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MCM-41 silica as a host material for controlled drug delivery systems

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The adsorption and release of Naproxen as a model drug was studied. The MCM-41 silica was chosen as a model adsorbent. The synthesis of mesoporous silica was performed by template method using cetyltrimethylammonium bromide CTAB as a pore directing agent. Synthesized MCM-41 material of high quality was used as a carrier for Naproxen. The loading procedure was performed at normal conditions and under vacuum. The release of drug was measured for differentially prepared samples. The results for MCM-41 are compared to those measured for silica gel for column chromatography Si-100 containing substantially larger pores. The results are discussed taking into account the penetration of pore system by loading solution as well as in terms of the proportion of dimensions of Naproxen molecule and pore dimensions of MCM-41.

Keywords: MCM-41 silica, Naproxen, adsorption, drug loading, release systems.

1. INTRODUCTION

Almost a quarter of a century has passed since a first drug delivery system DDS (Liposomal amphotericin B) was approved [1]. The most important functions of drug delivery systems are to control and make targeted the drug transport into cells, maintain drug concentration within the therapeutic level and reduce side effects [2]. Generally, DDS is built of 2 components: carrier and drug substance. The carrier matrix plays a crucial role in proper functioning of DDS. For the carrier is expected to be biocompatible, non-toxic, thermally and chemically stable. The drug release takes place from them in targeted and very often stimuli-responsive manner [2–4]. Important is fact that the cost and time of creation a new DDS (about $20–50 million and 3–4 years, respectively) is much lower than to develop of a new drug (about $500 million and over 10 years) [1]. It is obvious that scientists (especially material chemists and nanotechnologists) around the world are constantly working to create newer and better drug carriers and DDS. In the last decade one of the most popular matrices used as potential carriers in drug delivery system and in other biomedical applications are silica materials, especially mesoporous silica nanoparticles (MSNs) [5, 6]. Ordered mesoporous silica materials from the time of first synthesis in the early 90's are commonly used in adsorption, catalysis, separation and recently in biomedicine. MSNs like MCM-41, MCM-48, SBA-1, SBA-3, SBA-15, SBA-16 are tested to drugs delivery for different diseases e.g. inflammation, cancer, diabetes, neurological disorders and even as a carriers in gene therapy or biosensor in diagnosis. The reasons of their popularity are that these materials have a several advantages, such as unique ordered structure of high specific area and pore volume and consequently high sorption capacity. Moreover production of these materials is relatively simple, inexpensive and easy controllable. Finally, they are nontoxic and biocompatible which are the key requirements [5–7]. Therefore great number of papers is addressed to drug release from mesoporous silica nanoparticles. The great interest in regularly arranged silicas started in 2001 when Vallet-Regi and coworkers as a first reported the MCM-41 as Ibuprofen delivery system. They received a relatively high release percent of drug up to about 70 and 91 after 24 h and 72 h respectively. Since these investigations MCM-41 silica material and its variety modifications is the most frequently used as carriers for many types of medicaments i.e. Ibuprofen, Aspirin, Naproxen, Doxorubicin,

Captopril, Erythromycin [6, 8–10]. Vallet-Regi et.al/Zeng et.al./Halamova et.al. studied the amine modified MCM-41 materials respectively as Ibuprofen, Aspirin and Naproxen carrier. They observed the decrease of drug release, because the ionic interactions between amine groups and carboxylic groups of drugs, and increase the total amount of drug loaded into silica material, because of better adsorption of anionic drugs on modified MCM-41 material of cationic character [11, 12]. Horcjada et.al studied also the modified MCM-41 silica with different organosilanes (Ph, But, Cl-Prop, SH-Prop, CN-Prop) as Ibuprofen host material. In this case they had drawn similar conclusions. Ibuprofen was better adsorbed on polar group of modified MCM-41 material than on modified of non-polar character. The drug release from material modified with non-polar groups was higher than from modified matrix with polar species [13]. Horcjada et.al also investigated the influence of pore size MCM-41 on Ibuprofen rate delivery. They synthesized MCM-41 materials with different pore size (with diameter range from 2.5 nm to 3.6 nm), by using various types of surfactants containing different number of carbons in tail (from C8 to C16). Delivery rate of ibuprofen was increasing with increasing pore size of silica matrix [14]. Le-Le Yu Hong Bi developed the hybrid nanospheres MCM-41/iron oxide as a magnetic controlled DDS, to the target delivery of doxorubicin hydrochloride, which is a common anticancer drug. Amount of released drug in magnetic field was about 20% higher (at pH = 5.5) than in sample without field. They also examined the cytotoxicity of MSNs on human cells (HepG2) and they proved that the mesoporous silica nanoparticles are characterized by low cytotoxicity and high biocompatibility [15]. Summing up, one can say that silica materials, especially MCM-41 and its modifications, are still one of the most popular potential host materials for therapeutic substances.

Below we presented information about mesoporous silica MCM-41 and adsorption process of drug on these materials. Naproxen was used as a model drug in our experiments. In experimental part we presented results obtained for silica materials used as host material for Naproxen delivery system.

2. MCM-41 SILICA MATERIALS

2.1. Synthesis and features

The MCM-41 material was synthesised by a liquid crystal templating (LCT) in 1992 by scientists from Mobil Oil Company [16]. Their procedure of production consists in the formation of micelles in aqueous solution of surfactant, followed by the hydrolysis and polycondensation of a silica source in alkaline solution and finally the removal of surfactants from the pores of the material by calcination in 500-550°C Fig. 1 [5, 17–20].

