Solid-State Emulsions: Evaluation by ^{1}H and ^{13}C Solid-State Nuclear Magnetic Resonance

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The molecular environment of sucrose and mineral oil within sucrose and mineral oil solid state emulsions was investigated by NMR techniques. The ^{13}C and ^{1}H chemical shifts of sucrose and mineral oil to those observed in solid state emulsions (comprised of sucrose and mineral oil) were equivalent, indicating that the local structure of sucrose is unaffected by the presence of mineral oil in the solid-state emulsion. Cross-polarization, magic angle spinning ^{13}C (CP-MAS) in conjuncton with single-pulse studies indicated that the ^{1}H-^{13}C dipole-dipole interactions are very weak, i.e., mineral oil is highly mobile. Spinning side bands were observed, however, in ^{1}H single-pulse, magic angle spinning (SPMAS) spectra of the solid-state emulsion, indicating that the mineral oil has solid properties. Although the mineral oil was shown to be highly mobile, it also appears to be constrained or included by the sucrose.

KEY WORDS: emulsifiable glass; self-emulsification; solid state emulsion; inclusion compound and CRAMPS.

INTRODUCTION

Solid state emulsions are comprised of a matrix material and an oil phase that have been suitably processed to yield a solid. Upon addition of an aqueous phase to these solids, surprisingly stable dispersions are formed. The unique self-emulsification properties of these systems, in the absence of emulsifying agents, has prompted the physical properties of solid state emulsions to be characterized, e.g., the particle size (1) as a function of the matrix and oil phase (2), process and appropriate storage conditions (3) and the modification of aging properties (4). Solid state emulsions are amorphous, i.e., lack long range order, as determined by X-ray diffraction, yet exhibit short range order as determined by differential scanning calorimetry. Calorimetric results also indicate that the glass transition of sucrose does not change post-processing with mineral oil. The methods to prepare solid state emulsions that result in oil-in-water and water-in-oil-in-water emulsions have been reported (5).

Although the physical characteristics of these systems have been reported, a rationale that adequately describes the observed properties has not been elucidated. It is anticipated that an investigation of the interactions between the mineral oil and sucrose comprising the solid-state emulsion will provide information about the environment of the mineral oil and sucrose at the molecular level. One such analytical technique that can provide information about molecular interactions is solid-state nuclear magnetic resonance (NMR). Numerous recent advances have enabled high resolution spectra of solids to be made (6,7). The most common pharmaceutical applications of solid-state NMR have been for the detection of polymorphs (8). Solid-state NMR has also been used for trace quantitative analysis (9), conformational analysis (10), drug-excipient interactions (11) and interactions within complexes and inclusion compounds (12).

The intent of this report is to communicate our NMR findings for solid state emulsions comprised of sucrose and mineral oil.

METHODS AND MATERIALS

Materials

Mineral oil (USP, Fisher Scientific) and sucrose (reagent grade, EM Science) were used as supplied. Double distilled, de-ionized water was used throughout.

Preparation of Solid State Emulsion

The procedure to prepare the solid state emulsion is analogous to that previously described (5). Mineral oil (1.0 g.) and sucrose (3.5 g) were added to a 100 ml rotary vacuum flask. Sufficient water to dissolve the sucrose (~3 ml) was added to the flask. The flask was then fitted to a rotary evaporator (Buchi model 142) and lowered into a thermostatically-controlled bath and maintained at 60°C while vacuum was applied (5 mm Hg). The resulting solid (or foam) was removed from the flask and stored desiccated until required (3).

NMR Experimental Procedures

Both solid-state and liquid-state ^{13}C NMR spectra were recorded on a modified Nicolet NT-150 NMR spectrometer operating at 37.7 MHz for ^{13}C. A ^{1}H decoupling field of 50.4 kHz was used. All reported chemical shifts are relative to liquid TMS.

Solid-state ^{1}H NMR spectra were collected on a hand-built NMR spectrometer operating at 360 MHz for ^{1}H. A ninety degree pulse of 1.26 microseconds and a tau value of 2.4 microseconds were used with the BR-24 pulse sequence (13) to record ^{1}H CRAMPS NMR spectra (7). A ninety degree pulse of 1.26 microseconds was also used to record single-pulse magic-angle spinning (SPMAS) ^{1}H NMR spectra. Chemical shifts were referenced to external tetrakis (trimethylsilyl) methane (TTMSM), which has a chemical shift of 0.38 ppm relative to liquid TMS. Thus, ^{1}H chemical shifts are relative to TMS.

