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Physicochemical Characterization and In Vitro Release of Salicylic Acid from O/W Emulsions Prepared with Montanov 68®: Effect of Formulation Parameters

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ABSTRACT

Montanovs® are surfactants consisting of a combination of alkylpolyglucosides and long chain saturated alcohols. They are used to formulated oil in water (O/W) emulsions where they generate liquid crystals. Emulsions containing 5% Montanov 68® with 40% Lanol 1688® were prepared and salicylic acid (SA) was incorporated at different stages of the O/W emulsion preparation. This study highlights the effects of formulation parameters on the microscopic characteristics, particle size and rheologic properties of Montanov 68® O/W emulsions. Diffusion studies with these emulsions showed the influence of SA incorporation at different steps on the release kinetics. Montanov® enabled the release of SA to be controlled when it was solubilized in the internal phase. The presence of a physical barrier formed by the Montanov® at the interface between the oil and water appeared to modulate the SA passage to the external phase.

Key Words: Alkylpolyglucoside; O/W emulsion; Salicylic acid; Montanov®.

INTRODUCTION

In recent times, advances have been made in the formulation of topical preparations and interest has been focused on the excipients used as the vehicles for the drugs.[1] The appropriate choice of vehicle results in better drug availability, more activity, better stability and controlled release. Gallordo[2] has determined the effects of excipients on salicylate release from topical formulations and showed that the use of lipophilic

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excipients (cetyl alcohol, lanolin and white petroleum jelly) slowed down the release of the active substance by comparison with the use of hydrophilic excipients. This variation in salicylic acid release was related to the vehicle and not to the receptor phase used.

Clément[3] determined the effect of some formulation parameters on caffeine release from W/O emulsions. This author changed the emulsifier used in the emulsions and defined the influence on particle size, rheologic and active substance release characteristics. With these kind of emulsions, the concentration of emulsifier did not have a significant effect on the release of caffeine, but the diffusion of caffeine from the emulsion was found to be highly dependent on the volume of the internal phase.

The purpose of the current study was to investigate the effects on particle size, rheological properties and drug release, of a novel emulsifier, Montanov 68® when used in the preparation of oil in water emulsions. The idea was to control the release of the drug from emulsion by creating a physical barrier at the interface between the dispersed and continual phases. The emulsifier chosen was Montanov 68® which generates liquid crystals that could act as physical barrier to drug diffusion.[4–6] The first aim of this study was to investigate the physicochemical characteristics of Montanov 68® O/W emulsions according to formulation parameters. Salicylic acid (SA) was added at different stages of the emulsion preparation to evaluate the release of an active substance by these systems. Finally the study was conceived to add further to the understanding of the advantages of lyotropic liquid crystals in O/W systems.

MATERIALS AND METHODS

Montanov® or Alkylpolyglucoside (APG)

Montanovs® are non-ionic glucolipidic surfactants of vegetal origin used to formulate O/W emulsions.[4] They are constituted by combining alkylpolyglucosides with long-chain saturated alcohols (Fig. 1). Montanov 68® is the combination of cetyl and stearyl alcohol with cetearylglucoside.[5,6]

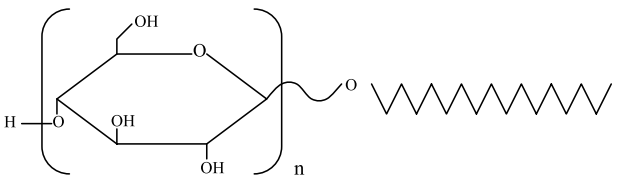

Figure 1. Alkylpolyglucoside structure.

The Preparation of Montanov 68® O/W Emulsions

The continuous phase (H_20) contained 0.15% (w/w) sorbic acid as a preservative. The O/W emulsion consisted of 40% (w/w) of Lanol 1688® and 5% (w/w) of Montanov 68®. Lanol 1688® (SEPPIC) is of semi-synthetic origin (cetearyl octanoate) and has a viscosity of 10.4 mPa.s. The two phases were separately heated up to 70°C, (70°C=Montanov 68® melting temperature) and were mixed at a high stirring speed (2000 rpm) for 4 minutes. Finally the emulsion was maintained under slow stirring at 200 rpm for 40 minutes to ensure a homogeneous cooling. At the end of this step, the emulsion temperature was 30±2°C.

