Research Article

Calorimetric Study of Mesoporous SBA-15 Modified for Controlled Valproic Acid Delivery

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Received 4 July 2012; Revised 7 October 2012; Accepted 7 October 2012

Academic Editor: Jose Alberto Pereira

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SBA-15 ordered mesoporous silica functionalized with (3-aminopropyl)triethoxysilane (APTES) was used as the carrier for anticonvulsant drug 2-propylpentanoic acid (valproic acid). The surface of SBA-15 containing free silanol groups was modified with 3-aminopropyltriethoxysilane via postsynthetic reaction. Functionalization of the carrier with basic aminopropyl groups resulted in an ionic interaction with acidic valproic acid. The samples of carriers and carrier-drug complexes were characterized by elemental analysis, N₂ adsorption, FTIR, and UV spectroscopy. The adsorption of valproic acid on modified mesoporous matrix was proportional to the amount of introduced aminopropyl groups. A thermodynamic study with isothermal titration calorimetry (ITC) was made to characterize the modification and encapsulation of SBA-15 with APTES and valproic acid, respectively. The maximum content of deposited drug in modified SBA-15 was close to 30 wt.%. Tests performed in acidic solution (pH 2.0) showed the best pharmaceutical availability.

1. Introduction

Controlled drug-delivery systems (DDSs) are one of the most promising applications for human health care and represent an ever-evolving field for biomedical material science [1–4]. The development of new active molecules and potential treatments, such as gene therapy, is leading to the development of new therapeutic agents and the enhancement of the mechanisms to administer them. Basically, a drug delivery system can be described as a formulation that controls the rate and period of drug delivery (i.e., time-release dosage) and targets specific areas of the body. Unlike traditional therapies, which show a saw-tooth curve of drug concentration in plasma, DDSs are designed to maintain therapeutic levels during the treatment period [4, 5].

Furthermore, the isothermal titration calorimetry (ITC) is now routinely used to directly characterize the thermodynamics of biopolymer binding interactions [6–10]. This is the result of improvements in ITC instrumentation and data analysis software. Modern ITC instruments make it

possible to measure heat effects as small as 0.1 μcal (0.4 μJ), allowing the determination of binding constants, K_s , as large as 10^8 – 10^9 M⁻¹.

The extended use of mesoporous materials as adsorbents of drug agents is due to both its texture and the chemical properties of the surface, which also depend on the original materials and the method used to prepare the mesoporous solid, which can be modified with physical and chemical treatments to improve the adsorbent properties. The factors which influence the encapsulation process in the solution include the SBA-15, the adsorbate, the chemist who prepared the solution, and its temperature [10–12]. The use of isothermal titration calorimetry (ITC) has become the gold standard for the thermodynamic investigation of binding interactions. A total of 623 articles were cited in an ITC literature review in 2007 written by Bjelic and Jelesarov showing the value of the use of ITC [13–16]. When ITC is used to determine the thermodynamic parameters of a binding interaction, typically a ligand is titrated with a receptor. ITC measures the heat of the interactions of each injection and calculates the

enthalpy change since this takes place at constant pressure. By plotting the enthalpy changes for each injection against the amount of ligand versus receptor, an equilibrium binding association constant (K_a) and the stoichiometry (n) can be modelled from the shape of the curve [14–24].

SBA-15 mesoporous silica has been investigated as the potential drug carrier material due to large surface area, large pore size, thick walls, and easy surface modification [25, 26]. Some insoluble drugs, such as ibuprofen, nimodipine, itraconazole, and so on, have been applied to control the delivery from SBA-15 into simulated biological fluids [26–29]. Then, the introduction of appropriate organic compounds into SBA-15 has presented excellent results regarding drug release control. The choice of appropriate functionalizing agent can generate the inner channel surface acidic [30], basic [31], as well as hydrophobic [32]. Furthermore, the functionalized surface groups can interact via ionic interactions with desired drug. For example, mesoporous materials modified with amine groups were applied as carriers for adsorption of drugs with acidic character [33]. In contrary, modification of the surface of SBA-15 or MSU with acids (e.g., with carboxylic groups) increases the adsorptive properties of drugs with basic properties [33–36]. For example, valproic acid (VPA) is one of the most widely used anticonvulsants in our country. Serious adverse effects include hepatotoxicity, hyperammonemic encephalopathy, coagulation disorders, and pancreatitis.

