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Solid-state NMR characterization of drug-model molecules encapsulated in MCM-41 silica*

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Abstract: In this contribution, we present a solid-state NMR approach to characterize drug-model molecules as ibuprofen, benzoic acid, and lauric acid, encapsulated in MCM-41 silica and submitted to strong confinement effects. In particular, we show that by a careful choice of the solid-state NMR sequences, it is possible to efficiently characterize these highly mobile molecules and their interactions with the pore surface. Thus, we demonstrate that ^{13}C NMR spectroscopy is a powerful tool to characterize and even quantify entrapped and non-entrapped species by using either single-pulse excitation (SPE) or cross-polarization (CP). Whereas the standard $\{^1H\}$-^{13}C CP experiment is of poor efficiency for mobile species, we show that ^{13}C signal-to-noise (S/N) ratio can be significantly improved through ^1H-^{13}C cross-relaxation (namely, nuclear Overhauser effect, nOe) by using a ^1H power-gated technique. The long transversal relaxation times [$T_2(^1H)$ up to 22 ms] observed allow the set-up of *J-coupling*-based experiments such as 2D $\{^1H\}$-^{13}C heteronuclear multiple-quantum coherence (HMQC) in order to fully characterize the encapsulated molecules. Thus, we demonstrate that the use of sequences derived from solution-state NMR such as these two latter experiments is highly efficient to characterize highly mobile organic molecules trapped in mesopores. Finally, we show that ^1H spin diffusion-based experiments can give useful information on the proximities between trapped molecules and the silica surface.

Keywords: solid-state NMR; porous silica; encapsulation; confinement; drug delivery.

INTRODUCTION

Since their discovery in 1992, mesoporous silica materials such as MCM-41 [1] are widely used by researchers for their ability to encapsulate different chemical species such as small organic molecules, drugs [2], or even proteins [3]. These systems can find their applications as sensors for pollutant extraction [4,5], drug storage and release systems [6], or enzymatic heterogeneous catalysts [7]. In the pharmaceutical field, MCM-41-based drug-release systems are used to increase efficiently the solubility of hydrophobic drugs in biological fluids [8]. For such application, it is of high importance to characterize the physical state of the encapsulated entities, as well as their possible interaction with the sil-

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ica surface that will modulate their ability to be released in physiological fluids. Indeed, an unexpected physical state for the encapsulated molecules was already observed in these materials at ambient temperature due to the existence of confinement effects [9]. These effects are generally observed for pore diameters ranging from 1 to 20 nm, and they imply the depression of the phase-transition temperatures [10,11]. Thus, a "liquid-like" behavior is observed for the trapped molecules, whereas the bulk substance is a solid at ambient temperature. As a consequence, encapsulated species act as isolated molecules rather than bulk crystals, which leads to fast release kinetics in a biological medium.

In order to study these particular systems, we encapsulated ibuprofen (a common analgesic and anti-inflammatory drug) as well as benzoic acid and lauric acid (Fig. 1) in MCM-41 silica mesoporous materials using an "incipient" wetness method previously described [8]. We use benzoic acid and lauric acid as model molecules for drugs such as ibuprofen, as 80 % of drugs possess a carboxylic acid group. The ^{1}H and ^{13}C solid-state NMR characterization of the loaded samples revealed that the corresponding molecules behave like liquids once encapsulated, and are thus submitted to confinement effects, whereas the three bulk substances are indeed crystalline solids at ambient temperature.

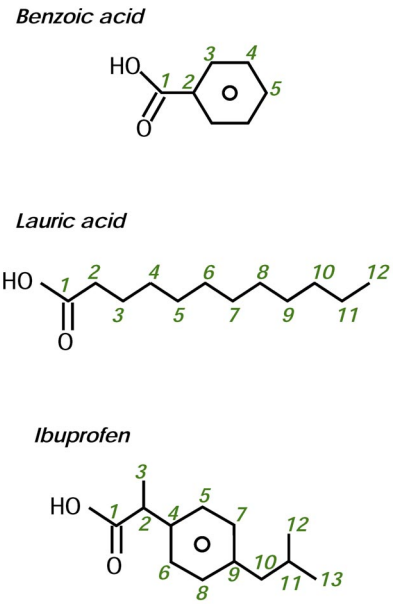

Fig. 1 Schematic representation of benzoic acid, lauric acid, and ibuprofen with the respective labeling of the C atoms.

