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Thermal gelation of aqueous hydroxypropylmethylcellulose solutions with SDS and hydrophobic drug particles

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ABSTRACT

The thermal gelation of hydroxypropylmethylcellulose (HPMC) solutions has been studied as a function of sodium dodecyl sulfate (SDS) concentration with and without griseofulvin, a model particulate BCS Class II drug by rheological measurements of gelation temperature (T_{gel}), steady-state viscosity (η) at 25 °C, and ζ-potential. Polymer adsorption on the drug was demonstrated by a decrease in η and potential in the absence of SDS. Griseofulvin had a synergistic effect on gelation which was attributed to an effective spanning of associated hydrophobic polymeric regions through interactions with the adsorbed polymer. Adding SDS offsets this effect on T_{gel} shielding hydrophobic interactions. Higher SDS concentrations had no effect on the particles surface as evidenced by constant ζ-potential and T_{gel}. Yet, polymeric chains are saturated and larger surfactant aggregates account for the increase in viscosity. Understanding the gelation mechanism and complex interactions of HPMC with surfactants and drugs is necessary for the design of pharmaceutical products and optimization of their performance properties.

1. Introduction

The development of potent and water insoluble drugs has created the need for the development of new drug delivery systems. Amongst the alternatives is the casting of edible biopolymer films in which a solid active ingredient is suspended and physically stabilized in a gel network. The advantages of loaded films over conventional dosage forms, such as tablets, capsules, or solutions, include: fast dissolution providing rapid bioavailability, easy dosification, long-term stability, and fewer formulation components. Nevertheless, they have a low maximum loading due to their poor flavor masking capacity. Also, high concentrations of drug particles can be detrimental to the gelling capacity of the polymer and the mechanical properties of the formulation or final product.

In many of these systems the use of surfactants to stabilize and disperse the solid particles is unavoidable. Surfactants play an important role as dispersing agents improving the separation of particles and promoting long-term stability. The latter are extremely important properties in the development of reproducible homogeneous and stable pharmaceutical products. However, surfactants can interact with polymers, more so if the polymer contains both polar and non-polar functional groups. When surfactants and non-ionic polymers are mixed two competing phenomena take place, either self-aggregation of surfactant molecules to form micelles or interaction of individual surfactant molecules with the monomer units of the polymer chain (Gangopadhyay, Gong, & Osada, 2004).

Self-aggregation into micelles in aqueous media occurs at a characteristic concentration for each surfactant denoted the critical micelle concentration (CMC) (Miller & Neogi, 2007). On the other hand when the surfactant interacts with the polymer, complexes may be formed. Interactions between non-ionic polymers and surfactants are affected by surfactants head group charge and tail length (Brackman & Engberts, 1989). If the surfactant concentration exceeds a characteristic value, polymer–surfactant micelles are produced. This concentration is denoted as the critical aggregation concentration (CAC) and it is lower than the CMC (Griffiths & Cheung, 2002). The presence of a surfactant can affect the physicochemical properties of the product, such as surface tension (Miller & Neogi, 2007), conductivity (Wang, Wei, Chen, & Tsao, 2004), rheological properties (Bu, Kjøniksen, Knudsen, & Nyström, 2005), and optical properties (Lay-Theng, 1999). Consequently, the performance properties, such as release rate, permeability, elasticity, or optical transparency to name a few, are also affected.

Of particular interest to the fore mentioned application is the identification of the interactions of surfactants and polymers, in the absence and presence of active pharmaceutical ingredients (APIs), and their effect on the gelation process. In our current research efforts, the effect of an anionic surfactant on the gelation temperature and viscosity of an aqueous non-ionic polymer solution

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are evaluated by rheological measurements, with and without the particulate griseofulvin. Griseofulvin is a model Biopharmaceutics Classification System (BCS) Class II (i.e. high permeability–low solubility) drug with negligible dissolution in water, $\sim 10^{-5}$ M (Rytting, Lentz, Chen, Qian, & Venkatesh, 2005).