The incidence of VPA-associated pancreatitis has been estimated to be 1 : 40,000. The incidence of acute pancreatitis (AP) in children is estimated to be 2–2.7 : 100,000 [26]. The literature medical reports say that 11-year-old boy admitted to hospital with complaints of acute abdomen and diagnosed acute hemorrhagic pancreatitis after laparotomy. This has been a of first cases documented case with VPA-associated pancreatitis in Turkey.

It can be noted in the valproic acid structure shown in Figure 1 that the OH its structure may serve as proton donors to form hydrogen bonds with carriers [30].

Therefore, mesoporous SBA-15 material may be a good candidate for valproic acid adsorption because of its relatively large pore size, abundant hydroxyl groups, and easily modified surface with silanes. In this work, a simple and effective approach has been developed for controlled drug delivery carrier through local surface modification in mesoporous silica SBA-15 with aminopropyl groups.

Moreover, in this work calorimetric measurements are performed to establish the thermodynamics of encapsulation with APTES on SBA-15 and valproic acid.

2. Experimental

2.1. Materials. SBA-15 mesoporous silica was synthesized following the procedure introduced in [36]. 2.7 g of poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (also known as P123) was dissolved in 65 mL of 2.5 M HCl at room temperature, and 10.0 g of KCl was added to the solution. Then, 5.7 g of tetraethyl orthosilicate (TEOS) was added under vigorous stirring.

FIGURE 1: Exploded view of the isothermal titration calorimeter: 1, 2: Electronic terminals and support. 3: Superior lid. 4: Internal lid of calorimeter. 5: Tube and extension. 6, 7: Guides of tube. 8: Microcalorimeter lid. 9: Bulb cell. 10: Cell microcalorimetric. 11: Themopiles. 12, 13, 14: Lids inferior. 15: Telon isolated. 16, 17, 18: Titration parts. 19: Controller of titration.

The final reactant molar composition was 0.03 P123/5 KCl/7 HCl/177 H₂O/2 TEOS. After stirring at room temperature for a day, the mixture was transferred into an autoclave and heated at 110°C for 48 h. The product was, then, collected by filtration and washed with both ethanol and water (to remove unreacted P123 and KCl) and dried. The as-made powder was calcined at 620°C for 12 h to remove the organic template.

2.2. Modification of SBA-15 with APTES. 7.0 g of dry SBA-15 (dried at 110°C for 48 h) was introduced into 70 cm³ solution containing different amounts of (3-aminopropyl)triethoxysilane (APTES) in water-free toluene while continuously stirring. The molar ratio of SiO₂ to APTES varied between 1 : 25 and 1 : 2 (Table 1). The reaction of SBA-15 with APTES was performed in closed system at 100°C for 48 h. After cooling and filtration samples were five-fold washed with toluene (5 × 250 cm³) and dichloromethane (5 × 250 cm³). Samples were next dried for 48 h at 120°C (heating rate 0.5°C/min). Next, samples were treated (5 × 200 cm³) with methanol-water solution (1 : 10, v/v) and soaked for 6 h with this mixture (200 cm³, stirring condition) in order to purify and hydrolyze the possible residue of ethoxyl groups. The carrier was filtered

TABLE 1: Characterization of modified SBA-15 with aminopropyl groups and the carriers loaded with valproic acid.

