Preparation and Characterization of Pluronic–Colloidal Silicon Dioxide Composite Particles as Liquid Crystal Precursor

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ABSTRACT

The purpose of this study was to produce spray-dried Pluronic–colloidal silicon dioxide (Aerosil) composite particles as a liquid crystal precursor that would form a liquid crystalline phase upon hydration. A Pluronic–colloidal silicon dioxide dispersion in isopropyl alcohol was spray-dried to obtain composite particles using different concentrations of Aerosil. Polarizing microscopy, gelation, gel melting, and rheological studies were employed to characterize the composite particles. The composite particles obtained were irregular, with concave depression. Gelation was found to decrease with the addition of Aerosil, while gel melting was found to increase with the concentration of Aerosil. Rheological studies showed an increase in elasticity as well as viscosity with an increase in the concentration of Aerosil. Composite particles showed improved gelation and rheological properties. These composite particles and the process by which they were obtained may be useful for designing various drug delivery systems.

KEYWORDS: precursor, spray-drying, liquid crystal, Pluronic, Aerosil, rheology.

INTRODUCTION

Amphiphilic surfactants and block copolymers exhibit liquid crystalline arrangements. Different mesophases formed include lamellar, cubic, and hexagonal. These mesophases exhibit different thermal and rheological properties.[1-5] Because of their biodegradability, ability to incorporate a variety of drugs, drug release retardation, and possible enhancement of the stability of incorporated drugs and proteins, liquid crystalline mesophases have been of interest for use in drug delivery.[1,6,7] Applications of mesophases in pharmaceutical drug delivery systems depend upon their properties. The relatively low-viscosity lamellar phase has good syringeability and bioadhesivity. Norling et al have reported lamellar phase injectable dental gels containing glyceryl monooleate (GMO), which upon administration was transformed into the highly viscous cubic phase.[8] The cubic phase, in contrast, has lower bioadhesivity than the lamellar phase.[6,9] The cubic arrangement provides high viscosity and is widely used for controlled drug release systems.[10-12] Cubic phases are also applied for protection of labile moieties like enzymes and other drugs sensitive to hydrolysis and oxidation.[13] However, because of their highly viscous nature, cubic phases are restricted to certain applications. This restriction stimulated research into the design of precursors that are transformed into liquid crystals upon hydration.

Shah and Paradkar have reported GMO matrices for oral administration of serratiopeptidase, which undergo transformation to the highly viscous cubic phase in situ and provide sustained release from the microenvironment-controlled highly viscous cubic phase.[14] The limitation with precursors is intermediate low-viscosity lamellar phase transformation, which causes faster drug release and does not provide adequate protection to drug molecules. Spicer et al reported dry powder precursors in which monoolein was combined with an aqueous starch solution to avoid sticking of molten monoolein during spray-drying. On reconstitution, these precursors formed a low-viscosity dispersion that could provide controlled drug release.[15]

Self-assembling block copolymers exhibiting a wide range of morphologies and rheological behaviors have attracted significant attention because of their advantages, such as controlled drug release, bioadhesivity, and protection of sensitive drug molecules. Pluronic F127 exhibits a thermoreversible gelation property in water, with high solubilizing capacity. It can form liquid crystalline mesophases with high viscosity, which enhance protein stability and provide controlled drug release. Hence, this polymer is of special interest to the pharmaceutical industry.[16-21] The presence of drugs and excipients in the Pluronic gel significantly affects the properties of the system.[4] Pisal et al have reported the effect of the addition of vitamin B_{12} and other excipients on various pharmaceutical properties of a gel.[21] Pandit et al have reported the effect of salt on Pluronic F127's gelation behavior.[22] The major limitation in the Pluronic gels is the

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high concentration of polymer required to obtain the viscosity needed to achieve the desired pharmaceutical performance. Therefore, attempts have been made to reduce the polymer concentration by combining it with Carbopol, hydroxypropylmethylcellulose, and carboxymethylcellulose.[23,24] These polymers are added in the concentration range of 1% to 5% wt/wt. Colloidal silicon dioxide (Aerosil 200) is a popular gelling agent that has been shown to gel in a wide range of solvents.[25] The addition of any other component to a liquid crystalline system is expected to alter the liquid crystalline phase and in turn the properties of the system. Therefore, it is necessary to study the effect of the additive on the liquid crystalline phase.