The non-ionic hydroxypropylmethylcellulose (HPMC) was chosen since it is widely used in the pharmaceutical industry as a viscosity modifier and structural constituent for films. HPMC is a biopolymer derived from cellulose in which the hydroxyl groups are replaced by hydroxypropyl and methyl groups. HPMC gels upon heating (Haque & Morris, 1993; Sarkar, 1979). When heated, the mobility of the chains increases. The polymer swells increasing its hydrodynamic volume and exposing its hydrophobic groups. As these groups are exposed structured water cages are formed around them. After further increase of the temperature disrupts the cages, intermolecular hydrophobic groups aggregate to form a percolated network. Due to its more polar character (less hydrophobic than methyl), larger size, and molecular flexibility, increasing amounts of hydroxyprol substituents inhibit intermolecular association increasing the transition temperature (Haque, Richardson, Morris, Gidley, & Caswell, 1993). On the other hand, increased substituent heterogeneity has being reported to promote gelation (Viriden, Larsson, Schagerlof, & Wittgren, 2010). The physical properties of the solutions are significantly altered during the transition. This allows for the determination of thermal transitions by various methods including optical rotation, turbidimetry, differential scanning calorimetry (DSC), and dynamic rheometry, amongst others (Bajwa, Sammon, Timmins, & Melia, 2009; Chen, Lin, & Kang, 2009; Haque et al., 1993; Pérez, Wargon & Pilosof, 2006; Silva et al., 2008).

In general, the gel transition of HPMC is affected by the amphiphilic nature of additives and their charged groups, which cause a disruption of the polymer-bound water cages by a Hofmeister effect. Recently, it was demonstrated that a series of common salts in HPMC follow the order of the Hofmeister effect (Joshi, 2011; Liu, Joshi, & Lam, 2008). To date only a few studies have dealt with the interaction of active drug molecules and HPMC or cellulose derivatives in solution and most of them report on water soluble or poorly soluble drugs. Felbinac (4-biphenylacetic acid) was found to have a negligible effect on the gel transition, while other additives, such as buffering excipients like sodium citrate and tris(hydroxymethyl) aminomethane (THAM) showed a Hofmeister effect (Pygall, Kujawinski, Timmins, & Melia, 2009, 2010). Multivalent citrate ions promoted hydration of the polymer by disruption of the water cages promoting hydrophobic association, while monovalent THAM does not promote salting-out. Whereas a salting-in effect was reported for nicotinamide, which inhibited gelation (Hino & Ford, 2001). In another study, Pygall, Griffiths, Wolf, Timmins, and Melia (2011) showed that addition of meclofenamate lowers the gelation temperature, increases viscosity, and reduces the diffusion of the drug, which are indications of aggregation on the polymer. No such effects were reported when diclofenac Na was added. The difference was attributed to the ability of meclofenamate to form tautomers resulting in a wider distribution of electrons across the amine and carboxylic functional groups which effectively promotes association with the polymer. It was previously inferred from studies of the distribution of water in gels that diclofenac Na had a salting-out effect on the polymer, which was not observed with propranolol hydrochloride (McCrystal, Ford, & Rajabi-Siahboomi, 1999a,b). Non-cooperative solubilization of HPMC by ibuprofen sodium below its CMC, which increases solution viscosity and inhibits gelation, was also reported (Ridell, Evertsson, Nilsson, & Sundelof, 1999).