We show in this paper that solid-state NMR spectroscopy is an efficient tool to characterize such materials and, in particular, we demonstrate that ^{13}C NMR allows a fine characterization of the organic part of the loaded samples if NMR sequences are properly chosen. For instance, the classical {^{1}H}-^{13}C cross-polarization/magic-angle spinning (CP/MAS) solid-state experiment is particularly efficient to detect non-encapsulated molecules in the as-prepared sample, which will crystallize outside the pores. On the other hand, the CP technique is inefficient to detect the encapsulated molecules because of their high mobility, which causes an averaging of the heteronuclear ^{1}H-^{13}C dipolar interaction, driving force for the magnetization transfer. In the case of as-prepared samples, the ^{13}C single-pulse excitation (SPE) allows the quantification of encapsulated vs. non-encapsulated molecules. However, the low natural abundance of ^{13}C implies a low signal-to-noise (S/N) ratio of the latter experiment particularly in the case of low organic amounts. We show in this paper that the low sensitivity of the ^{13}C SPE experiment can be circumvented by using a technique based on nuclear Overhauser

effect (nOe) that is classically used in solution-state NMR. Indeed, the use of a power-gated technique—which consists of a low-power irradiation of the proton spins prior to the acquisition of the ^{13}C signal—allows a ^{1}H-^{13}C cross-relaxation phenomenon that enhances the ^{13}C signal up to two times in the case of our samples.

In addition to the ^{13}C NMR spectra, the ^{1}H NMR spectra can also bring important information. Because of the high mobility of the encapsulated molecules, the spectra are characterized by extremely sharp lines, with line widths down to 30 Hz. Indeed, the relative degrees of mobility of the encapsulated molecules can be probed by apparent transverse relaxation time $T_2'(^1H)$ measurements obtained through an echo sequence. We observed $T_2'(^1H)$ up to 22 ms, unusually long values in the framework of solid-state NMR but which are characteristic of mobile species. These long $T_2'(^1H)$ allow performing 2D $\{^1H\}$-^{13}C experiments based on J_{C-H} *couplings* that require a long magnetization evolution period and that are commonly used in solution-state NMR such as heteronuclear multiple-quantum coherence (HMQC) or insensitive nuclei-enhanced polarization transfer (INEPT). In this paper, we used 2D MAS $\{^1H\}$-^{13}C HMQC experiments to assign unambiguously ^{1}H and ^{13}C resonances. Additionally, $\{^1H$-$^{29}Si\}$-^{1}H double-CP and 2D ^{1}H exchange spectroscopy (EXSY) experiments were performed in order to probe the direct proton environment in the silica matrix and to characterize the proximity between the encapsulated molecule and the silica surface.

The possibility of playing with all these NMR experiments to selectively reveal one piece of structural information will be illustrated with three different MCM-41 samples loaded with ibuprofen, benzoic acid, or lauric acid. More generally, the objective of this paper is to show how the use of an appropriate combination of NMR experiments can help to efficiently characterize molecules encapsulated in porous media and subjected to confinement effects.

EXPERIMENTAL

MCM-41 synthesis and loading procedure

The synthesis of the MCM-41 materials and the loading procedure with the organic molecules were already described in previous papers [8]. Typically, MCM-41 is obtained by mixing under stirring at room temperature H_2O, NaOH, cetyltrimethylammonium bromide, and silica (Aerosil 200), in a given molar ratio of 20:0.25:0.1:1, respectively. The resulting white precipitated powder is filtered and plentifully washed with distilled water up to neutral pH, then dried at 70 °C for at least 48 h. Samples are then calcined at 600 °C for 6 h under air flux to remove the surfactant.

The loading of MCM-41 calcined materials was realized according to the incipient wetness procedure previously described [8]. The mesoporous samples are loaded using a solution of ibuprofen, benzoic acid, or lauric acid in ethanol (~0.310 mol l^{-1}). Then, 0.500 g of MCM-41 is impregnated four times successively, with a small amount of the solution just allowing the powder to be wetted. The solvent is removed between two impregnations by heating the sample at 70 °C overnight. Then, samples are quickly washed with 5 ml of ethanol to remove the excess of non-encapsulated molecules. The control of this step is particularly crucial as an insufficient amount of ethanol can cause crystallization of the organic molecules in the samples, whereas an excess of ethanol leads to the partial release of the molecules. The MCM-41 samples loaded with ibuprofen, benzoic acid, and lauric acid will be referred to in the forthcoming text as MCM-Ibu, MCM-BA, and MCM-LA, respectively.

Sample characterization

Nitrogen adsorption/desorption isotherms were recorded at 77 K with a Micromeritics ASAP 2000 apparatus, after activation of the sample under vacuum (1×10^{-3} torr) at 150 °C for the calcined samples or at room temperature during 15 h for the encapsulated systems. The specific surface area S_{BET} is calculated according to the standard Brunauer–Emmett–Teller (BET) method [12], while the mean pore

diameter ϕ is estimated by the Barrett–Joiner–Halenda (BJH) method using the desorption branch of the isotherm (Table 1) [13].

Table 1 Textural characterization of MCM-41 and encapsulated samples.

