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Viscoelastic Evaluation of Topical Creams Containing Microcrystalline Cellulose/Sodium Carboxymethyl Cellulose as Stabilizer

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ABSTRACT The purpose of this study was to examine the viscoelastic properties of topical creams containing various concentrations of microcrystalline cellulose and sodium carboxymethyl cellulose (Avicel® CL-611) as a stabilizer. Avicel CL-611 was used at 4 different levels (1%, 2%, 4%, and 6% dispersion) to prepare topical creams, and hydrocortisone acetate was used as a model drug. The viscoelastic properties such as loss modulus (G''), storage modulus (G'), and loss tangent (tan δ) of these creams were measured using a TA Instruments AR 1000 Rheometer and compared to a commercially available formulation. Continuous flow test to determine the yield stress and thixotropic behavior, and dynamic mechanical tests for determining the linear viscosity time sweep data, were performed. Drug release from the various formulations was studied using an Enhancer TM Cell assembly. Formulations containing 1% and 2% Avicel CL-611 had relative viscosity, yield stress, and thixotropic values that were similar to those of the commercial formulation. The elastic modulus (G') of the 1% and 2% formulation was relatively high and did not cross the loss modulus (G''), indicating that the gels were strong. In the commercial formulation, G' increased after preshearing and broke down after 600 seconds. The strain sweep tests showed that for all formulations containing Avicel CL-611, the G' was above G'' with a good distance between them. The gel strength and the predominance of G' can be ranked 6% > 4% > 2%. The strain profiles for the 1% and 2% formulations were similar to those of the commercial formulation. The δ values for the 1% and 2% formulations were similar, and the formulations containing 4% Avicel CL-611 had lower δ values, indicating greater elasticity. Drug release from the commercial preparation was fastest compared to the formulations prepared using Avicel CL-611, a correlation with the viscoelastic properties. It was found that viscoelastic data, especially the strain sweep profiles of products containing Avicel CL-611 1% and 2%, correlated with the commercial formulation. Rheological tests that measure the viscosity, yield stress, thixotropic behavior, other oscillatory parameters such as G' and G'' are necessary tools in predicting performance of semisolids.

Key Words: Viscoelastic, Microstructure, Cream, Avicel CL-611, Hydrocortisone acetate, Storage modulus, Loss modulus, Thixotropic, Bridging flocculation

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INTRODUCTION

Products such as topical creams are designed for protracted residence on the skin and undergo a wide variety of stresses during removal from the container and application to the affected area. Therefore, it is important to consider the effects of such stress on the microstructure of products.

Microstructural characteristics (e.g, lamellar gel phase, interfacial layer or membrane of the dispersed phase, micellar formation and physical stability, flocculation, ratio of free and bound water to surfactants) of topical creams-pharmaceutical, cosmetic, or food-have been evaluated using several analytical methods. These methods include viscoelastic measurements [1-4], low- and high-angle X-ray diffractometry [2], confocal laser scanning microscopy [5], thermogravimetry [6], low-temperature scanning electron microscopy [1,7,8], differential scanning calorimetry [9], and ^{17}O nuclear magnetic relaxation [10]. More microstructure investigations have focused on foods than on pharmaceuticals. Therefore, microstructural characterization of topical pharmaceutical creams using methods such as rheology is necessary. Rheological or viscoelastic measurements are generally done to quantify the effects of aging, temperature, ingredients, and processing parameters on formulations. Additionally, they are performed to describe quantitatively the flow of a material for the purpose of quality control (e.g., pumping through pipes or tubes during processing; ease of dispensing of product from tubes, bottles, or jars; and spreadability on the skin surface) [11]. Additionally, textural analysis can be used for selection of candidate formulations for clinical applications [12,13].

Viscoelastic properties are derived from testing of materials without destroying the structure (i.e., the structure is flexed and material is measured in its "ground state"). The measurements are done through rheological flow and dynamic mechanical tests. The former investigates the flow viscosity, whereas the latter evaluates small periodic deformations that determine breakdown or rearrangement of structure or hysteresis.

