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Determination of optimal combination of surfactants in creams using rheology measurements

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Abstract

The effect of surfactant on the rheological properties of some cream formulations was studied. Two surfactants from two different series were combined to determine the combination which yielded the most viscoelastic structure for creams. The surfactants were the soybean derivatives soya sterol, polyethylene glycol 10 soya sterol and polyethylene glycol 25 soya sterol and the sorbitol derivatives sorbitan monooleate and sorbitan trioleate. The rheological properties of the creams were studied using oscillation stress sweep, oscillation frequency sweep and viscosity tests. Droplet size distribution and conductivity of the creams were also determined. The combination polyethylene glycol 10 soya sterol and sorbitan trioleate yielded the most viscoelastic structure with linearly viscoelastic behaviour.

Keywords: Rheology of creams; Surfactants; Storage modulus; Loss tangent; Hydrophile–lipophile balance

1. Introduction

Rheological properties can be divided into viscous, elastic and plastic properties and combinations of these, viscoelasticity being the most important for semisolids. Semisolids, like emulsions, combine solid behaviour and liquid properties in the same material (Barry, 1983). Viscoelasticity is defined as the simultaneous existence of viscous and elastic properties (Barnes et al., 1989). The dominating properties and the values for rheological parameters depend on the stress and the duration of stress application (Barnes et al., 1989). Analysis of viscoelastic materials is designed not to destroy the structure, so that measurements can provide information on the intermolecular and interparticle forces in the material (Martin, 1993).

Linear viscoelastic behaviour can be determined with dynamic and static tests. Static tests involve the imposition of a step change in stress (or strain) and the observation of the subsequent development in time of the strain (or stress) (Barnes et al., 1989). Dynamic tests involve the application of a harmonically varying strain (Barnes et al., 1989). Oscillation tests are dynamic

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methods for determining the rheological properties of the material in its rheological ground state. In rheological ground state the method of testing does not significantly alter the static structure of the material (Barry and Warburton, 1968).

In an oscillation stress sweep test the response of the material (strain) is measured while exposing the material to an increasing stress and a constant frequency. In the linear viscoelastic area the ratio of stress and strain is a function of time alone (Kobayashi et al., 1982). At the critical stress point the linear viscoelastic area ends and the dominant property changes from elastic to viscous. In an oscillation frequency sweep test the material is exposed to a stepwise increase in frequency and a constant sinusoidally varying deformation in stress (or strain). Whichever method is used, the measurements have to be made in the linear range of the material (Barnes et al., 1989). Kobayashi et al. (1982) and Gasperlin et al. (1997) have dealt with viscoelastic parameters in detail.

Surfactants affect the rheological properties of creams (Barry and Saunders, 1971; Barry and Eccleston, 1973a,b,c; Eccleston and Beattie, 1988; Kallioinen et al., 1994). Combinations of surfactants are often more effective in cream stabilisation than single surfactants by complementing the properties of each other. The ability of the blend to pack more tightly between formed phases contributes to the strength of the surfactant film and so to the stability of the cream (Rieger, 1986).

2. Materials and methods

2.1. Materials

The surfactants used were polyethylene glycol 10 soya sterol (Generol® 122 N E 10 D, Henkel KGaA, Germany), polyethylene glycol 25 soya sterol (Generol® 122 N E 25 D, Henkel KGaA, Germany), soya sterol (Generol® 122, Henkel KGaA, Germany), sorbitan monooleate (Kosteran® -O/1, Ph. Eur., Dr W. Kolb AG, Germany) and sorbitan trioleate (Kosteran® -O/3, Ph. Eur., Dr W. Kolb AG, Germany). Polyethylene glycol 10 soya sterol has an average of 10 moles of ethylene oxide and polyethylene glycol 25 soya sterol an average of 25 moles of ethylene oxide (Wenninger and McEwen, 1993). Sorbitan monooleate is a monoester of oleic acid and hexitol anhydrides and sorbitan trioleate a triester of oleic acid and hexitol anhydrides (Wenninger and McEwen, 1993). The soybean and sorbitol derivatives used are non-ionic surfactants.

