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Research paper

Hierarchical silica monolithic tablets as novel carriers for drug delivery

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ABSTRACT

This paper proposes the use of carriers with hierarchical porous structures as novel monolithic tablets for modified drug release. The influence of pore structure on the tamsulosin release profile is presented. The hierarchical arrangement of porous structure in monolithic tablets and the deposition of tamsulosin inside the silica carrier enable to control the kinetic of release and the amount of tamsulosin released. We developed a mathematical model of tamsulosin release from two carriers with different hierarchy of meso- and macropores. A model of this nature will allow to predict the release of tamsulosin from other carriers with a similar pore structure. We hope this research will improve the design process of novel carriers, and thus, will allow to tailor the porous structure of a carrier to achieve the desired release profile.

1. Introduction

Carriers for the controlled release of drugs have been well-established in pharmaceutical sciences for over 50 years [1–3]. Since their introduction, carriers have significantly improved the results of pharmacotherapy by aligning the concentration of drug substance in the blood (rapidly reached steady state), improving comfort by reducing the frequency of dosing and minimizing the risk of missing a dose or overdosing. The most frequently used oral formulations are tablets and/or capsules based on polymers that slow down or temporarily bind the active drug with a vehicle (methylcellulose, HPMC, PVP, PEG, etc.) and, thus, delay the release of the active drug into the gastrointestinal tract [4]. There are also known formulations that use the natural porosity of the carrier, so called monolithic matrix tablets [5], in which the process of the sustained release of the drug is obtained by varying the pore size (the smaller pore diameter the longer time to releasing the drug) and/or changing the distance between pores and contact surface of the gastrointestinal tract (pores located outside the tablet will quickly release the active substance, whereas those located inside of the tablet, due to the much elongated diffusion path, will release the drug much slower). For the optimal control such a system requires the use of a carrier with an appropriate pore size, so that it can release the same dose of the drug at similar time intervals, and does not unduly restrict the diffusion of drug molecules while ensuring sustained release through an elongated diffusion path. These requirements should be fulfilled by carriers with a hierarchical pore structure [6,7], that have large channel-like macropores, with diameters of 1–50 μm, and smaller mesopores, with diameters of 2–50 nm, guaranteeing high surface area. Large macropores facilitate drug transport from mesopores (pores with a diameter in the range of 2–50 nm), while high surface area enables adsorption of big quantities of the drug per mass of carrier [8]. Hierarchical silica monolithic materials were successfully used as supports in (bio)catalysis [9,10], chromatography [11] and, most recently, as chemical microreactors [9,12,13], but to the best of our knowledge, have not been comprehensively studied as carriers for the controlled release of drugs.

In literature [14], there is relatively little discussion regarding the use of monolithic porous tablets for pharmacotherapy even though they can negate the use of polymers and, therefore, simplify the formulation and eliminate the irritant effects of the excipients on the walls of the gastrointestinal tract. Apart from publications describing the use of meso- and microporous materials as drug carriers [15–17], only a few involve materials with hierarchical porous structure [18–22], but none of them were in the form of monolithic tablets. Some these carrier types have already been examined in the context of the sustained or controlled release of drugs. However, the results for non-modified porous silicas were not satisfactory [19], due to the presence of large macropores with a wide diameter distribution releasing nearly a whole drug dose in a short time. Using carriers with homogeneous and hierarchical porosity, many drugs can be delivered in ways that permit new and more effective therapies – for example it is believed that modification of release patterns (e.g. pulsatile, continuous) is an effective method to improve therapeutic responses [23].

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The pharmaceutical technology available offers diverse methods for the preparation of monolithic matrix tablets [5]. Unfortunately, most of these methods fail to ensure homogeneous pore size distribution and open-through pore structure, which are crucial parameters for monolithic tablets to be used as drug delivery systems. Implementation of monolithic silica with a hierarchical pore structure is a promising material for use in the controlled release of drugs due to the high repeatability of the synthesis and the homogeneous distribution of pores [24]. In this paper, we present a novel approach to the release of drugs from silica with hierarchical porous structure. We chose tamsulosin as a drug model, an antagonist of the α_1 receptor (therapeutic group Alpha-adrenoreceptor antagonists ATC code G04CA02 [25]), that is used by men to treat the symptoms of an enlarged prostate (benign prostatic hyperplasia – BPH). We studied two carriers with hierarchical porous structure to modify the tamsulosin release profile, and we devised a mathematical model of tamsulosin release in different conditions. This research may serve as a hint of how to modify the release profile by altering the structure of the porous media. We focus on the use of silica as a precursor for monolithic matrix tablets. However such an approach does not exclude its use in other therapeutic systems as an excipient, that, apart from its basic function, may facilitate controlled/modified drug release.

2. Materials and methods

Silica monoliths, having a hierarchical structure with different sizes of macro- and mesopores, were proposed as potential carriers for controlled/modified drug release. The conception of monolithic tablet with hierarchical porous structure was presented on Fig. 1. Two structures with diverse distribution of macro- and mesopores were synthesized, and we assigned them as A and B.

2.1. Materials

Tamsulosin hydrochloride was synthesized by Pharmaceutical Research Institute. Tetraetoxysilane (TEOS), poly(ethylene glycol) (PEG) with average molecular weight 35000 g/mol and cetyltrimethylammonium bromide (CTAB) were supplied by Sigma Aldrich (Poland). Nitric acid (65%), ammonia solution (33%) was supplied by Avantor Perfomance Materials Poland S.A. (Gliwice, Poland). All other agents were provided by Sigma Aldrich (Poland). Chemicals were used without further purification.

Table 1
Compositions (molar ratios) of silica A and B carriers.

Carrier	TEOS	HNO_3	H_2O	PEG*	CTAB
A	1	0.25	14.7	0.26	0.19
B	1	0.25	14.7	0.54	0.029

* The values given for the PEG were calculated on the basis of the monomeric units.

2.2. Carrier preparation

Materials were prepared according to the procedure given by Smatt et al. [26] and modified by Pudlo et al. [9]. In a typical synthesis of A and B materials, polyethylene glycol (PEG) was dissolved in 1 M nitric acid, and then tetraetoxysilane (TEOS) was added dropwise. When the solution was homogenic in the whole volume, cetyltrimethylammonium bromide (CTAB) was dissolved (the starting compositions are listed in Table 1). The sol generated was sonicated for 5 min, then gelled and aged for 7 days at 40 °C. After that time, gels were treated in 1 M ammonia for 12 h at 90 °C, then neutralized in 0.1 M nitric acid and water, and, finally, dried for 5 days at 60 °C and calcined at 550 °C at a rate of 1 K/min. Before pharmaceutical testing, silica monoliths were divided into tablets with a height of 2.3 mm and a diameter of 5 mm (Fig. 2a). Some of the wet gels were extruded and spheronized to obtain pellets with hierarchical porous structure (Fig. 2b).

