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Preparation and Physicochemical Characterization of Dioctyl Sodium Sulfosuccinate (Aerosol OT) Microemulsion for Oral Drug Delivery

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ABSTRACT

The performance of dioctyl sodium sulfosuccinate (aerosol OT) in the development of a pharmaceutically acceptable, stable, self-emulsifying water continuous microemulsion with high dilution efficiency was assessed. A pseudoternary microemulsion system was constructed using aerosol OT/medium-chain triglycerides with oleic acid/glycerol monooleate and water. The model microemulsion was characterized with regard to its electroconductive behavior, eosin sodium absorption, interfacial tension, and droplet size measurements after dilution with water. The percolation transition law, which makes it possible to determine the percolation threshold and to identify bicontinuous structures, was applied to the system. The interfacial tension changes associated with the microemulsion formation revealed ultralow values up to 30% oil at a surfactant/cosurfactant ratio of 3:1. Moreover, the investigated particle size and polydispersity using photon correlation spectroscopy after dilution with excess of the continuous phase proved the efficiency of the microemulsion system as a drug carrier that ensures an infinitely dilutable, homogeneous, and thermodynamically stable system.

KEYWORDS: microemulsions, phase diagram, conductivity, eosin sodium absorption, photon correlation spectroscopy

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INTRODUCTION

Microemulsions are transparent fine dispersions of oil and water droplets stabilized by surfactant molecules. They are macroscopically monophasic, are isotropic, and possess a flexible interfacial film that is characterized by ultralow interfacial tension values (10^{-2} mN/m).[1] Such dispersions are easy to formulate, and various structures (oil/water or water/oil) can be obtained. In contrast to emulsions, microemulsions are thermodynamically stable. This stability makes them interesting as drug carrier systems.

In recent years, lipid microemulsions incorporating medium-chain glycerides have attracted much interest as oral dosage forms to improve drug dissolution and/or intestinal absorption[2] because (1) they are stable food grade products and generally recognized as safe by the US Food and Drug Administration; (2) microemulsions incorporating these excipients can be formulated at ambient temperature over a wide range of compositions; and (3) early studies have shown that medium-chain glycerides and fatty acids improve intestinal absorption of many drug molecules.[3-5] In the small intestine, they are hydrolyzed by intestinal lipases to generate monoglycerides and free fatty acids that can be directly absorbed through the portal route and detected in the plasma.

Dioctyl sodium sulfosuccinate (aerosol OT) has been reported to increase the intestinal absorption of many drugs.[6,7] While the number of publications on the possible application of aerosol OT microemulsions for topical drug delivery is already extensive,[8-10] aerosol OT applicability for oral microemulsion drug delivery still needs to be studied. Recently, a patent cooperation treaty (PCT) provided a stable, self-emulsifying water/oil microemulsion in which the surfactant with high hydrophile lipophile balance (HLB) comprises a medium-chain alkyl/dialkyl sulfate, sulfonate, or sulfosuccinate salt dissolved in a polyhydric alcohol to improve the delivery characteristics of a therapeutic peptide drug.[11]

Table 1. Composition of the 2 Investigated Microemulsion Systems

System	Surfactant (% wt/wt)	Cosurfactant (% wt/wt)	Oil (% wt/wt)	K_m Ratio
System 1	60	20	20	3:1
System 2	40	30	30	1.3:1

The purpose of this study was therefore to assess the ability of aerosol OT to develop a pharmaceutically acceptable, stable, self-emulsifying water continuous microemulsion with high dilution efficiency. Characterization of the prepared system inside and outside the microemulsion domain after dilution with water was another objective; I hoped to find a microemulsion containing a low amount of surfactants and cosurfactants for possible oral delivery purposes.

MATERIALS AND METHODS

Materials

Aerosol OT was from American Cyanamid Company (Bridgewater, NJ), medium-chain triglyceride oil (Miglyol 812) from Hüls AG (Witten/Ruhr, Germany), oleic acid and eosin sodium from Merck AG (Darmstadt, Germany), and glycerol monooleate (Monomuls 90-018) from Henkel KGaA (Düsseldorf, Germany). All other chemicals used were of analytical reagent grade.

