

# IPM/DOSS/Water Microemulsions as Reactors for Silver Sulfadiazine Nanocrystal Synthesis

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**ABSTRACT:** The first goal of this work was the preparation of a water-in-oil microemulsion from components generally regarded as safe for use in humans. Stable formulations without need of a co-surfactant were prepared from isopropyl myristate (IPM), dioctyl sodium sulfosuccinate (DOSS), and water. A ternary phase diagram was prepared for the IPM/DOSS/water system. The IPM/DOSS/water microemulsions were characterized by conductivity and dynamic laser light scattering (DLS). The results obtained from conductivity experiments indicate conductivity values of less than 1  $\mu\text{S}/\text{cm}$  and were consistent with the formation of w/o microemulsions. The DLS results showed that the emulsified water droplets had an average diameter range of 9.2 to 19.7 nm, depending on composition. Modulation of the droplet size is possible by varying the water to DOSS molar ratio and DOSS to IPM ratio. The second goal of this work was the preparation of silver sulfadiazine (AgSD) nanoparticles. It was hypothesized that two separate microemulsions containing dispersed aqueous droplets of either sodium sulfadiazine or silver nitrate would react when mixed. The DLS results are consistent with the successful formation of submicron AgSD crystals. © 2005 Wiley-Liss, Inc. and the American Pharmacists Association *J Pharm Sci* 94:1310–1320, 2005

**Keywords:** microemulsion; electrical conductivity; particle size; dynamic light scattering; nanoparticles

## INTRODUCTION

Microemulsions are optically transparent, isotropic, kinetically stable systems of water, oil, and surfactant. They may have either major component as the internal phase. A particular formulation may also require a co-surfactant. This system was first reported by Schulman in 1943 and labeled microemulsions by his group in 1959.<sup>1,2</sup> When an appropriate intermediate HLB surfactant is mixed with water and a suitable oil, gentle mixing will rapidly produce a translucent liquid that visually appears to be a single-phase system. Water-in-oil microemulsions appear clear although the morphology of the internal aqueous microstructure may be diverse.<sup>3</sup> Depending on the physico-

chemical nature of the surfactant, the temperature, and the presence of salts and other agents, such as polymers, the amount of emulsified water will vary.<sup>4–6</sup> Based on the nature of the components and temperature, slight modifications in composition can result in w/o or o/w microemulsions, reverse micelles, rod-like micelles, or cubic, hexagonal, or bicontinuous phases.<sup>7</sup> Microemulsions can be easily prepared and have demonstrated desirable biopharmaceutical properties due to their unique physico-chemical characteristics.<sup>8,9</sup>

Chemical engineers and material science groups have used such microemulsions as reactors for synthesizing magnetic particles,<sup>10</sup> semiconductors,<sup>11</sup> and polymeric nanoparticles.<sup>12</sup> The microemulsions reported in the cited works used dioctyl sodium sulfosuccinate (DOSS) with organic solvents such as iso-octane and n-hexane. The composition of the microemulsions was found to alter the size, shape, and some physico-chemical

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properties of the nanoparticles produced. However, these microemulsions are not particularly suitable for direct use in drug formulations due to the unfavorable properties of the hydrocarbons.

Within the pharmaceutical sciences, microemulsions have been a topic of interest for several years.<sup>13</sup> There has been a renewed interest in microemulsions as researchers attempt to manipulate existing materials to facilitate drug delivery.<sup>14</sup> Different hydrophilic and lipophilic drugs have been incorporated into microemulsion formulations and evaluated for delivering therapeutic agents *via* the oral, topical, and parenteral routes. In most cases, further product development of the evaluated systems for human use was hampered by concerns about the toxicity of components in the formulations.

This work reports the development of pharmaceutically relevant microemulsions using isopropyl myristate (IPM). DOSS was used as the surfactant since it forms stable microemulsions without the need of co-surfactants. These w/o microemulsions were used as reactors for the synthesis of silver sulfadiazine (AgSD) nanocrystals. The reaction is hypothesized to proceed *via* diffusion controlled mass transport of emulsified water droplets containing either sodium sulfadiazine or silver nitrate. Brownian forces lead to collisions that result in the interdroplet exchange of reactants whereby the reaction occurs with precipitation, since the AgSD product is present at a concentration greater than its solubility product. This project was motivated by results from earlier work that demonstrated increased antimicrobial effectiveness of a smaller particle size AgSD product and stabilization of these smaller particles by adsorbed surfactant.<sup>15,16</sup> Further size reduction of AgSD particles may result in greater antimicrobial effectiveness based, in part, on enhanced solubility of AgSD due to the Kelvin effect.<sup>17</sup>

## MATERIALS AND METHODS

### Materials

Isopropyl myristate (IPM, Super Refined Crodamol IPM) was obtained from CRODA, Inc. (Parsippany, NJ). The Crodamols are non-polar esters widely used in cosmetic preparations and in drug formulations suitable for use *via* the oral, parenteral, and topical routes. Dioctyl sulfosuccinate, sodium salt (DOSS) was purchased from Sigma Chemical Co. (St. Louis, MO). Silver

nitrate was purchased from J. T. Baker Chemical Co. (Phillipsburg, NJ). Sulfadiazine sodium USP (NaSD) and glycerol were purchased from Spectrum Chemical Co. (Gardena, CA). All materials were used as received. Water used in the work was rated ultrapure and obtained from a Barnstead Nanopure<sup>®</sup> (Dubuque, IA) water purification system.

