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Modified SBA-15 as the carrier for metoprolol and papaverine: Adsorption and release study

Michał Moritz, Marek Łaniecki *

Faculty of Chemistry, A. Mickiewicz University, Grunwaldzka 6, 60-780 Poznań, Poland

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ABSTRACT

A series of modified SBA-15 materials were applied in drug delivery systems. The internal surface of siliceous hexagonal structure of SBA-15 was modified with different amount of (3-mercaptopropyl)-trimethoxysilane (MPTMS) and oxidized in the presence of hydrogen peroxide. The sulfonated material was loaded with metoprolol tartrate or papaverine hydrochloride. Both drugs indicated strong chemical interaction with modified mesoporous surface. The characteristic of the obtained materials was performed with XRD and DRUV-vis spectrometry, themogravimetry and nitrogen adsorption (BET) measurements. The obtained results show that modification of the mesoporous materials leads towards significant decrease of the drug delivery rate.

1. Introduction

Majority of drug delivery systems consists of polymeric matrices or polymer-based composites containing different materials such as silicas or other non-harmful inorganic oxides [1,2]. Among many different inorganic materials also silica aerogels and xerogels were studied as carriers for controlled drugs release [3]. In drug formulation the materials characterized by uniform pores distribution providing homogenous drug distribution inside the channels are usually applied. However, in drug formulation, apart from materials with uniform pores distribution heterogenous matrix systems are applied. Characteristics of these materials is described by use of such parameters as porosity and tortuosity [4].

The discovery by Kresge et al. [5] from Mobil of the uniform mesoporous siliceous materials started a new era in nanomaterial science. The pioneering study by Vallet-Regí et al. [6] on the application of MCM-41 as ibuprofen delivery system showed that with these studies a new era in generation of new pharmaceutical systems just has been launched. Since that time the MCM-41 and SBA-15 siliceous mesoporous materials became the subject of numerous studies in embedding of organic molecules with therapeutic activity inside these siliceous matrixes.

Inorganic silica-based materials exhibit some specific properties such as very high stability, biocompatibility and lack of toxicity making them useful as potential carriers. In recent years many studies were concentrated either on adsorption or release of drugs from siliceous mesoporous materials. The drug molecules can be easily introduced into porous system of MCM-41 [7,8] or SBA-15 [9,10] but their release usually do not fulfill the expectations. The "once daily" formulation in drug delivery systems (DDS) for oral administration requires zero-order kinetics and linear release of drugs during 24 h. These requirements were achieved only in few cases [11,12]. The release of drugs was very fast in first few hours in majority of the studied systems in which mesoporous siliceous materials were applied as carriers. The porous system architecture, thickness of walls, amount of surface silanol groups, amount of the adsorbed drug, type of bonding (physical or chemical) and many other parameters can influence on the kinetics of the drug release. Therefore, in order to be close to the "one day "dose, the synthesis of siliceous materials must be strictly controlled. Moreover, all the hydrophilic silanol groups existing on the surface of these siliceous carriers can be modified either during synthesis or post-synthetically. Such procedure can help significantly during drug adsorption and optimization of their release. The choice of appropriate functionalizing agent can generate the inner channel surface acidic [13,14], basic [15–17] as well as hydrophobic [18,19]. The functionalized surface groups can interact *via* ionic interactions with desired drug. The strength of such bond as well as additional presence of certain polymers can lead towards zero-order kinetics during drug release. Because majority of contemporary drugs is produced in forms of organic salts and indicate either acidic or basic properties, it is important to adjust surface with appropriate properties. Siliceous mesoporous materials modified with amine groups were applied as a carrier for adsorption of drugs with acidic character [20–23]. 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 [24,25].

* Corresponding author. Fax: +48 61 8291505.
E-mail address: laniecki@amu.edu.pl (M. Łaniecki).

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This paper describes the adsorption of metoprolol tartrate (β-blocker, applied in hypertension [26]) and papaverine hydrochloride (smooth muscle relaxant [27]and vasodilatator [28]) on the non-modified and sulfonic acid modified SBA-15. The aim of this work was to achieve desired drug formulation (powder, granulate and tablets) with prolonged release of the drug from the carrier.

2. Experimental

2.1. Synthesis of SBA-15

Synthesis of SBA-15 was performed according to the method of Zhao et al. [29]: 48 g of block copolymer of Pluronic P-123 was dissolved in 360 cm^3 of water and 1440 cm^3 of 2 M HCl at 35 °C. After complete dissolution 102 g of TEOS were added and the obtained mixture was stirred 20 h at 35 °C. Next, the suspension was transferred into tightly closed vessel and kept for 24 h at 105 °C without stirring. The obtained white solid was filtrated and washed repeatedly with distilled water. After drying in air the white powder was next calcined at 500 °C for 6 h (heating rate 1 °C/min.).

