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Unassisted Solventless Mesopore Filling of SBA-15 with Ibuprofen: A Solid-State Study and Long-Term Characterization

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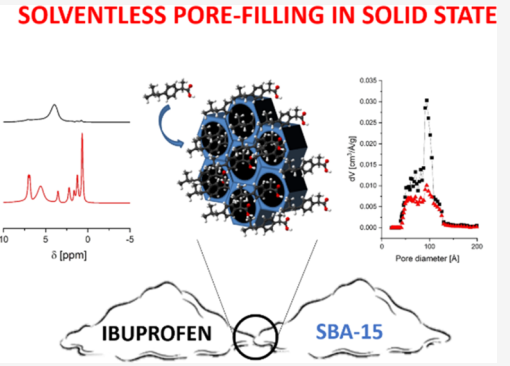
ABSTRACT: Herein, the incorporation of ibuprofen into mesopores of the SBA-15 material was observed in systems where both organic and inorganic phases were in the solid state. The filling of pores was ascribed to sublimation and adsorption in the pores. The loading of pores increased with the mixing time during the preparation of the physical mixture. Regardless of the mixing duration, after 1 month on the shelf, every sample exhibited the same porosity and intensities of ^{1}H MAS NMR spectra. Long-term studies of the physical mixture of ibuprofen and SBA-15 included X-ray diffraction (XRD), N_2 adsorption, MAS NMR, electron microscopy, and energy dispersive X-ray (EDX) characterization. The studies unequivocally showed that ibuprofen spontaneously enters the mesopores over time without any additional treatment. After 1 month, the sample resembles the reference, with the pores filled using the melting method. These results are potentially significant for every solid-state method of preparation of drug delivery systems.



INTRODUCTION

One of the most important uses of porous materials is drug delivery. Materials with high porosities are vessels for medicinally active compounds that could be released into the human body in a controlled way, ensuring a stable drug concentration. The size of the pores is essential for controlled drug delivery. It is known that micropores (less than 2 nm of pores diameter) have relatively low adsorption capacity for drug molecules, and their release is slower than in materials with larger pores.[1] On the other hand, macroporous materials have very accessible pores, but the release of the active compound is very fast.[2,3] Mesoporous materials with pores between 2 and 50 nm are a good compromise between the accessibility and kinetics of release.

The potential for the release of active compounds is also governed by interactions between the guest molecules and the surface of the pores in the host material. It is known for example that zeolites who have a charged surface (and possible extra-framework alumina species) interact so strongly with the drug molecules that not all guest molecules are released.[4] The main interactions between ibuprofen and the silica surface are thought to be hydrogen bonds between the carboxyl group of the drug and silanol groups of silica.[5]

Another factor that needs to be addressed in terms of drug release is how molecules behave when they are introduced into pores (finite-size effect).[6] Molecules in confinement behave differently from those in the bulk. They do not form crystals inside mesopores but create an amorphous state characterized by different physicochemical properties compared to crystalline materials, like a shift of phase-transition temperatures,[7−9] or even a presence of forms that are metastable in bulk.[10,11]

There are plenty of methods for loading drug molecules to mesoporous materials. The methods use solvent or solventless strategies. The summary of the methods used is presented in an excellent review.[12] When solvents are used, they have to be evacuated from this system. Moreover, the solvents' remains could increase the cytotoxicity of such drug delivery materials.[13] In the second solventless group of methods, intense treatments like ball milling or heating are used, which could deteriorate the host or the guest phase.[14] These methods are considered environmentally friendly, as they do not use possibly toxic solvents and are in compliance with the rules of green chemistry.[15]

The anomalous behavior of the physical mixtures of drug molecules and porous matrices was discovered during the examination of solventless systems. It was shown that in the mixtures of porous silica glass powder with benzoic acid, ethyl *p*-aminobenzoate, and benzophenone organic phases lose their crystallinities. For a low content of the guest phase (from 5 to 10 mass %), no diffraction peaks were observed, accompanied by a decrease in the porosity of the host. For higher

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concentrations of the drugs, the diffraction peaks were observed, but after 1 month of storage at room temperature, their crystallinities decreased. The authors claimed that organic molecules occupied pores in the amorphous phases. The transition to the amorphous phase was not observed for the mixture of organic molecules with nonporous silica beads.[16] No reflexes were recorded for a physical mixture of 5% benzoic acid and controlled porous glass.[17] Konno et al. examined the behavior of the physical mixtures of porous materials, magnesium aluminum silicate, and activated carbon with medicinal molecules, aspirin, and phenacetin. The crystallinities of such mixtures decreased with time, eventually obtaining amorphicity. The time of amorphization is a function of vapor pressure of the drug, suggesting that this phenomenon was driven by sublimation.[18] At reduced pressure, the amorphization was quicker.[18−20] Partial amorphization of indomethacin was noticed in the physical mixture of this drug with silica gels with pores from 40 to 100 Å.[21] Only the earliest works characterizing the changes in the physical mixtures of drug compounds with porous matrices examined their behavior at room temperature.[16−18] Most of them treated the physical mixtures at higher temperatures and/or reduced pressures.[19−24]

This process was further examined by Bogner et al. in a series of papers.[25−27] Driven by the previous suggestion that vapor pressure is the key feature in this phenomenon, the organic compound in the form of a powder was placed in the same chamber as the porous material without physical contact between them. Gas-driven filling of pores of the porous material with the amorphous phase of the organic material was observed. This way, the adsorption capacities were determined. Physical mixtures of solid compounds were also investigated. Mesoporous silica with 5 nm pores was physically mixed with naphthalene, 1-naphthol, 1-naphthalic acid, ibuprofen, and diflunisal and stored at 40 °C under a water-free atmosphere. The amorphization of organic molecules took place. The amorphization time differed from 1−2 days for 1-naphthol to 7−14 days for naphthalene.[25] It was proved that the amorphization time of the organic drugs in the physical mixtures with mesoporous materials is the function of vapor pressure of the drug but only when the content of the guest phase is lower than the adsorption capacity. When the content is near the maximum uptake, other properties of the guest compounds could be essential for amorphization time and filling of the pores.[26] Generally, it was proved that the vapor phase governs the amorphization of the organics in the presence of mesoporous materials. It is driven by the interplay of enthalpy and entropy of the system.[25] The adsorption capacity is higher for smaller mesopores and a higher value of enthalpy of condensation of organic compounds.[26] It was also proved that water vapor decreases the maximum uptake of naphthalene when gas-phase loading in the adsorption chamber is performed.[27] The most widely examined compound in these articles was naphthalene, as it has the highest vapor pressure.

