

NSAID naproxen in mesoporous matrix MCM-41: drug uptake and release properties

Dáša Halamová · Vladimír Zeleňák

Received: 7 December 2010 / Accepted: 17 May 2011 / Published online: 8 June 2011
© Springer Science+Business Media B.V. 2011

Abstract Hexagonally ordered mesoporous silica material MCM-41 ($S_{\text{BET}} = 1090 \text{ m}^2/\text{g}$, pore size = 31.2 \AA) was synthesized and modified by 3-aminopropyl ligands. The differences in an uptake and subsequent release of anti-inflammatory drug naproxen from unmodified and amino modified MCM-41 samples were studied. The prepared materials were characterized by high resolution transmission electron microscopy (HRTEM) and scanning electron microscopy (SEM), nitrogen adsorption/desorption, Fourier-Transform Infrared Spectroscopy (FT-IR), Small-angle X-ray scattering (SAXS), thermoanalytical methods (TG/DTA) and elemental analysis. The amount of the drug released was monitored with thin layer chromatography (TLC) with densitometric detection in defined time intervals. The amounts of the released naproxen from mesoporous silica MCM-41/napro and amine-modified silica sample A-MCM-41/napro were 95 and 90% of naproxen after 72 h. In this study we compare the differences of release profiles from mesoporous silica MCM-41 and mesoporous silica SBA-15.

Keywords Mesoporous silica · MCM-41 · Drug delivery · Naproxen · Amine modification

Introduction

In the recent years, ordered mesoporous materials were investigated as materials for applications in many areas,

such as catalysis [1, 2], sorption [3], separation [4], drug delivery or controlled release [5, 6]. The drug delivery systems are of special interest since controlled and prolonged release of the drug could lead to prolonged efficiency, less frequent doses and consequently to minimalization of the side, negative effects of the drugs. Several mesoporous materials were studied as drug delivery supports such as MCM-41, SBA-15, SBA-16, MSU-3, FDU-12 [7–18]. First who dealt with mesoporous silica as drug delivery support were Regí et al. [5] They used hexagonal mesoporous silica MCM-41 for controlled release of analgesic drug, ibuprofen. The released amount of ibuprofen was 70 and 90.72%, after 24 and 72 h, respectively. Muñoz et al. [10] studied the amine modification of mesoporous silica MCM-41 materials with different pore size. Their results showed, that amino functionalization decrease the rate of drug release. This observation was explained by interactions of the amine groups with acidic groups of ibuprofen. Manzano et al. [19] deal with ibuprofen delivery from amino-modified MCM-41 with different particle diameter. It was found out that a higher amount of ibuprofen (up to 10%) can be loaded into the amino modified mesoporous silica MCM-41 than into the unmodified mesoporous material.

Wang et al. [20] presented comparative study of synthesis procedures (grafting or co-condensation method) to functionalize mesoporous silica MCM-41 with various functional groups (3-aminopropyl, 3-mercaptopropyl, vinyl and secondary amine groups). Two different molecules (ibuprofen and rhodamine) were used as model drugs to investigate adsorption and release properties. Their results showed that while mercaptopropyl and vinyl functionalized samples showed high adsorption capacity for rhodamine, amine functionalized samples exhibit higher adsorption capacity for ibuprofen. On the other hand the tested

D. Halamová (✉) · V. Zeleňák
Department of Inorganic Chemistry, Faculty of Science,
P. J. Šafárik University, Moyzesova 11, 041 54 Košice,
Slovak Republic
e-mail: dasa.halamova@upjs.sk

samples functionalized with vinyl and mercaptopropyl by post grafting method released rhodamine faster than the corresponding sample synthesized by co- condensation.

Doadrio and Regí [6, 12] prepared mesoporous silica SBA-15 and used it for gentamicin and amoxicillin delivery. The authors applied two forms of mesoporous silica SBA-15, powder and disk. In the case of gentamicin, they found no significant differences between release rates from the both forms. But in the case of amoxicillin, the release rate from disk was faster.

Yu et al. [21] studied release of ninodiphine from SBA-15 mesoporous silica. The external surface of the SBA-15 was modified with phenyl-trimethoxysilane or trimethylchlorosilane. No difference in the release properties has been found for the samples after modification. The release efficiency was 100% in 24 h.

In our work we are interested in investigation of drug delivery of non-steroidal anti-inflammatory drugs. Recently we have reported the detailed study of the naproxen delivery using hexagonal SBA-15 silica [22]. In this study we report uptake and subsequent release of naproxen by MCM-41 silica, which has a narrower pore size in comparison with SBA-15. We modified prepared mesoporous silica with aminopropyl groups and we compared the release profiles of naproxen from these two hexagonal ordered mesoporous matrices. The administration of the naproxen molecules by a mesoporous silica matrix MCM-41 would provide advantages over conventional drug therapies. It can enhance curative effect of the naproxen, because this NSAID drug is insoluble in water.

Naproxen (S)-6-Methoxy- α -methyl-2-naphthalenacetic acid (Fig. 1) belongs to the group of nonsteroidal anti-inflammatory drugs (NSAID). This group of drugs is widely used to treat arthritis, musculoskeletal and post-operative pain, as well as headache and fever. NSAIDs include acetylsalicylic acid, traditional NSAIDs (e.g. diclofenac, ibuprofen, indomethacin and naproxen) and inhibitors of the COX-2 isoform of cyclo-oxygenase (celecoxib, lumiracoxib, etoricoxib, rofecoxib) [23]. Control and optimization of the drug release requires selective high-throughput analysis of the drug in the release media. Several methods have been published for determination of naproxen in pharmaceutical formations and biological fluids. Most of these methods are based on high performance liquid chromatography (HPLC) [24–26], gas chromatography with mass spectroscopy (GC–MS) [26, 27], or thin layer chromatography [28–30]. Our previous studies have confirmed that TLC is suitable and reliable method for analysis of drugs in various complex samples [31]. In the present study the amount of the drug released was monitored with fast and simple method TLC chromatography with densitometric detection. We have chosen a TLC chromatographic method for the release study, because it

presents the advantage over spectrophometric and potentiometric method to permit the detection of degraded compounds of the naproxen molecule, which can be produced throughout the time of release.