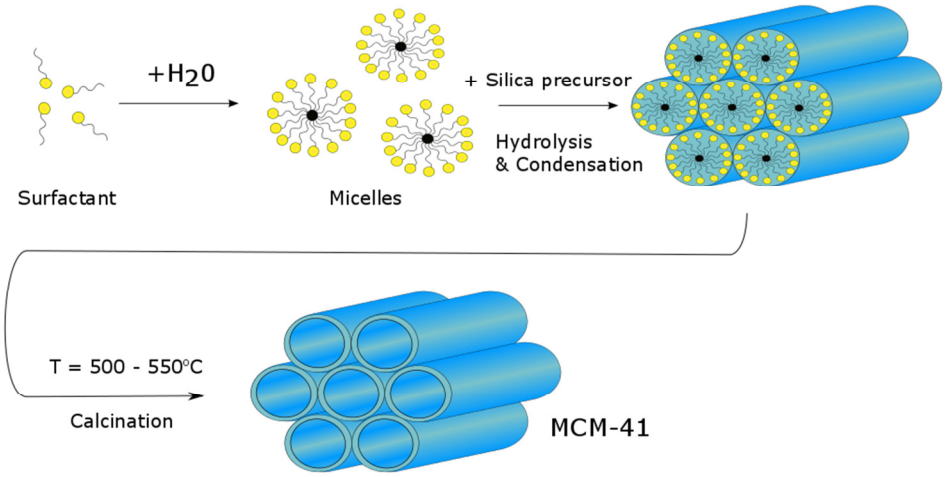

Fig. 1. Scheme of synthesis the MCM-41 silica material.

It is worth to pay attention to these silica due to their extremely high pore volume (~1-2 cm^3/g) and consequently high adsorption capacity (high specific surface area ~1000 m^2/g). Very useful feature is also the regularity of pore shape and uniformity of pore dimension. MCM-41 materials posses hexagonally arranged pores with long-range structural regularity. Both ends of cylindrical pores are likely open. As synthetized very fine particles of this silica can be easily formed in tablets or pellets without the deformation or collapse at pore system due to their mechanical stability, which is not insignificant in creating new drug delivery systems [1, 5, 18, 19].

2.2. Drug adsorption process

Most commonly used method for drug loading is impregnation in drug solution. Usually drugs are not satisfactory soluble in water. Thus, impregnations are performed using typical solvents like ethanol, acetonitrile or hydrocarbons like n-hexane. To facilitate the increase of drug loading from the aqueous solutions, salt of drugs are used, which are easy soluble in water and polar solvents. For solids equilibrated with binary solution containing drug both components are present in the surface phase. For solids where pores are large enough and their dimensions are within mesopore range there existing possibility to form the multilayer of preferentially adsorbed component (drug) on the pore walls. In the case of MCM-41 the formation of multilayer is strongly restricted from steric reasons. Thus adsorption of drug and competition for silica surface become most important factor regulating the amount of drug deposited. The aim of the experimental efforts is to optimize satisfactory the adsorption process and to cause that adsorption of drug is strongly preferential. The adsorption of relatively large drug molecules is determined by several factors, which may be summarized as follows:

1. The interactions of adsorbate/drug molecule with the silica surface. Walls of pores in MCM-41 consist an amorphous silica gel. Thus the surface of silica gel condensed around micelles of pore directing agent contains the surface silanol groups of acidic character. The presence of hydroxyl groups enhanced the interactions with polar compounds like water, alcohols, amines and other chemical species containing heteroatoms. However, the hydroxyls originated from silica acid easily condense. Condensation starts, according to the literature data above 200°C and is followed by formation at siloxane bridges which are of hydrophobic character. The conventional procedure of the MCM-41 synthesis is completed after calcination at 550°C for 8 h causing the degradation and removal of surfactant molecules. Calcination causes the increase of hydrophobic properties of silica surface. On the other hand the water treatment at acidic conditions makes possible partial rehydroxylation process. As a result the MCM-41silica adsorbs quite noticeably water. The state of silica surface in pore interior is a crucial parameter for adsorption of drug molecules. Thus, the state of silica should be carefully controlled [18, 21].
2. The adsorption of drug molecules is strongly determined by pore dimensions. In MCM-41 silica the pore diameter is dependent on the chain length of surfactant molecules being the basic element of pore

micellar matrix. The longer is the hydrocarbon chain in surfactant molecule the larger diameter of pores is created in MCM-41 silica. Additionally, the increase of pore dimensions may be realized by swelling of micelle template in auxiliary organics. Typically used surfactants in MCM-41 synthesis contain 12, 14, 16 or 18 carbon atoms in hydrophobic tail. All these pore directing agents lead to very narrow pores which may be ascribed to the lower limit of mesopores. If the pore diameters are too small during adsorption from gas and liquid phase the sieve effect may be expected. For example for standard drug molecule of ibuprofen the size of one molecule is as follows: 1 nm length and 0.6 nm width. The mix surfactants with 8 and 10 (85% : 15%) carbon atoms as leads to the MCM-41 material with hexagonally arranged pores of 2.5 nm pore diameter. Thus, one can say that the adsorption of ibuprofen in pores of this material is more difficult from geometrical reasons than in the MCM-41 material with 3.6 nm pore diameter synthesised from C16 surfactant [9, 14]. One can assume that MCM-41 silica prepared with higher member of homologous series of the same type of surfactant will be adsorbed with same restriction due to the small ratio of the dimension of pores and cross-section of drug molecules.

