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Research paper

Inclusion of ibuprofen in mesoporous templated silica: drug loading and release property

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Abstract

The aim of this study is to determine the feasibility of loading biologically active molecules into templated mesoporous silica (MCM 41). This material shows an important mesoporosity associated to hexagonally organized channels, a narrow pore size distribution and a large surface area. Ibuprofen was selected as a model molecule since it is a well documented and much used anti-inflammatory drug. Furthermore, it has a lipophilic character and its molecular size is suitable for inclusion within the mesopores of the MCM 41 material.

In order to load ibuprofen within the mesopores, adsorption experiments using various solvents or successive impregnations with solutions of ibuprofen in ethanol were performed. At each step of the loading process, the pore filling was characterized by nitrogen adsorption experiments and by X-ray diffraction. The impregnation procedure results in a significant improvement of the amount of ibuprofen loaded into MCM 41. The in vitro drug release was investigated with simulated biological fluids (gastric and intestinal). Hundred percent release is observed at the end of the in vitro experiment.

Keywords: Drug loading; Mesoporous silica; MCM 41; Ibuprofen

1. Introduction

Since drug-loaded particles appear particularly suited for controlled release and drug targeting, they have been the focus of research on drug delivery systems [1]. Developments in encapsulation technology have allowed the preparation of a large range of submicron-sized drug-loaded particles. These nanoparticles may have wide-spread potential as drug carriers due to the presence of an organic shell or to their organization (colloidal systems, liposomes, microemulsion, etc.) [1–4]. All these systems are expected to enhance the bioavailability of poorly absorbed drugs, entailing a lowering of the therapeutic dose. These nanoparticles are also efficient for entrapping slightly water-soluble drugs [4–6]. This technique represents an alternative to the traditional formulation processes involving cosolvents or micellar solubilization [7,8].

Among these drug delivery systems, inorganic porous materials are emerging as a new category of host/guest systems. Due to some interesting features such as their biological stability and their drug-releasing properties [9], there is a significant and increasing interest in these potential carriers. Several porous minerals have been used including synthetic zeolithe, silica xerogel material and porous ceramic [9–14]. MCM 41 is a typical mesoporous templated silica which has been largely investigated. This material presents nanosized pores that allow the inclusion of drug into the pores. With a pore size in that range, it presents an alternative to nanoparticles as a drug delivery system. Release properties of MCM 41 have been studied recently [15,16]. They suggest that this material may be used as a drug carrier.

In contrast to most porous minerals, which show disordered pores with a broad size distribution and irregular shapes, the MCM 41 type materials exhibit exciting structural features like their large specific surface area (up $1000\ m^2\ g^{-1}$) and ordered cylindrical mesopores with a narrow size distribution. Indeed, their inner structure consists of unidirectional channel-like pores that form a hexagonal pattern [17]. These mesoporous templated

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materials are synthesized by self-assembly of silica and surfactant micelles used as structure directing agents. For instance, the synthesis of MCM 41 type material was performed under hydrothermal conditions in presence of cationic surfactants, such as tetradecyl- or hexadecyltrimethylammonium bromide. The structure of these ordered mesoporous materials results from a cooperative organization process between the negatively charged silicate species interacting with the positively charged quaternary ammonium micelles [17–19]. The porosity of the material is available after surfactant removal via calcination. Owing to the structural features of these recent materials, research interest has been focused on the particle morphology and on the control of pore size. Indeed, ordered mesoporous materials provide the unique opportunity to tailor the pore width (ca. 20–100 Å) by the choice of appropriate alkyl chain length of surfactants or by solubilization of organic substances into the micelles to increase their size. In addition, it is possible to chemically modify their surface properties through covalent grafting of organic species to various functional groups onto the surface free silanol groups of MTS [20,21].

Therefore, highly ordered mesoporous silica appear very suitable as host materials and important applications are contemplated namely in heterogeneous catalysis, adsorption, ion exchange, and inclusion chemistry [22]. On account of their well-defined and large inner porosity, and consequently their large surface area, templated mesoporous silica exhibits structural properties required for drug carriers. Moreover, silica, such as aerosil, is a widely used pharmaceutical excipient; therefore, it would be interesting to use ordered mesoporous silica in alternative formulations for drug delivery systems.

The aim of this study is to determine the loading capacity of biologically active molecules of mesoporous templated materials and to characterize the drug-loaded materials. For this purpose, we chose a MCM 41 solid with a distribution of pore sizes in the range from 3 to 3.6 nm. This choice was directed by the fact that the MCM 41 structural features have been widely studied and characterized. Ibuprofen, an anti-inflammatory drug, was selected as a model drug for its low solubility in water and its molecular size; the latter is suitable for its incorporation within the pores of MCM 41. In the first part of the study, adsorption of ibuprofen on the channels surface of MCM 41 have been carried out using various solvents as the interactions between the solute and the mineral surface depend on the solvent properties. In the second part, successive impregnations of the MCM 41 particles have been performed with a solution of ibuprofen in ethanol. In addition, at each step of the loading process, the pore filling with ibuprofen molecules was characterized by nitrogen adsorption isotherms and by X-ray diffraction. This study particularly emphasizes the inclusion of the drug molecules within the pores of MCM 41 particles. Finally, the in vitro drug release was performed using a flow-through dissolution test (USP 4) with simulated gastric (pH 1.2) and intestinal (pH 7.4) fluids.