All substances were used as received. All solvents were of analytical grade.

Construction of Phase Diagrams

Pseudoternary phase diagrams were constructed with systems comprising 4 components: aerosol OT (a high HLB surfactant), Monomuls 90-018 (a low HLB surfactant), an oily phase consisting of a blend of Miglyol 812 and oleic acid in 1:1 ratio, and an aqueous phase (double distilled). Oleic acid was added to the oily phase because it has been reported to enhance permeation[12,13] and oral absorption[14,15] of many drugs. Appropriate amounts of surfactant, cosurfactant, and oil were weighed into screw-capped vials and were shaken to ensure thorough mixing. Phase diagrams were constructed by titrating these samples with aliquots of water according to the method mentioned by Aboofazeli and Lawrence[16] in 10% increments in the range from 10% to 100% wt/wt. Mixing was enhanced by vortex (Julabo Para Mix II, Munich, Germany) for 2 minutes, and the samples were stored at 37 ºC ± 1ºC for 24 hours for equilibration.

Clear, transparent formulations were indicative of a stable microemulsion when under polarizing light they were examined and found to be nonbirefringent, as would be expected from their isotropic nature.

The top peak of the phase diagram represents the cosurfactant component, and the other 2 peaks represent oil and high HLB surfactant.

Electroconductive Measurements

Conductometry is a useful tool to assess microemulsion structure.[17,18] It has been previously demonstrated that a consistent correlation does exist between structure type and microemulsion electroconductive behavior.[17] The conductivity measurements were carried out using a Tinsley conductivity bridge (Model LF 4896, Copenhagen, Denmark). The measurements were made at a constant frequency of 1 Hz at constant temperature of 37 ± 0.1ºC. The cell constant was ascertained by using a standard potassium chloride solution.

Two basic preconcentrate microemulsion mixtures with different surfactant/cosurfactant ratios (K_m ratios) inside (K_m 3:1) and outside (K_m 1.3:1) the microemulsion domain were selected for their electroconductive measurements while these mixtures were titrated with water (**Table 1**). The adherence effect of the surfactant and the cosurfactant upon the cell inner wall and the electrodes was avoided by prewashing the cell twice with the sample to be measured before each measurement.

Eosin Sodium Absorption

The levels of maximum absorption of the 2 basic microemulsion mixtures containing 10^{-5} mol L^{-1} eosin sodium as a function of water content were determined after 24 hours' storage at 37ºC ± 1ºC for equili-

bration using Beckman Du-7 spectrophotometer (Irvine, CA).

Interfacial Tension Measurements

The microemulsion formation is associated with changes in the interfacial tension where minimum interfacial tension is directly related to the microemulsion formation[19,20] and would provide the first determination of the microstructure of mixed oil/surfactant films.[21]

The microemulsion system under investigation was subjected to interfacial tension measurements using the spinning drop interfacial tensiometer (Krüss, Hamburg, Germany) at the 2 different Km ratios outside and inside the microemulsion domain, with the goal of exploring the interfacial tension changes associated with macro- and microemulsion formation. Furthermore, blends of oil with either surfactant or cosurfactant in different ratios were subjected to the same measurements. The measurements were performed by injecting the oil/surfactant or oil/cosurfactant mixture into the tensiometer capillary filled with water and at a temperature of 37 ± 0.5ºC by the oil circulation. Measurements of the drop diameter were achieved at different speeds ranging from 1000 to 3500 rpm. Densities were measured using a method based upon the Archimedean principle.

Dilution Effect and Particle Size Measurements

The particle size and the polydispersity of the 2 investigated microemulsion systems were determined using photon correlation spectroscopy after dilution with excess of water or 0.1N HCL excess of the continuous phase. Microemulsion preconcentrate basic mixture (oil, surfactant and cosurfactant) was diluted with excess water or 0.1N HCl to simulate body fluid dilution. This diluted microemulsion system was then measured using photon correlation spectroscopy. N.B. no special procedure was applied but the regular and the normal measurements using photon correlation spectroscopy was followed. This provided useful background on the efficiency of these systems as drug carriers that allow infinite microemulsion dilution when the systems are diluted by body fluids.

