A New Property of MCM-41: Drug Delivery System

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A new application of MCM-41 mesoporous materials has been developed. Two kinds of surfactants, C16TAB and C12TAB, have been employed to get different pore sizes. The samples were disk-shaped conformed before and after charging with ibuprofen, an anti-inflammatory drug. In all the cases the weight percent ratio of drug/MCM-41 was 30%. The drug release plots show a different behavior depending on the method for charging the drug in the material but not on the employed surfactant.

Introduction

Since the discovery of the M41S family by Mobil Corporation scientists in 1992,[1,2] synthesis and applications of mesoporous molecular sieves have received much attention. Among this family of materials, the one that has been more extensively studied is MCM-41, showing hexagonal arrays of cylindrical mesopores. Typically, these materials are synthesized by self-assembly[3] of silica−surfactant in which inorganic species simultaneously condense, giving rise to mesoscopically ordered composites formation.

Because of their potential applications in several fields such as adsorption, ion exchange, catalysis, and sensing, many efforts have been made to tailor both pore size and structure of these materials. Pore size depends basically on the surfactant employed in the synthesis, which means that pore size increases with the chain length of the surfactant, but also on other parameters of the synthesis process.[1,2] Lately, different methods have been reported to control the pore size by adding auxiliary organic molecules, which are solubilized in the hydrophobic region of the templating aggregates, thus increasing the micellar size,[2,5,4] or via hydrothermal restructuring of the as-synthesized material in the mother liquor[5,6] or water.[7] On the other hand, the structure has been modified, introducing functional groups to the pore surface by different routes.[8,9]

Although the feasibility of choosing the pore size offers a wide range of possibilities for hosting different molecules, references dealing with the inclusion chemistry of MCM-41 are not abundant and usually involve structure modification.[10] The structure of the wall of the pores consists of a disordered network of siloxane bridges and free silanol groups that could act as reacting nuclei against appropriate guest chemical species. This fact allows original MCM-41 material to behave as a matrix for controlled adsorption and liberation of organic molecules itself, with no need for pore-wall functionalization.

Therefore, it seemed primal to us to make a previous study about unmodified MCM-41 behavior toward organic molecules, such as drugs, as a function of pore size and investigate inclusion and delivery mechanisms, which should depend on the potential interactions between free silanol and the organic functional groups of the guest molecule.

Usually, drug delivery systems consist of a polymeric matrix from which the drug is released under appropriate conditions.[11] A wide number of materials have been employed, including mixtures of polymers and polymer-based composites with different material such as bioactive glasses or ceramics.[12,13] In these cases the drug is deposited by means of direct compression, wet granulation, or mechanical mixture of both matrix and drug. These methods have in general the disadvantage of heterogeneity of samples due to the difficulty of ensuring homogeneous distribution of the drug through the matrix, which can affect the release rate between different samples. Therefore, much improvement in this field would be expected if chemically homogeneous materials possessing well-defined porosity to accept

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organic guest molecules would be available. Clearly, ordered mesoporous materials fulfilled these conditions.

The aim of this work is to explore a new potential property of MCM-41, its capability of acting as a convenient reservoir for controlled drug delivery systems. For this purpose, we will introduce ibuprofen, an extensively employed analgesic and anti-inflammatory drug, into two MCM-41 materials with different pore sizes and subsequently the in vitro drug release process to a simulated body fluid will be studied. The choice of this drug is due not only to its pharmacological activity but also to its molecular size, which lies in the range of mesoporous material. MCM-41 materials will be synthesized by using two different surfactants (leading to two different pore sizes) and will be characterized at every step of the process by XRD and N_2 adsorption techniques.

Experimental Section

Gels with the molar composition 1.0/0.12/0.28/26.2 SiO_2/C_{16}-TAB (or C_{12}TAB)/TMAOH/H_2O were prepared as follows: 5.139 g of hexadecyltrimethylammoniun bromide (C_{16}TAB, Aldrich) was dissolved in 46.4 mL of water. A solution of 10% of calculated tetraethyl orthosilicate (TEOS, 25 mL) in 11.8 mL of tetramethylammonium hydroxide (TMAOH, Aldrich) was prepared and added to the former dissolution when the hydrolysis was completed. Afterward, the rest of TEOS (22.5 mL) was added slowly to prevent silica condensation and stirred until the TEOS hydrolysis was completed.