High-resolution, liquid-state ^{1}H NMR spectra were recorded on a Brüker AM-600 NMR spectrometer operating at 600 MHz for ^{1}H. Chemical shifts are relative to internal TMS.

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RESULTS AND DISCUSSION

^{13}C NMR Studies

A ^{13}C cross-polarization, magic angle spinning (CP-MAS) NMR spectrum for crystalline sucrose collected in this laboratory was equivalent to that previously reported for sucrose (14). The chemical shift region for sucrose was in the range of 50 to 100 ppm. Using the same probe as above, a ^{13}C single-pulse, non-spinning NMR spectrum of neat mineral oil was obtained (data not shown). Using this probe with mineral oil resulted in a poorly resolved manifold of resonance intensity in the 10–50 ppm region. The observed range of chemical shifts are in the region expected for a saturated hydrocarbon material.

Having individually identified the chemical shift regions for sucrose and mineral oil, the ^{13}C CPMAS of the sucrose:mineral oil::3.5:1 solid-state emulsion spectrum was determined (Fig 1). Analysis of Fig 1 indicates that only the resonance peaks of sucrose are observed in this spectrum while the resonance peaks of the mineral oil are not observed. In addition the ^{13}C chemical shifts of sucrose in the sucrose:mineral oil::3.5:1 solid-state emulsion are virtually identical to those of pure sucrose. This indicates that the local structure of sucrose in the solid state emulsion is the same as crystalline sucrose.

The failure to observe resonance intensity from the mineral oil in the ^{13}C CPMAS NMR spectrum of the solid state emulsion (Fig. 1), implies that either the ^{1}H-^{13}C dipole-dipole interaction in the mineral oil is weak, due to molecular motion, or that the ^{1}H spin-lattice relaxation time in the rotating frame, $T_{1\rho H}$, is very short. In order to determine the most likely case, ^{13}C CPMAS NMR spectra were obtained for the solid-state emulsion as a function of the contact time and relaxation delay. The spectra for contact times of 50 μsec., 0.5 msec., 5 msec. and 10 msec. are essentially the same as shown in Fig. 1. The inability to observe resonance intensity for the mineral oil at a very short contact time, e.g., 50 μsec., implies that the mineral oil $T_{1\rho H}$ is not very short. The inability to observe a resonance intensity for mineral oil at a relatively long contact time, e.g., 10 msec., suggests that the ^{1}H-^{13}C dipole-dipole interaction in the mineral oil is very weak.

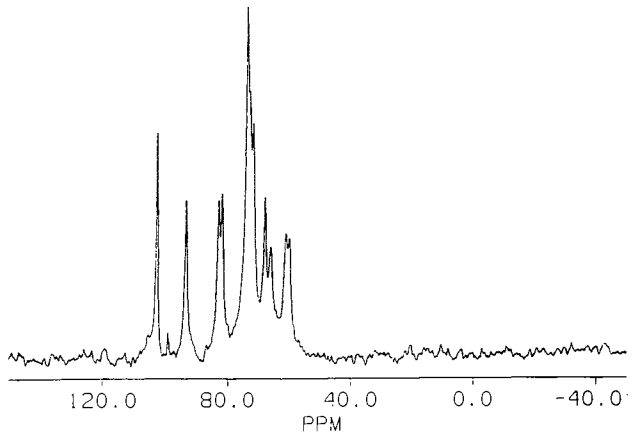

Figure 1 ^{13}C cross-polarization, magic-angle spinning (CPMAS) NMR spectra of 3.5:1::sucrose:mineral oil solid-state emulsion using an MAS speed of 2.0 kHz. Parameters: 120 sec relaxation delay; 8.5 μsec. decoupler "ninety" degree pulse; 2 msec contact time.

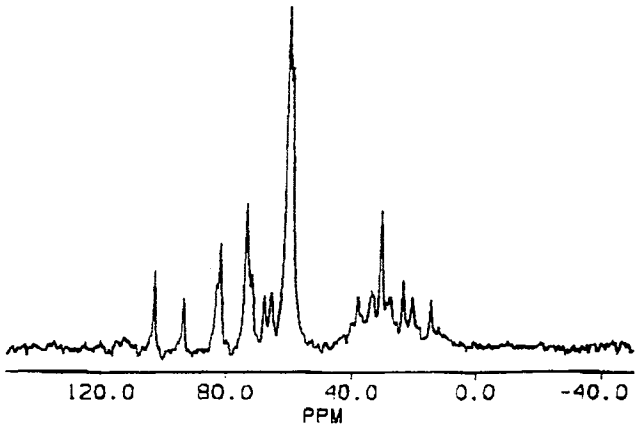

Figure 2 ^{13}C single-pulse, magic-angle spinning (SPMAS) NMR spectra of 3.5:1::sucrose:mineral oil solid-state emulsion utilizing a relaxation delay of 5 sec. Parameters: 4.9 μsec. decoupler "ninety" degree pulse; 2.0 kHz MAS.