Berglund, Przybycien, and Tilton (2003a,b) have studied the coadsorption of cellulose derivatives and SDS on selective hydrophobic and negatively charged silica, and non-selective hydrophobic PDMS surfaces. They reported that the bulk surfactant concentration controls adsorption on both types of surface. Their results indicate that at low SDS concentrations the mass of adsorbed polymer–surfactant complexes is similar to that of polymer in the absence of SDS. Furthermore, increases in concentration cause a reduction of polymer adsorption as more surfactant molecules bind to the polymer, due to a combination of mechanisms which include: shielding of hydrophobic interactions, repulsion of polymer–surfactant complexes from the surface, and, to a minimum, lateral repulsion from bound complexes. Yet, when the surfactant concentration surpasses the CAC adsorption is limited. Thus, it is expected that similar interactions will be present on a solution containing dispersed hydrophobic and charged particles, surfactant and polymer. Understanding of these complex interactions is needed to provide background information for formulation of new pharmaceutical products and for transport studies of drug–polymer systems.

2. Experimental

2.1. Materials

An 86 kDa hydroxypropylmethylcellulose (Cat# 423203, Batch# MKBB0393/MKBC7873) and sodium dodecyl sulfate (SDS) were purchased from Sigma–Aldrich. Distributor's specification data sheet showed a 1.8–2.0 methoxyl DS (i.e. 28.0–30.0%) and 0.20–0.30 hydroxypropyl MS (i.e. 7.0–12.0%), and a viscosity from 3 to 5.6 Pa s for a 2 wt% aqueous solution at 20 °C. The samples were used as purchased. The critical micelle concentration (CMC) of SDS has been reported in the literature as 8.08 mM (Fuguet, Rafols, Roses, & Bosch, 2005). The model drug used was griseofulvin. It is a commercial antifungal with a low water solubility (Boullata & Armenti, 2010). Micronized griseofulvin was donated by a local pharmaceutical industry. The average particle diameter of griseofulvin was determined by optical microscopy to be approximately 1.5 μm.

2.2. Sample preparation

Surfactant stock solutions were prepared by mixing the surfactant with deionized (DI) water and stirring for at least 30 min at room temperature. Griseofulvin stock suspensions in DI water were prepared by sonicating at least for half an hour using a Branson 450 W high power sonicator. HPMC was dissolved in hot DI water at 50 °C and stirred overnight at room temperature. Afterwards, all stock mixtures were magnetically stirred continuously at room temperature. Aqueous ternary mixtures of surfactant, polymer and drug were prepared by mixing each component to obtain the desired final compositions. Final HPMC and griseofulvin concentrations for rheological measurements were held constant at 1 wt% for both. Surfactant concentration was studied up to the CMC.

2.3. Rheology and gelation temperature

Rheological characterization was performed on a Rheologica StresTech HR stress-controlled rheometer equipped with an extended temperature cell for temperature control using a double gap Couette (V = 11 mL) fixture. The rheometer geometry was set to the desired temperature before loading the solution. Solutions were left at rest for at least 5 min to relax and equilibrate.

Dynamic rheological measurements were used to determine gelation temperatures of biopolymers during heating ramps. This technique is a widely used non-destructive method frequently used to study the gel evolution (Lapasin & Pricl, 1999). T_{gel} is typically taken as the temperature where the storage modulus, G', and loss modulus, G'', are equal. The storage and loss moduli were measured during a heating ramp from 25 to 75 °C at a rate of 0.5 °C/min. Frequency and strain were fixed at 1 Hz and 1%, respectively.

