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Progesterone inclusion into cyclodextrin-functionalized mesoporous silica

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Abstract SBA-15 type mesoporous silica has been modified to produce a covalent bond with β-cyclodextrin by two different synthetic approaches to obtain an hybrid system able to work as a drug delivery system for progesterone. In the first approach, SBA-15 silica was first let to react with 3-glycidyloxypropyltrimethoxysilane to produce an epoxide ring functional group on mesoporous silica. The latter was then reacted under basic conditions with mono-6-deoxy-6-mercapto-β-cyclodextrin (β-CDCH$_2$SH), prepared in its turn in two steps from β-cyclodextrin (β-CD) through monotosylation to give β-CDCH$_2$OTs followed by thiolation with thiourea. In the second approach, a silica suitably functionalized with a terminal thiol group (obtained by the reaction of SBA-15 silica with 3-mercaptopropyltrimethoxysilane) was reacted with β-CDCH$_2$OTs. The obtained materials were characterized by X-Ray powder diffraction, nitrogen adsorption, ^{13}C Cross Polarization Magic Angle Spin Nuclear Magnetic Resonance (^{13}C CP/MAS NMR). Progesterone was loaded on the materials producing complete filling of mesopores and cyclodextrin cavities. Its release was studied at different pH values. Only one of the two progesterone-loaded delivery device is able to retain the drug in the system during the first period at acid pH (2 h) and release it after pH increase.

Keywords SBA-15 · Hybrid mesoporous silica · Progesterone-loaded cyclodextrins · Progesterone release

1 Introduction

Several different kinds of mesoporous silicas [1, 2] have been studied as matrices for drug inclusion to the aim of producing systems able to modify drug diffusion after administration [3, 4].

Drug inclusion has been, very often, obtained through adsorption but, in some cases, the drug has been also adsorbed on the modified surface of hybrid mesoporous silica. Quite recently the incorporation of some active principles has been also ensured through the use of host–guest interactions, opening the possibility of designing new drug-targeting devices able to deliver the drug after specific irradiative or chemical stimuli. One major goal is to obtain important drug loadings specially when the drug molecule shows too low affinity for the silica surface, so suitable chemical pore surface modifications is requested.

Nanoparticle systems constituted of poly(isobutylcyanoacrylate) and hydroxypropyl-β-cyclodextrin, in the presence or absence of surfactant, have also been investigated with the aim to increase the drug loading of hydrophobic substances in the nanoparticles, using progesterone as model molecule. The results showed that this new type of nanoparticles may offer an opportunity for increasing the loading of nanoparticles with various lipophilic drugs [5]. Furthermore, a novel carrier system based on a mucoadhesive polymer exhibiting improved properties concerning drug delivery to the vaginal

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mucosa has been prepared by the covalent attachment of L-cysteine to commercially available polyacrylic acid (Carbopol 974P) [6]. This modified polymer was a promising carrier for progesterone providing a prolonged residence time and a controlled drug release. Cyclodextrins (CDs) are cyclic oligosaccharides able to form non-covalent inclusion complexes with several lipophilic molecules, and CD-based materials can be used as drug delivery systems [7]. Inclusion complexes of hydrocortisone and progesterone were formed with β-cyclodextrins and incorporated in solid lipid nanoparticles, the incorporation of the more hydrophilic drug, hydrocortisone, was higher than that of progesterone and the release lower when the drugs were incorporated as inclusion complexes than as free molecules [8]. According to a different approach, a biomineral-binding alendronate-β-cyclodextrin conjugate (ALN-β-CD) was developed as a novel drug delivery system [9] able to gradually release dexamethasone (Dex).

The ability of cyclodextrins to host molecules has been also evaluated in the development of a photochemical biovector in which a photoactive component is assembled together with an organized receptor (cyclodextrin aggregate), which at the same time can act as an organizing system. As photoactive component the authors have used a porphyrin which photosensitizes the production of singlet oxygen, whose manifold oxidative effects are the basis of photodynamic therapy of tumors [10].

In this work, SBA-15 type mesoporous silica has been modified to produce a covalent bond with β-cyclodextrin residues so that the whole hybrid system can work as a drug delivery system for progesterone. Progesterone release has been studied at different pH values.

2 Experimental

2.1 Materials

All reactants were commercially available and were used without further purification.

Hybrid materials SC1 and SC2 were prepared as described below.

2.2 Preparation of the samples

2.2.1 Synthesis of mesoporous materials

SBA-15 mesoporous material has been synthesised using a triblock-copolymer neutral surfactant PEO_{20}–PPO_{70}–PEO_{20} (Pluronic P123) in accordance with the procedure described by Zhao et al. [11].

In a typical preparation 4.0 g of Pluronic P123 was dissolved in 30 g of water and 120 g of 2 M HCl solution with stirring at 35 °C. Then 8.50 g of TEOS was added into that solution under vigorous stirring at 35 °C for 20 h. The mixture was aged at 80 °C overnight without stirring. The solid product was recovered, washed and air dried at room temperature.

The obtained materials has been calcined at 550 °C for 6 h to remove the structuring surfactant.