The present study sought to obtain spray-dried composite particles as liquid crystal precursors containing Pluronic and Aerosil that would spontaneously form liquid crystals upon hydration. This precursor system avoids the need for transport and processing of bulk water and enables a wider range of applications (eg, drug delivery via inhalation). These spray-dried composite particles were evaluated as liquid crystal precursors using polarizing microscopy, and rheological and gelation behavior.

Materials and Methods

Materials

Pluronic F127 was a gift sample from BASF (Svenska, Sweden). Aerosil 200 was obtained from Get Rid Pharmaceuticals (Pune, India). Isopropyl alcohol was purchased from Merck (Mumbai, India) and was of analytical grade.

Method of Preparation

An organic phase was prepared by dissolving Pluronic F127 in isopropyl alcohol. Aerosil was uniformly dispersed in this organic phase by continuous stirring. The prepared phase was then spray-dried using a laboratory-scale spray-dryer equipped with a spraying nozzle (Jay Instruments and System Private Limited, Mumbai, India). The following conditions were used during spray-drying: inlet temperature, 75°C; aspirator, 65%; and atomization air pressure, 2 kg/cm^2. The dispersion to be spray-dried was kept under stirring on a magnetic stirrer. The feed rate was maintained at 2 mL/min. Four batches of spray-dried composite particles were prepared using 4 different concentrations of Aerosil (0.0%, 1.0%, 1.5%, and 2.0% wt/wt).

Hydration of Composite Particles

To evaluate the various parameters (eg, gel point, gel melting, polarizing microscopy, rheology), the gels were prepared by hydrating the composite particles equivalent to 20% wt/wt of Pluronic F127.

Characterization

Surface Topography

Particles were coated with a thin gold-palladium layer by a sputter coater unit (VG-Microtech, Uckfield, East Sussex, UK), and the surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (Cambridge, UK) operated at an acceleration voltage of 10 kV.

Residual Solvent Content

The amount of isopropyl alcohol remaining in the composite particles following spray-drying was determined using thermogravimetric analysis (TGA-50, Shimadzu Corporation, Nakaguo-ku, Kyoto, Japan). The flow rate of nitrogen employed for flushing was 30 mL/min in the temperature range of 25 to 100°C. The heating rate was 5°C/min, and the weight of the sample was ~10 mg.

Diffused Reflectance Infrared Fourier Transform Spectra

Diffused reflectance infrared Fourier transform (DRIFT) spectra of Pluronic F127, Aerosil, and spray-dried composite particles were obtained after appropriate background subtraction using a Fourier transform infrared (FTIR) Spectrometer (FTIR 8400, Shimadzu Corporation) equipped with a diffuse reflectance accessory (DRS-8000, Shimadzu Corporation) and a data station. About 2 to 3 mg of the sample was mixed with dry potassium bromide, and the sample was scanned from 4000 to 400 cm^{-1}.

Polarizing Light Microscopy

The hydrated samples were examined under a polarizing light microscope (Nikon, Melville, NY) using a λ¼ compensator to study the existence of birefringence under crossed polarized light employing a magnification of 200×. The lamellar, cubic, and hexagonal phases were identified according to the classification established by Rosevear.[26]

Gelation and Gel Melting

Gelation and gel melting were assessed using a modification of the Miller and Donovan technique.[27] Equilibrated composite particles with water were transferred to a test tube, immersed in a water bath at 4°C, and sealed with aluminum foil. The temperature of the water bath (Haake Phoenix C 25P, Karlsruher, Germany) was increased in increments of 0.5°C and left to equilibrate for 2 minutes at each new setting. The samples were then examined visually for gelation, which was said to have occurred when the meniscus would no longer move upon tilting through 90°. The gel melting temperature, the critical temperature when a gel starts flowing upon tilting through 90°, was recorded.