The dynamic mechanical "strain sweep" test examines the microstructural properties of the material under increased strain. It measures the storage modulus, G', which is an indicator of elastic behavior and reveals the ability of the polymer system to store elastic energy associated with recoverable elastic deformation. The loss modulus, G'', is a measure of the dynamic viscous behavior that relates to the dissipation of energy associated with unrecoverable viscous loss. The loss tangent (tan δ) is defined as the ratio of the loss modulus to the storage modulus and is dimensionless. It is a measure of the ratio of energy lost to energy stored in a cycle of deformation and provides a comparative parameter that combines both the elastic and the viscous contribution to the system [11,14]. The relationship between G', G'', and tan δ is shown in equations 1 and 2:

$$\tan\delta = \frac{G''}{G'} \tag{1}$$

$$G^* = G' + iG'' \tag{2}$$

G^* is the complex modulus, a measure of the material's overall resistance to deformation, and i is the imaginary number, $i = \sqrt{-1}$ [12]. Tan δ values were found to be of great interest in modeling viscoelastic behavior and were successfully used by Gasperlin et al [15] to study lipophilic semisolid systems.

The dynamic viscosity η' is a function of the complex viscosity η" and is related to the steady shear viscosity. It measures the rate of energy dissipation in a viscoelastic material. The relationship between η' and loss modulus (G'') is given in equation 3:

$$\eta' = \frac{G''}{\varpi} \tag{3}$$

Various cellulose derivatives such as hydroxypropyl methylcellulose, hydroxyethyl cellulose, and sodium carboxymethylcellulose (NaCMC) have been used in the development of topical pharmaceutical cream emulsions. However, newer excipients such as Avicel CL-611 have not been well characterized as a dispersion stabilizer in topical preparations. Avicel CL-611 is microcrystalline cellulose coprocessed with a portion of NaCMC (11.3%-18.8%) that provides thixotropic behavior to the corresponding semisolid structural network formed [16,17]. The

hydrocolloids, the group to which colloidal Avicel CL-611 belongs, generally favor oil/water emulsions. They form very good hydrophilic barriers via adsorption on drug particles to form a 3-dimensional network structure within the system, thus sterically stabilizing the system. The consequence is increased viscosity (due to particle-particle interaction) or stabilization of the system without a corresponding increase in the oil phase of emulsions.

The aim of the present work was to investigate the rheological properties of creams (oil/water emulsions) prepared using various levels of Avicel CL-611 as the phase stabilizer and to study the drug release of the various formulations in comparison to a marketed formulation.

MATERIALS AND METHODS

Materials

Avicel CL-611 was supplied by FMC Corporation, Princeton, NJ. Hydrocortisone acetate was purchased from Sigma Chemical Co., St. Louis, MI. Propylene glycol, methylparaben, propylparaben, cetyl alcohol, and glyceryl monostearate were all purchased from Spectrum Quality Products, New Brunswick, NJ. All solvents used in High Pressure Liquid Chromatography [HPLC]. Analysis were HPLC grade unless otherwise noted and were used as received. The commercial (oil/water) cream used in this study was Lanocort 10 containing 1% hydrocortisone acetate. Other ingredients in the formulation included aloe, ceteareth-20, cetearyl alcohol, cetyl alcohol, methylparaben, propylparaben, sorbitol, water, and zinc pyrithione.

Methods

Preparation of creams

The oil phase ingredients and the aqueous phase ingredients (containing the Avicel CL-611 dispersion) were mixed separately and heated to 70°C. The aqueous phase and the oil phase ingredients are listed in Table 1. The oil phase was then added to the aqueous phase and mixed with a Lightnin mixer (Aldrich Chemical Co., Milwaukee, WI) at 500 rpm for 2 minutes followed by increasing the speed to 1000 rpm for 10 minutes. The hot creams were poured into ointment tubes and allowed to cool for solidification. Different levels of Avicel CL-611 (1%, 2%, 4%, and 6% w/w) were used to develop oil/water creams. Based on a preliminary study, 4 replicate batches of creams containing 1% and 2% Avicel CL-611 only were made. Each formulation contained 1% hydrocortisone acetate as model drug.

Table 1. Cream Formulation

Aqueous phase	Percentage
Avicel CL-611 dispersion	To 100.0% w/w
Methylparaben	0.25
Hydrocortisone acetate	1.0
Propylene glycol	10.0
Polysorbate 80	5.0
Oil phase	
Cetyl alcohol	2.50
Propylparaben	0.15
Glyceryl monostearate	15.0

Rheological studies

Rheological testing of the various cream formulations was performed at ambient temperature using a control-stress rheometer (TA Instrument AR 1000N). The general conditions for all tests included the use of a 4-cm acrylic plate with solvent trap and 1600-μ gap.