2.3. Structure characterization

Materials were analyzed by mercury porosimetry, low temperature nitrogen adsorption and scanning (SEM) and transmission (TEM) electron microscopy to determine their porous structure and its impact on the process of drug release. Scanning electron microscopy (TM 3000 Hitachi) was used to examine the macroporous structure (Fig. 2c and d). Transmission electron microscopy (S/TEM TITAN 80-300) was used to examine the mesoporous structure (Fig. 2e). In the SEM analysis the samples were cut into small slices, coated with a thin layer of gold, then degassed in high vacuum and analyzed at 40-5000x magnification with an accelerating voltage of 5 kV. In the TEM analysis, the carriers were

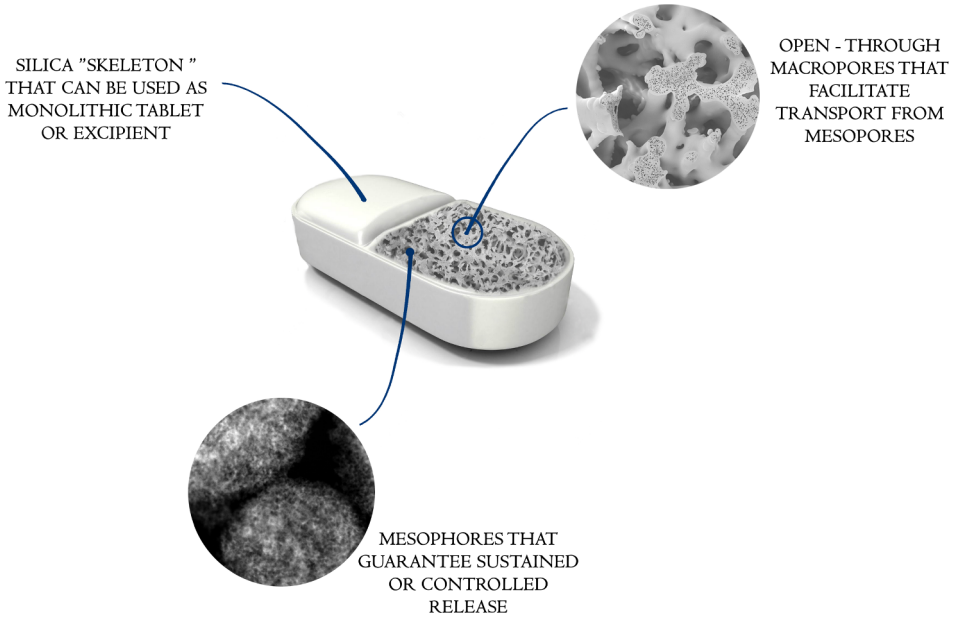

Fig. 1. The conception of monolithic tablet with hierarchical meso-macroporous structure.

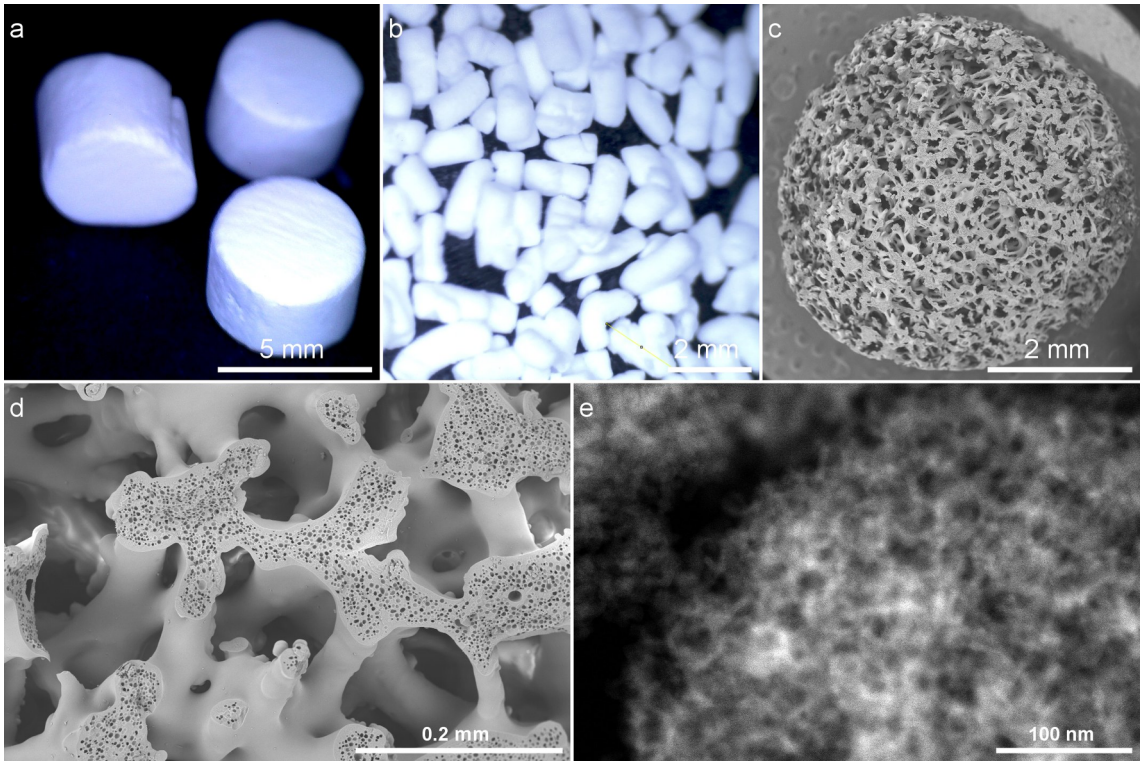

Fig. 2. Hierarchical silica monolithic tablets (a) and pellets (b). Structure of silica B tablet (c) with open-through macropores (d) and big mesopores (e) (Figures c and d – SEM micrographs, Figure e – TEM micrograph).

crushed, suspended in ethanol, settled on grids, followed by evaporated solvent and analyzed at the magnification range 10,000–1,000,000 with the accelerating voltage of 300 kV.

