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RESEARCH ARTICLE

Characterization of ternary phase diagrams by means of thermal and rheological analyses

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Abstract

Context: Mixtures made of oil, water and surfactants give rise to a wide range of structure with different characteristics and phase manifestations.

Objective: Aim of this paper is to build up and understand the phase diagram of a model ternary system (Water, Polysorbate 80 and isopropyl myristate) by the use of common techniques such as thermal analysis and rheology, in comparison with visual assessment and polarized light microscopy.

Methods: Different ternary systems were prepared and analyzed by means of DSC and rheology in order to highlight the state of water (free, interphasal, bound water) and the samples structural characteristics.

Results: The resultant phase diagram is divided into four different zones. Bound water zone is predominant at elevated surfactant/oil ratios, while as the surfactant/oil ratio decreases, DSC reveals the presence of free water. Interphasal water prevails at intermediate water and surfactant content which corresponds with gels systems. Mechanical spectra allow to discern between cubic (true gel) and lamellar mesophases (weak gel), while flow curves allow to distinguish among microemulsions, emulsions or lamellar mesophases.

Discussion: A deeper characterization of a model ternary phase diagram is possible, with respect to the simple visual inspection, by the use of thermal analysis and rheology. The state of water molecules and the viscoelastic characteristics of the system allow to obtain important structural considerations.

Conclusions: In conclusion, the knowledge of the state of water and of the viscoelastic characteristics of the systems allow a deeper understanding of the structural features of the ternary phase diagram.

Keywords: Ternary phase diagram, DSC, Rheology, Free/bound water

Introduction

Microemulsions are thermodynamically stable systems, which form spontaneously in presence of surfactants because of the low surface tension values due to the diffusion of surfactant itself in the interfacial layer and to the dominant entropy contribution that depends on the mixing of one phase in the other as a large number of very small droplets.[1] From the pharmaceutical point of view lyotropic liquid crystals and microemulsions show several advantageous features that make them drug delivery systems suitable for different administration routes. In fact they are able to incorporate and deliver drugs of different sizes and polarity since they posses lipophilic, hydrophilic and amphiphilic domains.[1,2]

Thus, microemulsions have been exstensively studied for transdermal, parenteral and oral delivery of drugs,[2,3] to enhance drug solubility and control proteins and peptides delivery.[1–4]

Mixtures made of oil, water and surfactants give rise to a wide range of structures such as regular emulsions, anisotropic crystalline lamellar, hexagonal, or cubic phases[5] and can have different characteristics and phase manifestations depending on constituents proportions. For example, systems with more similar content of water

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and oil have shown bicontinuous structures having microstructures which continuously change with time.[6,7]

The relationships between the phase behavior of a mixture and its composition can be depicted with the aid of a phase diagram. The phase diagram is strongly affected by the molecular design of the surfactant that is the major factor in determining the nature of the dispersion formed. In fact, droplet shape depends on the curvature of the water/oil interface. For example a strong surfactant is able to form microemulsions at low concentration and lamellar phases at higher concentration, making the phase diagram more complex.[6,7]

At low water content, elongated, rod-like micelles are present, but water in oil spherical droplets, smaller than in classical emulsions, can also be observed. Whereas, the formation of a lamellar phase is observed when there is a significant surfactant content with a consequent general increase in viscosity of the system.[8]

Usually in pharmaceutics phase diagrams are constructed in order to check in which area of the diagram systems called microemulsions are present. This zone is generally identified by visual observation and recognized with the systems considered completely transparent.[5] However, using this approach it is not possible to obtain information about the structure of these systems. As an example, in the case of w/o microemulsions it is not possible to know if the water molecules form nanodroplets or join a mesophasic structure because both these systems appear transparent.

Differential scanning calorimetry (DSC), has been largely used for the determination of the state of water into a system.[9–11] Considering that the main component of surfactant-based systems is water, the characterization of its behavior in the presence of adjacent interfaces appear to be of utmost importance.

