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Coagels from alkanoyl–6-O-ascorbic acid derivatives as drug carriers: structure and rheology

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Abstract

6-O-Ascorbic acid alkanoates (ASC*n*, where *n* is the number of carbon atoms in the alkyl chain) behave as surfactants and form stable supramolecular assemblies in water, depending on chemical structure, concentration and temperature. In concentrated water dispersions, ASC*n* form liquid crystalline structures ('coagels'), below the critical micellar temperature (CMT), with a typical Krafft phenomenon. Such semisolid systems incorporate and stabilize drugs like anthralin, which is insoluble and unstable in aqueous media. The rheological behavior of coagels obtained from aqueous ASC8, ASC10, ASC11, ASC12, ASC14 and ASC16 was evaluated and related to the coagel structure. For ASC8, ASC12, ASC14 and ASC16 complex rheology was observed and spur values were determined. This behavior is indicative of a high three-dimensional structure. The spur value represents a sharp point of structural breakdown at low shear rate. At this point the semisolids acquire pseudoplastic flow with a very low viscosity. Instead, ASC10 and ASC11 coagels showed pseudoplastic flow and—in the case of ASC11—thixotropy was observed. The ASC*n* coagel rheological behavior and their capability to load pharmacologically active compounds point to a potentially valuable capacity for such systems as drug carriers.

Keywords: Surfactants; Ascorbyl derivatives; Coagel; Rheology; Drug carrier

1. Introduction

6-O-Ascorbic acid alkanoates (ASC*n*, Scheme 1) behave as amphiphilic molecules in water. They possess both a hydrophobic moeity (aliphatic chain) and a polar group (ascorbic acid) [1,2].

These derivatives were synthesized in our laboratories [3] with the main aim of preparing vitamin C-based amphiphiles that combine the powerful antioxidant properties of ascorbic with sufficiently good solubility in lipophilic media.

The solubility of ASC*n* decreases with the alkyl chain length, and increases with temperature. These compounds form transparent dispersions in water, above the critical micellar concentration (CMC) and critical micellar temperature (CMT) [4]. If the dispersions are cooled down below the CMT, a semicrystalline mesophase (coagel) is obtained. Upon heating, coagels may form either liquid and homogeneous micellar solutions ($n \leq 10$), or gels ($n \geq 11$), depending on chain length n, temperature, and the addition of other solutes. In a recent paper we investigated the phase behavior of coagels as a function of the alkyl chain length, and in the presence of sucrose and urea [5]. The effect of different salts is now being tested on ASC12 coagels. Further, these coagel systems are able to increase substantially the apparent solubility [6], and the stability of certain drugs [7]. They therefore present a promising tool as drug carriers in pharmaceutical dosage formulations.

In this paper we evaluate the rheological behavior of coagels obtained from different ascorbyl–alkanoates ($n = 8$, 10, 11, 12, 14, 16). We interpret the results in terms of their structural features.

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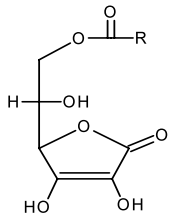

R = $(CH_2)_x$-CH_3

x		*n*
6	(ASC	8)
8	(ASC	10)
10	(ASC	12)
12	(ASC	14)
14	(ASC	16)

Scheme 1.

2. Material and methods

2.1. Materials

Alkanoyl–6-O-ascorbic acid esters (ASC*n*, with $n = 8$, 10, 11, 12, 14 and 16) were made in our laboratories. The procedure [3] uses condensation between the corresponding carboxylic acid ($H_3C(CH_2)_{n-2}COOH$) and the C_6–OH primary group of L-ascorbic acid, in sulphuric acid at 40 °C. Purity was assessed through TLC and elemental analysis. All reactants (analytical grade) were purchased from Fluka (Milan, Italy), and used without further purification. Bidistilled water was purified with a MilliQ apparatus.