The specific surface area and pore size distribution were determined from the low nitrogen adsorption (ASAP Micromeritics 2010). The BET specific surface area (S_{BET}) and the volume of monolayer coverage were determined using the Brunauer-Emmett-Teller (BET) equation [27]. The pore volume versus diameter distribution was calculated by analyzing the desorption branch of the isotherm using the Barrett-Joyner-Halenda method [28]. The size distribution of pores larger than 10 nm and total pore volume of silica carriers were measured by a mercury intrusion porosimetry (Quantachrome, PoreMaster 60).

2.4. Absorbency

The absorbency of carriers was examined for water, 2% hydroxypropylocellulose (HPMC) E5 solution in water, 2% hydroxypropylocellulose (HPMC) E15 solution in water, ethanol, propylene glycol, dimethyl sulfoxide (DMSO), and paraffin.

2.5. Loading carrier with drug and fluorescein

The release profile was made on model using fluorescein and tamsulosin hydrochloride. In the first case, 1 mg of dye solution (fluorescein in methanol) was added dropwise onto the silica, and then released into 500 mL of acceptor medium (potassium phosphate buffer at pH = 6.8).

For tamsulosin, we prepared four series of samples (A(M), B(M), A(D), B(D)) to obtain the release profile:

- A(M) and B(M) − 0.4 mg tamsulosin in a methanol solution (10 mg/ml concentration) was added dropwise to silica A or silica B using an electronic serial dispenser (Brand HandyStep®) to obtain A (M) or B (M), respectively. In each experiment, we used 40 µL per one silica tablet and waited about an hour for the proper distribution of the drug in the tablet. Monolithic tablets (A (M) and B (M)) were then placed in a tray dryer and dried at 80 °C overnight.
- A(D) and B (D) − 0.4 mg of tamsulosin in DMSO solution (concentration 10 mg/mL) was dropped into silica A or silica B using an electronic serial dispenser (Brand HandyStep®) to obtain A(D) or B (D) samples, respectively. In each experiment, we used 40 µL per one silica tablet and waited about an hour for the proper distribution of the drug in the tablet. In this case, there was no drying step because the solution trapped in the pore structure does not tend to evaporate due to the high boiling point of DMSO.

2.6. Dissolution of fluorescein

Fluorescein release studies carried out using Symphony 7100 dissolution tester (Distek Inc.). Each unit was selected and individually placed in the dissolution vessel containing 500 mL of potassium phosphate buffer (250 mL 0.2 M KH_2PO_4 + 112 mL 0.2 M NaOH, diluted to 1000 mL with water) at pH 6.8 or 0,1 M HCl at pH 1.2 at 50 rpm and 37 ± 0.5 °C. Aliquots (5 mL) were manually collected at 1, 2, 4, 6 and 8 h time intervals and filtered through a paper filter. Each aliquot withdrawn was replaced with 5 mL of acceptor medium.

The content of released fluorescein was determined using a HPLC Shimadzu LC-20 Prominence UV–VIS (Shimadzu) equipped with Hypersil Gold column (150 × 4.6 mm, particle size 5.0 µm) (Thermo Scientific). The mobile phase consisted of a mixture of octanosulfonic buffer pH 2.6 and methanol (45:55, v/v) with flow rate of 1.0 mL/min. The injection volume was 100 µL and the column temperature was maintained at 25 °C.

2.7. Dissolution of tamsulosin

Drug release studies carried out using Symphony 7100 dissolution tester (Distek Inc.). Each unit was selected and individually placed in the dissolution vessel containing 500 mL of potassium phosphate buffer at pH 6.8 or 0.1 M HCl at pH 1.2 at 50 rpm and 37 ± 0.5 °C. Aliquots (5 mL) were manually collected at 1, 2, 4, 6 and 8 h time intervals and

filtered through a paper filter. Each aliquot withdrawn was replaced with 5 mL of acceptor medium.

The content of released tamsulosin hydrochloride was determined using a HPLC Shimadzu LC-20 Prominence UV–VIS (Shimadzu) equipped with Synergi Max RP column (150 × 4.6 mm, particle size 4.0 µm) (Phenomenex). The mobile phase consisted of a mixture of phosphate buffer pH 6.8 and methanol (65:35,v/v) with flow rate of 1.2 mL/min. The injection volume was 100 µL and the column temperature was maintained at 35 °C.

2.8. Mathematical modeling

To model the release from silica A and B, we performed a random walk simulation [29–31] on a 3D lattice of size 200 × 200 × 200 nodes (8 mln nodes). The spacing between the nodes was set to $\delta = 4$ nm, so that the physical dimensions of the simulated domain equal to 0.8 × 0.8 × 0.8 µm. Such dimensions are suitable to simulate the interactions of mesopores but are insufficient to model macropores. Unfortunately, extending the size of the simulated domain to millimeters results in a unacceptable computation time and memory requirements.

The effect of macropores is introduced by adding a free volume at the edge of a chosen wall of the porous structure domain. In fact, the diffusion in macropores is much less time limiting than the diffusion in the mesopores (diffusion in macropores is less affected by blocking transport through adsorption/desorption processes), so this approximation does not introduce any serious errors.

The pores in the simulated domain (4 nm and 20 nm in size) were introduced according to the distributions in Fig. 3 in such a way that the number of pores multiplied by the volume of a single pore was proportional to the measured volume fraction. To account for the presented volumes on the simulation lattice, we have put $N_{1A} = 1950$ pores of diameter 4 nm and $N_{2A} = 10$ pores of diameter 20 nm for silica A, as well as $N_{1B} = 56$ pores of diameter 4 nm and $N_{2B} = 16$ pores of diameter 20 nm for silica B. These pores were aligned along with the x, y or z axes and extended from one wall of the domain to another – the application randomly selects one of three directions (x-axis, y-axis, or z-axis), and then draws the location of pores (e.g. (y, z) for the x-axis, (x, z) for the y-axis, and (x, y) for the z-axis.