3. Further complication of embedding of drug molecules in pore interior of MCM-41 silica follow by the competitive adsorption of drug molecules and solvent molecules for silica surface. Typically, as for all processes of adsorption from the liquid mixtures both components of the bulk solution being over the solid, are present in the surface phase. This effect diminishes substantially the adsorption of preferentially adsorbed component. The competition being the characteristic phenomenon in adsorption from solutions, play an important role during impregnation of porous solid with drug solution. Thus, it is very important to match appropriately the solvent to drug character. Solvent should be minimally active for silica surface and easy removable at lower temperatures [21].
4. Not without consequence is the shape of pores in solid carrier of the drug. The shape of pores influences mainly the accessibility of pore interior by drug molecules, as well as the diffusion into and out of pores. Pores with constricts or partially closed may be only partially filled with drug molecules. In this case a great part of pores may remain empty and inaccessible for larger molecules. Additionally, when the geometrical restrictions are comparable with the dimensions

of drug molecules, their presence may be the reason of irreversibility of adsorption. In this case part of entrapped molecules can't be desorbed even at higher temperatures or at presence of active components like those presented in body fluid or salt water solutions. The presence of the restrictions causes that diffusions deviate from the Fickian mechanism [21].

5. Finally, all above mentioned factors related to solid carriers of organic molecules strongly depend on the temperature. The higher temperature diminishes the adsorption of preferentially adsorbed component due to heat motion of molecules or changes the competition of both components for the surface. This last effect is very sensitive on temperature especially for solids exhibiting high energetic heterogeneity of the surface. It is obvious, that in the case of silica material the energetic heterogeneity of surface species is high and is the result of presence of different types of silanols Q^4, n <0-4>, as well as relatively high roughness of silica surface being the result of the irregular growth of silica skeleton during condensation process [18, 21].

On the other hand all listed features of porous silica materials offer a great possibility of the modelling of pores and silica surface character to fulfil the specific requirements of drug release systems.

2.3. Modification of MCM-41 silica materials

To facilitate more effective loading of drug molecules into MCM-41, the pore system of silica, the shape of pores and the chemical state of silica surface may be modified in different ways: modifying synthesis in the mother solution (changing temperature, pH or aging time or co-condensation with other silanes) and by post-synthesis treatment of as-synthesized silica:

1. The modification of pore dimensions on the stage of synthesis may be realized by, as it was mentioned earlier, by change of the surfactant. This is a main method for tailoring of the pore diameter. However, also important is the modification of the surface character by treatment with different chemical species. In addition, to typically used in MCM-41 synthesis tertaethyl orthosilicate (TEOS) another silane containing in the molecule organic ligand which is bonded directly to silicon atom and doesn't hydrolyse e.g. $(C_2H_5O)_3CH_3$~Si is commonly used as a method of chemical modification during sol-

gel process. As a result we obtain silica surface with desired organic groups enhancing the interaction with specific drug molecule. Using appropriate silane it is possible to introduce on the internal pore wall surface appropriate active ligand. Very often the organic ligands like: $-CH_3$, $-NH_3$, -SH, $-SO_3H$ are introduced. [9, 10, 18].

2. Post synthesis modification include usually the chemical modification of calcined mesoporous silica by using silanizing agents e.g. 3-aminopropyltriethoxysilane (APTES) [9].

Distribution of functional groups on MCM-41 surface varies depending on the method of modification. In the case of co-condensation modification the functional groups are more evenly distributed inside pores of mesoporous silica than in post-synthesis modification [10]. Both modification procedures in which organic ligands are used cause the change of pore diameter. In post-synthesis modification by APTES the MCM-41 pore diameter decreases from 2.5 nm to 1.7 nm, in contrast to co-condensation modification, where the pore diameter decreases only to 2.2 nm [22]. If the bonded phase is dense the reduction of pore diameter may be substantial. The adsorption on chemically bonded silica surface depends on the density and thickness of the organic phase. On modified silica surface takes place between organic deposits or between long alkyl chains of modifier. In this last case the adsorption is especially sensitive on the temperature.

Adsorption on silica surface depends mainly on surface silanols. Their number for fully hydroxylated silica is practically constant and equal to 7.8 $\mu mol/m^2$ [23]. Thermal treatment diminishes the concentration of silanols due to their condensation into siloxane bridges. Thermal treatment practically does not change the dimensions of pores. Additionally, the silica surface may be modified without reduction of pore dimensions in following ways [24, 25]:

- addition of metal ion like Al, Zr, during sol gel process and entrapment these ions in silica network,
- co-condensation of silane being silica source with silane containing no hydrolysing ligand e.g. alkyl(trimethyl/ethyl) silane.

The compatibility of interactions between silica surface and drug may be enhanced by suitable modification of capillary channels of silica. However, as it was mentioned earlier the introduction of large organic groups in MCM-41 causes the decrease of pore dimensions and

additionally worsening of pore shape regularity and ordering. For full understanding of the procedures related to the loading of organic molecules into pore system of MCM-41 one have to take into account the proportion of the dimensions of organic molecule and pore diameter being the result of the modification procedure.

