DOI: 10.1002/ejic.200501035

Drug Self-Templated Synthesis of Ibuprofen/Mesoporous Silica for Sustained Release

Fengyu Qu,[a,b] Guangshan Zhu,*[a] Huiming Lin,[a] Jinyu Sun,[a] Daliang Zhang,[a] Shougui Li,[a] and Shilun Qiu*[a]

Keywords: Template synthesis / Ibuprofen / Mesoporous materials / Silica

The synthesis of Ibuprofen/mesoporous silica has been achieved by a drug self-templated one-step co-condensation process. The drug template of Ibuprofen, a co-template of 3-aminopropyltriethoxysilane (APTES), and tetraethoxysiliane (TEOS) were self-assembled into Ibuprofen/mesoporous silica in a neutral aqueous reaction system. This drug/mesoporous silica was characterized by powder XRD diffraction, FTIR spectroscopy, N_2 adsorption/desorption, TEM, and ^{29}Si/MAS and ^{13}C/MAS NMR spectroscopy. The Ibuprofen/mesoporous silica system gives a well-sustained release profile.

Introduction

Over the past three decades there has been rapid growth in sustained/controlled drug delivery in the field of modern medication and pharmaceuticals since sustained/controlled release can bring both therapeutic and commercial value to health-care products.[1] Among a wide number of materials, micelles, liposomes, and polymeric and co-polymeric nanoparticles are widely employed as drug carriers for sustained/controlled delivery. Recently, a new application of mesoporous silica as a drug-delivery system has been explored,[2] and there is now growing interest in the use of mesoporous silica as a sustained/controlled drug delivery system due to its several attractive features, such as stable uniform mesoporous structure, high surface area, tunable pore sizes with narrow distributions, well-defined surface properties,[1,3] nontoxic nature,[4] and good biocompatibility.[5–7] Several research groups have reported on the design of mesoporous silica-based carriers for sustained/controlled drug-delivery systems.[1–3,6,8–12]

Up to now, the loading of drugs into the channel of mesoporous silica was mainly post-synthesis, that is, the mesoporous silica carrier was synthesized first followed by storage of the drug molecules. The post-synthesis introduction of drug molecules has been achieved by two general strategies: (i) by physical adsorption of drug molecules in the pure mesoporous silica[2,5,8,10,12] or by an acid-base interaction of the drug molecules with amine-supported mesoporous silica,[1,3] or (ii) by anchoring the drug molecules with modified mesoporous silica by covalent attachment to form a pro-drug with release potential.[11]

Ibuprofen is frequently employed as a model drug for sustained/controlled delivery owing to its suitable molecule size of about 1.0×0.5 nm,[2] good pharmacological activity, and short biological half-life (2 h).[13]

Here, we propose a novel approach to encapsulating Ibuprofen in the channels of mesoporous silica by a one-step, drug self-templating technique. The Ibuprofen/mesoporous silica sample was characterized by powder XRD diffraction, FTIR spectroscopy, N_2 adsorption/desorption, TEM, and ^{29}Si/MAS and ^{13}C/MAS NMR spectroscopy. Drug-release profiles have also been determined.

Results and Discussion

Figure 1 schematically illustrates the one-step, drug self-templated synthesis of our mesoporous silica drug-carrier system. The synthesis is based on $S^-N^+–I^-$ template pathways,[14–16] where S^- denotes the anionic drug template and N^+ and I^- represent the protonated amine group and negatively charged silane group, respectively. The formation mechanism is thought to be controlled by the electrostatic interaction between the negatively charged carboxylic headgroup of the drug template (Ibuprofen) and the protonated amine group of the organoalkoxysilane (APTES). Condensation occurs preferentially at the alkoxysilane sites in APTES to onset the formation of the silicate framework. Meanwhile, drug molecules are encapsulated in the channels of the mesoporous silicate to finally give the drug-encapsulated Ibu/MS system.