Sample	S_{BET} (±10 m^2 g^{-1})	V_P (±0.05 cm^3 g^{-1})	Average diameter (±2 Å)	Amount of encapsulated molecules (± 10 mg g^{-1})
MCM-41	950	0.85	30	–
MCM-Ibu	135	0	–	670
MCM-BA	160	0.15	–	680
MCM-LA	35	0.11	–	1015

Thermogravimetric analysis (TGA) was carried out on a TA instruments SDT 2960 and on a SETARAM TG-DTA instrument under an air flow with a heating rate of 5 °C min^{-1} up to 1000 °C.

The different NMR sequences used to study the encapsulated samples are schematically described in Fig. 2: SPE, SPE with power gate (SPE-PG), {^{1}H}-^{13}C CP, {^{1}H}-^{13}C HMQC, {^{1}H-^{29}Si}-^{1}H double-CP, and ^{1}H EXSY. All ^{13}C spectra were recorded with ^{1}H TPPM decoupling during acquisition [typically, $\nu_{RF}(^1H)$ = 60 kHz]. For SPE-PG experiments, PG proton radio-frequency was set to 2.5 kHz during the recycle delay. For ^{13}C-{^{1}H} MAS HMQC and ^{1}H EXSY experiments, evolution and mixing delays (τ) were rotor-synchronized in order to avoid reintroduction of unwanted interactions. ^{1}H and ^{13}C solid-state NMR experiments were performed on an AV300 Bruker spectrometer operating at $\Xi(^1H)$ = 300.13 MHz and $\Xi(^{13}C)$ = 75.48 MHz. 4-mm zirconia rotors were spun at MAS frequency of 5–14 kHz. Recycle delay for ^{1}H and ^{13}C experiments was set to 2 s. The chemical shift reference (0 ppm) for ^{1}H and ^{13}C was tetramethylsilane (TMS).

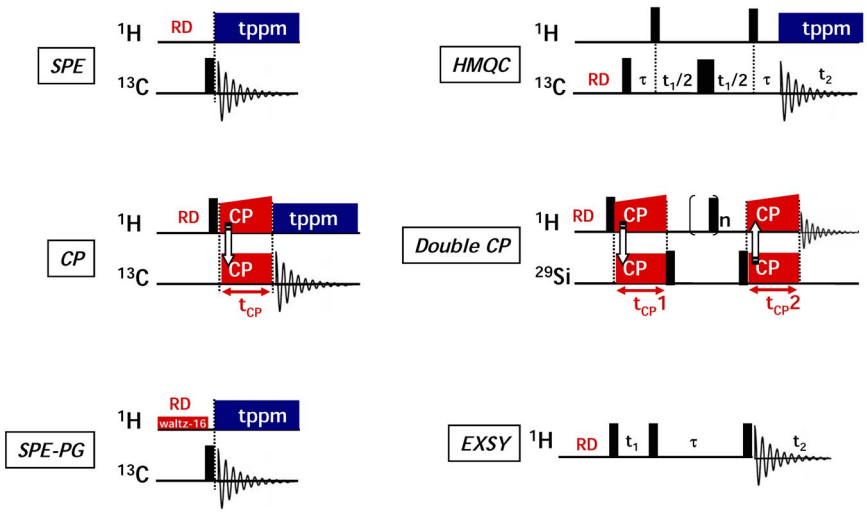

Fig. 2 Schematic description of NMR sequences used in this study.

RESULTS AND DISCUSSION

Porosity characterization and TG measurements

Nitrogen adsorption/desorption isotherms of calcinated MCM-41 revealed a type IV isotherm (not shown) with a specific surface area (S_{BET}) of 950 m^2 g^{-1}. The mean pore diameter is 30 Å with a narrow distribution of uniform pores. The mesoporous volume (V_p) is 0.85 cm^3 g^{-1}. After the loading procedure, a decrease of the porosity parameters is observed, which demonstrates that ibuprofen, benzoic acid, and lauric acid have been encapsulated in the mesopores (Table 1). TG measurements (not shown) allow determination of the encapsulation yield (670, 680, 1015 mg of molecules per gram of silica, for MCM-Ibu, MCM-BA, and MCM-LA, respectively, see Table 1).

^{13}C SOLID-STATE NMR

^{13}C solid-state NMR is a useful technique for probing the physical state of the organic molecules in our loaded samples and in particular before and after the washing step. As an example, we show in Fig. 3 the ^{13}C SPE and CP/MAS spectra of unwashed MCM-Ibu samples. CP experiment is based on ^{1}H to ^{13}C magnetization transfer driven by ^{1}H-^{13}C heteronuclear dipolar interaction. As mobility averages out this interaction, the CP technique is only sensitive to rigid molecules. On the other hand, SPE is able to detect all kinds of molecules, rigid as well as mobile ones. The CP and SPE spectra of unwashed MCM-Ibu samples are clearly different. The CP spectrum is similar to that of bulk crystalline ibuprofen and is characteristic of the part of ibuprofen molecules that have crystallized outside the mesoporous matrix. Instead, the SPE spectrum shows signals from all ibuprofen molecules, including those trapped in the mesopores, leading to a different spectrum in terms of number of peaks and chemical shift values. For instance, the chemical shift of the carboxylic carbon has shifted downfield from 184 to 181 ppm between the crystalline form and encapsulated one. A simple integration of peak areas allows the quantification of two forms (60 % of encapsulated vs. 40 % of crystallized ibuprofen in this sample).