2.2. Modification of SBA-15 with MPTMS

5 g of dry SBA-15 (dried at 110 °C for 24 h) was introduced into 50 cm^3 solution of (3-mercaptopropyl)trimethoxysilane (MPTMS) in water free toluene while continuously stirring. The molar ratio of SiO_2 to MPTMS varied in five samples from 1:30 to 1:2 (see Table 1; SiO_2 represents here water free SBA-15). Saturation of SBA-15 with MPTMS was performed in closed system at 100 °C for 24 h. After cooling and filtration samples were four-fold washed with toluene and dichloromethane. Samples were next dried 24 h at 60 °C and treated with 80 cm^3 of hydrogen peroxide (30 vol.%). The oxidation reaction of deposited MPTMS was performed at room temperature (24 h) and followed by filtration with subsequent drying at 60 °C for 24 h.

2.3. Adsorption of metoprolol tartrate and papaverine hydrochloride on SBA-15

The powdered SBA-15 samples modified with MPTMS and oxidized with hydrogen peroxide (2.0 g) were saturated at room temperature with solutions containing either metoprolol tartrate or papaverine hydrochloride for 24 h. In each case saturation was performed with water solution containing 10 mg/cm^3 of the studied drug. After filtration samples were initially dried at room temperature (24 h) and next at 60 °C for another 24 h. The amount of adsorbed drugs was estimated spectrophotometrically from absorbance values before and after the adsorption. For these reasons, samples containing suspensions were centrifugated (17.000g) for 3 min and measurements of absorbance of supernatant were performed at 275 and 250 nm for metoprolol and papaverine, respectively.

2.4. Drugs release

The release of the supported powdered drugs was performed in Erweka DT 60 apparatus (paddle method) in water (500 cm^3) at 37 °C with stirring rate of 50 rotations per minute. The amount of samples for drug release experiments was adjusted to 50 mg of medicament adsorbed within non-modified or modified SBA-15 nanoporous channels. After indicated period of time samples were centrifugated and the amount of the released drug was measured spectrophotometrically similarly like in the previous section. After 24 h of drug release in water, further release was performed in the presence of HCl. This was realized by adding of 4.3 cm^3 of 37 wt.% HCl into initial 500 cm^3 of water.

2.5. Characterization of the modified SBA-15

Samples were characterized by thermogravimetry in air (Setsys-TG-DSC from Setaram), XRD powder measurements (AXS D8 Advance spectrometer from Bruker, Cu$K\alpha$ = 1.5406 Å), elemental analysis (C, H, N, S)-Vario EL III Elemental Analyser. Both transmittance spectra and DRUV-Vis spectra were recorded on Cary 100 UV–vis spectrophotometer. The FTIR measurements applying KBr technique were recorded with 640-FTIR spectrometer from Varian. Adsorption–desorption measurements of N_2 at −196 °C were realized with ASAP 2010 sorptometer (Micromeritics).

3. Results and discussion

3.1. Modification of SBA-15

Both MCM-41 and SBA-15 materials are described in literature as large surface area (~1000 $m^2\,g^{-1}$) mesoporous siliceous materials with hexagonal array of pores of ~3.5 and ~6.5 nm of pores, respectively. In contrast to MCM-41, the SBA-15 materials with uniform mesoporous channels are described as more stable mechanically and thermally. Significant surface area, the presence of uniform cappilary channels and micropores cause that these materials are characterized by good absorption properties. The presence of free silanol groups in pure silica of SBA-15 or MCM-41 enable forming of hydrogen bonds between the adsorbed drugs and the walls of silanol matrix. Free silanol groups might be modified by attachment of trialkoxysilan. It can markedly increase adsorption properties of these materials relatively to certain substances. The bonding of these groups with appropriate organic

Table 1
Characterization of modified SBA-15 with $-SO_3H$ groups.