Steady shear

A flow test was used to determine the relative viscosity of all formulations with the following parameters: For the upcurve, a continuous ramp with shear rate as controlled variable (0-100 1/sec), log mode, 2 minutes ramp duration at 25°C was applied. The same procedure was used for the

downcurve with reversed shear rate (100-0 1/sec) to measure thixotropy and yield stress.

Dynamic Mechanical Testing

Strain sweep

All test samples were subjected to constant frequency (10 rad/sec) using an amplitude ramp with 0.2%-100% strain at 25°C. The aim was to investigate the structural properties of the creams under increased strain.

Time sweep

Each sample was subjected to preshearing (1 minute applied value of 20 1/sec shear rate at 25°C). The aim was to examine the structure recovery after the structure was broken down. The samples were subjected to a frequency of 10 rad/sec, with a 1.0% strain (this value was part of the established procedure in the laboratory used) as controlled variable for 30 minutes at 25°C.

Drug Release Study

The drug release from various formulations was evaluated using United States Pharmacopoeial [USP] Type II apparatus and an Enhancer Cell assembly [18]. The release medium consisted of 200 mL of 60% vol/vol ethanol. A polyethylene membrane (CoTran, 3M Pharmaceuticals, St. Paul, MN) was used as the permeating membrane. A 1-mL sample was withdrawn at 1, 2, 3, 4, 6, and 8 hours. The analysis sample (50 µL) was directly injected into the HPLC for analysis. Drug release from a commercial formulation was compared to that of the creams prepared in the laboratory.

HPLC Assay

The concentration of hydrocortisone acetate released was quantified by a reverse-phase HPLC method. A C18 column (4.6 x 100 mm, 5 µm) (Phenomenex, Torrance, CA) was used. The mobile phase consisted of methanol:water:acetonitrile (3:6:2.5) with a flow rate of 1 mL/min (Shimadzu Liquid Chromatography LC 10AS, Columbia, MD). The eluent was monitored with an UV detector at 242 nm (Shimadzu UV-VIS Detector SPD-10A), and chromatograms were analyzed using EZChrome software (Shimadzu Scientific Instruments, Columbia, MD).

RESULTS AND DISCUSSION

Rheological Evaluation

Steady shear

Based on a preliminary screening, we found that formulations containing 1% and 2% Avicel CL-611 had viscosity and yield stress similar to those of the commercial formulation (Table 2). Hence, replicate batches were made only for creams containing 1% and 2% Avicel CL-611. The thixotropic values for 1% or 2% Avicel CL-611 creams were lower than those of the commercial formulation,indicating that these formulations had better structure recovery properties. However, creams containing 4% and 6% Avicel CL-611 had much higher thixotropic values, implying that these formulations took longer to rebuild viscosity at rest after being sheared, which is potentially an undesirable property. A typical flow curve (shear rate vs shear stress) of the cream containing 1% Avicel CL-611 is shown in Figure 1.

The yield stress values for the various formulations are reported in Table 2. The magnitude of yield stress relates to the strength of interparticle interaction in the three-dimensional network microstructure of the creams. Both 4% and 6% creams had higher yield stress values compared to the other three formulations, indicating more contact surfaces, stronger packing between particles, lower packing fraction (Φ_m), and less tendency for bridging flocculation. This is to be expected, since greater concentration of hydrocolloid will cause better interpenetration of the polymer coils. In contrast, the yield stress of the

Table 2. Relative Viscosity/Yield Stress/Thixotropy of Various Formulations and Commercial Cream

Levels of Avicel CL-611	Relative Viscosity† (Pa.s)			Yield Stress,‡ Apparent (Pa)	Thixotropy (Pa/s)
	6 sec^{-1}	12 sec^{-1}	100 sec^{-1}		
1%	22.7 (5.4)	11.9 (2.9)	1.58 (0.29)	101.1 (22.1)	1818 (262.9)
2%	28.3 (1.5)	15.3 (1.3)	1.9 (0.1)	121.8 (9.1)	2257 (154.9)
4%	58.4	22.5	2.1	235.1	9578
6%	89.5	36.9	3.04	355.3	14,710
Commercial	13.5	11.2	2.4	121.1	5020

*Values in parentheses are standard deviations (n = 3).
† At selected points (6 sec^{-1}, 12 sec^{-1}, 100 sec^{-1}).
‡ Bingham statistical model ($\sigma = \sigma_y + K_y$, where σ = shear stress, σ_y = yield stress, K = Bingham viscosity, γ =shear rate).