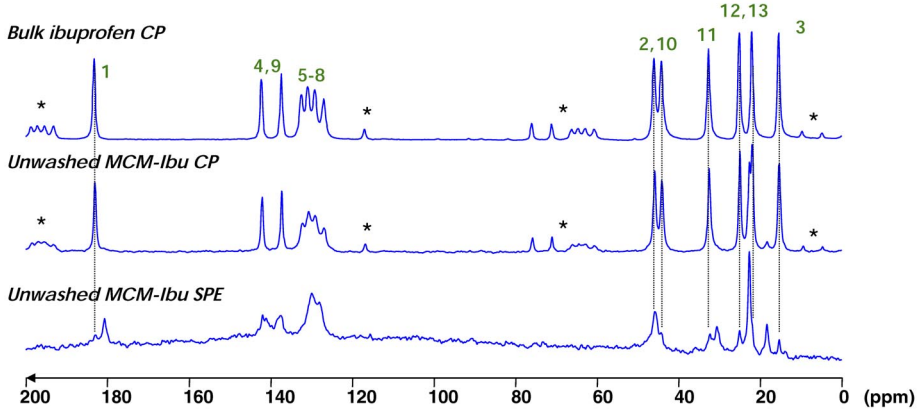

Fig. 3 ^{13}C CP/MAS NMR spectrum of bulk ibuprofen (with ^{13}C resonance assignment) and ^{13}C MAS NMR spectra of unwashed MCM-Ibu sample recorded with CP and SPE sequences.

The SPE spectrum of the washed sample MCM-Ibu (Fig. 4) proves that residual crystalline molecules are efficiently removed by the washing step, as resonances due to bulk ibuprofen are absent. Thus, this simple experiment allows the control of this delicate purification step at the end of the synthesis procedure. But more interestingly, the resonances are identical to those obtained from a solution

of ibuprofen in $CDCl_3$, confirming the highly mobile behavior of the encapsulated molecules. A comparison of the ^{13}C spectra of bulk and mobile ibuprofen shows that the methyl carbons labeled 12 and 13 of the isopropyl group are magnetically equivalent in the trapped form (Fig. 4), thanks to fast reorientation, whereas they are crystallographically distinct in the bulk form (Fig. 3). The same observation can be done for carbons of the aromatic ring labeled from 5 to 8: they are magnetically distinct in the crystalline form and correspond to four distinct peaks, while the fast reorientation due to high mobility in the encapsulated form leads to only two distinct resonances for carbons 5 and 6 on one hand, and 7 and 8 on the other hand.

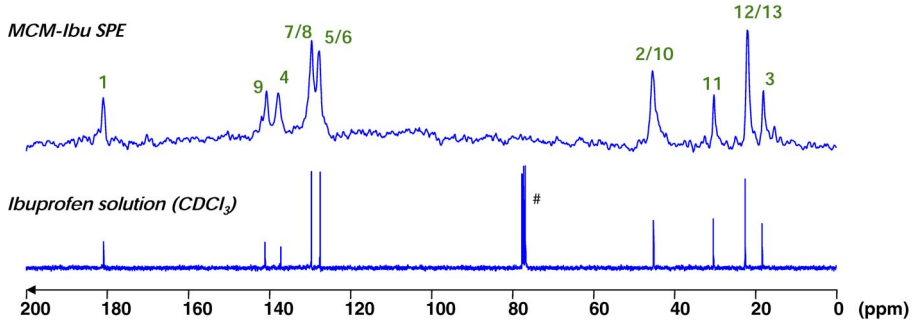

Fig. 4 ^{13}C SPE MAS NMR spectrum of MCM-Ibu with ^{13}C resonance assignment and ^{13}C solution-state NMR spectrum of a $CDCl_3$ solution of ibuprofen. # denotes the solvant resonance.