2.2.2 Preparation of 3-glycidyloxypropyl silica S1[1]

Silica SBA-15 (10 g) was activated at 150 °C and then was suspended under nitrogen in 100 mL of anhydrous toluene. To the resulting suspension were added 4.7 g (19.9 mmol) of 3-glycidyloxypropyltrimethoxysilane, and the resulting mixture was refluxed with stirring for 24 h. After cooling, the suspended solid was recovered by filtration and washed with toluene, ethanol, toluene and diethyl ether in this sequence. Eventually, the solid was purified by toluene Soxhlet extraction and then dried under vacuum at 70 °C for 5 h.

2.2.3 Preparation of 3-mercaptopropyl silica S2[6]

Freshly activated (at 150 °C) silica SBA-15 (10 g) and 3-mercaptopropyltrimethoxysilane (10.6 g, 26.9 mmol) were added under nitrogen to 100 mL of anhydrous toluene, and the resulting mixture was refluxed for 24 h. After cooling, the suspended solid was recovered by filtration, washed with toluene and dried at 120 °C for 12 h.

2.2.4 Preparation of monotosyl-β-cyclodextrin β-CDCH$_2$OTs[4]

Dried β-cyclodextrin (13.0 g, 11.5 mmol) was added in portions with stirring to a 500 mL round bottom flask containing 100 mL of anhydrous pyridine until complete dissolution was achieved. Tosyl chloride (1.7 g, 8.9 mmol) was then added in portions over a period of 40 min with stirring. The resulting clear solution was allowed to stand at room temperature for 18 h. Pyridine was then removed in vacuum, and the residual oil was triturated with acetone. The resulting solid, consisting of a mixture of β-CD and β-CDCH$_2$OTs (as confirmed by TLC analysis), was filtered, dried and then transferred into a 500 mL flask together with 200 mL of water. The resulting suspension was heated with stirring until gentle refluxing was observed. After a few min under reflux, complete dissolution was observed. The solution thus obtained was then allowed to cool to room temperature overnight. The resulting precipitated solid (consisting of β-CDCH$_2$OTs with some traces of unreacted β-CD) was filtered, washed with cold water and dried under high vacuum for 2 days (yield: 4.5 g, 30 %). The product was characterized by comparison with literature data.

2.2.5 Preparation of mono-6-deoxy-6-mercapto-β-cyclodextrin β-$CDCH_2SH$[5]

β-$CDCH_2OTs$ (4.0 g, 3.1 mmol) and thiourea (4.0 g, 52.6 mmol) were dissolved in 200 mL of a 8:2 mixture of MeOH:H_2O. The resulting mixture was allowed to reflux for 2 days with stirring. After cooling, the solvent was removed in vacuo. MeOH (60 mL) was added to the residue followed by stirring for 1 h at RT. The resulting solid was filtered, washed with MeOH and dried under vacuum for 1 h. The solid was then dissolved in 140 mL of 10 % aq NaOH, and the resulting solution was heated at 50 °C for 5 h with stirring. After cooling, the pH of the solution was adjusted to 2 by addition of 10 % HCl, and 10 mL of trichloroethylene were added dropwise. After stirring overnight at RT, the resulting precipitate was filtered, washed carefully with cold water and then dried overnight for 2 days (yield: 2.0 g, 56 %). The comparison with the spectra reported in literature confirmed the formation of β-$CDCH_2SH$.

2.2.6 Preparation of hybrid material SC1

To a solution of mono-6-deoxy-6-mercapto-β-cyclodextrin (β-$CDCH_2SH$, 1 g, 0.95 mmol) in anhydrous DMF (13 mL) was added under nitrogen K_2CO_3 (0.6 g, 4.34 mmol), and the resulting mixture was stirred at RT for 0.5 h. 3-Glycidyloxypropyl silica S1 (1 g) was then added, and the suspension was heated at 120 °C for 3 h with stirring. After cooling, the suspended solid was recovered by filtration, washed with methanol, DMF, methanol, water, methanol in this sequence, and eventually dried under high vacuum for 24 h.

2.2.7 Preparation of hybrid material SC2

A stirred suspension of 3-mercaptopropyl silica S2 (1.0 g) and K_2CO_3 (0.6 mg, 4.34 mmol) in anhydrous DMF (60 mL) was heated at 80 °C for 0.5 h. Monotosyl-β-cyclodextrin (β-$CDCH_2OTs$, 4.0 g, 3.1 mmol) was then added at 80 °C, and the resulting mixture was heated at the same temperature for 24 h with stirring. After cooling, the suspended solid was recovered by filtration, washed with DMF and water, and eventually dried under high vacuum for 24 h.

2.3 Drug loading and release

Progesteron (60 mg) was dissolved in distilled water (30 mL) then 300 mg of SBA-15 or β-CD were soaked in the solution and stirred for 24 h. In the case of SC1 and SC2 materials, the solutions were obtained dissolving 80 mg of progesterone in 40 mL of distilled water and suspending, under stirring for 24 h, 400 mg of each hybrid mesoporous compound.