Due to the lack of resonance intensities for mineral oil in the ^{13}C CPMAS experiments, a ^{13}C SPMAS spectrum was collected for the solid state emulsion. Spectra collected using relaxation delays of 120 sec, 10 sec. and 5 sec. were essentially identical. A representative ^{13}C SPMAS spectrum (relaxation delay of 5 sec) is shown in Fig. 2. In contrast to the ^{13}C SPMAS NMR spectra of this sample, the twelve resonance lines from sucrose and as many as seven resonance lines from mineral oil may be observed in the ^{13}C SPMAS NMR spectra (Fig. 2). This result indicates that the solid state emulsions were comprised of mineral oil.

The ^{13}C NMR results obtained for the mineral oil, sucrose, and the 3.5:1::sucrose:mineral oil solid-state emulsion indicate that the local structure of sucrose in the solid-state emulsion is similar to that of pure sucrose. The ^{13}C NMR results also indicate that mineral oil has no solid properties in the solid state emulsion.

^{1}H NMR Studies

High resolution ^{1}H NMR in solids has been made possible through a combination of magic angle spinning and multiple-pulse spectroscopy, namely ^{1}H CRAMPS (combined rotation and multiple-pulse spectroscopy) (16,7). A series of experiments were therefore designed in which high-resolution liquid-state ^{1}H NMR spectra of mineral oil could be compared to the CRAMPS spectra of sucrose based solid-state emulsions using various experimental conditions.

High-resolution ^{1}H CRAMPS spectrum of neat mineral oil resulted in two sharp peaks at 0.50 and 2.00 ppm (data not shown). The observed spectrum was typical of a saturated hydrocarbon material. The ^{1}H CRAMPS NMR spectrum of sucrose resulted in approximately ten peaks between 3.5 and 8.2 ppm (data not shown).

Having generated baseline spectra for mineral oil and sucrose, the ^{1}H CRAMPS spectrum for the 3.5:1::sucrose: mineral oil solid-state emulsion was measured (Fig. 3). The ^{1}H CRAMPS NMR spectrum of the solid state emulsion (Fig. 3) reveals resonance intensities from sucrose (3.5 to 8.2

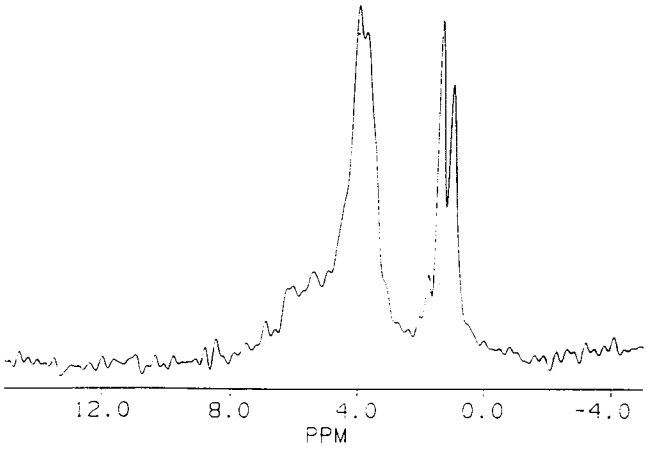

Figure 3 ^{1}H combined rotation and multiple-pulse spectroscopy (CRAMPS) NMR spectra of 3.5:1::sucrose:mineral oil solid-state emulsion. CRAMPS data collected using the BR-24 multiple-pulse program. Parameters: 300 sec relaxation delay.

ppm) and mineral oil (0.5 to 3 ppm). Since the chemical shifts for sucrose and mineral oil are essentially the same in the solid state emulsion, the structure of sucrose and mineral oil in the solid state emulsion is similar to that of the pure materials. These findings are consistent with the ^{13}C NMR results.