If the ^{13}C SPE NMR experiment is particularly useful for characterizing mobile entrapped species, the use of this method can be problematic as soon as small quantities of drug molecules are encapsulated. Indeed, ^{13}C is only 1 % abundant, and thus SPE experiments can be time-consuming to reach a correct S/N ratio. Thus, to enhance the ^{13}C signal, we use the SPE-PG sequence that is routinely used in solution-state NMR, in which a continuous low-power (2.5 kHz) proton decoupling sequence (waltz 16 [14]) is applied during the recycle delay [15]. The signal intensity enhancement is achieved by a cross-relaxation phenomenon—namely, nOe—between ^{13}C and neighboring protons. Figure 5 displays the ^{13}C SPE and SPE-PG spectra of the MCM-LA sample. The heteronuclear ^{1}H-^{13}C nOe enhancement factor η is indicated for each carbon. η is experimentally determined according to the following definition:

$$\eta = (S - S_0)/S_0$$

where S refers to the ^{13}C intensity following proton saturation, i.e., ^{13}C intensity corresponding to the SPE-PG experiment, while S_0 is the ^{13}C intensity without proton irradiation prior to excitation, i.e., ^{13}C intensity corresponding to the SPE experiment. The nOe between coupled ^{1}H and ^{13}C spins is maximized for molecular motions with fast correlation time ($\tau_C < 10^{-10}$ s). In this extreme narrowing motional regime, η reaches a maximum value of 1.99. Usually, this phenomenon is not observed in the solid state as the molecular reorientation time is too long or inexistent ($\eta = 0$) [16]. For the MCM-LA sample, we observe intermediate η values that vary between 0.38 and 0.94. These intermediate values prove the existence of moderate τ_c and confirm a viscous-like behavior—rather than a pure liquid behavior—of the encapsulated molecules at room temperature. Practically, the S/N ratio of the SPE-PG spectrum is almost twice higher for carbons 4 to 10 of the *n*-alkyl chain of lauric acid, compared to the SPE spectrum. More interestingly, we observe that the heteronuclear ^{1}H-^{13}C nOe still exists for the carboxylic carbon C_1. Indeed, we found a η value of 0.38, indicating the occurrence of cross-relaxation with not directly bounded protons, thanks to a sufficient mobility of C_1.

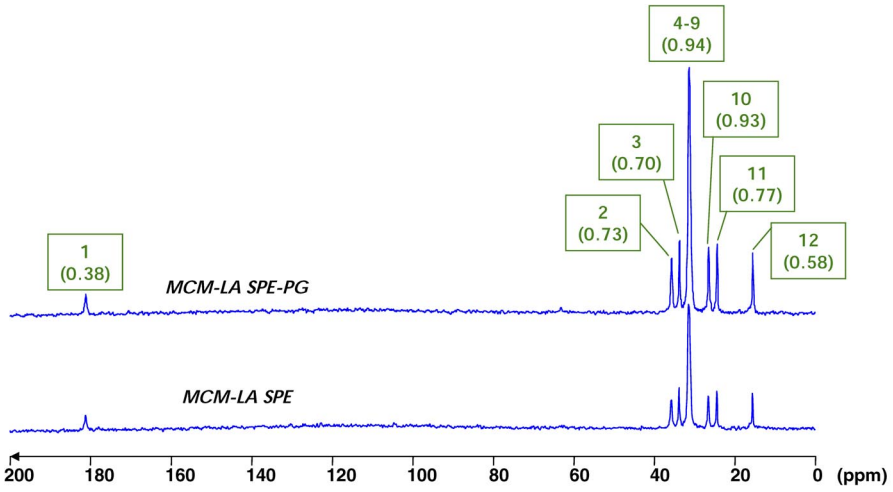

Fig. 5 ^{13}C MAS NMR spectrum of MCM-LA recorded with SPE and SPE-PG sequences. Insets display the ^{13}C resonance assignment together with the corresponding ^{1}H-^{13}C nOe enhancement factor value (η).

^{1}H solid-state NMR

^{1}H MAS NMR spectra also reflect the high mobility of the encapsulated species. Figure 6 displays the ^{1}H MAS spectra of MCM-Ibu, MCM-AL, and MCM-BA samples together with the spectra of the corresponding bulk crystalline samples. We note that if the spectra of the crystalline acids are broad due to the presence of a strong homonuclear ^{1}H-^{1}H dipolar coupling, the resonances of encapsulated molecules are extremely sharp because of the molecular motion in the pores that leads to a very efficient average of that latter interaction. The observed line widths range between 30 and 100 Hz. Furthermore, the proton signal coming from COOH groups is absent for the three encapsulated samples, whereas it is observed around 13 ppm as a broad resonance for the bulk samples. This result suggests that for the encapsulated molecules, this proton is in chemical exchange at room temperature, possibly with the Si–OH surface groups of the silica matrix [9]. In Fig. 6, a detail of the MCM-LA ^{1}H spectrum is enlarged with the proton assignment and the corresponding $T_2'(^1\mathrm{H})$ values. $T_2'(^1\mathrm{H})$ is defined as the apparent transverse relaxation time that is measured using a solid echo sequence ($\pi/2$-τ-π-τ-acquisition with τ corresponding to an entire number of rotor cycles). In the solid state, $T_2'(^1\mathrm{H})$ is characteristic of the mobility in the sense that the longer the $T_2'(^1\mathrm{H})$, the higher the mobility. The measured long values, ranging from 13.1 to 22.8 ms, are unusual for a solid sample and are significative of the "viscous-like" behavior of the encapsulated molecules. Indeed, the $T_2'(^1\mathrm{H})$ values of bulk lauric acid are around 150 μs, whereas in solution these values can go up to several hundreds of milliseconds. More interestingly, we note an increase of the $T_2'(^1\mathrm{H})$ values, 13 ms from protons near the carboxylic head (H2, H3) up to 20 ms for protons of the alkyl chain (H4–H11), and even 23 ms for protons of the methyl end group (H12). This indicates an increase of the mobility of the protons along the *n*-alkyl chain of lauric acid.