In each formulation there were 12% soybean derivatives and 7% sorbitol derivatives. The exact formulations are presented in Table 1 and the HLB (hydrophile–lipophile-balance) values of the

Table 1
Formulations of creams (g)

Raw material	Formulation					
	I	II	III	IV	V	VI
Polyethylene glycol 10 soya sterol	12.0	12.0	–	–	–	–
Polyethylene glycol 25 soya sterol	–	–	12.0	12.0	–	–
Soy sterol	–	–	–	–	12.0	12.0
Sorbitan monooleate	7.0	–	7.0	–	7.0	–
Sorbitan trioleate	–	7.0	–	7.0	–	7.0
Caprylic triglyceride	8.0	8.0	8.0	8.0	8.0	8.0
Isopropyl palmitate	8.0	8.0	8.0	8.0	8.0	8.0
Glycerin (85%)	12.0	12.0	12.0	12.0	12.0	12.0
Cetostearyl alcohol	8.0	8.0	8.0	8.0	8.0	8.0
Methylparaben	0.1	0.1	0.1	0.1	0.1	0.1
Propylparaben	0.02	0.02	0.02	0.02	0.02	0.02
Aq. Purif.	ad 100	ad 100	ad 100	ad 100	ad 100	ad 100

Table 2
HLB values of surfactant blends

Formulation	HLB
I	9.2
II	8.2
III	12.3
IV	11.4
V	3.5
VI	2.6

blends of surfactants in Table 2. The HLB values were calculated as an algebraic mean of the HLB values of single surfactants (Attwood and Florence, 1983).

The creams manufactured are identified as formulations I–VI. Polyethylene glycol 10 soya sterol and polyethylene glycol 25 soya sterol are referred to in Section 3 as PEG 10 soya sterol and PEG 25 soya sterol, respectively.

2.2. Preparation of creams

The creams were manufactured using an instrumented mixing pan (Molto-Mat Universal 5, O. Krieger, Muttenz, Switzerland) connected to a PC (HP 85 P, Hewlett Packard, Waldbronn, Germany). The PC was used for recording the in-process parameters, such as temperature of the product, chamber and cooling/heating jacket, total-resistance of the mixer, mixing and homogenising speeds and chamber pressure.

All formulations were manufactured similarly. For each formulation, two batches of 3 kg were manufactured.

2.3. Analytical methods

The creams were analysed for rheology, droplet size distribution and conductivity. Analytical determinations were made either 1 or 2 days after cream manufacture. For one batch of formulation III, analyses were made both 1 and 2 days after cream manufacture to determine the influence of measuring time on the results. Statistical analyses were performed using two-way analysis of variance with two between factors (soybean derivatives and sorbitol derivatives).

2.3.1. Rheological properties

Rheological properties were determined using a rheometer (StressTech, ReoLogica Instruments AB, Lund, Sweden, Stress RheoLogic Basic software, version 2.2, RheoLogica Instruments, Lund, Sweden) with parallel plate system. The temperature of the base plate was 25.0 ± 0.1°C. The tests used were as follows: oscillation stress sweep test, oscillation frequency sweep test and viscosity test. The tests were done at least in triplicate for each batch and all measurements were made from separate samples.

In the oscillation stress sweep test the stress was increased from 0.03 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). In the viscosity test, shear rate was recorded as a function of shear stress.

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

2.3.2. Droplet size distribution

Droplet sizes were determined using a light microscope (Olympus BX40F, Olympus Optical Ltd., Tokyo, Japan). A 10% water suspension was prepared and the measurement was performed immediately after sample preparation. The diameter was determined from 200 randomly chosen droplets. Droplet size determinations were made at least once from each batch and all determinations were made from separate samples.

2.3.3. Conductivity

Conductivity was measured with a portable conductivity instrument (Mettler Check Mate 90, Mettler Toledo, Essex, USA). An ion-sensitive transistor was used. Conductivity determinations were made at least in triplicate for each batch and all measurements were made from separate samples.