### Microemulsion Formulation

All microemulsions were formulated at ambient laboratory temperature, which was approximately 23°C. Appropriate quantities of DOSS (HLB > 20) were weighed out and dissolved in IPM to form solutions with varying surfactant:oil compositions. Accurately weighed amounts of water were added to the surfactant-oil mixtures in small increments followed by vortexing. The maximum amount of water added to each surfactant-oil mixture, before which turbidity appeared, was noted. A ternary phase diagram was constructed to identify the isotropic microemulsion forming region.

### Conductivity Measurements

Microemulsions with different values of  $W_o$  ( $W_o$  is the molar concentration of water to molar concentration of surfactant ratio) were prepared in DOSS:IPM mixtures of varying surfactant concentration. Conductivity measurements were performed on microemulsions to verify that w/o systems were formed when the components were mixed in the stated proportions. These measurements are widely used to determine the phase inversion temperature of commercial detergents since a sudden change in the conductivity is seen in microemulsions within a narrow range of change in composition at constant temperature, or variation in temperature at a fixed composition.<sup>18</sup> An YSI 3200 conductivity meter (YSI Instruments, Yellow Springs, OH) and YSI 3256 conductivity cell were used to obtain the data. The cell is capable of measuring conductivity in the range 0  $\mu$ S/cm to 10 mS/cm. The cell was calibrated using an YSI 3161 conductivity calibrator solution which has a conductivity value of 1000  $\mu$ S/cm at 25°C.

### Droplet Size Analysis of IPM/DOSS/Water Microemulsions by Dynamic Light Scattering (DLS)

Microemulsions were prepared in surfactant-oil mixtures by adding appropriate amounts of water

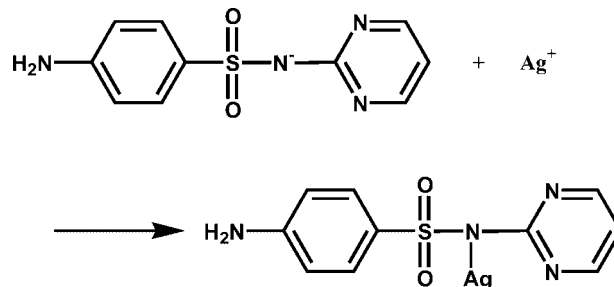
to prepare systems with a particular value of  $W_o$ . Samples of microemulsions were taken and placed in  $6 \times 50$  mm cylindrical glass cuvettes and centrifuged at 6000 rpm for 10 min. This treatment has no effect on the size distribution of the microemulsified droplets and only serves to minimize the potential interference of any extraneous suspended dust particles on the scattering intensity.

Light scattering experiments were performed using a NICOMP<sup>TM</sup> 380 submicron particle sizer (Particle Sizing Systems, Santa Barbara, CA) equipped with a He-Ne laser (15 mW, 632.8 nm wavelength), an avalanche photodiode detector (APD) optimized for wavelength, and a goniometer. All DLS experiments were performed at 25°C. The refractive index and viscosity values for IPM at 25°C are 1.4347 and 5.6 cP, respectively. The experiments were run in the auto mode of the instrument, and the digital correlator analyzed the intensity of scattered light collected at an angle of 90 degrees. To prevent damage to the detector, the photon count of the scattered laser light at the collector was capped at 300 kHz. When making measurements in the automode, the instrument controls the photon count by adjusting the position of a neutral density filter placed in the path length of the laser. All samples exhibited scattering over the range of 25–150 kHz and the neutral density filter was kept in the fully open position throughout the study. The autocorrelation data for the neat microemulsions are unimodal and estimation of the Gaussian parameters was performed using the cumulants technique. The limits of the particle size analysis are a function of the laser power output and the number density of the particles present in the sample. With the number of particles present in these samples, the equipment used in this work can effectively determine particle diameters with a minimum size of 3 nm.

### Synthesis of Silver Sulfadiazine Nanocrystals Using Microemulsions as Reactors

When equimolar aqueous solutions of silver nitrate (mw 169.87) and sodium sulfadiazine (mw 272.26) are mixed, AgSD (mw 357.14) is produced and precipitates because of its low solubility product ( $K_{SP} \sim 8E-12$  at pH 7 and 25°C) (Figure 1).

