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European Journal of Pharmaceutics and Biopharmaceutics 59 (2005) 333–342

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Viscoelastic and structural properties of pharmaceutical hydrogels containing monocaprin

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Received 4 March 2004; accepted in revised form 30 July 2004
Available online 2 October 2004

Abstract

The purpose of this study was to characterize the rheological and structural properties of a pharmaceutical multicomponent hydrogel formulation. This formulation consists of a hydrogel-forming poly(acrylic acid) polymer (Carbopol® 974P), microbicide (monocaprin), non-ionic surfactant (Tween® 20 or Tween® 40), and preservatives. The effects of surfactant addition, monocaprin concentration, and pH on the formulation are investigated with the aid of various rheological methods and small angle neutron scattering (SANS). A change of pH from 4 (reduced electrostatic interactions) to higher pH values (prominent electrostatic forces) resulted in a marked impact on both the structural and rheological characteristics, with higher values of the dynamic moduli. At pH 4, the rheological features were strongly influenced by the addition of surfactant and monocaprin concentration, whereas at higher values of pH the effect of additives was modest. The picture that emerges from SANS and rheology is that enhanced association structures evolve at pH 4, while at higher pH the tendency to form associations is inhibited. At all the conditions, the rheological results suggest a viscoelastic solid behavior, which is typical for many gels.

Keywords: Monocaprin; Hydrogel; Rheology; SANS; Pharmaceutical formulation; Drug

1. Introduction

The use of bioadhesive polymers in the formulation of dosage forms for mucosal drug delivery has received increasing attention in recent years. Bioadhesive polymers ensure a large area of contact with the surface and prolonged residence time at the site of administration of the active compound [1–4]. Poly(acrylic acid) polymers belong to this family of substances and are extensively utilized in pharmaceutical formulations because of their hydrophilic nature, biocompatibility and great mucoadhesive strength [5,6]. In this work, we have chosen an anionic polyacrylic derivative (the chemical structure is given in Fig. 1), Carbopol® 974P (p$K_a \approx 4.5$) [7], in which the degree of ionization depends significantly on the pH of the media. Carbopol is a loosely cross-linked poly(acrylic acid) with allylsucrose or allylpentaerythriol as cross-linking agent. This polymer has been widely used as a thickener in pharmaceutical formulations [8], and in the semidilute concentration regime it may form a hydrogel in water or in alkaline solution due to the ionization of the carboxylic groups.

In a study [9] of the interaction of carbopols with surfactants it was reported that the addition of a small amount of a non-ionic surfactant in carbopol dispersion could alter the polymer structure and the viscosity of the system. Both hydrophobic interactions and electrostatic forces may be responsible for this effect. It has been argued [10] that the surfactant–polymer binding occurs mainly through a stoichiometric hydrogen-bonding interaction between the oxyethylene and carboxylic groups.

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doi:10.1016/j.ejpb.2004.07.011

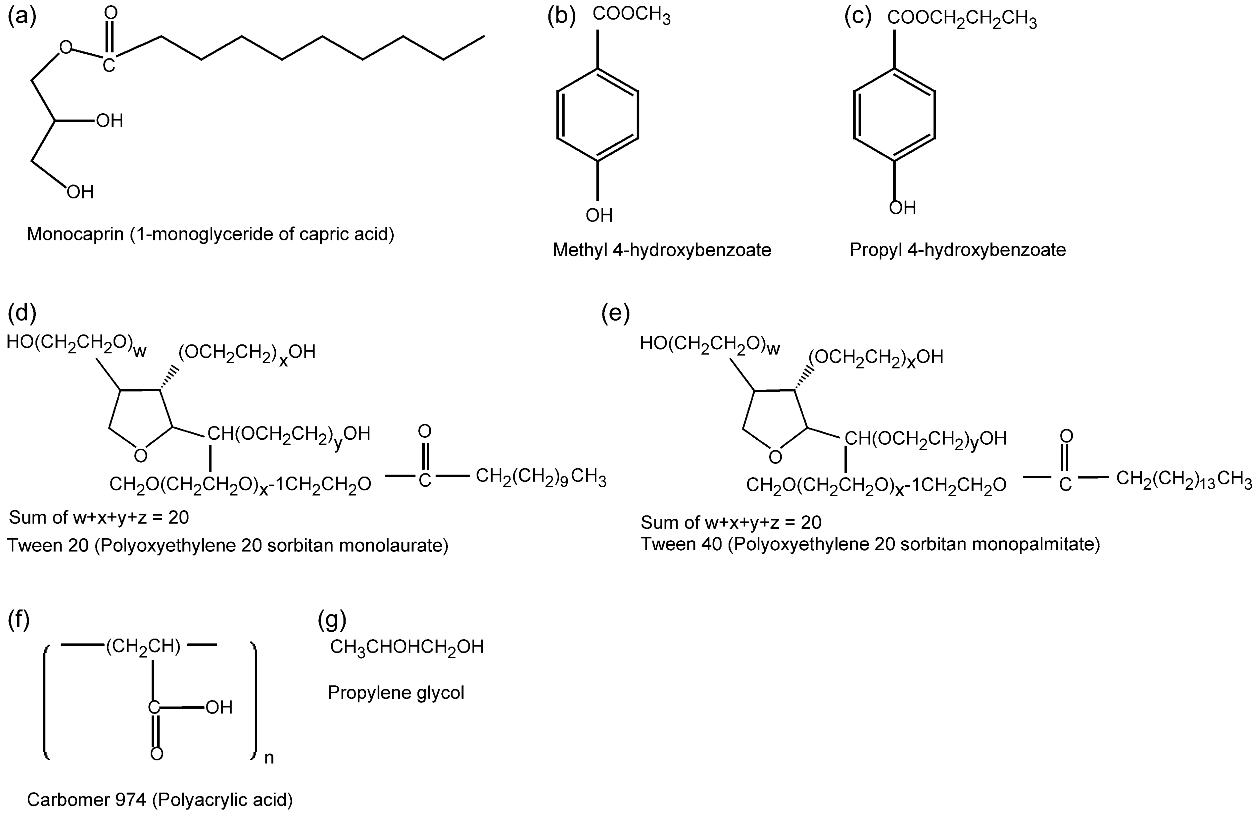

Fig. 1. Chemical structures of the components in the pharmaceutical formulation.