The transport properties of the system, besides of the structural relations in the pore hierarchy, depend upon two factors: diffusion coefficient $D = \delta x^2/6/\delta t$ (where δx is the lattice spacing, and δt is the time step of the simulation) [29] and adsorption probability, here varied between $P_{ads} = 0.9999$ and $P_{ads} = 0$. Correspondingly, the desorption probability was taken $P_{des} = 1\text{-}P_{ads}$. In the equilibrium, when the desorption and adsorption fluxes equal each other, this corresponds to a simple Henry isotherm of adsorption for the volume associated with a simulation node $P_{des}n_{ads} = P_{ads}n_{des}$, ($n_{ads}$ – number of adsorbed molecules in simulated volume associated to a given node that neighbors to the pore surface; n_{des} – number of desorbed molecules in that volume), i.e. we don't take saturation into account (this seems to be fine according to the simulation results).

The release time is scaled in such a way to correspond to the release time of macroscopic object like the investigated tablet. The simulated domain is less than 1 µm^3, so the simulated release is faster (by the nature of diffusion scaling of displacement with time [29] by the ratio $T_{simulated}/T_{real} = \delta^2_{simulated}/\delta^2_{real}$.), for example in the considered case it is 39 mln times faster. This means that in the case of the fluorescein simulation, that required 181,818 simulation steps, the simulation time

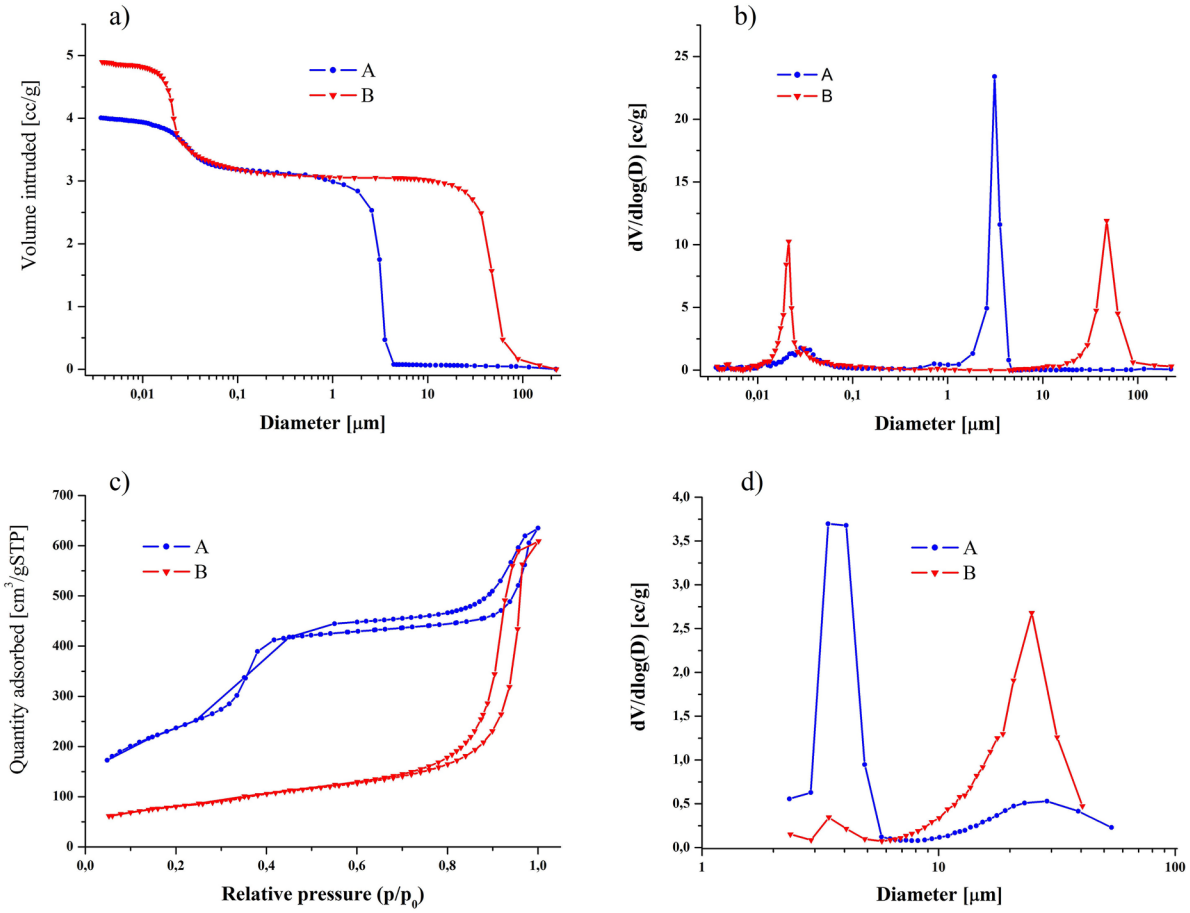

Fig. 3. Material properties of hierarchical porous monolithic tablets: Mercury porosimetry plots for A and B carriers – cumulative pore volume (a) and pore size distribution (b); Adsorption-desorption isotherm (c) and pore size distribution (BJH) (d) for A and B carriers.

