Chem. Mater. **2004,** *16,* 4160−4167

Influences of Material Characteristics on Ibuprofen Drug Loading and Release Profiles from Ordered Micro- and Mesoporous Silica Matrices

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Received January 27, 2004. Revised Manuscript Received July 27, 2004

A series of mesoscopically ordered silicas with different pore sizes, pore connectivity, and pore geometry have been studied as carrier matrices for controlled drug delivery systems. Ibuprofen was used as a model drug, and the release processes were monitored under in vitro conditions. The adsorption of ibuprofen from hexane was shown to be of Langmuir type in all cases, and the degree of drug loading was dependent on the specific surface area and the pore diameter of the host matrix. The release process is found to be mainly diffusion controlled, but clear differences were observed between the studied materials, which we mainly ascribe to differences in the pore connectivity and pore geometry of the materials, and the aqueous stability of the matrix. The studied nanostructured silicas display a high degree of drug loading, and, depending on the host material, a controlled drug release can be provided for time periods varying from hours to weeks.

Introduction

During the past decades, a diversity of polymer-based pharmaceutical carrier systems has been developed as new means of controlling temporal or distributional (site-specific) drug delivery.[1] Pharmaceutical controlling delivery systems offer numerous advantages as compared to conventionally administrated drugs in dosage forms, such as improved efficiency and reduced toxicity.[1] Polymeric cross-linked carrier matrices, such as hydrogels and supramolecular polymer aggregates as well as different types of microencapsulation vehicles, are typical examples of common drug delivery devices.[1−4] Besides the purely organic matrices, several sol−gel-derived silicon oxide-based materials have subsequently been investigated as alternative controlled drug release systems.[5−9] These materials are potentially multifunctional, because another possible application area for these types of silica ceramics is as bioactive bone-generating implants or bone-filling materials.[10−12] Introducing a pharmaceutical to such a matrix could therefore make it possible to combine bone-generating ability with controlled release properties.[13,14] Recently, the release studies on sol−gel-derived materials were extended to a new class of ordered nanostructured silica materials.[15−20] These materials are synthesized in the presence of supramolecular surfactant aggregates, which serve as structure-directing agents for the polymerizing silica. A mesoscopically ordered porous material is obtained upon removal of the surfactant, where the pore diameter is determined by the diameter of the supramolecular surfactant aggregate.[21,22] The interested reader is referred to some of the recent reviews covering various aspects of these materials, from synthesis to applications.[23−26] In contrast to most organic polymer-

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10.1021/cm0401490 CCC: $27.50

derived matrices, these highly porous materials exhibit a narrow pore size distribution in combination with a high specific pore volume. This feature could ease an even incorporation of organics into the structures and, further on, provide a controlled release. Furthermore, the high adsorption capacity of this class of materials facilitates a high loading of drug. The silica materials used in this study exhibit a narrow pore size distribution within the micro- or mesoporous range and a high surface area. The main body of the present work concerns materials denoted MCM-41[21,22] and SBA-3,[27,28] which both exhibit a uniform, hexagonal arrangement of cylindrical pores. However, in addition, also SBA-1,[28] which exhibits a micellar cubic arrangement of spherical cavities connected through smaller pores, has been investigated. MCM-41 is synthesized at elevated pH, whereas SBA-3 and SBA-1 are synthesized under acidic conditions. The study is focused on the drug adsorption and release characteristics having the pore dimension, connectivity, and geometry as the main parameters. Because the release rates are expected to be highly system dependent, ibuprofen was chosen as the model pharmaceutical to allow a comparison of the obtained results with literature data, where similar siliceous mesoporous carriers were investigated.[18] Furthermore, we also address some important aspects of the adsorption−desorption process, like the connection between pore size and the degree of ibuprofen loading, the influence of solubility of the silica matrix, the effect of sample size on the observed release rates, and the possibility of nucleation and growth of calcium phosphates on the silica carrier during the in vitro experiments. The microstructures of the materials were investigated by X-ray diffraction (XRD) and N_2-physisorption. The adsorption and subsequent release processes were monitored by UV−vis spectroscopy and gravimetry.

Materials and Methods

Materials. Tetraethoxysilane (TEOS) and hexadecyltrimethylammonium bromide (CTAB) were obtained from Aldrich, Germany. Ammonia (25%) and hydrochloric acid (36−38%) were purchased from J. T. Baker, Germany. Decanoic acid and toluene were obtained from Fluka, Great Britain, and phenyltriethoxysilane (PhTES) was from ABCR GmbH & Co, Germany. Ibuprofen was kindly supplied by Orion OY, Finland. All chemicals were used as received without further purification.