In order to study the effect of formulation parameters on the characteristics of Montanov® O/W emulsions, several process were used to incorporate 3% (w/w) SA, with this active substance incorporated into 1 of 3 different steps of the emulsion manufacture:

1. In the lipophilic phase: the active substance was incorporated into the mixing of Lanol 1688 and Montanov 68® at 70°C, i.e. at the beginning of the preparation. This preparation mode is defined as ''Start Mode.''
2. In the emulsion during the preparation at 70°C: the active substance was incorporated into emulsion under rapid stirring (2000 rpm), 2 minutes after the mixing of the 2 phases, i.e. at the middle of the preparation. This preparation mode is defined as ''Middle Mode.''
3. At the end of emulsion preparation at ~35 to 40°C: the active substance was incorporated into emulsion during the cooling after 20 minutes of mixing at 200 rpm. This preparation mode is defined as ''End Mode.''

Characterization of O/W Emulsions

Optical Microscopy

Samples were examined at ×100 magnifying power with an optical microscope (Hund Wetzlar Will h500) connected to a video camera (Sony). The microscope was fitted with a light polarizer in order to visualize liquid crystals. This mesophase is a material state halfway between a solid and liquid state. The lamellar phase (classical lyotrope) is composed of a periodic stacking of surfactant molecules in a double layer. The stack constitutes an anisotropic structure which is optically birefringent and can therefore be visualized by optical microcopy using polarized light.

Table 1. Emulsions studied.

Emulsion name	Dispersed phase	Emulsifier quantity	Active substance	Moment of active substance incorporation
Without SA	40% Lanol 1688®	5% Montanov 68®		
Start mode			3% Salicylic acid (SA)	Beginning
Middle mode				Middle
End mode				End

This type of analysis enabled the droplet forms to be seen or if there was crystallization of the active substance (SA).

Particle Size Study

Each O/W emulsion was analyzed with a laser granulometer, in order to study the evolution of the size of the dispersed phase droplets with respect to the formulation parameters. The analysis was carried out with a Coulter LS 100 laser diffraction granulometer equipped with a microvolume cell of 15 mL designed for liquid samples. A small quantity of emulsion was diluted in 3 mL of distilled water. One drop of this preparation was introduced into the cell, which was filled with 15 mL of distilled water, and the sample was stirred by using a magnetic stirrer placed under the cell. The analysis model used to characterize the globule size distribution was the Fraunhofer model. This model is used to characterize particles with a diameter greater than 1 μm.

Distributions were given as a function of the volume and the diameter of the globules. The parameters used in this study were the mean diameter D(3,2) that is defined as:

$$D(3,2) = \frac{\sum_i n_i d_i^3}{\sum_j n_j d_j^2}$$

n_i is the number of droplets having d_i diameter, n_j is the number of droplets having d_j diameter.

Particle size analysis was also used to determine the polydispersity of each emulsion. Diameters D(10), D(50) and D(90) were determined. D(X) represents a diameter such that X% of globules in the emulsion have a diameter smaller than it. The polydispersity index (PI) was calculated according to equation:[7]

$$PI = \frac{D(90) - D(10)}{D(50)}$$

Rheological Study

The rheological characteristics were determined with a Haake 75 controlled stress rheometer at 25°C. The geometry used was a stainless steel cone/plate geometry (d=60 mm, θ=1°), which was able to reach high shear rates (2000 s^{-1}). The viscosity determinations were carried out with shear stress sweep. In order to illustrate numerically the rheological analysis results, the apparent viscosity value was given for a shear rate value of 200 s^{-1} on the up curve (increasing shear step). The rheological study was performed 24 hours after the emulsions were prepared.

The Measurement of Salicylic Acid (SA) by UV

SA was measured by uv absorbance at a wavelength of 296 nm. A standard curve was constructed in the concentration range 5.0–62 mg/L (R^2=0.9998). A control emulsion containing no sa was used to verify that there was no interference in the sa absorbance by the excipients.