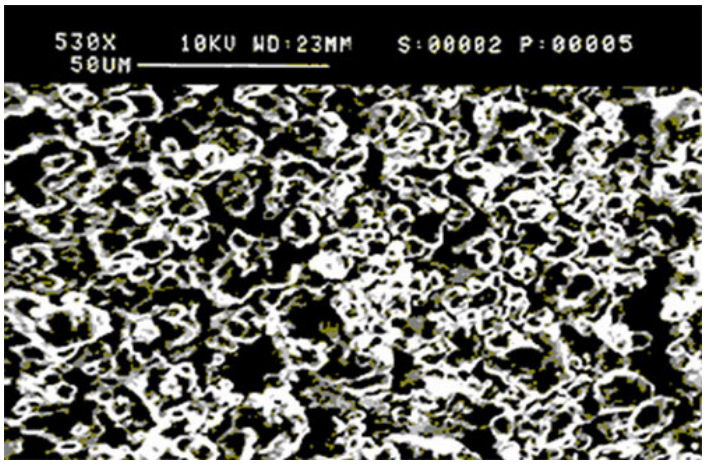

Figure 1. Scanning electron microscopy photographs of Pluronic–colloidal silicon dioxide composite particles.

Rheology Study

The rheological properties of hydrated samples were studied using an advanced rheometric expansion system (ARES) strain control rheometer (Rheometric Scientific, Piscataway, NJ) with parallel plate geometry (plate diameter: 25 mm). Samples were transferred onto the parallel plate and carefully overlaid with a silicone oil to minimize water evaporation. The silicone oil was immiscible with the aqueous solution and was not solubilized into the cores of the F127 micelles. Two types of oscillatory measurements were performed. An oscillatory strain sweep was applied in which the dynamic moduli were recorded at a constant frequency of 1 Hz. Strain sweep was used to determine the linear viscoelastic region. In the linear viscoelastic region, the response of the material is characteristic of its microstructure at rest. The relative magnitude of the moduli is a quantitative indication of the structure in the sample. For any system, 3 situations can be encountered (G′ is the energy stored per unit volume; G′′ is the energy dissipated per unit deformation rate per unit volume): G′ >> G′′ for a chemically cross-linked system, G′ > G′′ for a network consisting of secondary bonds, and G′≤ G′′ for a physically entangled system.[28,29] A second dynamic study (frequency sweep) was performed in which strain amplitude was kept constant and the frequency was varied. The structure of the system can be kept intact during the measurement by choosing the amplitude of strain within the linear viscoelastic region. In general, the material can respond to deformation on applied stress through 2 mechanisms: elastic energy storage and viscous energy dissipation. Quantitatively, these responses can be represented as elastic modulus G′, which provides information about the elastic properties of the material, and viscous modulus G′′, which provides information about the viscosity of the material.[30] The strength of the interaction of the internal structure in a system is measured by the magnitude of the ratio G′′/G′, which is called the phase angle (tan δ). All measurements were performed at 20°C and 30°C.

Results and Discussion

The process yield of the various batches was in the range of 42% to 56%. The percentage yield increased with an increase in the amount of Aerosil. Aerosil provided a large surface area for Pluronic to adsorb or coat on the surface, which prevented the loss of Pluronic due to sticking on the dryer wall. Thermogravimetric analysis indicated that residual solvent in the spray-dried composite particles was 0.083% wt/wt. According to International Conference on Harmonization (ICH) guidelines (1997), isopropyl alcohol is a class III solvent with a permissible limit of 0.5%, so the spray-drying method used for these batches was found to be suitable.

Scanning electron microscopy photographs of the liquid crystalline precursor are shown in Figure 1. The liquid crystalline precursor particles obtained were irregular, with concave depressions on the surface. DRIFT spectra of Pluronic, Aerosil, and the liquid crystalline precursor are shown in Figure 2. Pluronic showed characteristic peaks at 3491 cm^{-1} (O-H stretching), 2885 cm^{-1} (C-H stretching), and 1132 cm^{-1} (C-O-C stretching). Aerosil showed a prominent characteristic peak at 1107 cm^{-1} (Si-O linkage). DRIFT spectra of the precursor revealed broadening and shift of the O-H stretching