Sample	Initial molar ratio APTES SBA-15 ^a	Amount of aminopropyl group in the carrier ^b (mol·g ⁻¹)	S _{BET} (m ² ·g ⁻¹)	BJH pore volume (cm ³)	t-plot micropore volume (cm ³)	Average pore diameter (nm)
SBA-15	—	—	825	1.08	0.0776	6.9
SBA-15-AP(1:25)	(1:25)	6.37×10^{-3}	635	1.01	0.0277	6.2
SBA-15-AP(1:15)	(1:15)	1.74×10^{-3}	575	0.88	0.0232	6.0
SBA-15-AP(1:5)	(1:5)	2.01×10^{-3}	540	0.77	0.0186	5.8
SBA-15-AP(1:1)	(1:2)	2.09×10^{-3}	510	0.73	0.0094	5.7
SBA-15-VA	—	—	640	1.04	0.0297	6.4
SBA-15-AP(1:15)-VA	—	—	360	0.58	0.0000	6.4

^a SBA-15 expressed as SiO₂.^b Calculated from elemental analysis.

and the excess of solvent was evaporated for 48 h at 110°C (heating rate 0.5°C/min). These samples were marked as SBA-15-AP(X), where X corresponds to the molar ratio of SiO₂ to APTES used in the synthesis [37].

2.3. Adsorption of Valproic Acid on SBA-15 Carriers. 5.0 g of powdered SBA-15-AP samples modified with APTES (different molar ratio) or non-modified SBA-15 were introduced to 150 cm³ of 2-propanol solution of valproic acid (15 mg/cm³). The adsorption was performed at room temperature for 48 h. Samples were next filtered, dried at room temperature (48 h), and finally at 70°C for another 48 h. The samples (modified with APTES) containing valproic acid were marked as SBA-15-AP(X)-VA. The sample of non-modified SBA-15 loaded with valproic acid was described as SBA-15-VA. The amount of adsorbed drug in adsorption equilibrium state was estimated spectrophotometrically as a difference in drug concentration before and after drug adsorption. Before spectrophotometric measurement the samples were centrifuged (15,000 ×g) for 10 min and the supernatant was diluted with 2-propanol [37]. Measurements of absorbance were performed at 260 nm. Moreover, the total amount of adsorbed valproic acid after drying in all studied samples was calculated from elemental analysis.

2.4. Characterization. X-ray powder diffraction patterns were obtained using a Rigaku Ultima III diffractometer with Cu α radiation ($k = 1.5418 \text{ \AA}$) and operating at 40 kV and 44 mA. All XRD patterns were collected in the 3 h range between 0.5° and 3° with a scanning rate of 0.01°/min. The textural properties of the samples were measured via nitrogen adsorption isotherms at -196°C (77 K) using a IQ2 sortometer (Quantachrome Inc. USA, Boynton Beach, FL). Prior to each adsorption measurement, the SBA-15 and grafted samples were each degassed under vacuum for 12 h at 250°C and 110°C, respectively. The total surface area S_t , external surface area S_{ext} , and primary mesopore volume V_p of the samples were calculated using the as-plot method [38]. Pore size distributions (PSD) were calculated from the desorption branch of the N₂ isotherm data using the Barret-Joyner-Halenda (BJH) method applying the Kruk-Jaroniec-Sayari correction [39]. Images of the materials particles were

obtained using a JEOLJSM-6930 scanning electron microscope (SEM) operating with a secondary electron detector and an accelerating voltage of 15 kV.

FT-IR spectra were obtained in a Nicolet 6700 FT-IR instrument loaded with a Praying Matins attachment operated at ambient conditions. Powder samples were analyzed at 4 cm⁻¹ resolution and average of over 400 scans in the absorption band range of 4000–400 cm⁻¹.