In general, water interacting with polymers, molecules, macromolecules, colloidal particles and solid-liquid interfaces can display interactions of different nature and at least three types of thermodynamic water are recognized and quantified by DSC[12] free water, bound and interphasal water.[13] When describing the state of water in relation to any surface, it is necessary to distinguish between "bulk" and "bound" water. Bulk or free water possesses physicochemical properties (heat of fusion, freezing temperature, etc.) not much different from those of pure water,[14] while bound water (also known as "hydration shell", "vicinal water") shows a modification of its thermodynamic, hydrodynamic and kinetic properties due to the presence of a substrate in contact with the water itself.[15] Water whose properties are intermediate between free water and bound water may be defined also as "interphasal" water (freezing temperature about −10°C).[15]

The knowledge of the proportions between the three types of water is important in order to get information on the different phases formed, which allow to build and understand the relative phase diagram. At the same time, rheology is the most appropriate technique for rating structural rearrangements, defining viscoelastic properties of such ternary systems and classifing the different phases formed. In fact, variation in the ratios of the three components gives rise to a variety of structures all characterized by different degrees of consistency. Rheological analysis, in particular the investigation of the flow behavior of a three components system, has been utilized to model the lamellar structure, which has been intended as flexible layers subjected to frictional forces in the liquid layer.[16] For example, several nonionic surfactant/water lamellar liquid-crystalline phases characterized by shear thinning and yield stresses have been reported,[17] while another study reported the viscoelastic behavior of a lamellar anionic surfactant AOT (sodium *bis*(2-ethylhexyl) sulfosuccinate) as a function of surfactant concentration. Dynamical measurements indicated that the AOT/water lamellar phase behaved like a "weak gel".[18] Shear and elongational rheology studies of ternary systems composed of dodecane, didodecyldimethylammonium bromide and water has been performed as well.[19] Viscosity values outlined that dilute microemulsions were shear thinning and the critical shear rate depended on whether the liquid showed a bicontinuous or droplet structure. In another work, different rheological models have been applied in order to investigate the complex rheological behavior of a liquid crystalline surfactant-water system in the linear and in the nonlinear viscoelastic regions.[20]

The aim of this paper is to show which information can be drawn from the use of two rather common techniques such as DSC and rheology, used with visual assessment, for the understanding of the phase diagram of a model ternary system made of water/Polysorbate 80/isopropyl myristate (IPM). These components were chosen because they are well-known products and have been already studied in other phase diagrams.

Polarized microscopy was also carried out just to confirm the characteristics of the phase diagram as they have been depicted by thermal and rheological analysis.

Materials

Polysorbate 80 (TEGO SMO 80) and IPM were supplied by A.C.E.F s.p.a Piacenza (Italy). All chemicals were used without further purification. The water was deionized water.

Methods

Sample preparation

Polysorbate 80 and isopropylmiristate were mixed in order to obtain the following surfactant/oil ratios: 10/90, 20/80, 30/70, 40/60, 50/50, 60/40, 70/30, 80/20, 90/10. All the systems were prepared at room temperature under mechanical stirring at 200 rpm. An increasing amount of water was then added to the same portion of each of the above mentioned S/O ratios, in order to obtain systems having a final water content of 10, 20, 30, 40, 50, 60, 70, 80, 90%. In practice all these surfactant/oil/water systems are those represented by colored dots in Figures 1, 2 and 4.

They cover the whole ternary diagram. All these final systems were stored in closed vials in order to avoid water evaporation. Before testing, they were allowed to equilibrate at room temperature for 24 h.

Visual analysis

All the systems were first analyzed by visual assessment in order to classify them for transparency and consistency.

DSC analysis

Ten milligram of each ternary system was analyzed using a power compensation differential scanning calorimeter (DSC Pyris1, Perkin-Elmer US Instrument Division, Norwalk, CT, USA). Additional DSC analyses of pure surfactant, pure oil and water were also performed. The instrument was previously calibrated for melting enthalpy and temperature using high grade purity Indium and HPLC grade water as standards.

The enthalpy of fusion has been calculated by integrating the area under the endotherm of fusion by using a Pyris Series (Perkin-Elmer) software. Samples were accurately weighted using a Mettler Toledo balance (AX-26), then closed in aluminum pans and analyzed using the following procedure: (A) cooling ramp from 20 to −45°C at 2°C/min, (B) isothermal step for 30 min at −45°C, (C) heating ramp from −45 to 20°C at 2°C/min. All systems have been analyzed in triplicate.