2. Experimental section

2.1. Materials

Aerosil 200 (Degussa) was used as silica source. The quaternary ammonium surfactant hexadecyltrimethylammonium bromide (CTAB) was obtained from Sigma Aldrich (98%) (Saint Quentin Fallavier). Ibuprofen is commercially available from Sigma Aldrich. The solvents used in the adsorption experiments, i.e. hexane, ethanol, dimethylsulfoxide (DMSO), dimethylformamide (DMF) and dimethylacetamide (DMA), were purchased from Sigma Aldrich (HPLC grade). All chemicals were used as received.

2.2. Synthesis of mesoporous silica MCM 41 and calcination

MCM 41 silica was prepared by hydrothermal synthesis using CTAB micelles as a template. In a typical synthesis, 45 g of silica was added to a stirred solution of 7.5×10^{-2} mol of CTAB and sodium hydroxide (0.2 mol) in deionized water (500 ml) at the following molar ratio: $H_2O/NaOH/CTAB/SiO_2$ 20:0.3:0.15:1. The mixture was heated in a stainless autoclave at 115 °C for 20 h. The resulting white powder was filtered, washed successively with deionized water and ethanol and air dried at 50 °C. Afterwards, the solid was calcined at 550 °C for 7 h in under airflow to remove the surfactants.

2.3. Loading procedures

Two procedures were used to load MCM 41 material with ibuprofen. In the first method, 0.05 g of MCM 41 were added to 2.5 ml of an ibuprofen solution of concentration C_0 ($C_0 = 65$ mg/ml). The adsorption procedure was carried out by using successively DMSO, DMA, DMF, ethanol, and hexane as solvent. Afterward, the suspensions were brought to equilibrium under gentle stirring for 24 h. Subsequently, the suspensions were filtered (Acrodisc CR PTFE, pore size 0.2 μm, Fisher Bioblock, Illkirch) and ibuprofen that remained in the supernatant phase were determined using HPLC analysis with UV detection at 254 nm. The amount of ibuprofen adsorbed onto MCM 41 is determined by the depletion method.

In the second procedure (incipient wetness), 0.5 g of MCM 41 were impregnated several times with a solution of ibuprofen in ethanol of concentration 65 mg/g. The ethanol solvent was evaporated at 50 °C between each impregnation. In order to achieve pore filling an excess amount of ibuprofen was added to the sample. Then, the powder was quickly washed on a filter with 5 or 10 ml of ethanol to

remove the excess ibuprofen molecules coating the outer surface. The powder obtained was then dried at 50 °C. The amount of ibuprofen loading in the channel pores can be assessed by subtracting the amount of ibuprofen removed off the surface in the washing step from the total amount added to the sample.

2.4. Instrumentation

Powder X-ray patterns have been recorded using an INEL XRG 3000 instrument (monochromated Cu Kα radiation). Typically the diffractograms have been collected in a 2θ range of 1–6.5° with a resolution of 0.02°.

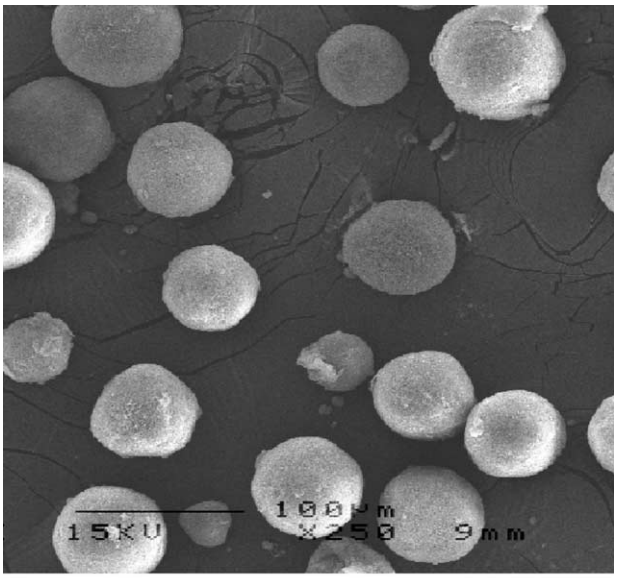
The nitrogen adsorption–desorption isotherms have been collected at 77 K using an adsorption analyzer ASAP 2010 from Micromeritics. The specific surface area is assessed according to the standard BET method. The pore size distribution is obtained by the Broekhoff and de Boer (BdB) method. The pore volume and the external surface area are computed using the *t*-plot method. For the characterization of the porous material, the MCM 41 particles have been degassed at 250 °C for 8 h under vacuum (10^{-2} Torr). For the pretreatment of the samples loaded with ibuprofen, the same conditions prevailed except for the degassing temperature which was set at 35 °C in order to avoid the sublimation of ibuprofen.