2.2. Rheology

Coagels were prepared by heating ASC*n* aqueous suspension above the phase transition temperature, the samples were then placed into the sensor cup and kept for three hours at 8 °C and then assayed. Rheological assays were performed at 20 °C in a Haake (Karlsrube, Germany) viscometer VT500 equipped with a VT500/VT 3.01 software, and an NV sensor. The curve fittings and statistical analyses were performed using a Microcal Origin® version 3.5.

2.3. ESEM

Environmental scanning electron microscopy experiments were performed on coagels using an XL 30 ESEM Philips apparatus at 10 kV, at about 10 °C, with a relative humidity ranging between 45 and 85%.This corresponds to a pressure of 2.9–6.0 mm Hg.

2.4. Drug incorporation into coagels

ASC*n* suspensions at different concentrations were heated above the CMT, until the gel phase was formed. Then an excess of anthralin was incorporated into the samples.

After 2 h, the samples were filtered and system was permitted to reach room temperature. Then, a weighted amount of the loaded coagel was placed into a volumetric flask, diluted with ethanol and transferred to a Shimadzu UV-160-A spectrophotometer. All measurements were performed three times.

3. Results and discussion

ASC*n* coagels and gels can be obtained through a sequence of heating-cooling cycles of the aqueous suspensions around the CMT. In previous work, we determined the CMT values for ASC8, ASC10, ASC11, ASC12, ASC14 and ASC16 using differential scanning calorimetry (DSC) and conductimetry. The results are summarized in Table 1 [8].

3.1. Preliminary examination of the coagels

Qualitative information can be gained by observing the macroscopic behaviour of the coagels. Coagels obtained from ASC8, ASC12, ASC14 and ASC16 remain at the bottom of the container even when the container is inverted upside-down and shaken. By contrast coagels from ASC10 and ASC11 show an apparent pseudoplastic flow and can be easily poured from the vial after shaking. All coagels decreased in apparent consistency with time on rubbing, suggesting thixotropy or irreversible shear breakdown. Before shear stress, coagels from ASC8, ASC12, ASC14 and ASC16 appear homogeneous. No phase separation is observed, even after a long period (> 7 days). When shear stress is applied, macroscopic structural changes can be observed. After a brief pause (< 30 minutes), free water is released and phase separation occurs. Unlikely as it seems, coagels from ASC10 and ASC11 form semisolid systems where phase separation is observed before shear stress and the formation of the coagel is faster than for the other derivatives.

Structural differences can be tracked also at a microscopic level. Fig. 1 shows the ESEM micrographs of coagels from ASC8, ASC10, ASC12 and ASC16. For ASC8 and ASC10, the coagel structures can be depicted as a planar continuous lamellar phase, where bilayers are ordered in sheets [9]. However, important size differences in the plates are observed (see Fig. 1a and 1c).

Table 1
CMT values for the phase transitions of coagels of ASC*n* in water

n	CMT (°C)	
	DSC	Conductivity
8	18.5	19.3
10	34.5	36.8
11	40.0	38.5
12	47.3	44.5
14	56.0	54.2
16	63.8	61.3

3.2. Continuous shear analysis

The rheological behavior of the coagels was evaluated by recording the shear rate vs. shear stress flow curves. The results are shown in Fig. 2. All coagels show a non-Newtonian flow. The differences are directly related to their structure.

Coagels from ASC10 and ASC11 (Fig. 2b and c) showed pseudo-plastic flow, and in the case of ASC11 thixotropy was detected as well.