Experimental part

Chemicals and materials

Tetraethyl orthosilicate (hereafter denoted as TEOS) was selected as a source of silica. Cetyltrimethylammonium bromide (CTAB) was used as the structure directing agent. 3-aminopropyl-triethoxysilane was chosen for silica modification. All these chemicals were obtained from Aldrich. Physiological solution (infusion intravenous solution of 0.9% NaCl) was obtained from Braun (Germany).

Synthesis and functionalization of the samples

MCM-41 mesoporous silica was synthesized according to the literature [32]. The TEOS/CTAB/NaOH/H₂O molar ratio was (1/0.12/0.33/601.3). In the typical synthesis, 0.56 g NaOH was dissolved in 486 ml of distilled water and then 1.99 g of CTAB was added into this solution. When the solution became homogenous, 9.33 g of TEOS was added and the mixture was stirred for 2 h. After this time the formed white solid product was filtered off, washed with distilled water and dried at laboratory

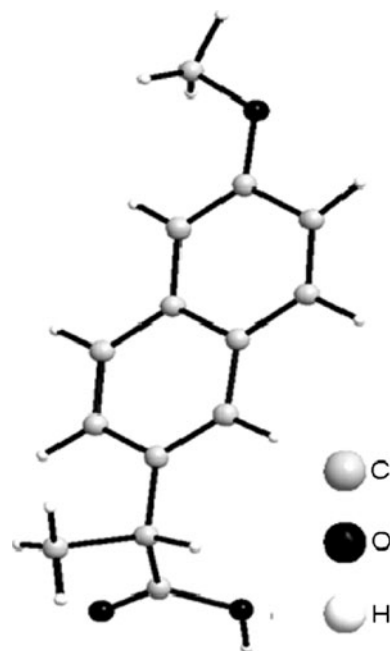


Fig. 1 View of naproxen structure

temperature. The porous MCM-41 sample was prepared by calcination of as-synthesized sample at 500 °C for 7 h.

The surface modification of silica was carried out by grafting. Before grafting of the sample by 3-aminopropyl ligands, silica matrix was thermally treated at 200 °C for 3 h. Then 1 g of mesoporous silica was dispersed in 50 cm³ of toluene dried over zeolite sieves. In the next step 3 cm³ of 3-aminopropyl-triethoxysilane were added to dried toluene and this mixture was refluxed for 20 h. The solid product was filtered off, washed out with toluene and dried at laboratory temperature. The sample was denoted as A-MCM-41.

Loading of naproxen into mesoporous silicas and study of release

For the loading of mesoporous supports with naproxen, 200 mg of mesoporous silica MCM-41 or A-MCM-41 was added into the solution of naproxen in ethanol (1 mg/mL) and stirred slowly for 24 h at laboratory temperature. The obtained products were filtered off, gently washed with ethanol and dried at laboratory temperature. The respective samples were denoted as MCM-41/napro and A-MCM-41/napro.

Naproxen release was received by treating of 150 mg of the samples MCM-41/napro, A-MCM-41/napro in 10 mL physiological solution at room temperature under stirring. The released amount of naproxen was determined in 1, 3, 5, 7, 24, 48 and 72 h. Infusion intravenous solution of 0.9% NaCl was chosen as physiological solution.

Characterization

The textural properties of the investigated materials were determined by nitrogen adsorption–desorption at 77 K using Quantachrome NOVA 1200e analyzer. Before the experiment, the samples were outgassed at 110 °C for 12 h. The specific surface area, S_{BET} was estimated using the Brunauer-Emmett-Teller (BET), pore size distribution and pore volumes were calculated using BJJ (theory of Barrett, Joyner, Halenda). Infrared spectra were obtained using Avatar FT-IR spectrometer. The powder samples were pressed in KBr pellets for IR analysis. Thermogravimetric (TG) analysis was carried out in air atmosphere at the heating rate of 9 °C/min using Netzsch 409 PC instrument. The elemental analysis was measured using the CHNS Elementar Analyser Flash 1112 (Finnigan). Small-angle X-ray scattering was carried out in Hasylab (Desy, Hamburg) using the B1 beamline. The HRTEM micrographs were taken with a JEOL JEM 3010 (LaB₆ cathode) microscope operant at 300 kV. The SEM micrographs were taken with JEOL JSM 35 CF (wolfram cathode) microscope operant at 25 kV. Chromatographic analysis was performed

on silica/glass F₂₅₄ TLC plates (10 × 10 cm², Kavalier, Czech Republic). The samples were spotted using a 2 μL microsyringe. The plates were developed at room temperature in the vertical trough glass developing chamber (20 × 20 cm²) with benzene-tetrachlormethane-acetic acid (35: 5: 5, v/v/v) as mobile phase to the distance of 8 cm. Visualization was performed by illumination with UV light source (254 nm) using UV scanner (Krüss, Germany). Densitometric analysis was performed at 260 nm by Shimadzu CS-930 TLC Scanner used in the absorbance mode. The obtained peak areas served for quantitative evaluation of the drug into physiological solution with help of calibration curve of naproxen standards.

Calibration standards were prepared daily by diluting solution of naproxen (1 mg/mL of ethanol) to yield concentrations of 25, 50, 100, 300, 500 ng per spot of naproxen. These standards were used to construct calibration curve. This curve was constructed by plotting the peak area against the corresponding concentrations of the analyte by means of the least-square method.