3. NAPROXEN

Naproxen (S)-6-Methoxy-α-methyl-2-naphtalenacetic acid ($C_{14}H_{14}O_3$) [Fig. 2] is well-known member of non-steroidal anti-inflammatory drug (NSAID). Its activity consist in inhibition of enzymes cyclooxygenase 1 and 2. Thanks its anti-inflammatory, analgesic and antipyretic properties this drug is widely used to reduction pain, fever, inflammation and stiffness, caused by conditions such as osteoarthritis, rheumatoid arthritis, gout and injury [26]. NSAIDs are the most commonly used drugs in the world. Unfortunately, they cause serious side effects especially from gastrointestinal tract. It is estimated that about 1100 people die every year from complications after taking NSAIDs [27]. Therefore still ongoing studies to improve forms of these drugs by creating a novel carriers or more advanced drug delivery systems (DDS).

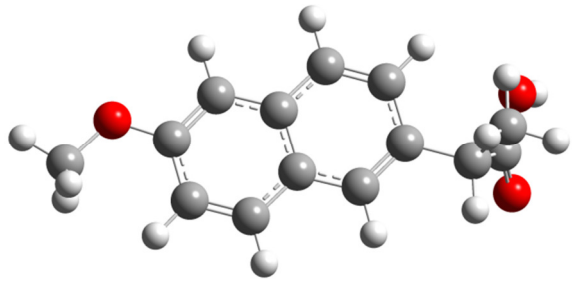

Fig. 2. Structure of the Naproxen molecule (white balls – hydrogen atoms, grey balls – carbon atoms, black balls – oxygen atoms).

In the present paper we present the influence of two different drug loading methods on efficiency of adsorption and release of this medicament from MCM-41 matrix. Mesoporous MCM-41 silica material was used as a drug carrier. Naproxen was used as a model drug. Drug loading process into MCM-41 material was performed from the ethanol solution at different conditions. Release process was realized to the phosphate buffer pH = 7.4 at 37°C.

4. EXPERIMENTAL

4.1. Synthesis of MCM-41

MCM-41 silica material was prepared according to the following procedure [28]: 2.4 g of C_{16}TAB was dissolved in 120 cm^3 of deionized water. After that 11 ml of NH_4OH (25%) was added to the surfactant solution. The solution was stirred for 15 min then 10 g of tetraetoxysilane TEOS was added dropwise for 30 min. Reaction mixture was stirred for 2 h to get white precipitate. Then the solid, white product was filtered, washed with deionized water and dried at 60°C. As synthesized material was calcined at 550°C for 8 h. Finally, a white pure silica product was obtained.

4.2. Characterization of MCM-41

4.2.1. Nitrogen adsorption

Nitrogen adsorption isotherms was measured at –196°C using Micromeritics apparatus ASAP 2420 (USA 2012). Prior experiment the sample was outgassed at 200°C in a vacuum for 1h.

4.2.2. X-ray diffraction

Powder X-ray diffraction was used to characterize the regularity of pore and dimension of pores. The measurements were performed with PANalytical apparatus Empyrean (Netherlands 2012).

4.2.3. SEM electron microscopy

The morphology of the sample was observed using a FEI high-resolution scanning electron microscope Quanta 3D FEG working at 30 kV.

4.3. Drug loading and desorption

4.3.1. Drug loading

The model drug was loaded into silica matrix in the following two ways. In the first one Naproxen (NXA) was loaded into MCM-41 silica material by impregnation method. Silica matrix was wetted by ethanol solution of Naproxen (24 mg/cm^3). The amount of solution was equal to pore volume and final sample was visually dry. Prepared sample was left for 1h at room temperature then was dried for 12h at 60°C. The dried

sample was named as I.MCM-41-NXA. The amount of absorbed NXA in the sample was sample 5% NXA (54 mg NXA/1g MCM-41). The amount of solution was equal to solution volume required for full filling of the pores. In the second way Naproxen was loaded into MCM-41 silica matrix by immersion with ethanol solution of Naproxen (16 mg/cm^3) under vacuum for 0.5h, and then the mixture was left over night at normal conditions.The solution was added with excess and MCM-41 silica was equilibrated with the bulk solution present over the sample. Next the sample was dried for 12h at 60°C. The dried sample was named as II.MCM-41-NXA. The amount of absorbed NXA in the sample was 20% NXA (233mg NXA/1g MCM-41). One can expect that the vacuum conditions will improve the penetration of small pores of MCM-41by both solution components. Under vacuum the air present in pores is evacuated and after outgassing the inflow of solution into pore interior is facilitated. The aim of this paper was to test the efficiency of drug release depend on drug loading.

4.3.2. Drug desorption

The drugs desorption experiments were performed by adding 200mg of investigated sample to vessels containing 50 cm^3 (I sample) or 100 cm^3 (II sample) buffer solution pH 7.4 (77.4 cm^3 de 1 M Na_2HPO_4 + 22,6 cm^3 de 1 M NaH_2PO_4) placed in incubation shaker. The temperature was fixed to 37°C and a stirring rate of 250 rpm was applied. At predetermined time intervals 5 cm^3 of release fluid were taken out for analysis of the drug concentration with UV-Vis spectrometer (Varian Carry 100 Bio) at a wavelength of 330 nm for NXA. Taken aliquot were replenished with fresh dissolution medium. The concentration of drugs in each sample was determined by comparison with a calibration curves based on the absorption maximum at 330 nm.

