Viscoelastic Properties of a Virucidal Cream Containing the Monoglyceride Monocaprin: Effects of Formulation Variables: A Technical Note

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INTRODUCTION

Creams are often the formulation of choice for topical drug delivery, but they are complex systems and many factors must be considered in their formulations. The structure and rheological properties of creams are affected by several factors, among them the volume fraction of the disperse phase, the droplet size distribution, the viscosity and composition of the medium, as well as the type and concentration of surfactant.[1] The behavior of a semisolid such as a cream can be characterized with a combination of elasticity and viscosity, and those aspects can be measured with a rheometer.[2] Rheology measurements are a relatively simple and effective technique to compare the structural properties of creams and are an efficient way to obtain information about the resistance to external forces, and thereby an indication of the stability of the structure for a length of time.[3,4]

The lipid monocaprin (1-monoglyceride of capric acid) has been shown to be effective against enveloped viruses such as vesicular stomatitis virus, herpes simplex virus (HSV), and human immunodeficiency virus (HIV) in vitro.[5,6] Monocaprin has also been found to possess bactericidal activity in vitro against bacteria such as *Staphylococcus aureus* and Group B *Streptococcus*.[7]

It has previously been found that the antimicrobial effect of monocaprin can be diminished by excipients used in the formulation.[8,9] In a previous work the antimicrobial activity of oil/water (o/w)-cream formulations containing monocaprin were tested against HSV-1. The results showed that formulation variables affected the antimicrobial activity, but it was possible to obtain activity equal to that of monocaprin control in culture medium.[10] The present work is aimed at studying the rheological properties of the cream formulations in order to obtain information about the consistency and a prediction of stability. As monocaprin has limited solubility in water, it was solubilized in the aqueous phase using a combination of the cosolvent propylene glycol (5%) and the surfactant polysorbate 20 (1%). Since earlier work had indicated that the stability of monocaprin was improved by the presence of carbomer, the effect of carbomer as a stabilizing agent in the aqueous phase was studied.[11] The formulation variables in the creams were oil/volume fraction, amount of carbomer in the aqueous phase, and amount of monocaprin (Table 1).

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MATERIALS AND METHODS

Materials

Propylene glycol and polysorbate 20 were purchased from Sigma Chemical Co (St Louis, MO). Monocaprin (pharmaceutical grade) was a gift from Danisco Ingredients (Copenhagen, Denmark). Methylparahydroxybenzoate, propylparahydroxybenzoate, cetostearyl alcohol emulsifying wax, and paraffinum liquidum were purchased from NMD (Oslo, Norway). Carbomer 974P was obtained from BF Goodrich (Cleveland, OH). Distilled water was used in the aqueous phase.

Preparation of Oil/Water Creams

The oil phase consisted of equal amounts of paraffinum liquidum and cetylan, with the total amount represented in Table 1. The aqueous phase contained 5% propylene glycol, 1% polysorbate 20, and variable amounts of carbomer as shown in the table. Monocaprin and preservatives were dissolved in propylene glycol, and then 1% polysorbate 20 was added and mixed carefully. Carbomer 974P was allowed to swell in part of the water before the propylene glycol solution was gently stirred into the gel. Cetostearyl alcohol emulsifying wax was dissolved in paraffinum liquidum at 60°C. The aqueous phase was then heated to 40°C, and when the oil phase had cooled down to 40°C the 2 phases were mixed using a homogenizer.

Rheological Properties

Rheological properties were determined using a rheometer (StressTech and Stress Rheologic Basic software, Version 2.2; ReoLogica Instruments AB, Lund, Sweden) with parallel plate system; except in the shear viscosity test, a cone-and-plate system was used. The temperature of the base plate was 25°C ± 0.1°C. The tests used were as follows: oscillation stress sweep test, oscillation frequency sweep test, and viscosity test. All rheological determinations were made at least in triplicate for each cream using separate samples.