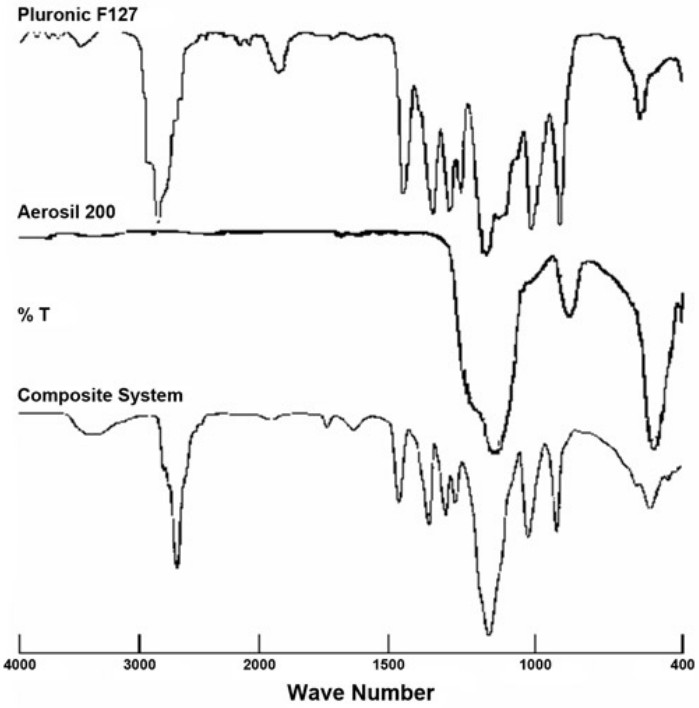

Figure 2. Diffused reflectance infrared Fourier transform spectra of Pluronic, Aerosil, and Pluronic–colloidal silicon dioxide composite particles.

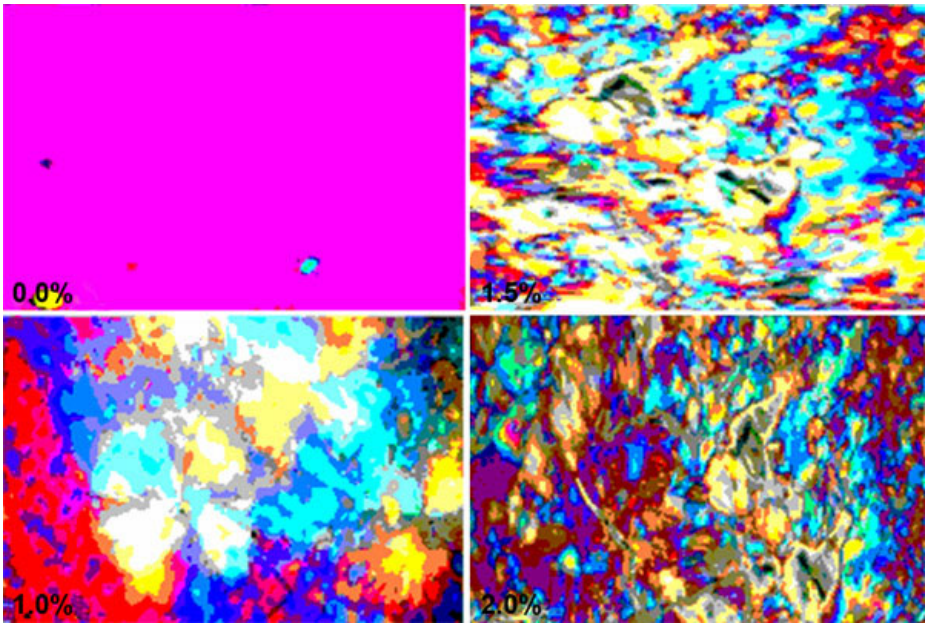

Figure 3. Polarizing photographs of hydrated Pluronic–colloidal silicon dioxide composite particles.

peak to a lower frequency at 3462 cm^{-1}, which was probably due to hydrogen bonding (OH-O).[31]