The three types of thermodynamic water are recognized.[12–15]

- Type 1: water which corresponds to bulk free water. It does not interact with other molecules and its thermal behavior (freezing and melting temperature) corresponds to that of normal water. The onset of the melting transition is 0°C.[21] In term of water activity (w_a), the term "free water" may describe a system with water activity close to 1. Water activity is $w_a = 1 - P/P_o$, where P is the partial pressure of water above the material and P_o is the partial pressure of pure water at the same temperature.[13]
- Type 2: water which is loosely bound to the molecules of the system. It melts at a temperature lower than that of bulk water. It can also display a significantly smaller enthalpy and can be named also "interphasal water".[13]
- Type 3: water that is strongly bound to the other molecules of the system and it freezes at temperatures lower than −50/−60°C. This kind of water does not show first order phase transition and is often termed "non-freezable water". Non freezable water may describe a system having low w_a, below the detection capability of the DSC. This water shows a crystallization/freezing behavior with considerably supercooling behavior and the areas under the peaks of all transitions are by far smaller compared to the bulk one. This happens because water interacts with specific functional groups of hydrophilic polymers, surfactants and other types of structures.[13]

The final heating step was particularly important because it allowed to estabilish the state of water and quantify it through its melting peaks unless other transitions superimposed. The enthalpy value associated with water endotherm allowed evaluation of the free water fraction (i.e. melting at 273°K), according to equation (1): bound water resulted from the difference between the "*a priori*" known water content of the sample and the amount of water that melted at 273°K.

Percent of free water =

$$\left(\frac{\Delta H_w^s \times \dfrac{sample\ wt}{water\ wt}}{\Delta H_w^T} \right) \times 100 \qquad (1)$$

where, ΔH_W^T = measured reference enthalpy of pure bulk water; ΔH_W^s = experimentally measured enthalpy value.

The intherphasal water was calculated according to the same criterion.[12–15]

Rheological analysis

Rheological analyses were performed on all the prepared ternary systems, using a stress control rheometer (Stress-Tech, Reologica). Cone-plate (4/40) with 150µm gap, plate-plate with 1 mm gap and bob and cup were the different geometries chosen depending on the system characteristics. Nondestructive oscillatory measurements, performed in this study, allowed obtaining the rheological main parameters such as the storage or elastic modulus (G'), the loss or viscous modulus (G") and the loss tangent (tan δ). The following tests were performed in triplicate:

Oscillation stress sweep

The sample was exposed to increasing stresses at a constant frequency (1 Hz frequency) and at 25°C. The range of stress was selected depending on sample properties. This test allows the determination of the linear viscoelastic regime of the sample, and therefore, the stress value to be used in the other oscillation tests.

Frequency sweep

The sample was exposed to a stepwise of increasing frequencies at a constant stress in the frequency range 0.01–50 Hz, in the field of linear viscoelasticity, at 25°C. The frequency range and the G'–G" curves were plotted in logarithmic scale.

Creep test

The sample was exposed for 100 s to a constant value of stress chosen in the linear viscoelastic regime at the temperature of 25° C. This test was used to determine sample viscosity.

Flow curve

The liquid samples were exposed to increasing stress (0.05–10 Pa) in order to study the flow behavior.

Optical polarized light microscopy

Samples were prepared by placing a drop of the different systems between a cover slip and a glass slide and then analyzed under polarized light by using an MT9200 (Meiji) microscope equipped with an Invenio 3S videocamera (DeltaPix). Ocular 10× was used corresponding to magnifications of 1.56 μm pixel heights.

Results and discussion

Visual analysis

Each different weight ratio mixtures that have been prepared are evaluated from a visual point of view and the results are shown in a phase diagram (Figure 1).

Different areas can be identified and correspond to different system types such as classical emulsions (white liquid emulsion, black symbol), emulsion-gel systems (red symbols), transparent gel systems (light blue symbols), turbid gel systems (pink symbols), transparent liquid systems (yellow symbols) and semisolid systems where phase separation occurs (green symbols).

High surfactant content generates transparent liquid or semisolid systems. In particular, 90/10 surfactant/oil weight ratio, for all water percentages, forms transparent systems that become liquid at high water concentration (70–90% w/w). Low water content brings to the formation of transparent thick gels; whereas, systems return liquid when only 10% of water is present.

The 80/20 surfactant/oil weight ratio shows a similar behavior in presence of low water amount; while a big area of liquid emulsions is present when the concentration of water increases above 60% (w/w). Decreasing the percentage of surfactant (from 70/30 to 30/70 surfactant/oil ratios) means lowering the amount of water that can be added without loosing system transparency (from 30 to 10% w/w). Most of the surfactant/oil ratios generate semisolid phases when added with 20 up to 50% w/w of water; however, their appearance changes with surfactant content. At elevated surfactant content (90/10 surfactant/oil ratios) systems are still transparent; then, as the surfactact content decreases, systems become turbid gels first and then completely white gels (emulsion gels). It is argued that in these samples water activity changes.[22]