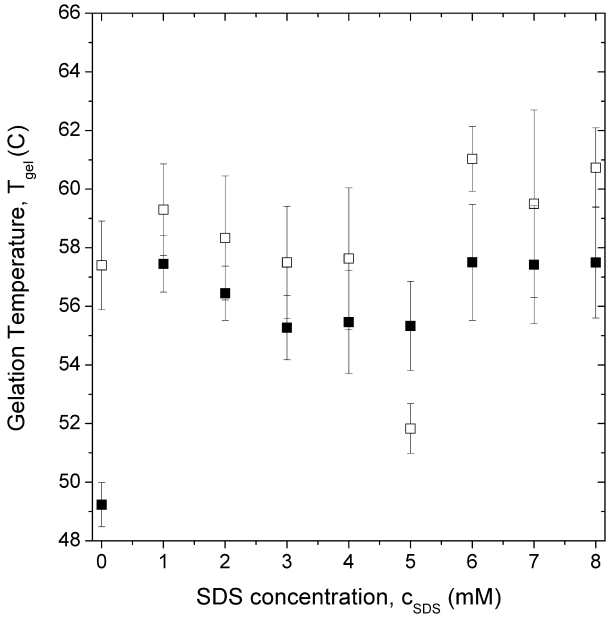

Fig. 1. Gelation temperature of 1 wt% aqueous hydroxypropylmethylcellulose solutions as a function of sodium dodecyl sulfate concentration in the absence (□) or presence (■) of 1 wt% griseofulvin.

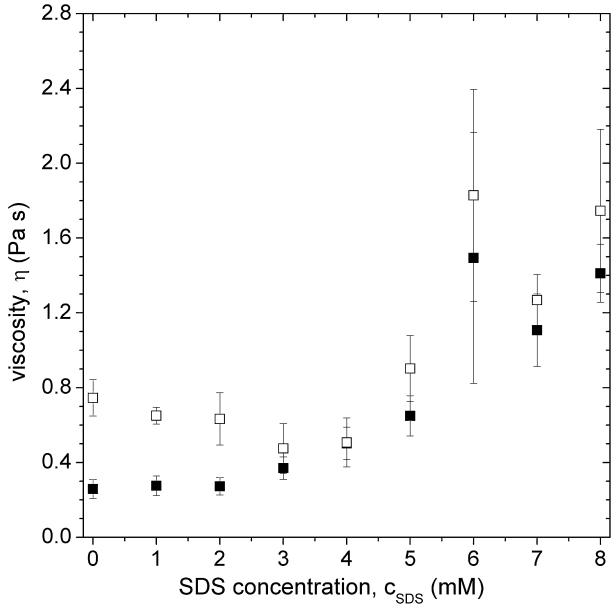

Fig. 2. Zero-shear steady state viscosity of aqueous hydroxypropylmethylcellulose solutions at 1 wt% with sodium dodecyl sulfate in the absence (□) or presence (■) of 1 wt% griseofulvin.

Steady-state viscosity was determined at 25 °C at shear rates from 0.1 to 100 s^{-1}. Viscosity can provide information about conformational effects due to polymer–surfactant interactions (Goddard, 1986). The steady-state viscosity of aqueous HPMC solutions showed a Newtonian plateau at low shear rates ($\dot{\gamma} < 10\,s^{-1}$) followed by a shear-thinning regime at higher shear rates, which is a characteristic behavior for most polymer solutions, including polysaccharides (Nishinari, 2006). No effect on the onset of shear thinning with the addition of surfactant was observed. Reported values correspond to the Newtonian plateau or, equivalently, the zero-shear steady-state viscosity. This regime provides more information about the component interactions, since it is assumed that they are not disturbed by shear.

2.4. ζ-Potential

ζ-Potential was determined at 25 °C in a Brookhaven Instruments BI-90 Plus particle size analyzer equipped with the BI-Zeta option. This instrument operates using a He–Ne red laser at a power, scattering angle, and wavelength of 35 mW, 90, and 633 nm, respectively. Solutions used for rheological tests were diluted by a one-hundredth factor for these measurements. Additional experiments were performed on a Beckman Coulter DelsaNano C particle analyzer.

Reported values of T_{gel}, viscosities, and ζ-potential correspond to the average of at least three measurements, while error bars correspond to their respective standard deviations. One-way ANOVA analyses were performed with 95% significance levels ($\alpha = 0.05$) on all data sets to determine the effects of surfactant concentration on T_{gel}, viscosity, and ζ-potential.