The general procedure involves the preparation of a 1:9 DOSS:IPM solution, which is divided into two aliquots. Separate aqueous solutions containing  $AgNO_3$  (1.183 mg/mL) and NaSD



**Figure 1.** Reaction scheme for preparation of AgSD.

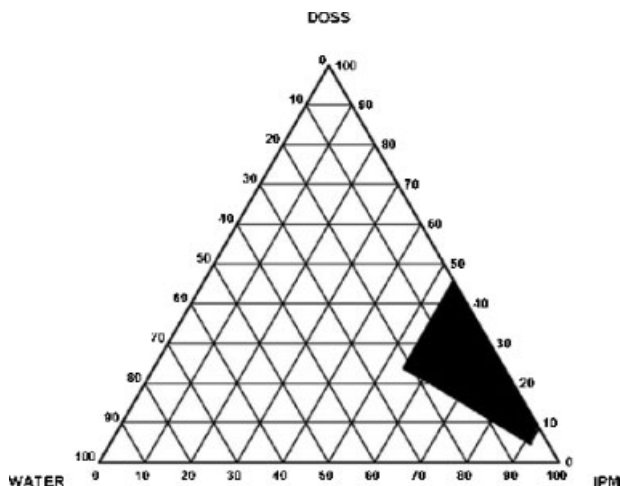
(1.908 mg/mL) are prepared (the slight stoichiometric excess of NaSD prevents any free silver ion being present at the conclusion of the reaction). These aqueous solutions are used to prepare separate microemulsions each with a  $W_o$  value of 15. Finally, the  $AgNO_3$  microemulsion is added to the NaSD microemulsion. The reaction proceeds *via* diffusion controlled mass transfer as has been reported for various other microemulsion reaction schemes.<sup>19</sup> Samples were taken for DLS analysis 15 min after mixing of the reagent microemulsions. Since the data obtained in this part of the work are, at least, bimodal, the NICOMP<sup>TM</sup> analysis method has been used. This method is a proprietary extension of the CONTIN technique involving the discrete Laplace transform inversion of the acquired autocorrelation data. Again, based on the number of particles in the scattering volume, the lower limit of detection is 3 nm.

The AgSD particles were isolated from the microemulsion by inducing phase separation by addition of glycerol to the microemulsion. The oil layer was siphoned off, and the glycerol layer was centrifuged at 12000 RPM for 30 min at 23°C in a temperature-controlled microcentrifuge. The nanocrystals were then washed with ethanol and mounted on glass slides and visualized with a Nikon Eclipse TE2000-U microscope at 20× magnification.

## RESULTS AND DISCUSSION

### Microemulsion Formulation

Figure 2 shows the phase diagram of the IPM/DOSS/water system. The shaded area represents the compositions where transparent formulations were produced. The boundary regions were verified by visual inspection of the samples. The efficiency of DOSS:IPM mixtures in forming stable microemulsions over a wide range of concentrations is evident from the phase diagram. When



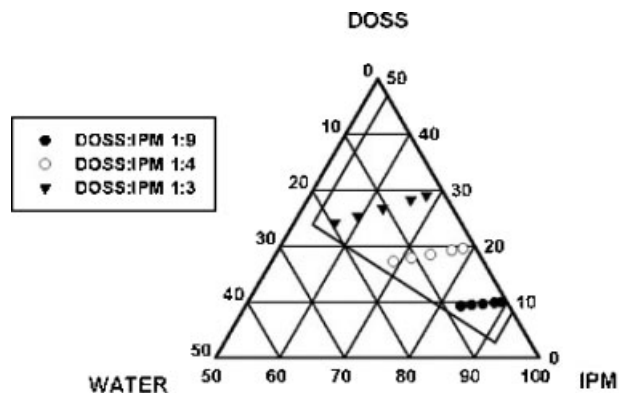
**Figure 2.** Ternary phase diagram of IPM/DOSS/water systems under study.

an amphiphilic molecule such as DOSS is dissolved in a non-aqueous solvent such as IPM, some ordering exists but the aggregation number is much less than that measured in the case with aqueous solvents. Hartley has proposed an “inverted micelle” model for these aggregates, and later experiments demonstrated aggregation numbers in the range 5–10.<sup>20,21</sup>

Formation of transparent and stable microemulsions requires low solubility of the surfactant in both the oil and water phases. This results in localization of the surfactant monomers at the oil-water interface.<sup>22</sup> Thus, an optimum balance of the hydrophilic and lipophilic properties of the surfactant reduces the interfacial tension to ultra-low levels resulting in spontaneous microemulsification.<sup>23</sup> DOSS and other dialkyl type surfactants are known to form reverse micelles and microemulsions resulting from a favorable balance of hydrophilic and lipophilic properties.<sup>24,25</sup>

### Conductivity Measurements

Water-in-oil microemulsions with a discrete droplet structure are characterized by very low conductivity values whereas oil-in-water and bicontinuous microemulsions exhibit significantly greater conductivity.<sup>18</sup> The structure and dynamics of water droplets within the formulation is a critical factor when nanoparticles are synthesized using reagent droplets microemulsified in surfactant-oil systems. Figure 3 shows the composition of all microemulsions used in the conductivity study. All microemulsions in this study had low conductivity values, less than 1  $\mu\text{S}/\text{cm}$ ,