The "amorphous" phase of ibuprofen located inside mesopores has its characteristic features. The most important is the high mobility of its molecules in confinement, which is easily seen in dielectric relaxation spectroscopy[28,29] or NMR spectroscopy.[30,31] It has been observed that ibuprofen displays very narrow lines in the ^{1}H NMR spectra and no signals in ^{13}C CP MAS NMR spectra when introduced into mesoporous silica MCM-41, suggesting a liquid-like behavior of the molecules at ambient temperature. The ^{13}C NMR spectrum with no cross-polarization showed signals characteristic of liquid ibuprofen.[32] In our previous studies, we found that water is essential for this effect to be observed. However, too much water can push ibuprofen out of the pores.[33−35]

Solventless methods have been used to introduce ibuprofen into the mesopores. The most important are melting[33,35,36] and comilling.[37] Melting is a simple method that relies on heating above the melting temperature of ibuprofen so that its molecules diffuse into mesopores. This method requires the preparation of a physical mixture of the mesoporous material (the most widely used are MCM-41 and SBA-15) with ibuprofen before heating. This step of preparation is frequently omitted in the physicochemical characterization of the samples, although it is known that organic compounds can diffuse into mesopores from a physical mixture without additional treatments (vide supra). This review aims to characterize the changes in the physical mixtures of ibuprofen and SBA-15 prepared only by simple mixing of two powders with a spatula or a simple contact between them, without any further treatment under the conditions that normally exist in the laboratory when the samples are prepared and stored (atmospheric pressure, humidity, and room temperature). The results are insightful for every mesoporous system prepared for drug delivery that uses ibuprofen.

A few features of ibuprofen will be used in this work as fingerprints of its location inside mesopores: (i) no reflexes in X-ray diffraction patterns, (ii) well-resolved signals in ^{1}H MAS NMR spectra, (iii) low signal-to-noise ratio in ^{1}H−^{13}C cross-polarization MAS NMR spectra, and (iv) specific signals in ^{13}C with proton-decoupling MAS NMR spectra similar to those obtained for the liquid phase.

EXPERIMENTAL SECTION

SBA-15 and ibuprofen were purchased from Sigma-Aldrich. SBA-15 was not dried before the procedure of mixing with ibuprofen. To obtain physical mixtures, ibuprofen and SBA-15 were placed in a plastic container and mixed with a spatula for different periods. For the evaluation of the mixing time, the mixtures of 10 and 100 mg of ibuprofen and SBA-15 were prepared. The "reference" sample was prepared in the same way, but additionally it was placed in an oven heated to 85 °C for 1 h. Long-term studies used the mixture of 100 and 1000 mg of the guest and host, respectively, mixed for 5 min with a spatula. All of the samples were stored in a laboratory in closed containers.

Solid-state NMR measurements were performed by using a Bruker Avance III spectrometer operating at 500 MHz (11.4 T). Approximately 30 mg powder samples were filled in 4 mm rotors that rotated at a speed of 10 kHz. ^{1}H MAS NMR spectra were normalized to 10 mg. ^{1}H and ^{13}C MAS NMR spectra were recorded with frequencies of 500.1 and 125.8 MHz, respectively. ^{1}H MAS NMR measurement used a single-pulse excitation with a pulse duration of 4 μs ($\pi/2$) and 10 s of recycle delay. Normally, 32 scans were recorded to obtain the spectrum. ^{13}C CP MAS spectra were obtained by recording 256 scans using 2 ms of contact time, ramped amplitude of 70−100%, and SPINAL64 for decoupling. The same decoupling scheme was used for the ^{13}C HPDEC MAS NMR method. For the latter, 410 scans were collected. ^{29}Si MAS NMR spectra were recorded at the frequency 99.37 MHz, using a $\pi/3$ pulse and a repetition time of 18s. 3584 scans were collected. For ^{29}Si CP MAS NMR spectra, different

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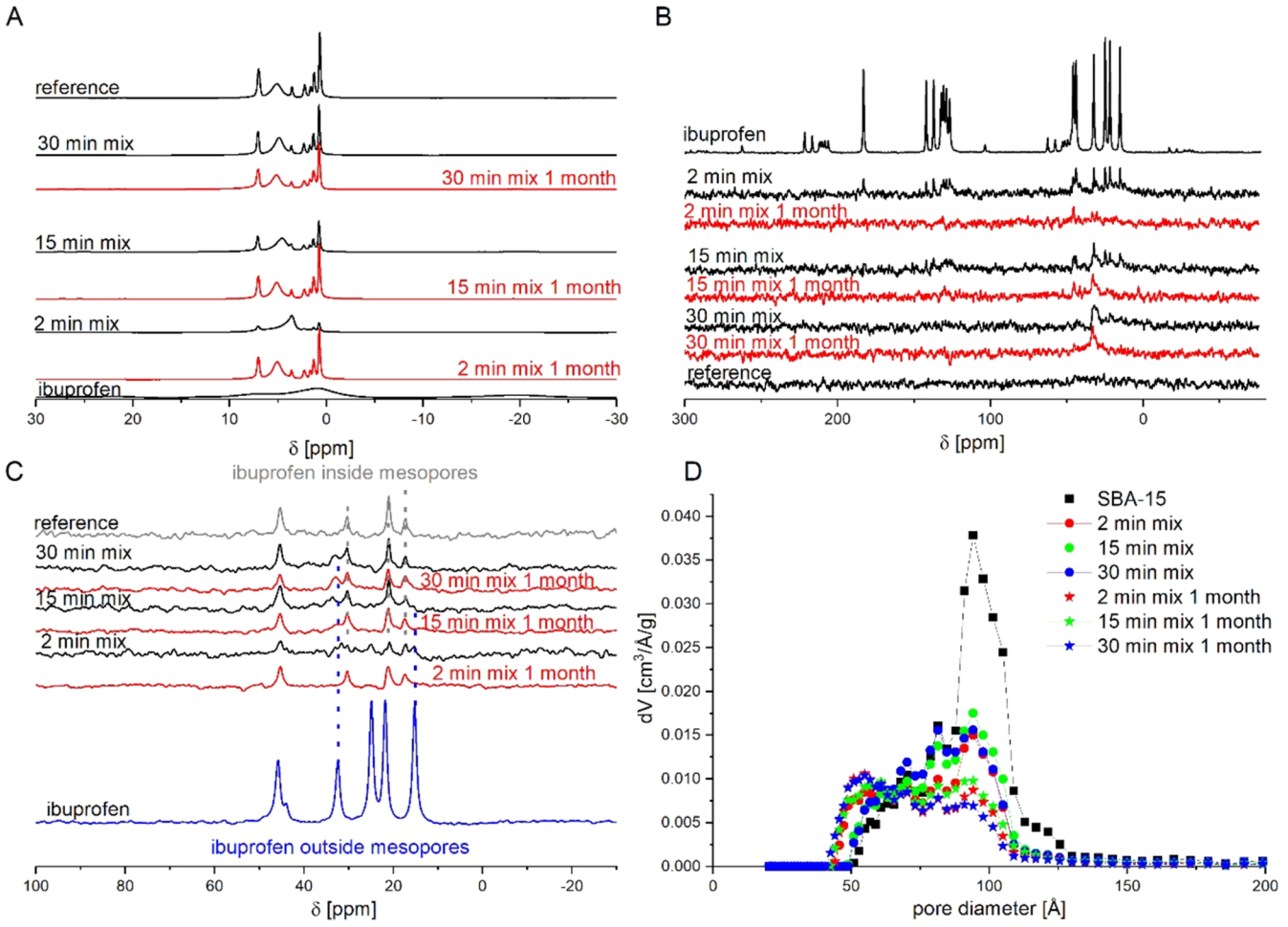