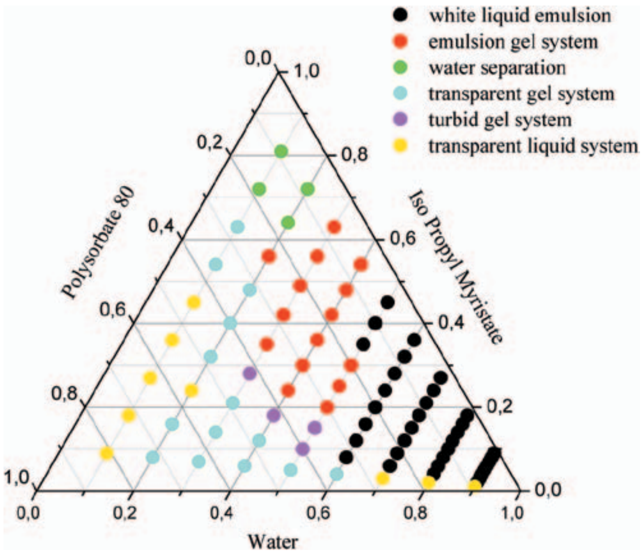

Figure 1. Phase diagram of the ternary system built by visual assessment of the mixtures at different weight ratio (w/w).

Very low surfactant content compromises systems and phase separation phenomena occur with the 10–20% w/w water content. Transparent systems, particularly the liquid ones, are usually defined microemulsions despite the real state of water is not fully established.

Thermal analysis

As already mentioned, before initiating the analysis of the different ternary systems, preliminary tests have been carried out on pure oil, surfactant and water. IPM showed an endothermic transition at 7.3°C during the heating run (data not shown), due to melting, deionized water melting onset is about 0°C, while Polysorbate 80 does not show any important transition in the range of temperatures in use.

Ternary systems show different thermal behaviors depending on the S/O ratio and on the amount of water content. Figure 2A is reported as an example of how water addition to a fixed surfactant/oil ratio (70/30) affects the thermal output.

From DSC curves, it is straightforward the identification of the three different types of water. Bound water, in this system, is interacting strongly with the surfactant chains, and for this reason, it is no more able to freeze above –45°C.

In the mixtures with 10 and 20% w/w of water, only melting of free oil is visible at about 6°C; thus, all water present is bound water and a water-in-oil system is formed. Interphasal bound water is the water surroundings the interface of a micelle or a drop in an emulsion; it is loosely bound and melts at a temperature below 0° (approximately –10° C). In Figure 2A, this kind of water is seen when a 30–60% w/w of water is added, thus the melting endotherm lies between –10° and –5°C.

Free water is not bounded; it can be bulk water of an oil-in-water microemulsion (or emulsion) or it can also be the water molecules inside the drop of a water-in-oil microemulsion (or emulsion). This kind of water should behave as a pure one and so it should melt around 0°C. In Figure 2A this behavior is shown for systems with high water content (70–90% w/w) and a significant endotherm appears at about 0°C.

Bulk water is observed also in systems titrated with 40–60% w/w of water, as a second peak that is shifted toward 0°C. Figure 2B shows the variation of freezable water, intended as free and interphasal water, versus the total amount of water for the 70/30 surfactant/oil ratio system. As expected, freezable water increases as added water increases. Similar trends are also seen for other surfactant/oil ratios; however, the curves are shifted along the y-axis depending on polysorbate 80 percentage (data not shown). In fact, at increasing polysorbate 80 content, curves are shifted to lower temperatures

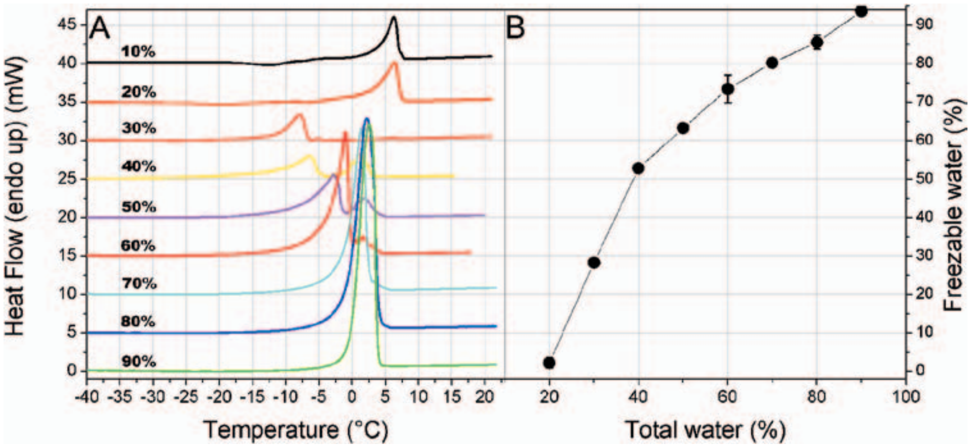

Figure 2. Heating cycles (using 2°C/min heating rate) of polysorbate 80/IPM in 70/30 titrated with increasing amounts of water (10–90%) on DSC.