The liquid crystalline phase can be identified by examining the texture under a polarizing light microscope. A lamellar liquid crystal displays a mosaic planar texture, while a hexagonal liquid crystal shows a fanlike angular or striated nongeometric texture. No texture is displayed by a cubic phase, and only a dark background is observed under a polarizing microscope.[32] Polarizing photographs of hydrated samples are shown in Figure 3. Photographs showed a dark background in the case of the plain system (0.0% Aerosil), suggesting a cubic phase, whereas some fanlike structures were observed in the polarizing photograph of the Aerosil-containing system (1.0%, 1.5%, and 2.0%). Thus, addition of Aerosil transformed the system from the cubic into the hexagonal phase. For a polyethylene oxide-polypropylene oxide-polyethylene oxide (PEO-PPO-PEO) block copolymer of a given composition and molecular weight, the type of structures obtained in the presence of selective solvents appears to be a function of the volume fraction of the polar/apolar component. This was attributed to the ability of the macromolecule blocks to swell to a different extent (based on the amount of solvent available) with the respective solvents and thus to modulate the interfacial curvature. The interfacial curvature is positive when the interface bends toward the apolar domains, that is, when the micelles are surrounded by the polar domains confining the apolar domains inside them, and is negative in the reverse case.[33,34] In the cubic phase, the interfacial curvature is highly positive because of the spherical micelles. A normal hexagonal phase has been obtained at a high content of Pluronic F127 because of decreased solvation of the PEO blocks. Aerosil having a large surface area absorbed water from the system; as a result, less water was available for Pluronic, which favored transformation from the cubic phase to the hexagonal phase.

Physically, gel formation is related to micellar packing and volume fraction. Researchers have attributed the gelation of Pluronic to the dehydration of PPO groups in the micelle core, a change in the micellar volume, or a decrease in the critical micelle concentration and an increase in the aggregation number.[34-36] The effect of Aerosil concentration on sol-gel and gel-sol transition is shown in Figure 4. The incorporation of Aerosil shifted the sol-gel transition to a lower temperature but increased the gel-sol transition temperature. Thus, the gelation range broadens with a higher concentration of Aerosil. Block copolymer Pluronic F127

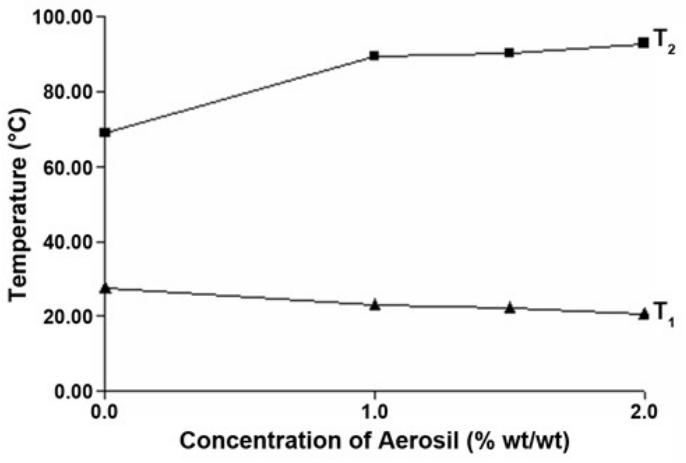

Figure 4. Effect of Aerosil concentration on gelation point (T_1) and gel melting point (T_2) of hydrated Pluronic–colloidal silicon dioxide composite particles.

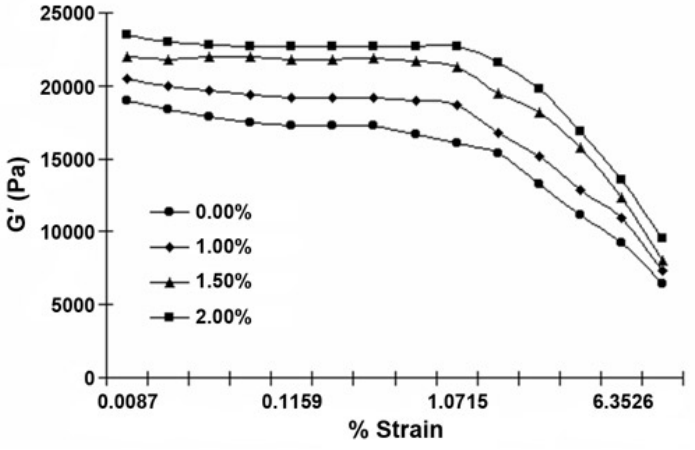

Figure 5. Effect of oscillatory strain sweep on elastic modulus G′ of composite particles containing different amounts of Aerosil.

