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Synthesis and characterisation of ibuprofen-anchored MCM-41 silica and silica gel

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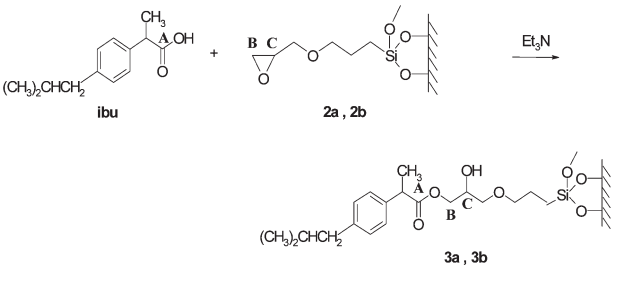
A non-steroidal anti-inflammatory drug (ibuprofen) has been anchored inside the mesoporous channels of MCM-41-type silica and on a silica gel surface. The relevant anchoring procedure through an ester function has been investigated. It uses the epoxide ring opening of 3-glycidoxypropylsilane grafted on the silica surface by the carboxylic-group-containing ibuprofen. The control of the surface modification and of the anchoring efficiency was achieved by comparison of spectroscopic data with those obtained using homogeneous counterparts. The use of nanostructured silica allowed an accurate verification of the different surface modifications and also a higher drug loading.

Amorphous colloidal and porous silica are used as adjuvants in pharmaceutical technology. Due to its properties, silica has been proposed as a drug delivery system on the basis of silica-embedding.[1] Drugs are known to adsorb on commercially available silica. Sol-gel processed sintered silica xerogel was studied as a controlled release material for drug delivery.[2] More recently, a copolymer–silica xerogel composite containing toremifene, an anti-estrogenic drug, was reported as a new drug-loaded material.[3] The discovery of highly structured mesoporous silicas produced by micelle templating, such as MCM-41 disclosed by Mobil researchers,[4] has opened up new possibilities for their use as supports or adsorbents. Such materials have been investigated for hosting non-steroidal anti-inflammatory drugs (NSAIDs) bearing a carboxylic acid, through a confinement procedure consisting in either physisorption on the pure silica surface[5,6] or *via* an acid-base reaction with aminopropyl chains tethered to the surface.[7] Recently, we have successfully encapsulated ketoprofen into nanostructured MSU-type silica by direct templated sol-gel synthesis.[8] Another attractive strategy to design desired controlled drug delivery systems involves linkage of the prodrugs onto the solid support. In this respect numerous studies describe the covalent attachment of the parent drug to chemical entities or polymers. Thus, NSAIDs were recently bound to methacrylic carriers[9] with the resulting material being presented as a drug release system.

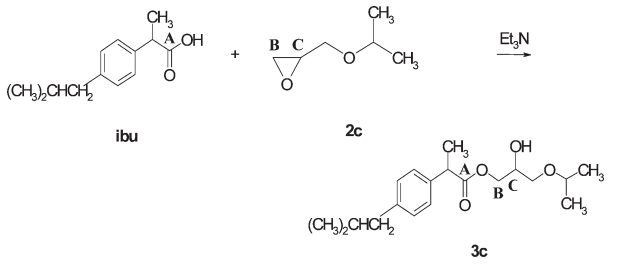
In this work, we have investigated the anchorage of moieties containing an ibuprofen residue onto the pore walls of MCM-41, the active molecule being linked by a labile ester function. The expected advantages of such a prodrug system are protection of the drug due to its location inside the pores of an inorganic material and its potential release induced by the cleavage of the ester bond by esterases *in vivo*. Taking into account our previous results on successful monoglyceride formation through epoxide ring opening of glycidol by a fatty acid, heterogeneously catalysed by amine-supported silica,[10] we have investigated the addition reaction of racemic ibuprofen *via* its carboxylic function to glycidoxy groups borne by propylsilane chains grafted onto the MCM-41 silica surface. A similar esterification reaction used as the coupling reaction has been reported for the anchoring of Rhodamine B on mesoporous silicas during the preparation of this manuscript.[11] In this communication, our results are compared with those obtained using homogeneous counterparts and using traditional silica as the support in order to control the surface modification and to see if mesostructuration brings any benefits for prodrug loading.

