. These are the mixtures of the MCC system and the Na-CMC system, the commercial Avicel 591 and SD(Na-CMC + MCC). These three compositions contain a similar ratio of Na-CMC and MCC (1:9). However, they give significantly different rheological profiles, implying that the interactions within these three systems are different. These interactions determine the physical behaviour of the hydrogels that are formed in these three systems. This physical behaviour demonstrates significance differences that depend on the composition and on the method of assembly.

The results that were acquired from the rheological study of the mixture of MCC (1.35%) + Na-CMC(0.15%), Fig. 4(d), show the effect of the combination of the Na-CMC (0.15%) solution, Fig. 4(c) with the MCC (1.35%) dispersion, Fig. 4(c). In addition, the SD (Na-CMC + MCC) sample (a dispersion of the spray dried mixture of the CMC and the MCC (1.5%)) shows the typical increased viscosity at lower shear rates. These viscosities were still significantly less than those of dispersions of samples of Avicel RC 591, indicating that the interaction between the Na-CMC and MCC influences the initial viscosity of the Avicel RC 591 suspension. The greater that this extent of interaction is, the greater is the initial viscosity. The extent of interaction is influenced by the form of the composition which is, in turn, influenced by the manufacturing process associated with the production of Avicel RC 591. These three types of suspension gave similar viscosity behaviour at relatively high shear rates, indicating that the interactions between the polymer and aqueous medium are dominant at high shear rates. Among these three samples, the greatest synergism is given by the commercial mixture of Na-CMC and MCC (Avicel RC 591).

It is clear that the rheological characteristics of the fluid systems under investigation owe much to the nature and to the strength of the intermolecular forces that operate under the test conditions and during processing. This is a point that has been raised by several research groups that have shown an interest in the characteristics of MCC–water combinations and MCC–CMC combinations. In several in depth studies, Watanabe et al. (2006a,b,c,d) have used spectroscopic methods (attenuated, total reflectance I.R. spectroscopy in different modes) to establish the nature of the relationship between the structural features of MCC and pertinent hydrogen bonded interactions. It is these interactions that have a significant impact on the rheological observations made in the current study and referred to above. Thus, Watanabe et al. (2006b,d) showed that in MCC–water compositions the hydrogen bonding interactions are stabilised by interchain H-bonds and that drying induces changes in the nature and the magnitude of the H-bonding