indicating an increase of bound water present in the sample. A decrease of the surfactant amount brought to an opposite behavior that is to an increase of free water.

Using the criteria of analysis described above, another ternary phase diagram (Figure 3) has been built, which takes into consideration the state of the water inside each sample. Obviously, systems showing phase separation phenomenon are not analyzed.

This diagram shows a big area made of samples rich in free water, at any surfactant/oil ratio, while water content is increased up to 60% w/w.

As surfactant/oil ratio decreases, free water appears even at lower water content; the hypothesis for this result is that surfactant gets saturated and it is no more able to keep the water "connected" to the system.

Whereas at 10% and also 20% w/w water content only bound water is present (except the zone of phase separation). Therefore, the zone of bound water becomes larger at elevated surfactant/oil ratio, up to 40% w/w water content. Overall, water can easily and totally interact with the surfactant and behave as bound water only when its amount is very low (10%-20% w/w) or when the polysorbate 80 is markedly predominant (90% w/w) or up to 40% w/w of water content.

At intermediate water and surfactant content, in the middle of the phase diagram interphasal water is largely present. Whether the phase diagram created by visual assessment and the one based on evaluation of the state of water by means thermal analysis are superimposed, another phase diagram (Figure 4) can be generated.

In the zone of the diagram where free water is prevalent is (on the right), samples are either white O/W liquid emulsions or emulsion gel systems. Then, oil-in-water microemulsion systems are formed when surfactant content is much higher than oil (90/10 surfactant/oil ratio) and in the presence of high water content (> 60% w/w).

The zone in the middle of the diagram, characterized by a prevalent amount of interphasal water, covers the area where systems are gels but with different appearance from transparent to opalescent or white. All these samples are characterized by apparent high consistency which might be related to the formation of cubic and bicontinuous phases. In fact in this zone of the phase diagram polarized microscopy shows the isotropic behavior typical of cubic phases (Figure 5B).

The filled zone on the left of Figure 4 represents systems with low water content, bound water is present and systems are transparent. Low water amount together with high surfactant percentage give rise to liquid systems, while a decrease in the surfactant/oil ratio brings to the formation of transparent structures with semisolid consistency. All these samples can be considered as having water-in-oil structures but, the type of mesophase changes between the two regions. Transparent gels may be associated with cubic phases while liquid systems may be formed by lamellar phases. In any case, bound water is always present; thus presumably no water nanodroplets can be found in these transparent systems.

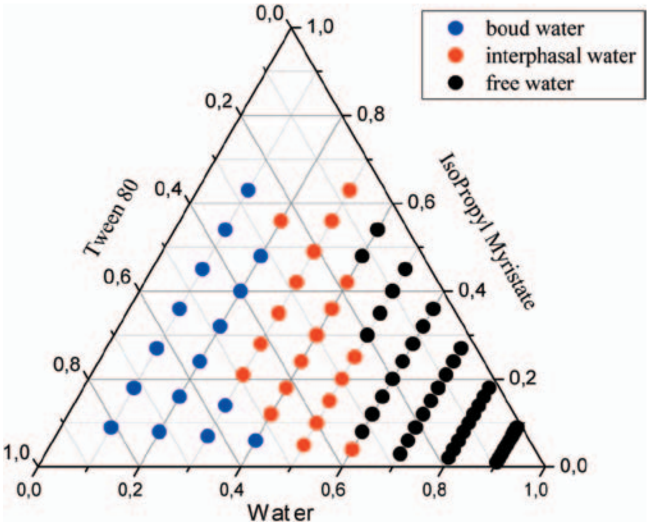

Figure 3. Phase diagram of the ternary system based on the different states of water within the ternary system in study measured by means of DSC.