One gram of each microemulsion system was diluted with either 500 g of water or 0.1N HCl using a magnetic stirrer. The samples were loaded into 1-cm^2 cylindrical cuvettes and placed in a scattering chamber. The aperture of the photomultiplier tube was set at 632.8 nm. The viscosity and refractive index were incorporated into the computer software, which calculates the mean particle size and polydispersity from intensity, mass, and number of bimodal distributions, assuming spherical particles. Light scattering was monitored at a 90º scattering angle at room temperature.

Stability Studies

Shelf life stability as a function of time and storage temperature was evaluated by visual inspection of the microemulsion system. Stability was monitored at 4ºC (refrigerator), 30ºC, 40ºC, and 60ºC.

RESULTS AND DISCUSSION

Development of Microemulsion Phase Diagrams

Figure 1 shows a pseudoternary phase diagram where the shaded area assigned on the phase diagrams was fluid, transparent, isotropic, nonbirefringent, and stable for more than 3 months. The unmarked areas indicate multiphase turbid regions. The microemulsion domain was determined by visual inspection for clarity and fluidity as well as through a cross polarizer for the absence of a liquid crystalline phase.

It is obvious that aerosol OT formed a clear isotropic microemulsion domain that extended over most of the whole range of surfactant/cosurfactant ratios, from 0.6:1 to 9:1. This region was capable of solubilizing up to 30% of the oil phase. At low water concentration, aerosol OT systems produced an enlarged microemulsion domain that achieved its maximum extension with low surfactant concentration and higher concentration of solubilized oil. When more water was added, the microemulsion existences field shrank, extending over a more limited area in the surfactant-rich part of the phase diagram. Moreover, the clear microemulsion region was critically dependent on the K_m ratio; at a K_m value of 1.5:1 the maximum solubilization peak moved toward the middle of the phase diagram, allowing maximum oil solubilization (30%) and maximum water inclusion.

Conductivity Measurements

The observed course conductivity curves of the 2 investigated systems as a function of water content vindicate the use of electroconductimetry to study structural changes in microemulsions. In system 1, the drastic changes in conductivity around a given water volume fraction ($Ø_p$) could be attributed to a phase