The flow-through cell dissolution (SOTAX CY 1-50) used in the in vitro experiments may be described as having three parts: the lower cone, the middle cylindrical portion and the filter head on top [23]. The dissolution medium enters the cone through a capillary bore situated on the bottom and flows upwards. The cone is separated from the cylindrical portion by a 40-mesh screen and a glass microfiber filter. The filter head on the top part also holds a glass microfiber filter. In all cases the lower cone holds a glass bead 6 mm in diameter, which serves to distribute the jet of fluid entering the cell.

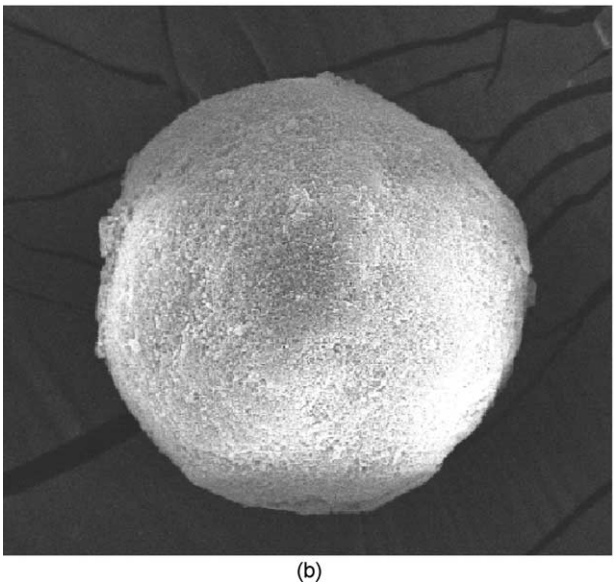
The powder was loaded into the flow-through cell on the bottom of the cylindrical portion and covered by a 1 mm round glass beads layer. The amount of drug used per experiment is around 50 mg. The flow rate of the dissolution medium across the cell is set at 6.5 ml/min and the cell is thermostated at 37 °C. During the first 30 min of the experiment, the dissolution fluid is a simulated gastric medium (pH 1.3) and in the subsequent one and a half hour, it is replaced by a simulated intestinal medium (pH 7.4) ($n = 3$). Experiments were carried out in an open loop setup and samples are collected over time during 2 h to measure the ibuprofen concentration. The HPLC used for the dosage consisted of a Shimadzu system. The column used is a Kromasil (C18 5 m) 250 × 4.6 mm with a guard column (ICS, Marseille). The absorbance value read at 260 nm in the UV visible detector were used for quantitative analysis of ibuprofen on the base of a calibration curve. The mobile phase for elution was acetonitrile (acetic acid 0.5%)/water (acetic acid 0.5%): 65%/35% at a flow rate of 1.2 ml/min. The injection volume of samples was in the range of 8–20 μl according to ibuprofen concentration.

3. Results and discussion

Fig. 1a and b displays scanning electron microscopy (SEM) observations of MCM 41 particles. MCM 41 silica material was obtained as small spherical particles with a size of a few microns. According to previous results [23], the TEM observations reveal a hexagonal periodic arrangement of the channels (honeycomb pattern). The structural properties of MCM 41 silica material used in this study have been determined by powder X-ray diffraction (Fig. 2a) and by nitrogen adsorption at 77 K (Fig. 2b).



(a)



(b)

Fig. 1. SEM pictures of the synthesized MCM 41 silica material.

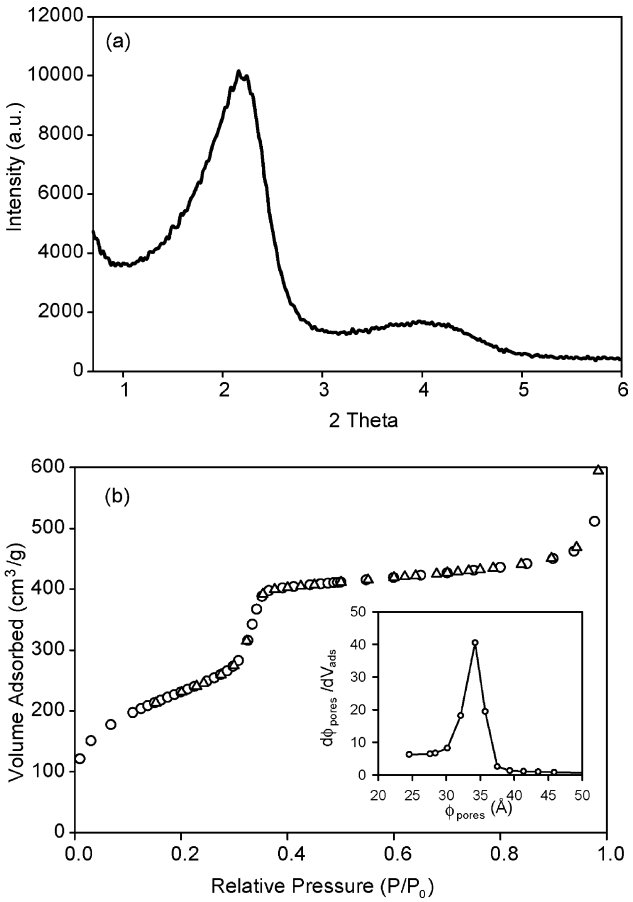


Fig. 2. (a) Typical XRD pattern of calcined MCM 41 material. (b) Nitrogen adsorption isotherm at 77 K, degassed at 523 K, for synthesized mesoporous silica calcined at 823 K. The insert shows the pore size distribution.