3. Results and discussion

3.1. SDS effect on the gelation of HPMC

Fig. 1 shows the gelation temperature, T_{gel}, of HPMC systems as a function of SDS concentrations, below the CMC, with (closed symbols) and without (open symbols) griseofulvin. Gelation temperature for the aqueous HPMC solution (from now on referred as pure HPMC) was found to be 57.4 ± 1.5 °C. At low SDS concentrations (i.e. <4.0 mM), no significant change in T_{gel} is observed without griseofulvin. At 5.0 mM a drop of 5.6 °C in T_{gel}, relative to that of the pure HPMC, was observed. Upon increasing SDS concentration to 6.0 mM, T_{gel} reaches 61.0 °C, surpassing the value for pure HPMC. Further increases of the SDS concentration up to 8.0 mM (or CMC) do not have an additional effect on T_{gel}.

These results are in agreement with gelation temperature results reported by other authors using calorimetric techniques (Joshi & Chen, 2009; Su, Liu, Joshi & Lam, 2008). Su and coworkers reported that low SDS concentrations (2 and 4 mM) do not have a significant effect on the gelation temperature (i.e. 55 °C for a 1 wt% 86 kDa HPMC solution). Joshi and Chen attribute the minimum and sudden increase in gelation temperature to adsorption of SDS molecules to the hydrophobic sites of the polymer followed by aggregate formation. The onset of aggregate formation denoted the critical aggregation concentration (CAC) for SDS in HPMC was reported as 6 mM by these authors. In addition, the increase of about 8 °C for HPMC solutions with SDS concentration above 6 mM, with reference to pure HPMC, was attributed to the higher energy that was necessary to displace aggregates and break water cages.

We also determined the effect of SDS concentration on the magnitude of the zero-shear steady-state viscosities of HPMC solutions at 25 °C, which are shown as open symbols in Fig. 2. Similar to T_{gel}, for SDS concentrations below 4 mM there was no significant effect on the viscosity. Above 5.0 mM, the viscosity increases up to a factor of 2 as it reaches the CMC. The increase in viscosity supports the proposed mechanism that higher order structures, such as aggregates, are being formed. Additional evidence is provided by the fact that the onset for the increase in viscosity is observed at the same concentration as the minimum in T_{gel}, which was attributed to formation of aggregates by Joshi and Chen.

3.2. SDS effect on the gelation of HPMC with griseofulvin

When griseofulvin is added to the polymer solution in the absence of surfactant a decrease in T_{gel}, or promotion of gelation, is observed. T_{gel} is 7.7 ± 1.7 °C lower than for pure HPMC. A decrease in viscosity (0.50 ± 0.21 Pa s) in the absence of surfactant, Fig. 2,

indicates adsorption of polymer on the particles surface. The latter can be attributed to a reduction in the effective viscosity of the medium or depletion to the particles surface, which will cause a decrease in the effective polymer concentration of the medium. Loose strands of the adsorbed polymer molecules can still interact with its surrounding. When heated, the hydrophobic groups of these loose strands are able to associate with the free polymer in solution. This might be repeated around the particles surface. As such, multiple hydrophobic clusters can be effectively spanned or bridged by the particle. Since the particle diameter and the radius of gyration of the HPMC, around 35 nm in water (Viriden, Wittgren, & Larsson, 2009), differ at least by three orders of magnitude, the length scale of the bridging is significant. Thus, a synergistic effect on the gelation process, which decreases transition temperature, is observed.

Our experiments show that when 1.0 mM of SDS are added to the HPMC–griseofulvin system T_{gel} increases by $7.7 \pm 1.2\,^{\circ}C$, above that of the HPMC–griseofulvin solution. Yet, the viscosity of the suspension is unaffected. The gelation temperature is similar up to 5.0 mM, after which a slight increase, without going through a minimum, of about 1.6 °C is observed above 7.03 mM. However, T_{gel} is statistically similar to that of the HPMC solution within the studied range of 0.1–1.0 mM SDS. On the other hand, the viscosity is unaffected up to 4 mM.