Release Study

The in vitro release of SA from Montanov 68® O/W emulsions was carried out with a paddle apparatus equipped with special cells for semisolids forms.[8] The SA release was performed with a hydrophilic cellophane membrane (regenerated cellulose, 30 μm thick (dry membrane, pore size 24 Å). This membrane was permeable to water and molecules with low molecular weight and impermeable to macromolecules. Cellophane membranes were wetted with the receptor phase 12 h before their use. About 2 g of emulsion was introduced in the diffusion cell. The membrane was fixed with the upper part of the diffusion cell on the preparation. This diffusion cell presented a donor surface area of 12.5 cm^2. The emulsion placed in the diffusion cell was positioned in a reactor containing the receptor phase, which was 0.15 M phosphate buffer, pH 7.4. The receptor fluid

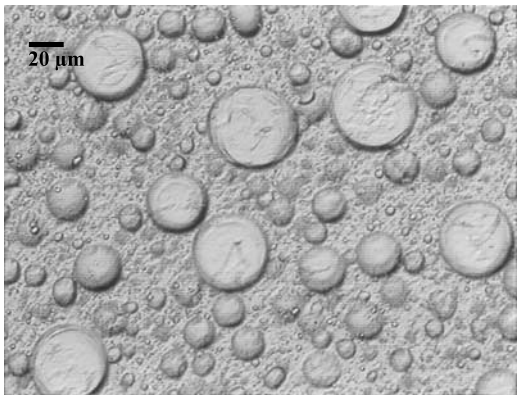

Figure 2. Visualization by microscopy of a Montanov 68® and Lanol 1688® emulsion.

was stirred constantly at 60 rpm and maintained at 32°C. The experiment was conducted under sink conditions, so that the receptor fluid was not rate-limiting in the diffusion process.

Ten sampling times were investigated (15 min, 30 min, 1 h and every hour up to 8 h), and the samples were immediately analyzed by UV spectroscopy for SA, with the experiment being performed simultaneously on six cells.

Salicylic Acid Partition Coefficient

The SA partition coefficient was measured as follows: a water phase corresponding to the water phase of the emulsions was prepared. The concentration of SA in this phase was measured by UV at the beginning and the end of the experiment. The water and the oil phases in proportion of the emulsion [Water: 129.45 g, Oil (Lanol 1688 ®): 120 g] were mixed together with a magnetic stirrer at room temperature. The mixture was centrifuged and the SA concentration in the water phase was measured. The partition coefficient is expressed as the ratio of the SA concentration in the oil phase over the concentration in the water phase. The partition coefficient of sa between lanol 1688 and water was 1.491 at pH 2.8.

RESULTS AND DISCUSSION

4 O/W emulsions as defined in Table 1 were studied: an emulsion without the active substance (SA) and 3 identical emulsions with 3% SA incorporated into the emulsion preparation at different stages. 24 hours after their preparation, these emulsions were characterized by microscopy, droplet size distribution and rheology.

Microscopical Characterization

Microscopy of Emulsion Without Active Substance

An emulsion without active substance was manufactured and its structure was observed by optical microscopy (Fig. 2). As can be seen this emulsion showed a wide distribution of droplet size up to 40 µm. The droplets were spherical and larger droplets showed a striated surface, which was related to the presence of liquid crystals.

Droplets are made of two parts: an anisotropic nucleus of the oil phase and a birefringence shell (mesophase or liquid crystals) which surrounds the nucleus. When this emulsion was gently crushed between the slide and the coverslip, the larger droplets were partially flattened. As the internal phase was incompressible, the