Acidic Synthesis. Micro- and mesoporous SBA-1 and SBA-3 types of materials were synthesized under acidic conditions according to the procedure described by Babonneau et al.[29−31] C_{16}TAB was used as structure-directing agent, and tetraethoxysilane (TEOS) and phenyltriethoxysilane (PhTES) were used as silica sources in the following molar ratios: 0.12/9.2/130/1 for C_{16}TAB/HCl/H_2O/Si. TEOS and PhTES were first prehydrolyzed in the presence of ethanol (molar ratios 4/1/1 for TEOS/PhTES/EtOH) to form co-condensed species to prevent phase separation.[32] The prehydrolyzation was performed at a pH of 1.2 adjusted by addition of HCl. The product is a 2D hexagonally ordered microporous material, denoted μSBA-3. When the same silane mixture is added directly to the acidic C_{16}TAB-solution without any prehydrolyzation step, a material possessing a cubic $Pm3n$ structure, denoted μSBA-1, is formed. When TEOS is used as a unique precursor and reacted with acidic C_{16}TAB-solution, a mesoporous material, denoted mSBA-3, with a hexagonally arranged pore structure is obtained. All of the acidic syntheses were performed at room temperature. The solutions were stirred for 3 h, filtered, rinsed with distilled water, and dried at 363 K for 20 h.

Alkaline Synthesis. The MCM-41 type materials were synthesized according to published synthesis routes.[33−36] In the synthesis of MCM-41, the template, C_{16}TAB, was first dissolved in deionized water by stirring (500 rpm) at 303 K before addition of ammonia. The silica source (TEOS) was slowly dripped into the solution, giving a final molar ratio of $157H_2O/0.15C_{16}$TAB/$3NH_3$/1TEOS. A similar synthesis was performed where 0.87 mmol of decanoic acid, DAc, was added to the surfactant solution as an anionic cosurfactant. After complete dissolution of the acid, 2.0 g of toluene was added to the mixture and stirring was continued for about 5 min. The pH was adjusted to 11.8 by addition of NaOH before addition of TEOS. The mixture was then continuously stirred for another 1 h. The molar ratio for the catanionic MCM-41 was $157H_2O/0.15C_{16}$TAB/$3NH_3$/6.6DAc/0.26toluene/1TEOS. The obtained powders were either directly filtered and washed with distilled and deionized water or aged at 363 K at a pH of 10 for 5 days before filtration. The aging process enhances condensation of the silica species and thereby stabilizes the matrix further. Filtered as-synthesized or aged materials were dried at 363 K for 20 h. The aged material is denoted MCM-41a to distinguish it from the MCM-41 sample. The material synthesized in the presence of decanoic acid and toluene was denoted c-MCM-41a, that is, catanionic MCM-41a, where the notation “a” refers to the aged material.

All materials were compressed into disks after the drying procedure. The SBA types of materials are calcined at 873 K (heating rate 1 K/min) for 4 h, and the MCM-41 types were calcined at 823 K, 5 h (heating rate 1 K/min). The cross section of the disks was 13 mm, and the thickness was varied between 1 and 3.5 mm. Depending on the disk size, the mass of the disks varied between 0.1 and 0.35 g, corresponding to a total porosity of about 65%, assuming a bulk density of silica of 2.2 g/cm^3.

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Characterization Procedures. XRD measurements were performed using a Kratky compact small-angle system (Hecus Braun, Austria). The system is equipped with a position-sensitive detector (PSD 50m) consisting of 1024 channels of 54.9 μm width each. A Seifert ID-300 X-ray generator, operating at a maximum intensity of 50 kV and 40 mA, provided the Cu Kα radiation at λ = 1.542 Å. A Ni filter was used to remove Kβ radiation, and a W filter protected the detector from the primary beam. The sample-to-detector distance was 277 mm. The sample holder was kept under vacuum during the measurements to minimize the background scattering from air.

Nitrogen physisorption measurements were performed at 77 K using an ASAP 2010 sorptometer (Micromeritics, USA). The calcined samples were outgassed at 423 K prior to the measurements, and the ibuprofen-loaded samples were outgassed at 333 K.

Impregnation. The impregnation process was performed according to one of the procedures described by Vallet-Regi et al.[18] Ibuprofen was dissolved in hexane (33 mg/mL), and the disk was soaked in the solution for 3 days (33 mg/mL silica/hexane) in a closed batch to prevent evaporation of the liquid. Longer impregnation times did not change the amount of ibuprofen incorporated; this is why an impregnation time of 3 days corresponded to equilibrium conditions. The drug-loaded disks were carefully washed with hexane to remove any adsorbed ibuprofen on the exterior surface. RAMAN spectroscopy (Bruker IFS66, Germany) and TGA-FT-IR (Bruker Equinox, Germany) were used to confirm complete evaporation of the hexane from the impregnated materials. The amount of incorporated ibuprofen was determined gravimetrically but also spectroscopically using a Perkin-Elmer UV−vis−NIR spectrometer, Germany, reading at 273 nm controlling the amount absorbed from solution.