1% Avicel CL-611 was the lowest, suggesting that a small stress is needed to initiate flow, which may be better in terms of applicability of the formulation to the skin. Although the stress values were the same for the cream containing 2% Avicel and the commercial formulation, the commercial cream took more time to rebuild its structure at rest after shear, as shown by the greater thixotropic value of the commercial cream.

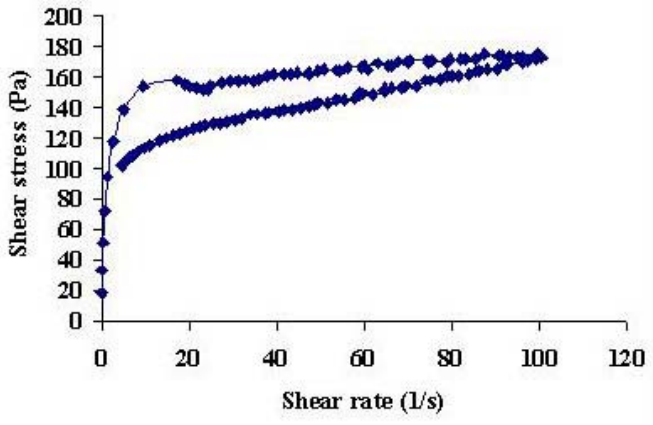

Figure 1. Typical flow curve (shear rate vs shear stress of a batch) of cream containing 1% w/w Avicel CL-611 [Top of the rheogram is the upcurve and the lower is the down curve].

Henderson et al [19] determined that creams generally encountered a shear rate of 120 sec^{-1} during topical application. Viscosity at this shear range could determine the ease of rubbing a cream or emulsion and hence influence the end-use performance of the product. Table 2 shows the viscosity of the various formulations used in this study at selected shear rates. The viscosities of the 1% and 2% formulations at shear rate of 100 sec^{-1} (1.58 and 1.9 Pa.s) were lower compared to the viscosity of commercial cream (2.4 Pa.s), indicating better spreadability upon topical application of the formulations.

Dynamic Mechanical Tests

Strain sweep

Creams prepared using 1% or 2% Avicel CL-611 had similar strain profiles (Figure 2A). The phase angle δ, which is a good indicator of the overall viscoelastic nature of the sample, was found to be 62° and 61° for the 1% and 2% Avicel, respectively, and 67° for the commercial cream (Figure 2D). These δ values range between 0° (ideal elastic solid) and 90° (completely viscous flow liquid), indicating that the creams are viscous enough to allow for

spreading and rubbing on the skin. Looking at the values of tan δ for the commercial cream (2.36) compared to the 1% and 2% Avicel CL-611 formulations (1.80 and 1.88), commercial cream is more viscous. Tan δ greater than 3 indicates that particles are nonassociated; $1 < \tan \delta > 3$ indicates that particles are weakly associated and $\tan \delta < 1$ signifies highly associated particles [20]. Therefore, it can be inferred that particles or the hydrocolloid polymer network within the laboratory-made cream products were more highly associated (more densely packed) or there was less bridging flocculation compared to the commercial cream [21].

The elastic modulus, G', for the 1% or 2% Avicel CL-611 and the commercial (Figures 2A and D) formulation was over G'' with a good distance between them, signifying strong thickening or solidifying behavior. However, at about 10% strain, the products started to break down, with G' and $'G''''$ crossing each other. The lower strain is a desirable feature since it simulates the onset of spreading of cream on the skin, as discussed earlier under Steady shear. This would also allow better absorption from the skin, considering the fact that the cream has to spread well on the skin surface before absorption could take occur.

In contrast, the 4% and 6% formulations did not show breakdown of elastic modulus (G') and crossing with the loss modulus (G'') until strain reached about 70% (Figures 2B and C). This demonstrates that greater strain is needed to cause effective spreading and rubbing, a correlation with the observed yield stress data discussed earlier under Steady shear above. The higher the percent strain, the stronger the cream structure. The greater strain is not desirable in a formulation, thus, 4% and 6% formulations were considered unsuitable. Therefore, knowledge of these viscoelastic indices could be used to predict the performance of topical delivery systems such as creams.