Release studies were carried out according to the method reported in USP XXII (*United States Pharmacopoeia*, drug-release test). First, 25 mg of the impregnated mesoporous sample were immersed in 10 mL of HCl 0.1 M solution (pH 1.0, simulating gastric fluid) and maintained at 37.0 ± ←0.5 °C in a water bath under magnetic stirring (∼←50 rpm). Finally, sodium phosphate buffer solution was added to raise pH to 6.8 (simulating intestinal fluid). At prefixed time samples were filtered and the obtained solutions were recovered.

Drug release has been determined by HPLC on the solutions obtained for different soaking times of the materials in solutions buffered at pH 1.0 and 6.8 at 37° C.

2.4 Characterization techniques

^1H NMR and ^{13}C NMR spectra were recorded on a Bruker DPX Avance 300 spectrometer at 25 °C in $CDCl_3$ solutions at 300 MHz and 75 MHz, respectively, with Me_4Si as internal standard. Chemical shifts (δ) and coupling constants (*J*) are given in ppm and in Hz, respectively.

^{13}C MAS NMR spectra were recorder on a Bruker Avance 500 spectrometer operating at 126 MHz with a 4 mm probe. The spinning frequency was 12 kHz. $^1H \rightarrow {}^{13}C$ CP/MAS experiment were performed with 2.5 ms contact time and 4 s recycle delay. The Hartmann-Han conditions were established on a sample of adamantine.

The N_2 adsorption–desorption volumetric isotherms at 77 K were measured on a Micromeritics Asap 2010 apparatus. Samples were pre-treated under vacuum at 110 °C to a residual pressure of 2×10^{-3} mm Hg. Surface area of the samples was calculated by BET linearization in the pressure range 0.05–0.2 P/P_0. Lattice pore volume was obtained from the amount of nitrogen gas adsorbed at the top of the rising section of the isotherm.

SEM micrograph has been acquired by a FEI Quanta 200 instrument.

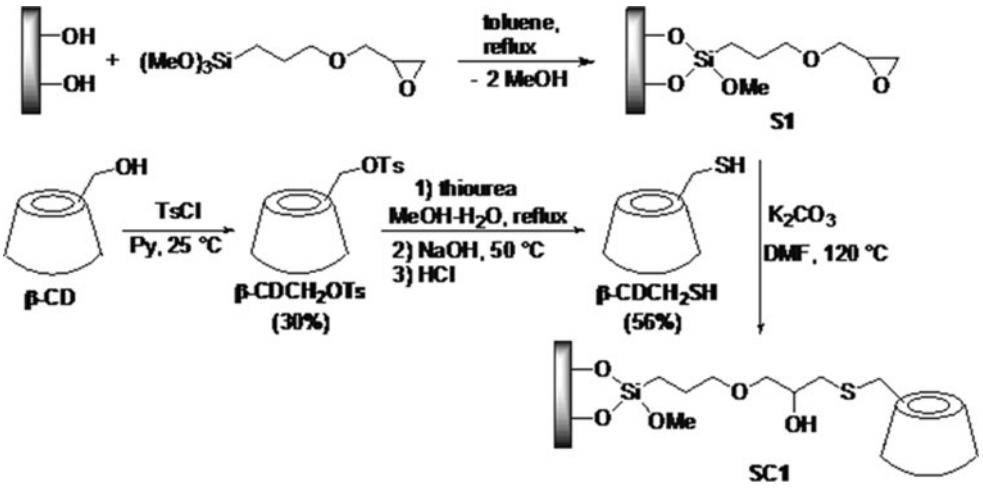
Progesterone release has been determined by High Performance Liquid Chromatography using a Jasco BS-997-01 instrument equipped with an UV-2075 Plus UV–Vis detector and a Lichrosorb RP 18 column.

3 Results and discussion

3.1 Functionalization of silica SBA-15 with β-cyclodextrin units

SBA-15 silica was functionalized with β-cyclodextrin residues by two different synthetic approaches, leading to the new materials SC1 and SC2. In the first approach, SBA-15 silica was first let to react with 3-glycidyloxypropyltrimethoxysilane to give functionalized silica S1,

Scheme 1 Synthetic strategy for the preparation of SC1 hybrid material



bearing a linker terminating with an epoxide ring moiety. The latter was then reacted under basic conditions with mono-6-deoxy-6-mercapto-β-cyclodextrin (β-CDCH$_2$SH), prepared in its turn in two steps from β-cyclodextrin (β-CD) through monotosylation to give β-CDCH$_2$OTs followed by thiolation with thiourea, to give β-CD-functionalized silica SC1 (Scheme 1).

In a similar way, β-CD-functionalized silica SC2 was prepared by reacting β-CDCH$_2$OTs with silica S2, suitably functionalized with a linker terminating with a terminal thiol group. The latter was easily obtained by the reaction of SBA-15 silica with 3-mercaptopropyltrimethoxysilane (Scheme 2).