Results and discussion

SAXS study

Fig. 2 shows SAXS patterns of the studied materials. The SAXS measurements of the unmodified, amine modified and drug loaded samples show that the periodicity of the porous structure of the modified materials was preserved after modification. The diffraction peaks of the modified samples have the same q value which indicates no change of the structural arrangement during the modification.

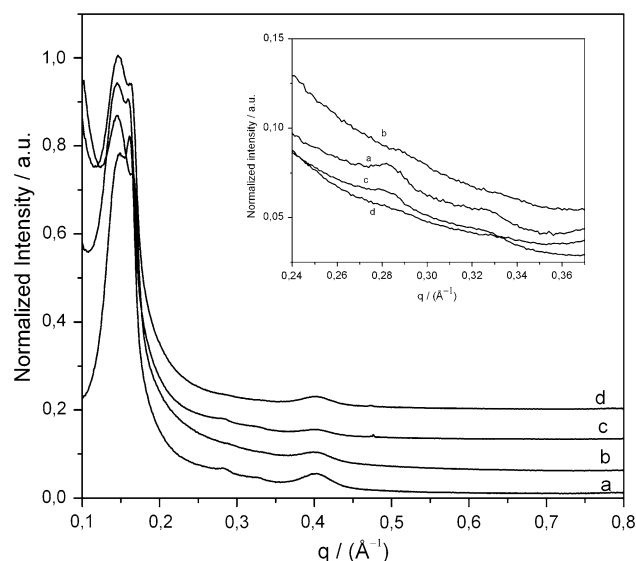


Fig. 2 SAXS patterns of the samples: MCM-41 (a), A-MCM-41 (b), MCM-41/napro (c), A-MCM-41/napro (d)

SEM and HRTEM measurements

Figures 3 and 4 show scanning electron micrograph and high resolution transmission electron micrographs of the calcined mesoporous silica material MCM-41. SEM micrograph shows that MCM-41 has shape of small spherical particles with a size of a few microns. From the HRTEM micrographs can be seen that this material has well ordered mesoporous structure of hexagonal symmetry with alternating channels and siliceous framework. The pore size, as determined from HRTEM micrographs was about 3 nm.

Nitrogen adsorption/desorption

The textural characteristics of the samples were determined by nitrogen adsorption/desorption and the results are summarized in the Table 1. The adsorption/desorption isotherms are shown in Fig 5.

The nitrogen adsorption/desorption isotherm of the MCM-41 mesoporous silica material (Fig. 5, isotherm a) is of type IV in the IUPAC classification with a typical adsorption step over a narrow range of relative pressures $p/p_0 = 0.2-0.4$, arising from the capillary condensation of nitrogen in the mesopores. The uniformity of desorption and adsorption curve in the full range of the measurement is characteristic for this mesoporous silica. BET surface area of MCM-41 sample was $1090 \text{ m}^2/\text{g}$, pore volume $0.72 \text{ cm}^3/\text{g}$ and pore diameter about 31.2 \AA , which corresponds with the estimated value from TEM micrographs.

The decrease of textural properties and the change of the shape of isotherms were observed after amine modification and loading the silica with naproxen (see Table 1 and Fig. 5).

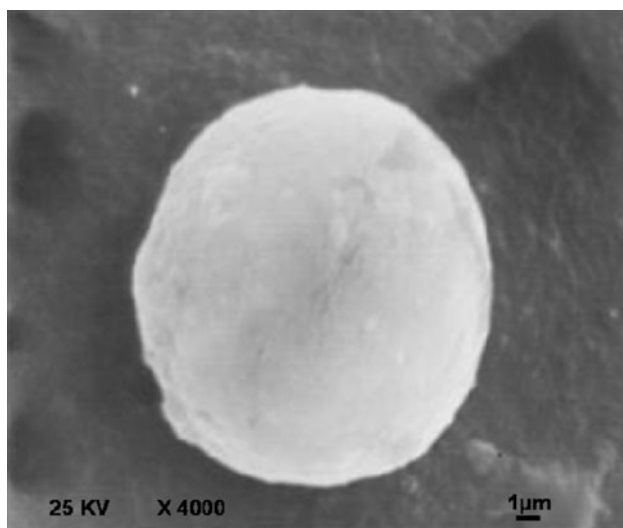


Fig. 3 SEM micrograph of MCM-41

The capillary condensation step was significantly reduced for the samples A-MCM-41 (Fig 5, isotherm b) and MCM-41/napro (Fig. 5, isotherm c), what showed on the decrease of the surface area and pore volume of the MCM-41 sample after modification. In the case of amine modified sample, A-MCM-41, the surface area decreased to $367 \text{ m}^2/\text{g}$ and pore size to 30.9 \AA . For the sample containing naproxen, MCM-41/napro, the value of the surface area was $185 \text{ m}^2/\text{g}$ and the pore size 30.3 \AA . The decrease of the textural parameters in the samples A-MCM-41 and MCM-41/napro is related to the filling of the pores by aminopropyl ligands or naproxen molecules.

In the case of sample A-MCM-41/napro (Fig 5, isotherm d) the simultaneous naproxen loading and amine modification of the mesoporous silica matrix produced filling of the pores and the hysteresis loop for this sample completely disappeared.

Elemental and thermal analysis

The quantification of naproxen and/or aminopropyl groups loaded/grafted in the silica was made by elemental and thermogravimetric analyses. According to the results of elemental analysis the sample A-MCM-41 contained 8.40% of carbon, which corresponds to the 13.5 wt% of the aminopropyl ligands grafted on the sample. This result is in an agreement with the results of the thermal analysis (see below). The amount of the carbon in the sample MCM-41/napro, as determined by elemental analysis represented 24.8%. This value corresponds to the 34 wt% of the naproxen loaded in the MCM-41 silica. Again this result well agrees with the amount of the naproxen as determined by TG and described below. For the sample A-MCM-41/napro the difference in the amount of naproxen determined by TG (27.6 wt% - see below) and elemental analysis (21.2 wt%) was observed. The difference can be explained by the non-homogeneity of the sample due to pore blockage. Since thermal analysis uses larger amounts of the sample, these results should be for the sample A-MCM-41/napro more reliable.