Time sweep

Creams prepared using 1% Avicel CL-611 had lower G', G'', and η' compared to creams prepared using 2% Avicel CL-611 and commercial formulation (Table 3, Figures 3A and C). Interestingly, in creams containing 1% or 2% Avicel CL-611, the structure recovered rapidly, G' (the solid-like component) never crossed G'' (the liquid-like component) during the test. This indicates a strong network of polymer entanglement and possibly better long-term stability compared to the commercial product. The commercial formulation had an increase in G' after preshearing that decreased substantially after approximately 600 seconds (Figure 3C, Table 3).

However, the formulations containing 4% or 6% Avicel CL-611 (Figure 3B) had much stronger solid-like properties (G' was very predominant) compared to other formulations. This is in agreement with the high yield stress values needed to initiate flow and the longer time needed to rebuild structure at rest after shear, as reflected in the high thixotropic values in Table 2.

The viscoelastic moduli, storage modulus (G'), and viscous modulus (G'') are direct measurements of particle-particle interaction (i.e., they measure structural characteristics of the cream formulations). The response is sensitive to the amplitude of applied deformation, that is, to strain or stress (γ or σ). Although the rheology is measured macroscopically, the measurement depends on microscopic considerations and it yields valuable information about the microstructure [22].

Drug release

The amount of the drug released (Q) was plotted against the square root of time (t), based on Fick's law of diffusion.

$$Q = AC_O(t)^{1/2} \quad (4)$$

In the above equation, A is the cross-sectional area of the Enhancer® Cell and C_0 is the initial concentration of the drug in the formulation.

