MCM-41 Organic Modification as Drug Delivery Rate Regulator

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Received May 27, 2002. Revised Manuscript Received September 24, 2002

Organic modification with aminopropyl group of two MCM-41 materials having different pore sizes (obtained from trimethylalkylammonium surfactants with different chain sizes (16 and 12 carbon atoms)) has been carried out in order to control the delivery rate of ibuprofen from the siliceous matrix. This functionalization was performed by two different methods: the as-synthesized MCM-41 sample was treated with aminopropyltrimethoxysilane (method *a*), and the MCM-41 was first calcined and then funtionalized by reaction with aminopropyltrimethoxysilane (method *b*). The amount of ibuprofen adsorbed from hexane solution is lower for the C12 derived materials. A slower delivery rate has been observed for method *b*, whereas a minor influence of the pore size on the delivery rate has been found.

Introduction

Ordered mesoporous materials are the object of an increasing number of studies diving to expand their potential application in fields comprising catalysis, adsorption/separation, and sensing.[1−3] The presence of pores of uniform size lined with silanol groups confers these materials potential interest as host of a variety of guest chemical species, such as organic molecules, semiconductor clusters, and polymers.[4] As an example, we have reported recently a new application of MCM-41 as a drug delivery system.[5] Ibuprofen has been shown to readily adsorb from an *n*-hexane solution into the porous matrix of MCM-41, and to slowly release into a solution simulating physiological fluid. Furthermore, it has been found that in this host/guest system there is a strong interaction between the silanol groups and the carboxylic acid of the ibuprofen molecule.

Having proven the feasibility of this system for drug retention and delivery, further effort should be made in gaining control of the amount of drug delivered, and, even more important, its release rate. It can be thought that this delivery rate could be modulated by modifying the interaction between the confined molecule and the MCM-41 matrix. This objective could be achieved by functionalization of the pore wall. As the ibuprofen contains one acid group, it is expected the host/guest interaction could be strengthened if basic groups are present in the pore wall.

Regarding the eventual influence of pore size on the delivery rate, no differences have been observed in the release profile of ibuprofen from MCM-41 extracted matrixes obtained from surfactants with 16 and 12 carbon atoms.[5] However, taking into account that in this case samples were calcined, and that the functionalization of the pore surface will decrease the pore size, it would be interesting to study how the reduction of the pore size of the C12-derived material would affect the delivery rate of ibuprofen.

To explore the validity of this strategy, samples of MCM-41 obtained from two different length chains of surfactant (16 and 12 carbon atoms) have been functionalized with aminopropyl groups, and the resulting hybrid materials have been used as matrixes for the controlled delivery of ibuprofen.

Two different functionalization methods have been used: modification of calcined materials and one-step anchoring of aminopropyl through template displacement, a method reported recently by Antochshuk and Jaroniec.[6] This method is claimed to produce high bonding density of silanes.

Experimental Section

MCM-41$_{16}$ and MCM-41$_{12}$ (with surfactant of 16 and 12 atoms of carbon, respectively) were synthesized as previously reported[5] from gels containing hexadecyltrimethylammonium (C16) and dodecyltrimethylammonium (C12) cations respectively, and the surfactants were removed by calcination (1 h at 550 °C under nitrogen, followed by 3 h in air). Pore wall modification was carried out by two different methods. Method *a* (reflux)[6] consists of the reaction between the as-synthesized MCM-41 materials before calcination (1 g) and the 3-aminopropyl-triethoxysilane (AP-TES, 50 mL) under reflux for 10 h, after which the suspension was filtered, and washed with hexane and ethanol, obtaining both the aminopropyl-modified MCM-41$_{16}$ and MCM-41$_{12}$, named MCM-41$_{16a}$ and MCM-41$_{12a}$, respectively. On the other hand, MCM-41$_{16b}$ and MCM-41$_{12b}$ were synthesized by reaction of calcined MCM-41 (1 g) and AP-TES (5 meq) in 10 mL of toluene under reflux and N_2 atmosphere (method *b*, calcination), and were washed with a mixture CH_2Cl_2/Et_2O (1:1). The as-obtained materials were