3.2 Characterization of the starting SBA-15 and hybrid materials SC1 and SC2

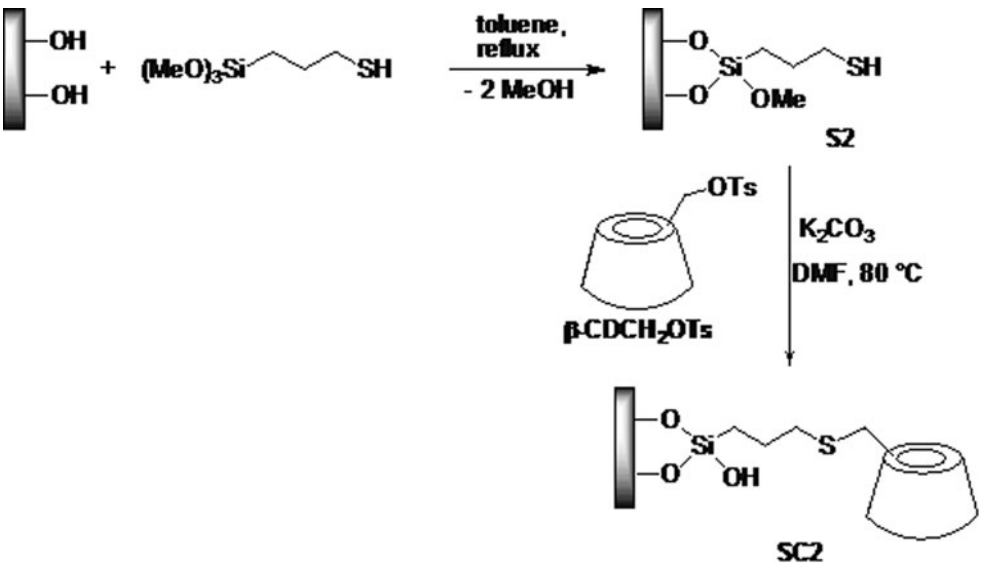
The X-ray powder diffraction patterns of hybrid SC1 and SC2 materials (not-shown) exhibit the expected (110) and (200) reflections of SBA-15 materials [11].

The nitrogen adsorption–desorption isotherms of the starting SBA-15 and of SC1 and SC2 hybrid materials are presented in Fig. 1, while Table 1 shows the structural data of SBA-15-type mesoporous material before and after the functionalization procedures.

In Fig. 1a the nitrogen adsorption–desorption isotherms of the starting calcined mesoporous materials is shown. It is a type IV not-reversible isotherm typical of SBA-15 type mesoporous materials.

From Table 1, it can be noted that the specific surface area and pore volume reductions of sample SC1 are dramatic if compared to the starting mesoporous material while the isotherm is still a not reversible type IV one (Fig. 1b). The nitrogen adsorption–desorption of sample SC2 exhibit lower specific surface and pore volume reduction, and the isotherm is still a not-reversible type IV one (Fig. 1c). The main nitrogen uptake corresponding to capillary condensation in mesopores occurs at a higher relative pressure if compared to material SC1 as confirmed from the higher value obtained

