Hydrophobicity-controlled Drug Delivery System from Organic Modified Mesoporous Silica

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A controlled drug release has been obtained from hybrid organic–inorganic mesoporous silica carriers under in vitro conditions. The control of drug release rate can be ascribed to the incorporation of different hydrophobic functional groups.

The discovery of mesoporous silicas, which possess a well-ordered pore structure with high specific surface areas, high specific pore volumes, and tunable pore sizes, has opened up new possibilities for their use as supports and adsorbents. Recent application of mesoporous silicas in controlled drug delivery has attracted much attention.[1–6] It has been shown that the textural characteristics of mesoporous silicas affect the release rate of the impregnated drugs.[3,4] Some other studies also revealed that the presence of organic functional groups, featured as containing one to three amino, could effectively control the impregnated ibuprofen release rate, due to the ionic interaction between carboxyl groups in ibuprofen and amine groups on mesoporous silica surfaces.[2,5] Moreover, further efforts have been made in developing the special target-drug delivery system controlled by the aid of magnetic field on the condition of entrapping magnetic species in mesostructures.[6] In this work, we have investigated drug delivery profiles from methylsilyl(MS)- or dimethylsilyl-(DMS)- modified mesoporous silicas. In such prodrug systems, obviously controlled drug release was obtained by retarding the process of release fluid penetrating into the mesoporous channels and delaying the process of drug diffusion out the mesoporous channels.

Purely siliceous MCM-41 (labeled as M41) was prepared according to the documented procedure in Ref. 7, except for different method used to remove the template. An ethanol solution of NH_4NO_3 was employed to remove the template according to Ref. 8, and this method was employed for the preparation of the following modified samples. The detailed preparation procedure for modified samples via post-grafting modification was similar to that for the grafting samples in Ref. 7, besides using different amounts of initial compositions. M41-1 was obtained by the addition of the compositions of 4.0 g of as-synthesized MCM-41 (before template removal), 100 mL of dry toluene and 1.95 mL (9.8 mmol) of methyltriethoxysilane (MTES). M41-2 was obtained by the addition of the compositions of 4.0 g of as-synthesized MCM-41, 100 mL of dry toluene and 2.30 mL (13.4 mmol) of diethoxydimethylsilane (DEDMS). Ibuprofen was adsorbed from a hexane solution as reported procedure.[1,3] The adsorption of ibuprofen was evaluated using UV–vis spectroscopy, and the detailed impregnated ibuprofen amounts referred to 1 g of the mesoporous solids were presented as A_t. The ibuprofen release profile was obtained by adding 0.3 g of the drug-impregnated powders in a 200-mL flask containing 100 mL of simulated body fluid (SBF) at 37 °C under continuous stirring (100 rpm). SBF has a composition similar to the human body plasma (pmm: 142.0/5.0/2.5/1.5/147.8/4.2/1.0/0.5 for $Na^+/K^+/Ca^{2+}/Mg^{2+}/Cl^-/HCO_3^-/HPO_4^{2-}/SO_4^{2-}$).

Table 1. Textural parameters of the samples and the impregnated ibuprofen amounts

Sample	D_{BJH} /nm	S_{BET} /$m^2\ g^{-1}$	V_{total} /$cm^3\ g^{-1}$	A_t /$g\ g^{-1}$
M41	3.4	953	0.78	0.29
M41-1	3.3	844	0.70	0.19
M41-2	3.4	860	0.73	0.17

Small-angle XRD of M41 shows a well-resolved pattern with reflections in (100), (110), and (200). This result reveals the successful preparation of the silica MCM-41, which presents a hexagonal mesoporous structures. The XRD patterns of the samples after modification with DMDES or MTES show no loss of structural ordering.

All the samples were further characterized by nitrogen adsorption studies, and the detailed textural chatacteristics are listed in Table 1. The modified samples present the slightly smaller BET surface areas in comparing with that of M41. And as expected, M41-1 and M41-2 possess the similar pore volumes and pore sizes compared to M41. Furthermore, according to the post-grafting modification procedure, it can be presumed that functional groups are mainly placed on the external pore surfaces and pore openings. Indeed, as an example, before the removal of the template for the sample modified using DEDMS, it shows the rather low BET surface area ($63.8\ m^2\ g^{-1}$) and pore volume ($0.06\ cm^3\ g^{-1}$), suggesting that the template keep inactive during the post-grafting procedure in this work. The observation reveals that the silylation reaction takes place on the external pore surfaces and pore openings.