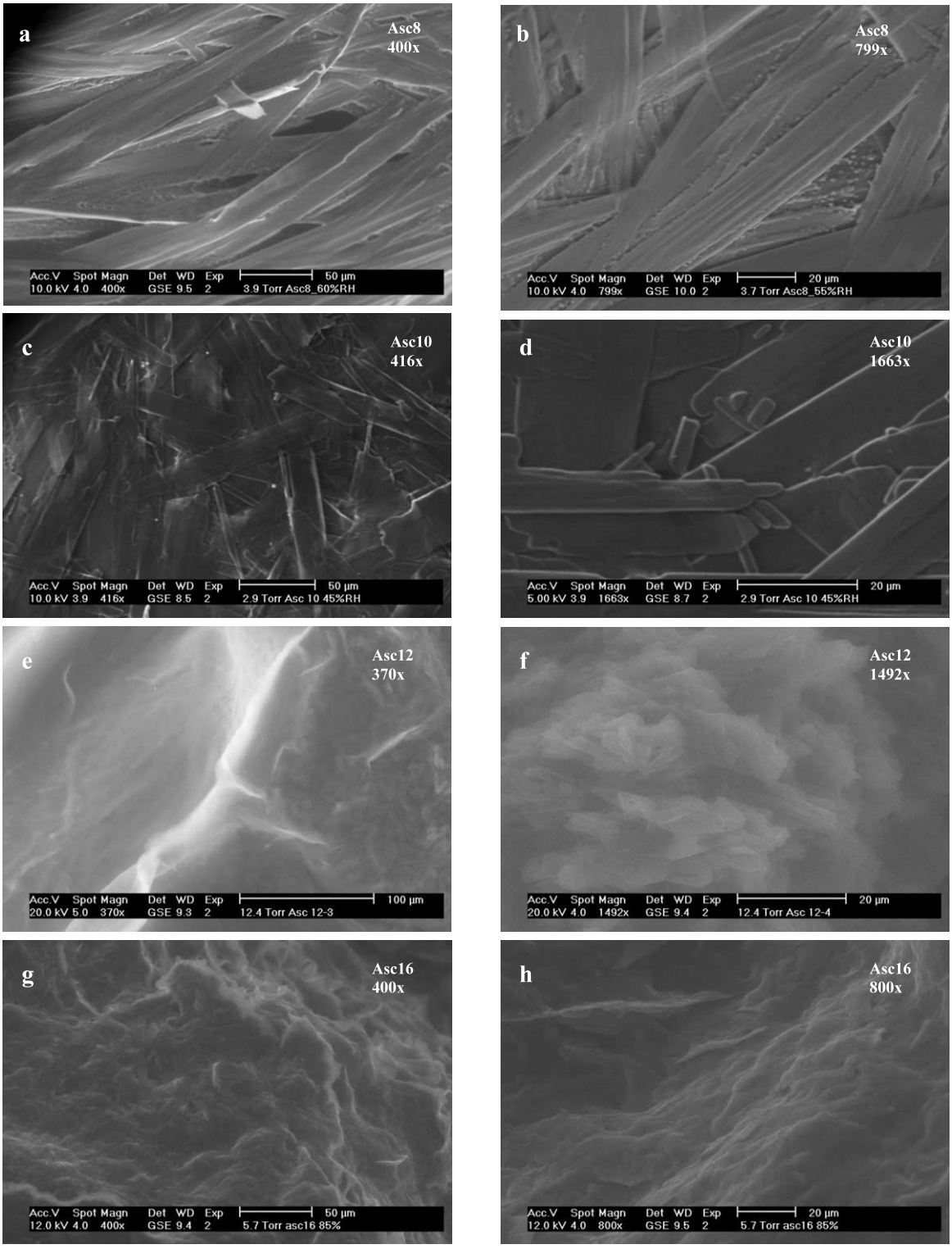

Fig. 1. ESEM for ASC*n* coagels.