After calcination of the solid at 550 °C a strong peak is observed at a 2θ angle in the range 2.2–2.4° and two additional reflections with a weaker intensity, merged into one broader peak. These diffraction peaks reveal a regular periodic variation of the electron density due to the long range ordering of the pores in the MCM 41 materials [17]. The intense reflection corresponds to the (100) diffraction peak with $d = 26$ Å leading to a lattice constant (the pore center distance) of $a_0 = 30$ Å according to the hexagonal unit cell relation ($a_0 = 2d_{100}/\sqrt{3}$). Fig. 2b shows the nitrogen adsorption–desorption isotherms of calcined MCM 41 and the pore size distribution. Characteristic type IV-isotherm of mesoporous materials are obtained for the pores filled (by capillary condensation), with a step in the range of $P/P_0 = 0.3–0.4$, typical of the filling of regular mesoporous systems. The specific surface area of the synthesized MCM 41 material is 920 $m^2\,g^{-1}$, with a measured mesoporous volume of 0.61 $cm^3\,g^{-1}$ and a narrow distribution for the pore size centered at 35 nm. A *t*-plot analysis does not reveal any microporous volume and indicates an external surface area of 104 $m^2\,g^{-1}$. In addition, the thickness of the pore wall can be estimated on the basis of the difference between the pore center distance and the pore diameter. The obtained value for this product is 0.34 nm. Therefore, all these data indicate that the MCM 41 type silica material used for this investigation exhibits a well-ordered mesoporous structure.

The adsorption of ibuprofen on mesoporous silica (MCM 41) or on non-porous silica (aerosil) was performed in solvents of different polarities. The two silica particles exhibit similar values of the external surface area and similar surface properties. The amounts adsorbed are reported in Table 1. When highly polar solvents like DMSO, DMF and DMA were used, the amount of ibuprofen adsorbed is weak or can even be neglected. In contrast, when ethanol or hexane was used, ibuprofen was adsorbed on both MCM 41 and aerosil. So, the adsorption varies in function of the solvent properties. Moreover, the amount of ibuprofen adsorbed on MCM 41 is higher than on aerosil suggesting that the adsorption should be done onto the outer surface and inside the MCM 41 channel pores. Actually, the pore size is large enough to allow access to the large internal surface area of these mesoporous materials and the diffusion of ibuprofen molecules is not restricted by the pore structure. However, the relative contribution of each of these two surfaces to the adsorption process was not estimated because adsorption onto external surface and into inner pores occurs spontaneously and uniformly, as previously reported [24–26].

Furthermore, in this study only the two less polar solvents allowed the adsorption of ibuprofen in sufficient amount to investigate its inclusion into the MCM 41 host and subsequently the drug release (Table 1). In the case of hexane, although the adsorbed amount achieved is attractive $\Gamma = 590$ mg g^{-1}, this solvent was not selected to pursue the study since hexane is highly toxic. Although adsorption carried in ethanol is less efficient ($\Gamma = 184$ mg g^{-1}), ethanol is a convenient and non-toxic solvent. A procedure of impregnation of MCM 41 particles was developed in order

Table 1
Effect of solvents on the adsorption of ibuprofen on MCM 41 and aerosil particles (T = 303 K)

Solvent	ε (25 °C)	C_i (mg/ml)	C_{eq} (mg/ml)	$\Gamma_{MCM\ 41}$ (mg/g)	C_i (mg/ml)	C_{eq} (mg/ml)	$\Gamma_{aerosil}$ (mg/g)
DMSO	46.7	35	34.7	25.5	32	32	0
DMF	37.8	28.9	28.4	47	28.9	28.3	34
DMA	37.8	30	30	0	30	30	0
Ethanol	24.5	32.6	30.9	184	31.2	30.5	42
Hexane	1.88	34.2	27	590	30.9	29.5	104

Table 2
Characteristics of MCM 41 before and after successive impregnation of ibuprofen (mg/g) and an ethanol washing: S_{BET} ($m^2\ g^{-1}$), V_{mes} ($cm^3\ g^{-1}$) and pore diameter (Å)

	Ibuprofen (mg/g)	S_{BET} ($m^2\ g^{-1}$)	V_{mes} ($cm^3\ g^{-1}$)	Pore Ø (Å)
MCM 41	0	850	0.62	34
Imp. 1	30	834	0.54	32
Imp. 2	133	768	0.425	30
Imp. 3	766	259	0.123	28
Imp. 4	1350	18	/	/
Wash 1	500	300	0.15	31

to enhance the inclusion of ibuprofen within the pores. Indeed, ibuprofen molecules diffuse with the solvent drawn into the pores by capillarity and after solvent removal, ibuprofen molecules remain trapped there. Successive impregnations enable to achieve a complete pore filling and result in a significant improvement of the amount of the drug molecules encapsulated (Table 2). Of course, with this impregnation procedure, a fraction of the drug molecules are deposited on the particle surface. Consequently, the loaded sample was quickly washed with 5 ml of ethanol to remove the ibuprofen from the outer surface.