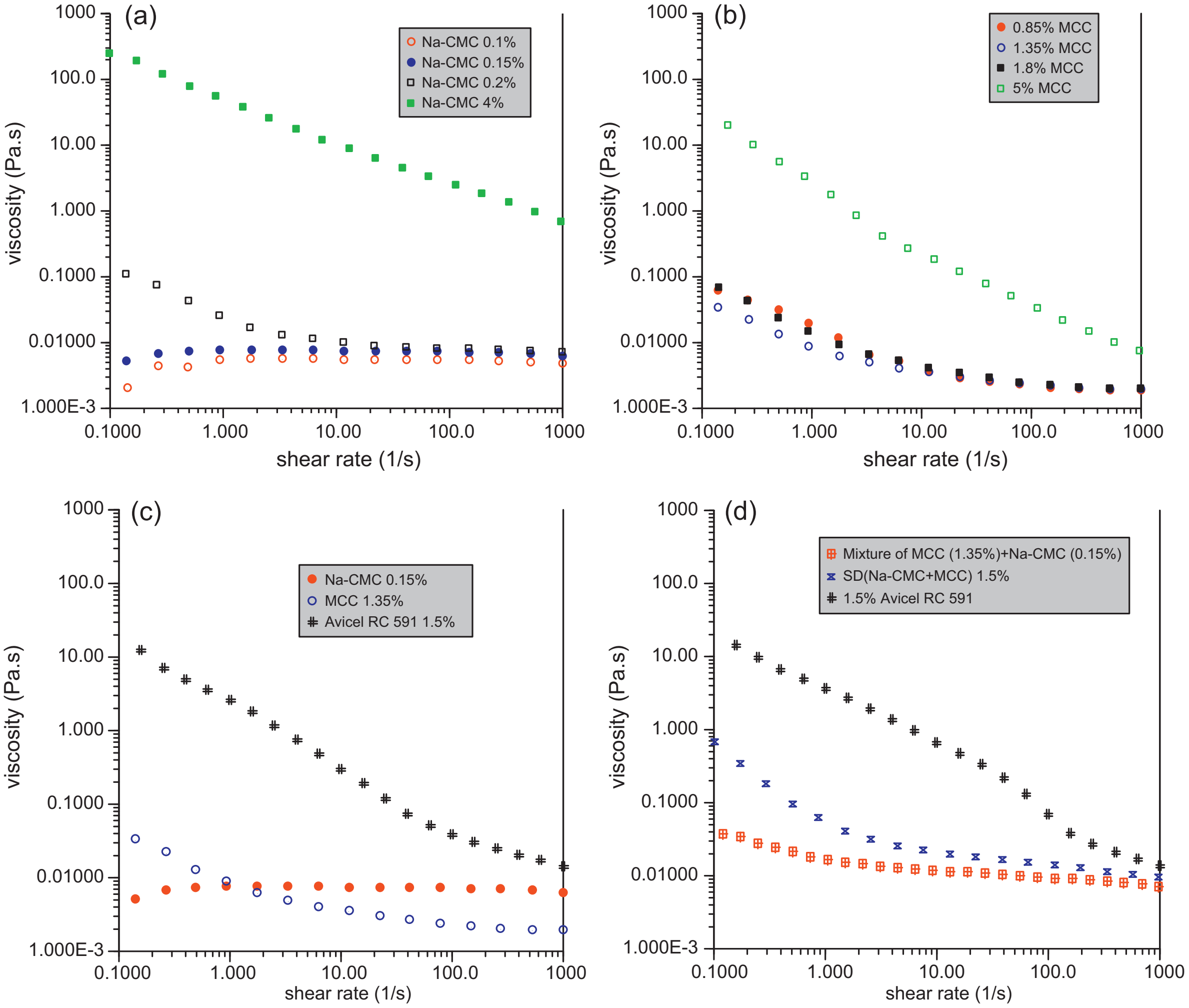

Fig. 4. The comparisons of the shear thinning profiles of the specified samples: (a) Na-CMC aqueous solutions at 0.1%, 0.15%, 0.2% and 4%, (b) MCC aqueous suspensions at 0.85%, 1.35%, 1.8% and 5%, (c) Na-CMC at 0.15%, MCC at 1.35%, and the dispersion of Avicel RC 591 at 1.5%, and (d) different combinations of MCC and Na-CMC.

network in the MCC, Watanabe et al. (2006a,c). Studies of adsorption and conformational changes in CMC, at solid–liquid (including water) interfaces have been reported by Wang and Somasundaran (2005). In their study, the authors approached their major objective using spectroscopic and atomic force microscopic techniques, supported by other related techniques. The overall conclusion that was drawn was that the results suggested that the main driving forces for CMC interactions were a combination of electrostatic interaction and hydrogen bonding. Thus, hydrophobic interactions were not the dominant source of the effects that arise through such interactions. One such effect is seen in the rheological behaviour of fluids that contain polymers such as MCC and CMC, coupled with other components. These intermolecular forces also have a marked influence on the behaviour of particle dispersions within varied shearing regimes, in drying, and in re-dissolution.

3.4. Particle dispersion characteristics

Fig. 5 gives confocal microscopy images of the dispersion of the MCC (5a), commercial Avicel RC 591 (5b), and SD (Na-CMC + MCC) (5c). Fig. 5(a) illustrates aggregates that were formed by the MCC particles after the settling of the dispersion. The stabilising function of the Na-CMC can be appreciated by comparing Fig. 5(a) for the MCC dispersion, with Fig. 5(b), for the Avicel RC 591, and Fig. 5(c), for SD (Na-CMC + MCC). Fig. 5(b) and (c) shows that the particles are uneven in their distribution. There is a lack of detail concerning the small particles due to the magnification limits of the confocal microscope that was used.