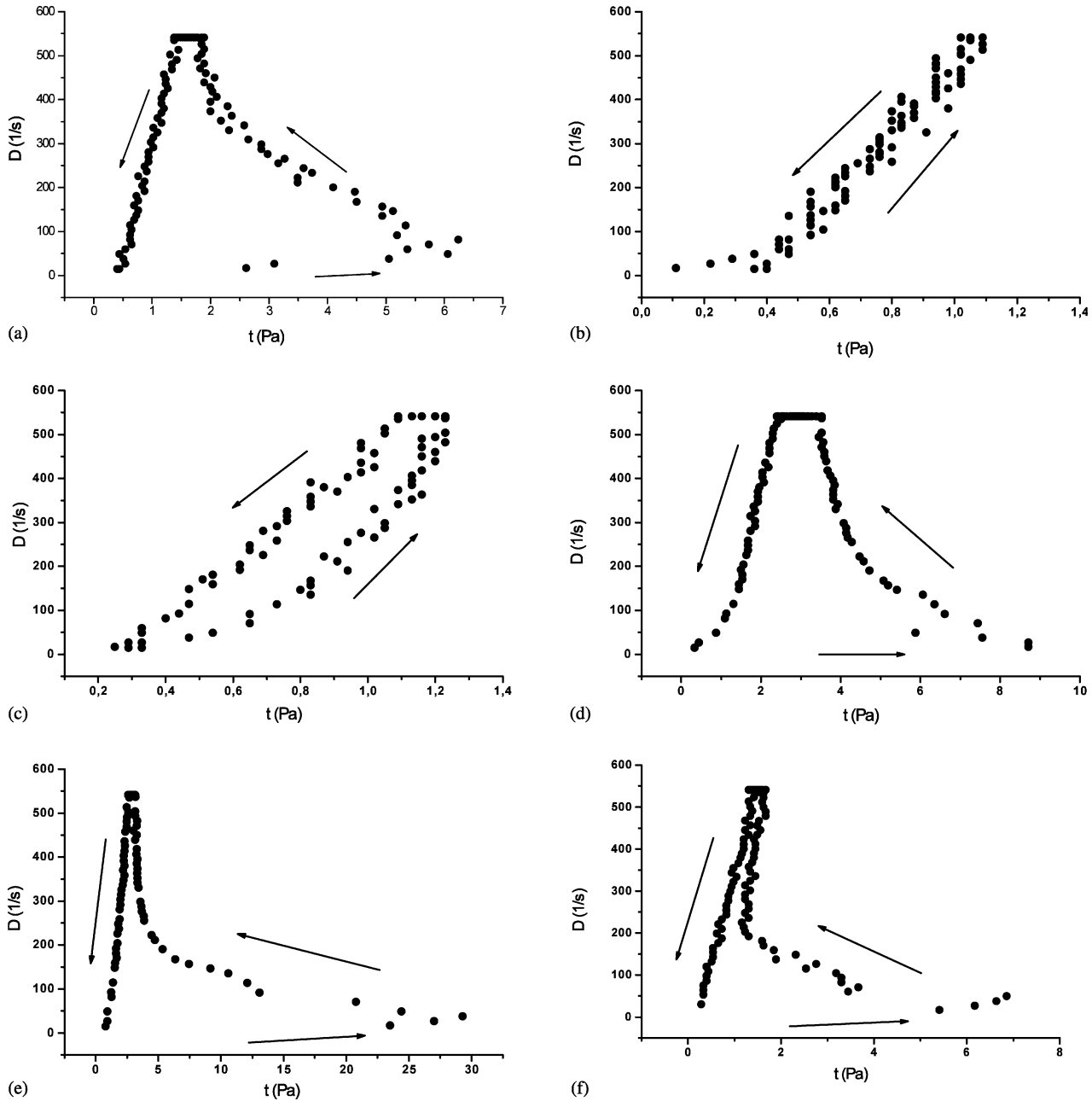

Fig. 2. Rheograms for ASC*n* coagels: (a) ASC8; (b) ASC10; (c) ASC11; (d) ASC12; (e) ASC14; and (f) ASC16.

Instead, coagels from ASC8, ASC12, ASC14 and ASC16 exhibit a much more complex rheology (Fig. 2a,d–f). This behavior is characteristic of highly structured semisolids and several reports for a wide variety of systems can be found in the literature [10–12]. The rheograms form a hysteresis loop in which the 'down' curve is displaced to the left of the 'up' curve. A characteristic feature of many such rheograms is the presence of a 'spur' point on the ascending curve. The rheology of these coagels displays a high yield or spur value. This can be taken as a measure of the strength necessary to break the ordered structure of the system before a significant flow occur. The shear stress at spur point is called the 'static yield value' (σ_S) [12].