2.5. Description of the Newly Built Isothermal Titration Calorimeter (ITC). We have modified our adsorption calorimeter [6–24] Figure 1 shows a complete exploded view of the calorimeter. It can work either as an adsorption or an isothermal titration calorimeter, making this versatile and new equipment. Its design is not very common and has not been previously reported in the literature. In this design we changed the calorimetric adsorption unit for a complete unit that allows the shots to take the action by titration. This is the main change, which led to slight changes in the main body of microcalorimeters, which are described below. A detailed view from the inside of the equipment to the exterior of the calorimeter is shown in Figure 1. In the diagram, Part No. 10 corresponds to the calorimetric cell made of stainless steel, which is embedded inside a large aluminium block that acts as a heat sink (4 and 12). Due to its thermal diffusion coefficient, the heat sink allows rapid heat conduction to the surroundings of the calorimeter. For this calorimeter, the nylon block (2 and 15) surrounding the equipment permits the rapid stabilisation of temperature. The thermal effects are sensed through the two thermopiles connected in series to increase the sensitivity of the microcalorimeter (11) (Thermoelectric Modules (peltier elements) are made of Bismuth Telluride alloys). These thermoelements generate a voltage signal through feedback, which is proportional to the heat flow produced in the cell. This thermoelectric potential is recorded by means of a 6.5 digit Agilent multimeter (model 34349) which is connected to a computer through an RS-232 interface. The upper part of the adsorption calorimeter consists of a nylon piece, which acts as a lid and at the same time has a conical device divided into two parts which permits the reception of the vial that contains the porous solid without leaving any empty space inside (1, 2 and 6).

FIGURE 2: XDR diffraction patterns (small angle) of SBA-15 loaded with valproic acid. (a) SBA-15-(1 : 15)-VA; (b) SBA-15-VA; (c) SBA-15.

2.6. Measurement with the ITC on SBA-15 Modified with APTES and the Encapsulation with Valproic Acid. The complete measurement process was fully automated with the aid of a personal computer that was also the controller element in the feedback power loop. After cleaning the vessel, the injection system was sealed with the titrant reactant solutions of APTES (in toluene) in other experiments with valproic acid in solutions buffered. Then, the adsorbent (SBA-15) to be titrated was placed (suspended in buffer) in the sample vessel. Buffer distilled water, acid, or basic solutions was put into the reference vessel for use as blank. The time required to reach thermal equilibrium was about 20 min. At that moment, the stirring system was switched on and after a waiting period of about 20–30 min, a good baseline was obtained. At this instant, the microcalorimeter was ready to carry out the experiment. It is worth indicating that at all times, the vessel contents were stirred and, therefore, an evaluation of the heat due to stirring was not needed. The software program stored all of the required parameters for each experiment run: parameters related to data acquisition (gain, channel, and sample period for the A/D converter, total measure time and baseline offset), with the compensation system (control parameters, depending on the control type: proportional, derivative, and integral) and with the injection system (injection number, injection volume, velocity, and time interval between injections). The recorded data were saved and collected automatically using the data acquisition and analysis software for calorimetry developed in our laboratory (ITC) in a program developed on a MatLab platform (DA-ITC).

3. Result and Discussion

3.1. Characterization of Mesoporous Carriers. Data presented in Table 1 as well as the diffraction pattern shown in Figure 2 indicate that the parent, non-modified material represents

typical mesoporous SBA-15 structure (pattern a). The low-angle XRD patterns of SBA-15 material show a well resolved peaks assigned to (1 0 0), (1 1 0) and (2 0 0) reflexes characteristic to the hexagonal ordered structure [40]. The properties of these materials are consistent with the data described in the literature [3–41].

The post-synthetic modification of SBA-15 with APTES was realized in the reaction of free silanol groups with ethoxysilanes and resulted in attachment of aminopropyl functional groups [28]. The amount of these groups attached to SBA-15 matrix was calculated from elemental analysis and varied between 6.37×10^{-4} and 2.09×10^{-3} mol of functional groups per gram of the carrier (Table 1). The amount of aminopropyl group in the carrier reached saturation when the APTES:SiO₂ molar ratio was lower than 1 : 5 (compare data in Table 1). This effect resulted from the partial replacement of free silanol groups in SBA-15 channels by modifying agent, therefore maximum of loaded aminopropyl groups was established for molar ratio 1 : 5. It is a consequence of the large molecule size of modifying agent (with aminopropyl chain) shielding close free silanol groups [30–43]. The XRD measurements (Figure 2, pattern b) confirm the hexagonal array of modified material.