Scheme 2 Synthetic strategy for the preparation of SC2 hybrid material



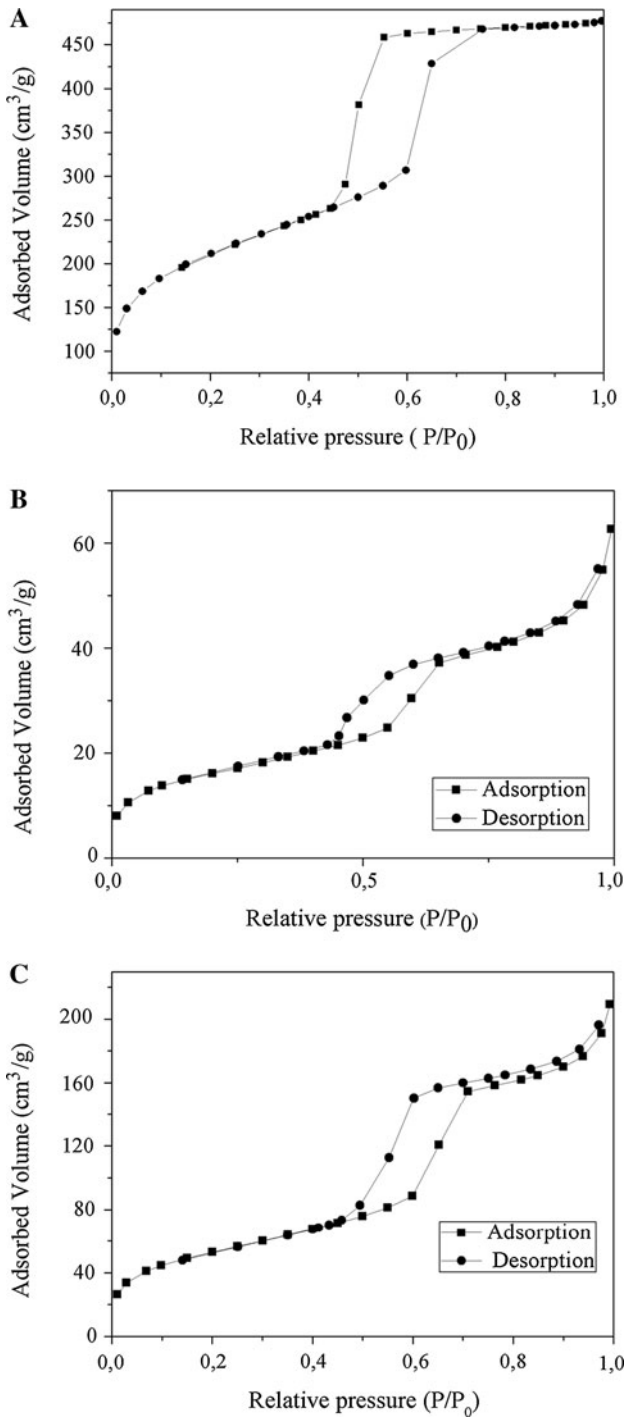


Fig. 1 Nitrogen adsorption–desorption isotherms of materials **a** SBA-15, **b** SC1, **c** SC2

for the average pore diameter (Table 1). The β-CD amounts in the samples SC1 and SC2 are shown in Table 1.

Both new materials SC1 and SC2 were characterized by ^{13}C CP/MAS NMR. The data are summarized in Table 2 and are compared to the ^{13}C NMR data obtained in solution for β-CDCH$_2$SH, 3-mercaptopropyltrimethoxysilane and 3-glycidyloxypropyltrimethoxysilane. A detailed comparison

Table 1 Pore volumes, Specific Surface Area S_{BET}, pore diameters and β-CD amounts of the different mesoporous materials samples

Samples	S_{BET} (m^2/g)	Pore volume ($P/P_0 = 0.9$; cm^3/g^{-1})	Pore diameter (nm)	Beta-CD amount (mol/g SiO_2)
SBA-15	766	0.68	6.0	–
SC1	150	0.08	5.0	1.5×10^{-4}
SC2	190	0.26	5.5	1.5×10^{-4}

these data shows that the materials obtained contain the cyclodextrin moiety. In particular, the ^{13} C CP/MAS NMR spectrum of material SC1 shows peaks centered at 103.2, 82.3, 64.2 and 62.1 ppm that cannot be assigned at the starting material S1 and are typical of cyclodextrin units. Moreover, a peak at 34.0 ppm is also present, which is assigned at the C_{7C} carbon of the thioethereal linkage (see figure SC1 material in Table 2). The signal related to the C_{6A} carbon of unreacted epoxide rings appears at 49.6 ppm.

In the case of SC2 material, the typical bands of cyclodextrin units appear at 102.9, 81.4, 72.2 and 62.1 ppm. The signals at 36.2 and 30.6 ppm are due to the C_{7E} and $C_{6E'}$ carbons of the thioethereal bond, respectively (see figure SC2 material in Table 2). Hydrolysis of Si-bonded methoxy groups was confirmed by the absence of signals around 50 ppm.

In Fig. 2 the SEM micrograph of starting SBA-15 material is shown. The observed morphology is similar to the expected ropelike one typical of SBA-15 materials synthesized using TEOS as silica source [12]. SEM observation of hybrid SC1 and SC2 materials (not-shown) do not evidence substantial variations in morphological properties.

3.3 Progesterone loading and release

In Table 3, pore volumes, specific surface area S_{BET} and pore diameters of different progesterone-loaded mesoporous materials are shown.

In Fig. 3, the nitrogen adsorption–desorption isotherms of progesteron-loaded SBA-15 (SBA-15-P), SC1 (SC1-P) and SC2 (SC2-P) materials are shown. Material SBA-15-P exhibits a not-reversible type IV isotherm and reduced pore volumes of and S_{BET} values. In the case of SC1-P and SC2-P materials, it can be observed, as expected, a further reduction of pore volumes and Specific Surface Areas S_{BET} if compared to the corresponding SC1 and SC2 materials. In both the cases a very low nitrogen volume is adsorbed and there is no evidence of capillary condensation. This behaviour is attributed to complete filling of mesopores by progesterone molecules included in pore volumes of mesoporous materials and cyclodextrin cavities.

Table 2 ^{13}C NMR chemical shift (δ) with assignment for the hybrid material SC1 and SC2