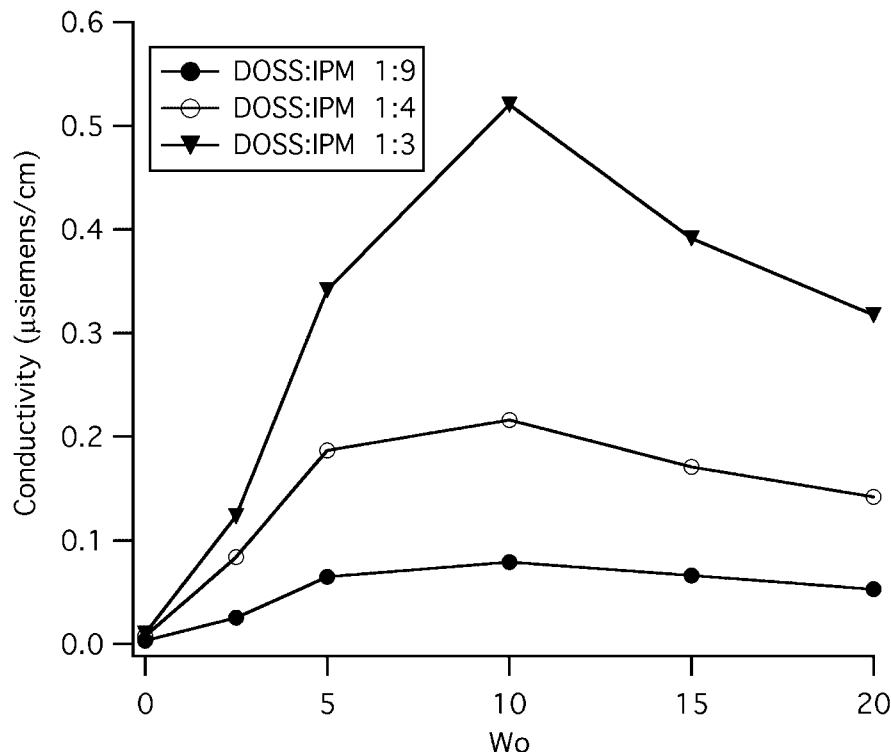


**Figure 3.** Ternary phase diagram of IPM/DOSS/water systems used in the conductivity study.

when the  $W_o$  is less than or equal to 20 (Figure 4). At a given value of  $W_o$ , the conductivity increases with increasing surfactant concentration. This is expected and reflects the increase in ionic species present within the water droplet. However, the conductivity levels off or slightly decreases beyond a  $W_o$  of 10. This effect is more pronounced in microemulsions made in surfactant:oil system 1:3. The slight decrease in conductivity could be attributed to water penetration into the interphasal layers of the surfactant. Highly variable and unstable conductivity values were observed in microemulsions with a  $W_o$  value of 25. This variability in conductivity is indicative of the presence of separate water domains within the system and possible fluctuating transitions to a bicontinuous structure. Microemulsions used in further studies were formulated with a  $W_o$  value less than or equal to 20.

### Droplet Size Analysis of IPM/DOSS/Water Microemulsions by Dynamic Laser Light Scattering

Dynamic light scattering (DLS) is a powerful tool for particle size analysis in the submicron region. Elegant mathematical formalisms have been developed to analyze monodisperse spherical, non-spherical, and polydisperse microemulsion droplets.<sup>26,27</sup> Typically a DLS measurement consists of obtaining the fluctuations in the intensity of scattered laser radiation at different time points as represented by an autocorrelation function (ACF). For random diffusion of non-interacting particles, the ACF is an exponentially decaying function with a characteristic decay constant,  $\tau$ . The decay constant is related to the diffusivity of particles through the relationship,



**Figure 4.**  $Wo$  versus conductivity profiles for microemulsions prepared in various DOSS:IPM systems.

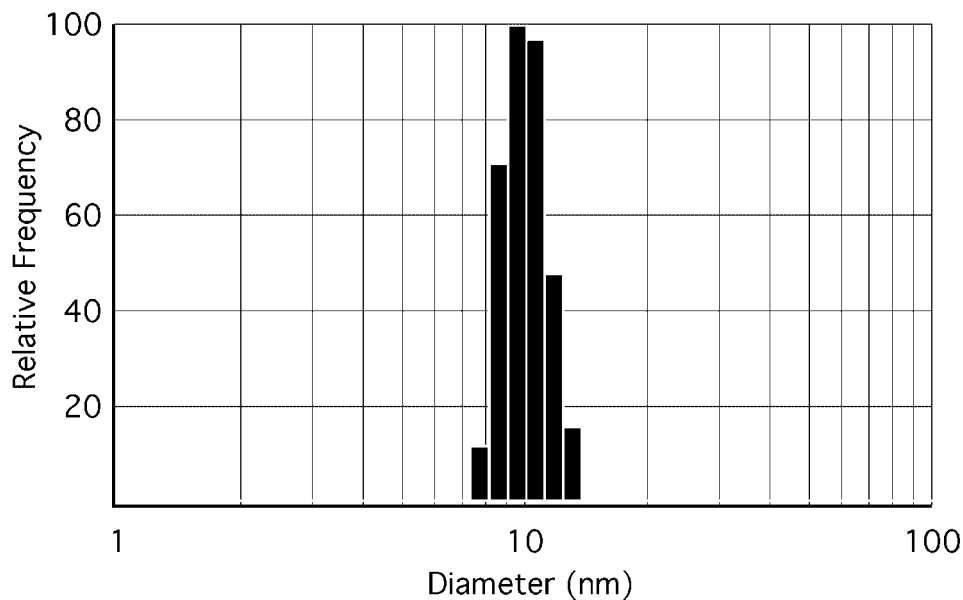
$1/\tau = 2DK^2$ , where  $D$  is the diffusivity, and the quantity  $K$ , the scattering wave vector, depends on the laser wavelength, scattering angle, and the refractive index of the dispersion medium. The diffusivity in turn is related to the particle radius *via* the Stokes–Einstein equation,  $D = k_B T / 6\pi\eta r$ , where  $k_B$  is the Boltzmann constant,  $T$  is the absolute temperature,  $\eta$  is the viscosity of the dispersion medium, and  $r$  is the particle radius. Obtaining a particle size from the ACF involves a sequential mathematical process whereby the  $D$ -value for the particle ensemble is related to the shape of the ACF and its decay parameter. Once the  $D$ -value is obtained, an equivalent spherical particle radius is calculated using the Stokes–Einstein equation.