Figure 3 shows the nitrogen adsorption-desorption isotherms of non-modified and modified SBA-15 whereas data in Table 1 present details of the textural parameters. In all cases the BET surface area, pore volume, pore size distribution (see side in Figure 3), and microporosity of modified samples were reduced after modification with APTES. The sample containing the highest amount of aminopropyl groups [SBA-15-AP (1 : 2)] showed reduction of BET surface area, pores volume and micropores volume by 38%, 34% and 92%, in comparison with non-modified SBA-15. The sharp shape of adsorption-desorption hysteresis loop (at P/P^0 from 0.60 to 0.85) is indicative for narrow mesopore size distribution of synthesized SBA-15 and modified materials [42–51]. The blockage of SBA-15 channels and especially of micropores by APTES is demonstrated by lower amounts of nitrogen adsorbed (Figure 3). Moreover, the shape of hysteresis loop and its position (P/P^0 0.5–0.8) were changed in comparison to SBA-15 and SBA-15-AP carriers. The similar effect was also described by Tang et al. [45] during adsorption of erythromycin on functionalized mesoporous matrix. The analysis of pore size and micropore volume proved that the adsorbed drug is deposited inside the mesoporous and microporous channels. These observations are compatible with the results reported by Qu et al. [48], Tang et al. [45] and Tang et al. [49] describing adsorption of other drugs on modified and non-modified SBA-15 and MCM-41 mesoporous materials.

The Figure 4(a) shows the particles SBA-15 synthesized that exhibit typical shapes and have diameters ca. 6 μm . After incorporation of APTES into the SBA-15 modified (Figure 4(b)), the channels are more thicker and the form change.

3.2. Valproic Acid Adsorption. The scheme presenting interaction of valproic acid (carboxylic acid) with basic aminopropyl-functionalized mesoporous silica is shown

FIGURE 3: N_2 adsorption-desorption isotherms (-196°C) of SBA-15 modified with APTES: (a) ■ SBA-15; (b) ● SBA-15-AP(1:25); (c) ▲ SBA-15-AP(1:15); (d) ▼ SBA-15-AP(1:5). Pore distribution.

FIGURE 4: SEM images of (a) SBA-15; (b) SBA-15-AP.

in Figure 5. Vallet-Regí et al. [44] indicate that in polar solvents such as 2-propanol used in this study the ionic interaction between drug and carriers was possible. The results of elemental analysis and spectrophotometric analysis in adsorption equilibrium state of valproic acid-containing sample are shown in Table 2; these calculations have been performed as reported in the literature by Zhao et al. [36]. The amount of valproic at equilibrium is proportional to the contents of aminopropyl groups located in modified SBA-15.

Table 2 is in good agreement with the literature data [25, 37]. This is demonstrated by the amount (~ 35 wt.%) of adsorbed valproic acid in samples fully saturated with APTES. The differences in amount of adsorbed valproic acid measured by spectrophotometric method and elemental analysis arise from the incomplete separation of the carrier suspension and the drug solution during adsorption experiments. Slightly higher values of adsorbed valproic

acid measured by elemental analysis suggest that incomplete elimination occurred after filtering as has been suggested by others authors [37]. The complete elimination of drug solution from the mesoporous capillaries of SBA-15 is very difficult [46].

Figure 6 shows the FTIR spectra of the modified and non-modified SBA-15 carrier before and after valproic acid adsorption. Adsorption of valproic acid on modified SBA-15 resulted in disappearance of the absorption band at 1670 cm^{-1} characteristic to carbonyl stretching vibrations in carboxylic groups in adsorbed drug ((SBA-15-VA(b)) [36–51]. Moreover, after drug adsorption on amino-modified SBA-15 (SBA-15-AP(1:15) (c)) characteristic band at 1600 cm^{-1} corresponding to stretching vibrations of ionized carboxylic groups was observed in the Figure 5 [37, 46]. These observations confirm the ionic character of the drug-carrier interaction [31, 37]. The appearance of

TABLE 2: Adsorption of valproic acid on SBA-15 material modified with with APTES.