The XRD pattern of Ibu/MS shows only one reflection (see Supporting Information Figure S1), with a *d*-spacing of

[a] State Key Laboratory of Inorganic Synthesis and Preparative and Chemistry, Jilin University, Changchun 130023, China
[b] Chemistry Department of Harbin Normal University, Harbin, 150080, China
Fax: +86-431-516-8331
E-mail: zhugs@mail.jlu.edu.cn
sqiu@mail.jlu.edu.cn
Supporting information for this article is available on the WWW under http://www.eurjic.org or from the author.

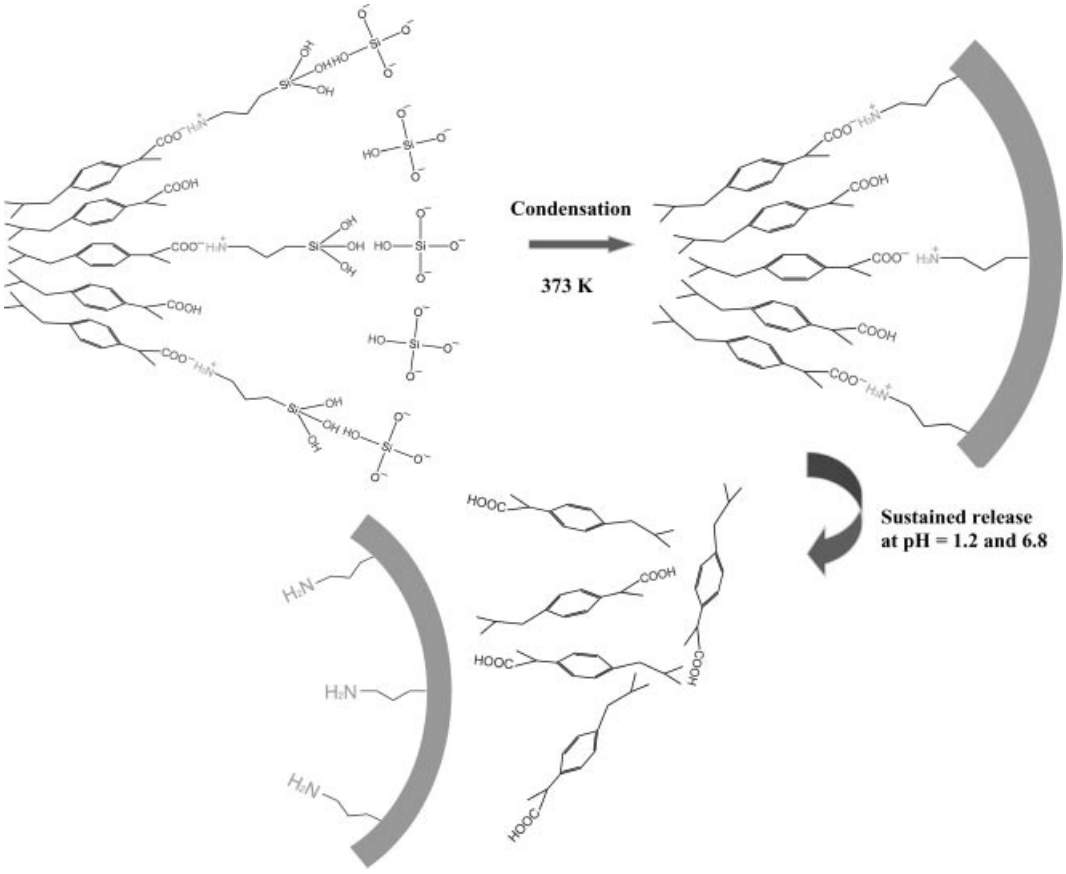

Figure 1. The one-step, drug self-templated synthesis of Ibu/MS system and sustained release.