This suggests that the addition of surfactant can be used to modulate the rheological and structural features of the carbopol–water system, and the gel network can be tailor made for a special task. Furthermore, the properties of the carbopol gel-network can be tuned in the presence of the co-solvent propylene glycol, which is known [11] to interact with the polymer.

The multicomponent systems, or pharmaceutical formulations that will be examined in this work have been developed with the intention to be used in connection with vaginally administrated drugs for the prevention of sexual transmission of various infectious pathogens [12,13]. For this purpose, the present hydrogel formulations contain the 1-mono-glyceride of capric acid (monocaprin; Mc), which constitutes an efficient microbicide [13] in pharmaceutical formulations. Monocaprin has been reported [13–16] to be effective against different bacteria and virus. This microbicide has a limited solubility in aqueous media, but it is important that the compound is solubilized in a pharmaceutical formulation so that it can be easily and effectively applied on, e.g. vaginal tissue for prolonged drug delivery. It is known that propylene glycol is an effective co-solvent for monocaprin, and by using a mixture of propylene glycol and a non-ionic surfactant it is possible to keep the concentration of co-solvent low in the formulation [17]. To store the pharmaceutical formulations over time, it is also necessary to add preservatives to the systems. The use of the polysorbates and monocaprin as ingredients in the present formulations is the result of years of experiments [14,17] in developing highly active antibacterial and antiviral dosage forms.

The hydrogel formulations that are investigated in this paper are multicomponent systems, consisting of a polymer gel matrix (Carbopol® 974P), microbicide (monocaprin), co-solvent (propylene glycol), non-ionic surfactant (Tween® 20 or Tween® 40), and preservatives (a mixture of methyl-4-hydroxybenzoate and propyl-4-hydroxybenzoate). The chemical structures of these components are all given in Fig. 1. The reason for choosing this complex multicomponent system is that we wish to be close to the conditions that are encountered in the pharmaceutical drug administration. In the experiments, the non-ionic surfactant is changed (Tween® 20 or Tween® 40) and the concentrations of the different components are kept fixed, except for the concentration of monocaprin that is altered. In addition, the effect of pH of the formulation is studied, because the pH of vaginal fluid ranges from 3.7 to 6.3 [18] and when semen is mixed with the vaginal fluid, the pH in the vagina increases to 7–8 [1]. In the light of this, it is worthwhile to scrutinize the effect of pH.

The aim of the present work is to elucidate the effects of type of non-ionic surfactant, concentration of monocaprin and pH on the rheological and structural features of a multicomponent pharmaceutical formulation. For this purpose, we have carried out oscillatory shear, viscosity, stress relaxation and a few small angle neutron scattering (SANS) experiments on the formulation under various conditions. Knowledge of rheological and structural characteristics may assist in improving the properties of pharmaceutical formulations, because the rheological and structural features of the system are essential for the effect of mucoadhesion [6] and vaginal applications. Furthermore, insights into rheological and morphological behaviors of hydrogel systems can also be helpful in the process of predicting which of the hydrogels can retain their structural stability over time. For a multicomponent system of this type, it is of course possible to change various components and to alter the concentrations of the ingredients and these variations may affect both the rheological and structural properties of the system. However, to mimic the conditions that will prevail for the pharmaceutical formulations in progress, we have kept most of the components and concentrations fixed.

2. Materials and methods

2.1. Materials

The gel-forming polymer Carbopol® 974P was provided by BFGoodrich Europe, UK. The two non-ionic surfactants: polyoxyethylene 20 sorbitan monolaurate (Tween® 20) and polyoxyethylene 20 sorbitan monopalmitate (Tween® 40) were both purchased from Sigma Chemical Co., St Louis, USA. The surfactants were fresh and of pharmaceutical grade and they were stored at 4 °C. The microbicide 1-monoglyceride of capric acid (monocaprin) was obtained from Danisco Ingredients, Denmark. The total concentration of the preservative agent was 0.1 wt%, and it consists of a mixture of methyl-4-hydroxybenzoate (0.08 wt%)/propyl-4-hydroxybenzoate (0.02 wt%), which both were purchased from NMD, Norway. The co-solvent propylene glycol was also obtained from NMD, Norway.

2.2. Methods

2.2.1. Preparation of hydrogels

Hydrogels containing different amounts of monocaprin were formed by allowing 0.65 wt% of Carbopol® 974P to swell in water for 24 h, before an aqueous mixture of the non-ionic surfactant (Tween® 20; 1 wt% concentration, or Tween® 40; 0.4 wt% concentration), propylene glycol (5 wt% concentration), monocaprin, and preservative agent (total concentration of 0.1 wt%) were exposed to the gel under gentle stirring. All the samples were stirred for the same period of time. The difference between Tween® 20 and Tween® 40 is that the number of carbon atoms is larger for the latter one (see Fig. 1) and this surfactant is more hydrophobic and less water-soluble. This is partly the reason for the higher concentration of Tween® 20 as compared to Tween® 40. Furthermore, the chosen concentration of each surfactant was also determined by the criterion that the antiviral and antibacterial effects [17] of the hydrogel formulation should not be affected. In the experiments, the concentrations of all the components, except for monocaprin, were kept constant. The pH of the formulation is approximately 3.5, and pH of the system was adjusted by dropwise addition of a small amount of 1 M NaOH. Finally, the formulations are centrifuged in a centrifuge for 1 h to remove air bubbles. In addition, all the hydrogels have been checked with HPLC for the assay of the active substance monocaprin. To check the reproducibility of the measurements for different manufacture of the hydrogels, one hydrogel was prepared twice and measured in the rheometer. The results were identical. To check possible time effects, the rheological measurements on some gels were repeated after several weeks but no change of the rheological characteristics was observed.