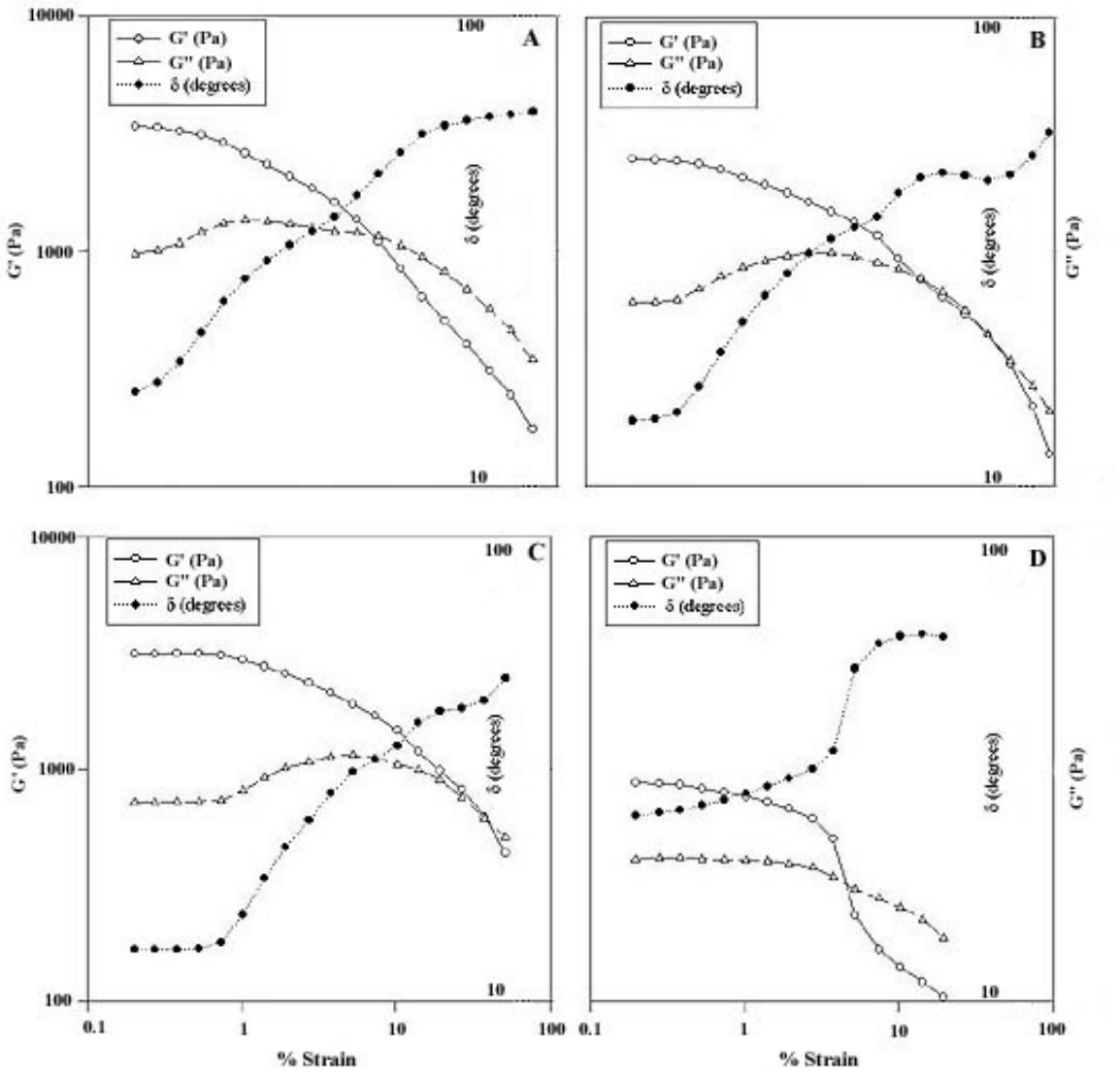

Figure 2. Typical strain sweep profiles for formulations containing Avicel CL-611, A - 1% & 2%; B- 4%; C - 6% and for the commercial cream - D.

The release of drug from the various creams fitted the square root of time relationship (Figure 4), indicating that the release was by diffusion. As expected, higher concentration of the Avicel CL-611 resulted in a slower drug release as a result of less bridging flocculation. This correlates with the relative viscosity data in Table 2, indicating that formulations with higher viscosity had lower release compared to the commercial formulation. The drug release profiles for creams containing 1% or 2% Avicel CL-611 were similar, while the release from the commercial formulation was faster than that of the other formulations. This could be due to the hydrophilic excipients such as ceteareth-20 (a surfactant) and sorbitol, a humectant that retards the recrystallization of dispersed solids, thus increasing the solubility of hydrocortisone acetate in the marketed product.

Table 3. Viscoelastic Properties of Various Formulations Containing Different Levels of Avicel CL-611 and the Commercial Cream

Levels of Avicel CL-611	Crossover Time (G'=*G″* Crossover) (sec)	Crossover Modulus G' = *G″* (at *y*-Axis) (Pa)	Dynamic Viscosity at G' =*G″* (η' at *y*-Axis) (Pa.s)	Elastic Modulus (G') 900 Sec (G' at y-Axis)(Pa)
1%	NC	NC	NC	739 (173)
2%	NC	NC	NC	1204 (252)
4%	NC	NC	NC	1484
6%	NC	NC	NC	1471
Commercial	556.4	963.5	93.89	639

*Values in parentheses are standard deviations of the elastic modulus (G')
NC indicates no crossover of G' with *G″*, G'> *G″*