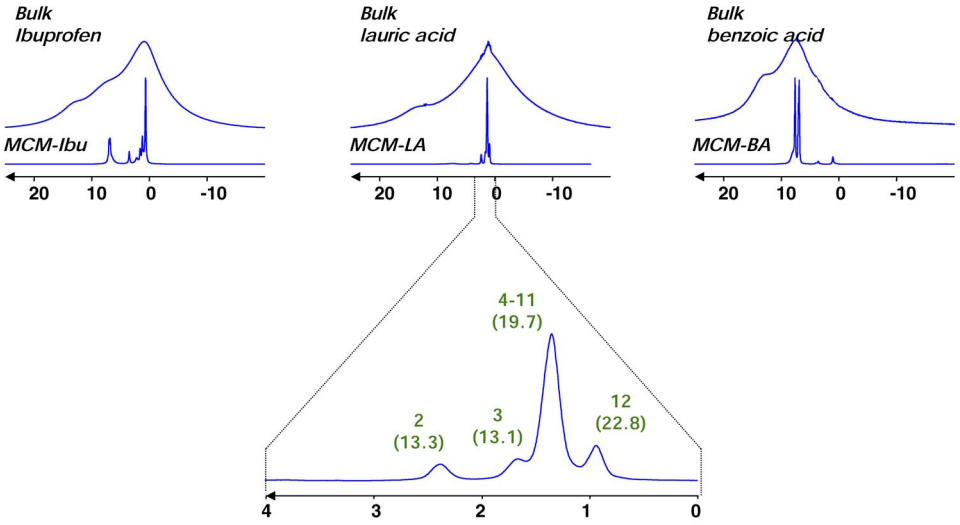

Fig. 6 ^{1}H SPE MAS spectrum of MCM-Ibu, MCM-LA, and MCM-BA and of the corresponding bulk samples (ibuprofen, lauric acid, and benzoic acid). The inset displays the expansion of the ^{1}H SPE MAS spectrum of MCM-LA with ^{1}H resonance assignment and corresponding $T_2'(^{1}H)$ values in ms.

2D solid-state NMR

In order to fully characterize encapsulated drugs, 2D ^{1}H-^{13}C NMR experiments can also be used. The long $T_2'(^{1}H)$ values allow running NMR experiments derived from solution-state NMR that require long coherences lifetimes such as {^{1}H}-^{13}C HMQC [17–19]. While the conventional 2D {^{1}H}-^{13}C HETCOR experiment based on CP transfer (*through space* magnetization transfer) is inefficient in our case, the HMQC sequence based on *through bounds* magnetization transfer using *J* couplings will be possible. This experiment needs long evolution times related to $(2 \times {}^{1}J_{CH})^{-1}$ and comprised between 3.2 ms for aromatic carbons and 4 ms for aliphatic carbons (corresponding to $^{1}J_{CH}$ = 155 and 125 Hz, respectively). These values usually cannot be used in solid-state NMR because of too short transversal relaxation times. Figure 7 displays the 2D ^{13}C-{^{1}H} MAS HMQC spectrum of MCM-Ibu where the evolution delay τ was set to 3.6 ms in order to optimize both the aliphatic and aromatic ^{13}C signals. Each ^{13}C signal correlates with one single proton peak except the quaternary carbons (C1, C4, and C9) that are not detected due to the absence of directly bonded protons. We note that the highly resolved proton dimension helps to assign unambiguously each ^{1}H and ^{13}C resonances. Such a *J couplings*-based 2D experiment is thus extremely relevant to characterize in details encapsulated molecules submitted to confinement effects in porous matrices.