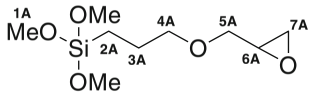
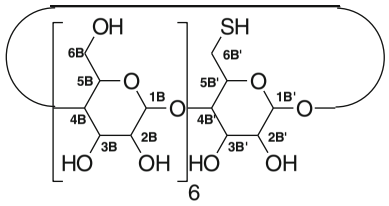
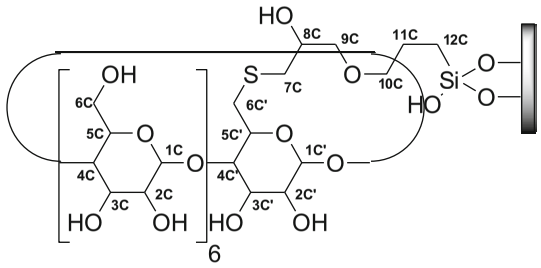
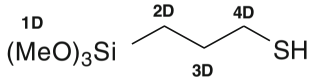
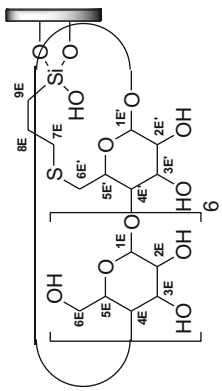
Sample	^{13}C CP/MAS NMR δ (ppm)	Assignment	^{13}C NMR in solution δ (ppm)	Assignment
			73.2	C_{5A}
(a) 			71.2	C_{4A}
			50.5	C_{6A}
			50.1	C_{1A}
			43.8	C_{7A}
			22.6	C_{3A}
			5.0	C_{2A}
(b) 			101.7	$C_{1B} + C_{1B'}$
			81.4	$C_{4B'}$
			81.3	C_{4B}
			72.3, 72.6, 72.9	$C_{2B} + C_{3B} + C_{3B'} + C_{2B'}$
			71.8	C_{5B}
			70.6	$C_{5B'}$
			59.7	C_{6B}
			25.5	$C_{6B'}$
	103.2	$C_{1C} + C_{1C'}$		
	82.3	$C_{4C} + C_{4C'}$		
	73.6	$C_{2C} + C_{3C} + C_{3C'} + C_{9C} + C_{10c} + C_{8c} + C_{2C'} + C_{4A} + C_{5A}$		
	64.2	$C_{5C} + C_{5C'}$		
	62.1	C_{6C}		
	49.6	C_{6A}		
	34.0	C_{7C}		
	23.3	$C_{6C'} + C_{11C} + C_{3A}$		
	8.5	$C_{12C} + C_{2A}$		
(c) 			C_{1D}	50.9
			C_{4D}	27.9
			C_{3D}	27.8
			C_{2D}	8.6

Table 2 continued

Sample	^{13}C CP/MAS NMR δ (ppm)	Assignment	^{13}C NMR in solution δ (ppm)	Assignment
	102.9	$C_{1E} + C_{1E'}$		
	81.4	$C_{4E} + C_{4E'}$		
	72.2	$C_{2E} + C_{3E} + C_{3E'} + C_{2E'}$		
	62.1	$C_{5E} + C_{5E'} + C_{6E}$		
	36.2	C_{7E}		
	30.6	$C_{6E'}$		
	24.2	C_{8E}		
	8.8	C_{9E}		

SC2

(a) ^{13}C NMR spectrum in $CDCl_3$ [1]
(b) ^{13}C NMR spectrum in d_6-DMSO [2]
(c) ^{13}C NMR spectrum in $CDCl_3$ [3]

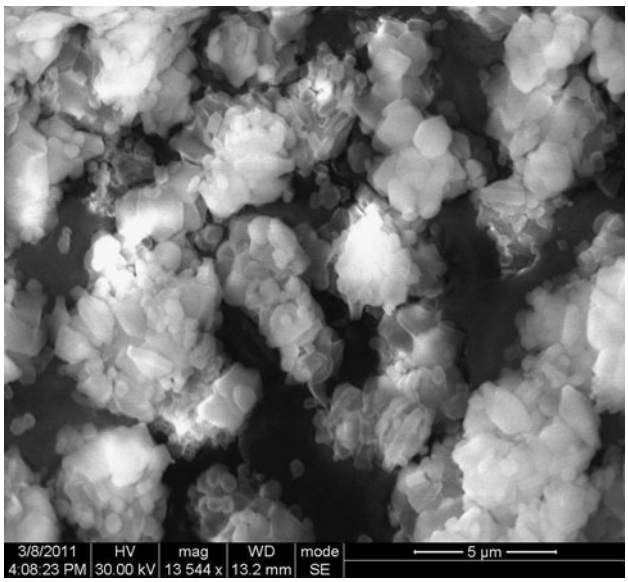


Fig. 2 SEM micrograph of starting SBA-15 material

Table 3 Pore volumes, specific surface area S_{BET} and pore diameter for each sample of different progesterone-loaded mesoporous materials

Samples	S_{BET} (m^2 g^{-1})	Pore volume ($P/P_0 = 0.9$; cm^3 g^{-1})	Pore diameter (nm)
SBA-15-P	227	0.32	4.5
SC1-P	7	0.008	–
SC2-P	18	0.022	–

The amounts of adsorbed progesterone for each sample are presented in Table 4. The X-ray diffraction patterns (not shown) of progesteron-loaded materials exhibit the characteristic peaks of progesterone in crystalline form only in the case of β-CD samples differently from the case in which mesoporous silica surface was able to promote crystallization [13]. It is worth noting that the presence of a drug in crystalline form is not desirable because of its low solubility and biocompatibility [14].

Drug release studies were carried out in vitro at 37 ± 0.5 °C at pH 1 (simulated gastric fluid) for 2 h and then at pH 6.8 (simulated intestinal fluid) using the pH change method.

Drug release rates are expressed as percent of drug delivered, related to the drug-loading value, as a function of time. The vertical bar at Time = 2 h indicates the pH change from 2 to 6.8.