Sample	Amount aminopropyl group in the carrier (mol/g) ^a	Valproic adsorption (wt%) ^b	Elemental analysis		
			Amount of C before drug adsorption (wt%)	Amount of C after drug adsorption (wt%)	Amount of valproic (wt%)
SBA-15-AP (1 : 25)-VA	6.37×10^{-3}	10.34	5.43	14.77	14.23
SBA-15-AP (1 : 15)-VA	1.74×10^{-3}	17.89	7.98	21.87	20.12
SBA-15-AP (1 : 5)-VA	2.01×10^{-3}	21.78	9.34	24.67	23.87
SBA-15-AP (1 : 2)-VA	2.09×10^{-3}	24.56	9.55	26.45	24.45
SBA-15-VA	—	6.45	0.00	7.56	9.12

^a Calculated from elemental analysis, before drug adsorption.

^b Calculated from spectrometric analysis (in the state of adsorption equilibrium). The amount of valproic acid was calculated from the formula $\%_{VA} = \{[(C_0 - C_1) \times V] / [W + (C_0 - C_1) \times V]\} \times 100\%$, where: $\%_{VA}$ is amount of valproic acid; C_0 is initial concentration of valproic acid; C_1 is concentration of drug after adsorption process; V is volume of drug solution; W is weight of the carrier. The concentration of valproic acid was estimated spectrophotometrically.

FIGURE 5: Interaction between SBA-15, APTES, and valproic acid.

absorption bands at 1462 cm^{-1} and 1680 cm^{-1} in samples loaded with valproic acid additionally (SBA-15-AP-(1 : 15)-VA(d)) confirm the presence of aromatic stretching C-C vibrations (Figure 6) and stretching vibrations of carbonyl related to aromatic rings, respectively [37, 46].

3.3. Valproic Acid Release. The cumulative release profiles of valproic acid from non-modified and aminopropyl-modified mesoporous SBA-15 in various solutions (water, pH 2.0 hydrochloric acid buffer, pH 5.0 acetic buffer, pH 9.0 phosphate buffer) are shown in Figures 7(a) and 7(b). Although the final pharmaceutical availability (80–95%) of valproic acid (after 24 h) from pure SBA-15 (Figure 7(a)) was similar in all samples it should be noticed that the shape of these curves was different. Valproic acid is a drug with weak acidic

properties ($\text{pK}_a = 4.7$), poorly soluble in water, therefore its release from non-modified SBA-15 in alkaline phosphate buffer was faster in comparison to acidic medium (pH 2.0 hydrochloric acid buffer, pH 5.0 acetic buffer) or water (pH ~ 7.0). The pH increase results in ionization of valproic acid carboxylic groups and in consequence the higher its solubility. Similar results were observed by Charnay et al. [51] in the work describing ibuprofen release from MCM-41 in various media and and Moritz and Łaniecki [37] in the work ketoprofen on SBA-15. It should be noticed that all of the samples exhibited prolonged valproic acid release from mesoporous matrix due to the limited diffusion of this drug from mesoporous and microporous channels. The release profiles of valproic acid adsorbed on aminopropyl-modified SBA-15 are shown in Figure 7(b). Due to the strong ionic

FIGURE 6: FTIR spectra of (a) SBA-15; (b) SBA-15-VA; (c) SBA-15-AP(1 : 15); (d) SBA-15-AP(1 : 15)-VA.

interaction of acidic valproic acid on the basic silica carrier the lowest release of the drug was observed in water. The pharmaceutical availability after 24 h reached is of 50% of adsorbed drug, which is of the highest reported about this type of work reported in the literature for example by Moritz and Łaniecki [37].