4.28 nm. The TEM image confirms that the Ibu/MS sample possesses an ordered mesoporous structure (Figure 2). Furthermore, the characteristic mesoporous system was also confirmed by nitrogen adsorption/desorption measurements (shown in Figure 3), which revealed that the samples possess a high specific surface area of 1262 $m^2 g^{-1}$, a large pore volume of 0.66 $cm^3 g^{-1}$, and an average pore size of 2.08 nm. It can be seen that a well-defined step occurs in the adsorption curve at a relative pressure, P/P_o, of 0.2–0.3, which indicates the filling of framework-confined mesopores.[17] This isotherm can be classified as type IV.[18]

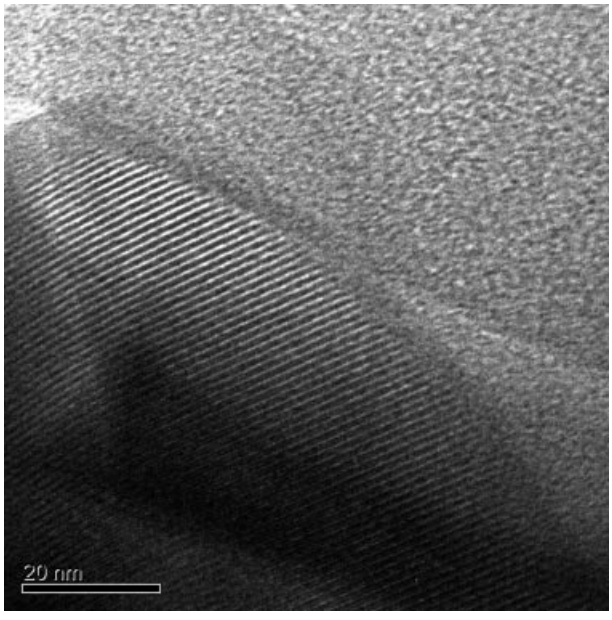

Figure 2. TEM image of Ibu/MS.

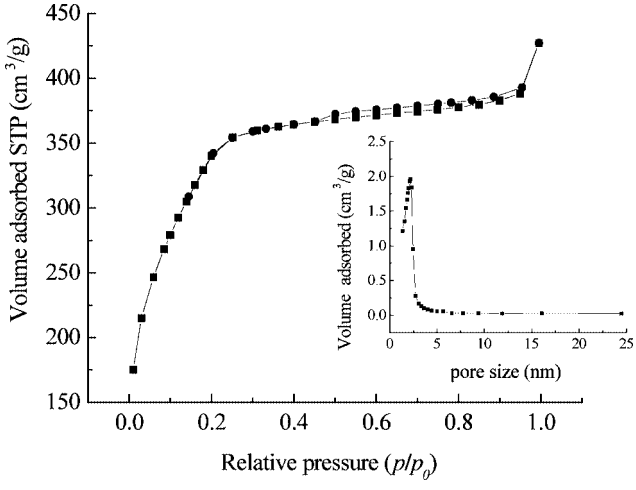

Figure 3. Nitrogen adsorption/desorption isotherm and pore-size distribution of Ibu/MS.

The FT IR spectra of Ibuprofen show that the band corresponding to a free carboxylic acid (1723 cm^{-1}) has changed to a carboxylate one (1463 and 1637 cm^{-1}) in the Ibu/MS sample (see Supporting Information, Figure S2), which suggests $COO^{-}\cdots N^{+}$ bonding between Ibuprofen and the co-template (APTES).[1,3,8,19] In addition, bands for the quaternary carbon atom of Ibuprofen at 1463 and 1519 cm^{-1} and bands for C–H_x of APTES at 2919 and 2962 cm^{-1} can be clearly seen in the Ibu/MS system.[20] These observations show that Ibuprofen and APTES are involved in the formation of the mesoporous phase.