At low SDS concentrations, surfactant and polymer–surfactant complexes can replace unbound polymer on the surface, which might effectively reduce the number of loose strands on the particles surface that can interact during gelation by shielding the hydrophobic interactions. Furthermore, as demonstrated by Berglund et al. (2003a,b) the amount of polymer adsorbed, either alone or bounded to surfactant, is similar; thus, viscosity is unaffected. As SDS concentration is increased, there is no more adsorption on the particles surface of either polymer, SDS, or their complexes. Excess SDS starts to saturate the polymer in solution promoting the formation of surfactant micelles. Thus, solution viscosity can increase without a significant effect on the transition temperature.

The ζ-potential of griseofulvin was measured as -18.20 ± 1.46 mV, consistent with values reported in the literature (Itoh, Pongpeerapat, Tozuka, Oguchi, & Yamamoto, 2003). Addition of SDS, without HPMC, to the griseofulvin increased the potential until it saturated above 4×10^{-2} mM to -27.75 ± 0.81 mV, shown as open symbols in Fig. 3. This indicates that the SDS hydrophobic tails sit on the particles surface exposing its negatively charged hydrophilic head. In multi-component system with both HPMC and SDS, the presence of the additional component impacts the observed process due to competitive adsorption on the griseofulvin surface. Addition of HPMC (closed squares in Fig. 3) without SDS decreases the value for griseofulvin to -4.77 ± 0.92, which indicates that the polymer adsorbs onto the drug's surface. When SDS was added, the suspension became slightly more negative, which shows HPMC replacement from the surface. A small change upon addition of SDS has also been reported for various drug/cellulose ether systems, including griseofulvin/HPMC (Meng, Chen, Chowdhury, Yang, & Mitra, 2009). Further increases in SDS reduced the charge until it saturated at around 4×10^{-2} mM. Alternatively, when HPMC was gradually added to SDS-stabilized griseofulvin the observed changes of ζ-potential indicate that competitive adsorption of SDS and HPMC on the particles occurs in several regimes, as shown in Fig. 4. Initially the griseofulvin particles were completely covered with 6 mM of SDS and their ζ-potential value was equal to -67 mV. Upon addition of HPMC, the attractive forces (i.e. Van der Waals forces) between the SDS and HPMC forced the SDS to leave the surface of the drug, and were replaced by the HPMC molecules. As a result, ζ-potential increased with the HPMC concentration. After a certain critical

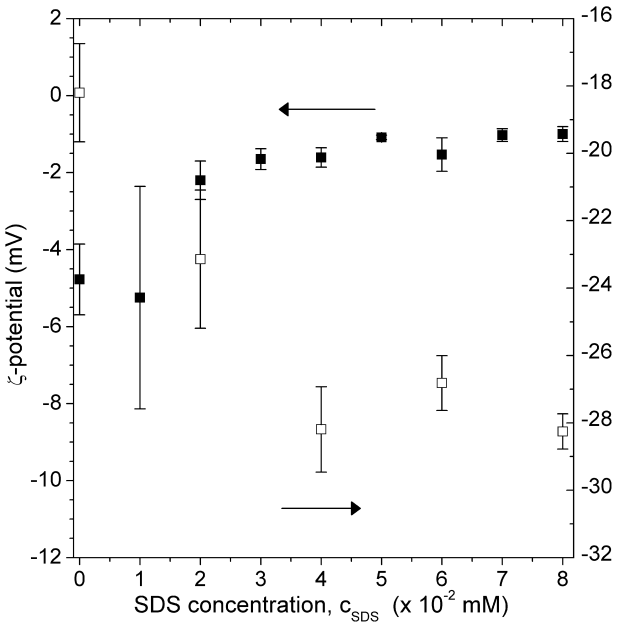

Fig. 3. ζ-Potential of 0.01 wt% griseofulvin suspension with 0.01 wt% hydroxypropylmethylcellulose (■, left axis) or without (□, right axis) as a function of sodium dodecyl sulfate concentration.

concentration, which was about 0.003% of HPMC, SDS started to adsorb onto HPMC molecules and form complex with slightly negative charges and ζ-potential began to drop as a result. This corresponds well with the competitive adsorption of SDS and polymer on drug particles previously reported in the literature (Terayama, Okumura, Sakai, Torigoe, & Esumi, 2001).