3. Results and discussion

The time of measurements (1 or 2 days after cream manufacture) did not affect the results. Formulation III, from which the influence of measurement time was tested, gave similar results regardless of the measurement time.

Formulations I–IV yielded o/w creams and formulations V and VI unhomogeneous systems. In formulations V and VI, both surfactants, soybean and sorbitol derivatives, were oil-soluble with low HLB values. These blends were not hydrophilic enough to bind the water phase and to form a cream.

3.1. Oscillation tests

Formulations I and II, which contained PEG 10 soya sterol, were more viscoelastic than formulations III and IV which contained PEG 25 soya sterol. In the oscillation stress sweep test the values of storage modulus (G′) showed a great difference in elasticity between formulations (Table 3). Storage modulus characterises the elastic behaviour of the material (Gasperlin et al., 1997). Loss tangents (tan δ) were similar depending on the surfactant of soybean derivatives (Table 3). Loss tangent is the ratio of loss modulus (characterises the viscous behaviour of the material) and storage modulus (Kobayashi et al., 1982; Rieger, 1991; Gasperlin et al., 1997). The smaller the loss tangent is, the more elastic is the material (Davis, 1971). The loss modulus dominated more in formulations which contained PEG 25 soya sterol.

At the stress of crossing over point, the loss modulus is equal in value with the storage modulus, and the loss tangent is 1 (Gasperlin et al., 1997). An increase in stress of the crossing over point is a sign of more lasting elastic properties. The crossing over point gave the same results as the storage modulus; the greater the elasticity of the cream, the more lasting was the elasticity under increasing stress (Table 3).

The values of storage modulus showed statistically significant interaction between soybean and sorbitol derivatives ($p < 0.05$). The mean level of storage modulus was 319 Pa when PEG 10 soya sterol was combined with sorbitan monooleate and 959 Pa when combined with sorbitan trioleate (Table 3). The corresponding mean levels of PEG 25 soya sterol were 56 and 120 Pa. At the crossing over point there was a statistically significant main effect in soybean and sorbitol derivatives ($p < 0.05$). The mean levels of PEG 10 soya sterol and PEG 25 soya sterol were 70.2 and 5.5 Pa and those of sorbitan monooleate and sorbitan trioleate 19.5 and 56.1 Pa, respectively (Table 3).

The oscillation stress sweep test showed that formulation II, containing PEG 10 soya sterol and sorbitan trioleate, had the most viscoelastic structure. In formulation II, the storage modulus and crossing over point values were about 3–4 times higher than in formulation I. Formulation I differed from formulation II only in the surfactant of sorbitol derivative. Unlike formulations I and II, formulations III and IV, which contained PEG 25 soya sterol, did not show any linearly viscoelastic behaviour.

In the oscillation frequency sweep test the elastic properties occurred even at the lowest frequencies in formulations which contained PEG 10 soya sterol (Fig. 1). The steadiest storage modulus values under increasing frequency were in formu-

Table 3
Results of oscillation stress sweep test[a]

Formulation	Storage modulus G′ (Pa)	Loss tangent tan δ	Crossing over point (Pa)	n
I	319 ± 13	0.07	36.2 ± 1.4	6
II	959 ± 32	0.07	104.1 ± 6.1	6
III	56 ± 16	0.59	2.8 ± 0.7	9
IV	120 ± 19	0.56	8.1 ± 1.9	6

[a] Means ± standard deviations are presented.