Release. The drug-loaded tablets were dried and immersed in simulated body fluid, SBF, for in vitro drug release studies (1 mg of ibuprofen/mL of SBF). The release processes were followed spectroscopically. The SBF solution has an ionic composition similar to that of human body plasma,[37,38] having a molar composition of 142.0/5.0/2.5/1.5/147.8/4.2/1.0/0.5 for $Na^+/K^+/Ca^{2+}/Mg^{2+}/Cl^-/HCO_3^-/HPO_4^{2-}/ SO_4^{2-}$, and a pH of 7.4.

SiO_2-Solubility and Bioactivity. The rate of silica dissolution in SBF of the different materials was studied for materials impregnated with ibuprofen. One milligram of sample (ibuprofen + silica) per milliliter of SBF-solution was used for the analysis. The silica contents were measured using molybdenum blue as a tracer, and the concentration was monitored by means of UV−vis spectrophotometry[39] (Hitachi model 100-60, Japan). Furthermore, to follow the potential formation of calcium phosphates on the silica during the release experiments, the calcium ion concentration in solution was followed as a function of immersion time. The calcium concentrations were determined by atomic absorption spectroscopy (Perkin-Elmer 460, Germany).

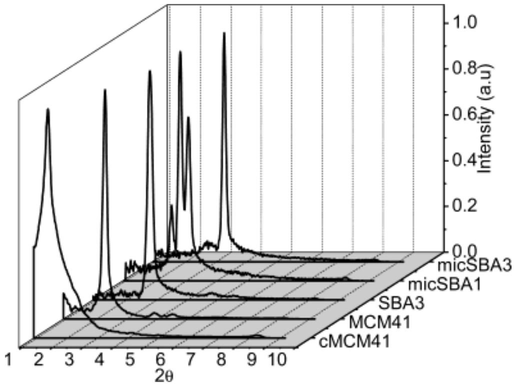

Figure 1. XRD diffractograms of the investigated mesoporous silica carrier matrices.

Results and Discussion

Material Characteristics. The materials in this study were synthesized according to already thoroughly documented synthesis routes. The materials were investigated by X-ray diffraction, XRD, and N_2-sorption, and the results were in perfect agreement with literature data.[28,29,33−35] The XRD diffraction patterns measured for the carrier matrices studied are shown in Figure 1. Some important material properties are summarized in Table 1. Most importantly, the pore sizes vary from micropores, less than 2 nm in diameter, to mesopores, up to 5 nm in diameter. There are important differences in the pore structure and pore connectivity between the studied materials. The MCM-41 and the SBA-3 type materials have straight one-dimensional cylindrical pores, while the SBA-1 materials have a 3D interconnected porosity, where close to spherical pores are connected through smaller windows. The c-MCM-41a material has also one-dimensional pores, but the cylinders are not straight but corrugated, which essentially is equal to a situation where larger pores are connected through smaller pore openings. This will be discussed in more detail later, but is important for the understanding of the drug release results presented below.

Adsorption of Ibuprofen. The adsorption of ibuprofen from hexane was studied by determining adsorption isotherms for the different porous silica matrices described in Table 1. An impregnation time of at least 3 days was used and found to be sufficient to reach equilibrium. In Figure 2, the corresponding isotherms are expressed as the amount ibuprofen adsorbed per weight silica, n/w, as a function of the equilibrium concentration of ibuprofen in hexane solution, c_{eq}. The isotherms were reversible and could therefore be further fit to a Langmuir-type adsorption isotherm.[40]

The isotherms reveal large differences in adsorption capacity between the materials. The microporous materials showed the lowest and the MCM-41 sample the highest ibuprofen adsorption capacity calculated on a weight percentage basis. For MCM-41, a drug loading degree of up to 41 wt % could be reached, while a maximum of 25 wt % of ibuprofen could be incorporated into the microprous SBA-1 and SBA-3 materials. The other materials reached loading degrees around 30 wt %, as listed in Table 2. It is clear that the microporous

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Table 1. Lattice Spacing, d_0; Specific Surface Area, a(BET); Pore Volume, V; and Pore Diameter, d(BJH), for Acid and Alkaline Synthesized Silica Materials (Drug Loaded Matrices Have Been Impregnated for 3 days in Ibuprofen/Hexane Solution (33 mg/mL))

sample	lattice structure	lattice parameter d_0 (nm)	pore diameter $d(\mathrm{BJH_{des}})$ (nm)	specific surface area a(BET) (m^2/g)	pore volume V (cm^3/g)
MCM-41	hexagonal	4.8	3.3	1200	1.0
MCM-41/ibuprofen			2.6	370	0.2
MCM-41a	hexagonal	4.8	2.8	~1050	1.0
MCM-41a/ibuprofen			2.3	450	0.2
c-MCM-41a	hexagonal	7.5	5.0[a]	650−800	1.0−1.2
c-MCM-41a/ibuprofen			3.0	400−650	0.4−0.6
m SBA-3	hexagonal	3.8	2.6	>1000	1.0
m SBA-3/ibuprofen			n.d.	440	0.35
μ SBA-3	hexagonal	3.0	1.7	>1000	0.51
μ SBA-3/ibuprofen			n.d.	220	0.11
SBA-1	cubic	6.9	1.8	>1000	0.54
SBA-1/ibuprofen			n.d.	240	0.13

[a] Determined from the adsorption branch.