Figure 1 displays the ^{29}Si MAS NMR spectra of the samples. For M41, three resonances appear at −111, −101, and −92 ppm, which could be assigned to the silicon sites of Q^4, Q^3, and Q^2,[9,10] respectively. In the case of M41-1, two new resonances at −64.1 and −55.4 ppm, corresponding to the silicon sites of T^3 [$(CH_3Si(OSi)_3)$] and T^2 [$(CH_3(OH)Si(OSi)_2)$], are detected.[11] The emergence of the T^3 and T^2 peaks and the simultaneous weakened Q^3 and Q^2 signals indicate the successful silylation. M41-2 contains an additional resonance at −16.8 ppm corresponding to D^2 [$(CH_3)_2Si(OSi)_2$], indicating that DMS groups are successfully incorporated onto the mesostructures.[12]

The impregnation results indicate that a maximum of 0.29 g of ibuprofen could be impregnated for 1 g of M41, which is in a good agreement with the adsorbed ibuprofen amount obtained for the comparable mesoporous carrier.[1] In addition, the impregnation experiments have shown that the incorporation of hydrophobic MS or DMS groups prevents the impregnation of ibupro-

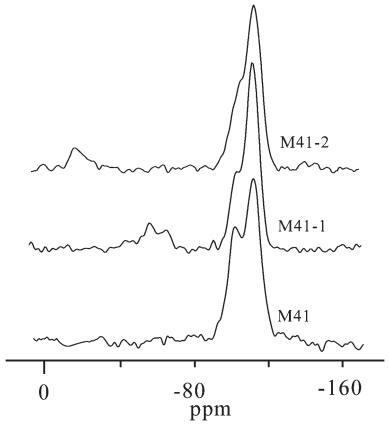

Figure 1. ^{29}Si NMR spectra of M41, M41-1, and M41-2.

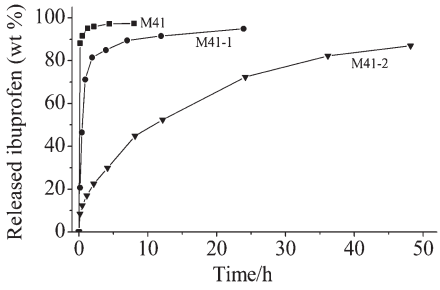

Figure 2. Ibuprofen release profiles from the different carriers.

fen. In comparison with M41, less impregnated ibuprofen amounts of 0.19 and 0.17 g are obtained corresponding to 1 g of M41-1 and M41-2, respectively. It has been shown by the former results[1,3] that the driving force for the inclusion of ibuprofen is the hydrogen-bond interaction between carboxyl groups in ibuprofen and silanols on the mesoporous silica surface. Indeed, for the modified samples, the reduction of the adsorption capacities can be partially ascribed to the decrease of surface silanols in the modified samples. The decrease of surface silanols is because part of surface silanols in M41 acted as anchoring points for organic functional groups.[13] Moreover, it should be noted that the decrease of the adsorption capacities of M41-1 and M41-2 could be linked to the steric hindrance derived from the close-packing of functional groups on the external pore surfaces and pore openings.

The release of the impregnated ibuprofen from M41 is almost completed after about one hour under the release conditions employed here. It should be noted that the drug delivery rate from M41 presented here is much faster than the previous results obtained with the comparable mesoporous matrices, where the ibuprofen delivery equilibrium need tens of hours.[1,4] The great differences would be attributed to the different release conditions, including the powder or disk of the ibuprofen-impregnated mesostructure and the release system investigated with or without stirring.

Figure 2 indicates that the modified samples show slower drug release rates than that of M41. The difference in the drug release rates between modified and unmodified samples would be attributed to the hydrophobic effect derived from the DMS and MS groups incorporated on the surface of mesopores. The release of the impregnated drug from the mesostructures occurs as follows: The release fluid penetrates into the drug-matrix phase through pores; then followed by the drug dissolve into the release fluid and diffuse from the system along the solvent-filled pore channels. Therefore, for the modified samples, the incorporated hydrophobic groups retard the penetration and diffusion processes mentioned at the above sentence. Moreover, it has been shown that the functional MS and DMS are placed on the external pore surfaces and pore openings, which are the first inevitable gateway for release fluid penetrating into the mesopores to take out the impregnated drug. Consequently, delayed ibuprofen release has been obtained from the hydrophobically modified samples.

On the other hand, the release rate of impregnated ibuprofen from M41-2 is observed to be slower than that from M41-1, which may be related to the fact that different hydrophobic groups of MS and DMS attached on the external pore surfaces and pore openings. Moreover, the molar ratio (14.9%) of $(\Sigma T^n)/[\Sigma(T^n) + \Sigma(Q^n)]$ in M41-1 is higher than that (8.2%) of $(D^2)/[(D^2) + \Sigma(Q^n)]$ in M41-2, which allows the quantitative assessment of the modification levels with DMS or MS in corresponding materials, confirming that DMS modification is more effective than MS modification in delayed ibuprofen release.

Therefore, it can be obtained that controlled drug release can be obtained by the modification of mesoporous silicas with different species of hydrophobic functional groups of MS and DMS.

This work was supported by the National Native Science Foundation (Grant Nos. 20133040 and 20573128).

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Published on the web (Advance View) April 1, 2006; DOI: 10.1246/cl.2006.474