Scanning electron microscopy (SEM) was used to ascertain any differences between the dispersions of commercial Avicel RC 591 and of SD (Na-CMC + MCC). Fig. 6(a) and (b) shows the SEM images of the dried dispersions of the commercial Avicel RC 591 and of SD (Na-CMC + MCC). Differences with respect to the nature of the film surfaces that were formed from those two dispersions were observed. Fig. 6(a) presents a network of the needle shaped particles of MCC. The pores shown in Fig. 6(a) have an average diameter of approximately 30 nm. Such topographical character would support the development of a network structure in wet dispersions of this type of polymer composition. Water molecules and any particles smaller than 30 μm in diameter in the wet dispersion could flow through those pores. Fig. 6(b) suggests that there are "needle shaped" MCC particles at the surface that is smoother and less structured than that shown in Fig. 6(a). That implies that a lesser network structure is built in the dispersion of SD(Na-CMC + MCC). This network could be compromised by the drying process.

3.5. Particle sizing study

The dynamic light scattering (DLS) technique (large angle) was used to detect the particle size distribution of small particles in the dispersions without interference from the larger particles on the distribution. Fig. 7 shows the results from the 150° detection of the

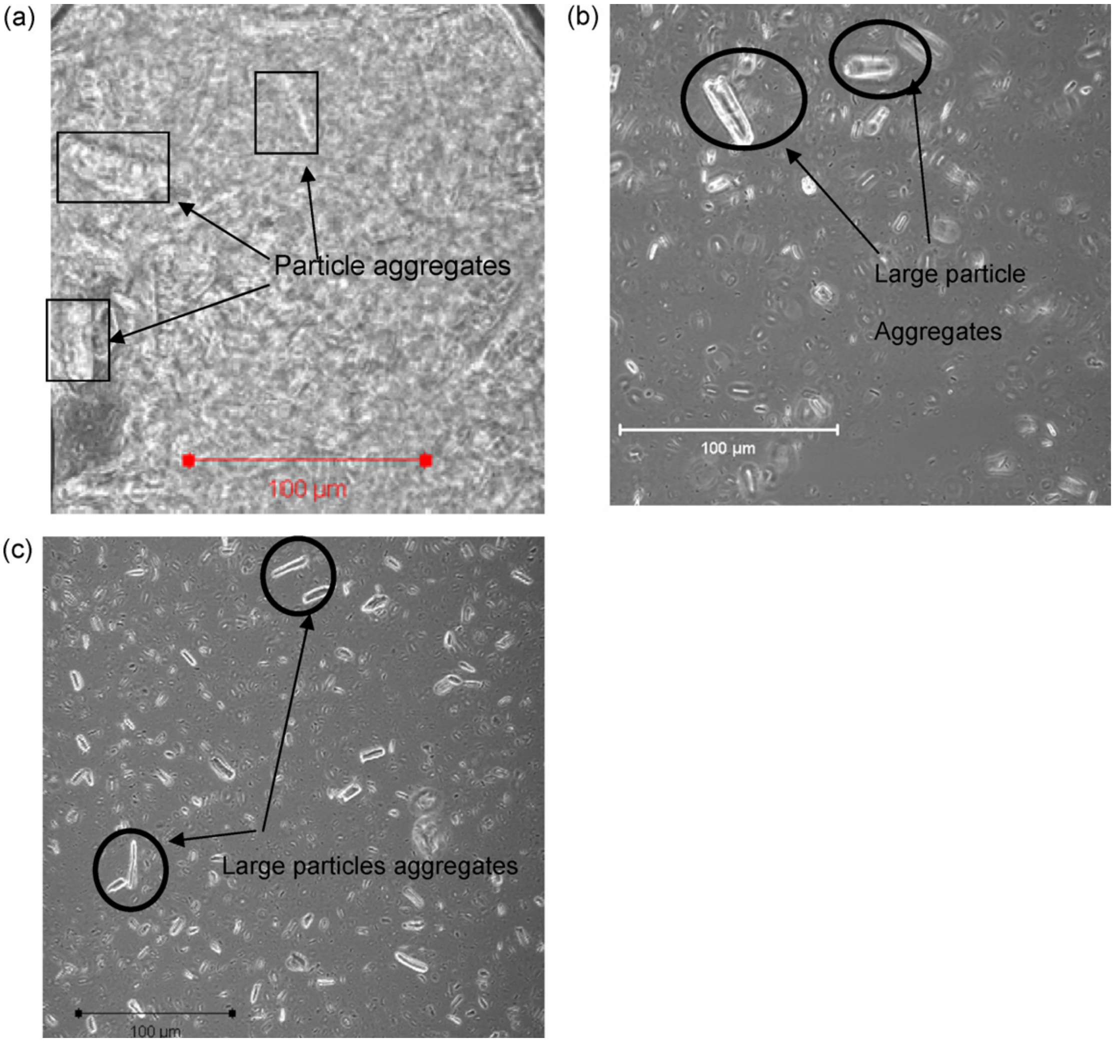

Fig. 5. Confocal laser scanning microscopy images: (a) a 1.8% dispersion of MCC in an aqueous medium, (b) a 1.5% Avicel RC591 dispersion in an aqueous medium, and (c) a dispersion of 1.5% SD (Na-CMC + MCC) in an aqueous medium.

dynamic laser light scattering by dispersion of the MCC, MCC + Na-CMC, Avicel RC 591, and SD (Na-CMC + MCC). Avicel RC 591 has a wider particle size distribution and smaller particle size than that of the other samples (mainly around 90–200 nm). The average particle size values of SD (Na-CMC + MCC), MCC + Na-CMC and MCC are 300 nm, 400 nm, and 500 nm, respectively. Dispersions of the commercial formulation, Avicel RC 591, contain 30% of particles that are less than 100 nm in size, Fig. 7. These could be the source of the contribution to the stabilisation of the 3D network structures that are formed by MCC and Na-CMC. The formed structures give a

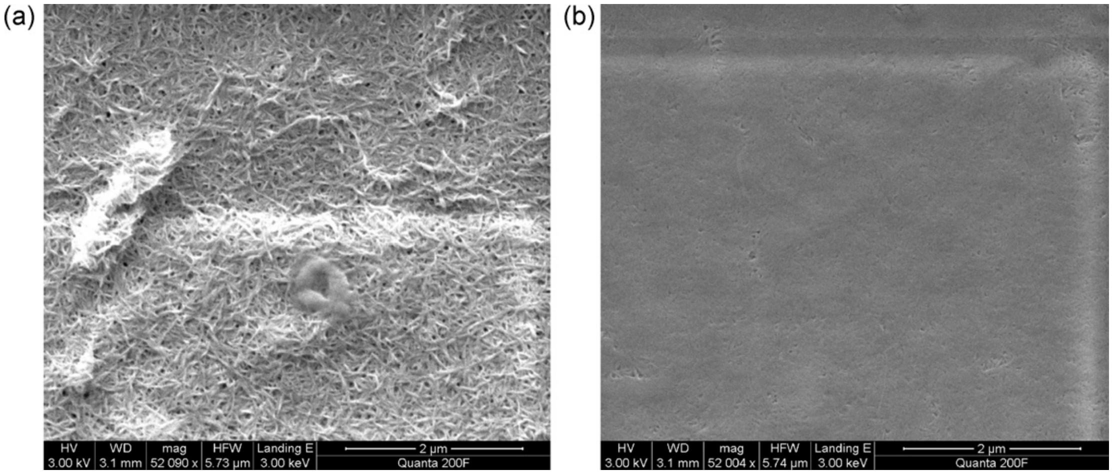

Fig. 6. The high resolution SEM images of the dried films of the following samples: (a) Avicel RC591 dispersion and (b) laboratory made SD (Na-CMC + MCC).