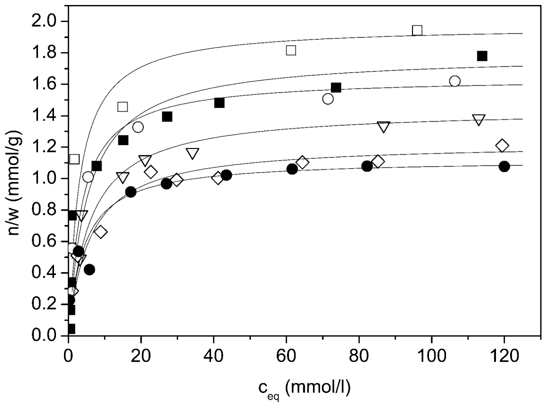

Figure 2. Adsorption isotherms of ibuprofen in hexane solution for the studied porous silica materials expressed as the amount of adsorbed ibuprofen/g of silica. (□) MCM-41; (○) MCM-41a; (▽) c-MCM-41a; (■) mSBA-3; (◇) μSBA-1; (●) μSBA-3.

Table 2. Langmuir Equilibrium Constants for Impregnated Samples (3 days) and Loading Degrees at a Concentration of 33 mg of Ibuprofen/mL for the Different Micro- and Mesoporous Silica Materials

sample	loading degree (wt %)	$K_{L,\Gamma}$
MCM-41	41	0.328
MCM-41a	31	0.277
C-MCM-41a	28	0.165
mSBA-3	33	0.184
μSBA-1	25	0.171
μSBA-3	22	0.235

materials exhibit the lowest loading degree of the materials studied, which can be linked to steric hindrance upon increasing ibuprofen loading. No clear dependency of loading degree on the pore diameter is observed for the mesoporous materials. However, although the often used mass/mass-measure of the amount of incorporated ibuprofen gives important information about the corresponding total loading degrees, it does not give a satisfactory description of the adsorption process. Hence, the ibuprofen adsorption data from Figure 2 are replotted in Figure 3 as the amount ibuprofen adsorbed per unit specific surface area a(BET), that is, the surface excess (moles per unit area of adsorbent), Γ, versus the equilibrium concentration, c_{eq}. The surface excess is based on a(BET) as

$$\Gamma = n/w\cdot a(\mathrm{BET})^{-1}\ (\mu\mathrm{mol/m^2}) \qquad (1)$$

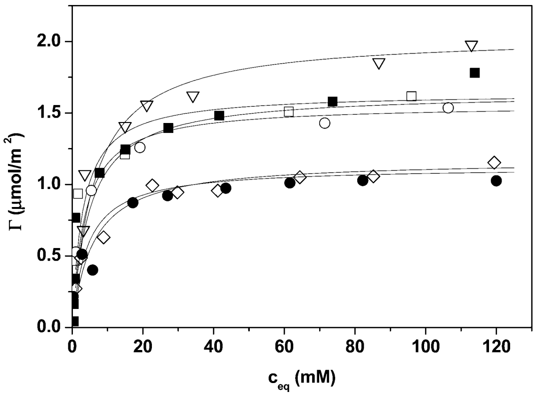

Figure 3. Ibuprofen adsorption isotherms expressed as the surface coverage Γ (amount of adsorbed ibuprofen/m^2) from solution. The surface area was determined using the BET-method. (□) MCM-41; (○) MCM-41a; (▽) c-MCM-41a; (■) mSBA-3; (◇) μSBA-1; (●) μSBA-3.

The Langmuir equilibrium constant, K_L, is obtained according to eq 1 from the two types of Langmuir isotherms. As seen in Table 2, the values of the equilibrium constant K_L do not vary significantly between the materials. This implies that the affinity of the different silicas for ibuprofen is very similar, as expected. The materials can be divided into three groups, according to their respective pore sizes. The microporous SBA-type of material displays plateau values between 1 and 1.2 μmol/m^2. As was already stated, this fairly low surface coverage is in this case probably due to sterical effects. With increasing ibuprofen loading, the adsorbing molecules experience steric hindrance when diffusing into small micropores that are less than double the length of a fully stretched ibuprofen molecule (~1 nm). Simple geometrical argumentation can be used to show that the steric requirements of the ibuprofen molecule will prevent a high surface loading in a small, highly curved, pore. The adsorption isotherms for materials having pore sizes in the 3 nm-range all display similar levels of adsorption. The MCM-41 and MCM-41a types of materials, as well as the mesoporous mSBA-3, display plateau values between 1.4 and 1.6 μmol/m^2. These values are similar to those results obtained by Vallet-Regi et al. if calculated on the basis of their adsorption data.[18] They used two MCM-41 materials with pore sizes within the same range as the MCM-41 and SBA-3 materials used in this study.