2.2.2. Rheology

Oscillatory shear, viscosity, and stress relaxation measurements were performed in a Paar-Physica MCR 300 rheometer using a cone-and-plate geometry, with a cone angle of 1° and a diameter of 75 mm. The formulation was applied on the plate and to prevent dehydration from the gel-like sample, the free surface of the sample was always covered with a thin layer of low-viscosity silicone oil (the viscoelastic response of the sample is not observed to be affected by this layer). The measuring device is equipped with a temperature unit (Peltier plate) that gives a very good temperature control over an extended time. All experiments were conducted at 25 °C.

The values of the strain amplitude were checked to ensure that all oscillatory shear measurements were performed within the linear viscoelastic regime, where the dynamic storage modulus (G') and loss modulus (G'') are independent of the strain amplitude. The oscillating sweep measurements were carried out in the approximate angular frequency (ω) domain 10–100 rad/s.

The shear viscosity experiments were carried out over an extended shear rate range (covering both the linear and nonlinear viscoelastic regimes). The shear rate dependence of the viscosity was usually registered as a function of increasing shear rate. To investigate possible hysterises effects, the shear rate dependence of the viscosity of the systems was monitored as a function of increasing shear rate (up-ramp curve), and the subsequent decline in shear rate (down-ramp curve) was also probed. Between measurements, the sample was allowed to equilibrate for some time before the experiments were commenced. No significant hysteresis effects were detected under the considered experimental conditions, and the up-ramp curve and the down-ramp curve coincided.

In a stress relaxation experiment, the sample is subjected to a rapid applied small strain, which is held constant for the remainder of the experiment, and the decay of stress in the viscoelastic material is monitored as a function of time. From this type of measurement, the stress relaxation modulus $G(t)=\sigma(t)/\gamma_0$, the ratio of stress to the constant strain, can be determined.

2.2.3. Small angle neutron scattering (SANS)

The SANS measurements were performed at the SANS installation (beam port 2) at the IFE reactor at Kjeller, Norway. The wavelength was set by means of a selector (Dornier), using a high FWHM for the transmitted beam ($\Delta\lambda/\lambda=20\%$), and maximized flux on the sample. The distance varied from 1.0 to 3.4 m and the wavelength between 5.1 and 10.2 Å, giving a wavevector (q) range from 0.008 to 0.3 Å^{-1}. The wavevector is given by $q=(4\pi n/\lambda)\sin(\theta/2)$, where θ is the scattering angle and n is the refractive index of the medium.

The gel-like systems were filled in 1 mm quartz cuvettes, which were equipped with a detachable sidewall to facilitate the introduction of the high-viscous samples. To avoid any leakage from the cuvette, a gasket of viton was placed between the sidewalls and this resulted in a pathlength of the cell of 1.5 mm. The measuring cells were placed onto a copper-base for good thermal contact and mounted in the sample chamber. The chamber was evacuated to reduce air scattering.

Standard reductions of the scattering data, including transmission corrections, were conducted by incorporating data collected from empty cuvette, beam without cuvette, and blocked-beam background. When relevant, the data were transformed to an absolute scale (coherent differential cross section ($d\Sigma/d\Omega$)) by calculating the normalized scattered intensity from direct beam measurements [19].

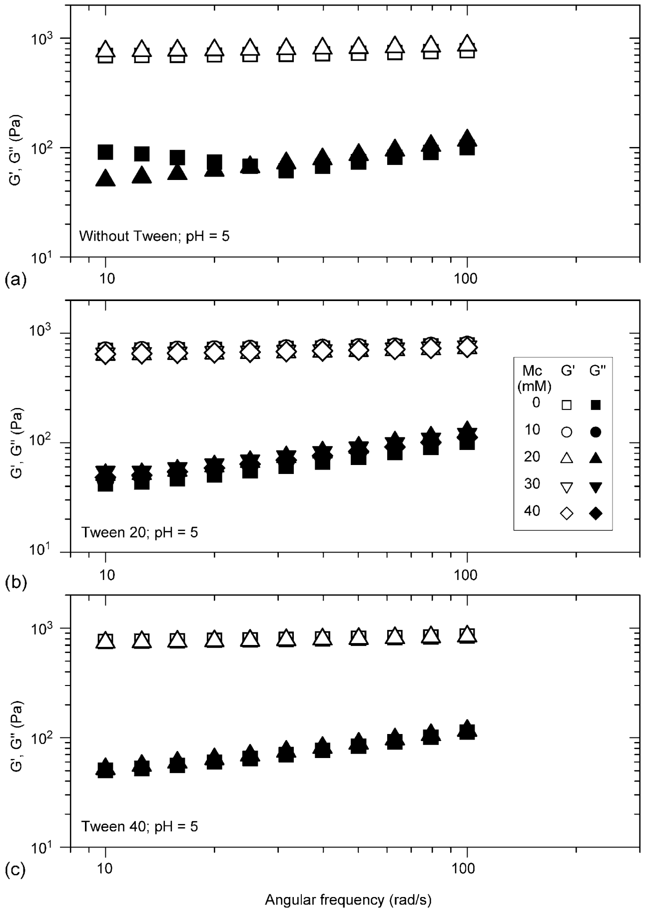

Fig. 2. Angular frequency dependencies of the dynamic moduli for the formulation at a constant pH (pH 5), different concentrations of monocaprin and with and without non-ionic surfactant (Tween® 20 or Tween® 40). The open and solid symbols represent G' and G'', respectively.

