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Confinement and Controlled Release of Bisphosphonates on Ordered Mesoporous Silica-Based Materials

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In modern societies, the development in science and medicine has resulted in an increase of life expectancy, which leads to an aging population and, subsequently, an increase in the incidence in bone diseases. This fact has raised a general concern about bone diseases, which has led to declare this decade as the "Bone and Joint Decade" in the USA. The current tendency in this area has shifted from tissue replacement to tissue regeneration.[1]

Today, one of the bone diseases with a major impact is osteoporosis, in which bones become fragile and are more likely to break. Within the several research efforts from the scientific community to find solutions to this disease, bisphosphonates are a family of drugs that inhibit bone resorption by osteoclasts. Bisphosphonates are analogues of pyrophosphates, with nonhydrolyzable P−C−P groups rather than P−O−P, which makes them resistant to hydrolysis and therefore showing a poor intestinal absorption, typically less than 1%.[2] They can also be useful to facilitate the regeneration of skeletal parts when it is needed for bone defects. Nowadays, bisphosphonates are orally administrated with the drawback of the very low adsorption. The possibility of using siliceous ordered mesoporous materials[3] for controlled delivery systems has been reported for a wide range of drugs.[4] The possibility of combining bisphosphonates with these systems seems to be very attractive. The confinement of bisphosphonates in the pores of silica-based ordered mesoporous materials for a local and controlled drug delivery would be a novel application for this kind of systems, useful for repairing bone defects and presumably showing a better adsorption behavior. Moreover, and enhancing this new application, silica-based ordered mesoporous materials have been found to induce apatite formation in physiological fluids,[5] opening the gates to new possibilities in tissue engineering. This feature together with the possibility of confining bisphosphonates in the pores suggests novel expectancies in bone tissue repairing and regeneration, which was the aim of this work.

Two types of hexagonal ordered mesoporous materials, MCM41 (D_P = 3.8 nm) and SBA15 (D_P = 9.0 nm), were used as matrices for alendronate (bisphosphonate) adsorption and release (Figure 1).[6] In both systems, the surfaces of the pore walls were organically modified with amine groups.[7] The amine functionalization was confirmed by FTIR, N_2 adsorption, and elemental analysis (see Supporting Information). XRD patterns ensured that the ordered mesoporous framework of the materials was unaffected by the modification conditions (Figure 2a). However, the total pore volume and diameter were considerably decreased, ca. 60% for MCM41 and ca. 40% for SBA15, as a consequence of the grafting of $PrNH_2$ to the pore walls in the modification process (Figure 2b).

After 24 h in an aqueous alendronate solution, the amine-modified materials showed a drug loading almost 3 times larger than that of the unmodified materials (Figure 3a). This different behavior could be explained by the different chemical interaction between the phosphonate groups in alendronate with the silanol groups in the case of unmodified materials and with the amine groups covering the surface of the mesopore walls of the modified materials.[8] In the loading conditions, at pH 4.8, the interaction between silanol in the substrate and phosphonate of the adsorbed drug is weaker than that of the amine to phosphonate. This leads

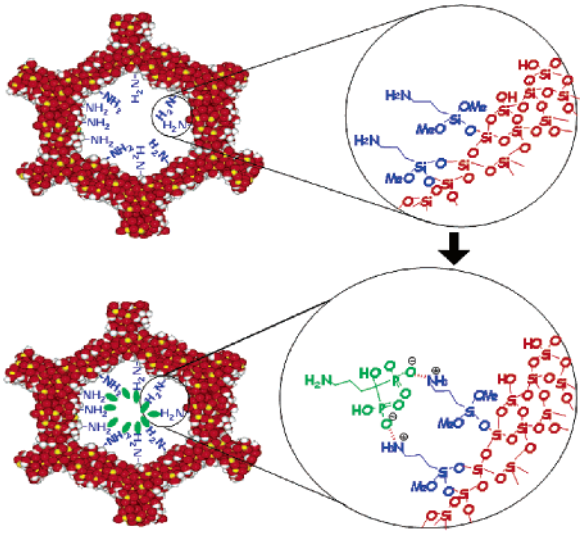

Figure 1. Alendronate adsorption on hexagonally ordered mesoporous silica functionalized with propylamine groups.