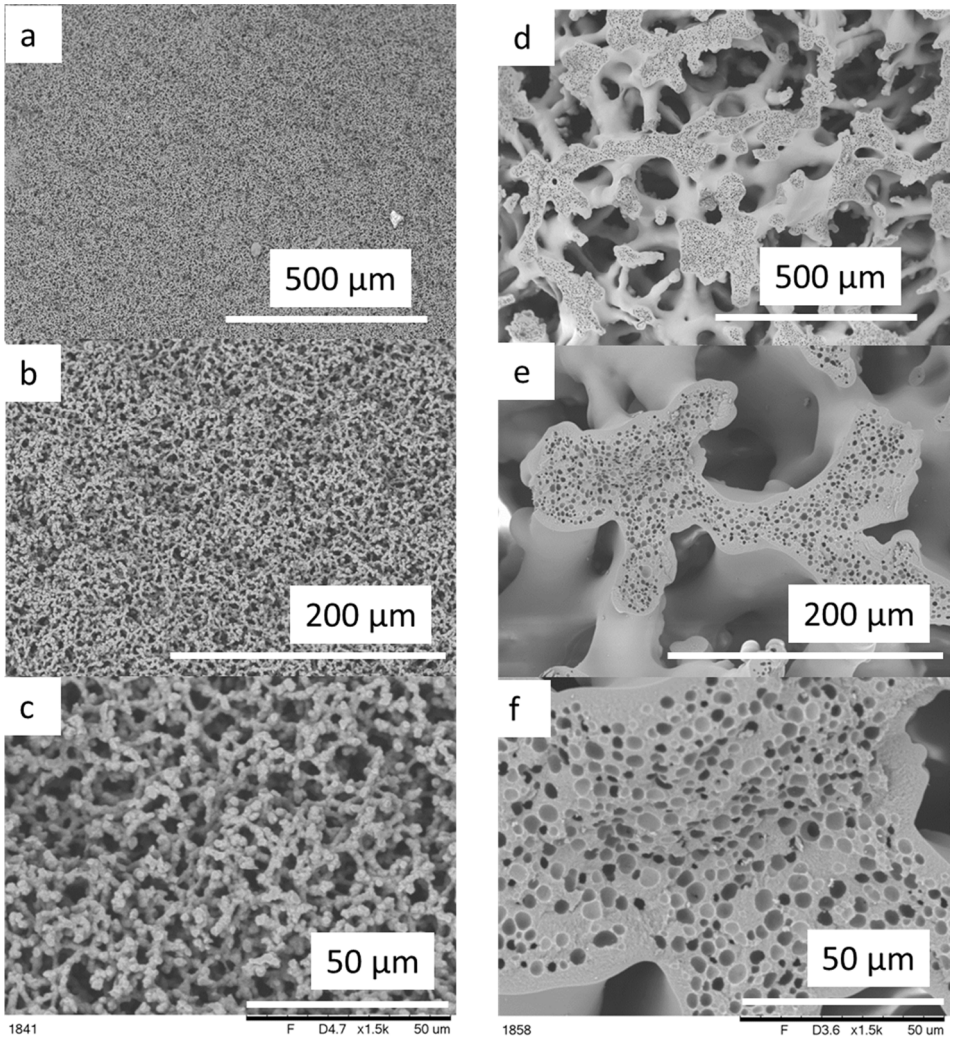

Fig. 4. Scanning electron microscopy of A (a–c) and B (d–f) silica carriers.

step related to $\tau = 8\,h/39\,mln/44998 = 16.4\,ns$, and the corresponding diffusion coefficient equals to $D = \delta^2/6/\tau = 6.6 \cdot 10^{-6}\,cm^2s^{-1}$ (where δ stands for the jump length or mean free path).

3. Results and discussion

3.1. Silica monolithic tablet characteristics

Silica monolithic tablets A and B were synthesized according to the same synthetic pathway [9,26], using sol-gel chemistry combined with phase separation to obtain hierarchical macro-mesoporous structures. The size and distribution of macropores were examined using mercury intrusion porosimetry (Fig. 3a) and SEM (Fig. 4). These methods showed large, 50 µm in size, macropores in silica B, and one order of magnitude smaller (d = 5 µm) macropores in silica A. Both materials have bimodal mesopore distribution with small (*ca* 4 nm diameter) and big (*ca* 20 nm diameter) mesopores in their structure (Fig. 3b). In silica A, smaller mesopores dominate and are responsible for huge surface area (850 m^2/g, Table 2), whereas silica B possess predominantly bigger mesopores with almost the same mesopore volume (Fig. 3b, Table 2).

Material characteristics of both carriers determine their dissolution results. Silica B showed better absorption of all solvents (with the exception of DMSO), which stemmed from the presence of the large macropores (Figs. 3a and 4d–f) as well as a high total pore volume (volume of macro- and mesopores, Table 2) in the carrier structure. It seems tricky to explain the greater absorption of DMSO by silica A, especially considering that carrier A has a smaller diameter of the macropores (Fig. 4a–c) and smaller mesopores (Fig. 3b). Most probably, the polar aprotic solvent interacts with the hydroxyl groups of the silica, whose proximity and large amounts are associated with increased specific BET surface area (Table 2), which enables penetration of greater volumes of solvent.

Table 2
Material properties of carriers A and B.

Sample	BET surface area m^2/g	Total pore volume* cc/g	Mesopore volume** cc/g
Silica A	850	4.05	0.96
Silica B	276	4.9	0.91

* Results taken from mercury intrusion porosimetry by adding volume of macropores and volume of mesopores.
** Results taken from low temperature nitrogen adsorption.

3.2. Using fluorescein as drug model

The release profile for the active pharmaceutical ingredient (API) model was performed with fluorescein. Although the dye amounts released from both carriers are almost similar (70% for A and 73% for B, Fig. 5), their release profiles are different due to the different structure of pore network. Release from carrier A, with smaller size of both

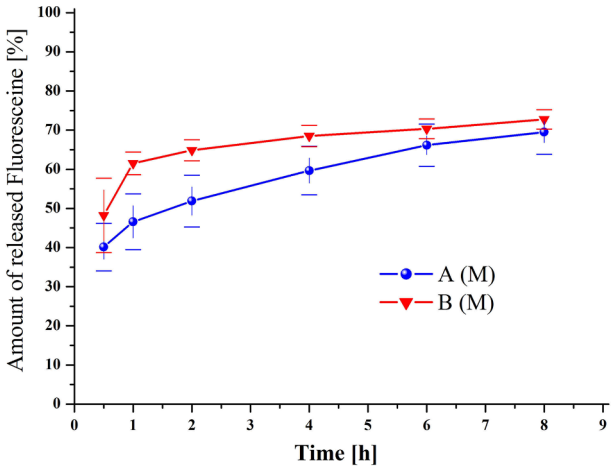

Fig. 5. Release profile of fluorescein from silica A and B (phosphate buffer solution pH 6.8).

macro- and mesopores (Figs. 3 and 4), resemble controlled release of drug with almost equal portions of drug released after unit time. Smaller size of macro- and mesopores hinder mass transport and, therefore, control release of drug into acceptor solution. For instance, release of fluorescein from the mesopores of sample A, is hampered by their size (average diameter of mesopores *ca* 4 nm, Fig. 3b). Although pores with this size are also present in sample B, its volume fraction is very low, and, therefore, release of dye is faster compared to the release from silica A.

Sustained release of fluorescein from silica A encouraged us to examine release of a drug available in the pharmacy market (tamsulosin hydrochloride).