However, when a considerable amount of interphasal water is present, the system starts to become opalescent. If one considers the 70/30 surfactant/oil ratio (Figure 2), it is clear that bound water is present at 10 and 20% w/w water content: no droplets forming a dispersed phase are present and the system is transparent. In fact, polarized microscopy analysis (Figure 5A) highlights the typical pattern of lamellar liquid crystalline structure, characterized by the presence of Maltese crosses. This transparency persists even at 30% w/w of water content despite interphasal water is present in the system; however, in this case, since interphasal water is a type of freezable water, nanodroplets could be present.

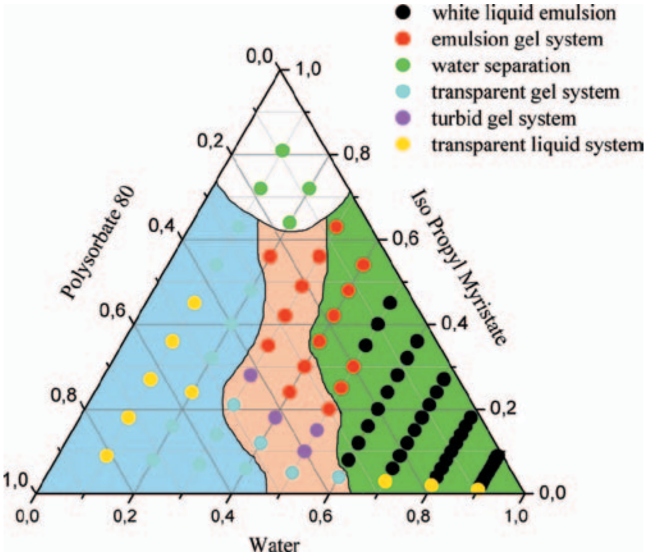

Figure 4. Phase diagram of the ternary system obtained by overlapping of the two phase diagrams reported in Figures 1 and 3.

When the amount of water in the system increases, interphasal water becomes predominant. In fact the system itself gets first turbid and then white. It is possible that water droplets increase in number and diameter before phase inversion occurs. Indeed from microscopy analysis it is possible to observe the presence of structures associated with classical emulsion systems (Figure 5C).

On the contrary, samples at 90/10 surfactant/oil ratio are transparent independently of the amount of water added, but also in this case the inner structure of the systems changes, since water behavior changes as well. As example, when the amount of water added is as high as 80% the polarization microscope image highlights the isotropic behavior usually associated with microemulsion systems (Figure 5D).

Rheological analysis

Dynamic rheological measurements have been performed on all Polysorbate 80/Isopropyl miristate ratios added with increasing amount of water (all the ternary systems) in order to identify and characterize from a rheological point of view the different regions of the phase diagram. Thus, modification of rheological parameters such as dynamic moduli, G' and G", together with viscosity are measured. In fact, different mesophases show different rheological properties and this study demonstrates that phase changes are strictly dependent on both water and surfactant contents. In general, oscillation frequency sweep analyses highlight that high surfactant/oil ratios give rise to gel-like systems but only when the amount of water is between 20 and 50% w/w. Whereas the presence

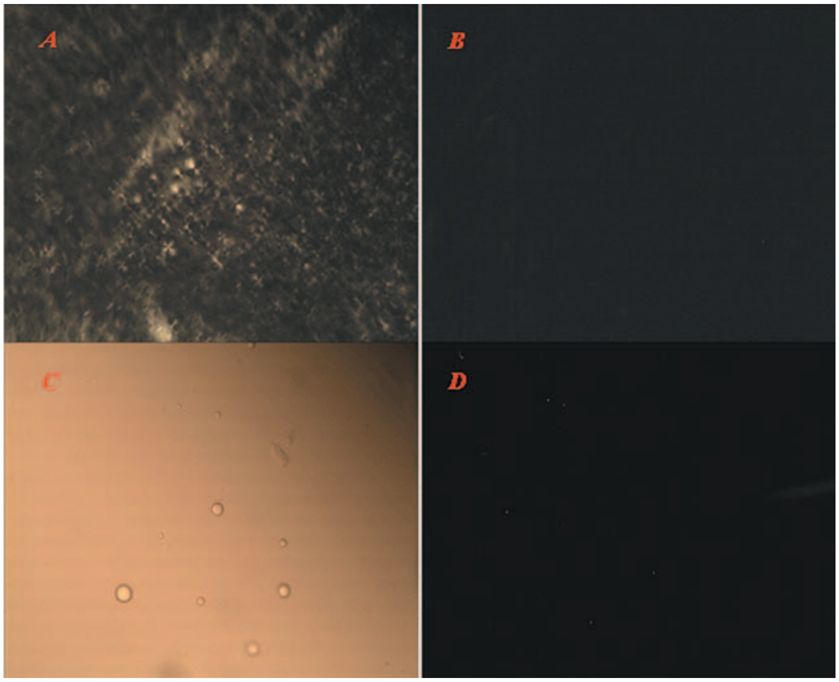

Figure 5. Polarized light microscopy images 70/30 S/O ratio containing 10 (A), 40 (B) and 60% (C) of water, and 90:10 S/O ratio with 80% of water (D).