3. Results and discussion

3.1. Oscillatory shear

The frequency dependencies of the storage modulus G' and the loss modulus G'' for the formulation at a fixed pH of 5, with different levels of added monocaprin, and with and without the non-ionic surfactant (Tween® 20 or Tween® 40) are depicted in Fig. 2. The general trend that emerges at all conditions is that G' is much larger than G'', suggesting that the elastic response dominates, which is typical for gels and solid-like materials. These results indicate that neither the addition of various amounts of the microbicide nor the presence of a non-ionic surfactant seem to affect the dynamic moduli considerably. In the formation of an incipient gel, the delicate interplay between connectivity and swelling of the network governs the characteristics of the gel network. However, for an annealed gel the rigidity of the network has been established, and small amounts of co-solute (monocaprin) and surfactant will probably not influence the rheological properties of the formulation to a large extent. This finding suggests that moderate concentrations of the added microbicide and surfactant will not change the properties of the gel-network significantly. Therefore, the impact on the drug release behavior in the formulation may be modest and should not constitute a problem in the dosage form development.

In Fig. 3, the frequency dependences of G' and G'' at different values of pH are shown for the formulation at a constant concentration (20 mM) of monocaprin, with and without surfactant. At a pH below the pK_a of the polymer (ca. 4.5), the polyelectrolyte effect is expected to be weak, while at higher values of pH, ionization of Carbopol® 974P occurs and the electrostatic repulsive forces become important and swelling of the gel is promoted. This effect can lead to extension of the polymer chains, which may facilitate formation of entanglements and thereby a stronger gel-network. The results in Fig. 3 reveal a conspicuous change of the linear viscoelastic response when pH is altered from 4 to 5. In this case, the values of both G' and G'' are significantly higher at pH 5 than their counterparts at pH 4, indicating reinforcement of the network. In the presence of Tween® 20, the effect of pH change on the dynamic moduli is much stronger than that observed

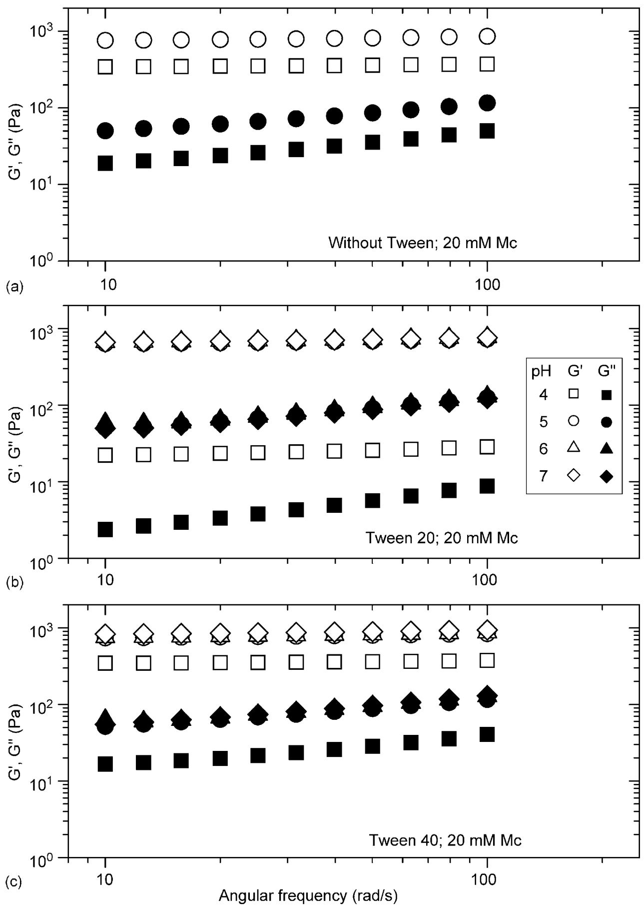

Fig. 3. Angular frequency dependencies of the dynamic moduli for the formulation at a constant concentration (20 mM) of monocaprin at various pH values, and with and without non-ionic surfactant (Tween® 20 or Tween® 40). The open and solid symbols represent G' and G'', respectively.