Figure 4 (part A) shows a typical ^{29}Si/MAS NMR spectrum for the Ibu/MS sample. In addition to the free hydroxy group (Q_3) at δ = –110 ppm and cross-linked silicon atoms (Q_4), a new peak group appears between δ = –50 and –80 ppm in Ibu/MS, which is assigned to the Si atoms covalently bound to organic groups {T_2 [$(SiO)_2Si(OH)CSi$] and T_3 [$(SiO)_3SiCSi$], respectively}.[21–23]

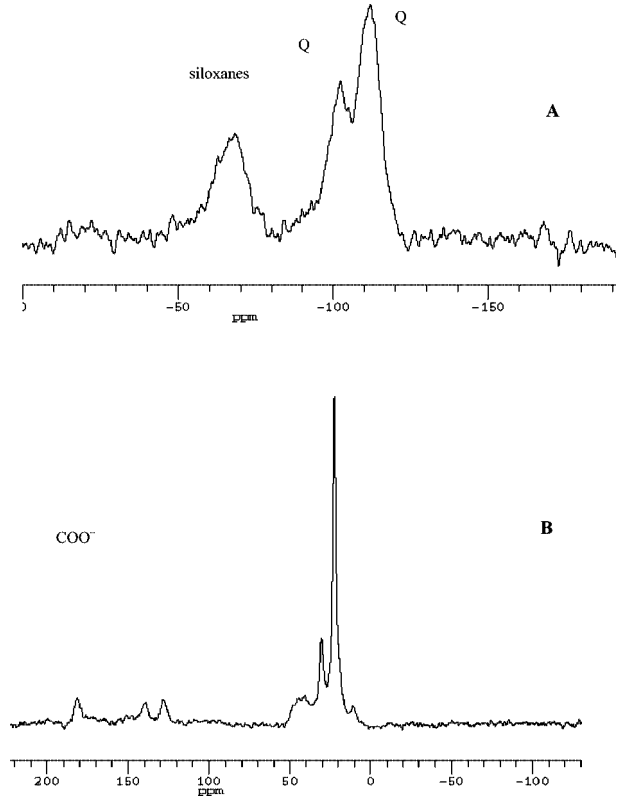

Figure 4. NMR spectra of Ibu/MS: (A) ^{29}Si/MAS NMR spectrum; (B) solid-state ^{13}C/MAS NMR spectrum.

The ^{13}C/MAS NMR spectrum of Ibu/MS is shown in part B of Figure 4. The peaks of $-CH_2CH_3$ at δ = 58 and 14 ppm of pure APTES have disappeared in the Ibu/MS system due to the condensation of APTES with TEOS, which is consistent with ^{29}Si MAS/NMR observations. Furthermore, the peak of the carboxylic acid group of pure Ibuprofen at δ = 183.22 ppm is shifted slightly to a higher shielding of δ = 181.16 ppm in the Ibu/MS system due to the shift of a proton from the carboxylic acid to the amine. These NMR spectra are in agreement with the results of the FT IR spectra, which further confirms the COO^{-}-N^{+} interaction between Ibuprofen and the co-template, as well as the encapsulation of Ibuprofen in the channels of the mesoporous silica.

The loading of ibuprofen in the Ibu/MS sample is about 24%, as determined from the drug released (M_∞) at infinite time. Since Ibuprofen is mainly adsorbed in the stomach and proximal intestine, the release profiles of Ibu/MS in simulated gastric and proximal intestine were determined; the cumulative release rates are shown in Figure 5. This diagram clearly proves that both systems exhibit sustained-release profiles. Only 8.61 wt.-% of Ibuprofen is released within 2 h, and it takes nearly 12 and 45 h to reach 45.06 and 95.2 wt.-% of drug released in simulated gastric fluid, respectively. The release rate in simulated proximal intestine fluid is higher than that in the simulated gastric fluid. Thus, 13.95 wt.-% of Ibuprofen is released within 2 h, 52.22 wt.-% of the drug is released in 12 h, and drug release is finished in 45 h. The difference of release profiles should be mainly due to the different solubility of Ibuprofen at different pH values. Additionally, the integrity of the drug molecules is maintained upon their release from the mesoporous silica (see Supporting Information, Figure S5).