The X-ray diffraction of ibuprofen crystals (1), of MCM 41 impregnated with ibuprofen (2) and then washed with ethanol (3) are displayed in Fig. 3. In the case of the loaded material (2), diffraction peaks characteristic for crystals of ibuprofen are obtained. The latter are formed on the particle surface during the solvent removal by evaporation. These diffraction peaks disappear after the flash washing step done with ethanol indicating that the crystals of ibuprofen have been removed from the surface particles. On washed samples, the lack of diffraction peaks indicates that no crystallization process occurred inside the pores. Thus, the ibuprofen molecules included within the pore channel are in a molecular amorphous state. This is in agreement with a crystallization study carried in confined space [27] that has shown that the crystallization can occur only for a channel pore size significantly larger than the molecular size, about 20 times the length of the molecules.

Successive washes with increasing ethanol amount allow the encapsulated molecules within the pores to be progressively extracted until their complete removal. X-ray diffraction (Fig. 4) and nitrogen adsorption–desorption isotherms (Fig. 5) are performed at each step in order to characterize the evolution of the structure and porosity of the loaded MCM 41. After the impregnation procedure, the most significant change in the XRD pattern (Fig. 4) of the silica host is the strong decrease of the diffraction peak intensity corresponding to the (100) reflection arising from the hexagonal pore arrangement. For each successive wash with ethanol, the intensities of the diffraction peak increase and they were nearly fully recovered after the total extraction of the ibuprofen molecules. The adsorption isotherms of nitrogen displayed in Fig. 5 are also hardly changed with the amount of ibuprofen included within the pores except for the step height. The characteristic pore-filling step of the nitrogen adsorption isotherm disappears after the loading of ibuprofen. Indeed, the characteristic type IV isotherm of mesoporous materials change with pore filling into a type I isotherm associated a microporous or non-porous solid. The adsorption isotherms obtained at each wash of the loaded sample reflect a progressive increase in

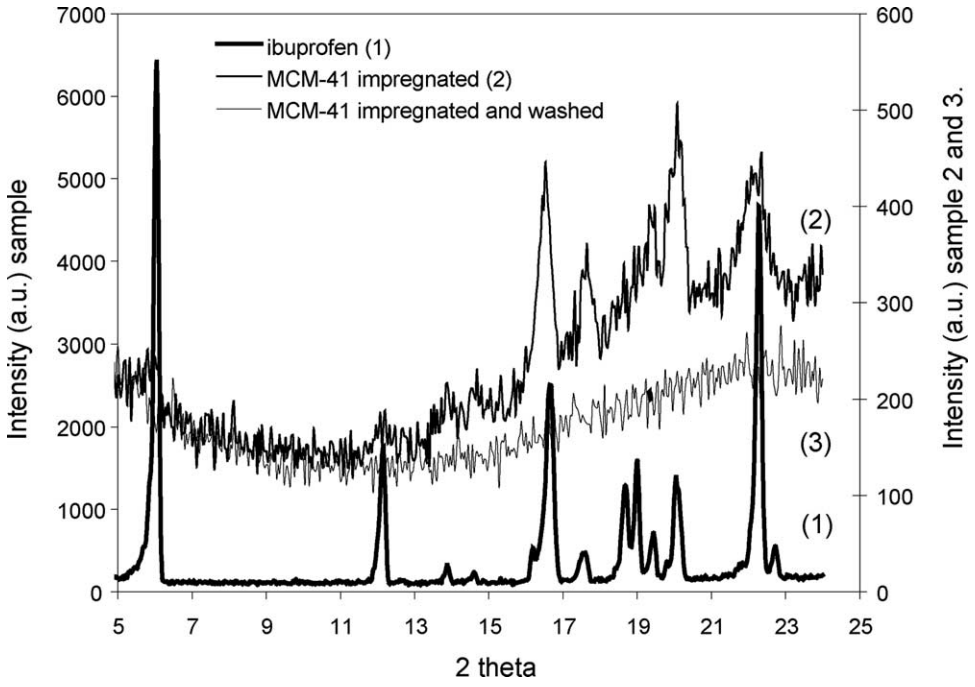


Fig. 3. XRD patterns (1) ibuprofen powder and (2) MCM 41 sample loaded with ibuprofen and (3) washed with 5 ml of ethanol.