The c-MCM-41a sample gives the highest loading degree per unit surface area with a plateau value close to 2.0 μmol/m^2, corresponding to an almost 2 times higher surface concentration of ibuprofen as compared to the microporous materials. Thus, if the ibuprofen adsorption is expressed as the amount of adsorbed ibuprofen per unit area, contradictory to earlier studies,[18] a clear dependency on the pore diameter is observed. The main interaction between the ibuprofen and the silica surface is thought to be from hydrogen bonding; that is, a single contact point of the ibuprofen molecule involving the formation of a hydrogen bond between the carboxylic acid group of the ibuprofen with surface silanol groups is energetically favorable.[18,41] For comparison, the surface silanol coverage for the investigated silica matrices has been reported to be in the range of 2−4 μmol/m^2 when calcined around 773 K,[42,43] which is close to but higher than the ibuprofen surface concentrations observed, and this is why the surface silanol concentration is not the limiting factor for the observed ibuprofen loadings for the materials under study. Indeed, it has recently been shown that hydrogen bonding between the carboxyl group of the drug and silanol groups of silica is essential for achieving high loading degrees for similar formulations.[44] The importance of the hydrogen-bonding interaction between the ibuprofen and surface silanols is further highlighted by the fact that loading degrees of less than 7 wt % can be achieved if the impregnation is performed in methanol,[19] evidently because the methanol competes with the ibuprofen for hydrogen bonding to surface silanols and the methanol is a very good solvent for ibuprofen. Furthermore, the adsorption capacity of hydrophobic silica carriers has in fact been shown to be lower, explained by the lack of surface silanol groups providing the active sites for the hydrogen bonding in the case of hydrophilic silica.[45] Further support for the importance of the surface silanol concentration on the ibuprofen loading is given by preliminary studies of ibuprofen adsorption to Grace silica powders,[46] where loading degrees of almost up to 20 wt % were achieved for fully hydroxylated surfaces as compared to about 5 wt % for that of a sample calcined at 1173 K where most of the free silanols have condensed.[47] In a recent communication, it was suggested the ibuprofen molecules are present as dimers in the pore channels.[48] However, it has to be kept in mind that here dried samples were investigated and the total interaction energies are clearly modified by the presence of a solvent. We therefore conclude that the pore size, surface area, and presence of silanol groups will be crucial factors for the drug loading. The difference in surface concentration of ibuprofen has important implications for the release process, because the higher the ibuprofen surface loading the more hydrophobic the pores will become, which could affect the kinetics of water diffusion into the matrix.

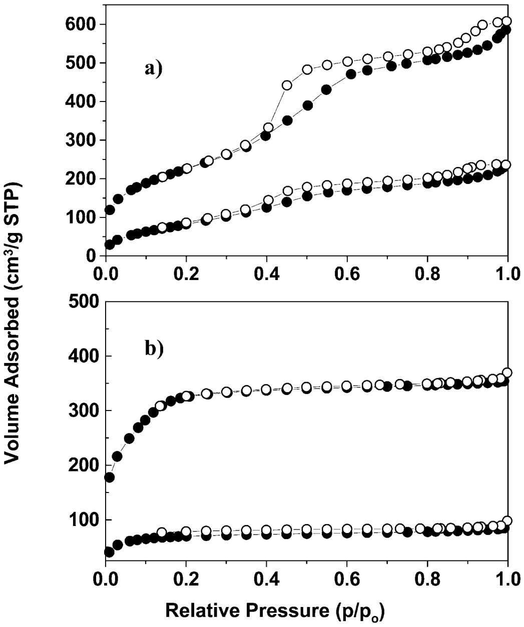

Figure 4. Nitrogen physisorption isotherms for c-MCM-41a and μSBA-3 materials. Closed symbols denote adsorption, and open symbols desorption. (a) Calcined c-MCM41a (upper) and impregnated c-MCM41a (lower). (b) Calcined μSBA-3 (upper) and impregnated μSBA-3 (lower).