Sample	Initial molar ratio MPTMS:SBA-15[a]	Yield of reaction (%)	Amount of SO_3H group in carrier (mol SO_3H/g carrier)[b]	S_{BET} (m^2/g)	BJH pore volume (cm^3/g)	t-plot micropore volume (cm^3/g)	Average pore diametre (nm)
SBA-15	–	–	–	807	1.04	0.0764	6.1
SBA-15–SO_3H (1:30)	1:30	28.84	1.53×10^{-4}	725	0.96	0.0653	6.1
SBA-15–SO_3H (1:20)	1:20	23.24	1.84×10^{-4}	715	0.95	0.0651	6.1
SBA-15–SO_3H (1:10)	1:10	16.37	2.56×10^{-4}	706	0.93	0.0605	6.1
SBA-15–SO_3H (1:5)	1:5	12.30	3.77×10^{-4}	683	0.89	0.0586	6.0
SBA-15–SO_3H (1:2)	1:2	5.72	4.34×10^{-4}	667	0.87	0.0561	5.9

[a] SBA-15 expressed as SiO_2.
[b] Calculated from elemental analysis.

or inorganic materials can lead to generation of surface acidic or basic sites. These sites can be used for accumulation of chemically bonded pharmaceuticals with appropriate opposite basic or acidic properties. Adsorption of metoprolol and papaverine on modified surface of SBA-15 is described in this paper. The MPTMS was applied as the reagent to modify the surface properties of SBA-15. The formation of surface sulfonic groups was realized by adsorption of MPTMS on SBA-15, followed by reaction with hydrogen peroxide. It was very important to establish the best concentration of surface sulfonic groups for drugs adsorption, therefore in the preliminary experiments five different concentrations of MPTMS were applied. Table 1 represents basic structural properties of the obtained modified samples of SBA-15. It was established that independently from the applied initial concentration of MPTMS only part of the assumed amounts can be adsorbed. Obtained data indicate that the best adsorption of the introduced surface modifier can be achieved for the lowest concentration MPTMS. It is due to the excess of modyfying agent (MPTMS) in the case of higher concentration relatively to free silanol groups at the surface of SBA-15 channels. Here, almost 29% of the initial amount of modifier is irreversibly connected with surface of SBA-15. Although an increase of molar ratio between MPTMS and SBA-15 results in lowering of the adsorption yield, the total amount of the adsorbed modifying agent (MPTMS) increases together with its concentration in an anhydrous toluene. This is demonstrated by increasing content of sulfur after oxidation of sulfhydryl groups (see Table 1). The increasing concentration of adsorbed MPTMS influences surface properties of SBA-15 by lowering surface area and meso- and micropores volume as well. The highest decrease of surface area was observed after deposition of MPTMS from solution with the lowest concentration. Here, the initial surface area of 807 m^2/g for non-modified SBA-15 was decreased by 10% for sample with 1.53×10^{-4} mol of $-SO_3H$ groups per 1.0 g of modified SBA-15. Further loading with MPTMS decreases surface area and pore size dimensions. Fig. 1 represents the nitrogen adsorption–desorption isotherms of the studied supports. The mesoporous character of the $-SO_3H$ modified SBA-15 is well preserved and this is documented by the shape and position of the hysteresis loop. The decreased amount of adsorbed nitrogen both at high and low p/p_o pressures shows that both mesopores and micropores are involved in this modification. The shape of adsorption–desorption isotherm indicates the preservation of mesoporous character of the carrier. The XRD diffraction patterns at low angle and TEM micrographs (not shown here) confirm that hexagonal array of the studied materials is well preserved after modification.

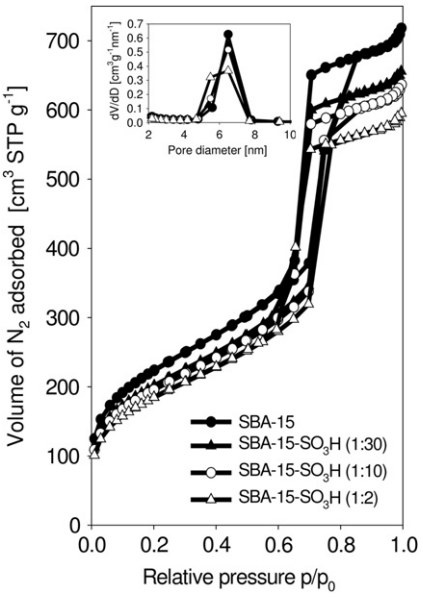

Fig. 1. N_2 adsorption–desorption isotherms (77 K) of SBA-15 modified with $-SO_3H$ groups. Inset: pores size distribution.

3.2. Adsorption and release of metoprolol

Metoprolol as the organic base should easily interact with acidic sulfonic groups (Fig. 2A) and generate stronger bonds than in the case of simple physical adsorption over the silanol groups of SBA-15. Table 2 shows the basic data concerning interaction of metoprolol with both modified and non-modified SBA-15 material. The obtained results show that the higher is the concentration of sulfonic groups, the better adsorption of metoprolol occurs. Molar ratio between metoprolol and sulfonated material indicate that at relatively low concentration of sulfonic groups the interaction with metoprolol is the best. It is connected with better availability (for drug) of rarely distributed functional groups.