5. RESULTS AND DISCUSSION

5.1. Nitrogen adsorption

The desorption of Naproxen from mesoporous silica in release solution is determined mainly by the geometrical structure of the carrier. Thus, first of all the basic parameters characterizing pore structure of silica under study were estimated. The adsorption/desorption isotherms of nitrogen on MCM-41 sample at –196°C were used to estimate the numerical values of the parameters characterizing porosity of silica. In

Fig. 3 the adsorption/desorption isotherms for sample under study are shown.

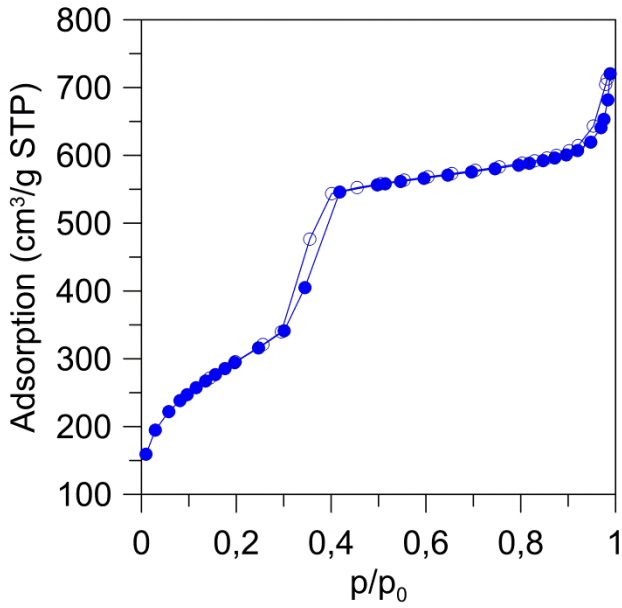

Fig. 3. Nitrogen adsorption (full points)/desorption (open points) isotherms at –196°C of MCM-41 silica.

As is seen in Fig. 3. the shape of isotherms is of type-IV, which is characteristic for mesoporous sorbents. The steep rise of isotherm at p/p_0 = 0.4 reflects the condensation of adsorbate in pores dominating in the pore system. Almost perpendicular rise of adsorption indicates that pores are very uniform in size and are regularly arranged. The numerical values of parameters characterizing pore system: specific surface area S_{BET} and total pore volume V_p were derived from adsorption data. S_{BET} was calculated using Brunauer-Emmett-Teller method in p/p_0 range from 0.05 to 0.25. Total pore volume was calculated from single point adsorption at p/p_0 = 0.985. Pore size distribution PSD was estimated using Barrett-Joyner-Halenda procedure from adsorption and desorption branch of isotherm within the condensation range i.e. for p/p_0 above 0.4. In calculations of S_{BET} the area of nitrogen molecule occupied in the surface phase was assumed as $\omega N_2 = 0.162$ nm^2. Calculated parameters for MCM-41 silica under study are as follows: S_{BET} = 1070 m^2/g, V_p = 1.1 cm^3/g, mean pore diameter $D = 4V_p/S_{BET} = 2$ nm. Mean pore diameter calculated in the above given manner represent the so called hydraulic diameter corresponding to cylindrical pore model. For solid characterized by

symmetrical pore size distribution this pore diameter is equal to the pore diameter at the peak of pore size distribution. In our case pore diameter at the peak of pore size distribution (Fig. 4) is centered at 2.8 nm for the desorption branch of isotherm and 3.2 nm for the adsorption branch [29].

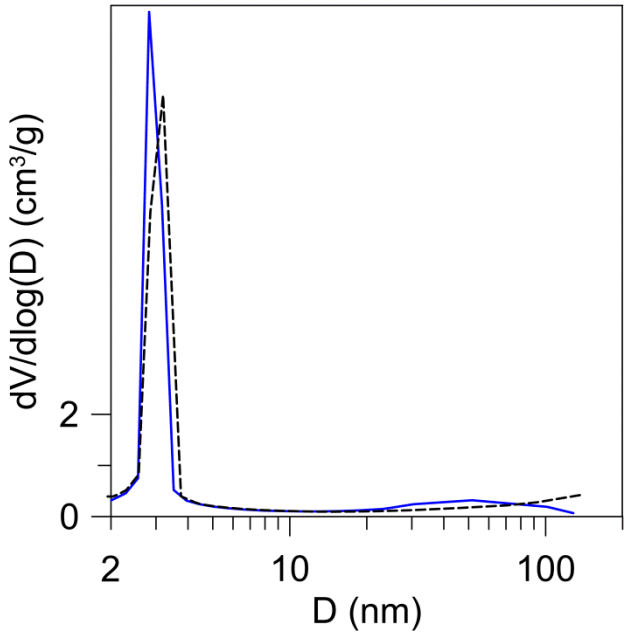

Fig. 4. The pore size distribution for MCM-41 silica calculated by BJH procedure – dash line - adsorption branch, solid line - desorption branch.

5.2. X-ray diffraction

For the same sample of MCM-41 silica was calculated the pore diameter from X-ray diffraction data XRD.