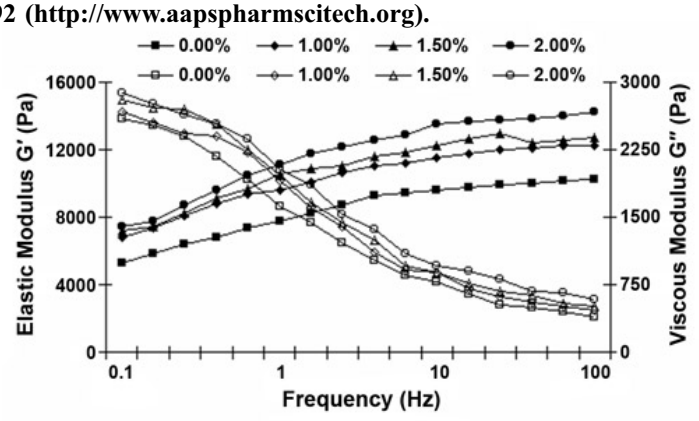

Figure 7. Influence of frequency on the elastic modulus G′ (filled symbols) and the viscous modulus G″ (unfilled symbols) of composite particles containing different amounts of Aerosil at 30°C.

gels are thought to be formed because of H-bonding in the aqueous system, caused by the attraction of the Pluronic ether oxygen atom to a proton of water. If the hydrogen bonding is supplemented by adding compounds with a hydroxyl group, the gelation point decreases.[23] The gel structure was thought to remain unaltered with temperature until an excessively high temperature caused the destruction of the gel structure. In our study at a higher temperature, the gel underwent a process of dehydration, but excessive hydrogen bonding and closely packed micelles restricted the destruction of the gel structure. As the concentration of Aerosil increased, the gel structure became more closely packed, arranged in a lattice pattern. In turn, the disruption of the lattice melting of the gel occurred at higher temperatures.

Before carrying out any oscillatory measurements, we checked each sample to ensure that it was within the linear viscoelastic region where the elastic modulus was independent of the applied strain. Application of stresses above the linear limit affects or even destroys the structure during the measurement. Analysis of viscoelastic material is designed to preserve the structure, so that measurements can provide information on the intermolecular and interparticle forces in the material.[37] The effect of oscillatory strain sweep on the elastic modulus (G′) is illustrated in Figure 5. Systems containing Aerosil exhibited significantly higher G′ values and longer linear viscoelastic regions than did the plain systems, and G′ values increased with an increase in the concentration of Aerosil in the composite system. This might have resulted from the stronger association of Pluronic with Aerosil via secondary bonds and physical entanglements. From the viewpoint of rheology, a high elastic modulus is an inherent characteristic of solid material, and a phase change from liquid to semisolid can be described via the changes to the elastic modulus.[38]

A dynamic oscillation frequency sweep test was used to determine the system's ability to resist structural changes under increased frequency. The strain selected was in the linear viscoelastic region of each formulation (0.25%). Oscillatory

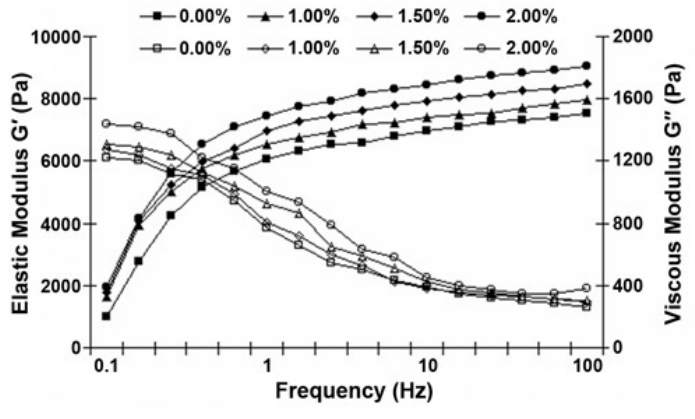

Figure 6. Influence of frequency on the elastic modulus G′ (filled symbols) and the viscous modulus G″ (unfilled symbols) of composite particles containing different amounts of Aerosil at 20°C.

