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Modified Silica Matrices for Controlled Release of Cephalexin

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Abstract: SBA-15 type ordered silicas possessing amino groups attached onto their surfaces were prepared by using two different functionalization methodologies. These matrices were used for the cephalexin adsorption from aqueous solution and further kinetic study of its release into physiological solution. The materials were characterized by nitrogen adsorption/desorption, scanning electron microscopy (SEM), Fourier-transform infrared spectroscopy (FT-IR), X-Ray photoelectron spectrometry (XPS) and thermo analytical methods (TG/DSC). UV–visible spectroscopy at 262 nm was used for quantitative determination of cephalexin present in liquid media. Results reveal that drug adsorption capacities and the corresponding release profiles are dependent on the number of loaded amino groups and their location, which in turn is determined by the functionalization procedure used. It was concluded that amino post-functionalization could enhance long-term cephalexin delivery in comparison with co-functionalization procedure.

Keywords: SBA-15, mesoporous silicas, surface functionalization, drug adsorption, drug release, cephalexin.

1. INTRODUCTION

In recent years, mesoporous materials, which have unique pore size, high surface area and pore volume, have been widely employed as carriers for controlled drug delivery. Compared with amorphous colloidal and porous silicas, mesoporous silicas exhibit higher loading of drugs and could provide a controlled drug release, sometimes improved by silica functionalization. The interaction between mesoporous matrices and drug molecules is decisive for designing controlled drug delivery systems for clinical applications. It is known that functionalization of mesoporous materials can change these interactions by changing the pore size and surface hydrophilic/hydrophobic properties [1].

Generally, surface functionalization of mesoporous silica materials via covalent bonding of organic groups can be achieved by two methods: i.e., post-grafting synthesis and co-condensation. Although the post-grafting method results in well-ordered functionalized mesostructured materials, it often produces non-uniformly distributed organic groups because the organic moieties can congregate more on the channel pore mouth and on the exterior surfaces. The co-condensation synthesis involves a one-step procedure and allows better control of the loading and distribution of the organic groups although it often produces materials with less ordered mesoporous structures. In particular, low degree of structural integrity and long-range periodicity as well as lower surface area would be produced when the organosilane concentration in the synthesis exceeds ~25% [2].

Previous results showed that the interaction forces responsible for the cephalexin retention onto ordered silica surfaces can be modified by changing the acidity of the adsorbent, with the drug adsorption noticeably enhanced when amino groups are present at the adsorption surface [3,4].

In this study, two aminofunctionalized SBA-15 ordered silicas were obtained by using the different methodologies previously detailed for the incorporation of amino groups.

Cephalexin, an antibiotic of the cephalosporin group, was selected as the adsorbate. This drug possesses great gram positive coverage and some activity against gram negative bacteria, and it is frequently indicated for the treatment of various infections. The cefalexin molecule (HCpx) contains NH_2, C(O)NH, and C(O)OH groups, as a result of which it is similar, in structure and acid-base properties, with dipeptide molecules [5]. The cephalexin structure is shown in (Fig. **1**).

Afterwards, the kinetic of drug release from these samples was measured in order to determine the influence of the aminofunctionalization procedure on the matrix performance.

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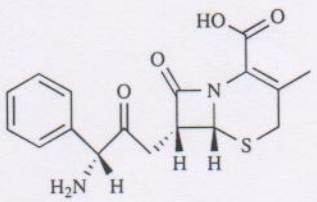

Fig. (1). Cephalexin structure.

2. MATERIALS AND METHODS

2.1. Chemicals

The chemicals used in this study include triblock copolymer poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide), Pluronics P123 (MW: 5800, Aldrich), tetraethyl orthosilicate (TEOS, 98%, Aldrich), hydrochloric acid (Merck), 3-aminopropyltriethoxysilane (APTES, Aldrich), 1,4-dioxane (Carlo Erba) and cephalexin monohydrate (Interlude Company S.A.).

2.2. Amino-functionalized SBA-15

2.2.1. Post-synthesis Grafting

Mesoporous silica SBA-15 was prepared according to the methodology described by Zhao [6], using TEOS and Pluronic P123 as organic structure–directing agent. The molar composition used was 1 TEOS:4.88 HCl:0.017 Pluronic:158.33 H_2O The solid material obtained was washed with water, dried at 120°C and calcined for 6 h at 550°C.

The SBA-15 was functionalized by anchoring aminogroups on the surface. In a typical procedure, 4 g of the calcined SBA-15 were refluxed in 120 mL of a 6.66% (V/V) solution of APTES in 1,4-dioxane for 16 h. The resulting solid was recovered by filtration, washed with the solvent and dried (40°C, vacuum) until constant weight [7]. This sample was named SBA_1.