The thermogravimetric curves are displayed in Fig. 6. In the case of sample MCM-41 (Fig. 6, curve a) the TG curve showed the mass loss in the temperature range $25-150 \text{ }^\circ\text{C}$ corresponding to the thermodesorption of water. This thermal change is characteristic of all other samples (A-MCM-41, MCM-41/napro and A-MCM-41/napro). After dehydration the pure mesoporous silica material MCM-41 is thermally stable in the temperature range from 150 to $900 \text{ }^\circ\text{C}$ without significant weight change. Slight mass loss at the temperatures above $650 \text{ }^\circ\text{C}$ (Fig. 6, curve a) corresponds to the loss of surface hydroxyls from the sample. For the amine functionalized mesoporous silica sample A-MCM-41 (Fig. 6, curve b) the mass loss of 12.5%

Fig. 4 HRTEM micrographs of the sample MCM-41. The view on the material along the hexagonal axis (a) and perpendicular to the hexagonal axis (b)

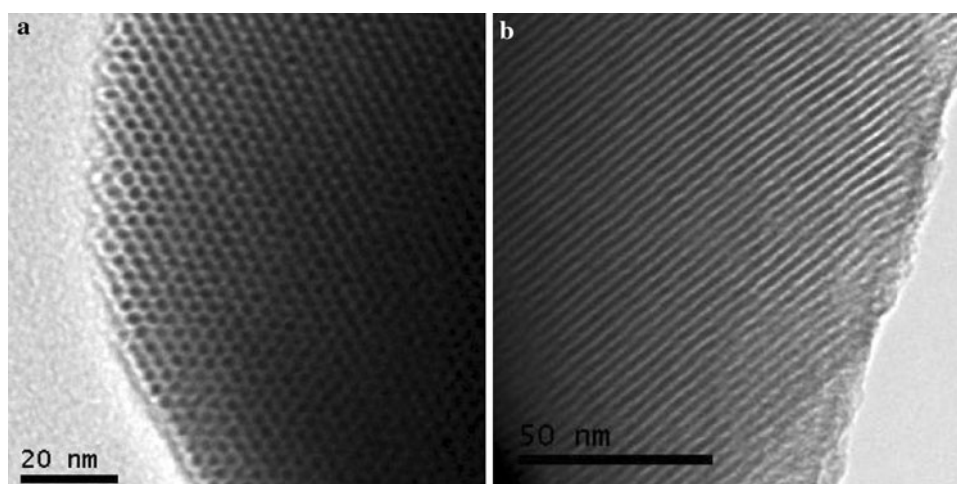


Table 1 Textural properties of MCM-41 and the modified samples

Silica	BET surface area (m ² /g)	External surface area (m ² /g)	Pore volume (cm ³ /g)	DV(d) diameter (Å)
MCM-41	1090	112	0.72	31.2
A-MCM-41	367	79	0.21	30.9
MCM-41/napro	185	64	0.11	30.3
A-MCM-41/napro	11	–	–	–

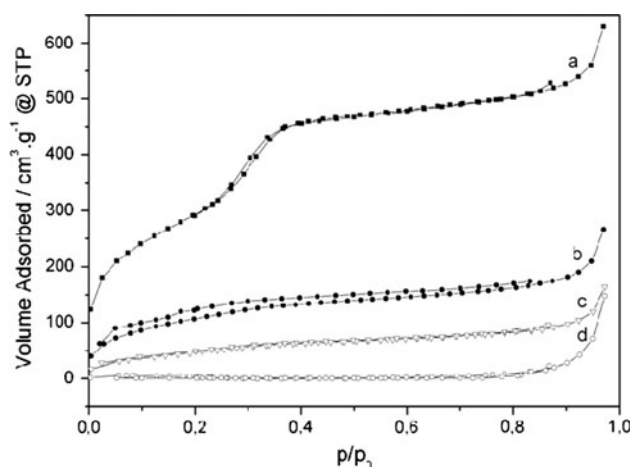


Fig. 5 Nitrogen adsorption–desorption isotherms of the samples: MCM-41 (a), A-MCM-41 (b), MCM-41/napro (c), A-MCM-41/napro (d)

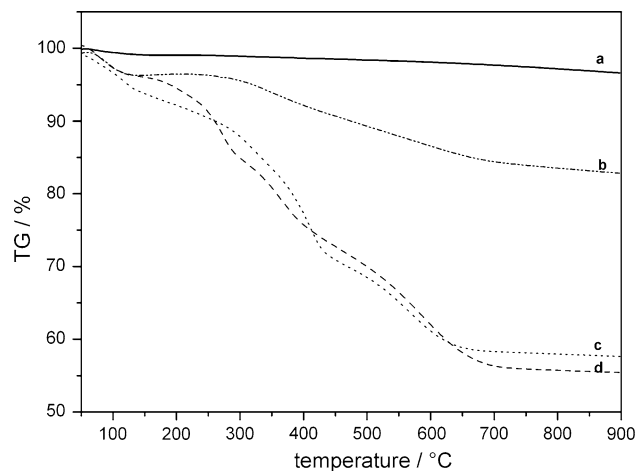


Fig. 6 TG curves of the samples MCM-41 (a), A-MCM-41 (b), MCM-41/napro (c), A-MCM-41/napro (d)

occurred in the temperature range 200 - 800 °C corresponding to the decomposition and release of amino ligands.