Figure 1. (A) ^{1}H, (B) ^{13}C CP, and (C) ^{13}C HPDEC MAS NMR spectra and (D) DFT pore size distribution from N_2 adsorption of the samples with different mixing times (2−30 min) shortly after the preparation and after 1 month on the shelf. The naming convention is explained in the text.

contact times from 300 to 8000 μs were used. ^{1}H−^{29}Si HETCOR was performed by the frequency-switched Lee Holdburg heteronuclear correlation (FSLG HETCOR) experiment with 4000 μs of contact time.

A Quantachrome AUTOSORB-1 device was used to determine the specific surface area and porosity (total pore volume and distribution of pore size) by analyzing gas sorption and liquid vapor. The measurement was carried out by adsorption of nitrogen at a temperature of liquid nitrogen. Before the measurement, each sample was activated for 18 h at room temperature in a vacuum. Pore size distributions were calculated by using the DFT method.

The morphology and chemical composition of the samples were investigated by means of a JEOL JSM-7500F field emission scanning electron microscope equipped with a retractable backscattered electron detector (RBEI) and an energy-dispersive spectroscopy (EDS) detector of characteristic X-ray radiation AZtec Live for the EDS system. The element (elemental) mapping analysis was carried out to obtain a two-dimensional distribution of the element in the micro areas of the samples.

RESULTS AND DISCUSSION

Physical Mixing as the Method of Introducing Ibuprofen to Mesopores. Figure 1A shows the ^{1}H MAS NMR spectra of crystalline ibuprofen (bulk) and the sample with ibuprofen introduced into mesopores (confined) using the melting method (named "reference"). The comparison of those spectra shows how remarkably they change after transporting ibuprofen into mesopores. High mobility makes the signals very narrow and the spectra well-resolved. Also, other NMR fingerprints of ibuprofen located inside mesopores are true for the "reference" sample: no signal in the ^{13}C CP MAS spectrum (Figure 1B), lower number, and specific chemical shifts of signals in ^{13}C HPDEC MAS NMR spectrum (Figure 1C), all in comparison to bulk ibuprofen.

Mixing two powders with a spatula for different periods changed the recorded ^{1}H spectra (Figure 1A). With an increase of the mixing time, the spectra are more resolved, with narrower signals and higher intensities that resemble the reference sample. This suggests that with the mixing time, the amount of ibuprofen localized inside mesopores increases as well. ^{13}C MAS NMR spectra support this hypothesis that the intensities of the peaks decrease for ^{13}C CP MAS NMR spectra (Figure 1B) with the mixing time. ^{13}C HPDEC signals from confined ibuprofen are more pronounced for samples mixed for a longer time (Figure 1C). Especially, the sample mixed for 2 min has detectable signals from both crystalline and confined ibuprofen. Nitrogen adsorption results show a pronounced decrease in the specific surface areas of all of the samples under

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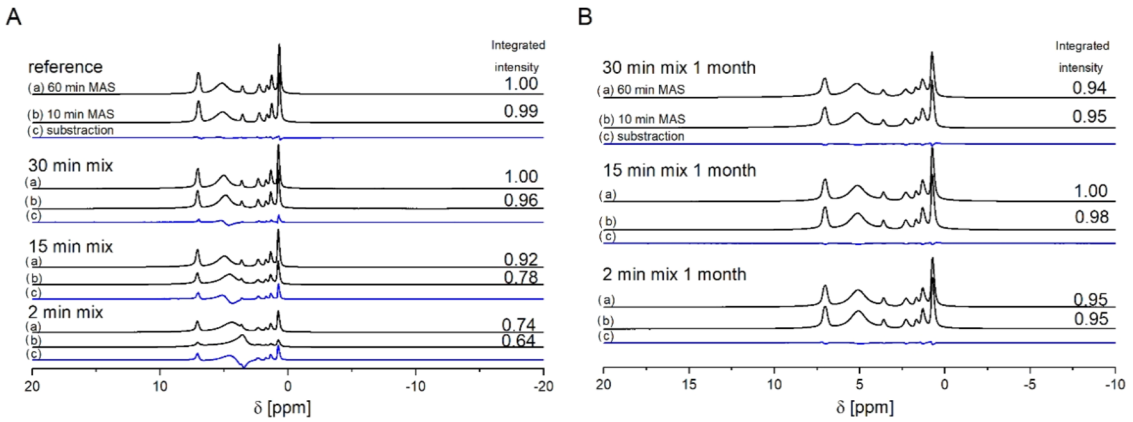

Figure 2. ^{1}H MAS NMR spectra of the reference and samples mixed for 2, 15, and 30 min after 10 min of constant rotation (a) and 60 min of rotation (b) recorded shortly after the preparation (A) and after 1 month (B). In blue (c), the subtraction between (a, b) is plotted.