Table 1. Formulation Variables of Creams: Results of Oscillation Stress Sweep Test*

Formulation	Carbomer in Aqueous Phase %	Oil Phase %	Monocaprin Concentration (mM)	Storage Modulus G' (Pa)*	Loss Tangent (tan δ)	Crossing-over Point (Pa)
1	0.5	2.5	20	73 ± 4	0.17	21.38
2	0.5	2.5	0	68 ± 2	0.16	21.75
3	0.5	5.0	20	82 ± 2	0.19	24.49
4	0.5	5.0	0	75 ± 3	0.16	21.68
5	0.5	7.5	20	107 ± 11	0.23	28.51
6	0.5	7.5	30	125 ± 5	0.21	35.34
7	0.5	7.5	40	120 ± 12	0.24	32.08
8	0.5	7.5	0	112 ± 2	0.17	34.26
9	0.5	10	20	159 ± 7	0.26	37.99
10	0.5	10	0	142 ± 8	0.21	37.67
11	0.33	10	20	106 ± 3	0.30	18.14
12	0.33	10	0	67 ± 2	0.20	13.87

*Values shown are mean ± SD.

In the oscillation stress sweep test the stress was increased from 0.06 to 300 Pa in 40 logarithmic steps, and the frequency was kept constant (1 Hz). In the oscillation frequency sweep test, the frequency was increased from 0.01 to 30 Hz in 16 steps, and the stress was kept constant (1 Pa). In the viscosity test, shear stress was first increased from 30 to 210 Pa (up curve) and then decreased from 210 to 30 Pa (down curve) to check possible hysterises effects. No significant hysterises effects were detected under the considered experimental conditions, and the up curve and down curve practically coincided. In the viscosity test, shear rate was recorded as a function of shear stress.

In the rheology measurements, the sample was first exposed to a shear stress of 1 Pa for 10 seconds, followed by a 15-second equilibrium period. A preshear period was used to standardize the handling of samples before measurements.

Results and Discussion

Rheology Measurements

The behavior of a semisolid is defined with a combination of elasticity and viscosity, and those elements can be measured with a rheometer. In oscillation tests, the elasticity part is defined as storage modulus (G′) and the viscosity part by loss modulus (G″). In viscosity measurements, the shear viscosity is defined as η.

Oscillation Tests

The results of the oscillation stress sweep test show a difference in elasticity between the formulations as expressed by the values of storage modulus (G′) (Table 1). Values for G′ decrease with decreasing oil volume fraction indicating decreasing elasticity (Table 1). In comparing creams with and without monocaprin, it is apparent that the inclusion of monocaprin in the formulations had little effect on the elastic behavior as expressed by the G′ values for formulations 5 to 8. An exception from this is the formulation in which the carbomer concentration was lowered to 0.33%. Then, the difference in elastic behavior between a control cream and a cream containing monocaprin was statistically significant (Formulations 11 and 12; Table 1), with monocaprin increasing the elasticity. The loss tangent (tan δ), that is, the ratio of loss modulus and storage modulus, increased with increasing oil volume fraction (Formulations 9, 5, 3, and 1; Table 1). The loss tangent values indicate that the storage modulus is the dominant feature in all the formulations (Table 1), as a small loss tangent indicates an elastic material. The values of the crossing-over point are all at rather high stress (Table 1), but an increase in stress of the crossing-over point is a sign of more lasting elastic properties for a formulation that has the elastic properties dominating in the linear range. The results show that the greater the elasticity (higher G′ value), the higher the crossing-over point (ie, the longer the elastic properties were dominating). The most elastic cream had the longest lasting elastic properties under increasing stress, and hence the results were the same as for the storage modulus (Table 1). The most viscoelastic formulation was Formulation 10, which is without monocaprin.

The results of the oscillation frequency sweep test showed that the elastic properties were present even at the lowest frequencies in all the formulations (Figure 1). The creams containing the lowest oil volume fraction showed the lowest storage modulus under increasing frequency and had the steadiest storage modulus values under increasing frequency (Figure 1). A steady storage modulus under increasing frequency indicates the ability of the creams to resist structural changes under stress. At the increasing frequency, the storage modulus was the highest in Formulation 10 (Figure 1), a cream containing 10% oil phase and