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(1) Corma, A. *Chem. Rev.* **1997**, *97*, 2373.
(2) Brunel, D. *Micropor. Mesopor. Mater.* **1999**, *27*, 329.
(3) Ying, J. Y.; Mehnert, C. P.; Wong, M. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 56.
(4) Moller, K.; Bein, T. *Chem. Mater.* **1998**, *10*, 2950.
(5) Vallet-Regi, M.; Rámila, A.; del Real, R. P.; Pérez-Pariente, J. *Chem. Mater.* **2001**, *13*, 308.
(6) Antochshuk, V.; Jaroniec, M. *Chem. Mater.* **2000**, *12*, 2496.

10.1021/cm021217q CCC: $25.00
Published on Web 12/21/2002

Table 1. Structural and Chemical Data for Mesoporous Materials

	D_p (nm)	S_{BET} (m^2/g)	V_p (cm^3/g)	a_0 (nm)	wt %N	IBU (mg)[c]
$MCM\text{-}41_{16}$	2.5	1157	0.98	4.42[a]		102
$MCM\text{-}41_{16a}$	2.2	793	0.65	4.47	2.9	100
$MCM\text{-}41_{16b}$	1.7	781	0.38	4.48	2.5	81
$MCM\text{-}41_{12}$	1.9	1099	0.84	3.84[b]		70
$MCM\text{-}41_{12a}$	1.7	865	0.50	4.14	2.6	70
$MCM\text{-}41_{12b}$	1.2	610	0.30	3.78	2.2	40

[a] Value of a_0 for the as-synthesized MCM-41A: 4.77 nm. [b] Value of a_0 for the as-synthesized MCM-41B: 4.07 nm. [c] Referred to 300-mg disks of each MCM-41.

conformed as 0.3-g disks by uniaxial (2.75 MPa) and isostatic pressure (3 MPa).

Ibuprofen was adsorbed from a hexane solution as already reported[5] and the amount adsorbed and delivered from the samples was monitored by UV spectrometry, thermogravimetry (TG), and elemental analysis. The release profile was obtained by soaking the samples in a 100-mL flask containing a solution simulating body fluid composition (SBF),[7] maintaining the ratio of mL SBF/mg IBU adsorbed equal to 1, and the temperature of 37 °C. To avoid limitation of the delivery rate by diffusion constraints through the pore system, continuous stirring (200 rpm) was maintained during the assays.

The samples were characterized by XRD, TG, FTIR, ^{29}Si MAS NMR, elemental analysis, N_2 adsorption, and TEM. The XRD patterns were obtained using a Philips X'Pert MDP (Cu Ka radiation) diffractometer with a multipurpose sample holder for nondestructive analysis. The thermogravimetric analyses (TGA) were carried out between 30 and 900 °C in air (flow rate 100 mL/min with a heating rate of 10 °C/min) using a Seiko TG/DTA 320. Surface area and pore size (BJH method) of the materials were determined by N_2 adsorption using a Micromeritics ASAP 2010 porosimeter. ^{29}Si MAS NMR spectra were recorded at room temperature on a Varian VXR-400S WB spectrometer at 79.5 MHz by using a pulse length of 4.0 microseconds and a recycle delay of 60 s. For the TEM experiments the samples were dispersed in acetone and dropped on a holey carbon copper microgrid. Micrographs and selected area electron diffraction patterns (SAED) were recorded in a Jeol JEM 2000Fx transmission electron microscope operating at 200 kV.

Results and Discussion

The synthesized functionalized materials were characterized by XRD, verifying that they maintain the hexagonal array of mesopores. The (100), (110), and (200) reflections are detected, with $d(100)$ spacings ranging from 39 to 35 Å. A unit cell contraction of 3 Å is observed upon calcination. However, the functionalization process, either on the as-made or on the calcined samples, does not affect the unit cell size (Table 1).