The surface of the mesoporous silica can as well be investigated by solid-state NMR [20]. In particular, silanol groups (SiOH) and adsorbed water can be probed using classical 1D or 2D ^{1}H-^{29}Si CP (HETCOR) experiments. Here, we use the newly developed {^{1}H-^{29}Si}-^{1}H double-CP approach that consists in two consecutive CP transfers, from ^{1}H to ^{29}Si and then back to ^{1}H [21]. The first transfer is used to maximize the ^{29}Si magnetization (the corresponding contact time $t_{CP}1$ is usually set to 5 ms) and the second transfer, from ^{29}Si to ^{1}H, allows the investigation of ^{29}Si-^{1}H proximities by varying the corresponding contact time $t_{CP}2$. The main advantage of this technique compared to conventional 2D HETCOR experiments is a much-reduced experimental time. 2D techniques usually require an overnight acquisition, while a 1D {^{1}H-^{29}Si}-^{1}H double-CP spectrum with a good S/N ratio is usually obtained in only 20 min. Figure 8 displays the series of experiments recorded on MCM-BA with contact times $t_{CP}2$ varying from 0.1 to 15 ms. A resonance at 9.5 ppm is clearly identified for $t_{CP}2$ = 0.5 ms, and its intensity increases up to $t_{CP}2$ = 9 ms (before decreasing due to $T_1\rho$ effect). In the 1D ^{1}H MAS

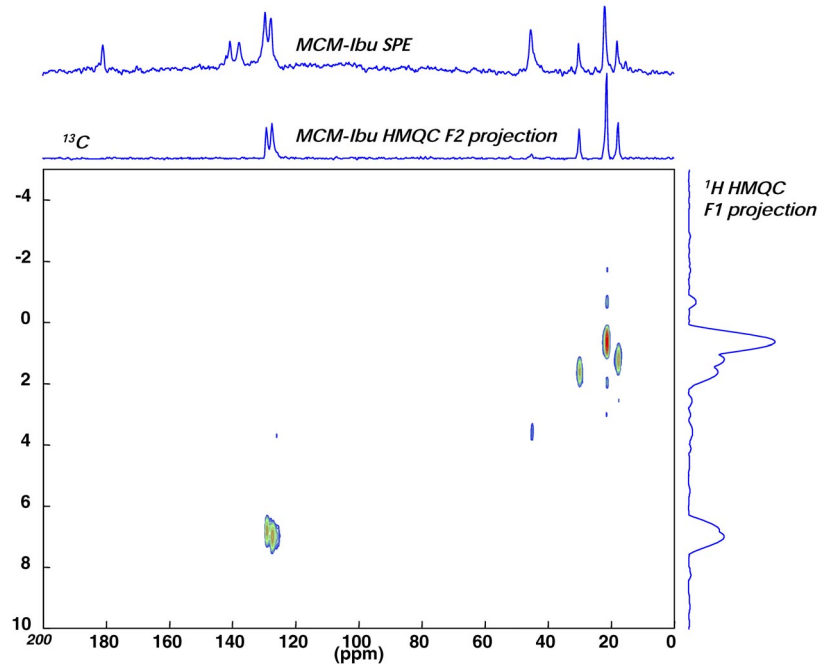

Fig. 7 ^{13}C MAS HMQC 2D spectrum of MCM-Ibu with the corresponding F1 and F2 projections. The ^{3}C SPE MAS 1D spectrum is also displayed for comparison.

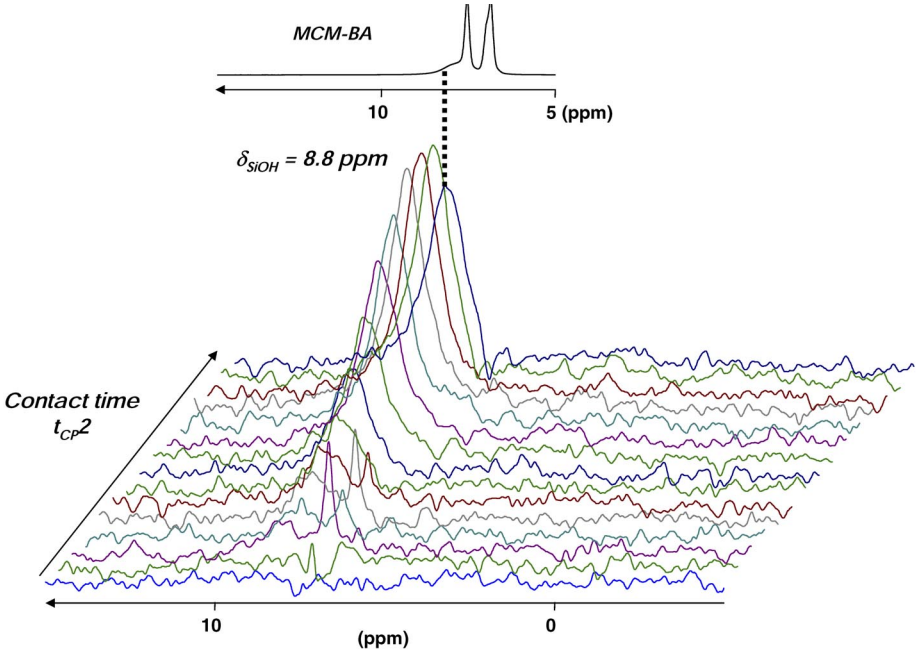

Fig. 8 {^{1}H-^{29}Si}-^{1}H MAS double CP spectra of MCM-BA recorded with $t_{CP}2$ = 0.1, 0.3, 0.5, 0.7, 1, 2, 3, 5, 7, 9, and 15 ms. ^{1}H SPE MAS spectrum is also displayed for comparison.