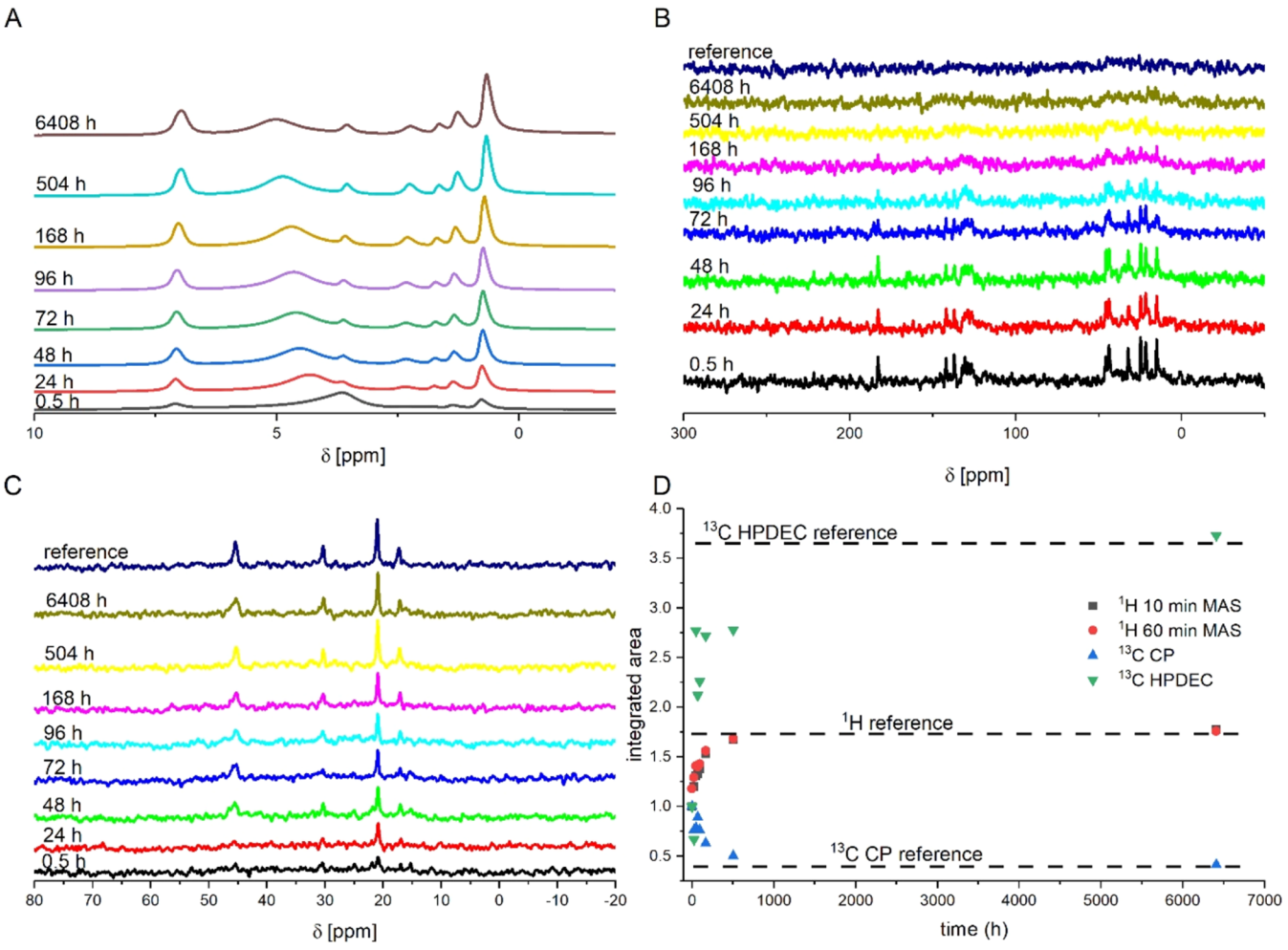

Figure 3. ^{1}H (A), ^{13}C CP (B), and ^{13}C HPDEC (C) MAS NMR spectra of the reference and samples after different times of shelf life. The integrated intensities of all of the spectra vs time are given in (D).

study in comparison to pure SBA-15, from 550 m^2/g to ca. 340 m^2/g (Table S1). There are no distinct differences between the mixed samples in pore size distributions, but it is clear that the volume of 94 Å pores diminished significantly in comparison to an empty SBA-15 sample (Figure 1D). From all these results, we can say that a simple physical mixing is sufficient enough to transport ibuprofen into mesopores. What is more, we also checked the impact of the rotation on the ^{1}H MAS NMR spectra. After 1 h of the MAS experiment and constant rotation at 10 kHz speed, the ^{1}H MAS NMR spectra of samples mixed for short times changed (Figure 2). The samples were compared using integrated intensities referenced to the reference sample. The spectrum of the sample mixed for 30 min exhibits the same line shape and intensity as the reference, and it hardly changes after rotation. Samples mixed for 2 and 15 min changed after rotation, got more resolved with

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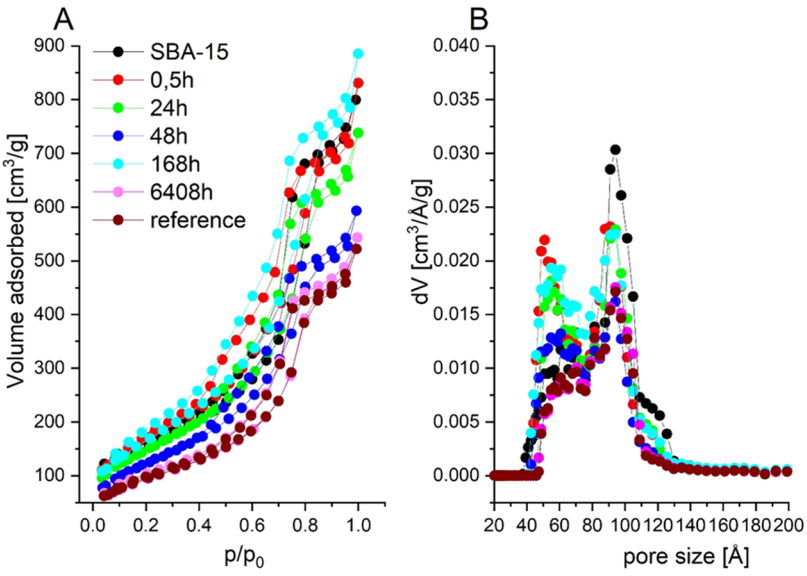

Figure 4. N_2 adsorption−desorption curves (A) and DFT pore size distributions (B) of the samples under study.

narrower signals, and their intensities increased. It proves that the rotation itself also transports ibuprofen into mesopores. That is why parts of the samples that were not used in solid-state NMR experiments were taken for characterization for other methods.