The mobility of mineral oil may also be studied using ^{1}H CRAMPS for sucrose and the solid state emulsion as a function of dipolar dephasing times, ie., 2, 10, 20, 40, 80, 160, and 320 μsec. The resulting ^{1}H CRAMPS spectra for the solid state emulsion are shown in Fig. 4. Analysis of Fig. 4 indicates that the ^{1}H-^{1}H dipole-dipole interaction is strong for sucrose. This conclusion may be made because of the loss of virtually all the intensity from sucrose at a dipolar dephasing time of 20 μsec. Further analysis of Fig. 4 indicates, for the same reason as above, that the ^{1}H-^{1}H dipole-dipole interactions of mineral oil are very weak. Even at the very long dipolar dephasing times, e.g., 320 μsec., very little of the resonance intensity of mineral oil has decreased (Fig. 4). Due to the fact that hydrogens in the mineral oil must be very close spatially to many other hydrogens, suggests that the mineral oil is very mobile in solid state emulsions. The high mobility of the mineral oil in the solid state emulsions, as determined by ^{1}H CRAMPS is consistent with our ^{13}C NMR results.

The nature of the mineral oil comprising the solid-state emulsion was further studied by doing a single pulse magic angle spinning (SPMAS) experiment as a function of the MAS speed. Figure 5 represent the ^{1}H SPMAS spectra for the 3.5:1::sucrose:mineral oil solid-state emulsion with MAS speeds of 1.4, 2.3 and 2.9 kHz, respectively. Analysis of Fig. 5 indicates that those peaks with chemical shifts of about 1.0 and 1.4 ppm and the shoulder at about 1.8 ppm are isotropic peaks. All other peaks in these spectra change position with the MAS speed and are thus spinning sidebands. More importantly, the existence of spinning sidebands demonstrates that the mineral oil in the solid-state emulsion has solid character. Also note that only very low MAS speeds are required to obtain a high-resolution, solid-state ^{1}H SPMAS NMR spectrum, which is in agreement with our findings that the ^{1}H-^{1}H dipole-dipole interaction in the mineral oil is weak because of molecular motion. One explanation for the observed solid character of the mineral oil may be that, even though the mineral oil in the solid state emulsion is highly mobile, it is constrained by the sucrose.

The ^{1}H NMR studies indicate that the local structure of sucrose in the solid-state emulsion has a structure similar to that of pure sucrose, in agreement with the ^{13}C NMR results. The ^{1}H NMR studies, however, indicate that the mineral oil is highly mobile but constrained in the sucrose matrix.

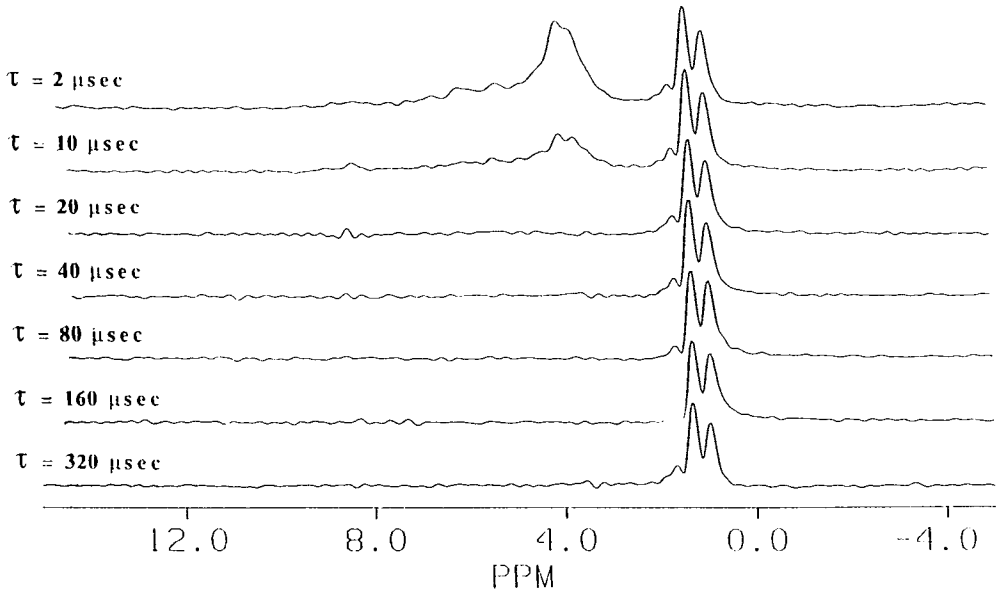

Figure 4 ^{1}H combined rotation and multiple-pulse spectroscopy (CRAMPS) NMR spectra of 3.5:1::sucrose:mineral oil the solid-state emulsion with TTMSM as a function of the dipolar dephasing time (τ). CRAMPS data collected using the BR-24 multiple-pulse program. Parameters: 300 sec relaxation delay.