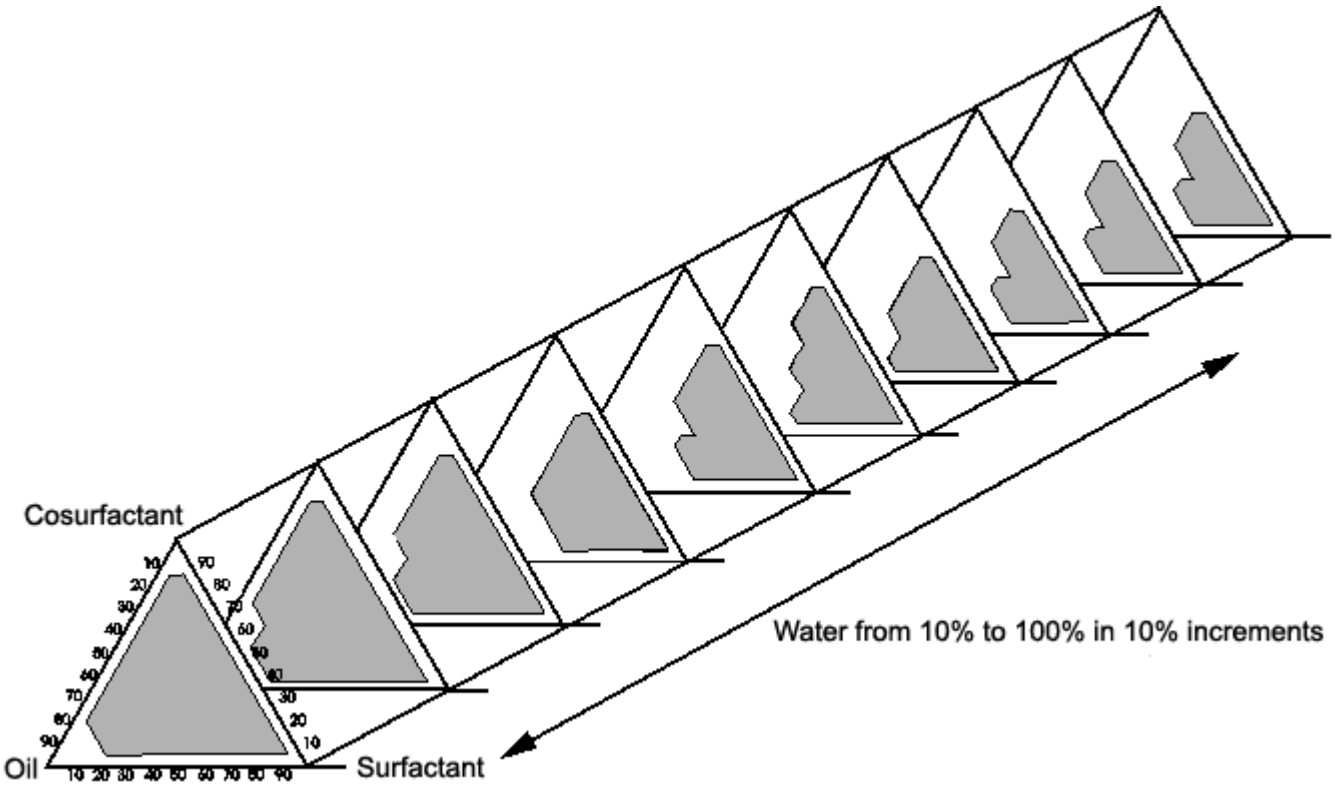

Figure 1. Quaternary phase diagram of aerosol OT microemulsion system.

inversion from reverse swollen micelles (water/oil) to direct micelles (oil/water) (**Figure 2**). This transition could be explained by the emergence of a bicontinuous structure where the "oil-rich" and "water-rich" zones merge into each other to form a unique domain.[22] These dynamic structures possess ultralow interfacial tension and are very promising for their wetting and substantive properties for biological membranes.[23]

The conductivity of this type is described on the basis of percolation and effective medium theories[24,25] that have been used for interpreting the conductivity of disordered media such as microemulsions.[26,27] The percolation transition signifies the first emergence of an infinite cluster for a critical value of water volume fraction ($Ø_p$) called the percolation threshold. This state characterizes bicontinuous structures. In such systems, conductivity is governed by a universal law independent of the physical properties of the medium. Near the percolation threshold, just before the medium suddenly becomes conducting:

$$\tilde{O} = (Ø_w - Ø_P)^t \qquad (1)$$

where $\tilde{O}$ is the conductivity (microsiemens), $Ø_w$ is the dispersed water volume fraction, $Ø_p$ is the dispersed volume fraction at the percolation threshold, and t depends on the system dimensionality (t = 1.5-1.6 for a 3-dimensional system).

To test the validity of the percolation theory, $\tilde{O}^{1/t}$ was plotted versus $Ø_w$. It is evident from **Figure 3** that system 1 undergoes a percolation transition, and it is possible to calculate the percolation threshold that corresponds to the bicontinuous phase. The middle part of the plot can be fitted by part of a straight line whose intersection with the $Ø_w$ axis provides the critical water volume fraction ($Ø_p$), which was found to be 8.9%.

The conductivity behavior of system 2, in contrast, showed a gradual linear increase in conductivity values up to 30% water, and then an abrupt increase was observed up to 70%. The strong increase in conductivity allows the assumption that there were increasingly mobile and changing sizes of surfactant associates. Further dilution of over 70% water leads to a decrease in the conductivity values with the formation of a macroscopic phase.