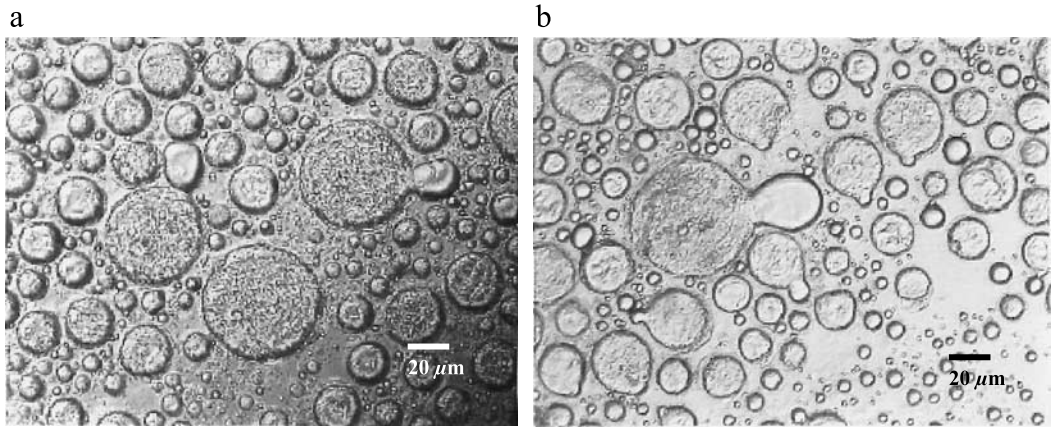

Figure 3. Visualization of the internal phase of the emulsion being expelled through the rigid structure formed by the liquid crystal layer under (a) slight pressure on the coverslip and (b) increased pressure on the coverslip.

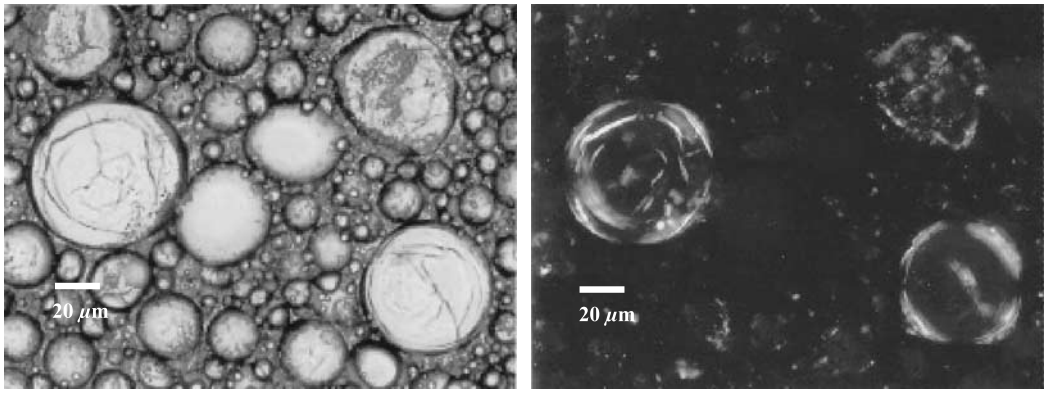

Figure 4. Visualization of liquid crystals by polarized light.

pressure excess inside the globule fractured the shell formed by the liquid crystals, causing the expulsion of the internal phase through the structure fractures (Fig. 3). When a part of the internal phase was forced out of the shell, the spherical structure of liquid crystals appeared empty but kept the same shape (Fig. 3b). Figure 4 shows the emulsion viewed with (left panel) and without polarized light (right panel). Under polarized light the rigid structure formed by the liquid crystals can be seen at the interface between the internal and the external phases, with the liquid crystals encapsulating the internal phase.

Microscopy of Emulsion with Active Substance (SA)

No SA crystals were observed when the SA was incorporated at the beginning (Start Mode: Fig. 5) and in the middle of emulsion preparation. On the other hand, when the SA was incorporated at the end of the preparation (End Mode) many needle shaped crystals were observed (Fig. 6). When the SA was added at the start and the middle of the preparation (Start Mode and Middle Mode), this active substance was totally solubilized in the oil phase droplets.

Particle Size Characteristics

Figures 7–9 present the results of the particle size studies. For the End Mode emulsion, SA crystals, which were present in the external phase, were solubilized by diluting the sample with water before the particle size measurement. Figure 7 shows a modification in the droplet distribution size of emulsions with SA added. Whatever the SA incorporation step (Start Mode, Middle Mode or End Mode) the mean size of the droplets and the size distribution were modified in comparison with the droplet size distribution of an emulsion without the active substance.