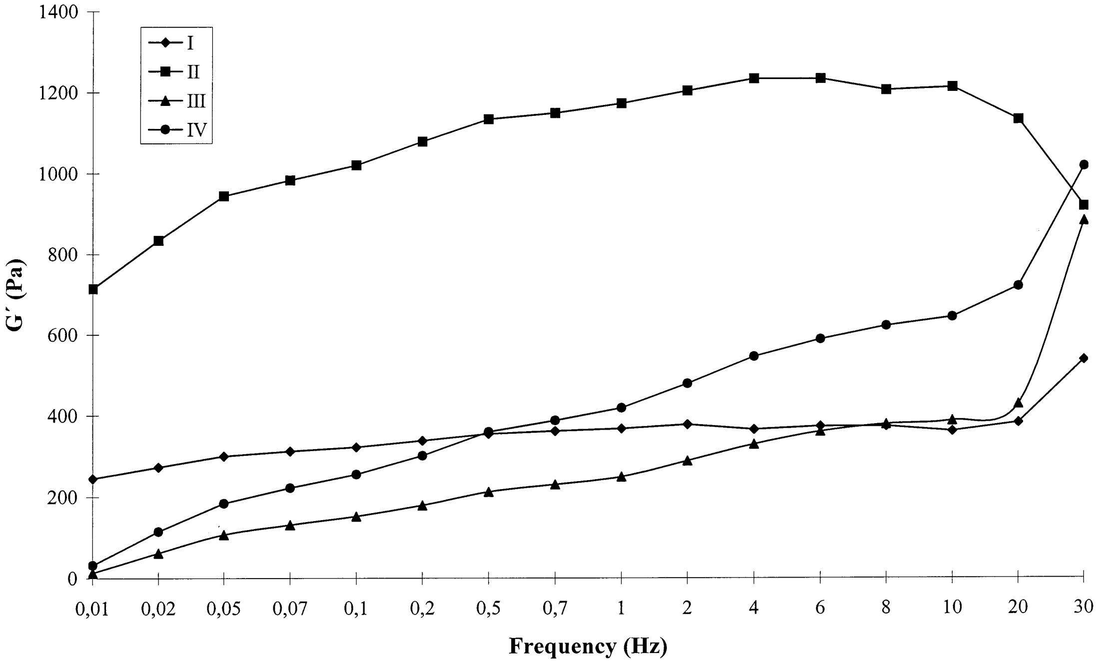

Fig. 1. Values of storage moduli (G′) in the oscillation frequency sweep test. Formulations I, II and IV: $n = 6$; formulation III: $n = 9$.

lation I. This shows the ability of the creams to resist structural changes under stress. Under the increasing frequency the storage modulus was clearly the highest in formulation II.

In the oscillation frequency sweep test, like in the oscillation stress sweep test, viscosity dominated more in formulations which contained PEG 25 soya sterol than in formulations which contained PEG 10 soya sterol. Both in formulations I and II and in formulations III and IV the loss tangent was on the same level and dependent on the surfactant of soybean derivative (Fig. 2).

The oscillation frequency sweep test supported the results of the oscillation stress sweep test. This is seen especially at lower frequencies. It is important to notice that the behaviour of formulations III and IV was not linearly viscoelastic. Therefore the results obtained from formulations III and IV were not independent of the stress used.

The increase of the ethylene oxide proportion from 10 to 25 moles decreased the elasticity. Usually an increase in the number of ethylene oxide groups of surfactants produces more consistent creams (Eccleston and Beattie, 1988). With increasing number of ester chains from one to three the elasticity of creams increased. Thus the increase in chain length of the surfactants increased the consistency of creams up to a certain limit. This can be due to the critical micelle concentration. Critical micelle consentration decreases as the chain length of the surfactant increases (Barry and Saunders, 1971).

The forming process of smectic structures is time-dependent (Barry and Saunders, 1971). The surfactants with long chain lengths give less time for water to penetrate deeper through the quickly formed viscous structures. Thus it is possible that, for higher homologies, there is less structural building during cream manufacture. For higher homologies also temperature ranges for interaction are shortened (Barry and Saunders, 1971). There is less time available for a smectic phase to form before the cream cools below the interaction temperature. However, with non-ionic systems, cold penetration might be more important than the high temperature interaction (Barry and Eccleston, 1973a).