2.2.2. Co-condensation

In a typical synthesis, 4 g of the structure-directing agent, Pluronic P123 were dissolved in a mixture of 125 mL of deionized water and 25 mL of hydrochloric acid (12 N). TEOS was added as the silica precursor at 40 °C. The functional silane, either APTES was added after a TEOS prehydrolysis period of one hour. The resulting mixture (1 TEOS:0.1 APTES:7.76 HCl:171 H_2O molar ratio) was stirred at 40 °C for 20 h and aged at 90 °C for 24 h before being filtered. The surfactant template was removed by refluxing in ethanol with 10 wt% hydrochloric acid for 24 h. The solid was then filtered and washed with ethanol [8]. This sample was named SBA_2

2.3. Characterization

The solid samples obtained before and after functionalization were analyzed by different techniques. The size and morphology of the particles were observed by SEM, using a Philips 505 microscope. The adsorption-desorption nitrogen isotherms were measured at the temperature of liquid nitrogen using a Micromeritics apparatus ASAP 2020. The surface area was determined by applying the Brunauer-Emmett-Teller (BET) equation, samples were outgassed by heating at 100°C in vacuum lower than 3 x 10^{-2} mm Hg (4.0 Pa) for 12 h. Composition and surface reducibility analyses were conducted by X-Ray photoelectron spectrometry (XPS). XPS spectra were collected using a Physical Electronics PHI 5700 spectrometer with non monochromatic Mg Kα radiation (300W, 15 kV, 1253.6 eV) for the analysis of the O 1*s*, Si 2*p*, S 2*p* and C 1*s* core level signals, and with a multichannel detector. Solids samples were introduced in a sample holder and degassed at high vacuum during 12 hours. Spectra of powdered samples were recorded with the constant pass energy values at 29.35 eV, using a 720 μm diameter analysis area. During data processing of the XPS spectra, binding energy values were referenced to the C 1*s* peak (284.8 eV) from the adventitious contamination layer. The PHI ACCESS ESCA-V6.0 F software package was used for acquisition and data analysis. A Shirley-type background was subtracted from the signals. Recorded spectra were always fitted using Gauss-Lorentz curves, in order to determine the binding energy of the different element core levels more accurately. The error in BE was estimated to be ca. 0.1 eV. Bruker IFS 66 equipment, pellets in KBr, and a measuring range of 400–4,000 cm^{-1} were used to obtain the FT-IR spectra of samples dried at 40 °C. Thermogravimetric analyses (TG-DSC) were performed with a SDT-Q600 analyzer from TA Instruments. Measurements were carried out on samples in open platinum crucibles under a flow of 100 mL min^{-1} of air with heating rate of 10 °C min^{-1}. All samples were heated from 25 to 900 °C in air.

2.4. Drug Adsorption and Release

The two modified SBA-15 samples were soaked in a solution of cephalexin in water (concentration 10 mg/mL). The resulting suspensions (prepared using a solid/liquid ratio = 5 mg/mL) were left at ambient temperature, without stirring. After a contact time of 20 h, the solid phases were separated from the liquids by filtration and dried at room temperature. The respective samples were denoted as SBA_1/cpx and SBA_2/cpx (where cpx means cephalexin).

The amount of drug loaded in the pores of the carrier was characterized quantitatively by thermogravimetry. For drug release experiments, the prepared samples (SBA_1/cpx and SBA_2/cpx) were put in contact with physiological solution [9], under stirring, at 37°C. The evolution of the drug content in the liquid phase was determined by UV–visible spectroscopy at 262 nm.

3. RESULTS AND DISCUSSION

SEM and Nitrogen Sorption Characterization

The scanning electron micrographs obtained for both supports before adsorption of the drug reveal a fibrous morphology, as usually is found for this type of solids; after adsorption of the cephalexin molecules the morphology of these solids is well maintained due to their adsorption takes place preferably into the pores (Fig. **2**).

The corresponding nitrogen adsorption isotherms of these materials are shown in (Fig. **3**), and the textural parameters derived from the analysis of them are listed in Table **1**. All the isotherms are of Type IV according to the IUPAC classi-