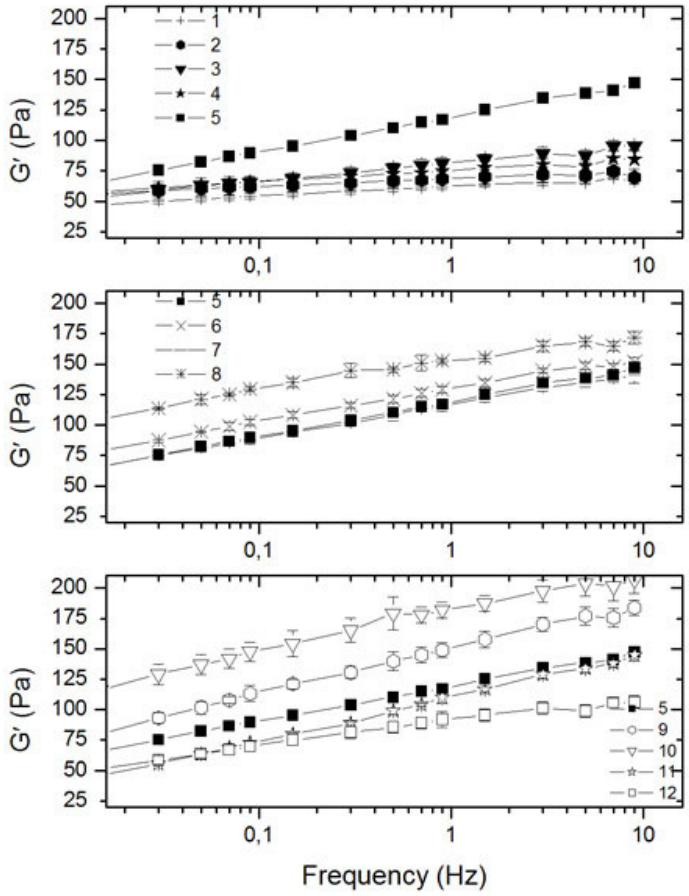

Figure 1. Values of storage moduli (G′) in the oscillation frequency sweep test. Formulations 1 to 12; n = 3.

0.5% carbomer but without monocaprin, monocaprin thus reducing the storage modulus. It is also apparent that under increasing frequency, monocaprin decreases the storage modulus when the oil volume fraction is 7.5% as the storage modulus is highest for the cream containing no monocaprin compared with the creams containing 20, 30, or 40 mM of the monoglyceride (Figure 1). When the oil volume fraction is 5.0%, the storage modulus for the formulations without monocaprin is slightly lower than for the formulations containing monocaprin under increasing frequency. When the oil volume fraction is 2.5%, the opposite is seen but in both cases the difference is not statistically significant (Figure 1). An increase in the oil volume fraction from 7.5% to 10% causes an increase in the storage modulus (cream 5 compared with cream 9) (Figure 1). The concentration of carbomer in the aqueous phase also affects the storage modulus, since a reduction in the carbomer concentration reduces the storage modulus under increasing frequency (Figure 1). Lowering the carbomer concentration also appears to induce elastic properties driven by monocaprin, as the cream with 10% oil volume fraction and reduced carbomer concentration shows higher storage modulus, under increasing frequency, with monocaprin than without monocaprin (Figure 1).

The oscillation frequency sweep test supports the results of the oscillation stress sweep test in that the elastic part dominated in all the formulations (Figure 2). There is little variation in the tan δ values, and the curves are similar for the different formulations, which further supports the stress sweep test in that these variations in formulations do not result in extreme variations in rheological properties.

Viscosity

The results of the viscosity test supported the oscillation test. The highest viscosity was observed in the formulations with the largest oil volume fraction (Formulations 9 and 10), and the least viscous creams were those with either lower oil volume fraction or less carbomer concentration (Figure 3). The effects of monocaprin on viscosity was not significant except in the cream with reduced carbomer amount, in which monocaprin seemed to increase viscosity (Figure 3). All the formulations were shear thinning pseudoplastic systems. In the viscosity test, shear stress was first increased from 30 to 210 Pa (up curve) and then decreased from 210 to 30 Pa (down curve) to check possible hysterises effects.