Table 1 contains the volume-weighted results (mean  $\pm$  standard deviation) from an emulsion droplet size analysis ( $n = 3$ ). All microemulsions demonstrated a  $Wo$  dependant increase in size. At a particular surfactant concentration, the formulations with a  $Wo$  value of 20 had larger droplet diameters when compared to the formulations with a  $Wo$  value of 15. These differences were statistically significant based on a one-way ANOVA at  $\alpha = 0.05$ . The increase in droplet size may be due to the swelling of the internal droplets

as the volume fraction of water is increased. Both DLS and small angle neutron scattering studies have confirmed this experimental finding for many microemulsions, including formulations made with DOSS.<sup>28,29</sup> When  $Wo$  is kept constant but the amount of DOSS is increased relative to the IPM fraction there also is an increase in the droplet size. This increase in droplet size, and not the formation of greater numbers of smaller droplets, can be partially explained by the inability of DOSS to stabilize a system with continually increasing interfacial free energy. This observation can be explained by the concepts of efficiency and effectiveness. A surfactant's efficiency

**Table 1.** Droplet Size Analysis Results ( $n = 3$ ) for IPM/DOSS/Water Systems

DOSS:IPM	Water Droplet Size Distribution (nm) (Mean $\pm$ SD)	
	$Wo = 15$	$Wo = 20$
1:19	Scattering intensity too low	$9.6 \pm 0.1$
1:9	$9.2 \pm 0.1$	$12.9 \pm 1.0$
1:4	$11.6 \pm 0.2$	$16.3 \pm 1.6$
1:3	$12.6 \pm 1.7$	$19.7 \pm 1.6$