Figure 4 displays N$_2$-physisorption isotherms for (a) the mesoporous catanionic c-MCM-41a and (b) the microporous hexagonally arranged μSBA-3. They both represent typical isotherms for the two ranges of pore sizes. The catanionic MCM-41 displays a type IV isotherm characteristic of mesoporous materials with its marked uptake at a relative pressure close to 0.4. The *a*(BET) is in this case about 750 m^2/g. The average pore size is determined to be 4.5 nm, which means that the ibuprofen molecule can easily fit inside the pores. However, it is evident from the shape of the hysteresis loop in the N$_2$-sorption isotherm shown in Figure 4 that the mesopores in this material are not straight cylinders as in normal MCM-41, but the one-dimensional pores are corrugated and the desorption is delayed due to the fact that the desorption pressure is determined by the openings of the smaller pores. This is discussed in more detail in ref 35, where a more extensive characterization of this type of material is reported. The desorption isotherm can thus not be used for a correct determination of the pore diameter.[49] Furthermore, as desorption occurs at a relative pressure close to the critical pressure of nitrogen, $p/p_o = 0.42$, the diameter of the pore window cannot be determined either. However, one can conclude that the diameter of the pore window in this material is less than 4 nm.

The μSBA-3 type displays a type I isotherm typical for materials containing micropores with a *a*(BET) slightly above 1000 m^2/g and an average pore diameter below 2 nm (BJH$_{des}$). The corresponding adsorption isotherms determined after incorporation of ibuprofen into the pores are also shown in Figure 3. The loading

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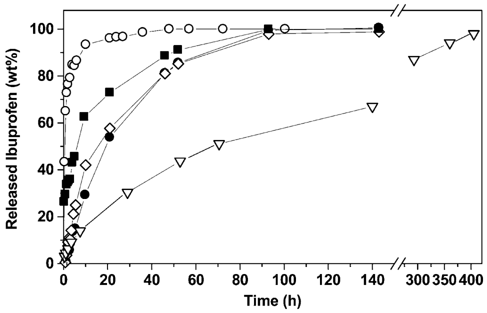

Figure 5. Ibuprofen release profiles for impregnated microporous and mesoporous materials in SBF at 37 °C. (○) MCM-41a; (▽) c-MCM-41a; (■) mSBA-3; (◇) μSBA-1; (●) μSBA-3. The release rate from the MCM-41 sample was similar to that from the MCM-41a sample and is omitted for clarity.

degrees for these samples are 28 wt % for the c-MCM-41 and 22 wt % for μSBA-3. The isotherms for the impregnated materials still display the presence of meso- and micropores, respectively. The marked uptakes have moved toward lower relative pressures, as expected. For the microporous SBA-3 type of material, the total uptake has been remarkably lowered as the total pore volume was reduced by almost 75% (based on calculations obtained from single point total pore volume at $p/p_0 \approx 0.97$). For the mesoporous c-MCM-41a, the reduction was approximately 60% (calculated from the plateau value obtained at a relative pressure $p/p_0 \approx 0.60$). For complete monolayer coverage of ibuprofen, the reduction in pore diameter should be at least 2 nm for head-on adsorbed ibuprofen to the pore walls. The reductions in the calculated average pore diameters (BJH desorption/adsorption plot for the pore size distribution, Table 1) were about 1−1.5 nm, giving further support for the conclusion that the ibuprofen molecules are not present as a close-packed monolayer due to steric hindrance connected to curvature effects and the possible formation of tilted ibuprofen due to dimer formation.[48]

Drug Release. Typical drug-release profiles for the different types of investigated materials are plotted in Figure 5, where all in vitro studies have been performed under the same conditions. The powders were compressed to disks with a diameter of 13 mm and a thickness of 3 mm. The respective loading degrees are given in Table 2. Depending on the material characteristics, a controlled release is observed for time periods reaching from 24 h for the majority of ibuprofen incorporated in the MCM-41a material to above 400 h for the catanionic c-MCM-41a. The microporous μSBA-3 and μSBA-1 materials and the mesoporous mSBA-3 material all display total release times in the range of 100 h. However, characteristic for mSBA-3 is the pronounced primary burst effect, corresponding to the intercept in Figure 5, where almost 20 wt % of the impregnated ibuprofen will be released within 1 h.

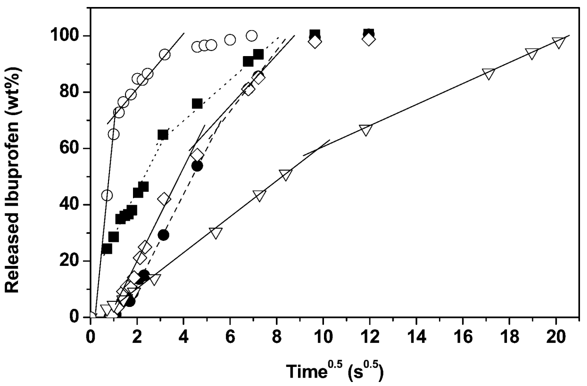

Figure 6. Higuchi square root of time plot for the release of ibuprofen from the studied microporous and mesoporous materials. (○) MCM-41a; (▽) c-MCM-41a; (■) mSBA-3; (◇) μSBA-1; (●) μSBA-3.