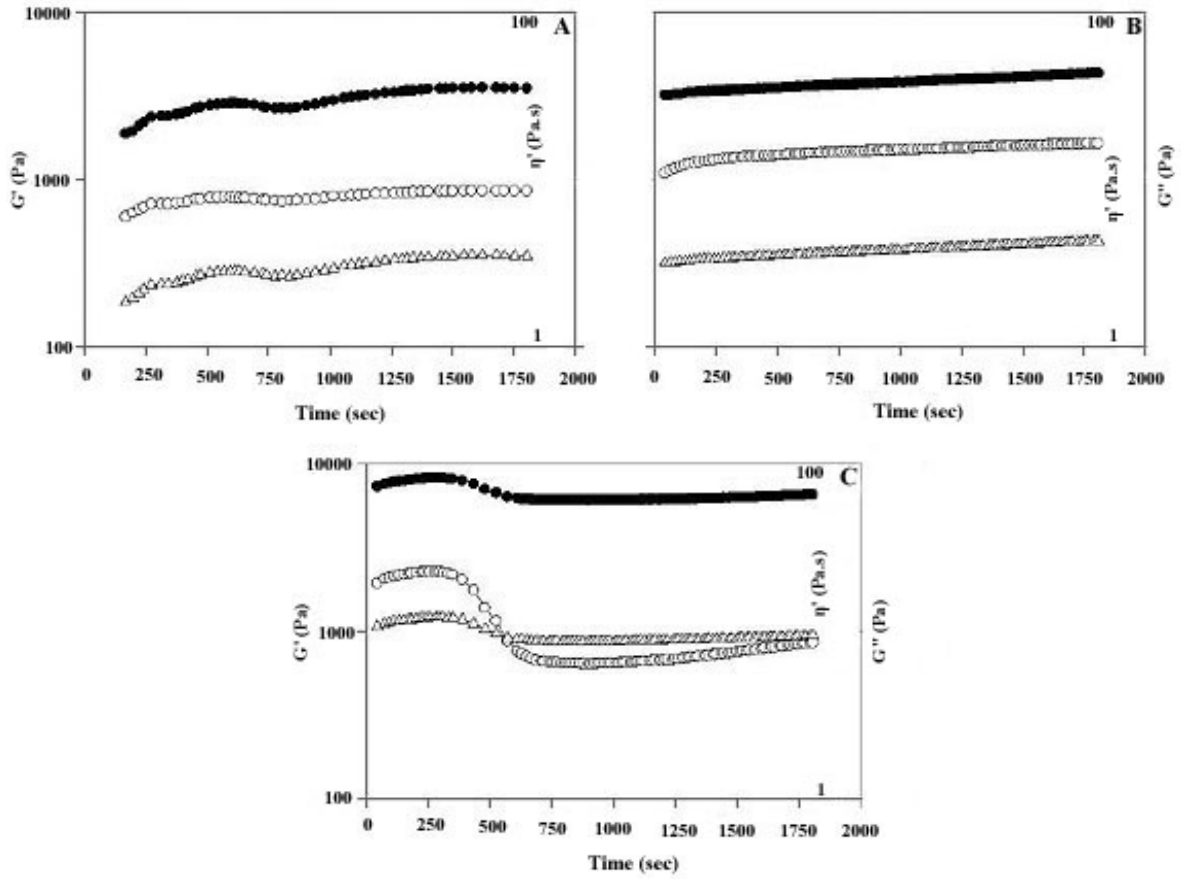

Figure 3. Typical time sweep profiles for formulations containing Avicel CL-611, A - 1% or 2%; B - 4% or 6%; and commercial cream - C. Closed circles - η', open circles - G' and open triangles - *G″*

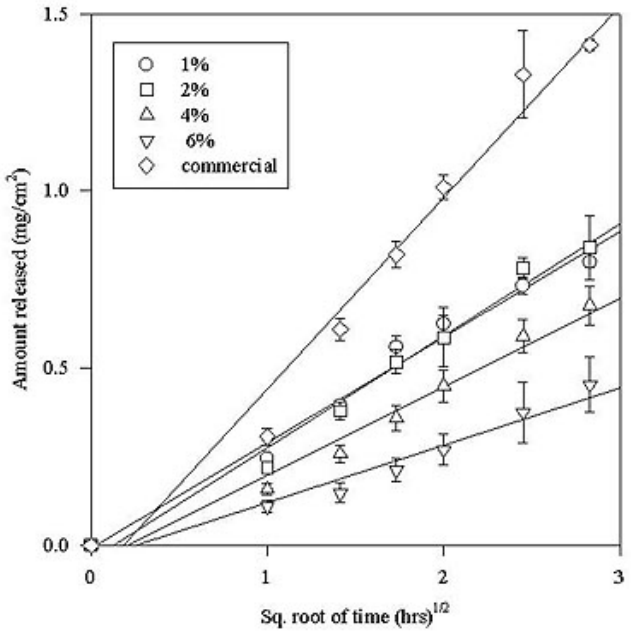

Figure 4. Drug release profiles of various cream formulations containing different levels fo Avicel CL-611 and commercial cream.

CONCLUSIONS

Microstructure characterization of the Avicel® CL-611 creams was investigated using rheological, dynamic mechanical viscoelastic measurements and drug release rate, and it revealed a dependence on the excipient level. Measurement of various rheological properties can serve as a good preformulation tool in predicting the performance of semisolids during processing, packaging, storage stability, spreadability during use, and subsequent absorption of the hydrocortisone. Such tests could also be considered for future regulatory guidance deliberations or USP specifications in addition to the current test for drug release.

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