Studies of D(3,2) and PI enabled this variation to be quantified. As can be seen, it appeared that the addition of SA to the Montanov 68® O/W emulsion generated an increase in droplet size. SA addition in the Start Mode of the emulsion caused an increase of

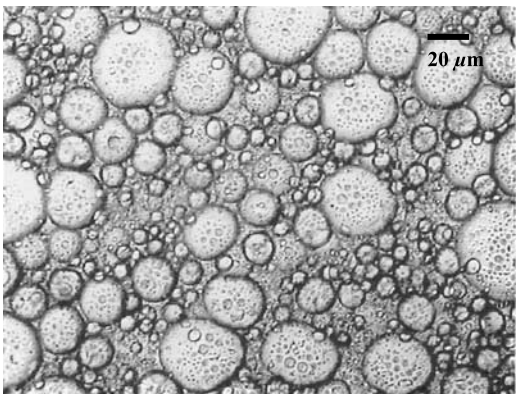

Figure 5. Emulsion with SA: ''Start Mode.''

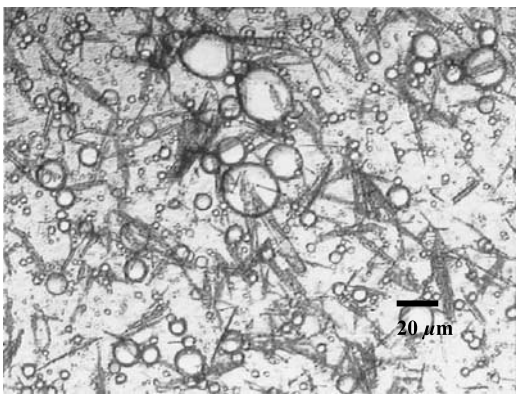

Figure 6. Emulsion with SA: ''End Mode.''

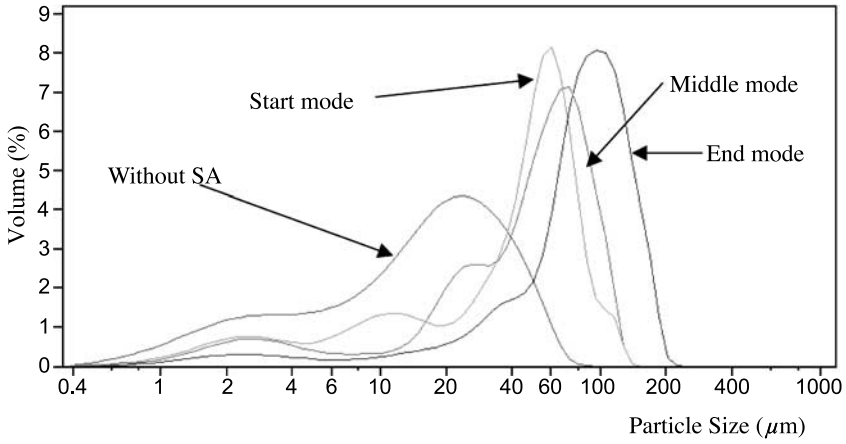

Figure 7. Droplet size distribution of each emulsion.

13% in D(3,2) when compared with the emulsion without active substance (Fig. 8), while droplet size increased by 27% when the SA was incorporated into the emulsion at the Middle Mode and the End Mode. The polydispersity study showed that the emulsion without SA and the emulsion with SA incorporated at the Start Mode have identical PI (Fig. 9). Both emulsions carried out with Middle Mode and End Mode addition of SA showed the same polydispersity. However, this PI value was 23% lower than the emulsion without SA. Thus, depending on the SA incorporation times, a modification in droplet size distribution (mean droplet size and polydispersity) was evident.

Rheological Characteristics

The rheological study showed the evolution of the viscosity of the emulsions after the incorporation of the active substance. Figure 10 shows the rising curves of the emulsions containing 3% SA and Table 3 the quantitative data. SA addition generated a viscosity decrease in the emulsions (Table 2 and Fig. 10), but between the Start Mode and the Middle Mode there was no difference in the viscosity. On the other hand the End Mode emulsion showed a lower viscosity than the other two. It was observed that SA addition, whatever the incorporation time, generated a decrease of over 50% in emulsion viscosity and a decrease in emulsion pH in comparison with the emulsion without SA.

The study of particle size [D(3,2) and PI] could explain some of the rheological characteristics. The comparison of the particle size characteristics between the Middle Mode and the End Mode emulsions showed no significant differences (Figs. 8 and 9). Since their droplet size and their polydispersity were similar, it was assumed that their viscosities should be similar.