Figure 4a, b show the drug release profiles of progesterone from SBA-15 material and β-cyclodextrin, respectively.

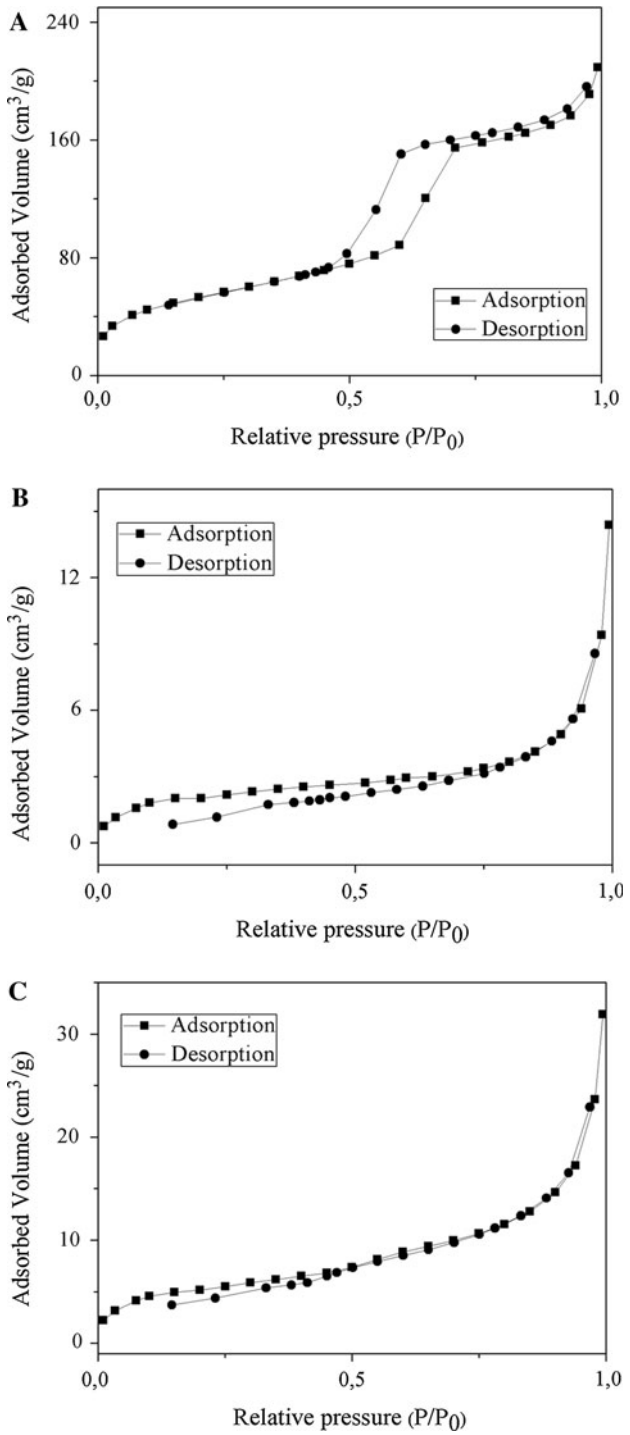


Fig. 3 Nitrogen adsorption–desorption isotherms of progesterone-loaded materials **a** SBA-15-P, **b** SC1-P, **c** SC2-P

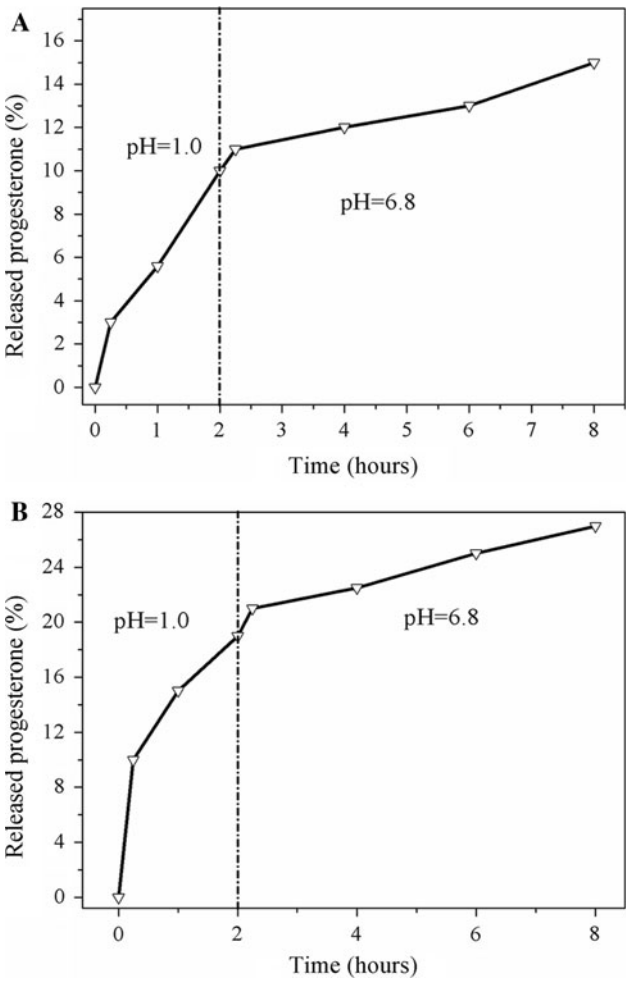


Fig. 4 Progesterone release versus time for the different progesterone-loaded samples **a** SBA-15-P and **b** β-CD-P