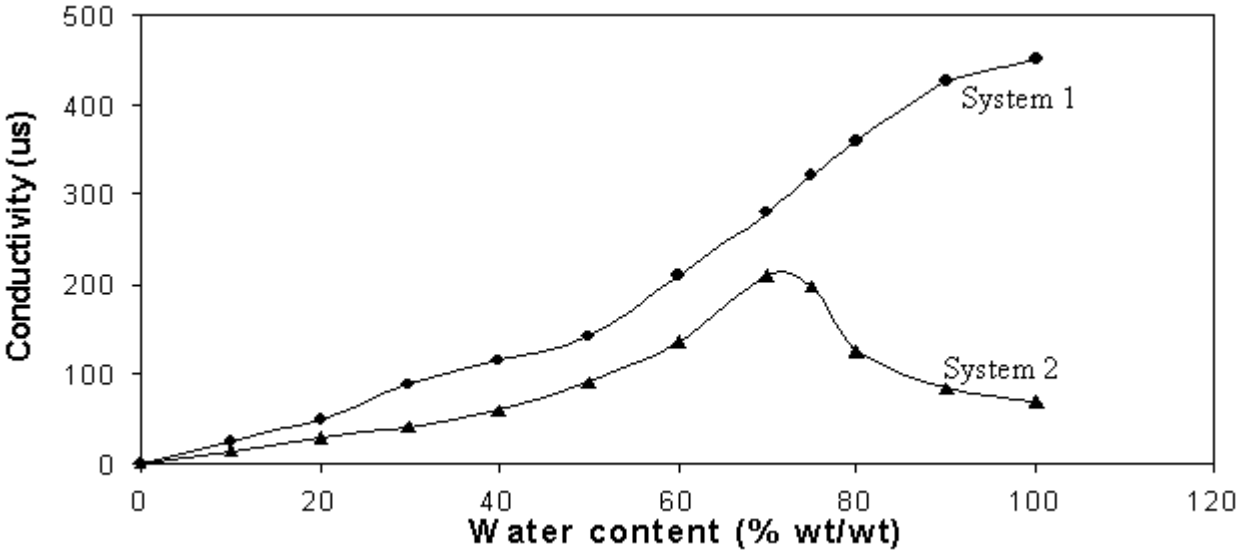

Figure 2. Conductivity as a funtion of water content.