After 1 month of resting on the shelf, the samples were characterized again. ^{1}H MAS NMR spectra of all of the samples looked almost identical. Figure 1A shows the ^{1}H MAS NMR spectra of these samples (red lines). No matter how long the sample was mixed, the ^{1}H spectra looked almost exactly the same after 1 month. The integrated intensities are also almost the same for all of the samples, and they do not change after 60 min of rotation (Figure 2B). ^{13}C CP and HPDEC spectra also changed after 1 month. Signals in ^{13}C CP MAS NMR spectra diminish (Figure 1B) and signals from confined ibuprofen in ^{13}C HPDEC MAS NMR spectra increase, which is especially pronounced for the sample mixed for 2 min (Figure 1C). The porosity of these samples also changed, showing in every sample a lower specific surface area and a lower volume of mesopores in pore size distributions compared to the samples measured right after mixing (Figure 1D and Table S1). The pores filled with the introduced species have a diameter reduced by 50% (around 5 nm) and are beginning to dominate in the pore distribution.

This experiment showed that physical mixing can introduce ibuprofen into mesopores, but it is more than that. Samples changed after being left to rest for 1 month in closed containers on the shelf. When the sample mixed for 2 min with an initially limited amount of ibuprofen located inside mesopores was characterized after 1 month, it resembled the sample that was mixed for 30 min. Ibuprofen in the physical mixture migrates toward mesopores without any help of mixing or other techniques. To examine that, further experiments performed over a long period were conducted.

Long-Term Studies of Ibuprofen Filling of Mesopores. For the long-term studies, 1 g of SBA-15 was mixed with 0.1 g of ibuprofen for 5 min. After that, the mixture remained untouched in a closed container on the shelf. A series of experiments, including solid-state NMR, XRD, and N_2 BET, were performed using a small amount of the sample taken each time from this parent mixture. The aim of this experiment was to monitor changes in the physical mixture with time. The experiment was conducted for 9 months.

Figure 3 shows the ^{1}H, ^{13}C CP, and ^{13}C HPDEC MAS NMR spectra of the sample during shelf life. The line widths of ^{1}H NMR signals get smaller, the overall intensity of the spectra increases, the intensities of ^{13}C CP signals decrease, and the intensities of ^{13}C HPDEC signals increase. All of the integrated intensities are summarized in Figure 3D. The observed intensities of ^{1}H and ^{13}C MAS NMR spectra of the sample after 6408 h of shelf life are almost identical to the reference sample, i.e., SBA-15 sample with ibuprofen located inside mesopores by the thermal treatment. The influence of long rotation was also checked. Figure S1 in the Supporting Information shows the zoom-in image of the integrated areas vs time for the samples spun for 10 and 60 min. There is an increase in the integrated areas of the spectra after prolonged spinning. However, this impact is most pronounced for the samples with short shelf life. After ca. 600 h, by the time the intensity of the spectrum achieves the intensity of the reference sample, the intensity of the ^{1}H MAS NMR spectrum does not change with the rotation. In essence, we can say that NMR spectroscopy shows that ibuprofen is located inside mesopores after 9 months of shelf life.

The filling of mesopores is evidenced in the N_2 adsorption data (Table S1). During 9 months of shelf life, the specific surface area decreases from 620 to 352 m^2/g. Figure 4 shows the N_2 isotherms and pore size distribution of the samples. All of the samples have hysteresis loops with the shape characteristics for SBA-15 material (H1 type),[38] although the sample after 0.5 h exhibits a characteristic increase in the hysteresis loop in the range 0.4 to 0.6 p/p_0, which resembles hysteresis loop type H5 due to blocked mesopores[39] (Figure S2 in the Supporting Information). The parent SBA-15 sample has only 1 maximum pore size at 94 Å in the pore size distribution. After mixing with ibuprofen, another maximum arises at 51 Å. It represents partially filled pores or blocked mesopores (vide infra). The volumes of both generations of pores diminish with time. After 9 months, the volume of the pores near 100 Å is 2 times lower than that in the parent sample. The maximum at ca. 50 Å is not present anymore; only a broad distribution starting from 50 Å and overlapping the

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100 Å maximum is present. The pore size distribution of the sample after 9 months is essentially the same as the reference sample obtained by the melting of ibuprofen. All of the other porosimetric data are comparable between those samples. It means that ibuprofen filled all of the available pores of the material during this time.

One of the characteristics of the "confinement effect" of ibuprofen in mesopores is that it does not form crystals. Therefore, there are no reflections from the confined drug. Figure 5 shows XRD patterns of pure crystalline ibuprofen and

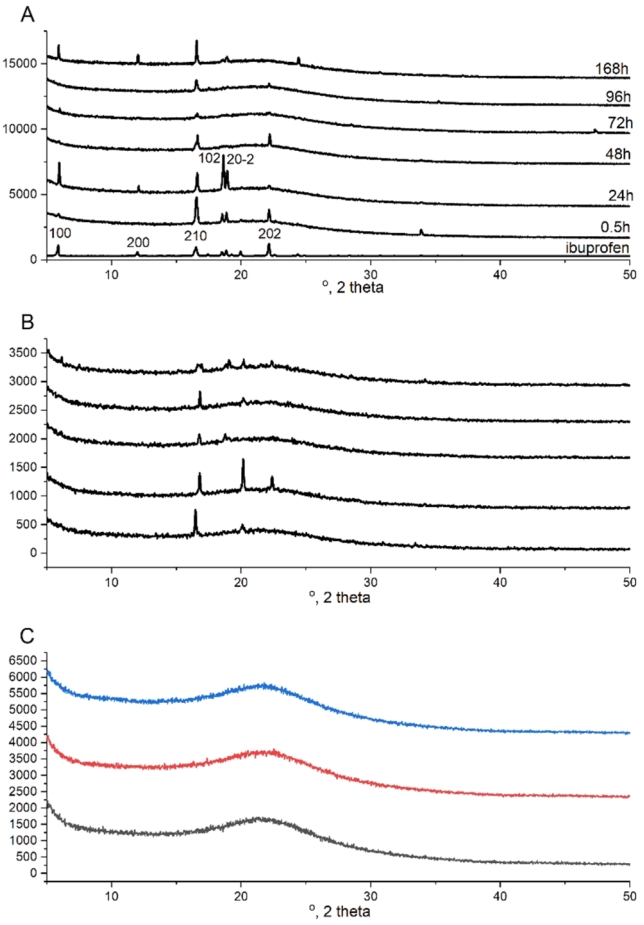

Figure 5. XRD diffractograms of the samples under study (A), 5 diffractograms recorded from 5 different parts of the sample after 48 h (B), and 3 diffractograms from different parts of the sample for the 6408 h sample (C).