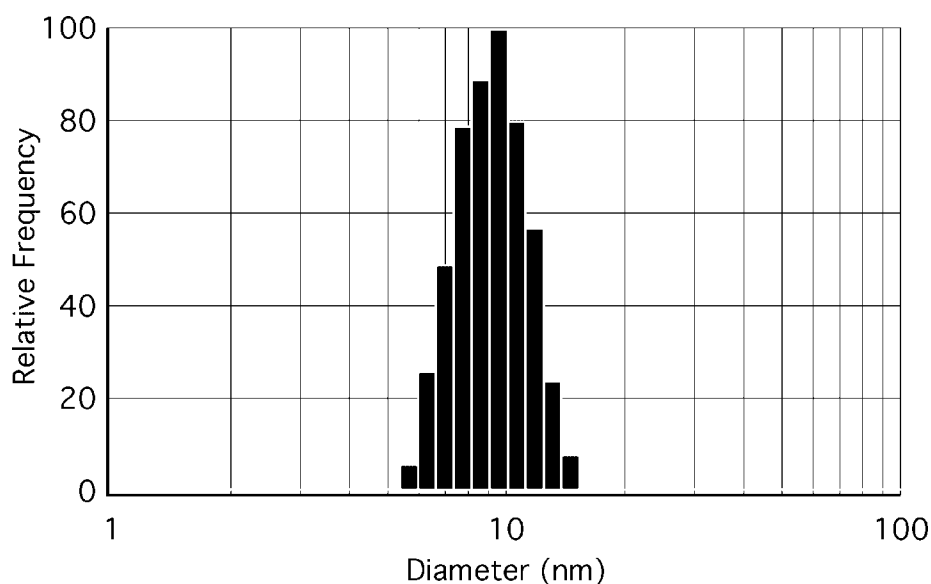


**Figure 5.** Droplet size distribution (volume-weighted) of a typical NaSD microemulsion.

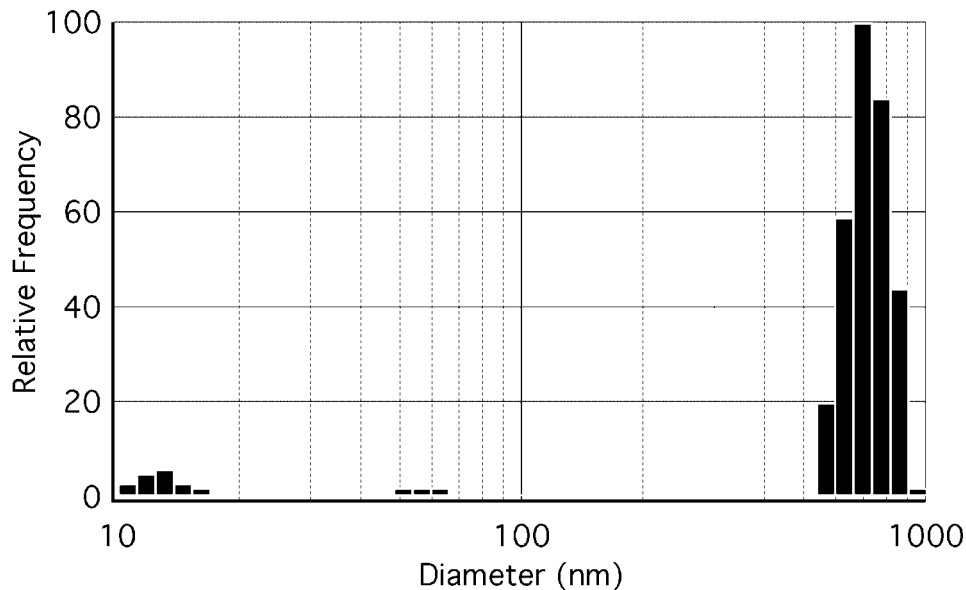
is the measure of the equilibrium concentration present necessary to effect a measurable change in a parameter. The surfactant's effectiveness is the measure of the maximum effect, in this case the stabilization of discrete water droplets that can be observed irrespective of concentration.<sup>30</sup> And it is worth noting that structural geometry and intermolecular interactions between a surfactant and a particular oil play important roles in the dispersed phase droplet size and stability.<sup>31</sup>

#### Synthesis of Silver Sulfadiazine Nanocrystals and Process Characterization

Reagent microemulsions used to synthesize AgSD nanocrystals were stable throughout the period of study. Figures 5 and 6 represent typical volume-weighted droplet size analysis data of a NaSD microemulsion and an AgNO<sub>3</sub> microemulsion, respectively. The NaSD microemulsion has a mean droplet diameter of 9.3 nm (SD = 1.2 nm),



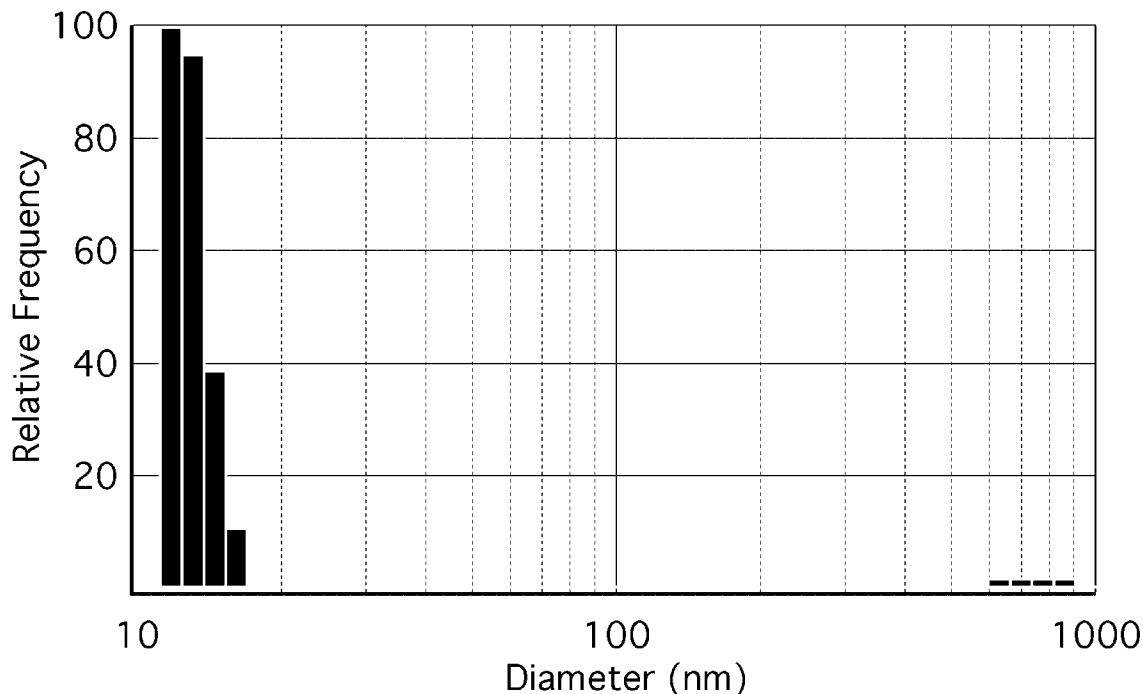
**Figure 6.** Droplet size distribution (volume-weighted) of a typical AgNO<sub>3</sub> microemulsion.