The sample loaded with the drug, MCM-41/napro (Fig. 6, curve c), shows in temperature range from 200 to 900 °C the mass loss 34.4 wt%, which corresponds to the 344 mg of loaded naproxen per one gram of the sample. More complicated thermal decomposition was observed in the case of the sample A-MCM-41/napro (Fig. 6, curve d). The total mass loss in the temperature range from 200 to 800 °C was 41.8 wt%. The corresponding amount of the

loaded naproxen was calculated from the mass differences observed for the samples A-MCM-41 and A-MCM-41/napro. This difference represents 29.3 wt%, which corresponds to 293 mg of naproxen per one gram of the sample A-MCM-41/napro.

From the results of TG analysis it can be seen that the higher amount of naproxen was loaded into unmodified MCM-41 silica. This indicates that for the studied MCM-41 sample, with pore size about 3 nm, the amine grafting results decrease of the pore diameters and the amine groups obstruct the loading of naproxen molecules.

FT-IR spectra

Organic functionalization and loaded with drug was evidenced by infrared spectroscopy which was carried out on all samples. Infrared spectra of unmodified and modified mesoporous samples as well as naproxen sample are shown in Fig. 7. From the FT-IR analysis, it is found that there is no structural collapse of the pore structure occurred by the incorporation of naproxen and aminopropyl groups. But, the naproxen components and aminopropyls were not homogeneously doped in the pores of the mesoporous silica as we described in follow text. MCM-41 The asymmetric stretching vibration $\nu_{as}(\text{Si-O-Si})$ at about 1000 cm^{-1} , the symmetric stretching vibration $\nu_s(\text{Si-O-Si})$ at about 800 cm^{-1} and the bending vibration $\delta(\text{Si-O-Si})$ at 500 cm^{-1} are characteristic for FT-IR spectrum of all studied mesoporous silica samples and correspond to the vibrations of the siliceous framework. The broad vibration bands at about 3400 cm^{-1} are due to stretching vibrations of physisorbed water in the samples.

The modification of the silica by amine was reflected in the infrared spectra of the samples A-MCM-41 and A-MCM-41/napro by the bands of the stretching vibrations $\nu(\text{C-H})$ of propyl chains at about $2980\text{--}2840\text{ cm}^{-1}$ and bending vibrations $\delta(\text{C-H})$ in the range from 1470 to 1450 cm^{-1} (Fig. 7, spectrum b and d). For the drug loaded

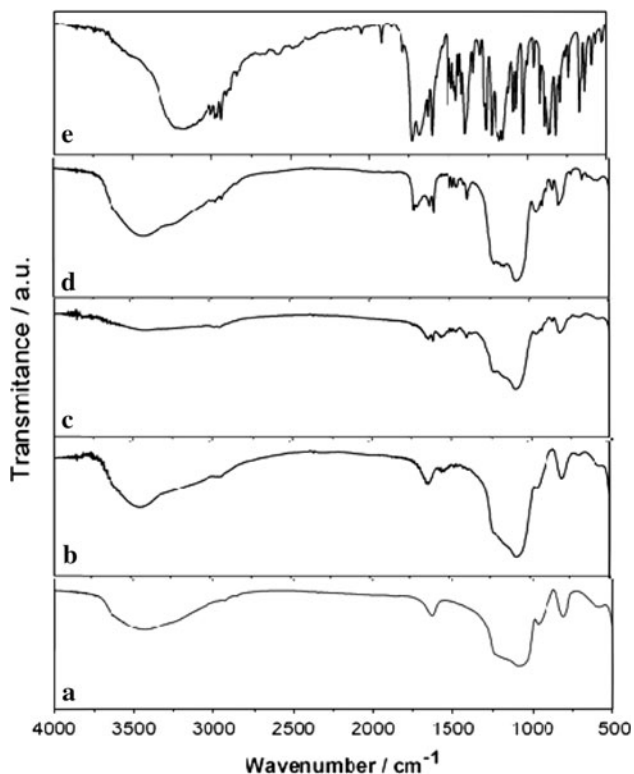


Fig. 7 FT-IR spectra of studied samples MCM-41 (a), A-MCM-41 (b), MCM-41/napro (c), A-MCM-41/napro (d), napro (e)

samples (MCM-41/napro, A-MCM-41/napro) the presence of naproxen in the samples was indicated by the bands of the stretching vibration $\nu(\text{C=O})$ of naproxen carboxylic group at 1720 cm^{-1} , the breathing vibrations of the aromatic rings at 1600 cm^{-1} and vibrations of naproxen $\nu(\text{C-H})$ at about 900 cm^{-1} .

As it follows from the results of TG analysis in the case of naproxen loaded samples the higher amount of drug was loaded in the sample MCM-41/napro (34.4 wt% of naproxen) in comparison to the amino modified sample A-MCM-41/napro (29.3 wt% of naproxen). On the other side in the amine modified sample A-MCM-41/napro the bands from FT-IR spectra corresponding to naproxen are more intensive in comparison with MCM-41/napro sample, even amine modified sample contained lower amount of the drug. This result suggests that in the amine modified sample larger amount of naproxen was immobilized on the surface of the sample. This immobilization of the amino groups on the surface accordant with the results of the SAXS measurements also.

Study of the drug release from MCM-41

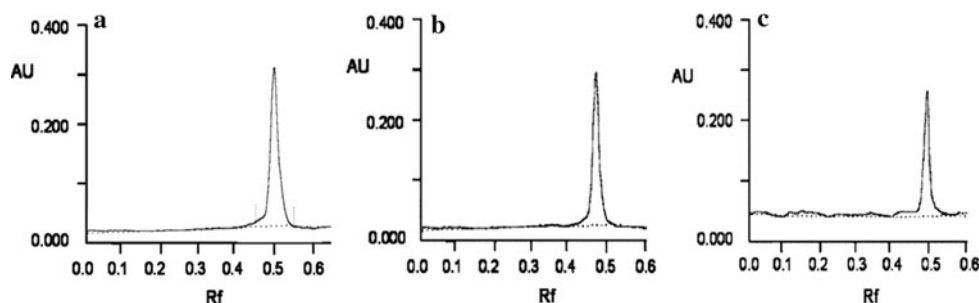
The amount of the naproxen released from the mesoporous silicas MCM-41 after immersion to physiological solution (0.9% NaCl) was determined by using TLC chromatographic method with densitometric detection in defined time intervals.