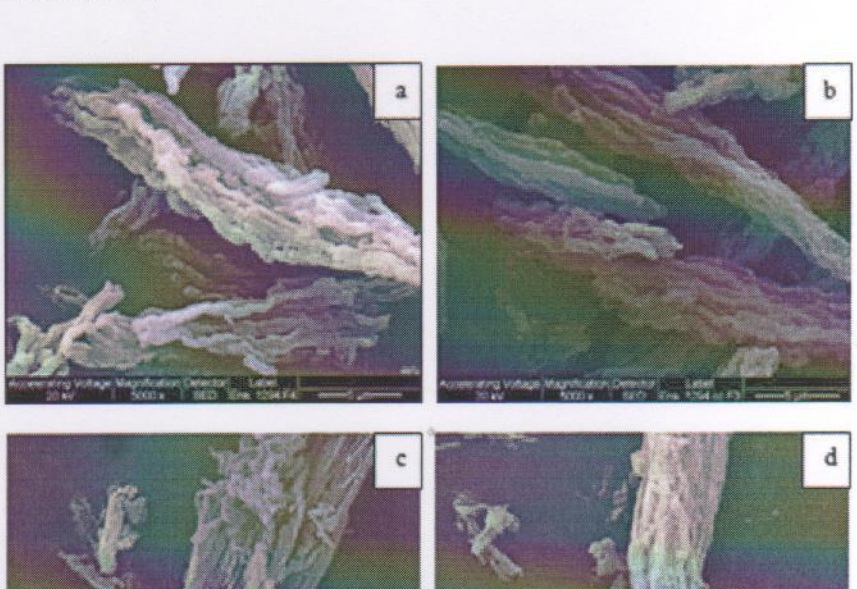

Fig. (2). SEM micrographs: a) SBA_1 b) SBA_1/cpx c) SBA_2 d) SBA_2/cpx.

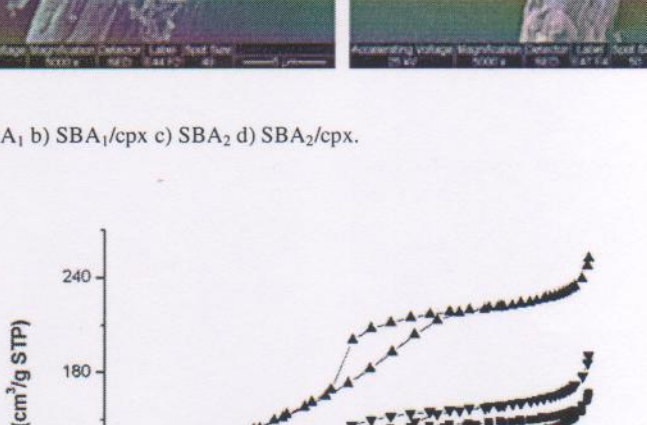

Fig. (3). Nitrogen adsorption/desorption isotherms: a) SBA_1 b) SBA_1/cpx c) SBA_2 d) SBA_2/cpx.

fication, with a sharp inflexion point at P/P_0 0.35-0.40 characteristic of capillary condensation of N_2 within uniform mesopores with constant cross section. The specific surface area is higher for SBA_2 indicating that when a higher amount of APTES molecules react with the surface of pores of SBA_1 their diameters are reduced and as a consequence the surface area and pore volume do it. All the isotherms show an H1 hysteresis loops, characteristic of mesoporous materials with a cylindrical pore arrangement. The pore size distributions shown in (Fig. **4**) display that SBA_1 leads to a narrower pore size distribution compared to SBA_2. After adsorption of cephalexin the surface areas of both solids are reduced, especially in the case of SBA_2, with 25 % of reduction, since this substance is preferentially adsorbed inside of pores. The pore volumes and pore sizes follow the same trend.

The skeletal FTIR spectrum of SBA-15 silicas (Fig. **5**) shows a large band ranging from 800 till 1250 cm^{-1} due to the Si-O-Si asymmetric and Si-OH terminal sylanol stretching vibrations. Signals at 460 and 800 cm^{-1} and at 1080 and

Table 1. Textural Characteristic of the Studied Mesoporous Silica Materials

Sample	S BET (m^2/g)	Pore Vol. (cm^3/g)	Pore size (Å)
SBA_1	308	0.25	3.8
SBA_2	491	0.38	4.5
SBA_1/cpx	266	0.14	3.5
SBA_2/cpx	368	0.28	4

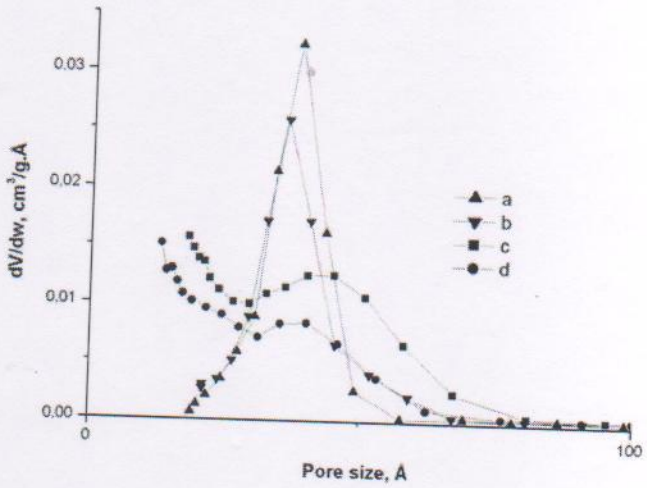

Fig. (4). Pore size distributions: a) SBA_1 b) SBA_1/cpx c) SBA_2 d) SBA_2/cpx.