SPE spectrum (Fig. 8), this resonance is barely visible as a shoulder. We note the absence of any resonance from isolated silanols (between 1 and 2 ppm) as well as resonances from the encapsulated molecules due to their mobility that averages the dipolar ^{1}H-^{29}Si interaction in that case. Thus, we can conclude that the 9.5 ppm resonance is due to protons present at the surface of the silica pores such as silanols and/or adsorbed water molecules that are strongly H-bonded [22]. It is worth noting that similar {^{1}H-^{29}Si}-^{1}H double-CP responses are found for MCM-LA and MCM-Ibu for which the resulting spectra exhibit the ^{1}H resonance between 7.5 and 9.5 ppm.

To gain more insight into the possible interactions of encapsulated molecules with the silica surface, ^{1}H EXSY NMR spectra have been recorded [23]. This technique is based on ^{1}H magnetization exchange driven by ^{1}H spin diffusion process and allows the investigation of ^{1}H-^{1}H proximities by inceasing the mixing time τ (see Fig. 2). Figure 9 shows the ^{1}H EXSY NMR spectrum of MCM-LA (τ = 200 ms) with close-up on the lauric acid proton alkyl zone (between 0 and 3 ppm) and on the proton silica surface resonance around 9 ppm. We observe as expected the presence of cross-peaks between the protons of the alkyl chain evidencing intramolecular magnetization exchange. But more interestingly, we observe cross-peaks between silica surface protons and alkyl protons. Their intensity is rather low, but they are clearly detected. In particular, we see that the SiOH resonance correlates with each alkyl resonance. This result denotes a spatial proximity between the silica surface and the encapsulated lauric acid molecules.

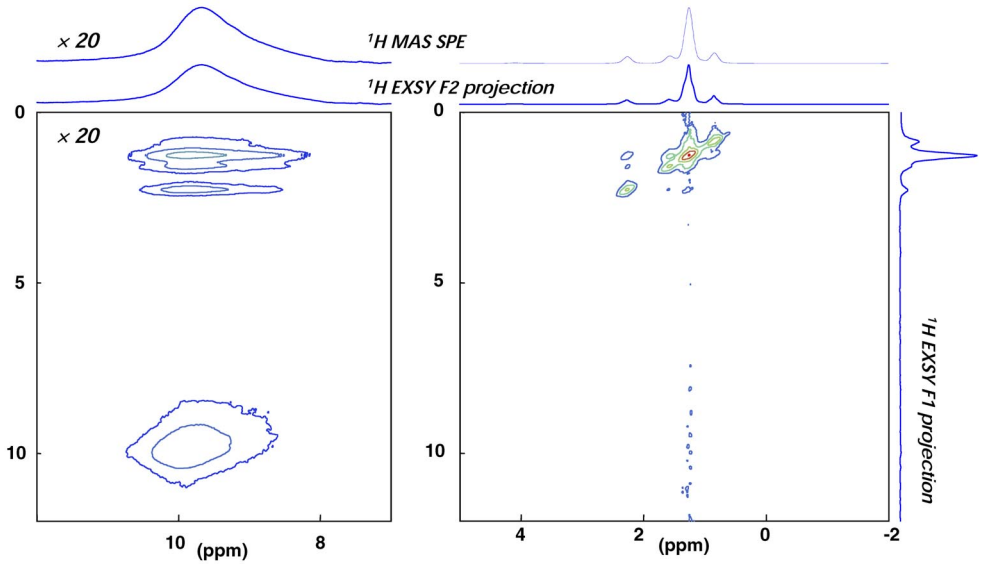

Fig. 9 ^{1}H EXSY 2D spectrum of MCM-LA with the corresponding F1 and F2 projections (τ = 200 ms). ^{1}H SPE MAS spectrum of MCM-LA is also displayed for comparison.

CONCLUSION

This contribution gave an overview of the solid-state NMR experiments that can be used to characterize drug-model molecules encapsulated in MCM-41 silica, and that can be easily extended to other confined molecules. Because of strong confinement effects, solid-state NMR sequences have to be carefully chosen to accommodate highly mobile behavior. In particular, whereas we demonstrated the poor efficiency of conventional {^{1}H}-^{13}C CP experiment to characterize these entrapped molecules, we proved the high efficiency of NMR sequences issued from solution-state NMR as ^{13}C nOe enhancement experiment or 2D {^{1}H}-^{13}C HMQC. Then, we showed that ^{1}H spin diffusion-based experiments such as EXSY could give useful information on the proximities between trapped molecules and the pore

surface. This study clearly shows that solid-state NMR can provide performing tools to investigate mesoporous silica-based drug delivery systems.

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