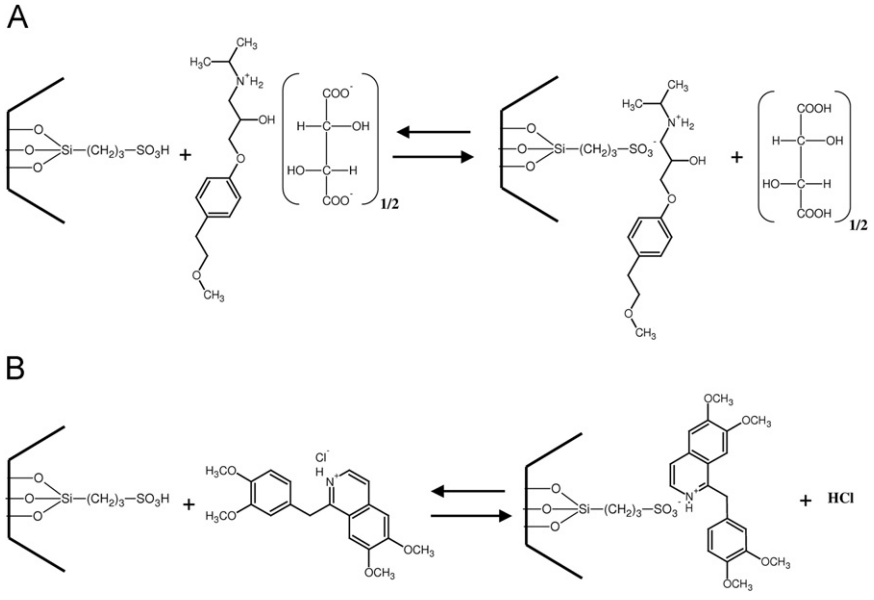

Fig. 2. Scheme of interactions of modified SBA-15 with metoprolol and papaverine.

Table 2
Adsorption of metoprolol tartrate on modified SBA-15-SO_3H materials.

Sample	Amount of $-SO_3H$ groups in the carrier (mol/g)[a]	Amount of N (after metoprolol adsorption) (wt.%)[a]	Metoprolol tartrate adsorption (wt.%)	Molar ratio Metoprolol: $-SO_3H$[a]
SBA-15–Meto	–	0.38	5.87/9.29[a,b]	–
SBA-15–SO_3H (1:30)–Meto	1.53×10^{-4}	0.35	6.30/8.56	1.28
SBA-15–SO_3H (1:20)–Meto	1.84×10^{-4}	0.37	6.95/9.05	1.18
SBA-15–SO_3H (1:10)–Meto	2.56×10^{-4}	0.39	7.09/9.53	0.87
SBA-15–SO_3H (1:5)–Meto	3.77×10^{-4}	0.44	8.12/10.76	0.68
SBA-15–SO_3H (1:2)–Meto	4.34×10^{-4}	0.47	9.34/11.49	0.69

[a] Calculated from elemental analysis.
[b] Calculated from spectrophotometric analysis (in state of adsorption equilibrium).

In the case of higher content of functional groups not all the sites available to adsorbate are used due to the steric hindrance effect resulting from the size of the drug molecule (0.610×1.347 nm [30]). The excess of modifying compound cannot interact with SBA-15 probably due to the limited access to silanol groups and steric hindrance. The discrepancies between the amount of adsorbed metoprolol tartrate measured by spectrophotometric method and by elemental analysis originate from deposition of certain amounts of this drug on the internal surface of the support. Higher content of drugs in the case of elemental analysis is due to the incomplete separation of carrier suspension and the solution in which the adsorption was taking place. It is connected with the preparation of the sample and with the difficulty of elimination of solution from the mesoporous cappilaries of SBA-15.

The series of thermogravimetric experiments was performed in order to establish thermal stability of the adsorbed drug, as well as possible maximum temperature for degassing in surface area measurements. Fig. 3A shows DTG curves of SBA-15 with metroprolol tartrate. It was found that in all cases, pores of SBA-15 (Fig. 3A, curves a–d) are filled with water and maximum of water desorption is ~120 °C, whereas non-modified or modified support with metoprolol can survive temperatures close to 170 °C (curves c and d) without drug decomposition. These results showed relatively high thermal stability of the adsorbed drug and simultaneously indicate the highest applicable evacuation temperature. Elemental analysis and thermogravimetric studies performed before and after evacuation of drug containing material (necessary for BET surface area measurements) showed that neither decomposition nor sublimation of the drug occurs.