The HLB values of surfactant blends correlated directly with the viscoelasticities of cream formulations I–IV. The smaller the HLB value, the more viscoelastic was the cream. Shinoda and Yoneyama (1980) showed that in the blend of surfactants Tween and Span the creams were more stable when the difference of HLB values of blended surfactants were smaller. As the HLB value was the highest in PEG 25 soya sterol, the difference in the HLB value of both sorbitol derivatives was the greatest. Thus, PEG 25 soya sterol as a highly hydrophilic surfactant dissolved mostly in the water phase and sorbitol derivatives as highly lipophilic surfactants in the oil phase. The interaction between these surfactants was not sufficient.

With non-ionic surfactants emulsion stabilization occurs through steric hindrance and hydrogen bonding (Fox, 1986). According to Fox (1986), the long zig-zag polyoxyethylene groups in the water phase set up a steric hindrance which inhibits the close contacts of oil droplets. Hydrogen bonding occurs between polyoxyethylene groups and water. Thus it can be expected that PEG 25 soya sterol with greater molecular structure would form a more effective steric hindrance and more viscosity in the outer phase. Boyd et al. (1972) reported that sorbitan trioleate did not form as condensely associated a structure with polyoxyethylene sorbitan monopalmitate or polyoxyethylene sorbitan monolaurate as sorbitan monooleate. This was due to the more open configuration of sorbitan trioleate at the interface of the phases. However, formulation II, which contained both PEG 10 soya sterol and sorbitan trioleate, had clearly the most elastic structure. The surfactants PEG 10 soya sterol and sorbitan trioleate showed the greatest interaction and the most suitable HLB values to form the most elastic cream. The structural interaction between single surfactants and their complementary hydrophile–lipophile balance, for example, influence the effectiveness of the blend of surfactants. Contributing factors are also the orientation of the surfactant

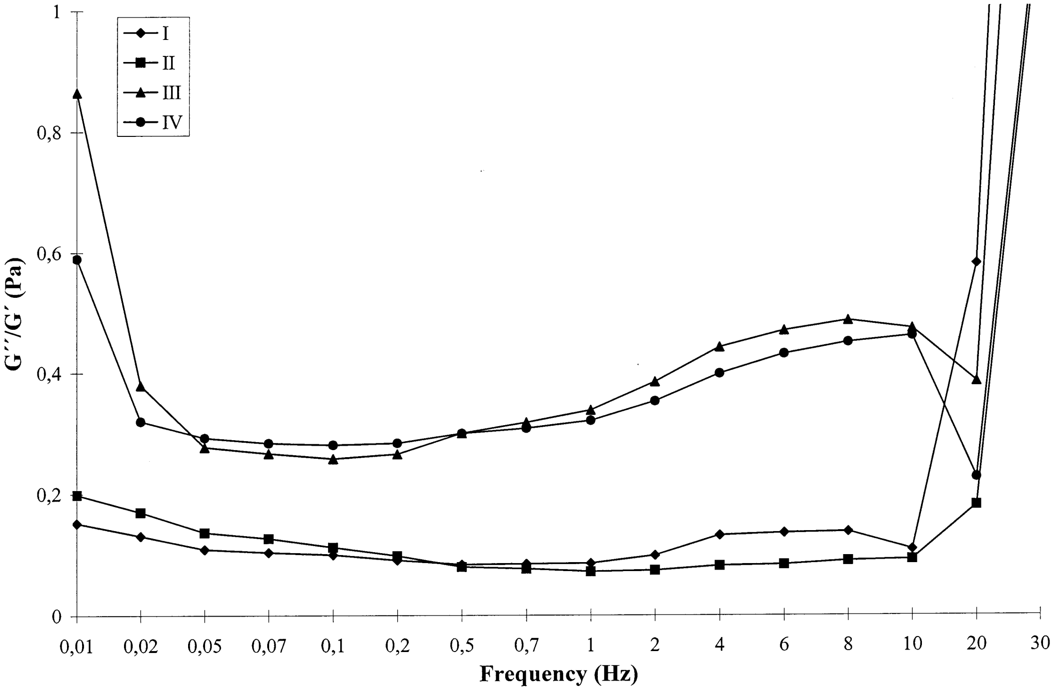

Fig. 2. Ratio of loss modulus and storage modulus (tan δ) in the oscillation frequency sweep test. Formulations I, II and IV: $n = 6$; formulation III: $n = 9$.