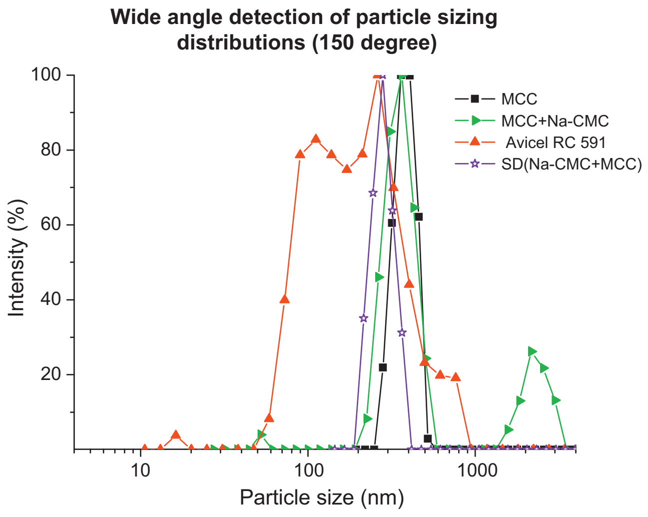

Fig. 7. The dynamic laser light scattering results of MCC, MCC + Na-CMC, Avicel RC 591 and SD (Na-CMC + MCC).

storage modulus of 2 Pa for a typical 1.5% dispersion. Such a storage modulus would be of help in stabilising the particles in the suspension. The dispersions formed from MCC, MCC + Na-CMC, SD (Na-CMC + CMC) show limited stability, with respect to standard storage conditions, relative to the stability provided by formulations of Avicel RC 591. This is because the formed structures are weak, compared to those in Avicel RC 591. Thus, the presence of networks in commercial grades of MCC + Na-CMC (Avicel RC 591) improves the stabilising action of the Avicel RC 591 dispersion.

4. Conclusions

MCC is widely used in pharmaceutical formulations as a suspending agent. The physical interactions that occurred during hydrogel formation, breakup, and recovery have been studied rheologically. Intermolecular interactions, including hydrogen bonding and ionic interactions play an important role in these processes. Dispersing Avicel RC 591, a commercial mixture of MCC and Na-CMC in water gives rise to hydrogels, having a 3D network structure. The network structure has been visualised by SEM and detected by DLS. The strength of the interaction between the Na-CMC and the MCC and the effect of this on hydrogel formation and stability has been identified by comparison of the commercial Avicel RC 591 with the laboratory formulated equivalent, SD (MCC + Na-CMC). The differences in the microscopic appearance, the morphology and the dispersion properties arise from the specific manufacturing process.

Acknowledgment

The authors acknowledge the valued contributions made by the EPSRC (Dorothy Hodgkin award for G.H.Z).

References

Avicel RC/CL, 1995. Specifications and Analytical Methods. FMC Biopolymer, Princeton, USA.

Badawy, S.I.F., Gray, D.B., Hussain, M.A., 2006. A study on the effect of wet granulation on microcrystalline cellulose particle structure and performance. Pharm. Res. 23, 634–640.

Barrista, O.A., 1961. Level-off D.P. Cellulose product, U.S. P. 2978446 (ed.), USA.

Biopolymer, F., 2008. FMC Microcrystalline Cellulose.

Durand, H.W., 1970. Dispersing and stabilizing agent comprising glucan and CMC and method for its preparation. U. S. P. 3539365 (ed.) United States Patent Office, USA.

European Pharmacopoeia, 2008b. ISBN: 10: 9287160546.

Hebeish, A.A., Guthrie, J.T., 1981. The Chemistry and Technology of Cellulosic Copolymers. Springer Verlag, New York, Heidalberg, ISBN: 10: 0387101640.

Kennedy, J.F., 1995. Cellulose and Cellulose Derivatives, Physical Chemical Aspents and Industrial Applications. Woodhead Publishing, ISBN: 10: 1855732122.

Manning, C.S., 1985. The interaction of cellulose and model compounds with N-methyl morpholine N-oxide. Ph.D. Thesis, University of Leeds, Leeds, LS2 9JT, UK.