Moreover, a 'dynamic yield value' (σ_D) can be obtained by extrapolating the linear portion of the down curve to the shear stress axis. σ_D measures the energy input that is necessary to achieve a constant τ/D ratio at which the structure has been partially or totally disrupted during the up curve stress [12]. Likewise, in general terms, the loop area (LA) may indicate the amount of structure breakdown that takes place during

Table 2
Area under curve (LA, from Fig. 2), static yield value (σ_S) and dynamic yield value (σ_D) for ASC*n* coagels

Coagel from	LA	σ_S (Pa)	σ_D (Pa)
ASC8	1253	6.24	0.42
ASC12	1574	8.71	1.06
ASC14	2977	29.29	1.02
ASC16	643	6.86	0.18

shearing. The values of σ_S and σ_D, for coagels from ASC8, ASC12, ASC14 and ASC16 are reported in Table 2.

For such systems, an irreversible structure breakdown is observed when the shear stress exceeds σ_S. The original coagel structure is not restored on rest. The values observed for σ_S are proportional to the alkyl chain length for ASC8, ASC12 and ASC14. The relatively low value for ASC16 coagel indicates a less structured network. The semisolids exhibit a pseudoplastic flow at $\tau \geq \sigma_S$.

3.3. Rheological behavior versus microstructure of coagels

The structural differences observed in ESEM images (see Fig. 1) can be related to the different rheological behavior of ASC*n* coagels. For ASC10, the coagel has a typical lamellar structure, with flexible, parallel bimolecular sheets [13]. These account for a pseudoplastic flow behavior.

A similar structure is observed for ASC8 as well. However this system shows a more complex rheology with a spur point. A reasonable explanation for this finding is the significant size difference of ASC8 coagel plates, with respect to those of ASC10 that are responsible for the formation of a three dimensional structure (see Fig. 1a and c). Coagels from ASC12, ASC14 and ASC16 behave similarly to ASC8 samples. However, ESEM images (Fig. 1e–h) show a very different arrangement of the lamellae that form a 'house of cards' structure. Swelling and strengthening of the semisolid network is owed to the presence of strongly bound water regions between the amphiphilic bilayers. Instead, for ASC10 and ASC11 coagels, this kind of arrangement are apparently not possible. When coagels of ASC12, ASC14 and ASC16 are subjected to shear stress ($\tau > \sigma_S$), the structure breaks irreversibly and the viscosity decreases significantly. The sample acquires a less ordered pattern, similar to that of ASC10. This phenomenon can be clearly observed with the ESEM micrograph of Fig. 3, where the structure of an ASC12 coagel after shear stress is depicted. This picture is similar to Fig. 1c, indicating that the ASC12 coagel acquires a pseudoplastic behavior after shear stress as in the case of ASC10 and ASC11 coagels. Such rheology is a characteristic feature of some coarse systems commonly used in pharmacy [14].

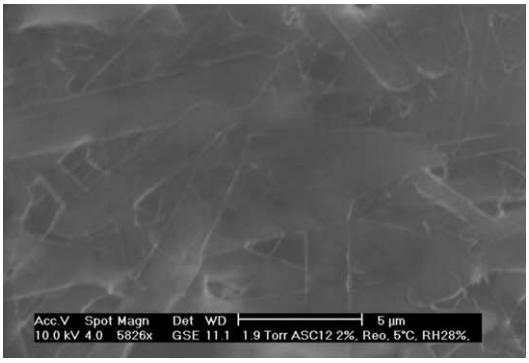

Fig. 3. ESEM for ASC 12 coagel after shear stress ($\tau \geq \sigma_S$).