3.3. Drug release test

3.3.1. Release of tamsulosin hydrochloride from monolithic tablets A and B

Tamsulosin hydrochloride release tests were performed in HCl at pH = 1.2 and in phosphate buffer at pH = 6.8 – the results are summarized in Fig. 6. For the series A(M) and B(M), where tamsulosin was dissolved in methanol and further evaporated, the release test in phosphate buffer was performed once and then extended from 4 to 8 h – the results are shown in Fig. 7. Based on the results presented in Figs. 6 and 7, we concluded that the samples A(M) and B(M) show favorable release profiles after 4 and 8 h of the test. Tamsulosin dissolved in DMSO solution showed a much faster release compared to the release seen in methanol. Such a situation is caused by mixing the DMSO with water and the evaporation of methanol during sample formulation. The rate of release from the silica in this case, is determined by the ease of buffer penetration through the pores of silica. In case of series A(M) and B(M), tamsulosin is dispersed in the carrier in solid form – this means that drug should be first dissolved in the buffer and then can diffuse through the pores in the carrier. The dissolution of drug in buffer is necessary to enable its diffusion through silica pores and, this process also slows the release of tamsulosin from silica carrier. In conclusion, we observe two “barriers” that control drug release in silica – one is carrier structure (hierarchical porous structure of silica A and B) that hampers diffusion of the drug, and the other is the physicochemical form of the API (series (D) and (M)), which regulates its dissolution.

3.3.2. Comparison of formulations

The comparison of two tablets with controlled porous structure sheds new light on the sustained drug release from silica carriers with hierarchical porosities. For example, the amount of tamsulosin released is always lower with the carrier A compared to the carrier B (compare A(M) with B(M), and A(D) with B(D) on Fig. 6a–d) – this effect is caused by the structure and the size of macro- and mesopores of both carriers (Figs. 3 and 4). The bigger the size of macro- and mesopores (silica B), the easier, faster and less controlled release of tamsulosin is. If we compare silica A(M) with silica A(D) at pH = 6.8 (Fig. 6c and d), we observe nearly 10% lower amount of tamsulosin released to the acceptor solution after 4 h just by changing solvent from DMSO to methanol. This effect is even greater for carrier B, in which the amount of released tamsulosin is nearly 20% lower for carrier B(M) comparing to B(D) after 4 h (Fig. 6c and d). The increased release from carrier B, in comparison with carrier A, by changing solvent from methanol to DMSO results from the bigger size of macro- and mesopores (compare carriers B(M) with B(D) and A(M) with A(D) in Fig. 6). Bigger pore size facilitates mass transport of the buffer to the interior of the pores, enabling faster release of the drug.

3.3.3. pH sensitivity

Fig. 6a–d shows the influence of pH on tamsulosin hydrochloride release. Tamsulosin HCl is a salt of strong acid and weak base with pKa equals 8.37 (secondary amine) and 10.23 (sulfonamide) [32]. Therefore its solubility is highly affected by pH – it increases when pH is more acidic, and decreases in moderate and high pH values. This phenomena explains the differences in release between pH = 1.2 and pH = 6.8. In pH = 1.2 release of the API dissolved in DMSO reaches a plateau after less than 1 h (Fig. 6b), i.e. there are small differences of released tamsulosin between first and fourth hour, and nearly the whole amount of drug is released during the first hour. The opposite situation is observed for tamsulosin hydrochloride dissolved in methanol and released in pH = 1.2 (Fig. 6a). In these conditions the release of tamsulosin salt is delayed – we assumed that the sharp decrease in solubility is caused by high concentration of chloride ions, so called common ion effect. This effect limits solubility of sparingly soluble hydrochloride salts in highly concentrations of HCl solution [33], making them even less soluble than free bases [34]. Common ion effect is not affecting on tamsulosin hydrochloride release in higher pH values (pH = 6.8), where concentration of chloride ions is very low. In nearly neutral pH values, the release of tamsulosin hydrochloride depends on the kinetics of dissolution ((M) samples) and/or diffusion ((M) and (D) samples), making this process more controllable (Fig. 6c and d). Fig. 6a–d indicates that pH modulates the kinetics of tamsulosin release by changing solubility of drug in acceptor solution.

3.4. Mathematical modeling

A sample chart for fluorescein (Fig. 8) shows that the simulation can reproduce the effects of variations in the pore hierarchy between material A and B, and we may take some conclusions about the mode of operation of these materials based on this template model, which may be applied to future drug release studies.

To understand the release profiles for tamsulosin hydrochloride, we fit the data along a spectrum of adsorption probabilities and diffusion coefficients. The larger the adsorption probability, the later steady state is attained, and the more discrimination between small and large diameter mesopores (in small diameter mesopores the frequency of adsorption events per molecule is larger than in wide mesopores, and diffusion is heavily impaired). Therefore, in measurements where we observe a pronounced transient period, we expect large adsorption or low diffusion coefficient. However, obtaining a long-lasting transient period results in a long time to reach the terminal release state.

The fit results were presented in Fig. 9, whereas the diffusion coefficients (D), desorption/adsorption probabilities (P_{des}, P_{ads}), and other control parameters of the simulation were presented in Table 3.

The analysis of the modeling results gathered in Table 3 contributes additional parameters concerning the mechanisms of tamsulosin hydrochloride release. The diffusion coefficients reveal a faster diffusion in case of the DMSO prepared samples, probably due to the mixing of DMSO with water. The probability of desorption (P_{des}) reaches the