of lower percentages of surfactant reduce the amount of water that can be added without decreasing systems consistency. This is in agreement with previous DSC and microscopy analysis results. It is possible that cubic liquid crystal phases are present, since a cubic structure gives a typical gel-like rheological behavior.

As an example, Figure 6 reports frequency sweep curves of the different 90:10 surfactant/oil systems. As can be observed, this ratio forms a gel-like structure with 20–60% w/w of water. In fact, mechanical spectra are characterized by a limited frequency dependence of G′ and G″ moduli and low values of tan δ which are indicative of a predominant elastic behavior. Such type of behavior is typical of cubic phase structures.

Furthermore, calculations of the slope of G′ versus frequency curves demonstrates a progressive structural modification of the studied systems as the water content increases (Figure 7) which suggests that changes in sample structural organization indeed occur. Higher slope values are typical of liquid phase, while low values are typical of structured systems.

While for water contents lower than 20% slope values are elevated, at 20% and higher water contents it can be observed a remarkable decrease of these slope values. This trend suggests the presence of a more organized structure evolving from lamellar mesophase, characterized by a mechanical spectra similar to that of a weak-gel system, to a cubic structure with slope values that became close to zero and thus typical of gel-like systems.[23,24] Thus, intermediate water percentages lead to the formation of true gels, from a rheological point of view. This is true also for other surfactant/oil ratios, particularly those higher than 50:50.

Now, these systems include the phase diagram regions characterized by the presence of bound (transparent gel) and interphasal water (emulsion gel and opalescent gel). Unfortunately, rheological analysis is not able to distinguish among transparent gel systems or emulsion gel systems. In fact, and the mechanical spectra of these samples are quite similar.

On the contrary, liquid systems are formed when water content is low (10%) or higher than 60%. In this last case, systems are not transparent but white. Yet at low S/O ratios, these white liquid systems already appear at a 40–50% water content. Independently of their classification, that is microemulsion or liquid crystals if transparent and classical emulsions if white, the mechanical spectra of both systems appear completely different from the semisolid systems (transparent and opalescent gel and emulsion gel systems) as proved by the presence of G′/G″ cross-over points in the frequency sweep plots.

As mentioned, the amount of water that can be added to the systems without affecting their mechanical properties gradually decreases as surfactant content decreases (Figure 8). For example, the ratio 30/70 surfactant/oil with 40% w/w water percentage is a definitively less structured sample, appearing more similar to a concentrated dispersion than a true gel. This drop of consistency may be due to a change from a cubic to an hexagonal mesophase or to the fact that the cubic phase is simply diluted by the presence of droplets of interphasal water.[23,24]

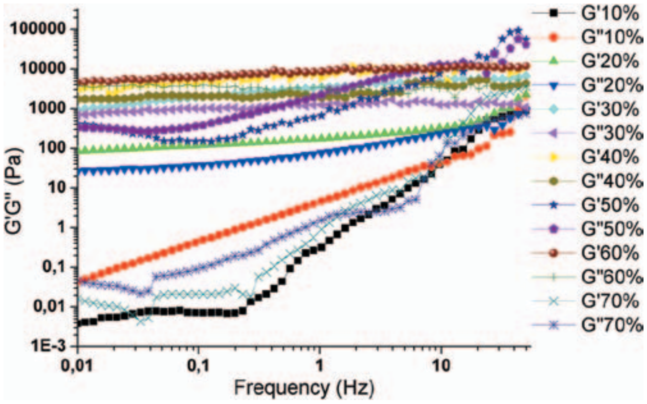

Figure 6. Frequency sweep of 90:10 surfactant/oil systems with a water content ranging from 10 to 70% (w/w).