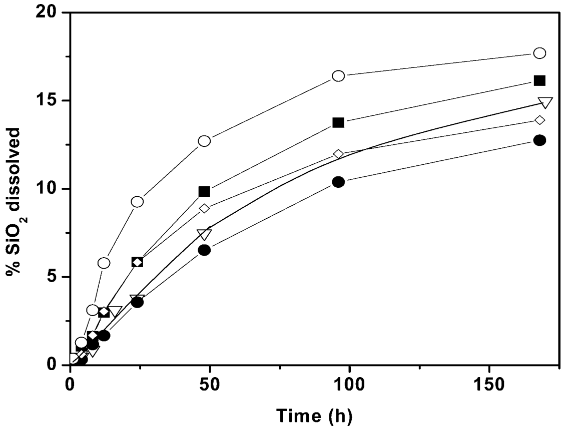

Figure 7. Amount of silica dissolved measured for ibuprofen-containing tablets in SBF at 37 °C. (○) MCM-41a; (▽) c-MCM-41a; (■) mSBA-3; (◇) μSBA-1; (●) μSBA-3.

The kinetics of the release of drugs from porous carrier materials is frequently described using the Higuchi model.[50,51] According to this model, the release of a drug from an insoluble, porous carrier matrix can be described as a square root of a time-dependent process based on Fickian diffusion. The amount of drug released, Q_t, per unit of exposed area at time t can then be described by the simple relation

$$Q_t = k_H \cdot \sqrt{t} \qquad (2)$$

where k_H is the release rate constant for the Higuchi model. Thus, for a purely diffusion controlled process, the amount of drug released exhibits a linear relationship if plotted against the square root of time. The use of this model should be beneficial for the system under study as the model is valid for releases of relatively small molecules that are uniformly distributed throughout the matrix.[51] However, from the Higuchi square root of time plots presented in Figure 6, it is clearly seen that all materials display a two-step release. This deviation from overall linearity is probably related to the dissolution of the silica matrices during the in vitro measurements, which will be discussed next.

The silica solubility rates determined for ibuprofen-containing matrices are shown in Figure 7. The rate of silica solubility is highest in the early stages, while the solubility rate decreases with time. This observation can be ascribed to the sink-type experiment and probably does not correspond to the dissolution rate in vivo. However, the rates of silica solubility for the different materials roughly follow the same order as the release rates of ibuprofen shown in Figure 5, but it is difficult to draw any lengthy conclusions on the basis of these

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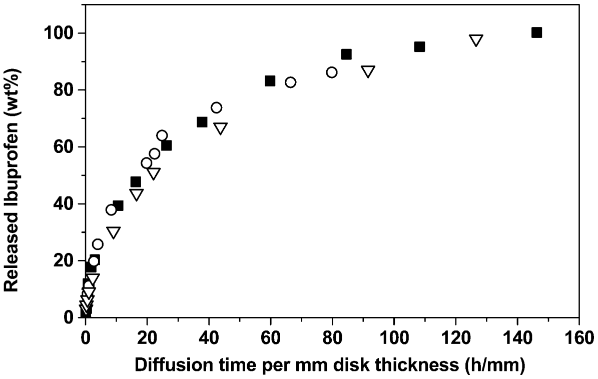

Figure 8. Ibuprofen release curves from c-MCM-41a normalized to the thickness of the compressed cylindrical tablets. The tablets had a constant loading degree of 270 mg of ibuprofen/g of silica. (○) 1.0 mm, (■) 2.0 mm, (▽) 3.0 mm.

differences. An initial induction period can be observed, which can be ascribed to the poor initial wetting of the ibuprofen-containing silica by the SBF. It should be noted that the solubility rates of the pure silica matrices were higher than those of the ibuprofen-containing matrices (results not shown), which can be ascribed to the same effect. The silica dissolution rate is significant for all of the materials, which can be related to the fact that they were synthesized at room temperature,[52] and is especially high for the MCM-41 sample that was not aged before impregnation. This MCM-41 sample also showed the fastest ibuprofen release kinetics of all matrices studied. We note that the presence of two steps in the Higuchi plot is less pronounced for the more stable materials, c-MCM-41a and μSBA-3. If the data presented in the study of Vallet-Regi et al.[18] are plotted against the square root of time, a straight line roughly passing through origin is also obtained. This would correspond to a pure Higuchi type of diffusion-driven release for a carrier where no alteration of the matrix occurs on the time-scale of the release. This is indeed in accordance with the fact that the materials used in ref 18 were hydrothermally processed and no loss of structural order after the release was reported. All in all, it can therefore be concluded that the rate of silica solubility has an influence on the observed ibuprofen release rates. However, another factor that is bound to influence the ibuprofen diffusion rate is the primary and secondary particle size of the substrate, an effect that we have not quantified in the present study, and why a one-to-one relation between the silica solubility rates and the ibuprofen release rates should not be expected. Furthermore, it is possible that the silica does not dissolve in a homogeneous manner, but preferentially from regions from which the ibuprofen has been released, because, as stated above, the rate of silica dissolution was clearly slower for materials containing ibuprofen as compared to the pure substrates.