Elemental analysis of the modified MCM-41 reveals the presence of nitrogen (Table 1). However, when the aminopropyl group is introduced before calcination, a fraction of the surfactant remains inside the pore structure, as the C/N molar ratio is 3.7, above that expected for aminopropyl moieties.

^{29}Si MAS NMR spectra of modified materials are shown in Figure 1, whereas positions and relative intensities of peaks are detailed in Table 2. Characteristic signals of completely (Q^4) and partially condensed Si (Q^3) are observed, together with those corresponding to the Si attached to the organic chain in two different

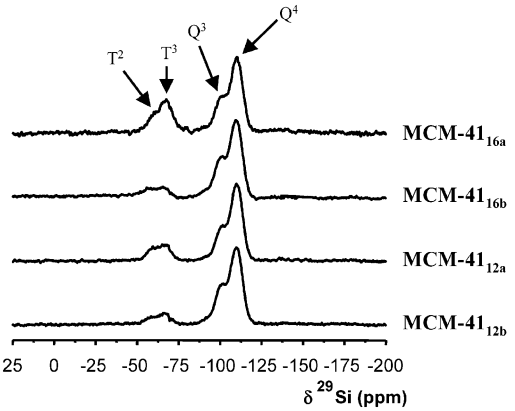

Figure 1. ^{29}Si MAS NMR spectra of modified $MCM\text{-}41_{16a}$, $MCM\text{-}41_{16b}$, $MCM\text{-}41_{12a}$, and $MCM\text{-}41_{12b}$.

Table 2. ^{29}Si MAS NMR Data of Modified MCM-41

	$\delta\ Q^4$ (int %)	$\delta\ Q^3$ (int %)	$\delta\ T^3$ (int %)	$\delta\ T^2$ (int %)
$MCM\text{-}41_{16a}$	−110.3 (47)	−109.9 (25)	−68.4 (14)	−61.9 (14)
$MCM\text{-}41_{16b}$	−110.2 (49)	−100.9 (36)	−66.7 (5)	−57.5 (10)
$MCM\text{-}41_{12a}$	−110.4 (55)	−101.0 (29)	−66.7 (5)	−57.5 (11)
$MCM\text{-}41_{12b}$	−110.1 (57)	−101 (31)	−66.4 (8)	−57.9 (4)

chemical environments, (T^3, Si−R; and T^2, Si(OH)R).[8] It can be seen in Table 2 that the functionalization efficiency of method *a* is higher than that of method *b*, for both C12- and C16-derived materials. Indeed, higher amounts of organosiloxane units are detected in the mesoporous material synthesized from C16 surfactant, owing probably to the lower condensation degree of the silica network (lower population of Q^4 environments). Relative population of T^3 and T^2 signals also changes according to the starting MCM-41 sample and synthesis procedure, but no clear trends are apparent.

Nitrogen isotherms and pore distribution of original MCM-41 and modified materials are shown in Figure 2, and Table 1 summarizes these results. As expected, the introduction of the organic fragment leads to a decrease in pore diameter, surface area, and pore volume, although there are significant differences between the materials modified by the two methods. Materials modified by method *b* display a lower pore volume and diameter than those synthesized by method *a*. This difference cannot be attributed to differences in the channel dimension between as-made and calcined samples. Indeed, it has been shown elsewhere[5] that the unit cell size of the as-made sample remains unchanged after acid extraction of the surfactant, whereas the pore size is the same as that of calcined sample (2.5 nm). Moreover, the functionalization degree of samples $MCM\text{-}41_b$ is lower than that of $MCM\text{-}41_a$ materials, which should lead to smaller average pore size of the latter. However, the opposite is actually found (see Table 1). These variations of the pore size and volume would be better explained by assuming that a significant fraction of the aminopropyl groups anchored in the sample following method *a* are located in the external surface of the material. Indeed, it is expected that the liquid-phase functionalization would take place more easily on the external surface than inside the channels, which are filled with surfactant cations. The 7−8 Å pore size decrease of the functionalized materials (method *b*) is

(7) Kokubo, T.; Kushitani, H.; Sakka, S.; Kitsugi, T.; Yamamuro, T. *J. Biomed. Mater. Res.* **1990**, *24*, 721.