Nitrogen adsorption–desorption curves presented in Fig. 4A show typical shape and position of the hysteresis loop characteristic for the mesoporous materials. Both functionalized and non-functionalized materials are capable to adsorb metoprolol. The presence of hysteresis loop indicate that mesoporous channels are not completely clogged, whereas certain part of micropores is blocked by the drug. The analysis of pores distribution (inset, see Fig. 4) indicates that the drugs are deposited on the internal surfaces of the channels accompanied by the shift of volume distribution in direction of smaller pores diameter. Additionaly, this phenomenon is also accompanied by BET surface area reduction. Similar observations were reported by Qu et al. [7], while adsorption of captopril on MCM-41 and SBA-15, Tang et al. [31] while adsorption of ibuprofen on MCM-41 and Xu et al. [32] while adsorption of famotidine on carboxyl-modified SBA-15.

Fig. 5 represents the XRD diffraction patterns within the wide angle range. The inset in Fig. 5 shows the results of DSC measurements. Only traces of the very complicated diffraction pattern, characteristic for the pure metoprolol tartrate (curve f), can be found in mechanical mixture of the drug and SBA-15 (curve e). In all other cases (curves c and d) no XRD reflexes were found. This is indicative for the amorphous form of the drug inside the mesoporous structure. Similar effect was observed by Charnay et al. [33] in the case of ibuprofen adsorbed on MCM-41. Additional confirmation of molecular dispersion of drug inside SBA-15 channels can be found while analyzing DSC measurements. The strong minimum at 125 °C (melting point of metoprolol tartrate) is followed by minimum at 230 °C connected with its partial evaporation. The endothermic peak around 65 °C for pure carriers corresponds to water desorption (see Fig. 5, curves a and b—in inset). The endothermic melting peak around 125 °C for drug containing sample (see Fig. 5, curves c and d—in inset) was absent. Similar results were reported by Mellaerts et al. [34] while examining adsorption and stability of itraconazole on SBA-15. Moreover, similar shape of DRUV spectra of the metoprolol supported on SBA-15 (see Fig. 6A, curves d and e) and transmittance spectrum of metoprolol tartrate recorded in water solution

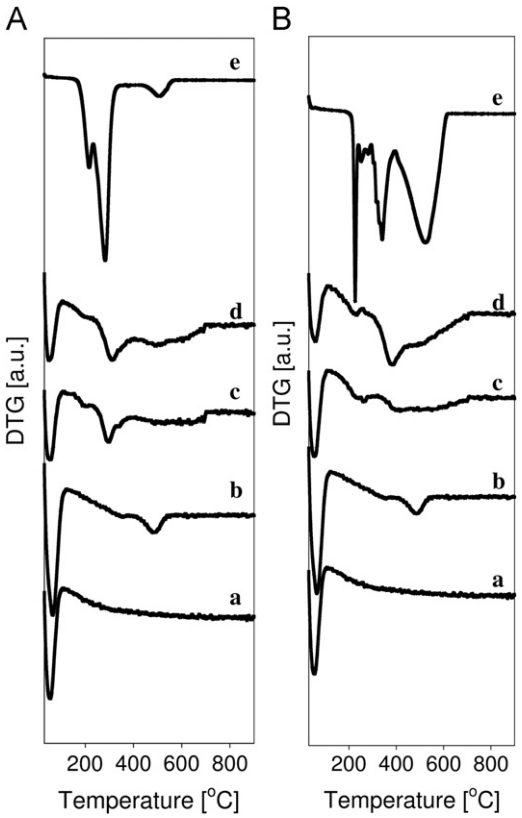

Fig. 3. Thermogravimetric analysis of metoprolol tartrate (A) and papaverine hydrochloride (B) loaded on non-modified and –SO_3H modified SBA-15: (a) SBA-15; (b) SBA-15-SO_3H (1:10); (c) SBA-15-metoprolol tartrate (A), SBA-15-papaverine hydrochloride (B): (d) SBA-15-SO_3H (1:10)- metoprolol tartrate (A), SBA-15-SO3H (1:10)-papaverine hydrochloride (B): (e) metoprolol tartrate (A), papaverine hydrochloride (B).