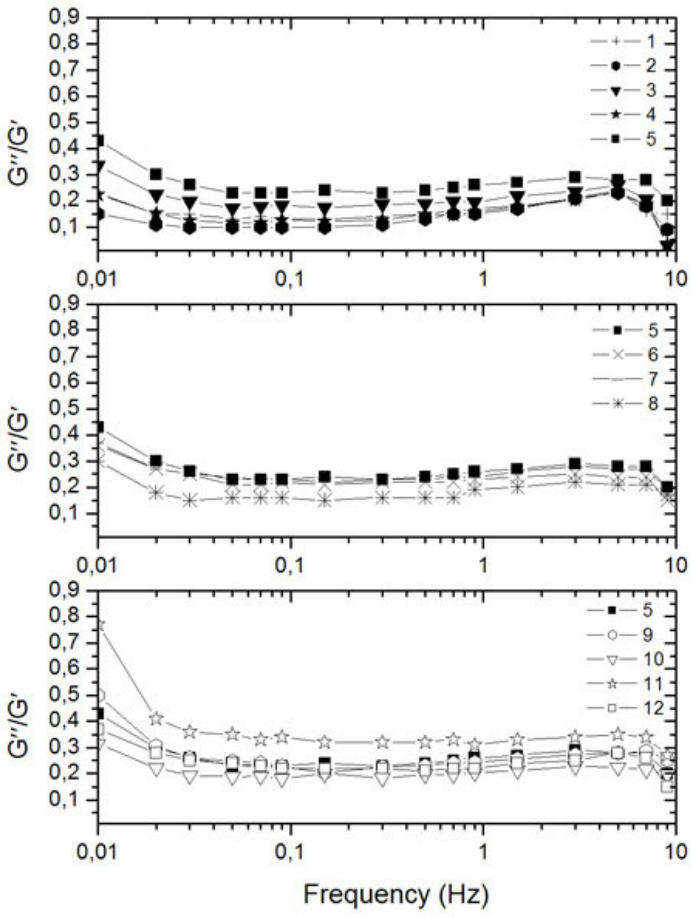

Figure 2. Ratio of the loss modulus and storage modulus (tan δ) in the oscillation frequency sweep test. Formulations 1 to 12; n = 3.

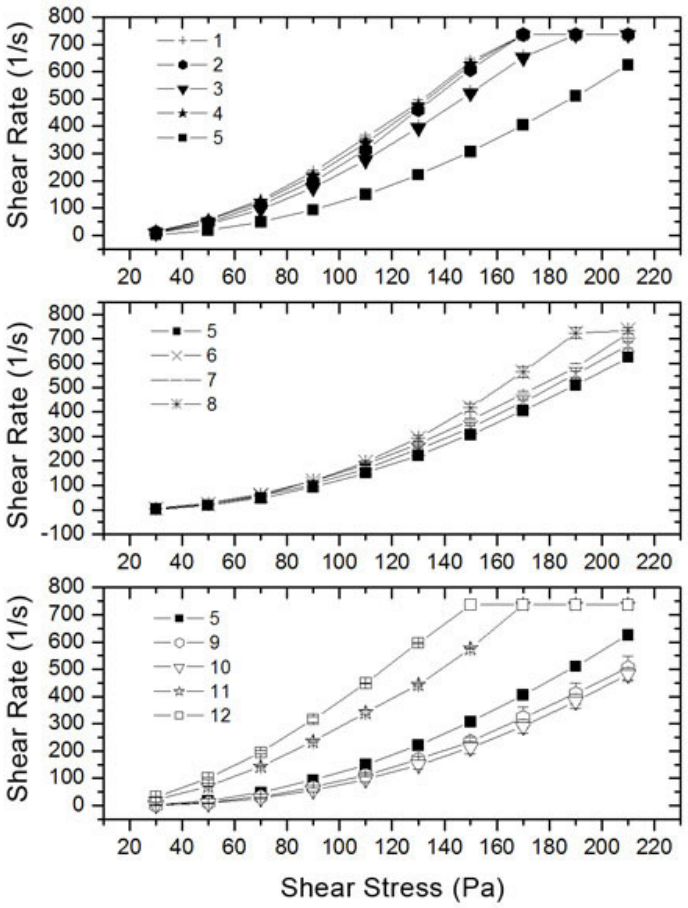

Figure 3. Viscosity of creams. Formulations 1 to 12; n = 3.

No significant hysterises effects were detected under the considered experimental conditions, and the up curve and the down curve overlapped.

Summary and Conclusions

The viscoelastic properties of the cream formulations were tested by 2 methods (ie, increased stress and increased frequency tests). The rheology experiments indicate that the formulations are stable; they show resistance to external forces, as their elastic properties are sustained whether or not the magnitude or frequency of external forces are increased. The results show that rheological properties of the formulations are affected by the proportion of the oil phase and the amount of carbomer in the aqueous phase, but the effect of monocaprin is modest. Increasing carbomer amount increases viscosity and elasticity. Increasing the oil volume fraction increased the structural stability of the creams. The formulation containing monocaprin, which yielded the most viscoelastic structure was a cream containing 10% oil phase and 0.5% carbomer (Formulation 9).

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