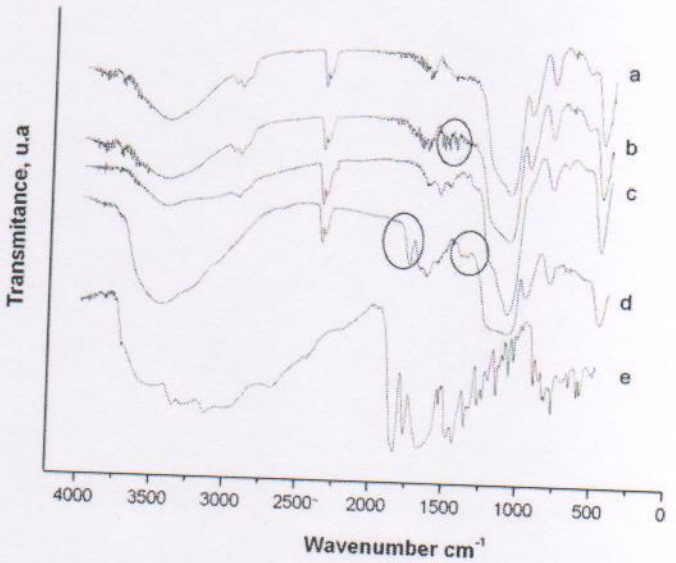

Fig. (5). FTIR spectra a) SBA_1 b) SBA_1/cpx c) SBA_2 d) SBA_2/cpx e) Cephalexin.

1220 cm^{-1} are associated to the torsion, symmetric stretching and asymmetric stretching of the Si-O bond, respectively; whereas in the hydroxyl range the large band from 3400 cm^{-1} till 3740 cm^{-1} can be assigned to sylanol groups; this band is enlarged due to strong interaction with residual water located in the channels although the more energetic part is attributed to non-interacting silanol groups [7].

The modifications of the samples by amino groups were reflected by appearance of characteristic bands of the amino