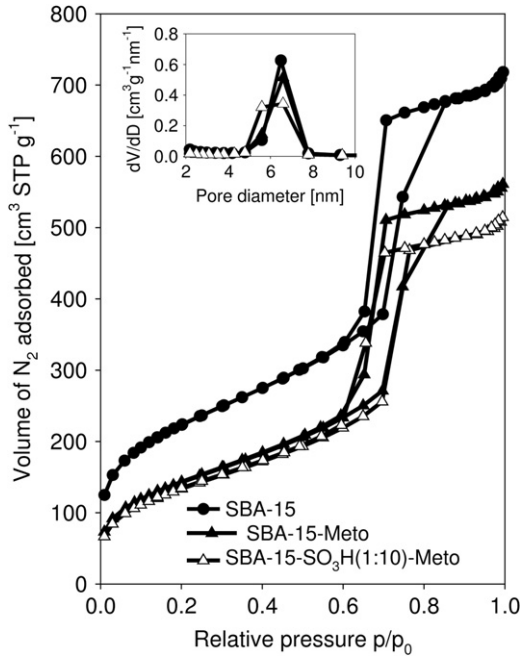

Fig. 4. N_2 adsorption–desorption isotherms (77 K) of modified SBA-15 loaded with metoprolol tartrate (inset: pore size distribution).

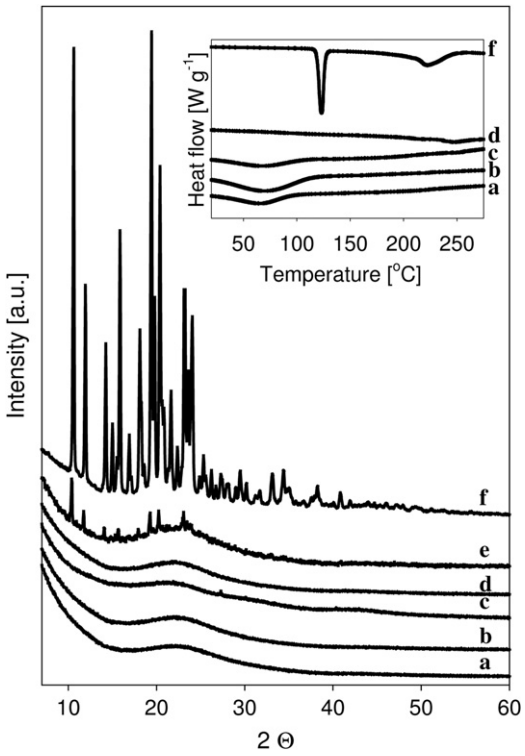

Fig. 5. XRD diffraction patterns (wide angle) of SBA-15 loaded with metoprolol tartrate (a) SBA-15; (b) SBA-15-SO_3H (1:10); (c) SBA-15-metoprolol tartrate; (d) SBA-15-SO_3H (1:10) metoprolol tartrate; (e) SBA-15+metoprolol tartrate (10 wt.% mechanical mixture); (f) metoprolol tartrate.

(curve f) confirm the similar character of interactions between the drug and the carrier as well as between the drug and the molecules of the solvent (hydrogen bonds, van der Waals interaction). Similar results of UV radiation adsorption by organic compounds adsorbed at the solid carriers are described by Ciani et al. [35] and Lacombe et al. [36]. The DRUV spectrum of pure metoprolol is shown in

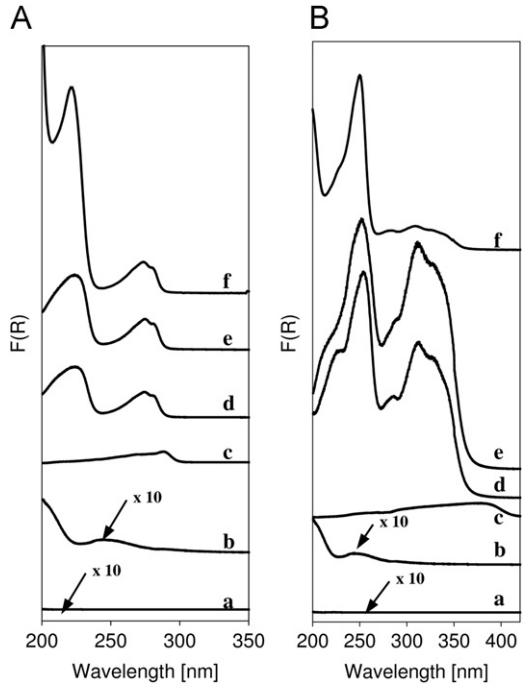

Fig. 6. UV–vis diffuse reflectance spectra of SBA-15 loaded with metoprolol tartrate (A) or papaverine hydrochloride (B): (a) SBA-15; (b) SBA-15-SO_3H (1:10); (c) metoprolol tartrate (A) (solid state), papaverine hydrochloride (B) (solid state): (d) SBA-15-metorpolol tartrate (A), SBA-15-papaverine hydrochloride (B): (e) SBA-15-SO_3H (1:10)- metoprolol tartate (A), SBA-15-SO3H (1:10)-papaverine hydrochloride (B): (f) metoprolol tartrate (A) and papaverine hydrochloride (B) (water solution).