To optimize TLC separation, several compositions of mobile phases were tried. A satisfactory separation of naproxen was obtained with a mobile phase consisting of benzene-tetrachloromethane-acetic acid (35: 5: 5, v/v/v) on aluminium backed TLC plates coated with silica gel. The R_F value at 260 nm was 0.50. Representative TLC chromatograms of released naproxen from the sample MCM-41/napro, amino modified sample A-MCM-41/napro and their comparison with naproxen standard are shown on Fig. 8.

For the additional information the UV adsorption spectrum of naproxen standard and released naproxen was measured. The overlaying of UV spectrum of naproxen standard and naproxen released from the mesoporous matrix MCM-41 confirmed the purity of released naproxen.

The experimental release profiles of naproxen from both forms of modified and unmodified mesoporous silica materials MCM-41 are shown on Fig. 9. From the picture can be seen that in the case of mesoporous silica MCM-41/napro larger amount of naproxen (45.6%) was released in the first 3 h than from amine modified sample A-MCM-41/napro (38.9%). This difference can be explained by the theory of Ronselholm and Lindén [33] considering the larger hydrophobicity and lower wettability of the amine modified sample. In the time interval from 3 to 7 h the

Fig. 8 TLC chromatograms of naproxen standard (a), naproxen released from mesoporous silica MCM-41 (b) and naproxen release from the matrix A-MCM-41/napro into the physiological solution (c)



kinetic of the release of the naproxen from the respective samples changed. Larger amount of naproxen was released from the amine modified sample (about 81.8%) than from unmodified one (65.2%). This fact is caused by releasing of naproxen molecules from the external surface of silica. Another reason is that the columbic interactions between the protonated aminopropyl groups and carboxylate anions would additionally contribute to the observed decrease of the delivery rate. After 7 h the release of the drug from the pores of mesoporous silica starts to dominate, however, the higher amount of naproxen was still released from the sample A-MCM-41/napro than from the sample MCM-41/napro. We suppose that in amino modified sample the naproxen release from the outer surface still continues until the 50 h. The total amount of the drug released after 72 h was 95% of the loaded amount in the case of MCM-41/napro and 90% for the sample A-MCM-41/napro.

Comparison of NSAID uptake and release from MCM-41 and SBA-15 matrices

In this part we compare the uptake and release of the naproxen from the mesoporous silica MCM-41 presented in this work and SBA-15 used in our previous study [22].

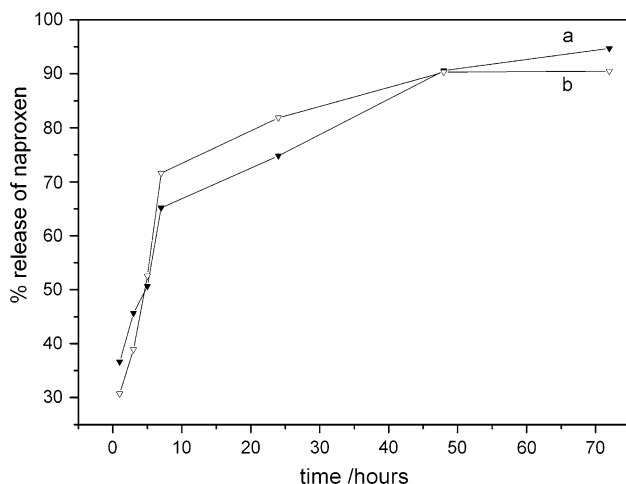


Fig. 9 Cumulative release rates of the samples MCM-41/napro (a), A-MCM-41/napro (b)

As it follows from our preceding study the adsorption capacity of naproxen in the sample SBA-15/napro was 37.3 wt% and in the amino modified sample 35.6 wt. %. The adsorbed amount of naproxen in SBA-15 was in both cases higher in comparison with the samples MCM-41/napro (34.4 wt%) and A-MCM-41/napro (29.3 wt%). The higher amount of adsorbed naproxen for the silica SBA-15 is related to approximately twofold larger pores in SBA-15 (71.3 Å) in comparison with MCM-41 (31.2 Å).

On contrary, when we compare the released amount of naproxen from the MCM-41 and SBA-15 silica, it is obvious that larger amount was released from the MCM-41 silica. The respective values of the drug release were 90.7% in the case of mesoporous silica SBA-15/napro, 80.9% in the case of mesoporous silica A-SBA-15/napro, 95% for MCM-41/napro and 90% for A-MCM-41/napro. This can be due to lower degree of assembly and higher disorder of the naproxen molecules in the channels of MCM-41 in comparison to SBA-15. According to the study of Salomen et al. [34], small pore size of mesoporous silica is an important factor in the stabilization of the drug. The small pores restrict the formation of an organized crystal structure inside them, and thus the loaded molecules are constrained to stay in the amorphous form and the phase transitions upon storage are prevented. Qiu et al. [35] explained similar observation by different mesoporous channel length. They suggest that the molecules of the naproxen would take less time to diffuse from smaller mesoporous silica (MCM-41).

Moreover the population of pore entrances on the external surface area of the mesoporous silica MCM-41 might be another reason of faster release [36]. The studied MCM-41 and SBA-15 samples have different external surface area (112 m²/g for the sample MCM-41 and 58.7 m²/g for the sample SBA-15). Since MCM-41 silica has larger external surface, lower wall thickness and lower pore size, more mesoporous entrances are supposed to be present on the external surface. This gives larger possibility of the fluid to penetrate inside channels, dissolve the drug release the naproxen into the solution. Therefore, the larger released amount of naproxen was determined for mesoporous silica MCM-41 with smaller pores in comparison with SBA-15 material.