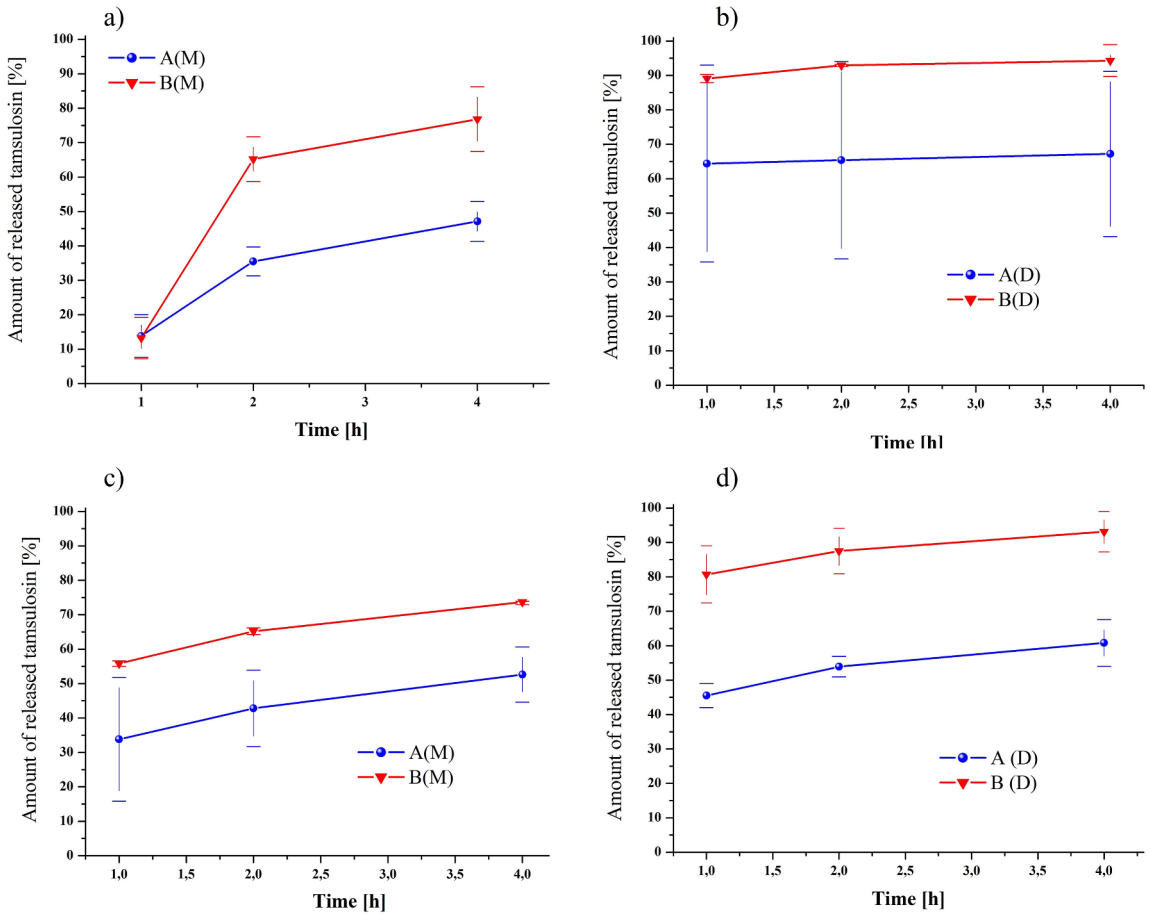

Fig. 6. Release of tamsulosin hydrochloride from monolithic tablets A (M) and B (M) into buffer solutions at pH = 1.2 (a) and pH = 6.8 (c); release of tamsulosin hydrochloride from monolithic tablets A (D) and B (D) to buffer solutions at pH = 1.2 (b) and pH = 6.8 (d).

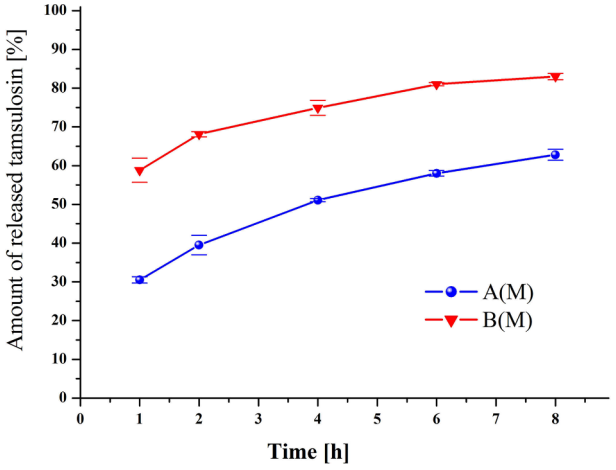

Fig. 7. Release profile of tamsulosin from hierarchical porous silica at pH = 6.8 – series A(M) and B(M).

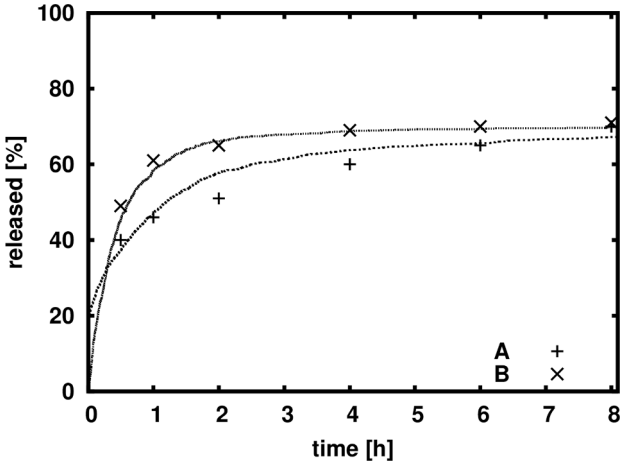

Fig. 8. Simulation of fluorescein release from A and B carriers.

highest values for samples prepared in methanol and decreases with pH. The Ov_A and Ov_B overshoot parameters were introduced to model disturbances in equilibrium initial concentration of the drug in the macropore compared to mesopores. The provided percentage of the mass is removed from uniform distribution over the whole simulation domain, and added to the macropore volume only to obtain vertical shifts of the measured release profiles due to rapid release from macropores. These parameters show that methanol solution can penetrate the porous structure to a larger extent than DMSO, increasing tamsulosin deposition in mesopores. The parameters also let us compare carrier A with B, showing a greater concentration of tamsulosin hydrochloride in bigger macropores of carrier B.

The t_0 parameter represents the time lag to observe the simulated behavior in real experiment. This is because we simulate a tiny subdomain of the porous medium, and we cannot model time lag related to the transport of the drug released from a mesopore through the macropore to the exterior. We assume time delays (t_0) as phenomena occurring during transport through macropores (this transport was not modeled due to limitations of the size of the simulated section and the