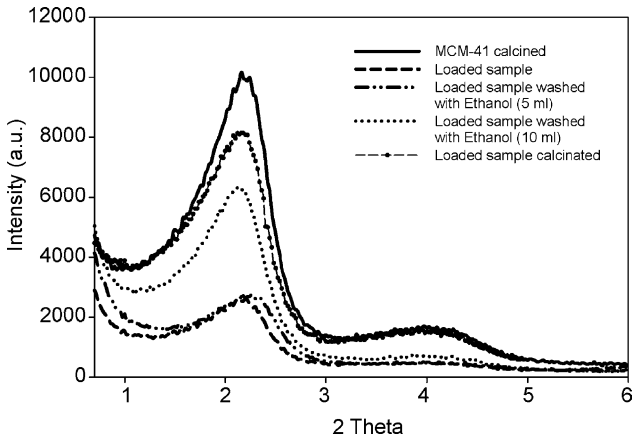


Fig. 4. XRD patterns of MCM 41 sample in the calcined state or loaded with ibuprofen and at different steps of the ibuprofen extraction with ethanol.

BET surface area and pore volume. Moreover, a shift of the relative pressure of the capillary condensation step is observed from 0.12 to 0.35.

All these data, obtained from X-ray diffraction and nitrogen adsorption are consistent with the pore filling with ibuprofen molecules. Indeed, the extinction of the intensities of X-ray diffraction peak results and depends on the amount of ibuprofen presents within the pores. These results are not surprising as similar results, concerning the filling of mesopores of MCM 41 with organic liquids of different scattering power have been previously observed [28]. This study has shown that the peak intensities could be correlated with the scattering contrast between the silicate wall and the sorbate inside the channel. Therefore, the decrease of the scattering contrast following the pore filling is correlated to the observed diffraction peak intensity. In the same way, the nitrogen adsorption isotherm of a loaded sample washed once, exhibits a dramatic decrease of the pore volume and specific surface area compared to the non-loaded MCM 41. These results suggest that a large amount of ibuprofen is included within the pore, even though a few ibuprofen molecules may still be adsorbed on the external surface of the MCM 41 particles. Surface area and mesoporous volume decrease as a result of the lining of mesopores by organic drug molecules. However, the pore size distribution, which decrease from 34.3 to 29 Å, is less affected than the mesoporous volume by the inclusion of ibuprofen until the saturation of the inner volume. This suggests that the ibuprofen molecules are packed inside the pore and not uniformly distributed on the inner surfaces.

Moreover, after the total removal of ibuprofen from the pores, the intensities of the diffraction peaks are nearly recovered as are the total mesoporous volume, the pore size distribution and the surface area. These results indicate that the regular mesoporous structure of the host material is preserved during all the impregnation procedure. Therefore, based on the X-ray diffraction data and nitrogen adsorption results for the loaded sample and for the samples washed in successive steps, it was demonstrated that the ibuprofen molecules were present within the pores in an amorphous state.

The in vitro release of ibuprofen has been performed in two simulated fluids: gastric fluid (pH 1.2) for 30 min and then intestinal fluid (pH 7.4) for 90 min, using dissolution in a flow-through cell [23], in order to simulate the behavior of the material after oral administration (Fig. 6). Ibuprofen (38 ± 2%) is released in the gastric fluid during the first 20 min of the kinetics. In an intestinal medium, the release is faster and reaches a plateau after 45 min at 91% (±8%) release. One may suppose that the increase in the aqueous solubility of ibuprofen (pK_a 5.6) at pH 7.4 ($s = 0.1$ g ml^{-1}) facilitates the transfer of the molecules from the silica matrix to the buffered solution. Finally, in the release tests, the diffusion of the encapsulated ibuprofen molecules does not seem to be restricted, a fact consistent with the well-defined porosity and channel size of the MCM 41 materials. This rapid kinetic profile presents a great interest for pharmaceutical application in order to improve a rapid drug delivery of poorly water-soluble drugs.

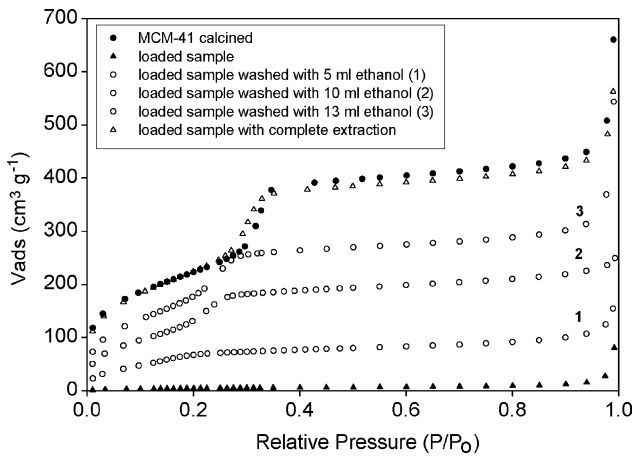


Fig. 5. Nitrogen adsorption isotherms at 77 K, degassed at 308 K for MCM 41 sample in the calcined state or loaded with ibuprofen and at different steps of ibuprofen extraction with ethanol.