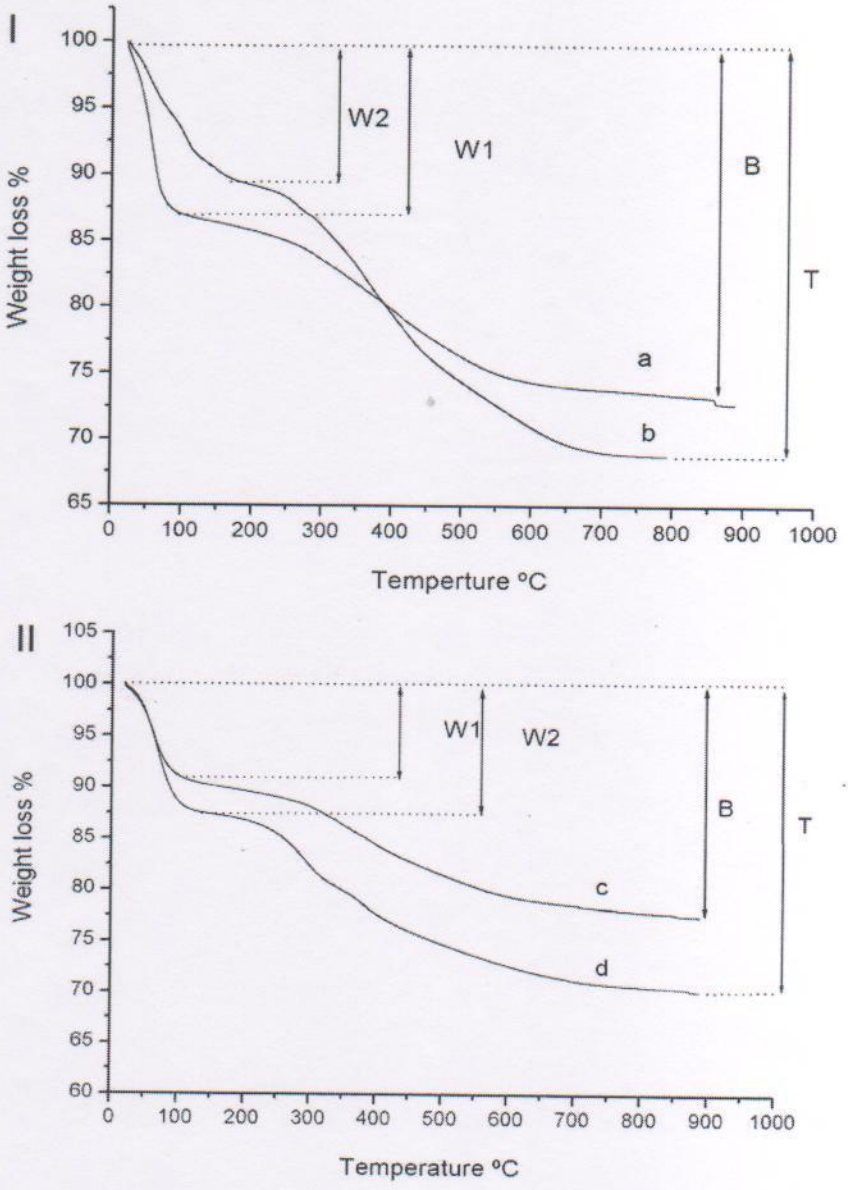

Fig. (6). TGA of amino-functionalized SBA-15 by I) post-synthesis and II) co-condensation. a) SBA_1; b) SBA_1/cpx; c) SBA_2; d) SBA_2/cpx.

groups in the IR spectra (Fig. **5**). There are several bands appearing in the aminofunctionalized SBA-15. Although it is difficult to determine the functional group $-NH_2$ attached to the mesoporous material surface by observing absorption around 3460 cm^{-1} because the band of $-NH_2$ overlaps with that of O–H stretching vibration. The signal that appears at 2937 cm^{-1} is assigned to the C-H bond stretching [10]. This band gives a direct demonstration of the presence of amino-propyl groups in SBA-15 framework.

Regarding the drug-containing materials, their spectra show peaks attributed to cephalexin. (Fig. **5.e**) shows the characteristic bands for this molecule. The bands appearing at 1758 and 1690 cm^{-1} are due to four-membered lactam carbonyl and secondary amide carbonyl groups, respectively. The bands appearing at 1455, 1 406, and 1350 cm^{-1} are due to C–H bending vibrations. As expected, additional peaks at 1763, 1695, 1425 and 1390 cm^{-1} appeared in the drugloaded materials, indicating the chemical stability of cephalexin after entrapment [11].

TG/DSC and XPS Analyses

To calculate the amount of cephalexin retained into both amine-modified mesoporous materials, thermogravimetric analyses (TG/DSC) were made. The results are displayed in (Figs. **6** and **7**). Firstly, the thermal analysis of both supports was performed (Figs. **6** and **7**); the weight loss observed over the temperature interval 100–200 °C for these samples corresponds to the thermodesorption of water from the mesoporous structure. The dehydration was accompanied by an endothermic peak at 100 °C on DSC curves. It is noteworthy that when the amine groups are introduced into the