Conclusion

The uptake and controlled release of the therapeutic drug as an active piece into/from the inert matrix has become still more important for the therapeutic system. The main advantages of this system is especially safety and efficiency and take control over the negative influence of the using drug.

Here, the adsorption capacity and release properties of NSAID drug, naproxen incorporated into amino modified and unmodified hexagonal ordered mesoporous silica material MCM-41 were studied. Our study shows that naproxen can be successfully incorporated into the pores of hexagonally ordered mesoporous silica material MCM-41, even if this material has smaller pore size in comparison with SBA-15. This incorporation was confirmed by elemental analysis, nitrogen adsorption/desorption measurements, small-angle X-ray scattering and FT-IR spectra. According to thermogravimetric analysis a larger amount of the loaded naproxen was determined for unmodified sample in comparison with modified one. The released naproxen was studied with TLC chromatography with densitometric detection. The larger total amount of the released drug after 50 h was observed from amine modified sample, which reflected larger amount of the naproxen immobilized on the external surface of the A-MCM-41/napro sample.

Finally we compared the release profiles of naproxen from two types of mesoporous silicas MCM-41 and SBA-15. The larger released amount observed for MCM-41 material can be explained when considering the differences in wettability and number of pores on the external surface of both materials as well as the different structural ordering of the adsorbed naproxen molecules in the pores of MCM-41 and SBA-15.

Our study can be useful in the biomedical applications. The storage and subsequent release of the studied NSAID drug from mesoporous matrix should decrease the negative effect of the drug using and also decrease the dose of the drug during the therapy.

Acknowledgments This work was supported by the VEGA project of Ministry of Education of the Slovak Republic (No. 1/058311), and by the ERDF EU grant under the contract No. ITMS26220120019. The authors would like to thank HasyLab laboratory (Desy, Hamburg), for the project no. I-20100131 to support measurements at the B1 beamline of HasyLab. The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement no. 226716.

References

- Nekoksová, I., Žilková, N., Zukal, A., Čejka, J.: Introduction of tin into mesoporous molecular sieves for oxidation of adamantanone. In: Safari A., Jaroniec, M. (eds.) NANO-IV Symposium. Stud. Surf. Sci. Catal. **156**, 779 (2005)
- Dai, Q., He, N., Weng, K., Lin, B., Lu, Z., Juan, Ch.: Enhanced photocatalytic activity of titanium dioxide supported on hexagonal mesoporous silica at lower coverage. J. Incl. Phenom. Macrocycl. Chem. **35**, 11–21 (1999)
- Ziółek, M., Sobczak, I.: Photochromism and hydrolysis of aromatic Schiff base N, N'- bis (salicylidene)-p-phenylenediamine (BSP) studied in heterogenous environments. J. Incl. Phenom. Macrocycl. Chem. **63**, 211–218 (2009)
- Gunko, V.M., Turov, V.V., Turov, A.V., Zarko, V.Z., Garda, V.I., Yanishpolskii, V.V., Berezovska, I.S., Tertykh, V.A.: Behaviour of pure water and water mixture with benzene or chloroform adsorbed onto ordered mesoporous silica. Cent. Eur. J. Chem. **5**, 420–454 (2007)
- Regí, M.V., Rámila, A., del Real, R.P., Pariente, J.P.: A new property of MCM-41: drug delivery system. Chem. Mater. **13**, 308–311 (2001)
- Raso, E.M.G., Cortes, M.E., Teixeira, K.I., Franco, M.B., Mohallen, N.D.S., Sinisterra, R.D.: A new controlled release system of chlorhexidine and chlorhexidine β cd: inclusion compounds based on porous silica. J. Incl. Phenom. Macrocycl. Chem. **67**, 159–168 (2010)
- Nguyen, T.P.B., Lee, J.W., Shim, W.G., Moon, H.: Synthesis functionalized SBA-15 with ordered large pore size and its adsorption properties of BSA. Microporous Mesoporous Mater. **110**, 560–569 (2008)
- Zhao, D., Feng, J., Huo, Q., Melosh, N., Fredrickson, G.H., Chmelka, B.F., Stucky, G.D.: Triblock copolymer syntheses of mesoporous silica with periodic 50–300 angstrom pores. Science **279**, 548–552 (1998)
- Zhao, D., Huo, Q., Feng, J., Chmelka, B.F., Stucky, G.D.: Nonionic triblock and star diblock copolymer and oligomeric surfactant syntheses of highly ordered hydrothermally stable mesoporous silica structures. J. Am. Soc. **120**, 6024–6036 (1998)
- Muñoz, B., Rámila, A., Pariente, J.P., Díaz, I., Regí, M.V.: MCM-41 organic modification as drug delivery system. Chem. Mater. **15**, 500–503 (2003)
- Wang, S.: Ordered mesoporous materials for drug delivery. Microporous Mesoporous Mater. **117**, 1–9 (2009)
- Regí, M.V., Doadrio, J.C., Doadrio, A.L., Barba, I.I., Pariente, J.P.: Hexagonal ordered mesoporous materials as a matrix for the controlled release of amoxicillin. Solid State Ionics **172**, 435–439 (2004)
- Tang, Q., Xu, Y., Wu, D., Sun, Y.: A study of carboxylic-modified mesoporous silica in controlled delivery for drug famotidine. J. Solid State Chem. **179**, 1513–1520 (2006)
- Budi-Hartono, S., Qiao, S.Z., Jack, K., Ladewig, B.P., Hao, Z., Qing, Lu G.: Improving adsorbent properties of cage-like ordered amine-functionalized mesoporous silica with very large pores for bioadsorption. Langmuir **25**, 6413–6424 (2009)
- Zelevák, V., Hornebecq, V., Llewellyn, P.: Zinc(II)-benzoate complexes immobilized in mesoporous silica host. Microporous Mesoporous Mater. **83**, 125–135 (2005)
- Thomas, M.J.K., Slipper, I., Šalunk, A., Jain, A., Favretto, M.E., Kallinteri, P., Douroumis, D.: Inclusion of poorly soluble drugs in highly ordered mesoporous silica nanoparticles. Inter. J. Pharm. **378**, 272–277 (2009)
- Tingming, F., Liwei, G., Kang, L., Tianyao, W., Jin, L.: Template occluded SBA-15: an effective dissolution enhancer for poorly water drug. Appl. Surf. Sci. **256**, 6963–6968 (2010)
- Xu, Z., Ji, Y., Guan, M., Juany, H., Zhao, Ch., Zhang, H.: Preparation and characterization of L-Leucine-modified amphiphilic bifunctional mesoporous SBA-15 molecular sieve as a drug carrier for ribavirin. Appl. Surf. Sci. **256**, 3160–3165 (2010)
- Manzano, M., Aina, V., Areán, C.O., Balas, F., Cauda, V., Collila, M., Delgado, M.R., Regí, M.V.: Studies on MCM-41