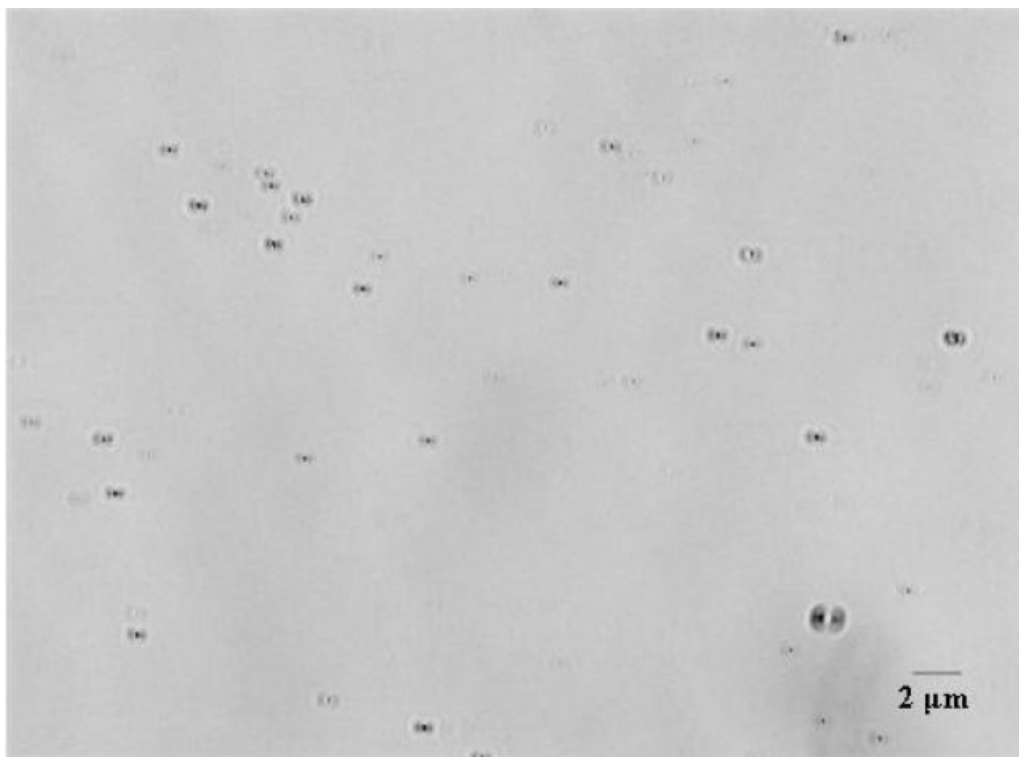
**Figure 7.** Particle size distribution (intensity-weighted) of AgSD nanocrystals.

and the  $\text{AgNO}_3$  microemulsion has a mean droplet diameter of 9.0 nm (SD = 1.6 nm). Figure 7 shows the intensity weighted particle size data obtained from samples of microemulsions taken 15 min after mixing of the reagent microemulsions. Two significant peaks are seen. The peak at 12.1 nm (SD = 1.3 nm) represents the large mass of initially emulsified water droplets. The other peak at

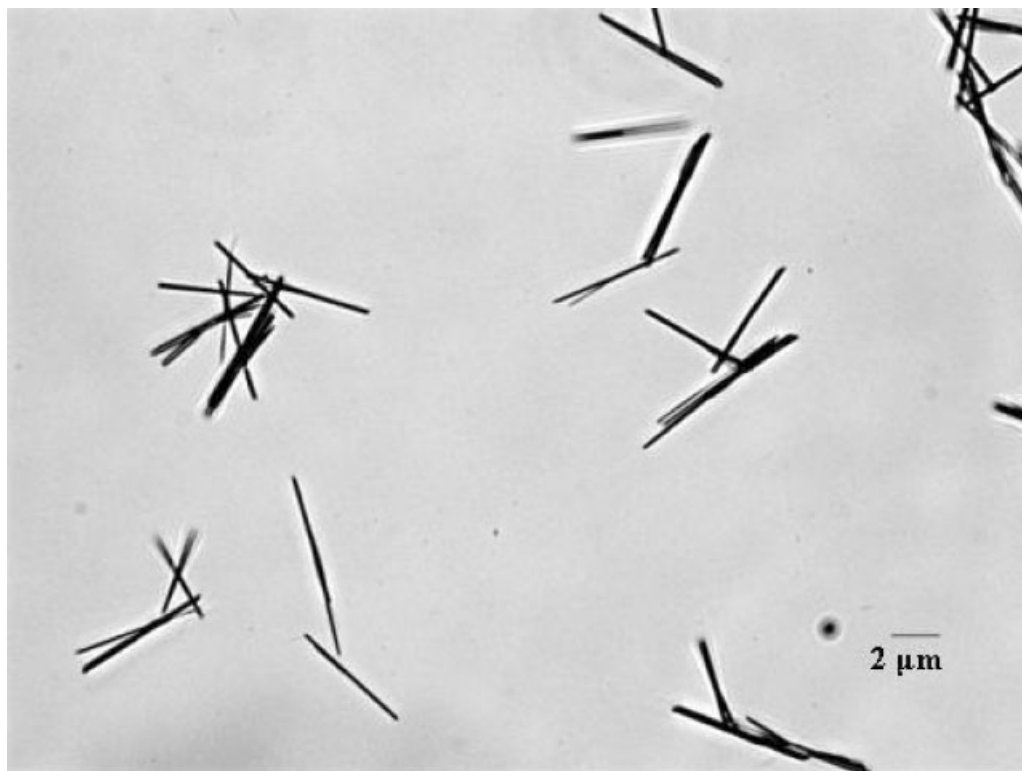
679.0 nm (SD = 78.9 nm) represents the AgSD nanocrystals. Figure 8 shows the corresponding volume-weighted particle size data. Two peaks are seen, one with a mean diameter of 12.0 nm (SD = 1.0 nm), and another peak at mean diameter 688.2 nm (SD = 73.1 nm). (The data reported in Figures 5–8 are well within the dynamic range of the light scattering instrument.) Slight