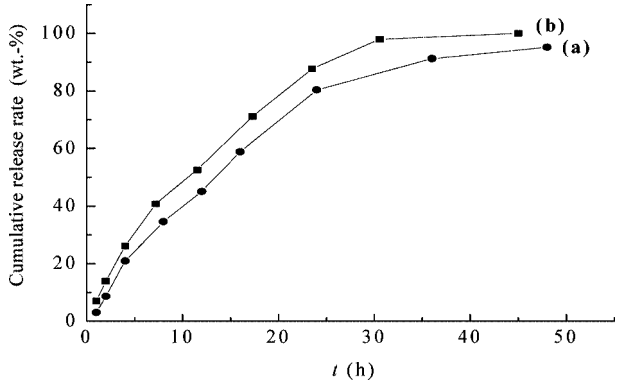

Figure 5. Cumulative release rates of Ibuprofen in simulated (a) stomach and (b) proximal intestinal fluid.

For comparison, MCM-41 was functionalized with APTES and the release kinetics were studied (see Supporting Information, Figure S6). It can be seen that this system shows a faster initial release rate than the Ibu/MS system, with 17.5 wt.-% of Ibuprofen released within 2 h and 55.56 wt.-% of the drug released in 12 h.

In order to investigate the release behavior of Ibuprofen, the drug-release kinetics were analyzed with the Korsmeyer–Peppas model.[24,25] This model often deviates from Fick's law and follows an anomalous behavior that follows the exponential model $M_t/M_\infty = kt^n$, where M_t is the drug released at time t, M_∞ is the quantity of drug released at infinite time, k is the kinetic constant, and n is the release exponent, which characterizes the drug-transport mechanism. When n = 0.5, the drug diffusion and release from the matrix follow Fick's law and drug initial release is slower, while for $1 > n > 0.5$ it follows an anomalous non-Fick-type transport and drug initial release is faster than that of n = 0.5. A relatively larger initial drug release is essential for sustained/controlled drug release. The ln(frac-

tional release of Ibuprofen) is plotted as a function of ln(time) with the data up to 45 h. The exponent for the Ibu/MS system is 0.763 and 0.876 at pH 1.2 and 6.8, respectively (Table 1), which suggests that Ibuprofen release from this system follows an anomalous non-Fick-type transport behavior.

Table 1. The Korsmeyer–Peppas model fit of Ibuprofen release.

Samples	Release medium	$\ln(M_t/M_\infty)$ vs. $\ln t$	n	R
Ibu/MS	pH 1.2	$y = 0.763x - 2.519$	0.763	0.9949
Ibu/MS	pH 6.8	$y = 0.876x - 3.094$	0.876	0.9775

Conclusions

In summary, we have achieved a novel and effective method that uses a drug in a one-step template synthesis that leads to an Ibu/mesoporous silica system. The reported Ibu/MS system possesses an ordered mesoporous structure and gives a well-sustained release profile. The release mechanism follows an anomalous non-Fick-type behavior. This new drug/mesoporous silica synthesis technique is likely find applications in the encapsulation of drugs, fragrances, nanoparticles, and (bio)macromolecules inside mesoporous silica systems.

Experimental Section

Materials: (3-Aminopropyl)triethoxysilane (APTES, Aldrich), tetraethoxysilane (TEOS, Tiantai Co., Tianjin), and Ibuprofen (Ibu, Tianzunzezhong, Chemical Co., Nanjing) were used as received.

Synthesis of Ibuprofen/Mesoporous Silica System: In a typical procedure, 0.11 g of Ibu was first dissolved in a mixture of 0.1 g of APTES and 0.5 mL of distilled water by stirring until a clear solution had formed. Then, 1.01 g of TEOS was added with continuous stirring for 24 h at room temperature. The pH value of the final gel was about 7. This white gel was sealed in a Teflon-lined stainless-steel autoclave and heated at 323 K for 8 h, followed by further heating at 373 K overnight under static conditions. The white precipitate obtained was filtered and washed extensively. The as-synthesized sample was air-dried at room temperature for 48 h.