In the first step, MCM-41 silica **1a** (surface area, $S_{BET} = 697$ $m^2 \cdot g^{-1}$; mesopore volume $V_{meso} = 2.2$ $mL \cdot g^{-1}$) and silica gel **1b** ($S_{BET} = 446$ $m^2 \cdot g^{-1}$; $V_{meso} = 1.9$ $mL \cdot g^{-1}$) surfaces were functionalised using a silanisation reaction with 3-glycidoxypropyltrimethoxysilane. The resulting functionalised samples **2a** and **2b** were then reacted with ibuprofen at toluene reflux (Scheme 1) using triethylamine as an activating agent to give samples **3a** and **3b**. These modified materials were characterised at each step by various physicochemical methods. First, in order to assess the chemical nature of the organic moieties linked to the mineral supports, a reference ester molecule was synthesised in the homogeneous phase. This allowed us (i) to control the efficiency of the epoxy ring opening by the carboxylic function and (ii) to obtain the spectroscopic data necessary to identify the grafted moieties.

Hence, ibuprofen addition on glycidyl isopropyl ether (**2c**), conceived as a model of the grafted 3-glycidoxypropylsilane (**2a** and **2b**), was carried out using the same conditions (Scheme 2). The yellow oily product **3c** was identified by its IR spectrum (Fig. 1), which exhibits a strong carbonyl



Scheme 1



Scheme 2

stretching vibration typical of an ester bond ($\nu_{C=O}$ 1740 cm^{-1}). The ^{13}C NMR chemical shifts [Table 1 and Fig. 2(a)] were assigned to carbon atoms A, B and C of molecule **3c**. These results demonstrate that the coupling reaction successfully occurred between the epoxy ring and the carboxylic function of ibuprofen in homogeneous conditions.

Furthermore, the various modified mesoporous silica materials were analysed by FTIR (Fig. 1) and ^{13}C CP/MAS NMR [Fig. 2(b)]. The data are summarised in Table 1 and compared to those of their homogeneously prepared counterparts. A comparison of the spectroscopic data for the hybrid materials **2a**, **2b** and **3a**, **3b** with those of **2c** and **3c** demonstrates that these solids contain glycidyl and 2-(4-isobutylphenyl) propionate functions, respectively. Thus, these results confirm the effective linkage of ibuprofen to the functionalised MCM-41 **3a** and to silica gel **3b** by means of an ester function.

Fig. 3(a) presents the nitrogen adsorption/desorption isotherms of samples **1a**, **2a** and **3a**. They exhibit a type IV pattern featuring a sharp step characteristic of a monodispersed pore size mesoporous structure. This result clearly indicates that the mesostructure is preserved during the surface modifications. The textural characteristics of these various materials are reported in Table 2 in addition to those of their silica gel counterparts. It is noteworthy that the surface areas and mesoporous volumes of both the MCM-41 and silica gel series decrease as the extent of organic lining increases. These variations are slight but definitively in agreement with the high initial pore diameter. Moreover, the C_{BET} value decreases with

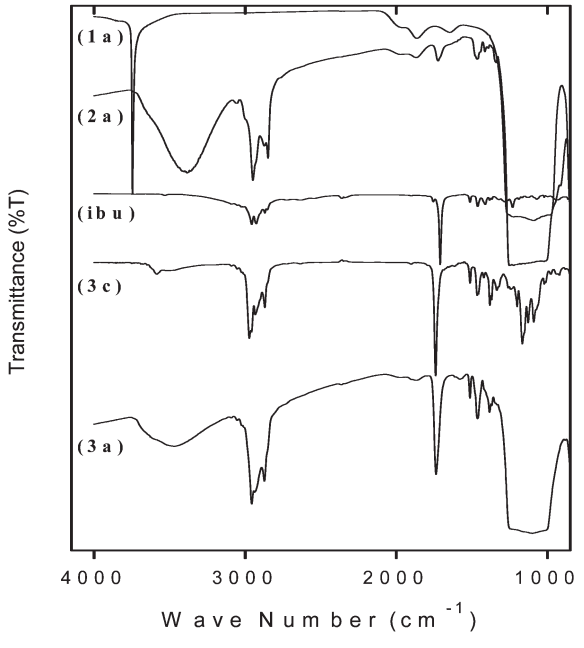


Fig. 1 FTIR spectra of MCM-41 (**1a**), functionalised MCM-41 (**2a**), ibuprofen (ibu) and ibuprofen ester (**3c**) in CCl_4, ibuprofen-anchored MCM-41 (**3a**).