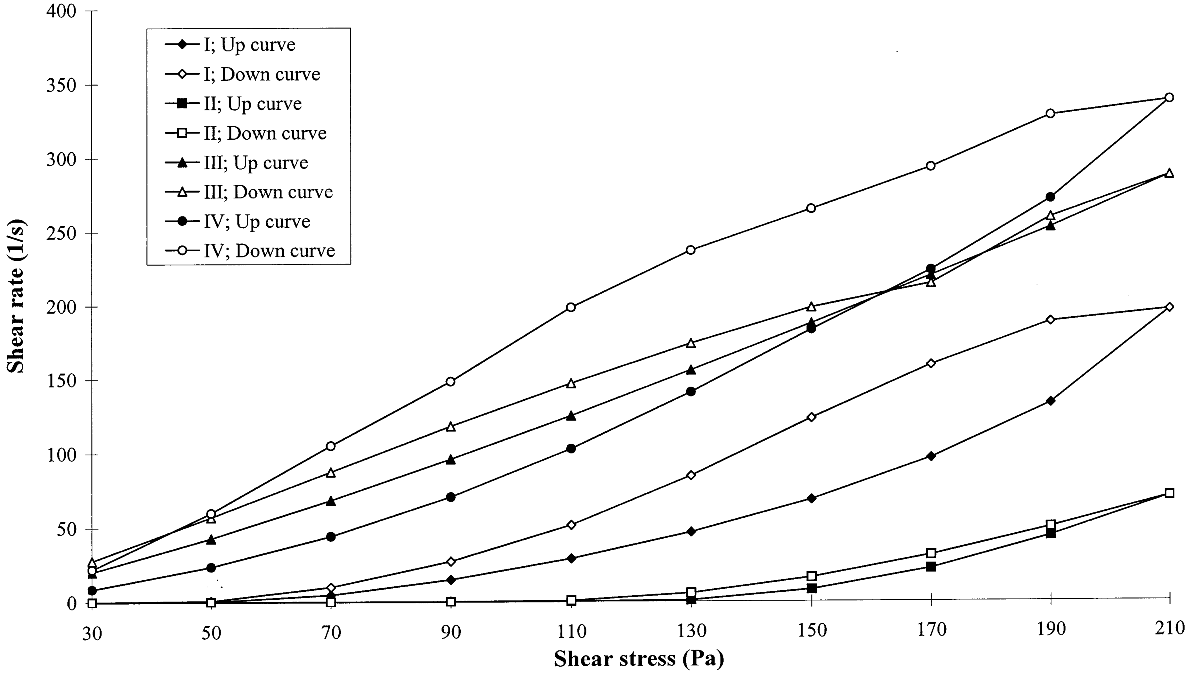

Fig. 3. Viscosity of creams. Formulations I, II and IV:$n = 6$; formulation III: $n = 9$.

molecules at the interface of phases and the suitability of the surfactant blend for the cream formulation.

3.2. Viscosity

The viscosity test supported the results of the oscillation tests. The greatest viscosity was observed in formulation II, which was a shear thinning, pseudoplastic system (Fig. 3). Formulations I and II which contained PEG 10 soya sterol, had a yield point. In formulation II, where PEG 10 soya sterol was combined with sorbitan trioleate, the yield point was greater than in formulation I where PEG 10 soya sterol was combined with sorbitan monooleate. The yield points correlated with the end points of the linear viscoelastic area in the oscillation stress sweep test.

Every formulation behaved thixotropically. Formulations I and IV were most thixotropic, with pseudoplastic behaviour in the up curve and dilatant behaviour in the down curve. The most linear shear rate under increasing shear stress was in formulation III. In formulation III the up and down curves intersected, implying that the shearing cycle itself caused some structural build-up (Eccleston and Beattie, 1988).