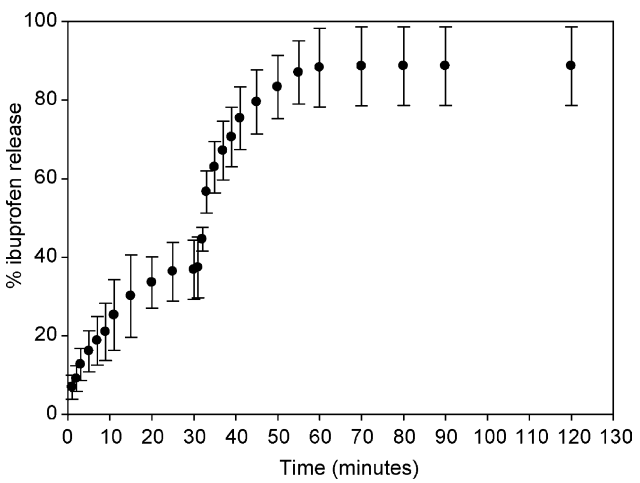


Fig. 6. Ibuprofen release profile into gastric fluid during 30 min (pH 1.2) and then intestinal fluid (pH 7.4) during 1 h.

After stirring the washed MCM 41 for 24 h in a buffer at pH 7.4, ibuprofen is quantified using HPLC in order to determine the 100% release of ibuprofen. The MCM 41 particles were filtered off the phosphate buffer solution, dried and characterized by nitrogen adsorption (data non-shown). A decrease in the amount of nitrogen adsorbed is observed. Moreover, the adsorption isotherm does not exhibit any more the adsorption step characteristic of the mesoporous materials. These observations suggest a collapse of the porosity due to the erosion of the solid. However, during this kinetics at pH 7.4, the release of the ibuprofen molecules from the particles seems to occur faster (20 min) than the degradation of the silica matrix by the erosion (a few hours). Therefore, the release of the drug during the dissolution kinetics is certainly due to a diffusion process.

4. Conclusion

The results obtained show that pharmaceutically active compounds could be loaded with a great efficiency into MCM 41 mesoporous silica. The loading extent is influenced by the loading procedure. Successive impregnations of the MCM 41 particles with a solution of ibuprofen in ethanol result in a significant improvement of the amount of the drug molecules encapsulated. Moreover, it has been shown using X-ray diffraction that the encapsulated molecules remain in a molecular and amorphous state because no crystallization process occurs within the pores. These physical properties of encapsulated ibuprofen allow a rapid liberation of the probe during the dissolution kinetics. Release experiments performed in a simulated gastric and intestinal fluid showed a rapid and complete release of the ibuprofen molecules included within MCM 41 mesopores principally by a diffusion phenomenon. The molecules can easily diffuse out of pores due to their well-defined amorphous and molecular state and to the size of the pores of the mesostructured silica.

Finally, for their high surface areas and ordered mesoporous structure, micelle-templated silica materials constitute a potentially interesting drug carrier for non-water-soluble drugs. This material allowed us to encapsulate a drug with a control of its physical state (molecular, in the case of ibuprofen) inside the pores so that the formation of a cristalline state is avoided. The stability of the silica material versus the gastric fluid leads to a release of only one-third of the drug, the larger part being freed in the intestinal fluid. The molecular state allows a rapid kinetic profile for the release. The association of a nanostructured mineral to the molecular state of the drug presents a great interest for pharmaceutical applications as it allows a control of the kinetic delivery of lipophilic drugs.