Table 1 IR and ^{13}C NMR spectroscopic data for the modified MCM-41 **2a** and **2b** and **3a** and **3b** compared to ibuprofen (**ibu**), glycidyl isopropyl ether (**2c**) and the reference compound **3c**

	ibu	2c	3c	2a, 2b	3a, 3b
$\nu_{C=O}$/cm^{-1}	1709	–	1740	–	1740
δ_A/ppm	182	–	173	–	174
δ_B/ppm	–	44	68	50	67
δ_C/ppm	–	51	64	43	74

each step of the modification procedure (Table 2), revealing a gradual surface modification towards a more hydrophobic/organophilic character as previously reported.[12] Actually, the C_{BET} parameter, expressed as $C_{BET} = \alpha\exp[E_1 - E_L/RT]$, where E_1 is the adsorption energy of the first monolayer adsorbed on the surface and E_L is the molecule interaction enthalpy in the liquid phase, is considered as a quantification of adsorbate-surface interactions. These strongly depend on the surface polarity for polarizable molecules such as nitrogen. Therefore, the decrease of the C_{BET} value is consistent with an improvement in the coverage of the more polar silica surface due to an increase of the organic moiety length. More importantly, the mesopore volume of the materials standardised *versus* the dry mineral oxide component [Fig. 3(b); Table 2] decreased as a function of the extent of the organic lining. Hence, such a result reveals that the major surface modification takes place on the silica surface inside the mesoporous channels of the nanostructured MCM-41-type silica.

The chemical composition of the hybrid organic-inorganic materials was determined by thermogravimetric and elemental analyses. Solids **2a** and **2b** contain 1.1 and 0.83 molecules of 3-glycidoxypropylsilane per square nm of dry silica MCM-41 and silica gel, respectively (Table 3). These loadings are expressed in terms of density for standardisation in order to compare the various materials coming from parent supports featuring different surface areas. Then, to these solids, 0.76 and 0.53 mmole of ibuprofen, respectiely, were added and anchored. These amounts are given per gram of dry pure silica contained in the two materials. These ibuprofen loadings correspond to epoxide ring opening reaction yields of 49% and 72% for MCM-41 and silica supports, respectively. This difference in epoxide conversion could result from differences in both the chemical nature of the silica surface and in the site accessibility. Indeed, the epoxide ring could be activated by

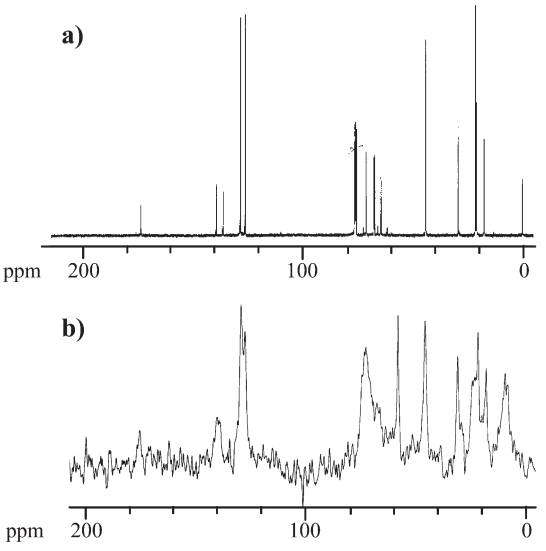


Fig. 2 (a) ^{13}C NMR spectrum of ibuprofen ester in $CDCl_3$ (**3c**); (b) ^{13}C MAS NMR spectrum of ibuprofen-anchored MCM-41 (**3a**).