Fig. 5 depicts the XRD pattern of investigated MCM-41. As it is seen in Fig. 5 the silica shows well defined three XRD peaks. First located at 2θ = 2.2 nm and indexed as (100) is assigned to hexagonally arranged pore structure p6mm. Two remaining peaks are located above 2θ = 4 nm. The d(100) spacing calculated according to Bragg's law for 2θ equal to 3.96 nm is typical for MCM-41 silica prepared with CTAB as template. On the basis of obtained d(100) value we can calculate additional parameters characterizing pore structure of investigated material i.e. unit cell dimension:

$$a_0 = \frac{2d_{100}}{\sqrt{3}} \quad (1)$$

and pore diameter [30]:

$$W_d = cd\left(\frac{V_p \cdot \rho}{1+V_p \cdot \rho}\right)^{1/2} \quad (2)$$

where: c – constant equal 1.213, V_p – pore volume resulting from N_2 sorption, ρ – pore wall density equal to 2.2 g/cm^3.

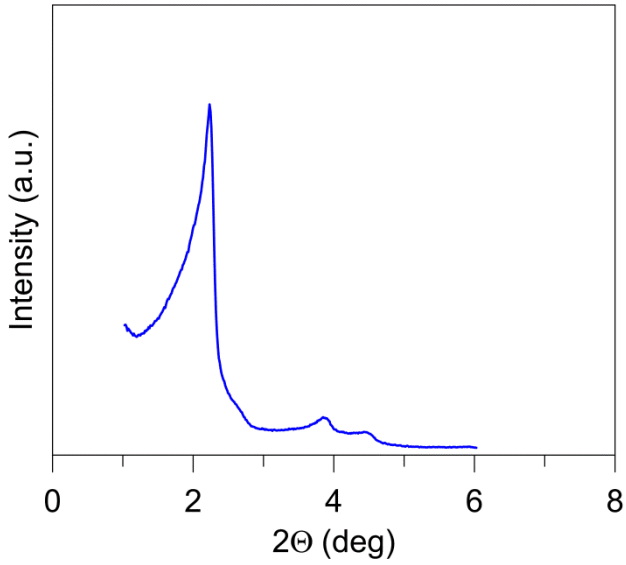

Fig. 5. X-ray diffraction pattern of MCM-41 silica under study.

Knowing both these values we can calculate the pore wall thickness:

$$b = a_0 - W_d \quad (3)$$

The results of our calculations based on XRD data indicate that the diameter of the pore is equal to 3.9 nm, and the thickness of the wall of pore is equal to 0.7 nm.

Comparing the adsorption data of nitrogen and the results of X-ray diffraction experiment (Table 1) one can observe that the values of pore diameter obtained by different techniques don't coincide. The pore diameter derived from XRD data is higher as compared with pore diameter calculated from desorption experiment but is congenial to adsorption results. This discrepancy is observed for many materials and discussed elsewhere [31]. Both used techniques confirm only that investigated silica material exhibits highly regular structure and contains mesopores of uniform size. It means, that desorption of Naproxen in the

liquid phase takes place similarly as in gaseous phase simultaneously from all pores and the desorption mechanism is for these pores the same.

Table 1. Structural parameters obtained from the nitrogen adsorption/ desorption and XRD data for MCM-41 sample under study.

Parameter	Value
S_{BET} [m^2/g]	1070
V_p [cm^3/g]	1.1
D_1 ($4V_p/S_{BET}$) [nm]	2
D_2 (PSD-adsorption branch) [nm]	3.2
D_3 (PSD-desorption branch) [nm]	2.8
D_4 (W_d XRD) [nm]	3.9
b [nm]	0.7

* D_1 – hydraulic parameter, $D_{2,3}$ – pore diameter at the peak of PSD adsorption/desorption branch respectively, D_4 – pore diameter from XRD data.

5.3. SEM electron microscopy

SEM experiment provides information on the morphology of MCM-41 particles. Two most representative pictures of MCM-41 silica after calcination are shown in Fig. 6.

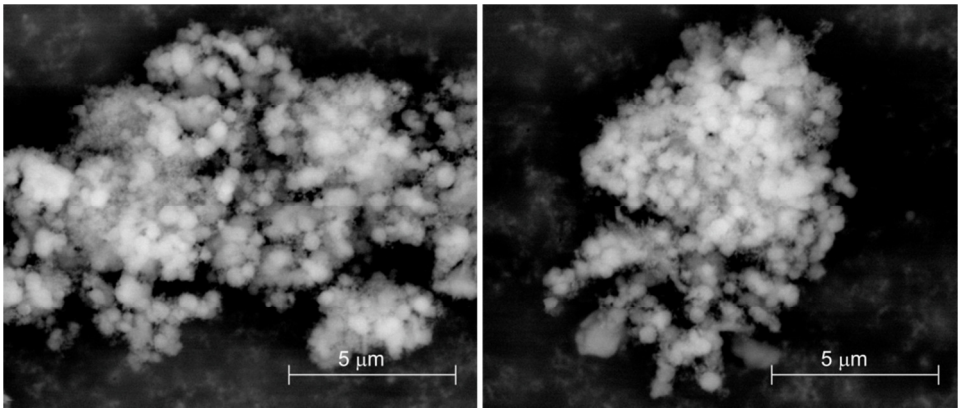

Fig. 6. Representative SEM images of MCM-41 silica material.

The SEM images shown in Fig. 6 indicate that the SiO_2 particles are very fine and approximately spherically shaped. The diameter of the particles is rather similar and do not exceeds 500 nm. The silica particles form aggregates which contain a large number of similar in size spherical particles and small amount of those irregularly shaped.