(8) Zhao, X. S.; Lu, G. Q. *J. Phys. Chem. B* **1998**, *102*, 1556.

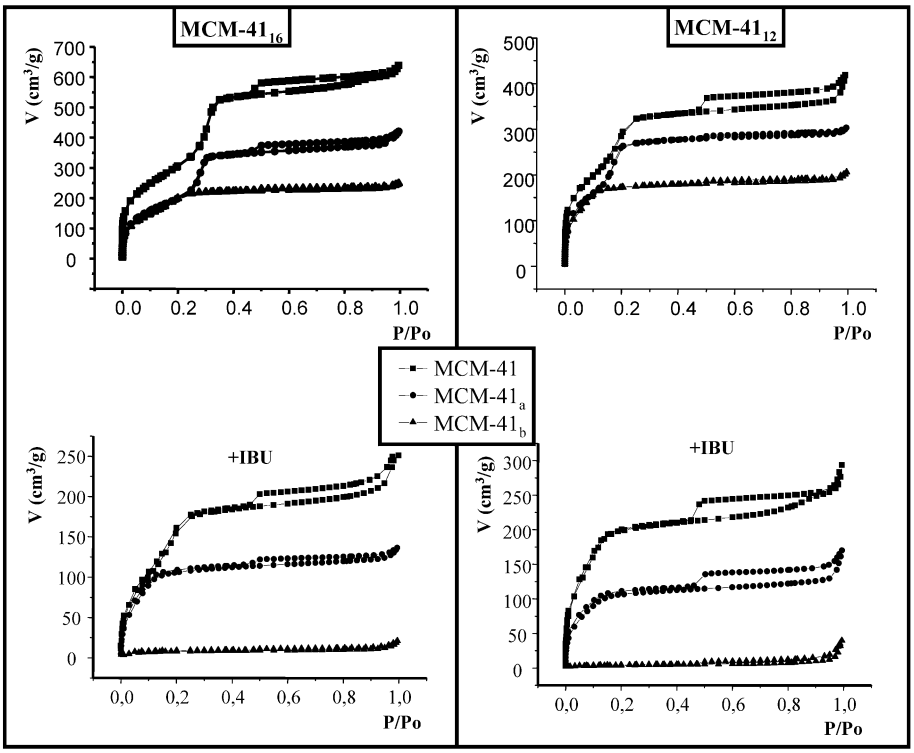

Figure 2. Nitrogen adsorption isotherms of mesoporous materials before and after Ibuprofen adsorption.

consistent with what is expected from the effective length of the aminopropyl moieties that cover the pore walls along the channels.

It has been shown that both organic modification methods lead to differences in pore size and functionalization degree and the distribution of aminopropyl groups. It could be thought that these differences would be reflected in their behavior of ibuprofen adsorption. When ibuprofen is introduced into the pore array of MCM-41 prepared following method *a*, it occupies only part of the pore volume, whereas this molecule fills completely the pores of the MCM-41 modified by method *b*, as it can be observed in the nitrogen isotherms shown in Figure 2. It is worth notice that the different behavior shown by the samples is not directly related to pore size or functionalization degree. As can be seen in Tables 1 and 2, samples MCM-41$_{16b}$ and MCM-41$_{12a}$ have the same pore size and a quite close amount of aminopropyl content, even the same T^3/T^2 ratio. However, they exhibit a very different behavior in ibuprofen adsorption (Figure 2). A lower density of aminopropyl groups inside the channels, as explained before, could account for these results. In any case, the method employed in the functionalization of MCM-41 determines the character of drug adsorption inside the mesopores, and could therefore control the rate of the drug delivery.