References

[1] S. Benita (Eds.), Microencapsulation, Drugs and the Pharmaceutical Sciences, Marcel Dekker, New York, 1996.
[2] V.-P. Torchilin, Structure and design of polymeric surfactant-based drug delivery systems, J. Control. Release 73 (2001) 137–172.
[3] T. Lian, R.J.-Y. Ho, Trends and developments in liposome drug delivery systems, J. Pharm. Sci. 6 (2001) 90.
[4] N. William Charman, Lipids, lipophilic drugs and oral drug delivery—some emerging concepts, J. Pharm. Sci. 8 (2000) 89.
[5] J. Ferezou, N.-T. Lai, C. Leray, T. Hajri, A. Frey, Y. Cabaret, J. Courtieu, C. Lutton, A.-C. Bach, Lipid composition and structure of commercial parenteral emulsions, Biochim. Biophys. Acta 1213 (1994) 149–158.
[6] A.-B. Dennis, S.-J. Farr, I.-W. Kellaway, G. Taylor, R. Davidson, In vivo evaluation of rapid release and sustained release Gelucire capsule formulations, Int. J. Pharm. 65 (1990) 85–100.
[7] S. Sweetana, M.-J. Akers, Solubility principles and practices for parenteral drug dosage form development, J. Pharm. Sci. Technol. 50 (5) (1996) 330–342.
[8] S. Nema, R.-J. Washkuhn, R.-J. Brendel, Excipients and their use in injectable products, J. Pharm. Sci. Technol. 51 (4) (1997) 166–171.
[9] K. Unger, H. Rupprecht, B. Valentin, W. Kircher, The use of porous and surface modified silicas as drug delivery and stabilizing agents, Drug Dev. Ind. Pharm. 9 (1983) 69–91.
[10] P. Kortesuo, M. Ahola, M. Kangas, I. Kangasniemi, A. Yli-Urpo, J. Kiesvaara, In vitro evaluation of sol gel processed spray dried silica gel microspheres as carrier in controlled drug delivery, Int. J. Pharm. 200 (2000) 223–229.
[11] M. Ahola, P. Kortesuo, I. Kangasniemi, J. Kiesvaara, A. Yli-Urpo, Silica xerogel carrier material for controlled release of toremifene citrate, Int. J. Pharm. 195 (2000) 219–227.
[12] V. Ambrogi, G. Fardella, G. Grandolini, L. Perioli, Intercalation compounds of hydrotalcite-like anionic clays with anti-inflammatory agents—intercalation and in vitro release of ibuprofen, Int. J. Pharm. 220 (2001) 23–32.
[13] K. Kawanabe, Y. Okada, Y. Matsusue, H. Iida, T. Nakamura, Treatement of osteomylitis with antibiotic-soaked porous ceramic, J. Bone Joint Surg. 80B (3) (1998) 527–530.
[14] C. Uglea, I. Albu, A. Vatajuna, M. Croitoru, S. Antoniu, L. Panaitescu, R. Ottenbrite, Drug delivery systems based on inorganic materials: synthesis and characterization of a zeolithe–cyclophosphamide system, J. Biomater. Sci. Polym. Ed. 6 (7) (1994) 633–637.
[15] L. Mollo, V. Levresse, M. Ottaviani, S. Ellouk-Achard, M.-C. Jaurand, B. Fubini, Study of the stability of a paramagnetic label linked to mesoporous silica surface in contact with rat mesothelial cells in culture, Environ. Health Perspect. 105 (5) (1997) 1031–1036.
[16] M. Vallet-Regi, A. Ramilla, R.-P. del Real, J.-P. Perez-Pariente, A new property of MCM 41: drug delivery system, Chem. Mater. 13 (2001) 308–311.
[17] U. Ciesla, F. Schüth, Ordered mesoporous materials, Micropor. Mesopor. Mater. 27 (1999) 131–149.
[18] A. Firouzi, D. Kumar, M. Bull, P. Seiger, Q. Huo, S.-A. Walker, J.-A. Zasadzinski, C. Glinka, J. Nicol, D. Margolese, G.-D. Stucky, B.-F. Chmelka, Cooperative organization of inorganic-surfactant and biomimetic assemblies, Science 267 (1995) 1138–1143.
[19] A. Galarneau, F. Di Renzo, F. Fajula, L. Mollo, B. Fubini, M.-F. Ottaviani, J. Colloid Interface Sci. 201 (1998) 105.
[20] D. Brunel, A. Cauvel, F. Di Renzo, F. Fajula, B. Fubini, B. Onida, E. Garrone, Preferential grafting of alkoxysilane coupling agents on the hydrophobic portion of the surface of micelle-templated silica, New J. Chem. 24 (2000) 807–813.

[21] A. Derrien, G. Renard, D. Brunel, Guanidine linked to micelle-templated mesoporous silicates as base catalyst for transesterification, Stud. Surf. Sci. Catal. 117 (1998) 445–452.
[22] K. Moller, T. Bein, Inclusion chemistry in periodic mesoporous hosts, Chem. Mater. 10 (1998) 2950–2963.
[23] S.N. Bhattachar, J.A. Wesley, A. Fioritto, P.J. Martin, S.R. Babu, Dissolution testing of a poorly soluble compound using the flow-through cell dissolution apparatus, Int. J. Pharm. 236 (2002) 135–143.
[24] F. Di Renzo, H. Cambon, R. Dutartre, A 28-years-old synthesis of micelle-templated mesoporous silica, Micropor. Mater. 10 (1997) 283–286.
[25] M.-J. Meziani, J. Zajac, S. Partyka, Adsorption and interfacial aggregation of cationic quaternary ammonium surfactant on powdered mesoporous MCM 41 aluminosilicates from dilute aqueous solution, Langmuir 16 (22) (2000) 8410–8418.
[26] H. Hata, S. Saeki, T. Kimuro, Y. Sugahara, K. Kuroda, Adsorption of taxol into ordered mesoporous silicas with various pore diameters, Chem. Mater. 11 (1999) 1110–1119.
[27] M. Sliwinska-Bartkowiak, G. Dudziak, R. Gras, R. Sikorski, R. Radhakrishnan, K.E. Gubbins, Freezing behavior in porous glasses and MCM 41, Colloid Surf. A: Physicochem. Eng. Aspects 187–188 (2001) 523–529.
[28] B. Marler, U. Oberhagemann, S. Vortmann, H. Gies, Influence of the sorbate type on the XRD peak intensities of loaded MCM 41, Micropor. Mater. 6 (1996) 375–383.