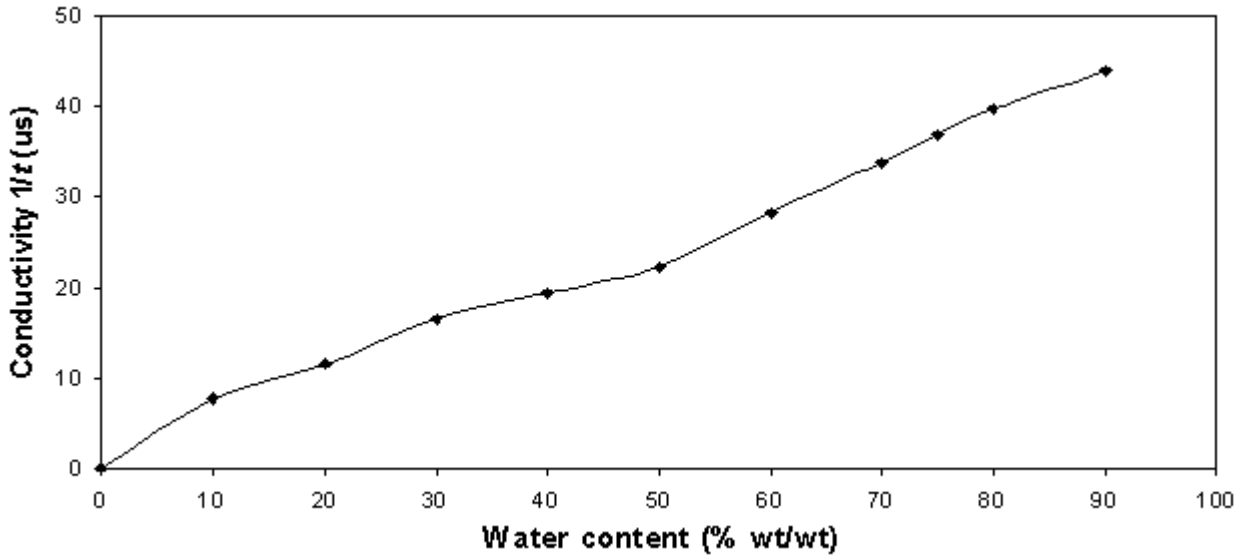

Figure 3. Percolation threshold determination.

Eosin Sodium Absorption

One way to study micelle formation and critical micelle concentration is by using dyes.[28,29] The absorption measurement of eosin sodium is supposed to function as an interpreting expedient for possible structures (eg, swollen micelles) in the one phase system where its absorption maximum is bathochromically shifted after association with micelles of nonionic surfactants.[30]

If one compares the course conductivity curve of system 2 as a function of water content with the result of eosin sodium absorption measurements, some similarities become clear. Eosin sodium possesses an absorption maximum of 524 nm in the microemulsion base. Addition of water up to 30% to the microemulsion base shifts the absorption maximum of eosin sodium bathochromically from 524 to 527 nm. In these ranges, hydration of the surfactant/cosurfactant mix-

Table 2. Interfacial Tension Measurements Inside and Outside Microemulsion Domain

Oil (% wt/wt)	Interfacial Tension (mN/m), mean ± SD			
	Oil: Cosurfactant Mixture	Oil: Surfactant Mixture	Oil:Surfactant:Cosurfactant Mixture	
			System 1	System 2
10	2.15 ± 0.23	0	0	0.03 ± 0.02
20	—	0	0	0.07 ± 0.02
30	2.35 ± 0.33	0	0	0.18 ± 0.06
40	—	0.04 ± 0.02	0.02 ± 0.01	0.3 ± 0.08
50	5.18 ± 0.75	0.09 ± 0.03	0.33 ± 0.04	0.70 ± 0.07
60	—	0.13 ± 0.03	0.49 ± 0.06	1.10 ± 0.11
70	6.37 ± 0.63	0.49 ± 0.08	0.69 ± 0.04	2.20 ± 0.15
80	—	0.80 ± 0.04	1.03 ± 0.06	2.70 ± 0.20
90	7.47 ± 1.10	1.37 ± 0.21	2.02 ± 0.71	3.20 ± 0.40
100	15.30 ± 2.60	15.30 ± 2.60	15.30 ± 2.60	15.30 ± 2.60

ture can be assumed. Further dilution from 30% to 70% water produces a bathochromic shift to 530 nm, in which a structuring of the system is possible. Dilution of over 70% water leads to a hypsochromic shift of the absorption maximum to 519 nm, which can be interpreted as a dissolution of associates; the surfactant mixture is not able to ensure stability, so the microemulsion droplets tend to coalesce and form clusters. It should be pointed out that system 1 showed no hypsochromic shift.

Interfacial Tension Measurements

One of the most fundamental properties of an oil/water system that forms a microemulsion is the interfacial tension between the oil and water phases where the phase behavior of such systems can be directly related to their interfacial tension. Schulman et al[31] postulated that interfacial tension is a key process in microemulsion formation and that the main role of the cosurfactant is to reduce the interfacial tension to very low values.

As shown in **Table 2**, pure oil had high interfacial tension—about 15.3 mN/m. This value was reduced to 2.2 mN/m by the increase in the concentration of the cosurfactant up to 90%. Moreover, the data for various oil-surfactant mixtures revealed that the incorporation of surfactant led to a dramatic decrease in the interfacial tension, which reached its minimum at 70% surfactant concentration. This result proves that the interfacial efficiency of the surfactant is better than the cosurfactant's. Hence, blends of oils with surfactants at certain ratios (30:70 oil:surfactant) could produce the minimum interfacial tension value needed for a microemulsion formation, without the need for a cosurfactant.[32] These results provide convincing evidence that the interaction of oils with the surfactant monolayer has important consequences for a wide range of phenomena, including microemulsion formation,[33] and that various physical processes can give rise to very low interfacial tension with the probability of oil spreading on the surface of the aqueous surfactant solution either as a continuous oil film over the surface or as discrete lenses.[34]