Characterization: Powder XRD diffraction data were collected on a SIEMENS D5005 diffractometer with Cu-K_α radiation at 40 kV and 30 mA. Nitrogen adsorption/desorption was measured with a Micromeritics ASAP 2010 M sorptometer. Before measurement, the samples was calcined at 723 K for 5 h, degassed at 373 K for 12 h, and the measurements were carried out at 77 K. Specific surface areas and pore-size distributions were calculated using the Brunauer–Emmett–Teller (BET) and Barrett–Joyner–Halenda (BJH) models from the adsorption branches, respectively. Solid-state/MAS NMR spectra were recorded on a Varian infinity plus 400 spectrometer. ^{29}Si/MAS NMR: resonance frequency: 79.41 MHz; spinning frequency: 4.00 kHz; pulse delay: 10.00 s; pulse width: 30°; ^{13}C/MAS NMR: resonance frequency: 100.52 MHz; contact time: 1.00 min; spin rate: 3.33 kHz. UV/Vis spectra were recorded with a UV-2450 visible spectrophotometer from Shimadzu. An FT-IR spectrometer (JASCOFT/IR-420) was used to record infrared spectra of the samples by the KBr method. Powder materials were pressed into a tungsten mesh grid and installed in an in situ FTIR transmission cell; the samples were outgassed in a vacuum system with a residual pressure of less than 3×10^{-4} Torr at ambient temperature. TEM images were recorded with a JEOL 3010 at an acceleration voltage of 300 kV.

Drug Release: After the Ibu/MS sample has been compressed into tablet with a diameter of 10 mm and a thickness of 0.5 mm, the release rate was obtained by soaking the sample tablets (150 mg) in 500 mL of simulated gastric and proximal intestinal fluid (pH 1.2 HCl and pH 6.8 buffer solution), respectively, at a temperature of 310 K. At predetermined time intervals, 3-mL samples were withdrawn and immediately replaced with an equal volume of dissolution medium to keep the volume constant. These samples were filtered (0.45 μm), diluted, then the Ibuprofen contents were analyzed at 222 nm using a UV/Vis spectrophotometer.

Supporting Information (see footnote on the first page of this article): Figure S1 shows the powder X-ray diffraction spectra of Ibu/MS, which confirms the mesoporous structure. Figure S2 shows the FTIR spectra of (a) pure Ibuprofen and (b) Ibu/MS. Figure S3 shows the ^{13}C/MAS NMR spectrum of neat APTES. Figure S4 shows the ^{13}C/MAS NMR spectrum of neat Ibuprofen, which may give information that ibuprofen and APTES may be involved in the formation of the mesoporous structure. Figure S5 shows the UV/Vis spectra of (a) neat Ibuprofen and (b) Ibuprofen released from the Ibu/MS system. Figure S6 shows the cumulative release rates of Ibuprofen from functionalized MCM-41 in simulated fluid. Figure S7 shows SEM images of the Ibu/MS sample.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant nos. 20571030, 20531030 and 20371020), and the State Basic Research Project (2006CB806100).

