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Characterization of nanoparticles of lidocaine in w/o microemulsions using small-angle neutron scattering and dynamic light scattering

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Abstract. Microemulsions (MEs) are of special interest because a variety of reactants can be introduced into the nanometer-sized aqueous domains, leading to materials with controlled size and shape [1,2]. In the past few years, significant research has been conducted in the reverse ME-mediated synthesis of organic nanoparticles [3,4]. In this study, a w/o ME medium was employed for the synthesis of lidocaine by direct precipitation in w/o microemulsion systems: water/isopropylpalmitat/Tween80/Span80. The particle size as well as the location of nanoparticles in the ME droplet were characterized by means of dynamic light scattering (DLS) and small angle neutron scattering (SANS). It is observed that lidocaine precipitated in the aqueous cores because of its insolubility in water. Hydrodynamic radius and gyration radius of microemulsion droplets were estimated as ∼15 nm and ∼4.50 nm from DLS and SANS respectively. Furthermore, different size parameters obtained by DLS and SANS experiments were compared

Keywords. Microemulsions; nanoparticles and drug.

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1. Introduction

Microemulsions (MEs) are thermodynamically stable systems consisting of a hydrophilic phase and a hydrophobic phase, stabilized with the use of surfactants. Regular MEs consist of nanometer-sized hydrocarbon domains (termed micelles) surrounded by amphiphilic molecules, stabilized in a continuous aqueous phase. In contrast, reverse (w/o) MEs consist of aqueous domains (termed reverse micelles) dispersed in a continuous oil phase. w/o MEs are of special interest because a variety of reactants can be introduced into the nanometer-sized aqueous domains for reaction confined within the reverse micelles, leading to materials with controlled

size and shape [1]. In the past few years, significant research has been conducted in the reverse ME-mediated synthesis of inorganic (metal halides, selenides, or sulfides) and organic nanoparticles (cholesterol, rhodiarome, or rhovanil, nimesulide) [1,4]. In this study, a w/o ME medium was employed for the synthesis of lidocaine. The interest of these organic nanoparticles lies in their pharmaceutical application as model drug delivery system. As organic substances are often insoluble in water, a classical method of drug delivery using aqueous solutions is not applicable. However, if nanoparticles could be prepared in suspension in water, they could be directly injected. The size of the particles is very important, because bigger particles could lead to embolism. To elucidate the structure and particle size as well as the location of nanoparticles in the ME droplet, SANS and DLS experiments were conducted [2].

2. Experiments

The basic w/o ME was prepared using H_2O or D_2O (5 wt%), isopropylpalmitat (IPP, 75 wt%) and a blend of high HLB Tween80 : low HLB Span80 surfactant (3 : 2, 20%). Different wt% of organic molecule of lidocaine hydrochloride are added to the w/o MEs in order to investigate the variation of the nanoparticle size as a function of the concentration of the organic molecules. SANS experiments were performed on the V4 at BENSC. Data were taken with 6.05 Å neutrons and sample-to-detector distances of 16, 4 and 1 m, which covered a range of scattering vectors q (0.03–5.0 nm^{-1}). The data were corrected for background, empty cell scattering, and sample transmission. Dynamic light scattering experiments were performed on a standard commercial apparatus (ALV) using a green Nd : YAG DPSS-200 mW laser emitting vertically polarized light at a wavelength of 532 nm. The intensity time autocorrelation functions $g_2(\tau)$ are recorded with an ALV-5000E multiple tau digital correlator with fast option. The minimal sampling time of this correlator is 12.5 ns. Temperature of all the measurements was controlled ($\pm 0.1^\circ$C) by a single thermostat with circulating water as the medium. The refractive index of all the samples was measured using a commercial Abbe refractometer at different temperature T°C $\pm 0.2^\circ$C.

2.1 *Characterization of droplet size by DLS and SANS*

All measurements were made at seven different scattering angles between 70° and 130° at a temperature of 25°C. The $g_2(\tau)$ corresponding to one set of experimental parameters have been measured five times and data used for fitting are averaged over these five measurements. Initial studies indicated that the microemulsions were too small to exhibit significant angular dependence, therefore results used for discussion are results obtained at scattering angle of 90°. The normalized field autocorrelation function $g_1(\tau)$ has been derived from the measured $g_2(\tau)$ via Siegert relation. The $g_1(\tau)$ (see figure 1) was analysed using regularization method (CONTIN) [5].

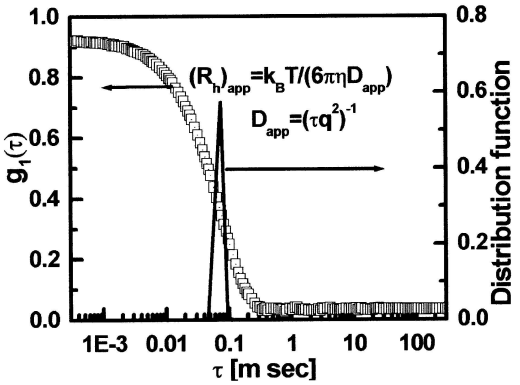

Figure 1. DLS data analysis using CONTIN fit.