On the other hand, it should be remarked that the amounts of ibuprofen adsorbed by the MCM-41 samples synthesized from the C16 and C12 long-chained surfactants are quite distinct (Table 1). As it can be observed, the differences in ibuprofen adsorbed between calcined MCM-41$_{16}$ and MCM-41$_{12}$ derived materials reach up to 20 wt %, depending on the method employed in the aminopropyl group introduction. In this sense, the drug dosage is dependent on the pore size. Differences between the inner surfaces of these different sized materials and the packing of ibuprofen inside the channels could explain the variations in the drug adsorption.

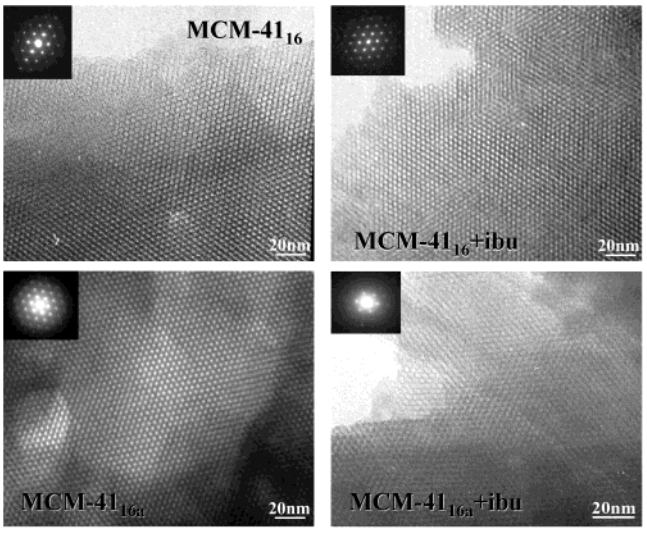

Figure 3. Images and selected area electron diffraction patterns of samples MCM-41$_{16}$ calcined, MCM-41$_{16}$ + ibu, MCM-41 calcined and loaded with ibuprofen, MCM-41$_{16a}$, and MCM-41$_{16a}$ + ibu, along the direction parallel to the c axis.

In addition, ibuprofen-containing and also calcined and modified MCM-41 were studied by transmission electron microscopy (TEM). Selected area electron diffraction patterns (SAED) showing high symmetry along the two possible orientations of *p*6*mm* plane group were obtained for all the functionalized and ibuprofen-containing MCM-41 materials described in this work, proving the hexagonal arrangement of the mesoporous channels. As an example, Figure 3 shows the images and SAED patterns along the direction parallel to the *c* axis of samples MCM-41$_{16}$, MCM-41$_{16}$ + ibu, MCM-41$_{16a}$, and MCM-41$_{16a}$ + ibu. This figure shows that both

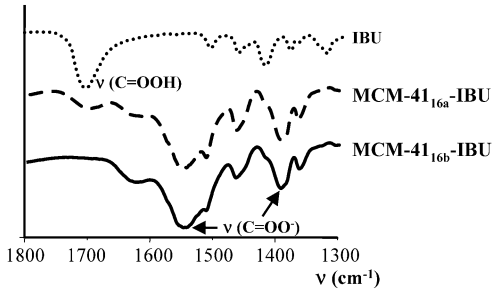

Figure 4. FTIR of MCM-41$_{16a}$ and MCM-41$_{16b}$ after Ibuprofen adsorption, compared with that of Ibuprofen itself.

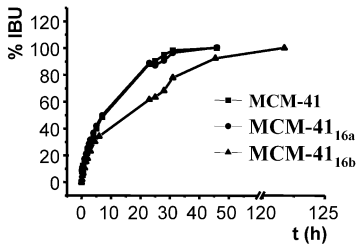

Figure 5. Ibuprofen delivery from MCM-41, MCM-41$_{16a}$, and MCM-41$_{16b}$.

the well-ordered pure silica and the functionalized MCM-41 materials maintain the structure after ibuprofen loading, whether they are functionalized by method *a* or *b*. Besides, the cell parameter measured from SAED is comparable to the value observed by XRD in all the cases.