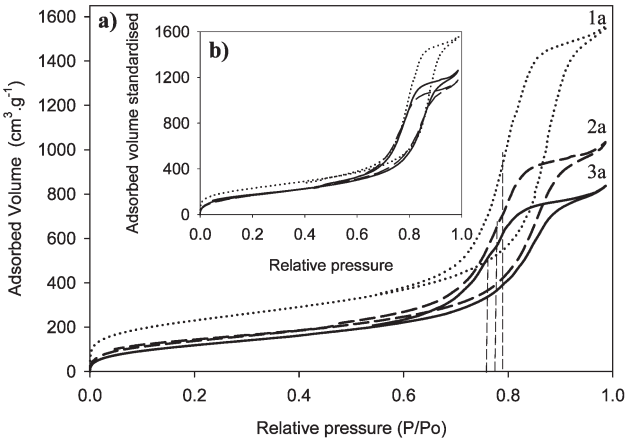


Fig. 3 N_2 adsorption-desorption isotherms at 77 K for calcined (**1a**), functionalised (**2a**) and ibuprofen-anchored (**3a**) MCM-41 *versus* sample weight (a) and standardised *versus* dried mineral oxide (b).

the residual accessible silanol groups, whose concentration and activity are higher in the case of silica gel.[13] Moreover, the denser the surface coverage with 3-glycidoxypropylsilane chains (**2a** *versus* **2b**), the less efficient is the conversion of epoxide by ibuprofen addition due to a lower accessibility resulting from steric hindrance. Hence, even though the coverage of the MCM-41 silica surface with 3-glycidoxypropylsilane moieties (**2a**) is significantly higher than that of the corresponding silica gel surface (**2b**), the lower epoxide ring opening yield in the case of the MCM-41-type materials leads to comparable ibuprofen loadings on the two silica surfaces **3a** and **3b** (0.53 and 0.59 molecule per square nm). Nevertheless, the use of MCM-41-type silica is preferred for anchoring ibuprofen with a higher loading per gram of mineral support due to a significantly higher surface area than any other silica material.

In conclusion, the innovations brought about by this study consist in both (i) the design of a potential pro-drug by a new and well-controlled coupling reaction of an organic acid with a functional alkylsilane chain grafted onto a silica surface and (ii) the use of a nano-structured silica as mineral oxide support in order to obtain an accurate description of the different surface modifications. The study of the release of ibuprofen from this pro-drug system is now in progress.

Experimental

Methods and materials

Adsorption/desorption isotherms for nitrogen at 77 K were performed with a Coulter SA 3100. Samples were previously heated at 373 K under vacuum overnight. FTIR spectra of organic samples in CCl_4 solution and FTIR spectra of self-supported wafers previously heated at 423 K under vacuum were obtained on a Brücker Vector 22 spectrometer. ^{1}H and ^{13}C NMR spectra of the samples in $CDCl_3$ solution were recorded on a Bruker DRX 400 spectrometer. A 135 DEPT pulse program was applied for the ^{13}C NMR spectra. ^{13}C MAS NMR of the modified solids were acquired on a Bruker Avance 300 DPX spectrometer operating at 75.467 MHz under cross-polarisation conditions. The instrument settings were: pulse length 4.2 μs (90°), contact time 3 ms, delay time 5 s, rotor 4 mm. Thermogravimetric studies were carried out on a Netzsch TG 209C IRIS balance under air flow. Elemental analyses were performed at the Service Central d'Analyses of the CNRS in Solaize.

Ibuprofen (2-(4-isobutylphenyl)propionic acid) and 3-Glycidoxypropyltrimethoxysilane were purchased from SIGMA, Glycidyl isopropyl ether, cethyltrimethylammonium (CTAB) and Trimethylbenzene (TMB) were from Aldrich. Aerosil 200 was obtained from Degussa and silica gel 1b from Grace Davison.