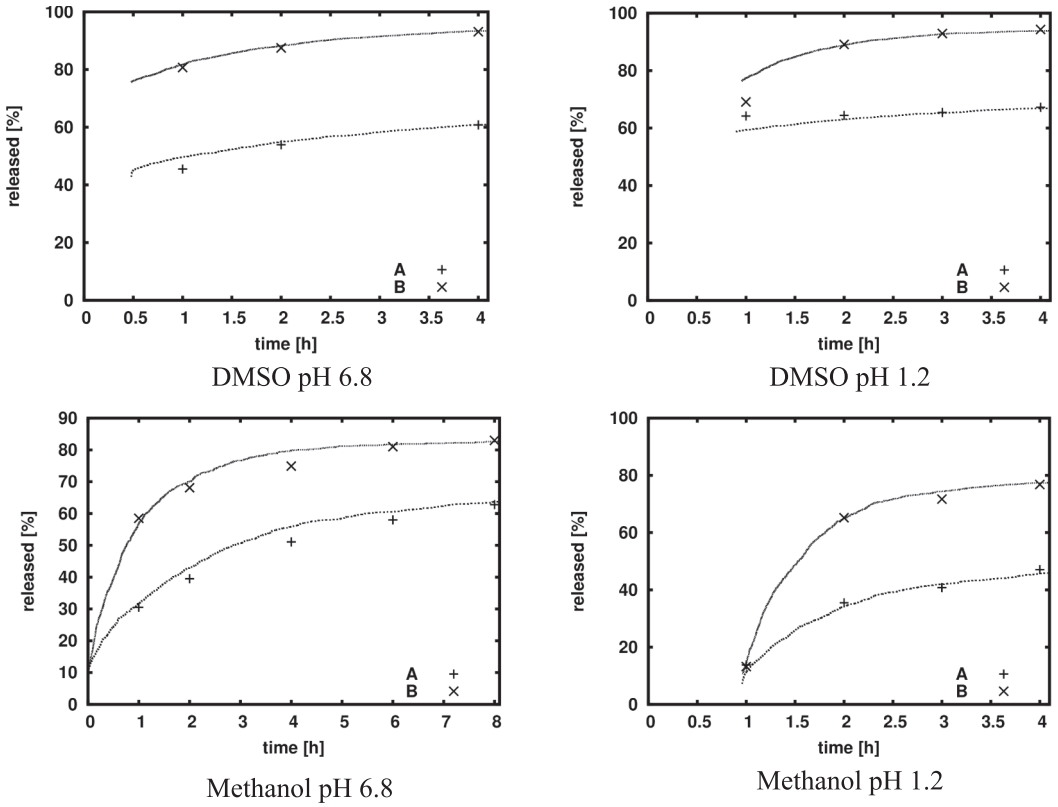

Fig. 9. Simulation of tamsulosin release from carriers dissolved in buffer solution at pH = 1.2 and pH = 6.8, prepared in DMSO (upper plots) and methanol (lower plots).

computing power of the hardware). The results in Table 3 may indicate that t_0 depends on the pH. At low pH values (pH = 1.2), the time delay resulting from transport through macropores is large reaching up to 0.96 h (situation for both samples prepared with DMSO and MeOH, except for the carrier A – however the error bars on Fig. 6b indicate, that the delay may occur in this case), while for a higher pH (pH = 6.8) the time lag is either 0.48 h (for DMSO samples) or 0 (for MeOH samples).

In other words, at pH = 1.2, release for about 1 h occurs mostly from macropores (for DMSO samples), whereas for pH = 6.8 release occurs simultaneously from macro- and mesopores (for MeOH samples) or occurs for 0.48 h mostly from macropores, then from mesopores (DMSO samples). For DMSO samples, the high t_0 can be explained by a large amount of the drug deposited in macropores (Ov_A and Ov_B – 50.3% and 76.4%, respectively), which release the drug in a short time due to direct contact with the external environment, and at the same time, may slow down transport of drug from mesopores to macropores (low concentration gradient between mesopores and macropores because of higher amount of tamsulosin located in macropores). On the other hand, for MeOH samples and pH = 1.2, the time lag may be caused by the common ion effect, that blocks the drug release from mesopores in the first hour (0.96 h). This effect does not occur for MeOH samples for pH = 6.8, hence the drug is released from meso- and macropores without delay (no t_0) – a large part of the drug is stored ($1 - Ov_A$ and $1 - Ov_B \approx 90\%$) in mesopores, increasing the release from these pores due to the higher concentration gradient compared to DMSO samples.

Moreover, the silica surface becomes increasingly negatively charged as the pH is increased above 2 ± 1 [35]. Hence it is probable, that at pH = 1.2 silica network and tamsulosin hydrochloride may be oppositely charged, and positively charged tamsulosin can be attracted by negatively charged silica network. This phenomena additionally

Table 3
The parameters of simulation of tamsulosin release from silica monolithic tablets.

Solvent	$P_{des} = 1 - P_{ads}$	$D \times 10^6$ ($cm^2 s^{-1}$)	Ov_A (%)	Ov_B (%)	Ch (%)	t_0 (h)	Sp_A (%)	Sp_B (%)
Methanol pH 1.2	0.0128	1.4	7.3	10.8	7	0.96	2	0
Methanol pH 6.8	0.0032	3.1	7.3	10.8	1	0	2	0
DMSO pH 1.2	0.0016	7.2	50.3	76.4	9	0.96*	0	0
DMSO pH 6.8	0.0016	4.5	50.3	76.4	2	0.48	14	1

P_{des} – probability of desorption.
P_{ads} – probability of adsorption.
D – diffusion coefficient in mesopores.
Ov_A – percentage of drug mass, that is added to macropores instead of mesopores in network A.
Ov_B – percentage of drug mass, that is added to macropores instead of mesopores in network B.
Ch – chemisorption/permanent immobilization of drug – percentage of the drug permanently associated with the tablet.
t_0 – time lag relative to release from mesopores due to transport through macropores.
Sp_A, Sp_B – possible spill of the drug from the tablet during loading
* Only for the B structure, A structure required a lag of 0.04 h.

hampers drug transport in mesopores, increasing time lag. In our simulation it was described as the chemisorption (*Ch*) parameter – the *Ch* parameter describes the fraction of the drug that undergoes permanent (i.e. stronger) immobilization in the porous structure. This effect is modelled as proportional to the pore surface and is mostly visible at low pH. The chemisorption can help to explain the difference between time lags in DMSO samples in different pH values. Lower time lag (t_0 = 0.48 h) for DMSO sample in pH = 6.8 is caused by low chemisorption (Table 3), therefore tamsulosin deposited in mesopores appears in the exterior environment after shorter time (0.48 h).

The Sp_A and Sp_B parameters represent a possible spill of the drug from the tablet while loading. This decreases the amount of drug that can be released in a way similar to chemisorption, but this effect is not proportional to the adsorbing surface.

4. Conclusion

The paper describes the process of the release of tamsulosin hydrochloride from the two monolithic tablets with a hierarchical pore structure. We focused on finding the relationship between the carrier's structure and its influence on the release profile of the drug deposited on them. The study results indicate that there are considerable possibilities for control over the speed and the amount of released tamsulosin using carriers with different pore sizes. The use of materials with a hierarchical porous structure as drug carriers will pave the way for their rational selection based on the desired release kinetics. The research will also improve the design of new carriers with the tailor-made structures adjusted to the release profile, as well as promote hierarchical silica as a drug delivery system.

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