3.3. Droplet size distribution

In formulations II and IV, the most frequent droplet diameter was < 1.7 μm while in formulations I and III it was 1.7–3.4 μm (Table 4). Formulations which contained sorbitan trioleate had smaller droplets than formulations which

Table 4
Droplet size distributions of creams

Droplet size μm	Formulation			
	I	II	III	IV
<1.7	128	290	198	246
1.7–3.4	170	88	314	128
3.5–6.8	88	18	88	26
>6.9	14	4	0	0
Sum	400	400	600	400

Table 5
Conductivities of creams[a]

Formulation	Conductivity μS	n
I	12.3 ± 0.8	6
II	19.3 ± 7.6	6
III	36.9 ± 0.9	9
IV	30.7 ± 12.7	6

[a] Means ± standard deviations are presented.

contained sorbitan monooleate. Droplet sizes over 3.5 μm occurred more often in formulations I and III than in formulations II and IV.

Viscosity increases when the particle size of the dispersed phase decreases (Rieger, 1986). As the number of droplets increases, the interactions between the droplets and the viscosity increase. This can be seen in formulation II which had the smallest droplets and the greatest viscosity. In formulations I, III and IV the results were opposite; the more mobile the formulations, the smaller were the droplets. According to Depraétere et al. (1980), the stability of creams was the greatest at the HLB values where the droplet sizes were the smallest.

Droplet size distribution is not the only explanatory factor when considering the rheological properties of creams. Creams are considered complex polydispersed multiple-phase systems containing additional phases of oil and water (Eccleston, 1990). Viscoelastic networks present in the continuous phases are responsible for the consistency of creams (Barry and Eccleston, 1973a). These networks are formed through interaction of fatty alcohol and surfactant solution (Barry and Eccleston, 1973a).

3.4. Conductivity

Conductivity is a measure of amount of free water and free ions. High conductivity values reveal that there is less lamellar water and more free water in the creams, which can be seen as a decrease in the consistency of creams (Eccleston and Beattie, 1988). Formulations which contained PEG 10 soya sterol (formulations I and II) had lower conductivity values than formulations which contained PEG 25 soya sterol (formulations III and IV) (Table 5). PEG 10 soya sterol bound water into lamellar water to a greater extent than PEG 25 soya sterol. The combination of PEG 10 soya sterol and sorbitan monooleate (formulation I) bound free water to the greatest extent.

In the conductivity values there was statistically significant interaction between soybean and sorbitol derivatives ($p < 0.05$). The mean level of conductivity was 12.3 μS when PEG 10 soya sterol was combined with sorbitan monooleate and 19.3 μS when combined with sorbitan trioleate (Table 5). The corresponding mean levels of PEG 25 soya sterol were 36.9 and 30.7 μS.

The results of the conductivity test supported the results of the oscillation stress sweep and viscosity tests. The highest consistencies were in formulations I and II which had the smallest conductivity values.

4. Conclusion

Rheology measurements provide a simple and effective means to compare the structural properties of creams. The oscillation stress sweep test and the oscillation frequency sweep test gave an exact presentation of the viscoelastic properties of the creams. In addition to oscillation tests, the viscosity test with yield values and droplet size distributions suggested that the cream, which contained polyethylene glycol 10 soya sterol and sorbitan trioleate, was the most viscoelastic cream. The most elastic structure is presumed to be able to maintain structural stability and resistance to external forces for longer periods of time.

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References

Attwood, D., Florence, A.T., 1983. Emulsions. In: Attwood, D., Florence, A.T. (Eds.), Surfactant Systems, their Chemistry, Pharmacy and Biology. Chapman and Hall, London, pp. 469–566.

Barnes, H.A., Hutton, J.F., Walters, K., 1989. Linear viscoelasticity. In: Barnes, H.A., Hutton, J.F., Walters, K. (Eds.), An Introduction to Rheology, vol. 3. Elsevier Science Publishers BV, Amsterdam, pp. 37–54.