The obtained gel was poured into a Teflon recipient hermetically closed and heated at 100 °C for 24 h. After this, it was filtered, washed with water, and dried at 60 °C. The surfactant was removed from mesopore material by extraction, suspending 1 g of sample in 50 mL of HCl (35% in weight)/ethanol mixture with a ratio of 1:10 for 24 h and kept at reflux. This process was carried out twice, and the quantitative removal of surfactant was assessed by TG and chemical analysis.

The obtained material was filtered, washed with H_2O and ethanol, and dried at 60 °C. The samples obtained from the C_{16} and C_{12} surfactants were denoted as MCM-41A and MCM-41B, respectively.

Two procedures were used to charge the material with ibuprofen. In method 1 the drug was dissolved in hexane (33 mg/mL) and the extracted MCM-41 sample was added (33 mg/mL of hexane), stirring for 24 h and preventing the evaporation of hexane. A Unicam UV 500 spectrophotometer was used to control the amount of ibuprofen absorbed by the sample, reading at 273 nm. That amount was determined by UV spectrometry and thermogravimetry, resulting, in both cases, in 30 wt % with respect to the powdered starting material.

For both MCM-41A and B the final amount of charged drug reached around 30% in weight. This drug-charged material was conformed in 0.3-g disks (13 × 3 mm) by uniaxial (2.75 MPa) and isostatic pressure (3 MPa) to improve the drug release process.

In the second procedure (method 2) the initial powder without drug was pressed at the same conditions as described below. The disks were soaked in a solution of ibuprofen in hexane (33 mg/mL) for 3 days. The absorption process is slower in this case, but it reached the same ratio in weight (30%).

The release profile was obtained by soaking the samples in 90 mL of a simulated body fluid, SBF (1 mg of ibuprofen of the sample per mL of fluid), and measuring the drug concentration in the fluid by means of a UV−vis spectrophotometer. Simulated body fluid (SBF) has a composition very similar to the human plasma[14] (pmm: 142.0/5.0/2.5/1.5/147.8/4.2/1.0/0.5 $Na^+/K^+/Ca^{2+}/Mg^{2+}/Cl^-/HCO_3^-/HPO_4^{2-}/SO_4^{2-}$).

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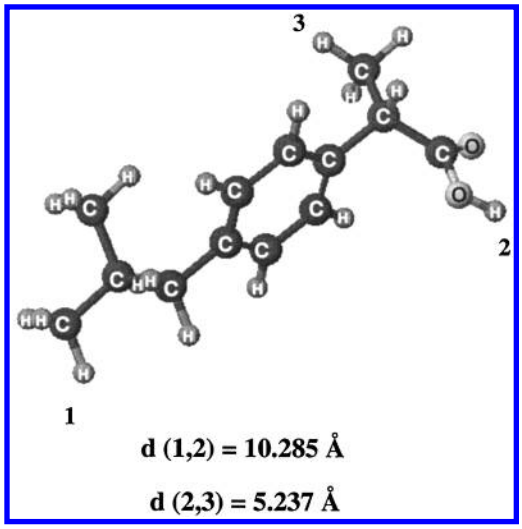

Figure 1. Three-dimensional ibuprofen molecule with corresponding interatomic distances.

Every sample (either powder or disk) was characterized by XRD, thermogravimetry, and N_2 adsorption.

The XRD patterns were obtained using a Philips X'Pert MDP (Cu Kα 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.

The surface area and pore size of the material were determined by N_2 adsorption using a Micromeritics ASAP 2010 porosimeter.

Results and Discussion

Both MCM-41A and B after surfactant extraction were characterized by XRD. Sample A showed (100), (110), and (200) reflections, whereas a less resolved pattern is obtained for sample B, prepared from C_{12}-TAB. The *d*(100) spacings were 39 and 36.5 Å for samples A and B, respectively. The nitrogen adsorption isotherms and pore size distributions showed the characteristic stepped pore filling in the range 0.2−0.35 p/p_0. BET surface areas were 1157 and 1099 m^2/g for MCM-41A and B, with a total volume of pores of 0.98 and 0.84 cm^3/g, respectively. The pore size distribution is centered at 2.5 and 1.8 nm for the samples prepared from C_{16} and C_{12}, respectively.