Small-angle neutron scattering (SANS) measures the absolute scattering cross-section $I(q)$ (cm^{-1}) of a sample as a function of the modulus of momentum transfer $q = (4\pi n/\lambda)\sin(\theta/2)$, where n is the neutron refractive index of microemulsion, θ is the scattering angle and λ is the wavelength. Data are analysed at small q (more exactly, at values of q smaller than the inverse of the characteristic dimension of the droplet, the so-called Guinier region $qR \leq 1$), and information about the size (radius of gyration R_{g}) were obtained.

3. Results and discussion

The maximum amount of the active organic compound (lidocaine) that can be added to the w/o MEs is 1 wt%. The w/o ME is destabilized (phase separation occurs), when the concentration increases (more than 1 wt%). Indeed, when the concentration increases, the number of active compound molecules per aqueous core also increases, which increases interaction with the surfactant at the interface. The optimal curvature radius is perturbated and a phase separation occurs. In this study, we investigated three samples, basic w/o ME, basic w/o ME with 0.25 wt% of active organic compound and basic w/o ME with 0.75 wt% of active organic compound. Figure 2 shows the obtained SANS curve from w/o ME and w/o MEs with different concentration of active organic compound. Two samples (basic w/o ME and basic w/o ME with 0.75 wt%) were measured both with light water and heavy water. Scattering curves shown in figure 2a indicate that organic compound formed nanoparticles in heavy water core. Thus, with increasing concentration the scattering intensity decreases due to direct precipitation of organic compound into the heavy water core. As shown in figure 2a, the change in scattering intensity of ME droplets having organic compounds by substituting the protonated water with heavy water is one order less than the change in scattering intensity of basic ME droplets by substituting the protonated water with heavy water. This also proves that organic compounds precipitated into aqueous core.

Figure 2b shows the best fitting and gyration radius R_{g} obtained using Guinier approximation which is listed in table 1. As shown in table 1, nanoparticle size does not change significantly as a function of the concentration of active organic

Table 1. Gyration radius of microemulsion droplets.

Microemulsions	SANS R_g (nm)
w/o ME (D_2O)	4.55 ± 0.62
w/o ME (D_2O) + 0.25 wt% lidociane–HCl	4.53 ± 0.57
w/o ME (D_2O) + 0.75 wt% lidociane–HCl	4.56 ± 0.44

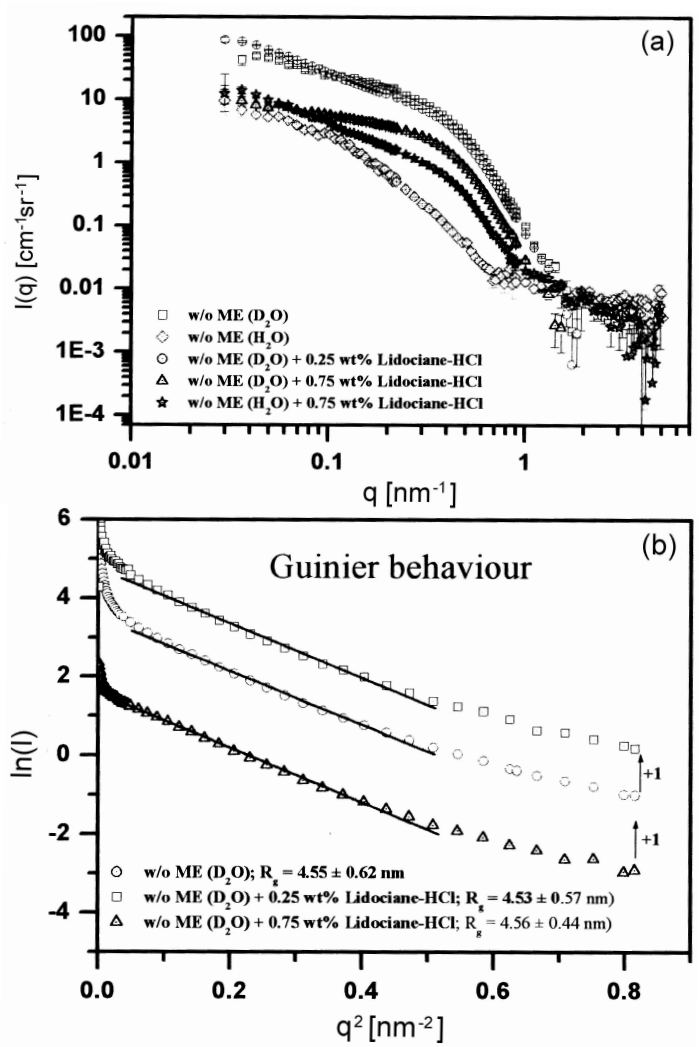

Figure 2. (**a**) SANS intensity as a function of q. (**b**) Guinier approximation fitting.

compound. Apparent hydrodynamic radius $(R_h)_{app}$, which is supposed to consist of the spherical inner core, a surfactant film including possible solvent molecules which migrate with the droplet obtained from DLS is about ∼15 nm and does not significantly change with the increase of the concentration of active organic compound too. As expected, R_g is substantially smaller than $(R_h)_{app}$. More detailed data analysis are in progress.

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