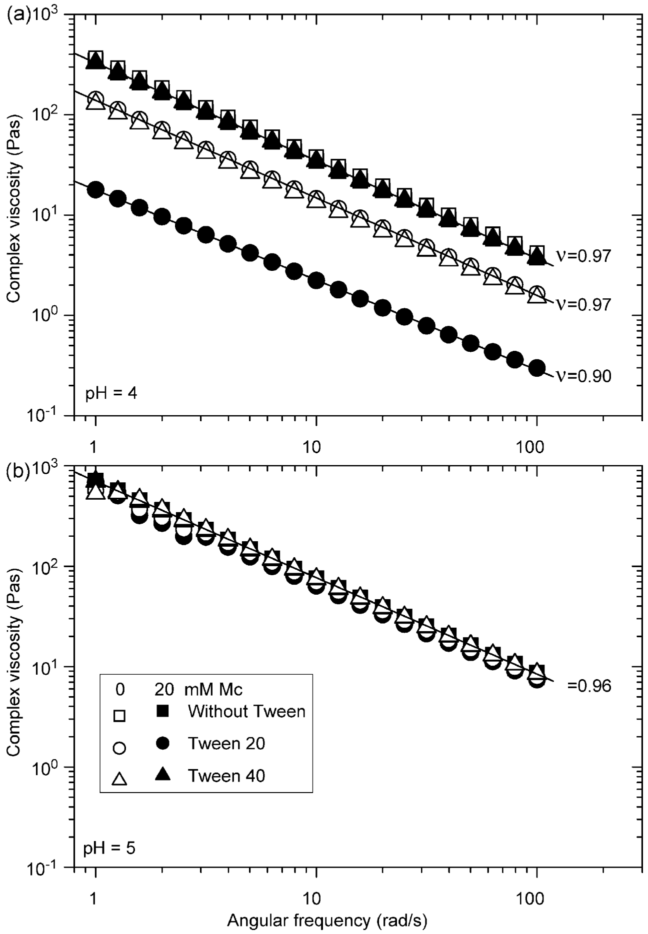

Fig. 4. Angular frequency dependencies of the complex viscosity for the formulation with and without non-ionic surfactant (Tween® 20 or Tween® 40) at pH 4 and 5 in the presence (20 mM) or absence of monocaprin.

with Tween® 40 or without surfactant. This may reflect that Tween® 20 gives rise to a stronger interaction with the polymer than the other surfactant. The structure of the two surfactants is similar, but the longer carbon chains in Tween® 40 make this surfactant more hydrophobic and stronger interactions should be expected. However, the lower concentration of Tween® 40 is probably responsible for the reversed trend. We should note that at pH values above 5, no further impact on the rheological behavior is found, but the data points can virtually be superimposed onto each other (see Fig. 3). This seems to indicate that there is no further pH-induced strengthening of the network.

To gain more information about the viscoelastic characteristics of the formulation at different conditions, it can be worthwhile to examine the frequency dependence of the complex viscosity ($\eta^*(\omega) = (G'^2 + G''^2)^{1/2}/\omega$). It is generally observed that the frequency dependence of the complex viscosity can be described in terms of a power law $\eta^* \propto \omega^{-\nu}$, where ν assumes the values of 0 and 1 for a liquid and a solid, respectively [20]. An illustration of the frequency dependence of η^*, at different pH of the formulation, with and without surfactant, and in the presence and absence of monocaprin, is given in Fig. 4. It is evident that all the data exhibit scaling law behavior in frequency over two decades. At pH 5 all the data points, representing different conditions, practically condense onto each other with a power law exponent $\nu = 0.96$. This suggests that the additives have no noticeable effect on the oscillatory shear rheology at this pH, and the systems exhibit a solid-like response that is typical for gels. At pH 4, a more intricate behavior emerges. The highest values of the complex viscosity and a condensation of the data points with a high value of ν ($\nu = 0.97$) are observed for the formulation in the presence of monocaprin with or without Tween® 40. The lowest values of η^* and the weakest ($\nu = 0.90$) frequency dependence of η^* are found for the formulation in the presence of Tween® 20 and 20 mM monocaprin. The addition of Tween® 20 in the presence of monocaprin at this pH seems to weaken the gel-network and the result is probably a 'softer' gel. In the absence of monocaprin, the data points representing different conditions collapse onto each other with Tween® 20 or Tween® 40 present, and intermediate values of the complex viscosity are displayed, showing a strong ($\nu = 0.97$) frequency dependence of η^*. These results reveal that at conditions where the polymer is practically uncharged, the presence of additives may have a significant impact on the rheological properties. In this case the co-solutes can be employed to tune the characteristics of the gel to a situation desired for a certain pharmaceutical application. It is reasonable to assume that at conditions where the repulsive interactions are suppressed, the system should be more susceptible to form association complexes (cf. the discussion below concerning the SANS results) in the presence of non-ionic additives than for a charged polymer.

3.2. Shear viscosity

In Fig. 5, the shear rate dependencies of the viscosity for the formulation at different monocaprin concentrations, with and without surfactant, are depicted. At all conditions, Newtonian behavior is observed at low shear rates (typically less than 10^{-3} s^{-1}), whereas at higher shear rates a progressive shear thinning occurs, i.e. the intermolecular junctions are disrupted at a rate faster than their rate of reformation, resulting in a decrease in the junction density and hence a drop in the viscosity. Rheological studies [21–23] of associating and gel-forming polymer systems of various natures often reveal shear thinning at much higher shear rates. Since the shear thinning effect for the present systems starts at fairly low shear rates, this seems to indicate that some of the network associations are fragile. Usually, beyond the Newtonian plateau, a monotonous decrease of the shear viscosity with increasing shear rate is observed, but for most of the present systems a more complex profile, with several relaxation stages, of the shear-viscosity curve emerges. The characteristic profile of a curve is reproducible, and even the down-ramp curve exhibits this feature, but we do not yet have a model for an explanation of this peculiar and novel phenomenon. It is only the curve representing the formulation without surfactant and with 20 mM monocaprin that shows a 'normal' shear thinning effect. A close inspection of the curves reveals that at a shear rate of approximately 0.1 s^{-1}, a plateau-like region appears before the viscosity proceeds to fall off. It is possible that the second plateau-like region announces stronger junction zones of the network than those broken up in the first stage, and higher shear rates are needed to disrupt the network structure. This behavior may indicate that the gel network structure is heterogeneous.