Table 2 Textural properties of parent and modified MCM-41 samples

Sample	S_{BET}/m^2 g^{-1}	V_{meso}[b]/mL g^{-1}	C_{BET}	V_{meso}[c]/mL g^{-1} *vs.* dry silica
1a[a]	697	2.22	85	–
2a	515	1.41	56	1.72
3a	457	1.13	37	1.59
1b[a]	446	1.89	98	–
2b	426	1.59	54	1.87
3b	298	1.45	53	1.73

[a] The surface area was calculated according to the BET equation. [b] The pore volume is based on the nitrogen volume adsorbed at the top of the filling step of the isotherms. [c] Area and volume are standardised *versus* dry mineral oxide weight.

Table 3 Chemical composition of different organic entities grafted on silica gel and MCM-41

		Silica gel	MCM-41
Epoxy groups	mmole (g sample)$^{-1}$ [a]	0.62	1.27
	mmole (g SiO_2)$^{-1}$ [b]	0.74	1.56
	molecule nm^{-2}	0.83	1.1
Ibuprofen	mmole (g sample)$^{-1}$ [a]	0.44	0.54
	mmole (g SiO_2)$^{-1}$ [b]	0.53	0.76
	mg (g SiO_2)$^{-1}$	109	156
	molecule nm^{-2}	0.53	0.59
Molar ratio ibuprofen/epoxy groups		0.72	0.49

[a] In mmole *versus* weight of hybrid material. [b] In mmole *versus* weight of dry silica.

Syntheses

Synthesis of 3-isopropyloxapropan-2-ol, 3-[2-(4-isobutylphenyl)propionate] (3c). Ibuprofen [2-(4-isobutylphenyl)propionic acid; 1 g, 4.85 mmol], glycidyl isopropyl ether (0.304 mL, 2.42 mmol) along with dried and freshly distilled triethylamine (0.343 mL, 2.42 mmol) were added to dry toluene (80 mL). The solution was stirred at reflux overnight under N_2. Toluene and triethylamine were removed under vacuum. The oily yellow product obtained was taken up with CH_2Cl_2. The acidic fonction of the excess ibuprofen was neutralised with a 1% KOH aqueous solution. The solution was then quickly washed at least 3 times with CH_2Cl_2 to avoid ester hydrolysis. Residual water in the organic phase was eliminated with $MgSO_4$. The solvent was removed under vacuum. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07 (d, $J = 8.0$ Hz, 4H; Ar*H*), 4.05 (m, 2H; OCH_2-CHOH), 3.81 (quint., $J = 5.0$ Hz, 1H; C*H*OH), 3.66 (q, $J = 7.2$ Hz, 1H; C*H*CH_3), 3.41 [sept., $J = 5.5$ Hz, 1H; $(CH_3)_2CHO$], 3.23 (m, 2H; CHOHCH_2OCO), 2.36 (d, $J = 7.0$ Hz, 2H; ArCH_2CH), 1.76 [sept., $J = 7.0$ Hz, 1H; $CH_2CH(CH_3)_2$], 1.42 (d, $J = 7.0$ Hz, 3H; CH_3CH), 1.02 [dd, $J = 6.0$ Hz, 2.4 Hz, 6H; $(CH_3)_2$CHO], 0.81 [d, $J = 7.0$ Hz, 6H; $(CH_3)_2CHCH_2$]. ^{13}C NMR (400 MHz, $CDCl_3$): δ 173.5 (*C*=O), 139.5 (*C*Ar$_1$), 136.6 (*C*Ar$_4$), 128.3 (*C*Ar$_{3,5}$), 126.1 (*C*Ar$_{2,6}$), 71.2 [$(CH_3)_2$*C*HO], 67.8 (CH_2*C*HOHCH_2), 67.5 [$(CH_3)_2$CHO*C*H_2], 64.5 (CHOH*C*H_2COOR), 44 (Ar*C*H_2CH), 29.1 [$CH_2CH(CH_3)_2$], 20.9 [(CH_3)$_2$CHCH_2, (CH_3)$_2$CHCO], 17.3 (CH_3CH). IR (CCl_4): ν 1740 cm^{-1} (C=O ester). MS (FAB$^+$): m/z 305 (MH$^+$), 263 (MH$^+ - 42$), 207 [MH$^+ - 98$ (M $_{ibuprofen} + H^+$)], 161 (MH$^+ - 144$).