The highest pharmaceutical availability of valproic acid after 12 h (95%) was observed for SBA-15-AP(1 : 15)-VA sample released in hydrochloric acidic buffer in comparison to other buffers. Although the release rate from this sample was initially the good (after 1 h–40%) the final effect was much better than with the other buffer solutions (32% at pH–5.0 and 35% at pH–9.0). This effect results from shifted ionic equilibrium in acidic medium (2.0 pH) and from precipitation of free acidic valproic. Significant content of valproic in SBA-15-AP(1 : 15)-VA sample (above 30 wt.%) caused local saturation of valproic solution and its precipitation in acidic environment. The possibility of drug precipitation from mesoporous matrix was considered by Moritz and Łaniecki [37]. In the next step the precipitated valproic was transformed into soluble form and simultaneously further amounts of drug were released from the pores of the support. Final release of valproic (after 24 h) at pH 2.0 and pH 5.0 was slightly lower in comparison to hydrochloric acid buffer and was equal to 80 and 90% of the drug in the sample, respectively.

The proposed mechanism of drug release in acidic or basic media is shown in Figure 8. However, further studies are required to prove or to reject the proposed mechanism.

3.4. Analysis of Calorimetric Data: Fixation of APTES onto SBA-15 and the Encapsulation of Valproic Acid. ITC data were collected automatically using the data acquisition and analysis software for calorimetry developed in our laboratory (ITC) in a program developed on a MatLab platform (DA-ITC). All data were corrected for the heat of dilution by subtracting the heat remaining after the saturation of binding sites on the adsorbent prior to further data analysis. Data were fitted using a nonlinear least-squares algorithm using a single-site or two-site binding model employed by the

TABLE 3: Thermodynamic parameters of phenol and catechol to activated carbon at 25°C, determined by isothermal titration calorimetry (ITC).

Compound	ΔG (kJ/mol)	ΔH (kJ/mol)	ΔS (J/K·mol)	n ($\mu\text{mol/g}$)
SBA-15-AP	–45.6	–34.7	–198.5	18
	–41.3	–39.8	–239.6	22
	–36.5	–43.9	–257.5	27
	–30.2	–48.6	–274.6	32
SBA-15-AP(1 : 15)-VA	–28.9	–25.6	–141.2	5

DA-ITC software that accompanies the calorimeter built by us. Fitting the theoretical data to the experimental data yielded the stoichiometry (n) as the amount of adsorbate (solutions of APTES, and valproic acid) per gram adsorbent (n/g) (SBA-15) or μmol of adsorbate/gram adsorbent, the equilibrium binding association constant (K_a), and the reaction enthalpy change (ΔH_r°) of the reaction, that is, when the data is worked up, the recorded differential power is integrated over each injection time interval, and the molar ratio of titrant to titrant versus ΔH is plotted for each injection event.

Ideally, this data can be fit to a sigmoidal-shaped curve from which the enthalpy of binding ΔH , the equilibrium constant K_a , and the stoichiometric factor n can be extracted (Figure 9). ΔH is simply the extrapolated y -axis intercept, n is the amount of adsorbate (phenol or catechol) per gram adsorbent (n/g) or μmol of adsorbate/gram adsorbent at the curve's inflexion point, and K_a is obtained from the slope of the curve at the inflexion point.

The changes in the reaction free energy (ΔG_r°) and entropy (ΔS_r°) were calculated using (1). Errors in ΔH_r° and K_a were obtained as the standard deviations of at least five experiments:

$$\Delta G_r^\circ = -RT \ln K_a = \Delta H_r^\circ - T\Delta S_r^\circ. \quad (1)$$

3.5. Binding of APTES and Valproic Acid to SBA-15. The typical thermograms (Figure 9(a)) clearly show that APTES binds to four distinct binding sites on the SBA-15, corresponding to the chemical bonds of each of the OH groups of SBA-15 with EtO– of APTES, one strong ($\Delta G = -45.6 \text{ kJ/mol}$ for one –OH group) and the fourth low value relatively weak ($\Delta G = -30.2 \text{ kJ/mol}$ for the other –OH) (Table 3).