its mixture with SBA-15 material measured at different times after the preparation. Every sample has a lower number of reflections in reference to the crystalline acid, but there is no correlation between the number of reflections and the time of the "shelf life" of the sample. For example, there is only 1 reflection at 16.5° (2 theta) in the sample after 72 h, but 5 peaks in the sample after 168 h. What is more, different peaks are present in the diffraction patterns of different samples, for example, reflections at 18.6 and 18.9° (2 theta) are very intense in the diffraction pattern of the sample after 24 h while not visible at all in samples after 48, 72, and 96 h. The only peak visible in all of the diffraction patterns is 16.6° (2 theta). It is also one of the most intense reflections in pure ibuprofen. It represents Miller indices 2 1 0 (as compared with the ICDD PDF 00-034-1728). This could indicate that ibuprofen crystals expose this surface when interacting with SBA-15 material.

The lack of correlation between the intensities or the number of reflections and the shelf life of the samples is the reason for examining the XRD homogeneity of the samples. The XRD patterns also changed when the same sample (on the same day after the mixing time) was measured 5 times from 5 different parts of the bulk sample. Figure 5B shows XRD patterns from the same sample (48 h). Every XRD pattern shows different reflections. This may indicate that the configuration of ibuprofen in the SBA pores changes over time and that this is a very dynamic process until there is balanced accommodation in the carrier channel. It is also likely that a simple mixing of two powders for 5 min is not enough to produce a homogeneous mixture, which is also (still) true for the sample after 48 h upon mixing. When crystalline ibuprofen is present in the sample, reflection peaks are present in the XRD patterns as well. The concentration of ibuprofen in the physical mixture is different in different parts of the sample and/or crystals obtained with different orientations toward the X-ray beam, in the mixture, therefore generating different XRD peaks. Such "heterogeneity" of the samples could also explain the higher porosity of the sample after 168 h in reference to other samples. This deviation could be due to the heterogeneity of the physical mixture. It may also indicate that status quo has not been achieved.

Nonetheless, after 9 months (6408 h), there are no diffraction peaks in the physical mixture. We measured 3 different parts of the sample, every time obtaining no diffraction peaks (Figure 5C). It means that after this time there are no crystalline ibuprofen in the sample detectable with the XRD method.

The penetration of SBA-15 by ibuprofen is evidenced by SEM−EDX mapping (Figure 6). The physical mixture right after mixing shows a clear distinction between inorganic (SBA-15) and organic (ibuprofen) parts of the mixture. Carbon is detected in parts of the sample, where silica is not present (Figure 6A−C). The sample after 6408 h of shelf life shows that carbon is spread evenly on different parts of the mixture, even on the SBA-15 particles (Figure 6D−F). That is yet another evidence of the migration of ibuprofen inside the voids of mesoporous material or on the outer surface of the particles.

Such an unassisted migration of organic molecules inside pores of SBA-15 does not change the characteristic features of the host material. Figure S3 shows low-angle XRD patterns of the pristine SBA-15 and the 6408 h sample with ibuprofen. The position of the reflections is not changed, indicating that the hexagonal structure of this type of material is preserved. However, the intensities of the reflections are diminished. This was already noticed in the samples with ibuprofen introduced into pores by using the melting method. The reflections regained intensities after the calcination of ibuprofen.[33] It could be another indication of pore filling with ibuprofen in the examined samples and covering the available external surface only with a monolayer, especially since the grain sizes and fwhm values of 001 reflections did not change after incorporation of ibuprofen. Figure S4 shows no changes in ^{29}Si MAS NMR spectra of SBA-15 without and with ibuprofen (6408 h). Signals from silica without (Q4 at −110 ppm) or with (Q3 at −101 ppm) protons in the near environment of silica atoms are present at the same chemical shifts for both samples.

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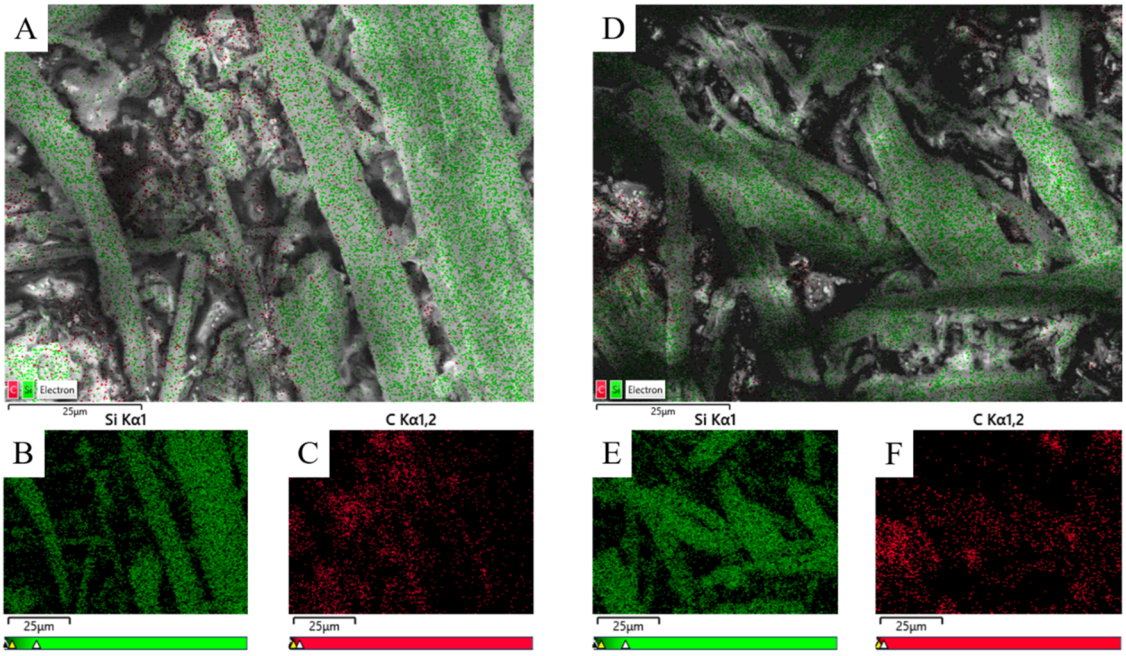

Figure 6. SEM images (A, D) and elemental mapping (B, C, E, F) of the sample shortly after mixing (A–C) and after 6408 h of preparation (D–F). Elemental mapping is shown as green dots (silica) and red dots (carbon) in SEM images (A, D).