Fig. 6A (curve c). Here, in contrast to the water solution spectrum, practically no electron excitation originating from aromatic compounds is observed [37].

Although differences in the DRUV spectra of metoprolol supported on non-modified and modified carrier are negligible, the rate of evolution of this drug clearly indicates the basic differences between these two materials. Fig. 7A shows the release profiles for metoprolol deposited on pure SBA-15 and two profiles from differently modified support (different amounts of –SO_3H groups). The evolution of metoprolol in water from SBA-15 is instant, because after first minutes almost 90% of deposited drug can be found in the solution. The amount of evolved drug reaches 95% after 10 h and is steady until 24 h of release. Modification of the internal surface of SBA-15 with –SO_3H groups results in much lower rate of the drug release in water. Moreover, the saturated surface of SBA-15 with sulfonic groups causes stronger interaction of the carrier with the studied drug. This effect is especially strong for SBA-15 modified with larger amounts of MPTMS. Much faster release of the supported drug is observed in acidic medium during next 24 h (see Fig. 7A). In all cases an instant increase in drug release was observed. Finally, a complete release was found for non-modified SBA-15, whereas in both cases of sulfonated samples certain amount was strongly anchored within the porous structure.

3.3. Adsorption and release of papaverine

Although papaverine interacts with surface sulfonic groups (Fig. 2B) on the same basis as metoprolol, the amounts of adsorbed and chemically bonded drug are much higher (see Table 3). This can originate from more basic character of papaverine and formation of stronger ionic bonds.

Thermogravimetric analysis (see Fig. 3B) of the adsorbed papaverine is very similar to the one with metoprolol. Thermal

treatment of papaverine supported on SBA-15 do not cause thermal decomposition up to 170 °C. Practically, the only difference can be found in thermal decomposition of non-supported drugs. DTG of papaverine shows more complicated decomposition pathways.

There are many similarities between metoprolol and papaverine adsorbed on SBA-15. Adsorption–desorption isotherms in both cases represent almost the same shape and surface area (compare Figs. 4 and 8). These results indicate a similar character of location of the drugs inside the hexagonal channels and practically the same type of interaction with silica walls.

The uniform distribution of papaverine inside the porous structure of SBA-15 is confirmed by XRD measurements (Fig. 9), similar to those effects found for metoprolol. The lack of characteristic reflexes after introduction of papaverine onto SBA-15 confirms amorphous form of the drug inside the pores. As in the case of metoprolol the DRUV-vis spectra of the supported papaverine (Fig. 6B) show very intense bands between 300 and 350 nm related to the presence of benzene rings in papaverine structure.

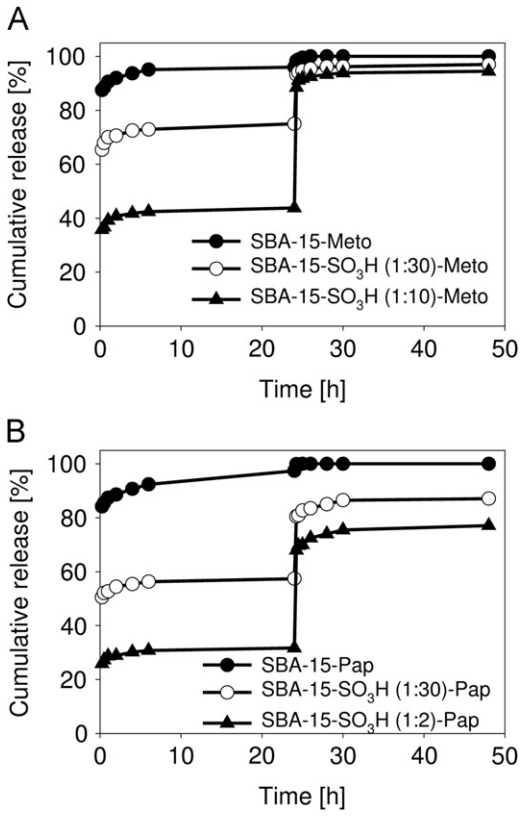

Fig. 7. Release of metoprolol tartrate (A) and papaverine (B) from modified SBA-15.

Comparison of the kinetics during drugs release (Figs. 7A and B) reveals that papaverine is much strongly bonded to the modified SBA-15 than metoprolol. This is demonstrated by much slower release of the drug after treatment with diluted hydrochloric acid. Even after 48 h cumulative release do not cross 80%. In the case of non-modified SBA-15 the drug release is very fast.