Figure 9(b) (enthalpy in terms of micromoles of valproic acid on SBA-15-AP(1 : 5) expressed in grams) for the valproic acid in solution shows an abrupt change that is characteristic of simple interaction between a single-NH₂ group (of SBA-15-APTES) and the adsorbent (valproic acid), but when the adsorbate or adsorbent has several functional groups, such as –NH₂ in of SBA-15, a competition is generated on the adsorbent surface, producing an initially strong enthalpic peak, and then smooth curves, which is associated with the presence of six binding sites on SBA-15. On the other hand, the valproic acid site shows only one chemical bond that we associated with the interaction of the –Si-(CH₂)₃– group on

FIGURE 7: Profiles of cumulatives release of valproic acid from (a) non-modified SBA-15-VA sample and (b) APTES-modified SBA-15-AP(1:15)-VAP sample.

FIGURE 8: Drug mechanism release of valproic acid from aminopropyl-modified SBA-15 in acidic and basic media.

SBA-15-AP; a value of $\Delta G = -28.9 \text{ kJ/mol}$ was obtained. Thermodynamic studies of this type using ITC have not yet been reported. This study provides a new perspective and a distinctive contribution to this field of research. On the other hand the values for the thermodynamic functions (enthalpy, free energy, and entropy) were negative, showing that the modification of the SBA-15 with APTES and the encapsulation of SBA-15-AP with valproic acid are spontaneous. When comparing the values thermodynamic obtained between SBA-15-AP and SBA-15-AP(1:15)-VA, ITC calorimetry was able to differentiate the results of the titration, as well as the effects of the presence of each of the OH groups of the SBA-15 and the interaction with APTES and the interaction of groups $-\text{NH}_2$ and $-\text{COOH}$ of valproic

acid. In the case of SBA-15/APTES system, the presence of different OH groups of SBA-15 determines six different values of enthalpy (-26.4 kJ/mol and -38.8 kJ/mol) which shows the different strength with which the $-\text{OH}$ is attached inside the pores of SBA-15. This research has established the equilibrium constants of the adsorption of the SBA-15-AP-VA and SBA-15-AP systems under study, which show that the reaction between the SBA-15 and APTES and SBA-15-AP and valproic acid are very stable.

Using the computer built (ITC) is possible to evaluate the isosteric heat of APTES and valproic acid on SBA-15 at constant coverage by varying the temperature using the temperature controller that was designed for this purpose. The titration calorimetry is useful in studies of chemical

FIGURE 9: Thermograms for the titration of (a) APTES and (b) valproic acid solution on SBA-15-AP(1 : 15) at 25°C.

kinetics, determination of reaction mechanisms, and in studies of structural rearrangements of the adsorbate upon adsorption/partition and the excluded water molecules or ions in the bulk solvent; the ITC also analyze of exclusion of water or ions surrounding the adsorbate and the hydrophobic interactions between the adsorbate and the hydrophobic parts of the adsorbent sites.

4. Conclusion

SBA-15 mesoporous material, both in non-modified or modified forms, can be used as the carrier for adsorption of acidic drug such as valproic. The modification of mesoporous and microporous channels of SBA-15 with 3-aminopropyl group leads towards formation of carriers with surface basic properties. High amount of adsorbed drug (~30 wt.%) showed that modified SBA-15 could be a suitable carrier for valproic. The valproic acid adsorption on the non-modified and modified carrier contributed to its increased thermal stability what can be a great advantage in drug formulation. Drug release rate was dependent on pH value of dissolution

medium. Obtained results give promising perspectives for future application of mesoporous materials in drug delivery systems. The use of ITC allowed for the determination of the thermodynamics of APTES and valproic acid reaction on SBA-15, which took place at a different-binding site that was relatively strong. The thermodynamic variables showed that adsorption was a spontaneous process; additionally, the goal of this research was to show that with this technique (ITC), is possible differentiate the adsorption of APTES and valproic acid on SBA-15.

Acknowledgments

The authors wish to thank the Master Agreement established between the Universidad de los Andes and the Universidad Nacional de Colombia and the Memorandum of Understanding entered into by the departments of chemistry of both universities. Additionally, thanks to the special fund "Proyecto Semilla" of the Sciences of Faculty the Universidad de Los Andes, for partial funding of this research.

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