Selection of ibuprofen was made according to its pharmacological activity and to its molecular size and structure. With that intention, a molecular modelization was carried out employing Cache Scientific 3.9, arriving at the lower energy configuration shown in Figure 1. From this model, the size of the ibuprofen molecules could be estimated to be ≈1.0 × 0.6 nm, which ensures that it could fit inside the material mesopore. Besides, the acid group present in ibuprofen could interact with the silanol groups present on the surface of the pore wall.

The effective uptake of ibuprofen by the mesoporous materials when immersed into the hexane solution of the drug can be monitored by TG, which indicates a maximum of 30 wt % of ibuprofen. Indeed, the mesopore filling with ibuprofen molecules can be assessed by N_2 adsorption. As shown in Figure 2, the characteristic pore filling step of the isotherm nearly disappears after ibuprofen adsorption for both methods 1 and 2. How-

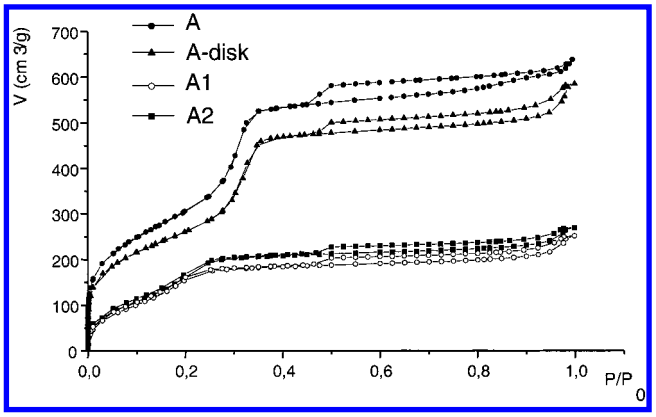

Figure 2. Nitrogen adsorption isotherms of different MCM-41A materials.

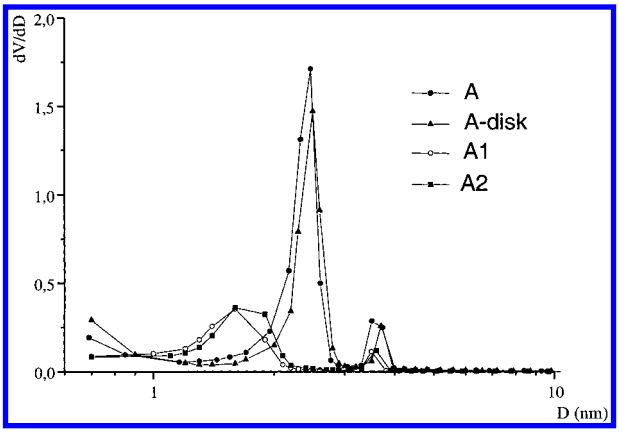

Figure 3. Pore size distribution of different MCM-41A materials.

ever, careful inspection of the isotherm shows a weak inflection point at ≈0.12 p/p_0. The pore size distribution (Figure 3) is nearly unaffected by the method used to incorporate the ibuprofen into the MCM-41 matrix, but in both cases a shift of the average pore size from 2.5 to 1.9 nm is observed. This result would suggest that the ibuprofen molecules packed inside the channels do not fully occupy the available space in such a way that there is still some room for N_2 adsorption. Indeed, the surface area and the pore volume drops only to 688 $m^2\ g^{-1}$ and 0.39 $cm^3\ g^{-1}$ after ibuprofen loading following method 1 and to 592 $m^2\ g^{-1}$ and 0.42 $cm^3\ g^{-1}$ according to method 2.

Besides, it should be pointed out that the XRD of MCM-41 after ibuprofen release showed no loss of structural ordering whereas the nitrogen adsorption isotherm was comparable with the original one.