Barry, B.W., 1983. Rheology of dermatological vehicles. In: Barry, B.W. (Ed.), Dermatological Formulations, Percutaneous Absorption, vol. 18. Marcel Dekker, New York, pp. 351–407.

Barry, B.W., Eccleston, G.M., 1973a. Influence of gel networks in controlling consistency of o/w emulsions stabilised by mixed emulsifiers. J. Texture Stud. 4, 53–81.

Barry, B.W., Eccleston, G.M., 1973b. Oscillatory testing of o/w emulsions containing mixed emulsifiers of the surfactant-long chain alcohol type: self-bodying action. J. Pharm. Pharmac. 25, 244–253.

Barry, B.W., Eccleston, G.M., 1973c. Oscillatory testing of o/w emulsions containing mixed emulsifiers of the surfactant/long chain alcohol type: influence of surfactant chain length. J. Pharm. Pharmac. 25, 394–400.

Barry, B.W., Saunders, G.M., 1971. The self-bodying action of alkyltrimethylammonium bromides/cetostearyl alcohol mixed emulsifiers; influence of quaternary chain length. J. Colloid. Interface. Sci. 35, 689–705.

Barry, B.W., Warburton, B., 1968. Some rheological aspects of cosmetics. J. Soc. Cosmet. Chem. 19, 725–744.

Boyd, J., Parkinson, C., Sherman, P., 1972. Factors affecting emulsion stability, and the HLB consept. J. Coll. Interface Sci. 41, 359–370.

Davis, S.S., 1971. Viscoelastic properties of pharmaceutical semisolids III: nondestructive oscillatory testing. J. Pharm. Sci. 60, 1351–1355.

Depraétere, P., Florence, A.T., Puisieux, F., Seiller, M., 1980. Some properties of oil-in-water emulsions stabilized with mixed non-ionic surfactants (Brij 92 and Brij 96). Int. J. Pharm. 5, 291–304.

Eccleston, G.M., 1990. Multiple-phase oil-in-water emulsions. J. Soc. Cosmet. Chem. 41, 1–22.

Eccleston, G.M., Beattie, L., 1988. Microstructural changes during the storage of systems containing cetostearyl alcohol/polyoxyethylene alkyl ether surfactants. Drug. Dev. Ind. Pharm. 14, 2499–2518.

Fox, C., 1986. Rationale for the selection of emulsifying agents. Cosmet. Toiletries 101, 25–44.

Gasperlin, M., Kristl, J., Smid-Korbar, J., 1997. Viscoelastic behaviour of semi-solid w/o emulsion systems. STP Pharma Sci. 7 (2), 158–163.

Kallioinen, S., Helenius, K., Yliruusi, J., 1994. Physical characteristics of some emulsion creams in which the length of ethylene oxide chain of emulsifier varies. Pharmazie. 49, 750–756.

Kobayashi, M., Ishikawa, S., Samejima, M., 1982. Application of nonlinear viscoelastic analysis by the oscillation method to some pharmaceutical ointments in the Japanese Pharmacopeia. Chem. Pharm. Bull. 30 (12), 4468–4478.

Martin, A., 1993. Rheology. In: Martin, A. (Ed.), Physical Pharmacy, Fourth ed. Lea and Febiger, Philadelphia, pp. 453–476.

Rieger, M.M., 1986. Emulsions. In: Lachman, L., Lieberman, H.A., Kanig, J.L. (Eds.), The Theory and Practice of Industrial Pharmacy, Third Edition. Lea and Febiger, Philadelphia, pp. 502–533.

Rieger, M.M., 1991. Stability testing of macroemulsions. Cosmet. Toiletries 106, 59–69.

Shinoda, K., Yoneyama, T., 1980. Evaluation of emulsifier blending. J. Disper. Sci. Tech. 1, 1–12.

Wenninger, J.A., McEwen, G.N. Jr. (Eds.), 1993. International Cosmetic Ingredient Dictionary, Fifth ed., Vol. 1, The Cosmetic, Toiletry and Fragrance Association, Washington D.C.