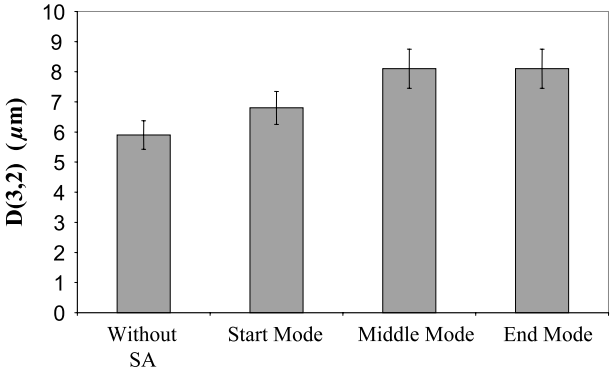

Figure 8. Effect of SA incorporation on emulsion droplets D(3,2): 9 measurements were carried out to calculate the means ± standard deviation.

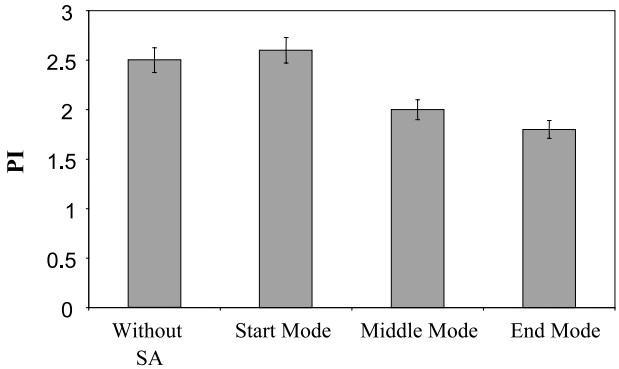

Figure 9. Effect of SA incorporation on emulsion PI: 9 measurements were carried out to give means ± standard deviation.

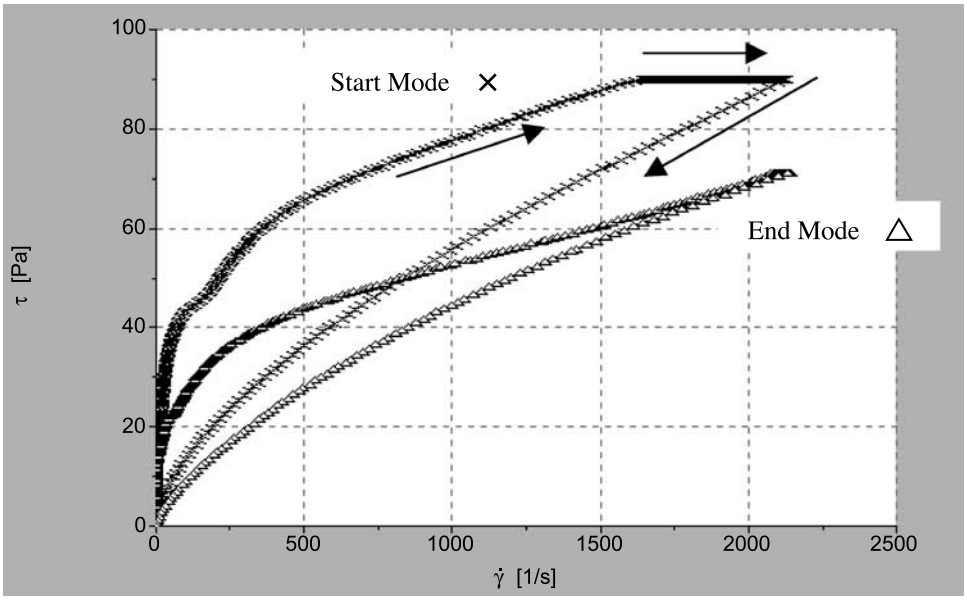

Figure 10. Rheograms of the montanov 68® emulsions with SA.

Rheological characterization of both systems showed that the End Mode emulsion viscosity was 28% lower than the viscosity of the Middle Mode emulsion. This viscosity decrease could be due to SA crystals present in the external phase. In fact these crystals generated a poor homogeneity in this system, which caused a low viscosity.