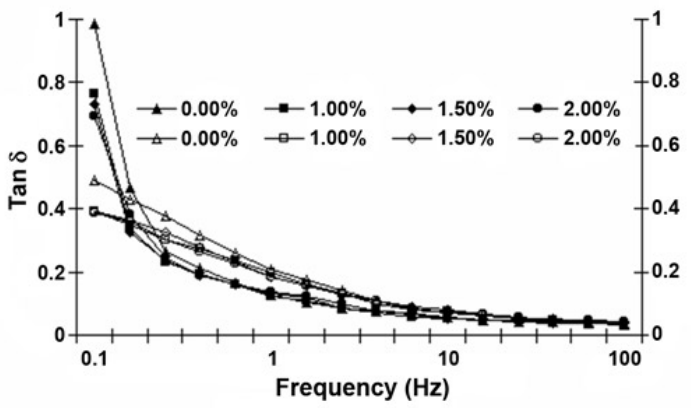

Figure 8. Effect of Aerosil concentration on tan δ at 20°C (filled symbols) and 30°C (unfilled symbols).

Table 1. Effect of Different Concentrations and Temperatures on Tan δ at Different Frequencies

Aerosil Concentration of Composite Particles	Frequency (Hz) at 20°C				Frequency (Hz) at 30°C			
	0.1	1.0	10	100	0.1	1.0	10	100
0.0%	0.984	0.127	0.056	0.034	0.492	0.207	0.080	0.038
1.0%	0.765	0.123	0.051	0.037	0.392	0.197	0.076	0.037
1.5%	0.729	0.133	0.053	0.035	0.389	0.185	0.072	0.040
2.0%	0.692	0.135	0.053	0.041	0.385	0.182	0.071	0.040

measurements in which the frequency was varied (0.1-100 Hz) showed that the viscous modulus (G´´) dominated in lower frequencies, while the elastic modulus (G´) dominated in higher frequencies (Figure 6 and 7), which indicated that the elastic component was more dominant than the viscous component.

The effect of Aerosil concentration on dynamic moduli at 20°C is shown in Figure 6. The elastic modulus and the viscous modulus increased with increases in the concentration of Aerosil. At lower frequencies, no significant effect of concentration on elastic modulus was observed. The rise in the elastic modulus was more prominent for systems containing 1.5% wt/wt and 2% wt/wt Aerosil at higher frequencies. There was no significant difference in the viscous modulus at 1% wt/wt Aerosil. After an initially slow change in the viscous modulus, it decreased sharply up to 10 Hz. Above 10 Hz the decrease in the viscous modulus was independent of the Aerosil concentration.

The viscoelastic behavior of the samples at 30°C is illustrated in Figure 7. The value of the elastic and viscous moduli increased with an increase in temperature, probably because of an accompanying increase in entanglement. At 30°C, the G´ values were significantly greater than those at 20°C, indicating the formation of a strong gel structure at higher temperatures, as observed during the gelation study. The gain in G´ value was linear with frequency. Also, at a 1% wt/wt Aerosil concentration the values were significantly higher than those for the system containing no Aerosil. The elastic modulus of the system with 2% wt/wt Aerosil was higher compared with those of the systems containing 1.5% and 1.0% wt/wt Aerosil. The different viscoelastic properties of the formulations might be attributed to the different gelation temperature. But Figure 7 shows that the viscous modulus decreases with increasing frequency. This observation confirms the shear thinning nature of the system, which is related to the formation of the large aggregates. It has been suggested that the elasticity was related to changes in the PEO mantle, hard sphere interaction between packed micelles, and hydrophobic interaction between the PPO core and water.

The changes in tan δ values of the gel containing different amounts of Aerosil at 20°C and 30°C are shown in Figure 8. Table 1 presents values of tan δ at different frequencies. The phase angle is a good indicator of the overall viscoelastic nature of the material.[39] The tan δ, which is a ratio of viscous and elastic properties, decreased with frequency. The decrease in tan δ was exponential: there was an almost sharp linear decline at low frequencies, followed by a small change at higher frequencies. The slow decline in the tan δ values at 30°C was an indicator of slow structural changes due to the resistance offered by the strong gel network. The well-formed gel structure at 30°C was responsible for lower tan δ values even at low frequency. The improvement of elastic and viscous properties with the addition of Aerosil may be attributed to the hydrogen-bonding capacities of the Si-OH group.

CONCLUSIONS

The spray-dried composites showed an increase in viscosity in the gel form when the hexagonal phase was exhibited instead of the cubic phase. The viscoelasticity and thermal gelation data explained the rheological behavior of the liquid crystal gels of composite particles obtained using spray-drying. These particles and the process by which they were obtained may be useful for designing various delivery systems for pharmaceutical applications.

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