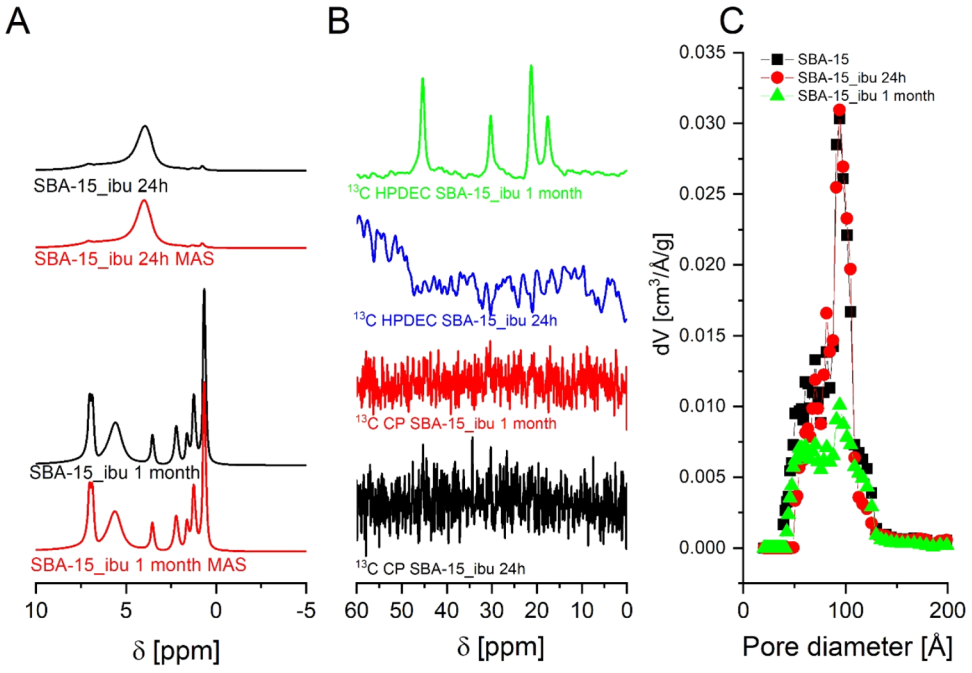

Figure 7. (A) ^{1}H MAS NMR and (B) ^{13}C MAS NMR spectra and (C) DFT pore size distributions of the SBA-15 disc after contact with ibuprofen powder for 24 h (SBA-15_ibu 24h) and 1 month (SBA-15_ibu 1 month) and after 60 min of constant rotation after contact for 24 h or 1 month (SBA-15_ibu 24h MAS and SBA-15_ibu 1 month MAS, respectively).

Transport of Ibuprofen Molecules inside Mesopores without Mixing or Rotation. Up to this point, we proved that ibuprofen molecules diffuse into mesopores during physical mixing. Two powder materials were mixed for a short time to prepare the physical mixture, so there was an "external driving force" that could transport ibuprofen into mesopores. Indeed, ibuprofen also flows into mesopores by the rotation inside a rotor, giving an undoubtedly different ^{1}H spectrum after 60 min of rotation. This treatment is much more intense than physical mixing by the spatula but suggests that this kind of procedure can facilitate the filling of pores with ibuprofen.

It was also proved that in the same physical mixtures, ibuprofen molecules diffuse without any external force during the "shelf life" to mesopores. To fully verify, if this phenomenon is "spontaneous", the experiments with no physical mixing were performed.

Self-supporting disks were formed from SBA-15. Then, ibuprofen powder was loosely placed on the top of the discs. After 24 h or 1 month, the disc was cleaned of the organic

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powder and characterized. By this, only ibuprofen molecules that diffused into the SBA-15 pores are visible in NMR spectroscopy. Figure 7 shows ^{1}H, ^{13}C CP, and ^{13}C HPDEC MAS NMR spectra of such samples after 24 h and 1 month of contact between ibuprofen and SBA-15 discs. The difference in the ^{1}H MAS NMR spectra is remarkable. For the sample after 24 h of contact (denoted as SBA-15_ibu 24h), there are only traces of ibuprofen in the sample. ^{1}H MAS NMR spectrum does not change after 1 h of constant rotation (the sample SBA-15_ibu 24h MAS). The sample after 1 month of contact (SBA-15_ibu 1 month) exhibits characteristic, intense signals from confined ibuprofen, which do not change after constant rotation for 60 min (SBA-15_ibu 1 month MAS). There are no signals in ^{13}C spectra for the sample after 24 h, while for the sample SBA-15_ibu 1 month, these spectra show characteristic signals for ^{13}C HPDEC and no signals for ^{13}C CP MAS NMR spectra. N_2 adsorption proves as well that the mesopores are filled after 1 month: the specific surface area drops to 247 m^2/g, and the volume of 94 Å pores decreases drastically after 1 month of contact (Figure 7C). For the sample with a short contact time, the porosity is hardly changed.

Sublimation and Hydrogen Interactions as Driving Forces for Filling of Mesopores with Ibuprofen. The filling of pores of a porous material when mixed with the organic phase was ascribed to a two-step mechanism: sublimation and adsorption onto the surface of the sorbent from the vapor phase.[25] Sublimation of most organic pharmaceutical compounds is not a fast process, but in many cases, the vapor pressure is not negligible, even at room temperature and atmospheric pressure. Konno et al. showed a linear correlation between vapor pressure and the time of amorphization (the time after which the organic material loses its long-range order and therefore resides in pores where it does not form crystals) of benzoic acid-like compounds mixed with porous activated carbon.[18] Later, Bogner et al. showed that it is not always true: the direct connection between vapor pressure and the time of amorphization is valid only for the systems where the amount of organic phase is much below the maximum uptake in the porous medium.[26] Near the maximum uptake, the amorphization time is shorter than its vapor pressure would suggest. For example, the amorphization time of ibuprofen in the mixture with mesoporous silica was 5 weeks and naphthalene was 2 weeks, although their vapor pressures are 1.7×10^{-2} Pa and 45 Pa at the temperature of 40 °C (so the temperature of the experiment), respectively.[25] The fast amorphization of ibuprofen was ascribed to a closer contact between the drug and porous material in the physical mixture. There is a shorter diffusion path for the molecules to travel before adsorption on the silica surface, or even the adsorption could take place without the gas phase, but directly from the solid state.[25]