5.4. Drug desorption

Fig. 7 shows the results of Naproxen release from both of MCM-41-drug conjugates (triangles and squares plots). The differentiation of the shape of desorption curves for Naproxen indicates that the evacuation mechanism of drug from MCM-41 silica is different. It should be mentioned that the amount of Naproxen loaded in impregnation process in vacuum is 4 times higher than during loading without outgassing. The release of Naproxen from I.MCM-41 sample is very fast and during twenty minutes almost 90% of drug is released. It means that Naproxen is located mainly on the external surface of particles or around the openings of pores. It is possible that during wetting process into pore interior penetrate mainly alcohol and large part of Naproxen remains out of pores. Much higher amount of drug about 20 w/w% recalculated on 1 gram of pure silica in II.MCM-41 sample is released much longer. Taking into account that the volume of the release solution is larger in the case of second sample one can assume that the final drug concentration in the bulk solution of this sample is similar to that for lower loaded sample. Thus, the shape difference of the release curves is the result of different release mechanism. As in the case of I.MCM-41 sample the drug crystals are located rather on the external surface of silica particles. However, in II.MCM-41 the drug is entrapped in the interior of narrow pores. The diffusion from these pores is substantially restricted. Release profile from I.MCM-41-NXA sample is characterized with strong initial burst effect followed by a very slow drug release. Fast and complete release of drug in a short time is characteristic for non-porous or macroporous silica adsorbents. That type of drug release can be use when initially is required a high dose drug e.g. in pain or inflammations. The rapid release of Naproxen was being the result of its location at least in part out of pores. This maybe also caused by strong competition of drug and ethanol for internal surface in wetting process. Much lower loading of Naproxen in I.MCM-41-NXA suggests also that part of pore system was not accessible for solution components. Thus, at restricted availability, when alcohol is strongly preferentially adsorbed Naproxen remains out of the pore system. The release in this case is determined mainly by dissolution

process. Release profile from II.MCM-41-NXA sample follows first-order kinetics and it is associated with dissolution and diffusion processes. The drug is released in a less rapid and more monotonic manner. The observed effect clearly indicate, that the release process is mainly determined by the porosity of the carrier. To verify of this hypothesis the release of Naproxen was measured for silica gel for column chromatography Lichrosorb Si-100 (from Merck, Darmstadt, Germany). This silica gel contains relatively large pores sized approximately 10 nm in diameter. For comparative purposes in Fig. 7 is presented the release curve for Naproxen from Si-100 silica gel (circles) loaded with 1.2% (13 mg NXA/g Si-100). As is seen the release of drug from Si-100-NXA was very fast and exhibits a characteristic burst effect (90 % drug was released within first 15 min). This type of profile is typical for macroporous silica adsorbents. The shape of release curve is similar to that for MCM-41 after simple impregnation. Thus, one can conclude that for continuous release within long period of time it is necessary to introduce of drug into pore interior of relatively narrow diameter.

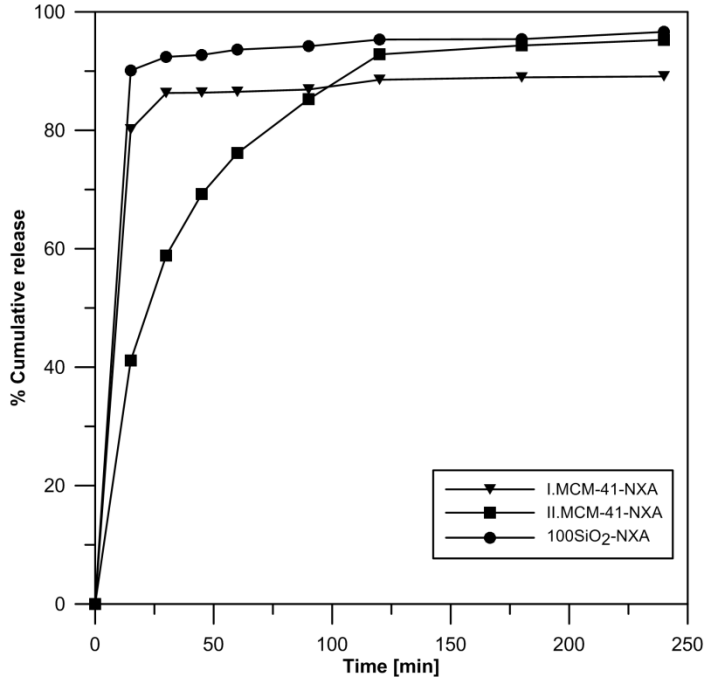

Fig. 7. Naproxen release curves from MCM-41(triangles – sample without outgassed; squares – sample with outgassed) and SiO_2-100 (circles) silica material.

As it was mentioned above in the outgassed sample it is possible to load up to 20 w/w % of Naproxen which is strongly entrapped in internal pore system of MCM-41. However, part of drug originating from the excess volume of solution probably occupies the external surface of particles. It is worth to notice that introduced drug does not fill totally the free volume in pores, which exceeds 1 cm^3 per gram. Due to restricted pore volume one can expect that Naproxen form is rather non-crystaline and the Naproxen clusters are distributed randomly along silica pores. It is also possible that Naproxen is incorporated into MCM-41 in the form of multi-molecular layer. Between drug particles or molecules still remain free volumes available for solvent molecules in desorption experiment. One can expect that density of packing of drug in pore interior is the factor regulating the release. Thus, interesting seems to be to compare the dimensions of Naproxen molecule in two dimensions, the cross-section and the length to pore dimension. The appropriate proportions are illustrated in Fig. 8.