**Figure 8.** Particle size distribution (volume-weighted) of AgSD nanocrystals.



**Figure 9.** Optical microscopy image of isolated AgSD nanocrystals at 20 $\times$  magnification.



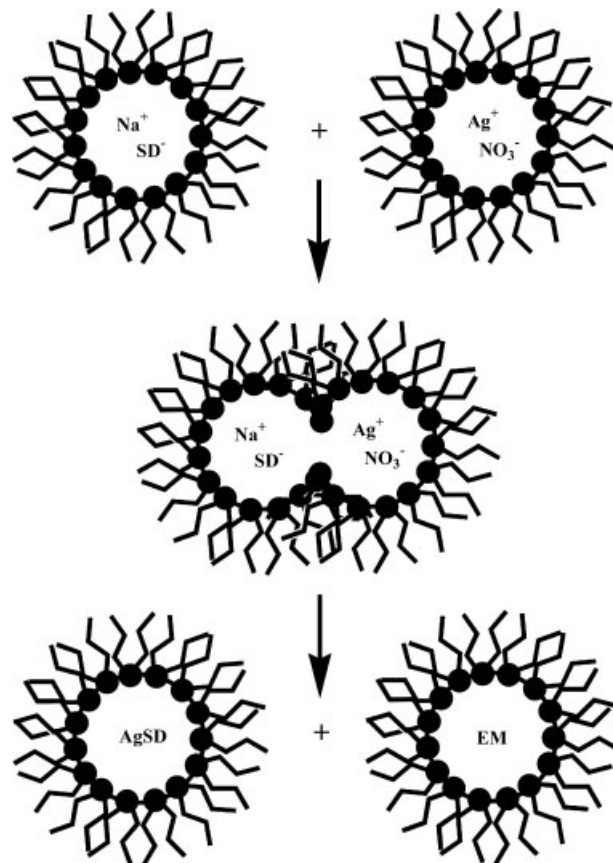
**Figure 10.** Optical microscopy image of AgSD crystals synthesized in water.



changes in the mean peak values are consistent with the differences observed when intensity-weighted data are converted to a volume-weighted distribution. The small peak seen at approximately 50 nm in Figures 7 and 8 is statistically insignificant. The contribution of this peak to the total intensity or volume is less than 0.1%. It may be evidence of a very small fraction of stabilized 50 nm particles. However, at this time, this cannot be unequivocally confirmed.

During the isolation of AgSD particles effected by the use of glycerol, the drug crystals could be seen adhering to the centrifuge tube at the area of the oil-glycerol interface. This suggests that the particles are coated with the surfactant and hence could be removed by washing with ethanol. This agrees with results obtained in a different study.<sup>16</sup> Figure 9 shows an optical microscopy image of AgSD nanocrystals. The particles are all in the submicron region and corroborate the particle size analysis results obtained using DLS. When the same amounts of aqueous AgNO<sub>3</sub> and NaSD were mixed in water, crystals of approximately 8 μm were obtained (Figure 10). A comparison of Figures 9 and 10 attests to the impact microemulsions have on controlled nucleation and growth of AgSD crystals.

When compared to reactions run in bulk water, the exchange of materials between microemulsion-based reactor systems occurs over a longer period of time. For example, the formation of silver chloride nanoparticles from DOSS-alkane microemulsions containing silver nitrate and sodium chloride has been reported to be complete in approximately 60 ms.<sup>32</sup> A proposed mechanism for this type of simple precipitation/neutralization reaction is shown in Figure 11. When the two reactor microemulsions are mixed, primary nuclei are formed by the exchange of reactant species between transiently aggregated droplets. The nuclei grow into nanoparticles that approach the diameter of the aqueous core of the micellar droplets. At this point, in various systems involving semiconductors, magnetic media, and quantum dots, the particle growth is arrested by the addition of a capping reagent. In the system reported in this work, continuing intermicellar exchange effected by Brownian motion leads to particle growth caused, in part, by the large surface free energy of the AgSD nanoparticles. This system is inherently unstable and seeks to minimize the free energy by particle growth. One way to stabilize the AgSD particles in the size range of 30–100 nm is to find an acceptable



**Figure 11.** Schematic illustration of nanoparticle formation mechanism. EM represents a micelle devoid of silver and/or sulfadiazine.

coating/capping reagent that will not interfere with the antimicrobial activity. The search for and testing of potentially compatible reagents is a continuing project.

While reactions in microemulsions have been investigated for approximately 30 years, each reactant system must be individually optimized. The reaction processes have been reported to be influenced by the droplet internal structure, volume fraction of the internal phase, the physicochemical nature of the oil and surfactant, the viscosity of the dispersed phase, and the chemical nature of the reactants, to name a few variables.<sup>33</sup> The influence of these factors on the particle formation and growth in the reported system continues to be investigated.

## CONCLUSION

In this study, stable microemulsions were prepared using pharmaceutically acceptable components.

The results obtained by the use of DLS and microscopy are consistent with the formation of submicron AgSD crystals when microemulsion-based reactors containing AgNO<sub>3</sub> and NaSD were mixed. These nanocrystals synthesized *in situ* could be formulated into various preparations using appropriate additives. This methodology could be used to produce other types of pharmaceutically interesting nanoparticles *via* a process that is neither energy nor heat intensive.

## ACKNOWLEDGMENT

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