Probably, for practical reasons (to obtain experimental results in a reasonable time), most of the studies focused on *amorphization* of ibuprofen in the presence of porous material and used heating of this system to a temperature higher than room temperature. For example, Bogner and Qian used 40 °C and a water-free environment. At this temperature, the vapor pressure of ibuprofen is 1.7×10^{-2} Pa.[25]

Our experiments go further and show that at room temperature where the vapor pressure of ibuprofen at 25 °C seems almost negligible (1.2×10^{-3} Pa (9×10^{-6} mmHg)[40]), ibuprofen still penetrates the mesopores of SBA-15 with time and forms layers of amorphous, mobile phase in the pores. The kinetics of this process is not fast; after 1 month, the mixture resembles the reference sample, but it is still significant. It is accelerated by direct contact with the porous SBA-15. It is very important to obtain a homogeneous physical mixture of ibuprofen and SBA-15. If the powders are mixed for a long time (e.g., 30 min), the ibuprofen is distributed evenly in the mixture; therefore, the formation of an amorphous, mobile phase in large quantities inside pores is almost instant. The samples mixed for shorter times needed more time to obtain a comparable amount of ibuprofen inside pores, but after 1 month NMR fingerprints of ibuprofen located inside pores evidenced comparable amounts of organics inside pores (Figure 1).

One month is a crucial time, after which a relatively high amount of ibuprofen filled the pores, even in the samples with initially not homogeneous mixtures or in samples where the contact between silica and ibuprofen is limited to the surface of the SBA-15 disc. This time is comparable to what was obtained for the mixture of porous silica and ibuprofen in a 2:1 ratio.[25] For the lower content of ibuprofen (7:1 ratio), a shorter *amorphization time* of 3 days was obtained.[26]

The intermolecular forces between ibuprofen and the surface of pores in the SBA-15 material are crucial to establishing the reason for ibuprofen adsorption in the pores from the vapor phase. There is a general agreement in the literature that hydrogen bonds are the main interaction in this system.[5] Only a few reports take into account that water molecules are also present in this system,[41,42] which is true, especially in our case where no other solvent or no increased temperature needed for dehydration is provided (the water content in pristine SBA-15 was 2.7%, as measured by thermogravimetry). The intermolecular interactions between mesoporous silica, ibuprofen, and water molecules were computationally examined by Tielens et al.[41] It was proved that it is more likely for ibuprofen to adsorb onto a nonhydrated bare silica surface ($dE_{ads} = -0.95$) than to form dimers ($dE_{ads} = -0.86$). This is true for adsorption at −273.15 °C (0 K). At higher temperatures (27 °C), molecular dynamics show that ibuprofen detaches from the surface of silica.

The impact of the presence of water in the silica−ibuprofen system was calculated as well. Water molecules very likely adsorb onto silica surfaces ($E_{ads} = -0.67$) and do not desorb even at 27 °C. On microsolvated silica surfaces, ibuprofen molecules adsorb less likely than on bare silica surfaces at −273.15 °C ($E_{ads} = -0.38$). Molecular dynamics show a significant difference in the behavior of ibuprofen molecules adsorbed at microsolvated surface in comparison to bare silica surface at 27 °C. Ibuprofen molecules at this temperature do not desorb immediately. They stay close to the microsolvated surface longer (t = 0.3 ps) than to the nonsolvated surface (femtoseconds). There is a higher number of hydrogen bonds between ibuprofen and water molecules adsorbed onto silica surfaces than between ibuprofen and bare silica. Water molecules are called an adhesive layer between organic molecules and the silica surface. Such interactions between the solvated silica surface and ibuprofen molecules could be the driving force for the adsorption of ibuprofen inside the pores of SBA-15.

We have to remember that ibuprofen molecules experience a confinement effect when located inside mesopores. They have high mobility. Water is essential for this phenomenon to be present.[33,42] Given the mentioned interactions between ibuprofen and the microsolvated surface, it is predicted that

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a series of adsorption and desorption of mobile ibuprofen molecules is taking place inside a pore.[41] High mobility of ibuprofen molecules inside the pores of SBA-15 is visible in ^{1}H MAS NMR spectra (vide supra) and also in ^{29}Si CP MAS NMR spectra, which are depicted in Figure S5A. The intensity of such a signal is visibly decreased for the sample with ibuprofen inside, even though this organic molecule has many protons that could be engaged in the polarization transfer. This is not the case because of the high mobility of introduced organics. The intensities of ^{29}Si CP MAS NMR signals are decreased in comparison to pristine SBA-15, regardless of how long the contact time was used (Figure S5B). ^{1}H−^{29}Si HETCOR MAS NMR of the sample with ibuprofen shows only the correlation between the water signal and the Q3 signal, which is further evidence that mobile ibuprofen is not visible by this technique (Figure S6).

This section explains a possible mechanism of the filling of pores of SBA-15 with ibuprofen molecules. At first, ibuprofen molecules sublime and penetrate the porous structure of SBA-15. Then, it adsorbs onto the pores of mesoporous material, which is driven by the intermolecular interactions (hydrogen bonds) with the solvated surface of the pore. At the same time, ibuprofen molecules achieve a state of high mobility inside pores.

CONCLUSIONS

This study proves that ibuprofen spontaneously fills the pores upon contact with mesoporous SBA-15 material. The mechanism relies on sublimation and adsorption of the substrate. Simple physical mixing is sufficient enough to transport ibuprofen to mesopores, especially when the mixing lasts more than 15 min. It produces a homogeneous physical mixture with extensive surface contact between the porous material and ibuprofen that facilitates the filling of pores. The rotation inside the NMR magnet also transports ibuprofen into mesopores. Long-term studies show that the drug molecules diffuse into cavities with time, which was evident for the physical mixture and the SBA-15 disc. One month (ca. 600 h) is the time after the mixing when the mixture resembles the reference sample obtained by the melting method. These results show that ibuprofen diffuses on its own to mesopores without any additional treatment. The physical mixtures frequently used as the starting points for different preparation methods change with time; therefore, spontaneous filling of pores should be taken into account in these systems. Further studies will be performed to examine the adsorption kinetics of filling ibuprofen into the SBA-15 discs.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.jpcc.4c06734.

N_2 sorption results; integrated areas of ^{1}H MAS NMR signals vs time for samples after spinning; nitrogen adsorption−desorption isotherms showing blocked mesopores; low-angle XRD diffractograms; ^{29}Si MAS NMR spectra; and the ^{1}H−^{29}Si HETCOR spectrum (PDF)

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Notes

The authors declare no competing financial interest.

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