Synthesis of a large pore MCM-41 (1a). The synthesis of a MCM-41 material (**1a**) with large mesopores (about 100 Å in diameter) was carried out according to the procedure of Desplantier-Giscard *et al.*[14] The reactants were added under stirring at room temperature in the following order: H_2O, NaOH, CTAB, TMB and SiO_2 (Aerosil) (molar ratio: 21 : 0.26 : 0.1 : 1.30 : 1). Swollen micelles were formed using a TMB/CTAB molar ratio of 13. After the addition of silica, the mixture was stirred for 30 min and then left to stand in an autoclave for 1 h at 388 K. The gel was then filtered, washed with distilled water to reach neutral pH and dried 10 days at 383 K. A thermal treatment at 823 K under air flow eliminated the surfactant.

Functionalisation of silica (2a and 2b). Freshly activated (30 min under N_2 flux) silica samples **1a** or **1b** (3 g) and 3-glycidoxypropyltrimethoxysilane (3.74 mL and 1.49 mL of silane for the preparation of **2a** and **2b**, respectively) were added to dried toluene (50 mL). After stirring the solution at toluene reflux for 1.5 h, the released methanol was distilled and then the reaction was heated again at 120 °C for 1.5 h. The modified silicas were filtered and first washed with toluene and diethyl ether. They were then submitted to a continuous extraction run overnight in a soxhlet apparatus using diethylether–dichlorometane (v/v, 1 : 1) and dried overnight at 433 K. ^{13}C solid state NMR: δ 73 [O*C*H$_2$(CH$_2$)$_2$], 70.4 (O*C*H$_2$epoxy), 50.1 (CH$_2$*C*epoxy), 47.6 (SiO*C*H$_3$), 43.5 (*C*epoxy), 22.7 (OCH$_2$*C*H$_2$CH$_2$Si), 6.2 [Si*C*H$_2$(CH$_2$)$_2$]. TGA (25–850 °C, 5 °C·min^{-1}): decomp. > 260 °C; mass change: −17.9% for **2a** and −10.2% for **2b**. Elem. anal.: C 10.73%, Si 37.20% for **2a**; C 5.33%, Si 40.20% for **2b**.

Preparation of ibuprofen-anchored silicas (3a and 3b). Functionalised silicas **2a** or **2b** was added to freshly distilled (2.5 g for **2a** and 1 g for **2b**) ibuprofen in a toluene solution (50 mL) with triethylamine (1.72 mL for **2a** and 0.687 mL for **2b**). The suspension was stirred overnight at reflux. The solid was filtered and carefully washed in sequence with different solvents (toluene, methanol, distilled water, dimethylformamide, methanol, diethyl ether) to remove any physically adsorbed residual ibuprofen. The washing step was completed with a continuous extraction run overnight in a soxhlet apparatus with diethyl ether–dichloromethane (v/v, 1:1). Samples **3a** and **3b** were dried for 2 days at 433 K. ^{13}C MAS NMR: δ 174 (*C*=O), 140 (*C*Ar$_{1,4}$), 129.3 (*C*Ar$_{3,5}$), 127.5 (*C*Ar$_{2,6}$), 75–67 [br., O*C*H$_2$(CH$_2$)$_2$, CH$_2$*C*HOHCH$_2$, CH$_2$*C*HOHCH$_2$, CHOH*C*H$_2$COOR], 50.9 (undetermined), 45.3 (Ar*C*H$_2$CH), 30.4 [*C*H(CH$_3$)$_2$], 23 (OCH$_2$*C*H$_2$CH$_2$Si), 21.1 ([*C*H$_3$)$_2$CHCH$_2$], 17.4 (*C*H$_3$CH), 9 (*C*H$_2$Si). TGA (25–850 °C, 5 °C min^{-1}), decomp. > 260 °C; mass change: −28.8% for **3a** and −15.1% for **3b**. Elem. anal.: C 19.83%, Si 31.70% for **3a** and C 9.07%, Si 31.70% for **3b**.

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