Fig. 6 shows the shear rate dependence of the viscosity for the formulation at different pH values in the presence of

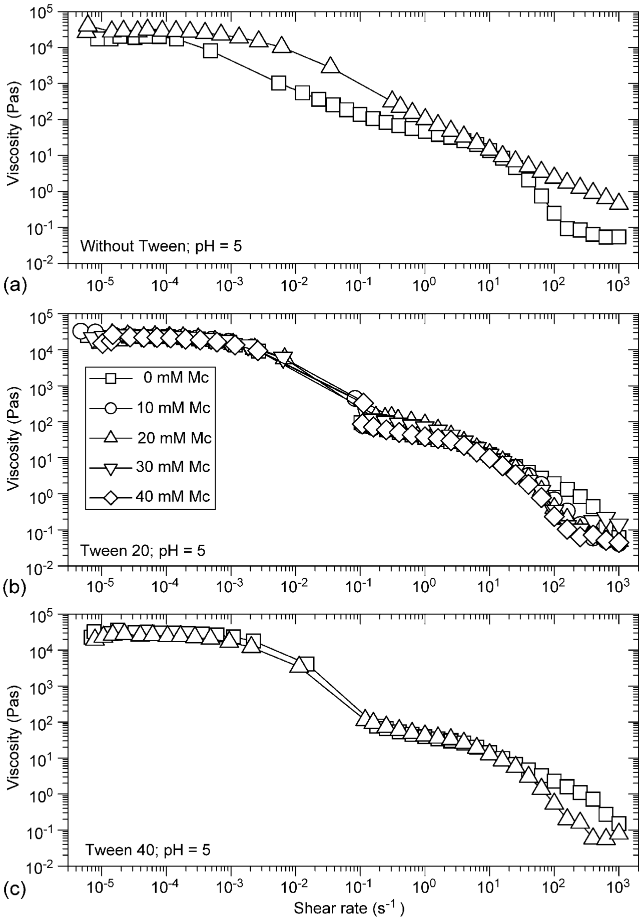

Fig. 5. Shear rate dependencies of the viscosity for the formulation at a constant pH (pH 5), different concentrations of monocaprin and with and without non-ionic surfactant (Tween® 20 or Tween® 40).

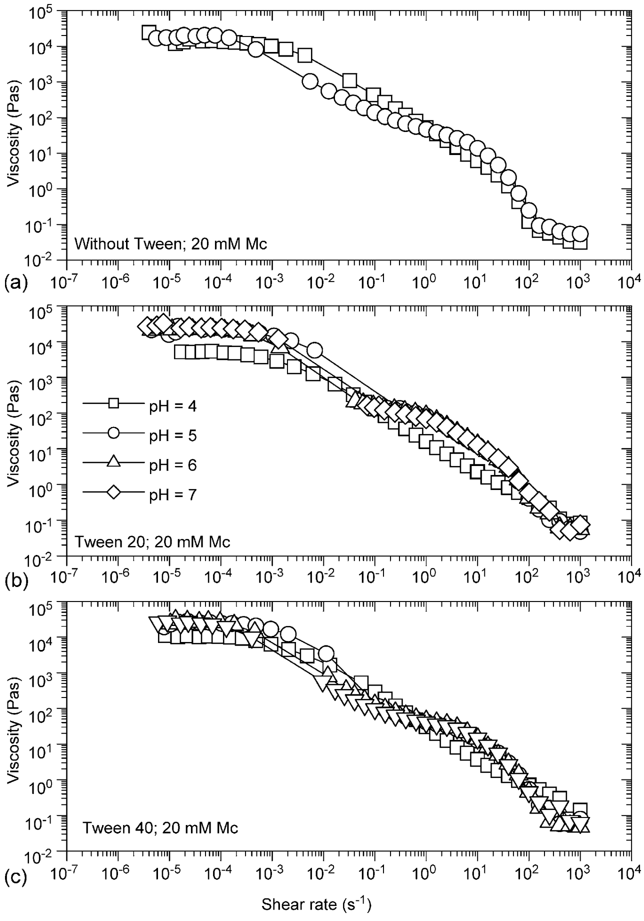

Fig. 6. Shear rate dependencies of the viscosity for the formulation at a constant concentration (20 mM) of monocaprin at various pH values, and with and without non-ionic surfactant (Tween® 20 or Tween® 40).

20 mM monocaprin, with and without surfactant. The general features are similar to those reported in Fig. 5. A salient feature is the lower values of the viscosity at low shear rates at pH 4 in the presence of surfactant. This finding again elucidates that stronger networks are formed at higher values of pH, where electrostatic interactions come into play. The polyelectrolyte effect can give rise to extension of the chains, and this may promote the growth of entanglement couplings.

For many solutions of non-associating polymers, the shear viscosity as a function of shear rate is virtually identical to the complex viscosity as a function of frequency, an empirical finding known as the Cox–Merz rule [24]. Deviations from this rule are frequently reported for more complex polymer systems, such as associating and gelling polymers systems [22,25–27]. Shear viscosity and complex viscosity properties of the formulation at different pH in the presence of non-ionic surfactant (Tween® 20 or Tween® 40), and at a fixed pH of 5.0 at various levels of added monocaprin are shown in Fig. 7 as a function of shear rate or frequency. At all conditions, more or less pronounced deviations from the Cox–Merz superposition rule are found and this type of anomaly has been reported for many associating polymer systems that display shear thinning effects. This behavior probably reflects that steady shear and oscillatory shear induce different types of structural reorganizations [28] of the network. This is a further evidence of that these systems are characterized by complex rheological features.