4. Conclusions

Siliceous, mesoporous SBA-15 material can serve both in non-modified or modified form as the carrier for such drugs as metoprolol or papaverine. Modification of the internal surface of the SBA-15 with sulfonic (–SO_3H) groups leads towards carriers with surface acidic properties. Adsorption of weak organic bases of metoprolol or papaverine occurs with much better yields on the modified surface. Although the release of the studied drugs from SBA-15 is still far from the zero kinetics order, the obtained results show that further modification of the mesoporous materials with other compounds might be promising. In future studies carrier systems providing constant drug release (for a few hours) required for oral administration will be of interest.

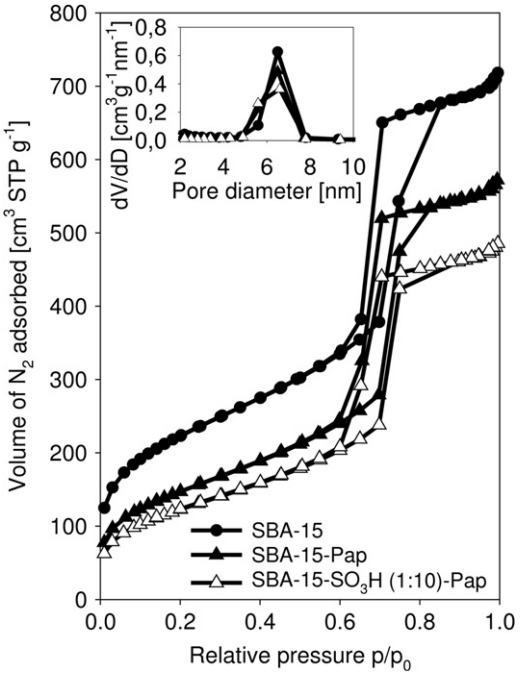

Fig. 8. N_2 adsorption–desorptions isotherms (77 K) of modified SBA-15 loaded with papaverine hydrochloride (inset: pore size distriburion).

Table 3
Adsorption of papaverine hydrochloride on modified SBA-15-SO_3H materials.

Sample	Amount of $-SO_3H$ groups in the carrier (mol/g)[a]	Amount of N (after papaverine adsorption) (wt.%)[a]	Papaverine hydrochloride adsorption (wt.%)	Molar ratio Papaverine: $-SO_3H$[a]
SBA-15-Pap	–	0.27	5.82/7.25[a,b]	–
SBA-15–SO_3H (1:30)-Pap	1.53×10^{-4}	0.38	8.35/10.20	1.58
SBA-15–SO_3H (1:20)-Pap	1.84×10^{-4}	0.43	8.94/11.55	1.42
SBA-15–SO_3H (1:10)–Pap	2.56×10^{-4}	0.39	8.59/10.47	0.97
SBA-15–SO_3H (1:5)-Pap	3.77×10^{-4}	0.47	10.22/12.62	0.80
SBA-15–SO_3H (1:2)-Pap	4.34×10^{-4}	0.56	12.15/15.85	0.85

[a] Calculated from elemental analysis.
[b] Calculated from spectrophotometric analysis (in state of adsorption equilibrium).

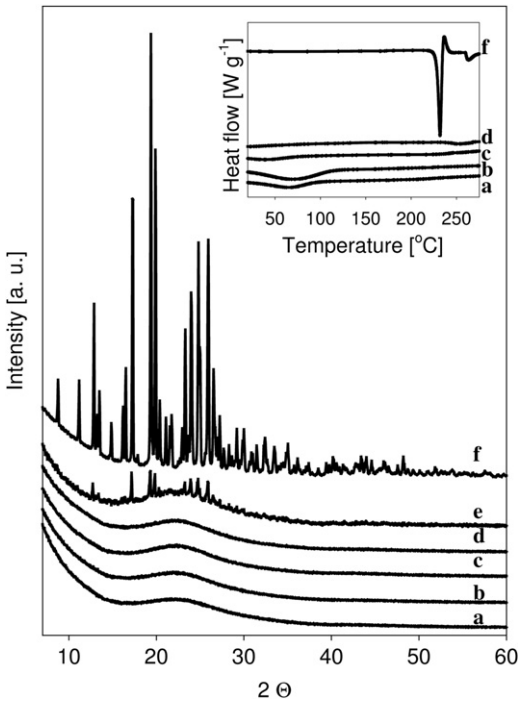

Fig. 9. XRD diffraction patterns (wide angle) of SBA-15 loaded with papaverine hydrochloride : (a) SBA-15: b/ SBA-15—SO_3H (1:10): (c) SBA-15—papaverine hydrochloride: (d) SBA-15—SO_3H(1:10) papaverine hydrochloride: (e) SBA-15+papaverine hydrochloride (10 wt.% mechanical mixture): (f) papaverine hydrochloride.

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