Fig. 5 shows a schematic representation of the proposed mechanism for HPMC gelation in the presence of SDS with and without griseofulvin at a temperature below (i.e. T_1) and above gelation (i.e. T_2). The gelation process is mainly affected by two competing processes: (1) griseofulvin acting as binding agent of associated hydrophobic polymer regions which include adsorbed polymers and polymer–surfactant complexes, and (2) SDS aggregating with the HPMC through hydrophobic interactions. At a temperature

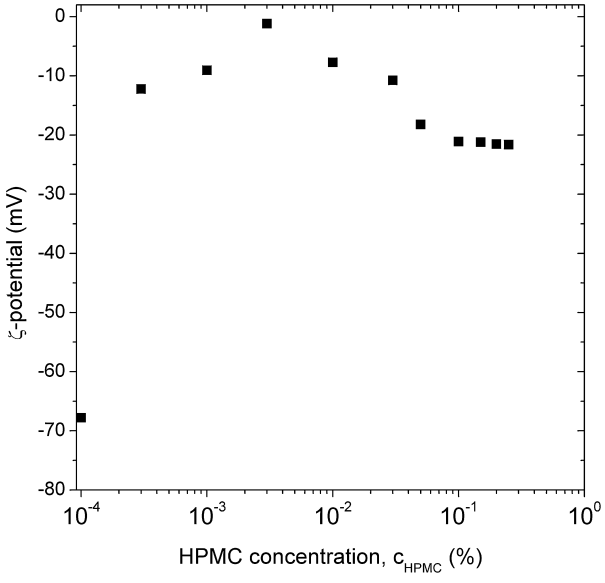

Fig. 4. ζ-Potential of SDS-stabilized griseofulvin particles as a function of hydroxypropylmethylcellulose concentration. The concentration of SDS was held constant at 6 mM.