Figure 4 shows the percentage of ibuprofen release as a function of time for the MCM-41A sample loaded with ibuprofen according to method 1 and immersed into the SBF solution. It is observed that the release is very fast during the first day, but decreases with time and reaches a maximum value of 80% the third day, remaining constant after that day. If the ibuprofen is loaded into the MCM-41A sample according to method 2 (a MCM-41 wafer is immersed into the ibuprofen solution in *n*-hexane), the delivering rate was higher (Figure 4), and the release reached 100% of the ibuprofen adsorbed.

The same two assays were carried out for MCM-41B, obtaining similar results (Figure 5). The difference

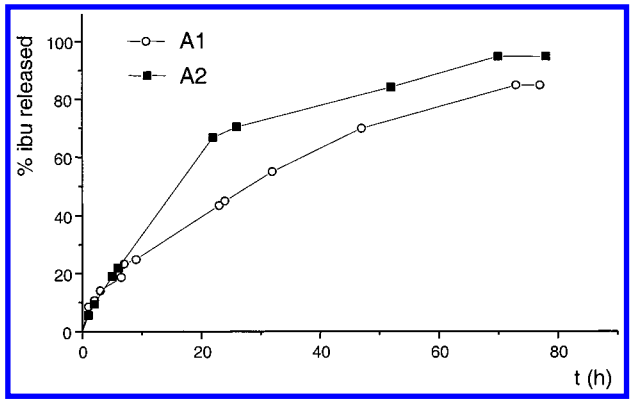

Figure 4. Ibuprofen % release from MCM-41A1 and 2.

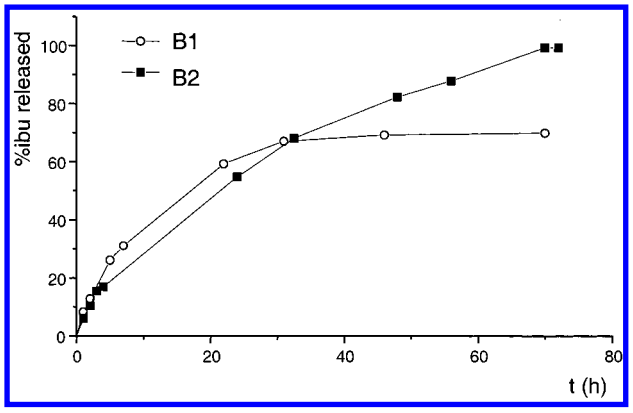

Figure 5. Ibuprofen % release from MCM-41B1 and 2

between MCM-41A and B is a slightly higher rate of release for A during the first day, reaching the value at 24 h of 68% for A and 55% for B.

The virtual absence of pore size effect for the ibuprofen releasing between samples A and B could be understood on the basis of the small molecular size of ibuprofen, 1.0 × 0.6 nm, compared with the pore size of 2.5 and 1.8 nm for the two samples. Indeed, in both cases the availability of free space inside the mesopore of the ibuprofen-containing samples accessible to the SBF solution would enhance the drug transport from the pores to the solution.

The different behaviors of the material when the ibuprofen was introduced before or after conformation could be explained by assuming that when the powdered material is charged with ibuprofen, the compression of the drug−matrix mixture leads to a decrease of pore size and, eventually, to a narrowing or closing of the pore cavity. This could induce a slow or even incomplete release of ibuprofen due to diffusion constraints. Nevertheless, if the starting MCM-41 material is compacted before ibuprofen loading, the uptake and release of the ibuprofen would take place following the same unrestricted diffusion pathway through the mesopore network.

Conclusions

A new property of MCM-41 materials has been developed, which is its capability for accepting and delivering organic compounds. This property has been evidenced by using two MCM-41 samples with different pore sizes, 2.5 and 1.8 nm, as hosts and the ibuprofen

molecule as the guest. The ibuprofen occupies partially the MCM-41 mesopores, and it can diffuse out of them when the ibuprofen-loaded samples are immersed into a simulated body fluid. By optimizing the method of ibuprofen loading, all the drug incorporated into the MCM-41 matrix can be released to the solution after 3 days, in the conditions prevalent in the in vitro test.

This preliminary study demonstrates the feasibility of designing reliable drug delivery systems by appropriate choice of the matrix and the organic molecule.

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