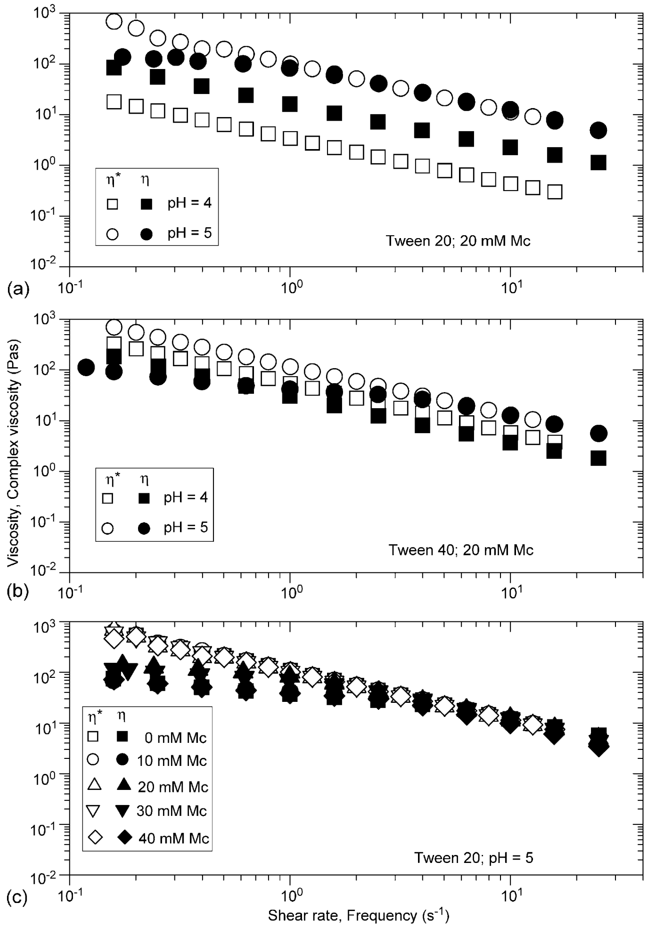

Fig. 7. Shear viscosity compared to the magnitude of the complex viscosity for the formulation at the conditions indicated. See text for more details.

3.3. Shear stress relaxation

The effects of pH and surfactant on the decay of the linear relaxation modulus $G(t)$ (determined from stress relaxation measurements) are depicted in Fig. 8. In the absence of surfactant and monocaprin (Fig. 8a), higher values of $G(t)$ are observed at pH 5, and only a slight relaxation of the modulus is detected at both pH values. The higher values of $G(t)$ found at pH 5, support the finding reported above, namely that a stronger network evolves in the presence of Coulomb interactions. The fact that there is only a very slight decay of the relaxation function, suggests an enhanced elastic response and viscoelastic solid behavior [29]. Our conjecture is that the gel-network is rather rigid and because of associations and entanglements it takes time for the chains to relax. A similar trend is observed for the formulation in the presence of Tween® 20 without monocaprin (Fig. 8b), but in this case the effect of pH is larger and a somewhat stronger decay is detected. The most striking feature is observed with the addition of Tween® 40 (no monocaprin) to the formulation at pH 4 (Fig. 8c), where a strong decay of the relaxation modulus is manifested after ca. 1 h. This indicates that after a long time, there is a reorganization of the network structure and junction zones may be disrupted in this process and even the connectivity of the network may be broken. At these conditions of pH (suppressed electrostatic interactions) and surfactant, the results suggest that the network matrix is rather sensitive to external perturbations and it seems that the addition of a small amount of Tween® 40 weakens the network structure.

Figs. 8d and e give a direct illustration of the effects of the non-ionic surfactants at the two different pH values. At pH 4, the addition of surfactant leads to weakening of the elastic response of the system and this effect is very prominent at long times for Tween® 40. These results reveal that the rheological properties of the formulation can be modulated by the addition of a non-ionic surfactant. At pH 5, the electrostatic interactions probably diminish the effect of surfactant addition, and there is only a slight effect at long times when Tween® 20 is added to the formulation.

3.4. Small angle neutron scattering

By using the SANS technique, structural characterization of polymer systems on the nano-scale can be accomplished.