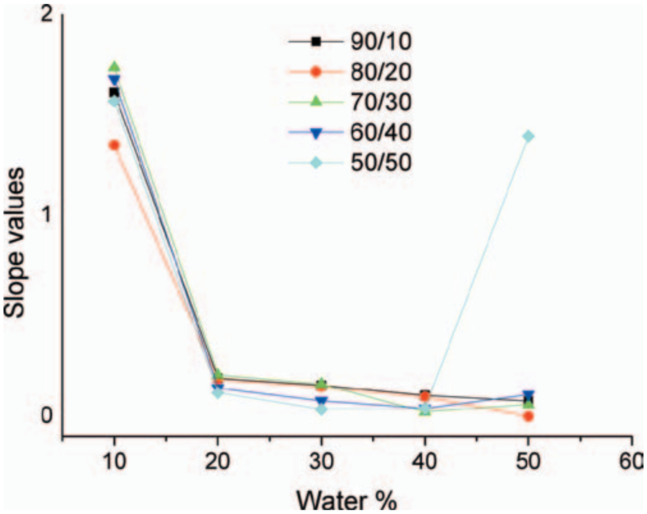

Figure 7. Slopes of G′ values of the surfactant/oil (w/w) ratios from 90/10 to 50/50 versus water percentage.

The viscosity values from the creep tests confirmed the frequency sweep results. Figure 8 reports these viscosity values.

Furthermore, for systems characterized by liquid-like behavior, the distinction between o/w emulsions, microemulsions and w/o lamellar mesophases can be performed by considering the viscosity values which are lower for emulsions. This can be attributed to the fact that w/o lamellar mesophases show higher level of structural organization compared to o/w emulsions or microemulsions.

Conclusions

This work pointed out what type of information can be drawn by the use of rather common techniques such as thermal analysis and rheology, in the construction of a

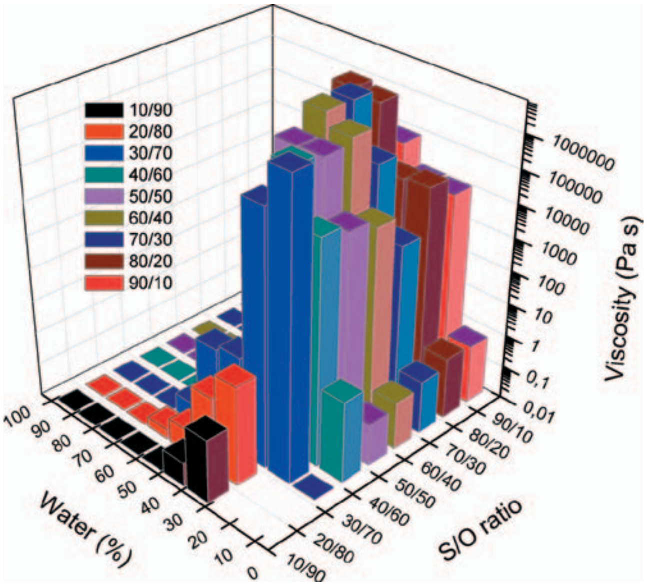

Figure 8. Viscosity values from the creep test for the different surfactant/oil (S/O) ratios as a function of water content. Only the range 0–50 Pa s has been selected to avoid bar overlapping in the plot.

ternary phase diagram. In this sense the two above mentioned techniques complemented by polarized microscopy analysis, which is also a simple and widely used methodology, permit a much accurate characterization with respect to the simple visual inspection which allows only to distinguish between liquid and transparent zones.

Deeper considerations, even of structural type, can be done on the basis of the state of water molecules and of the viscoelastic characteristics of the systems. As an example, nanodroplets, usually studied by light scattering techniques in order to determine their particle size, are not always present in transparent systems. At the same time, a transparent system can be either liquid or semisolid depending on the type of mesophase present and, in general, on the type of structure.

Surely, other techniques such as small angle x-ray scattering or neutron scattering give more complete structural information; however, they are not so common techniques. Nevertheless, a characterization and comprehension of the whole phase diagram is indeed necessary especially in the pharmaceutical field. In fact, when a drug is loaded into a so-called “microemulsion” and then administered in vivo, the system is diluted with water quickly or not, depending on the amount of water available. As it can be seen also from the diagrams reported in this work, a system can change in consistency from liquid to semisolid as a consequence of this dilution, slowing down the drug release. At the same time, a semisolid system can change to a liquid one if phase inversion occurs and this fact leads to a quicker drug release. Therefore, a correlation between pharmacokinetic data and system characteristics is rather complicated without an in-depth knowledge of the whole ternary phase diagram.

Declaration of Interest

The authors report no declarations of interest

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