The comparison between the Start Mode and the Middle Mode emulsion characteristics showed a PI decrease from 2.6 to 2 (23%) and a droplet size increase from 6.8 to 8.1 μm (16%). The emulsion D(3,2) increase should generate a viscosity decrease in this system. For a given volume fraction, if droplet size increases, the mean distance between the droplets increases and the interaction between droplets decreases, facilitating the flow of each droplet. This could explain how a droplet size increase generated a viscosity decrease in this system.[9] On the other hand the PI study of these two emulsions showed that the Middle Mode emulsion was less polydisperse than the Start Mode emulsion. In Luklam's opinion,[10] for a given volume fraction, a higher PI value generates a lower viscosity value. D(3,2) and PI evolution effects on viscosity are antagonistic. Between the Start Mode and the Middle Mode emulsions, the PI decreased and the D(3,2) increased and therefore the viscosities of these two systems remained constant.

Table 2. Rheological characteristics of Montanov 68® O/W emulsions: 3 measurements were carried out to give mean ± standard deviation.

Emulsion	η at 200 s^{-1} (Pa.s)	η at 1000 s^{-1} (Pa.s)	τ_0 (Pa)
Without SA	0.53±0.04	0.13±0.01	11
Start mode	0.24±0.01	0.06±0.01	27
Middle mode	0.25±0.01	0.08±0.01	13
End mode	0.18±0.01	0.05±0.01	11

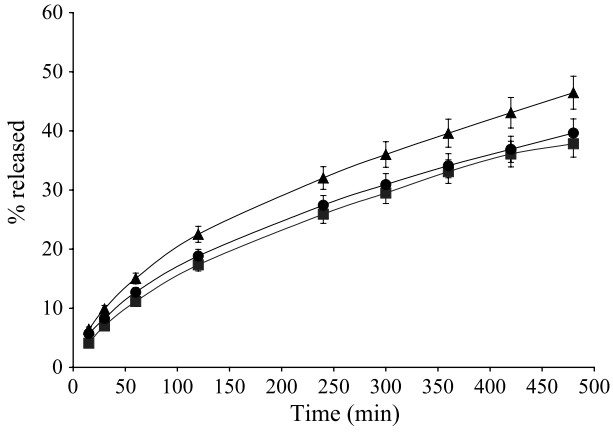

Figure 11. SA release profiles of the montanov 68® emulsions: effect of preparation mode. Each point = mean of 6 measurements ± standard deviation. ■ = Start Mode; ● = Middle Mode; ▲ = End Mode.

Table 3. F_1 F_2 factors.

Comparison of release kinetics with F_1 et F_2 factors	F_1	F_2	Comparison result
Start mode and middle mode	5.7	88.3	Insignificant
Start mode and end mode	24.3	61.6	Significant
Middle mode and end mode	17.2	66.7	Significant

Diffusion Studies

Diffusion studies were carried out with about 2 G OF O/W emulsion containing 3% SA. each release study was carried out in 1 Liter of 0.15 M Phosphate buffer, PH 7.4. Under these conditions, the final theoretical concentration at 100% of SA released would be 60 mg/L.

In pH 7.4 phosphate buffer solution, SA had a solubility greater than 300 mg/L and so sink conditions were respected and SA solubility in the receptor fluid was not rate-limiting in the diffusion process. The three studied emulsions had the same formulation and so their affinity with the cellophane membrane was identical and this membrane was not a limiting factor in SA diffusion. Most of the diffusion studies were undertaken 48 h after the emulsion fabrication. In this study, the mean release percentage of the three emulsions containing 3% SA were compared. Release profiles were determined with the mean, standard deviation and variation coefficient of SA cumulative percentage release for each time point. The results are shown in Fig. 11. Start Mode and Middle Mode emulsions showed similar release profiles. On the other hand, the End Mode emulsion released SA slightly more rapidly than the other two. The End Mode emulsion released up to 20% more SA than the Start and Middle Mode emulsions.