[1] S.-W. Song, K. Hidajat, S. Kawi, *Langmuir* **2005**, *21*, 9568–9575.
[2] M. Vallet-Regí, A. Rámila, R. P. Del Real, J. Pérez-Pariente, *Chem. Mater.* **2001**, *13*, 308–311.
[3] B. Muñoz, A. Rámila, J. Pérez-Pariente, I. Díaz, M. Vallet-Regí, *Chem. Mater.* **2003**, *15*, 500–503.
[4] C. Tourné-Péteilh, D. A. Lerner, C. Charnay, L. Nicole, S. Begu, J. M. Devoisselle, *ChemPhysChem* **2003**, *4*, 281–286.
[5] Y. L. Cheng, T. G. Brian, M. J. Dusan, J. Ksenija, X. Shu, J. Srdija, S. Y. L. Victor, *J. Am. Chem. Soc.* **2003**, *125*, 4451–4459.
[6] D. R. Radu, Y. L. Cheng, K. Jeftinija, E. W. Rowe, S. Jeftinija, V. S.-Y. Lin, *J. Am. Chem. Soc.* **2004**, *126*, 13216–13217.
[7] C. Barbé, J. Bartlett, L. Kong, K. Finnie, H. Q. Lin, M. Larkin, S. Calleja, A. Bush, G. Calleja, *Adv. Mater.* **2004**, *16*, 1959–1966.
[8] A. Rámilia, B. Muńoz, J. Pérez-Pariente, M. Vallet-Regí, *J. Sol-Gel Sci. Technol.* **2003**, *26*, 1199–1202.
[9] P. Horcajada, A. Rámila, J. Pérez Pariente, M. Vallet-Regí, *Microporous Mesoporous Mater.* **2004**, *68*, 105–109.
[10] J. Andersson, J. Rosenholm, S. Areva, M. Lindén, *Chem. Mater.* **2004**, *16*, 4160–4167.
[11] C. Tourné-Péteih, D. Brunel, S. Bégu, B. Chiche, F. Fajula, D. A. Lerner, J. M. Devoissele, *New J. Chem.* **2003**, *27*, 1415–1418.
[12] A. L. Doadrio, E. M. B. Sousa, J. C. Doadrio, J. Pérez Pariente, I. Izquierdo-Barba, M. Vallet-Regí, *J. Controlled Release* **2004**, *97*, 125–132.

[13] F. Highton, *The Pharmaceutics of Ibuprofen*, in *Ibuprofen. A Critical Bibliographic Review* (Ed.: K. D. Rainsford), Taylor and Francis, London, **1999**, pp. 53.
[14] S. N. Che, A. E. Garcia-Bennett, T. Yokoi, K. Sakamoto, H. Kunieda, O. Terasaki, T. Tatsumi, *Nat. Mater.* **2003**, *2*, 801–805.
[15] S. N. Che, Z. Liu, T. Ohsuna, K. Sakamoto, O. Terasaki, T. Tatsumi, *Nature* **2004**, *429*, 281–284.
[16] E. Alfonso, A. E. Garcia-Bennett, O. Terasaki, S. N. Che, T. Tatsumi, *Chem. Mater.* **2004**, *16*, 813–821.
[17] P. T. Tanev, T. J. Pinnavaia, *Chem. Mater.* **1996**, *8*, 2068–2079.
[18] M. Grün, K. K. Unger, A. Matsumoto, K. Tsutsumi, *Microporous Mesoporous Mater.* **1999**, *27*, 207–216.
[19] A. Matsumoto, K. Tsutsumi, K. Schumacher, K. K. Unger, *Langmuir* **2002**, *18*, 4014–4019.
[20] H. L. Li, A. P. Fu, D. S. Xu, G. L. Guo, L. L. Gui, Y. Q. Tang, *Langmuir* **2002**, *18*, 3198–3202.
[21] A. S. M. Chong, X. S. Zhao, *J. Phys. Chem. B* **2003**, *107*, 12650–12657.
[22] D. W. Sindorf, G. E. Maciel, *J. Am. Chem. Soc.* **1983**, *105*, 3767–3776.
[23] L. Ekkehard, S. Theodor, A. Friedrich, H. A. Mayer, *Angew. Chem. Int. Ed.* **1999**, *38*, 2154–2174.
[24] T. Higuchi, *J. Pharm. Sci.* **1961**, *50*, 874–875.
[25] T. Higuchi, *J. Pharm. Sci.* **1963**, *52*, 1145–1149.

Received: November 19, 2005
Published Online: August 18, 2006