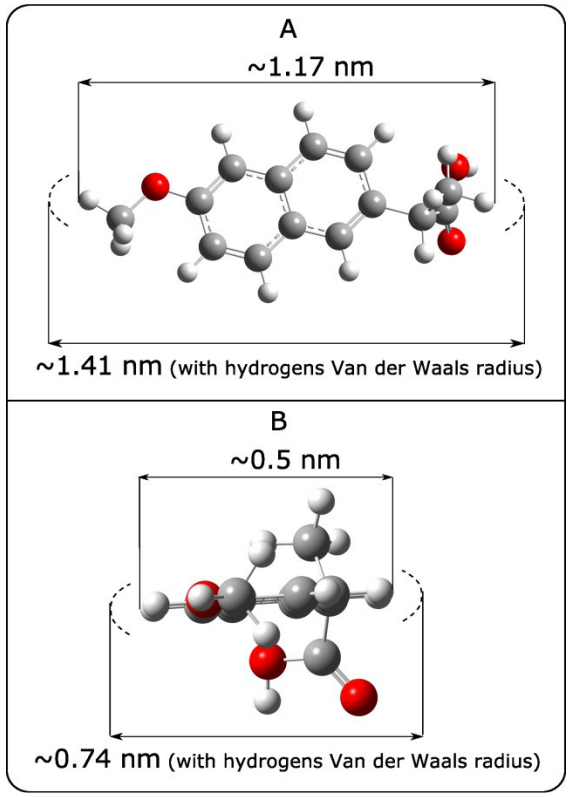

Fig. 8. Structure and size of the Naproxen molecule: A – the length and, B – the width. The reported values were found for the structure optimized at the DFT/B3LYP level [32] with 6-31G* basis set [33].

From the illustration presented in Fig. 8 and 9 one can conclude that the Naproxen molecule is relatively large if we relate its dimension to pore diameter of MCM-41 silica. The length of Naproxen molecule estimated from model calculations is ~ 1.17 nm and width is ~ 0.5 nm. However with consideration of dimension with Van der Waals spheres of extreme hydrogens atoms the size increases to ~ 1.41 nm in length and ~ 0.74 nm in width respectively. So that, the loading of Naproxen into MCM-41 pores is strictly dependent on the arrangement of drug molecules in internal pore space. Any constrictions or geometrical defects may reduce the drug loading or its release to external media.

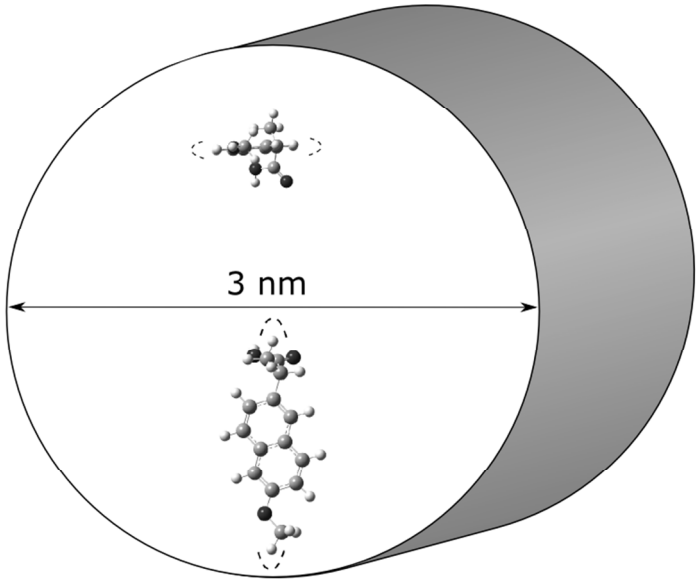

Fig. 9. Schematic comparison of the size (width and length) of Naproxen molecule to the diameter of MCM-41 pore (assumed as 3 nm).

6. CONCLUSIONS

Mesoporous silica materials of MCM-41 type are attractive from the point of view of drug loading in drug delivery systems. High pore volume and specific surface area are the important factors in drug loading process. Pore volume can't be totally filled with drug molecules in impregnation process and loading strongly depends on the interactions of drug with the mesoporous host and the rate of wettability by solution containing the drug. The wettability and the penetration of pores by wetting liquid are markedly improved in outgassed sample. Outgassing of

the system composed the porous solid and wetting liquid causes that Naproxen loading is many times larger than without outgassing. Moreover, the location of drug is dependent on the loading conditions. Wetting of mesoporous solid at normal pressure is incomplete and part of pores is inaccessible for solution. After outgassing under lower pressure the solution penetrates the silica pore system entirely. The amount of drug deposited in pores depends on equilibrium of adsorption process. In the case of highly porous solids containing pores of small dimensions very important is the relation of pore dimension to dimensions of adsorbed molecules. The dimensions of Naproxen molecules are comparable with MCM-41 pore diameter. Thus the competition of Naproxen and alcohol molecules for silica surface plays the main role in drug loading. In pore interior, over the adsorbed Naproxen molecules the presence of the bulk liquid is strongly limited. Maximal loading of MCM-41 under vacuum corresponds to 20 w/w % contamination of Naproxen. The release of Naproxen from this system takes a longer time than for wideporous silica nd takes place without burst effect.

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