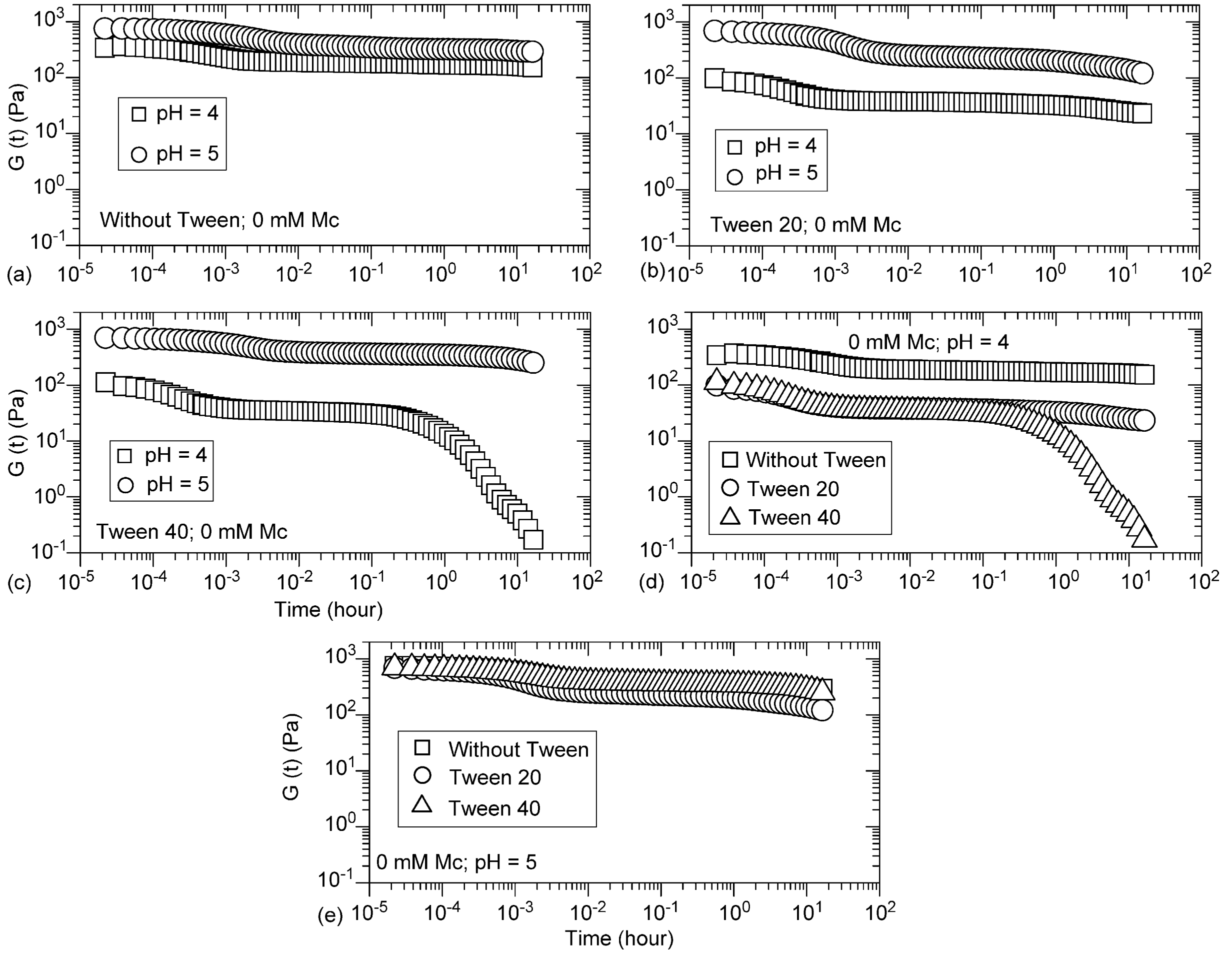

Fig. 8. (a–c) Plot of the shear relaxation modulus versus time for the formulation in the absence of monocaprin at two different pH values, and with and without non-ionic surfactant (Tween® 20 or Tween® 40). (d and e) The same plot at two different pH values. Every second data point is shown in the plots.

This method can provide important information about morphological differences between systems on different length-scales. The rheological results presented above have revealed dramatic changes of the formulation when pH is altered from 4 to 5. To gain more insight into possible pH-induced changes of the network structure when pH is changed from 4 to a higher value, the scattered intensity profiles at two different pH values (representing reduced electrostatic interactions and swollen gel network) for the formulation in the presence of Tween® 20 and 20 mM monocaprin are displayed in Fig. 9. A prominent feature of both curves is the marked upturn of the scattered intensity at low q values (larger length-scales are monitored). This excess scattering is usually attributed to ‘frozen-in’ large-scale heterogeneities [30] in gels. A stronger upturn of the scattered intensity at low q values is observed at pH 4, where the electrostatic repulsive forces are suppressed. This trend is expected, because under these conditions the formulation is more inclined to associate and produce large-scale structural heterogeneities than at pH 6, where repulsive electrostatic forces reduce the tendency to form chain associations. This supports the picture we have resorted to in the interpretation of the rheological results. At high q values (short length-scale; probing local structures), the scattered intensity curves merge into each other and this suggests that the structures are similar on short length-scales (ca. 1 nm).

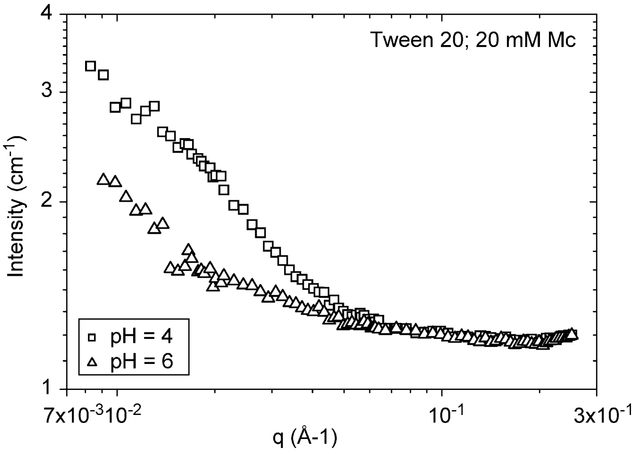

Fig. 9. SANS scattered intensity $I(q)$, plotted versus the scattering vector q for the formulation at two different pH values and in the presence of Tween® 20 and 20 mM monocaprin. See text for more details.

4. Concluding remarks

In this work, rheological methods and SANS were used to evaluate the effects of surfactant addition, monocaprin concentration and pH on the properties of the hydrogel-forming polymer Carbopol® 974P. It was found that a change of pH from 4 to values in the range 5–7 had a distinct effect on both the structural and rheological characteristics. The large-scale structures formed at pH 4 are weakened at higher pH and higher values of the dynamic moduli are favored at higher pH. At pH 4 the rheological features were strongly influenced by the addition of a non-ionic surfactant and monocaprin concentration, whereas at higher pH the effect of additives was modest. The results show that enhanced association structures evolve at pH 4, while at higher pH the tendency to form associations is inhibited due to repulsive forces between the chains. As the pH of the vagina, which is the target for the dosage form, is variable, knowledge of the rheological and structural properties of the hydrogel systems at different pH can assist in improving the pharmaceutical formulations.

These results reveal that the effects of the level of added monocaprin and the type of added nonionic surfactant (Tween® 20 or Tween® 40) are modest, whereas the effect of pH is strong at low pH. The future developments and suggested improvements will probably be the addition of a buffer in the pH 5 hydrogel.

Acknowledgements

This work was supported by grants from the Research Fund of the University of Iceland and the Icelandic Research Council, Students fund. T.O.T. received traveling support from NORFA. B.N. and K.D.K. gratefully acknowledge support from the Norwegian Research Council through a NANOMAT project (158550/431). K.D.K. thanks the Marie Curie Industry Host Project (Contract No. G5TR-CT-2002-00089) for support.

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