The interfacial tension measurements of a series of experiments in which oil was admixed with a blend of surfactant and cosurfactant showed slight variability in lowering the interfacial tension by changing the surfactant/cosurfactant ratios where the interfacial tension approached almost 0 in both systems with ncentrations up to 30% oil. Furthermore, the variation

Figure 4. Photomicrograph of microemulsion domain inside the tensiometer capillary using 25 magnification power.

of the Km ratio from 1.3:1 to 3:1 with the same oil resulted in a greater decrease in interfacial tension. Hence, it could be suggested that the cosurfactant helped decrease the interfacial tension of the microemulsion systems with a general relationships existence between interfacial tensions and concentration of both surfactant and cosurfactant.

The aforementioned results enabled the formation of a microemulsion when the oil and the cosurfactant were blended with a lower ratio of surfactant than that required when surfactant was used alone. Consequently, a reduction in biological hazard when high amounts of surfactants are used in microemulsion formations is anticipated.

Photomicrographs taken for oil/surfactant/cosurfactant mixtures inside the microemulsion domain (**Figure 4**) depict the changes in droplet shape caused by rotation inside the tensiometer capillary. It is clear that no boundaries between internal and external phases were observed, with phases overlapping those associated with 0 interfacial tension values. This would confirm that there was microemulsion formation.

Dilution Effect and Particle Size Measurements

The influence of the extent of dilution on the particle size as well as the polydispersity (system homogeneity) of the 2 microemulsion systems under investigation was monitored (**Figures 5** and **6**).