The reproducibility of the release process is illustrated in Figure 8. For a purely diffusion-controlled system, the relative amount of released ibuprofen per time from a cylindrical disk should be inversely proportional to the disk thickness. Indeed, for the c-MCM-41a sample, such a relationship exists, as seen in Figure 8, where the released amount of ibuprofen is plotted against the diffusion time divided by the disk thickness for three different tablets of c-MCM-41a with the thicknesses of 1, 2, and 3 mm, respectively. The data would be linear if plotted against the square root of time, as is expected for a diffusion-controlled process. That is, however, not the case for the part of the materials reported here which were not posttreated, and a reduction of the surface area and the pore volume is accompanied by an increase in the pore size of the silica matrix observed after the release. This lends support to the statement of the materials being degradable, but still preserving some structural properties during the period of the release.

Finally, to exclude the possibility of an influence on the ibuprofen release kinetics by nucleation and growth of hydroxyapatite on the silica during the in vitro experiments,[53] the Ca-ion concentration in SBF was followed during the ibuprofen release process. However, no, or negligible, precipitation was observed for any of the ibuprofen loaded samples during the release period, which is why this effect can be excluded in this investigation. Although, for the pure matrix, before or after the release, a Ca-loss from SBF-solution was detected, indicating bioactivity and nucleation of hydroxyapatite.

During the revisions of the present Article, we became aware of another paper dealing with the effect of pore size on the release of ibuprofen from mesoporous silica.[54] The main conclusion of the study was that the release rate of ibuprofen increases with increasing pore size for materials with pore diameters in the range 2.5−3.6 nm. In that study, the release data were plotted against the absolute amount of released ibuprofen, instead of the relative amount of ibuprofen released as a function of time. The different materials impregnated with ibuprofen exhibited different loading degrees, and the two materials with the smallest pore diameters, 2.5 and 2.7 nm, respectively, studied in ref 54 would actually show a very similar release behavior if the data would be plotted against the relative amount of ibuprofen released, which is why this conclusion is only approximately true. In any case, there are strong indications that the pore size has a pronounced influence on the release kinetics, as expected. This is also seen in our study for the materials exhibiting a 2D hexagonal structure with cylindrical pores, because the release rates increase in the order μSBA-3 < mSBA-3 < MCM-41. However, the much slower release of ibuprofen from the c-MCM-41a substrate can at first glance not be rationalized on the basis of a pore diameter argumentation, because the mesopore diameter of this material exceeds that of MCM-41. Thus, it is clear that the pore geometry has a pronounced influence on the release rates. The one-dimensional pores of c-MCM-41a are not straight, as evidenced from the N_2-sorption data given here and in ref 35, and contain smaller pore openings along the channel. Thus, it seems logical to conclude that the presence of this one-dimensional “cagelike” pore

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structure is very beneficial for supplying a slow release rate of ibuprofen from the material. Furthermore, the surface loading of ibuprofen in the c-MCM-41 sample is much higher than that of the other carrier matrices, and one more reason for the slow release kinetics could therefore be the more hydrophobic nature of the pore system leading to slower water penetration rates[17,44] in this sample. The μSBA-1 material, which has a 3D interconnected porosity where spherical pores of comparable pore diameter to the cylindrical pores of μSBA-3 are connected through smaller pore openings, shows a slightly faster ibuprofen release rate than μSBA-3, although the difference is quite small, and a clearly faster release than c-MCM-41a. We ascribe this observation to the faster diffusion in 3D interconnected pore systems and tentatively to the more hydrophilic nature of the pore system in the μSBA-1 due to the lower effective surface concentration of ibuprofen in this material. Our results thus indicate that a one-dimensional pore structure with cagelike pores is the most promising pore geometry for providing a slow release of drugs from mesoporous hosts. However, further investigations are clearly needed to validate this result.

Conclusions

A range of micro- and mesoporous silica matrices varying in pore size, pore connectivity, and pore geometry have been shown to function as suitable carrier matrices for controlled drug delivery systems under in vitro conditions. The drug release kinetics can be conveniently controlled by the choice of the carrier matrix. The achievable loading degree is related to both the surface area and the pore size of the silica matrix. The drug release process can be described quite satisfactorily as a diffusion-controlled process. Our results thus indicate that a one-dimensional pore structure with cagelike pores is the most promising pore geometry for providing a slow release of drugs from mesoporous hosts.

Acknowledgment. The Finnish Technology Center, TEKES, is acknowledged for financial support.

CM0401490