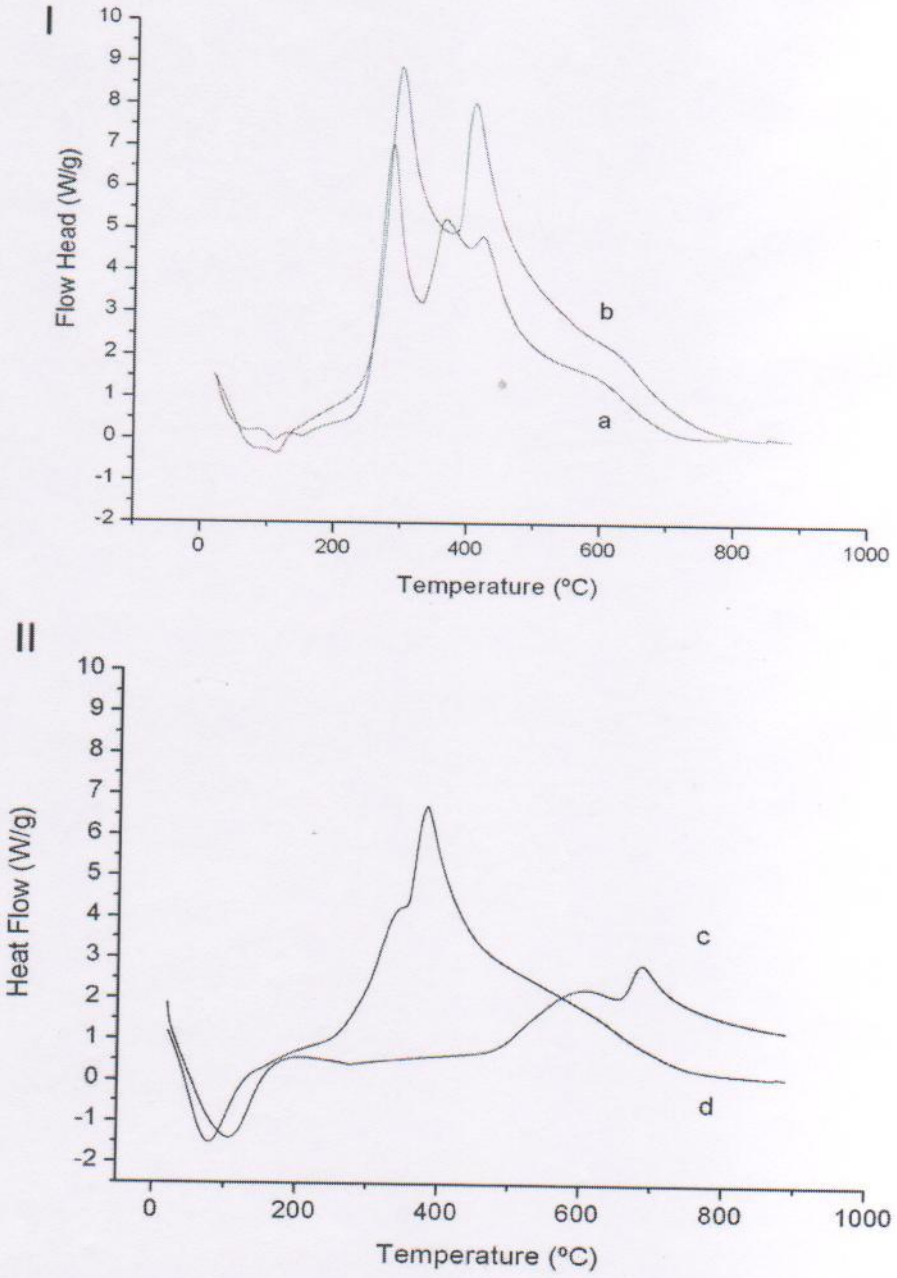

Fig. (7). DSC of amino-functionalized SBA-15 by I) post-synthesis and II) co-condensation. a) SBA_1; b) SBA_1/cpx; c) SBA_2; d) SBA_2/cpx.

silica by post-synthesis grafting (sample SBA_1) the amount of retained water is higher than when the silica is by co-condensation functionalized. This fact could be correlated with the amounts of amino groups incorporated in each case. The weight loss step observed above 300 °C corresponds to the thermal decomposition of aminopropyl chains anchored onto the surface of both SBA-15 supports. By comparing the weight loss corresponding to the combustion of the organic matter of both functionalized silicas it can be deduced that SBA_1 contains a higher amount of aminopropyl groups, i.e., the treatment of SBA-15 silica with APTES is more effective for the incorporation of amine groups. When the thermal analyses of materials containing cephalexin are considered, it is observed that the weight loss due to the adsorbed water is higher for SBA_2/cpx sample. The retention of cephalexin into the channels of SBA_2 material increased the degree of hydration with respect to the pristine support. The thermal decomposition of cephalexin was accompanied by an exothermic peak above at 400°C. However, the weight loss due to the combustion of the organic matter in the functionalized frameworks occurs almost simultaneously with that corresponding to the drug molecules retained in both samples. Therefore, the calculation process of loading weight percentage (W) is more complicated than in conventional silica

Table 2. Binding Energy Values (in eV)

Sample	C 1*s*	O 1*s*	N 1*s*	Si 2*p*	Cl $2p_{3/2}$	Na 1*s*	S $2p_{3/2}$
SBA_1	284.8 (79%) 286.2 (19%) 288.0 (2%)	532.5	399.0 (69%) 401.1 (31%)	103.0	197.6		163.2
SBA_2	284.8 (73%) 286.4 (24%) 288.0 (3%)	523.8	399.3 (57%) 401.7 (43%)	103.3	198.1		
SBA_1/cpx	284.8 (71%) 285.9 (22%) 287.7 (7%)	532.4	399.4 (84%) 401.2 (16%)	103.0	197.4		163.1
SBA_2/cpx	284.8 (72%) 286.1 (24%) 288.4 (4%)	532.5	399.4 (44%) 401.6 (56%)	102.9	197.7	1071.4	
SBA_1/cpx lib	284.8 (68%) 285.8 (25%) 287.5 (7%)	532.4	399.4 (79%) 401.3 (21%)	102.8	197.4	1071.4	
SBA_2/cpx lib	284.8 (76%) 286.4 (21%) 289.1 (3%)	532.6	399.3 (75%) 401.5 (25%)	103.0	198.0		