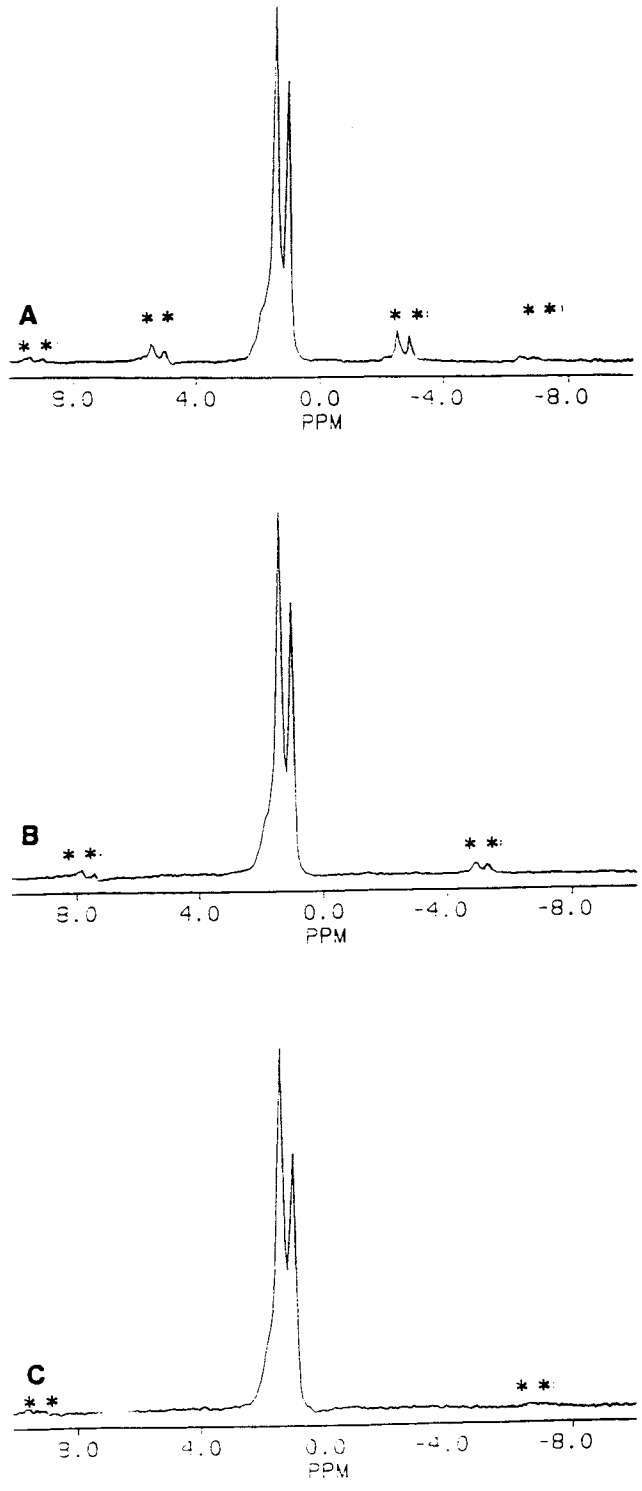

Figure 5 ^{1}H single-pulse, magic angle spinning (SPMAS) NMR spectra of 3.5:1::sucrose:mineral oil the solid-state emulsion with TTMSM as a function of the MAS. Parameters: 1.26 μsec ninety degree pulse; 10 sec relaxation delay; magic angle speed (MAS): (A) 1.4 kHz; (B) 2.3 kHz; (C) 2.9 kHz. (*denotes spinning sidebands)

Although other physical systems may be responsible for these properties (e.g., charge transfer complex or intercalates), one physical system that is consistent with our results is the formation of a multi molecular inclusion compound in which sucrose is the host molecule and mineral oil is the guest molecule. The formation of an inclusion compound is also consistent with the apparent lack of selectivity for the oil phase needed to prepare solid state emulsions (2). Reanalysis of infra red spectra physical mixtures of sucrose and oil and the corresponding solid state emulsion (1) is consistent with the formation of an inclusion compound (17). The classical inclusion compounds bound by intermolecular hydrogen bonds include urea (18,19) and thiourea (20) inclusion compounds. Due to the simplicity of urea and thiourea systems (e.g., urea or thiourea and octyl alcohol), the structure of these multi molecular inclusion compounds has been elucidated. As a result of the complexity of solid state emulsions, e.g., a disaccharide and a heterogenous oil phase, the organization of the inclusion compound will be extremely difficult to determine.

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