By comparing carefully the TEM results for sample MCM-41 calcined, where the channels are organic-free, with those of ibuprofen-containing and ibuprofen-containing-functionalized MCM-41, fully occupied by the ibuprofen, it can be concluded that no strong differences are observed in the images. The scattering of the matter that fills the pores (containing basically carbon, nitrogen, and oxygen) is not strong enough to inverse the contrast.

FTIR spectra of modified MCM-41$_{16}$ and MCM-41$_{12}$ are very similar, so only modified materials of the former are described. The ibuprofen-containing materials (Figure 4) reveal some differences in the chemical state of the adsorbed drug. In the sample prepared following method *b*, no band at 1706 cm^{-1} corresponding to the carboxylic group of ibuprofen is observed, whereas intense carboxylate bands at 1556 and 1397 cm^{-1} are detected, which indicates that proton transfer from the carboxylic acid of ibuprofen to aminopropyl groups has taken place. In contrast to this, a carboxylic acid band of low intensity is still observed in the spectrum of sample MCM-41$_{16a}$, which evidences a weaker average host/guest interaction.

The results of the in vitro study of ibuprofen released from the mesoporous materials are shown in Figure 5. As it can be observed, the material modified by method *a* has a delivery rate identical to that of the original MCM-41, whereas MCM-41$_{16b}$ material delivers the ibuprofen more slowly. In fact, whereas the former has released 50% of the ibuprofen after 7 h of assay, MCM-41$_{16b}$ needs almost 24 h to reach that percentage. Practically no differences are observed between C16 and C12 materials.

This fact is in agreement with the observations mentioned above. The slower delivery rate corresponds to the materials where the ibuprofen fills completely the MCM-41 channels (modified by method *b*). Besides, a fraction of the ibuprofen present in the samples obtained by method *a* would be adsorbed on the aminopropyl groups located on the external surface, so that it can be expected that the ibuprofen interacting with those groups would be more easily released to the SBF solution. Indeed, fully ionized ibuprofen chemical species are present in these samples. The culombic interaction between the protonated aminopropyl groups and carboxylate anions would additionally contribute to the observed decrease of the delivery rate.

It is observed in Figure 5 that the pore size of the functionalized MCM-41 does not seem to affect to the delivery rate. This suggests that even the smallest pore size here-obtained is still too large compared with the ibuprofen molecule to affect in a significant manner the release pattern of ibuprofen. On the other hand, it should be pointed out that even though the percentage of drug released to the media is the same for MCM-41 and MCM-41$_{16a}$, the actual concentration of drug in SBF is not. The different amounts of ibuprofen adsorbed by the materials in each case leads to different quantities delivered to the media. As an example, after 24 h of assay, unmodified MCM-41 has delivered about 90 mg, while this amount is reduced to 62 mg for MCM-41$_{16a}$, and less than 50 mg in the case of MCM-41$_{16b}$. From this point of view, it would be possible to choose the amount of drug to be delivered on the basis of the MCM-41 functionalization.

Conclusions

We have demonstrated the feasibility of controlling the delivery rate of drugs occluded in MCM-41 matrixes by functionalizing the pore wall with silane derivatives. In the case of ibuprofen, which contains an acid group, the functionalization of well-ordered MCM-41 matrixes with aminopropyl moieties allows decrease of the delivery rate. It has been shown that the functionalization procedure is determinant in both the adsorption of the drug and its release profile, which is also affected by the pore filling degree of the hybrid organic/inorganic matrix by ibuprofen.

On the other hand, it has been shown that the different pore sizes of the host material described in this work do not affect the delivery rate in the particular case of ibuprofen, probably due to the relative size of pore/drug, but are determinant in the drug dosage, being able to control it by choosing the adequate pore size.

Acknowledgment. This work is dedicated to Prof. Domingo González, from the University of Zaragoza, on the occasion of his retirement. We are grateful for financial support provided by CICYT MAT99-0461, and to Dr. T. Blasco for collecting the NMR spectra.

CM021217Q