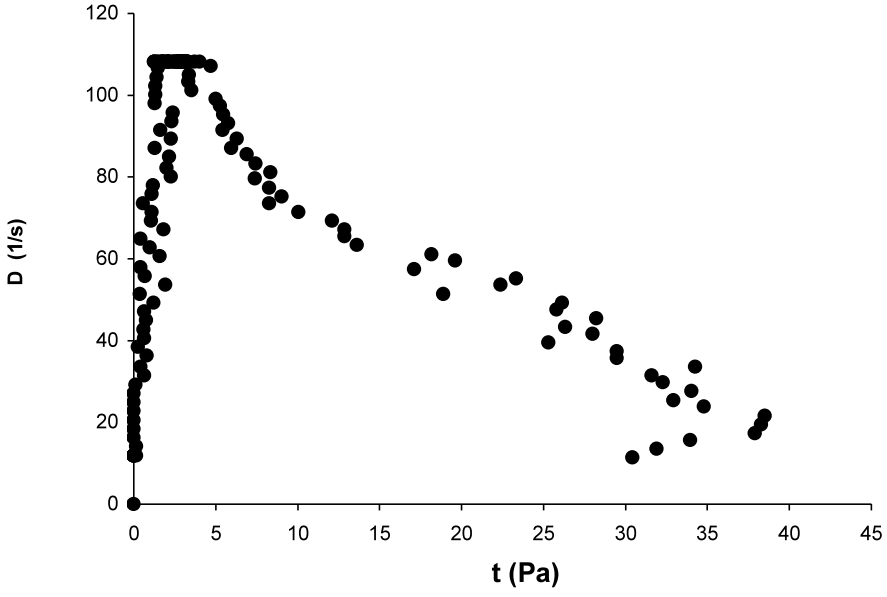

Fig. 4. Rheogram for anthralin loaded ASC14 coagel.

Finally, taking into account the potential utilization of these semisolids systems as drug carriers, the incorporation of an antipsoriatic drug (anthralin) [15] was evaluated as well as its influence in the rheology of the coagels.

The amount of anthralin loaded into ASC*n* coagels increased linearly with n. However, the load capacity is higher for $n > 12$ [16]. This behavior could be attributed to the gel configuration of ASC14 and ASC16 dispersions at temperature above TMC [8], where lamellar configuration would permit higher drug solubilization comparatively to micellar dispersions of ASC*n* with lower molecular weight.

Regarding the rheological properties of anthralin loaded coagels, the drug incorporation have no effect on the semisolid structure. In Fig. 4 the rheogram of anthralin loaded ASC14 coagel is depicted. As it occurs with ASC14 unloaded coagel (Fig. 2e), a spur value is observed and it is indicative of a high structured liquid crystal. This fact permit to infer that the solubilization of drug in the lipophilic portion of the coagel do not affect the interaction between the solvent (water) and the hydrophilic portion of ASC*n*.

4. Conclusions

Alkanoyl–6-O-ascorbic acid esters (ASC*n*) behave as amphiphiles in water dispersions, and form semisolid concentrated systems (coagels). These supramolecular assemblies, in which the surfactant molecules are arranged in closely packed lamellar structures, undergo either to a coagel-to-micelle or a coagel-to-gel phase transition depending on the aliphatic side chain length. In this work we studied the rheological behavior of ASC*n* coagels.

ASC8, ASC12, ASC14, and ASC16 coagels show a complex rheology, with the appearance of spur rheograms, while coagels of ASC10 and ASC11 exhibit pseudoplastic flow. ASC11 also shows thixotropy. The structural arrangement of these systems is the main factor that accounts for this behavior. Coagels of ASC12, ASC14 and ASC16 form a 'house of cards' structure, where swelling and strengthening of the semisolid network occurs, due to the presence of water pools between the amphiphilic bilayers. On the other hand, for ASC10 and ASC11 coagels, this kind of arrangement apparently is not permitted and flexible bimolecular sheets arrange parallel to each other.

When a spur value is reached, ASC12, ASC14 and ASC16 coagels acquire pseudoplastic flow. In this way, according to the handling of the semisolids, the rheological properties of the system can change.

This rheological behavior is a crucial factor for the use of ASC*n* coagels as efficient and stabilizing drug carriers, especially for rather hydrophobic and easily degradable products.

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