It can be noted that, after 8 h from the beginning of the release process that mimics an oral administration, only 15 and 25 % of the loaded progesterone are diffused from the mesoporous silica matrix and progesterone-loaded cyclodextrins, respectively. This effect can be due to the low solubility of progesterone in water at neutral pH. Drug retaining in SBA-15 mesoporous material could be attributed to the formation of hydrogen bond interactions between the silanol groups on silica surface and progesterone molecules adsorbed on the surface of silica or partially placed in microporous connections typical of SBA-15 porous system [15, 16].

When progesterone is loaded in cyclodextrin-functionalized mesoporous materials, only SC2 material (Fig. 5b) is able to retain the drug during the first period (2 h) (corresponding in the model to the crossing of the gastric region), while in the case of SC1 material a 70 % of progesterone is immediately released from the system (Fig. 5a). This latter behavior, very different from those ones presented in Fig. 4a, b for the systems SBA-15-P and β-CD-P, respectively, is surprising, considering the well-known low solubility of progesterone in water.

A possible explanation for the immediate release from system SC1 is the increase of solubility in acidic solution of progesterone adsorbed on the external surface and included in the hybrid material.

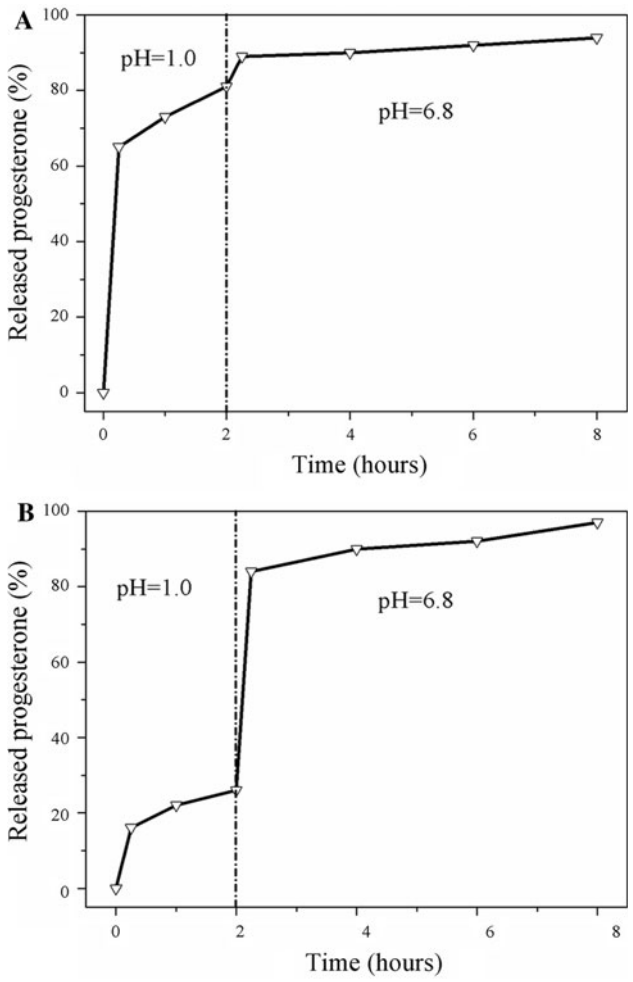


Fig. 5 Progesterone release versus time for the different progesterone-loaded samples **a** SC1-P and **b** SC2-P

Table 4 Amount of adsorbed progesterone for each sample

Sample	Amount of loaded progesterone (mg/100 mg of sample)
SBA-15-P	15.41
B-CD-P	10.45
SC1-P	16.55
SC2-P	15.36

It can be hypothesized, that, due to the long arm of the glicidoxypropyl functionalization, the progesterone molecule resides in the region comprised between the silica pore walls and the CD basket where it can interact by hydrogen bond with the hydroxyl group present in position 8c (Table 2). This hydrogen bond is produced during drug loading procedure that is carried out at neutral pH and is labilized at acidic pH so that the most part of progesterone is immediately released.

On the other hand, in the case of system SC2, progesterone is loaded both on the external surface of the mesoporous SBA-15 material and in the CD basket. This nano-environment allows at acid pH only diffusion of progesterone adsorbed on the external surface. The release is then completed after 2 h when the pH reach neutral values with both hybrid materials.

4 Conclusion

SBA-15 type mesoporous silica has been hybridized to produce a covalent bond with β-cyclodextrinresidues by two different synthetic approaches so that the whole hybrid systems can work as a drug delivery device for progesterone. Progesterone release has been studied at different pH values to mimics the oral administration. Only one of the two progesterone-loaded delivery device is able to retain the drug in the system during the first period at acid pH (2 h) and release it after pH increase.

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