- mesoporous silica for drug delivery: effect of particle morphology and amine functionalization. *Chem. Eng.* **137**, 30–37 (2008)
20. Wang, G., Otuonye, A.N., Blair, E.A., Denton, K., Tao, Z., Asefa, T.: Functionalized mesoporous materials for adsorption and release of different drug molecules. *J. Solid State Chem.* **182**, 1649–1660 (2009)
 21. Yu, H., Zhai, Q.Z.: Mesoporous SBA-15 molecular sieve as carrier for controlled release of nimodipine. *Microporous Mesoporous Mater.* **123**, 298–305 (2009)
 22. Halamová, D., Badaničová, M., Zelenák, V., Gondová, T., Vainio, U.: Naproxen drug delivery using periodic mesoporous silica SBA-15. *Appl. Surf. Sci.* **256**, 6489–6494 (2010)
 23. Rostom, A., Muir, K., Dube, C., Lanas, A., Jolicoeur, E., Tugwell, P.: Prevention of NSAID-related upper gastrointestinal toxicity: a meta-analysis of traditional NSAIDs with gastroprotection and COX-2 inhibitors. *Drug Healthc. Patient Saf.* **1**, 1–25 (2009)
 24. Monser, L., Darghouth, F.: Simultaneous determination of naproxen and related compounds by HPLC using porous graphitic carbon column. *J. Pharm. Biomed. Anal.* **32**, 1087–1092 (2003)
 25. Tashtoush, B.M., Al-Taani, B.M.: HPLC determination of naproxen in plasma. *Pharmazie* **9**, 614–615 (2003)
 26. Aresta, A., Palmisano, F., Zamboni, C.G.: Determination of naproxen in human urine by solid-phase microextraction coupled to liquid chromatography. *J. Pharm. Biomed. Anal.* **39**, 643–647 (2005)
 27. Sebök, Á., Vasanits-Zsigrai, A., Palkó, Gy., Zárny, Gy., Molnár-Perl, I.: Identification and quantification of ibuprofen, naproxen, ketoprofen and diclofenac present in waste-waters, as their trimethylsilyl derivatives, by gas chromatography mass spectrometry. *Talanta* **76**, 642–650 (2008)
 28. Singh, A.K., Jang, Y., Mishra, U., Granley, K.: Simultaneous analysis of flunixin, naproxen, ethacrynic acid, indomethacin, phenylbutazone, mefenamic acid and thiosalicylic acid in plasma and urine by high-performance liquid chromatography and gas chromatography-mass spectroscopy. *J. Chromatogr. Biomed. Appl.* **106**, 351–361 (1991)
 29. Guermouche, M.H., Atik, N., Chader, B.: Assay of naproxen in rat serum by high-performance thin-layer chromatography/densitometry. *J. AOAC Int.* **83**, 1489–1492 (2000)
 30. Jamshidi, A., Sharifi, S.: HPTLC analysis of tamoxifen citrate in drug-release media during development of an in situ-cross-linking delivery system. *J. Planar Chromatogr.* **22**, 87–189 (2009)
 31. Gondová, T., Halamová, D., Špacayová, K.: Simultaneous Analysis of New Antidepressants by Densitometric Thin-Layer Chromatography. *J. Liq. Relat. Technol.* **31**, 2429–2441 (2008)
 32. Qiang, C., Wen-Yong, L., Feng-Shou, X., Wen-Qin, P., Xi-Hua, Ch., Ben-San, Z.: The preparation of highly ordered MCM-41 with extremely low surfactant concentration. *Microporous Mesoporous Mater.* **32**, 1–15 (1999)
 33. Rosenholm, J.M., Lindén, M.: Towards establishing structure-activity relationships for mesoporous silica in drug delivery applications. *J. Control. Rel.* **128**, 157–164 (2008)
 34. Salonen, J., Laitinen, L., Kaukonen, A.M., Tuura, J., Björkqvist, M., Heikkilä, T., Vähä-Heikkilä, K., Hirvonen, J., Lehto, V.P.: Mesoporous silicon microparticles for oral drug delivery: Loading and release of five model drugs. *J. Control. Rel.* **108**, 362–374 (2005)
 35. Qu, F., Zhu, G., Lin, H., Zhang, W., Sun, J., Li, S., Qiu, S.: A controlled release of ibuprofen by systematically tailoring the morphology of mesoporous silica materials. *J. Solid State Chem.* **179**, 2027–2035 (2006)
 36. Lei, J., Fan, J., Yu, C., Zhang, L., Juany, S., Tu, B., Zhao, D.: Immobilization of enzymes in mesoporous materials: controlling the pore-mouth to nanospace. *Microporous Mesoporous Mater.* **73**, 121–128 (2004)