Table 3. Atomic Concentration (%) Determined by XPS

Sample	C 1*s*	O 1*s*	N 1*s*	Si 2*p*	Cl $2p_{3/2}$	Na 1*s*	S $2p_{3/2}$
SBA_1	35.11	35.37	4.92	21.88	1.71		0.82
SBA_2	10.83	57.63	1.58	28.58	1.36		
SBA_1/cpx	33.03	39.05	5.83	21.45	0.33		0.31
SBA_2/cpx	14.34	54.36	2.21	27.07	1.34	0.69	
SBA_1/cpx lib	18.00	51.20	3.37	26.33	0.71	0.39	
SBA_2/cpx lib	10.84	58.15	1.68	28.35	0.56	0.42	

hosts. To calculate the percentage of cephalexin adsorbed on amino-functionalized SBA-15, the method described in [12] was used. In (Fig. **6**), W_1 represents the percentage weight loss of physically adsorbed water (<100 °C) in both blank amino-functionalized SBA-15 silica, whereas W_2 means the weight loss of water for amino-functionalized SBA-15 containing cephalexin. On the other hand, B is the percentage weight loss corresponding to the adsorption of water and organic content of blank amino-functionalized SBA-15 samples, and T represents the percentage total weight loss of adsorbed water, organic content of the framework and drug loaded in amino-functionalized SBA-15 samples. In both amino-functionalized SBA-15 and amino-functionalized SBA-15/ cephalexin materials, the ratio of organic part to silica should be constant, thus the drug loading weight ratio (W) in SBA_1 and SBA_2 material can be calculated by the following equation:

$$\frac{B-W_1}{100-B}=\frac{T-W-W_2}{100-T}$$

The found values of W retained by SBA_1 and SBA_2 are 8.0 and 6.2 %, respectively. The SBA_2 support having lower amount of aminopropyl groups retains less cephalexin molecules especially due to these groups are preferably located onto the walls of the pores whereas in the case of incorporation of aminopropyl groups by post synthesis they could be located on the external surface and on the mouth of pores with an easy access for drug molecules.

To get insights on the chemical states of the elements and their relative abundance at the surface, XPS analysis was run out of supports and drug loaded samples. Table **2** includes the binding energy values in eV for C 1*s*, O 1*s*, N 1*s*, Si 2*p*, Cl $2p_{3/2}$, Na 1*s* and S $2p_{3/2}$, and Table **3** the surface composition in atomic concentration (%). The study of the chemical state of the constituent elements of SBA_1 and SBA_2 supports indicates that there are at least two types of nitrogen. One contribution at 399.0-399.3 eV assigned to the presence of free amino groups from APTES and a second one at 401.1 and 401.7 eV assigned to protonated amino groups. Concerning the surface chemical composition, it is clear that the post

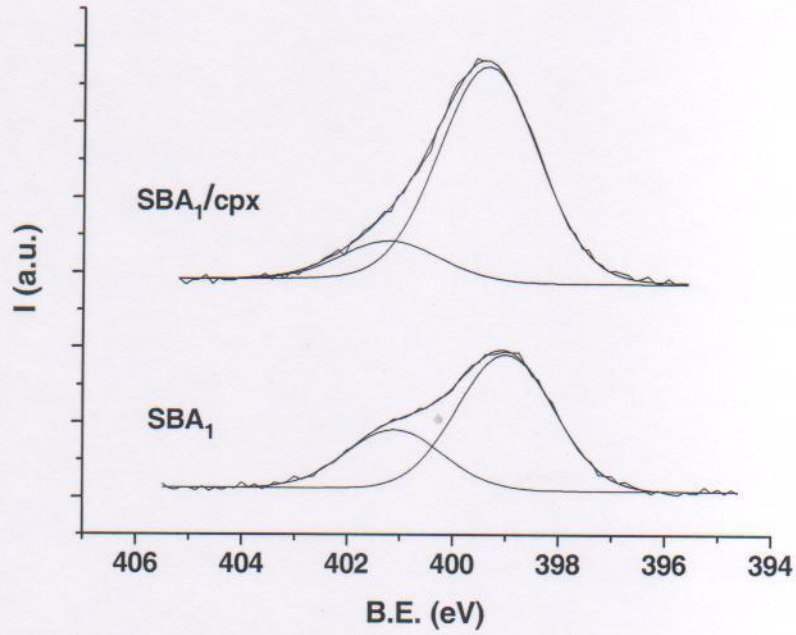

Fig. (8). N 1*s* core level spectra for samples SBA_1 and SBA_1/cpx.