Figure 5. Effect of dilution on (D) system 1 and (E) system 2

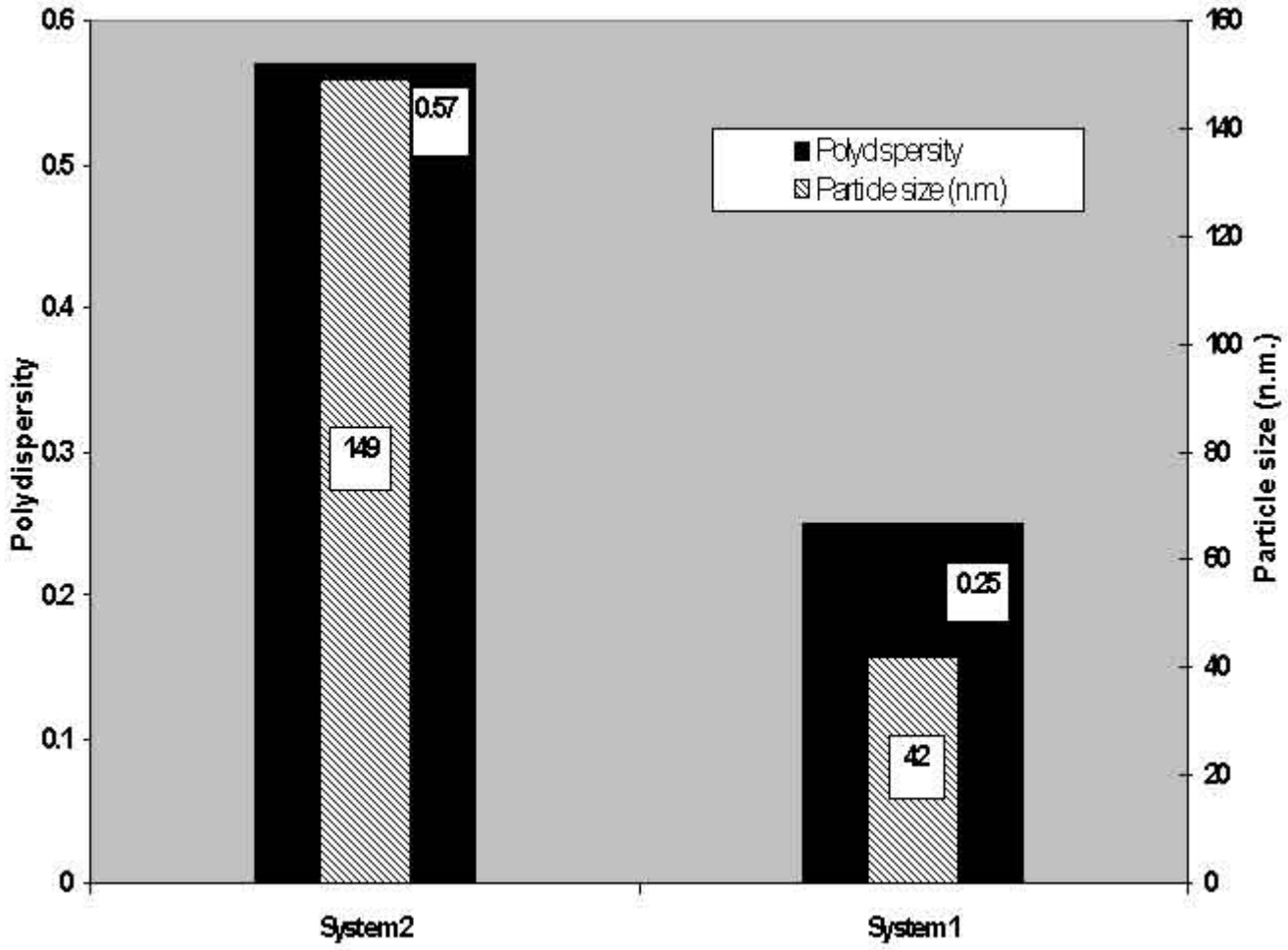

Figure 6. Dilution effect on the mean particle size and polydispersity of the 2 microemulsion systems.

System 1 appeared almost transparent, with a mean droplet diameter of 42 nm associated with a polydispersity of 0.25 (the polydispersity value varies from 0 to 1; the closer the value to 0, the more homogeneous the system). This signifies that dilution with the aqueous phase had an insignificant effect on the particle size when it resulted in infinitely dilutable, thermodynamically stable, and highly dispersed homogeneous systems without the formation of a turbid phase. Hence, reproducible pharmacokinetic and accepted bioavailability for these microemulsion systems is granted.[35]

On the other hand, dilution exhibited a more dramatic effect on system 2, where excessive dilution caused turbidity and microemulsion conversion to oil/water emulsion with a mean droplet diameter of about 149 nm and a polydispersity of 0.57. This would indicate the formation of a heterogeneous coarse dispersion. Moreover, the droplet size of system 2 prepared with a higher ratio of cosurfactant (40%, 50%) was larger than that prepared with a lower ratio (30%), even though both were converted to a heterogeneous oil/water emulsion upon dilution with water above 100%. This could be explained according to the hypothesis that the minimum droplet size should be reached when the continuous phase is nearly saturated with the cosurfactant; from then on virtually all the cosurfactant added should go into the internal phase, increasing the droplet diameter.[36]

The breakdown of system 2 upon high dilution was explained by the fact that when water was added a gradual transition from the oil-droplet-in-water continuum to mixed micelles took place. When water in excess of that required for such transition was added to the system, subaggregates were formed until the

breakdown of micelles occurred and turbidity appeared.[37]

Stability Studied

By visual inspection criteria, the microemulsion under investigation was identified as a stable system if it was free of any physical changes such as phase separation, flocculation, or precipitation for more than 6 months.

CONCLUSION

This investigation demonstrates the ability of aerosol OT to form an extended microemulsion area capable of solubilizing up to 30% of the oil phase. Because of the components used and the bicontinuous structure found in this study, this system is of great interest for pharmaceutical technology. The dilution effect and particle size measurements suggest that this system is a potential carrier for oral drug delivery.

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