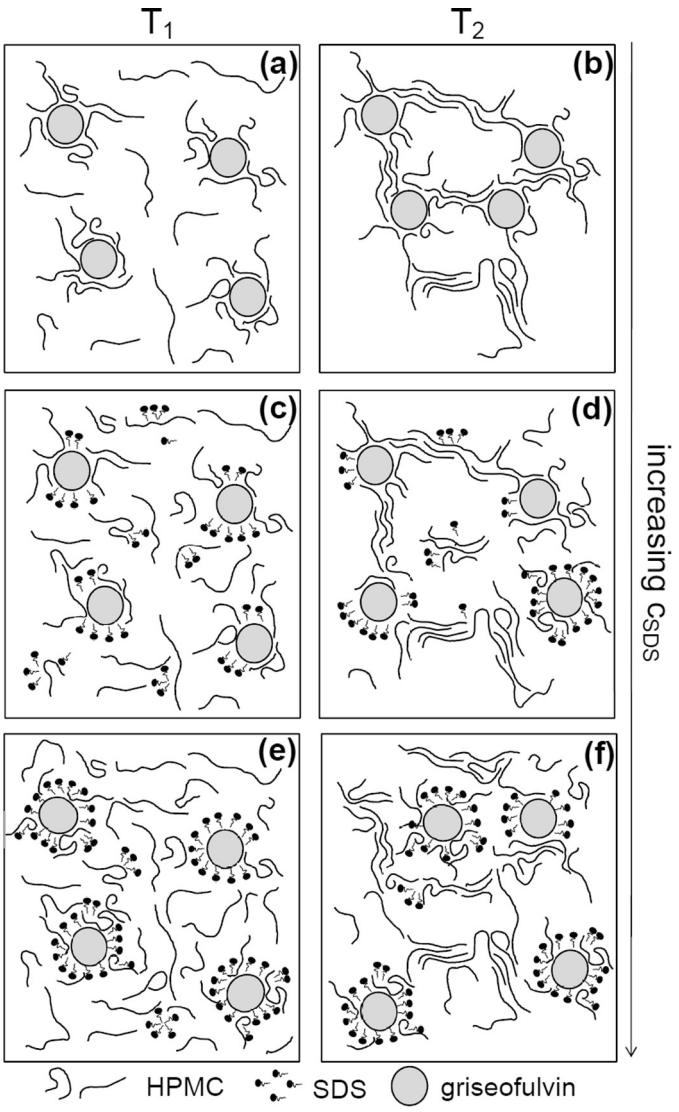

Fig. 5. Schematic representation showing the interactions between HPMC, SDS, and griseofulvin at T_1 and T_2, where $T_1 < T_{gel} < T_2$. Top panes, (a) and (b), represent the system with no SDS; middle panes, (c) and (d), represent the system with limited concentration of SDS; and bottom panes, (e) and (f), represent the system with higher concentration of SDS, but below the critical micelle concentration.

below T_{gel} and no SDS present, as shown in Fig. 5a, some HPMC bounds to the surface of the particles. The particles with adsorbed polymer help to bridge hydrophobic regions during gelation as shown in Fig. 5b. As SDS is added at low temperatures, Fig. 5c, some of it replaces HPMC from the particles surface and some of it forms polymer–surfactant complexes. In both cases SDS hinders gelation; nevertheless, bridging effects are still present as depicted in Fig. 5d. At a higher SDS concentration, Fig. 5e, the HPMC is free in solution and complexated with the bound SDS. When heated, the opposing effects mostly cancel each other.

4. Conclusions

The effect of a highly hydrophobic particulate drug, griseofulvin, on the thermal gelation of HPMC as a function of SDS concentration was determined in this work by dynamic rheological methods. Steady-state viscosity and ζ-potential measurements supplemented the study to provide additional information unto the complex interactions of the components in solution and on the drug surface, respectively. A decrease in viscosity and ζ-potential with addition of HPMC to a drug suspension demonstrated that HPMC adsorbs on the particles surface. Hydrophobic interactions between adsorbed polymer on griseofulvin and free polymer in solution during gelation account for the synergistic effect on gel transition. The particles aid in bridging hydrophobic regions separated by a distance of up to three orders of magnitude larger than the effective polymer size. The reduction in ζ-potential, no effect on viscosity, and increase in T_{gel} at low SDS addition suggest a replacement of adsorbed polymer by surfactant–polymer complexes and unassociated surfactant, and that free and surfactant-bound polymer concentrations remain constant, both in solution or adsorbed. SDS shields the polymer–polymer hydrophobic interactions inhibiting gelation. Nevertheless, as its concentration increases the polymeric chains are saturated and larger surfactant aggregates account for the increase in viscosity. No further effect on T_{gel} and ζ-potential was observed, which showed that the adsorbed layer has also saturated. The similarity of the T_{gel} to that of the HPMC solution also indicates that the bridging effect and the shielding by the associated SDS are not eliminated but offset each other. Thus, the complex interactions between these components have to be accounted for during the formulation of pharmaceutical products.

Understanding these complex interactions is important in the design and optimization of pharmaceutical formulations with hydrophobic drugs as they can affect processing and performance. For example, the increased viscosity improves physical stability of the particles, but requires higher energy consumption to process and clean. While in products formulated from these solutions, such as a film casted by solvent evaporation, there might be a reduction in particle mobility (caused by the larger particle size when polymer is adsorbed and the physical crosslinks with the surroundings) improving stability. Yet, wetting and drug release rate might be affected.

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