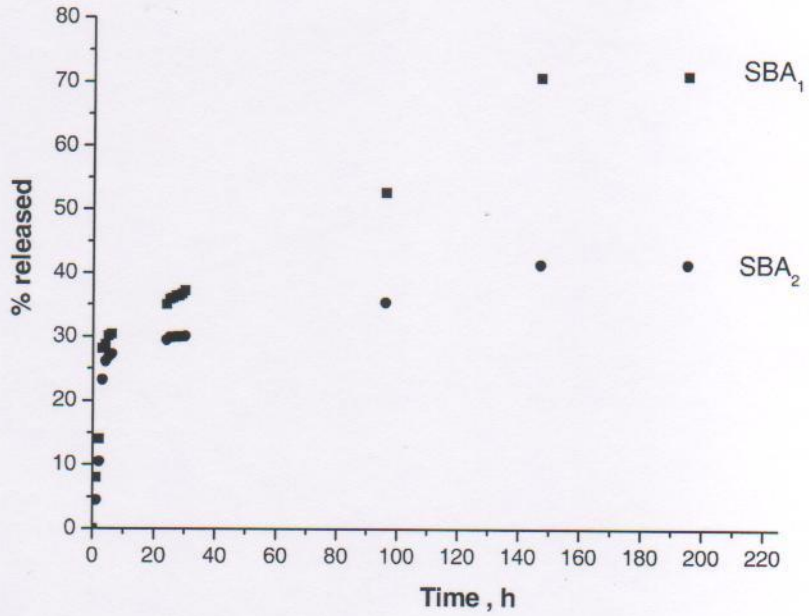

Fig. (9). Release profiles corresponding to the studied SBA samples.

synthesis grafting method gives rise to a higher incorporation of APTES than that observed in the co-condensation method (4.92 and 1.45 % of N for SBA_1 and SBA_2, respectively), as was observed from the TG analysis. Sample SBA_2, with a lower content of APTES, has a higher proportion of protonated amino groups than that of SBA_1. This fact indicates that SBA_1 has more available amino groups for the incorporation of new substances. The incorporation of cephalexin provokes some visible changes in the N 1s core level spectra. The spectra of the rest of the studied elements presents minimum or negligible modifications (see Table **2**). In the case of sample SBA_1, it is observed an increase of the intensity of the contribution at low binding energy in the N 1s signal (see Fig. **8**), and the atomic concentration of N increases from 4.92 to 5.83% upon incorporation of cephalexin. This increase is more moderate in the case of sample SBA_2 (from 1.58 to 2.21 %). The location of cephalexin molecules in the interior of the pores of this support could be responsible of this low response found by XPS analysis.

The drug adsorption is basically a surface phenomenon and would be a function of the support surface and the chemical affinity between this surface and the adsorbate. Undoubtedly, a higher loading of aminogroups in SBA_1 compared to SBA_2 was determined by thermal analyses and

XPS spectroscopy, and these values could be correlated with the cephalexin amounts retained by the two samples. The different location of aminopropyl groups in both supports is also responsible of SBA_2 support has lower loading drug.

Drug Release Experiments

As was mentioned above, for drug release experiments, the prepared samples SBA_1/cephalexin and SBA_2/cephalexin were put in contact with physiological solution under stirring, at 37°C. Release profiles of SBA_{A1}/cephalexin and SBA_{A2}/cephalexin as a function of time are shown in (Fig. **9**). For both samples the release rate exhibits two steps, in the early hours there is a rapid drug release, followed by a slow release rate. In the second stage, the release rate is slow reaching zero after 150 h. The total released amounts at this time ranged from 70% to 40% of the adsorbed weight, depending on the methodology used for silica functionalization. The amount of amino groups and their location in the materials affect the adsorption capacity, and also alter the amount of drug released. Additionally, the sample synthesized by post-grafting released cephalexin faster than the sample functionalized by co-condensation. SBA_2 support releases a lower amount of cephalexin according to the location of this substance in the interior of pores. On the other hand, it is observed that the drug is not 100% released, which is attributed to strong interactions between drug molecules and functional groups of silica.

The found surfaces atomic concentrations (%) values after 150 h of the release of cephalexin determined by XPS (see Table **3**) also corroborate these facts. The % of N decreases from 5.83 % (SBA_1/cpx) to 3.37 % (SBA_1/cpx lib) and from 2.21 % (SBA_2/cpx) to 1.68 % (SBA_2/cpx lib).

4. CONCLUSION

In this work the adsorption/desorption study of cephalexin on two ordered silica matrices possessing amine-groups on the pore walls was run for the first time. Adsorption/desorption measurements showed that cephalexin can be successfully loaded on the synthesized mesoporous silica materials and subsequently released from the samples in a simulated body fluid solution of pH of 7.40 at 37 °C. It was shown that drug adsorption capacities and the corresponding release profiles are dependent on the number and location of loaded aminogroups. It was concluded amino post-functionalization could enhance long-term cephalexin delivery in comparison with co-functionalization procedure.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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