The statistical significance of the difference is shown in Table 3. If F_1 values < 15 and $50 < F_2$ values < 100, release kinetics were not significantly different. (If $F_2 = 50$, the difference between the 2 curves was about 10%).[11]

DISCUSSION

In this study we have examined the effects of using Montanov® as a surfactant on the properties of oil in water emulsions. Montanovs® consist of AlkylPolyGlucosides (APG). Emulsions were prepared containing 5% Montanov® 40% Lanol 1688® and salicylic acid (SA) was used as a test drug. The incorporation of the SA into the emulsions at different stages of the preparation produced emulsions with different release characteristics. Thus as shown in Fig. 11, when the SA was incorporated into the emulsion during the early or mid preparation stage (Start Mode and Middle Mode) then the release of incorporated SA was significantly lower than when it was incorporated during the final stage of emulsion preparation (End Mode). One possible explanation was the Montanov® (APG) formed liquid crystals which acted as a barrier to the diffusion of the entrapped drug. Other researchers have observed that alkylpolyglucosides generated liquid crystalline phases with lamellar structures.[12,13] Liquid crystals have been used to improve emulsion stability, for example, by their covering the dispersed phase droplets and thus preventing coalescence. The improved stability seen in O/W emulsions could be due to the high viscosity of the liquid crystals which increased the interface rigidity. Thus liquid crystals are a novel way of controlling the structure and stability of dispersed systems.[14–16]

In Oil/Water emulsions, these liquid crystal layers are located on the oil water interface and generate an increased interface rigidity. This configuration increased the emulsion stability with the creation of a physical barrier between the internal and the external phases.[6,17] Indeed when the emulsions were examined under polarized light (Fig. 4) the bifringence seen surrounding the droplets suggested a layer of liquid crystals, which could form a ''rigid'' physical barrier. In addition, when the emulsions were gently squeezed by gentle pressure on the cover slip, it could be seen that the contents of the oil droplets was exuded through apparent breaks in the barrier (Fig. 3).

When SA was incorporated at the beginning of the emulsion reparation (Start Mode), it would be solubilized into the oil phase at 70°C. During the mixing of the two emulsion phases, the preparation temperature remained high, and given the SA partition coefficient (1.491) between Lanol 1688® and distilled water, the SA would be preferentially solubilized in the oil phase. The same applies to the SA added as the Middle Mode. In these cases, the drug release can be envisaged as taking place through a number of steps. Firstly, within each Lanol® droplet, SA diffused from the most concentrated zones to the droplet surface. Then the SA must go through the liquid crystal barrier formed by surfactant, before diffusing through the external phase. On the other hand, when SA was introduced into the emulsion at the end of the preparation, the emulsion temperature was much lower: 35 or 40°C and the SA remained in the external phase because it was not able to go through the barrier generated by the liquid

crystals. Since SA was less soluble in the external phase, it remained as crystals in the preparation. This could also explain why crystals of SA could be seen in the external phase in the End Mode preparation (Fig. 6). It would also explain why this End Mode formulation showed higher release kinetics, as the SA would have been more concentrated in the external phase and diffuse directly out of this phase.

Other properties of the emulsions might also influence the drug release. For example, Malzfeldt et al. observed that drug release rate was influenced by the viscosity with faster release from low viscosity formulations.[18] Thus the rheological properties might account for the faster release seen in the Start and Middle Mode emulsions. The rheological data, as seen in Table 2 and Fig. 10, showed that the End Mode preparation had a lower viscosity than the other two, but the difference may not have been sufficient to account for the different release rate of SA.[18] Other authors have observed that droplet diameter and viscosity had no direct influence on the release kinetics of an active substance. The results with the emulsions would support the contention that drop size is not a factor influencing release as the data in Figs. 8 and 9 show that the Middle Mode and the End Mode emulsions show the same droplet size and the same polydispersity.

CONCLUSION

Emulsions prepared with Montanov 68®, which generated liquid crystals, presented several advantages. Due to these liquid crystals, the emulsions are less likely to coalesce and the active substance is stably ''encapsulated'' in the internal phase (Lanol®). In addition, the presence of the liquid crystals results in a more controlled release of the incorporated drug. The release of drug from these emulsions was not influenced by the particle size of the droplets or the viscosity of the formulations. This rigid structure of liquid crystals at the interface between internal and external phases may enable the production of emulsions with the incorporation of two incompatible active substances, one located in external phase and another in the internal phase, separated by this mesophase.

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