Mihranyan, A., Edsman, K., Stromme, M., 2007. Rheological properties of cellulose hydrogels prepared from Cladophora cellulose powder. Food Hydrocolloids 21, 267–272.

Pramanik, A., Chowdhur, Y., 1969. Degradation of Na amylose xanthate in dilute caustic soda solution during ripening. J. Polym. Sci. Part a-1-Polym. Chem. 7, 1055–1073.

Rowe, R.C., Sadeghnejad, G.R., 1987. The rheology of microcrystalline cellulose power water mixes-measurement using a mixer torque rheometer. Int. J. Pharm. 38, 227–229.

Rudraraju, V.S., Wyandt, C.M., 2005a. Rheology of microcrystalline cellulose and sodiumcarboxymethyl cellulose hydrogels using a controlled stress rheometer. Part II. Int. J. Pharm. 292, 63–73.

Rudraraju, V.S., Wyandt, C.M., 2005b. Rheological characterization of microcrystalline cellulose/sodiumcarboxymethyl cellulose hydrogels using a controlled stress rheometer. Part I. Int. J. Pharm. 292, 53–61.

Sharpe, S.A., Sandweiss, V., Tuazon, J., Giordano, M., Witchey-Lakshmanan, L., Hart, J., Sequeira, J., 2003. Comparison of the flow properties of aqueous suspension corticosteroid nasal sprays under differing sampling conditions. Drug Develop. Ind. Pharm. 29, 1005–1012.

Suzuki, T., Kikuchi, H., Yamamura, S., Terada, K., Yamamoto, K., 2001. The change in characteristics of microcrystalline cellulose during wet granulation using a high-shear mixer. J. Pharm. Pharmacol. 53, 609–616.

United States Pharmacopeia–National Formulary (USP–NF), 2008a. U.S. Pharmacopeia, ISBN: 10:1889788694.

Walkling, W.D., Shangraw, R.F., 1968. Rheology of microcrystalline cellulose–carboxymethyl cellulose gels. J. Pharm. Sci., 57.

Wang, J., Somasundaran, P., 2005. Adsorption and conformation of carboxymethyl cellulose at solid–liquid interfaces using spectroscopic, AFM and allied techniques. J. Colloid Interface Sci. 291, 75–83.

Watanabe, A., Morita, S., Ozaki, Y., 2006a. Study on temperature-dependent changes in hydrogen bonds in cellulose I beta by infrared spectroscopy with perturbation-correlation moving-window two-dimensional correlation spectroscopy. Biomacromolecules 7, 3164–3170.

Watanabe, A., Morita, S., Ozaki, Y., 2006b. A study on water adsorption onto microcrystalline cellulose by near-infrared spectroscopy with two-dimensional correlation spectroscopy and principal component analysis. Appl. Spectrosc. 60, 1054–1061.

Watanabe, A., Morita, S., Ozaki, Y., 2006c. Temperature-dependent structural changes in hydrogen bonds in microcrystalline cellulose studied by infrared and near-infrared spectroscopy with perturbation-correlation moving-window two-dimensional correlation analysis. Appl. Spectrosc. 60, 611–618.

Watanabe, A., Morita, S., Kokot, S., Matsubara, M., Fukai, K., Ozaki, Y., 2006d. Drying process of microcrystalline cellulose studied by attenuated total reflection IR spectroscopy with two-dimensional correlation spectroscopy and principal component analysis. J. Mol. Struct. 799, 102–110.

Zhu, S., Wu, Y., Chen, Q., Yu, Z., Wang, C., Jin, S., Ding, Y., Wu, G., 2006. Dissolution of cellulose with ionic liquids and its application: a mini-review. Green Chem. 8, 325–327.

Zietsman, S., Kilian, G., Worthington, M., Stubbs, C., 2007. Formulation development and stability studies of aqueous metronidazole benzoate suspensions containing carious suspending agents. Drug Develop. Ind. Pharm. 33, 191–197.