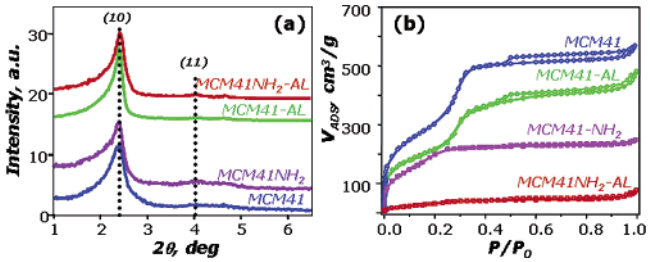

Figure 2. (a) XRD patterns of MCM41 materials before and after amine modification and further alendronate adsorption. (b) N_2 adsorption isotherms of MCM41 materials before and after amine functionalization and further bisphosphonate adsorption.

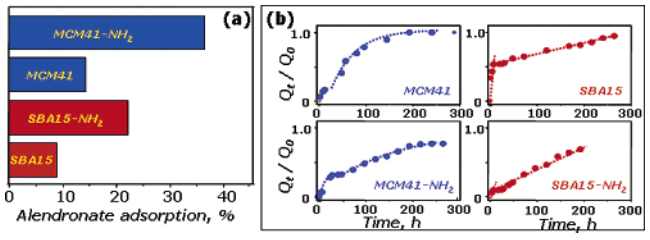

Figure 3. (a) Maximum load of alendronate in ordered mesoporous materials. (b) Release profiles of alendronate from the pure siliceous and amino-modified ordered mesoporous materials.

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to an adsorption of alendronate molecules when the materials are amine-modified, 22% in SBA15-NH_2 and 37% in MCM41-NH_2, that is greater than that when their surface remains unmodified, 8% in SBA15 and 14% in MCM41.

Loading on the mesoporous matrices was performed mainly in the inner surface of pores without affecting the hexagonal order of the mesopore channels on both materials, as it was confirmed by XRD (Figure 2a). Spacing of the main reflections attributed to the hexagonal *p*6*mm* symmetry group remained unaltered after both the surface modification with $PrNH_2$ chains and further alendronate adsorption in MCM41 and SBA15 materials. Bisphosphonate drug loading reduces the available inner surface of mesopores in materials (Figure 2b) as well as the volume of the primary mesopores, those produced by the template. The mesopore sizes, corrected using the KJS procedure,[9] show similar behavior, and both the silica surface modification and bisphosphonate adsorption reduce the mesopore widths according to the length of the $PrNH_2$ chains (ca. 0.82 nm) and that of the alendronate molecule (ca. 0.87 nm). The decrease of the pore size is more significant for SBA15, where amino-modified substrate shows a pore width 1.5 nm smaller than that of the raw material, almost twice the size of every $PrNH_2$ chain. For MCM41, the decrease in pore sizes is less noticeable (ca. 1.1 nm), which is attributed to some rearrangement of $Pr-NH_2$ groups in small mesopores. When both pure silica and modified materials are loaded with alendronate, the pore sizes are also noticeably reduced in an amount that is related to the total of adsorbed alendronate in every material. For high-loading materials, such as MCM41-NH_2, the initial pore width reduces to the micropore range which points out to an almost total occlusion of the pore entrance due to the adsorbed drug. Likewise, it could be observed that, as the pore size decreases from unmodified SBA15 to modified MCM41, the reduction on the pore diameter due to $PrNH_2$ grafting and sodium alendronate loading also decreases.

The interaction between surface and alendronate changes when materials are placed at pH 7.4 for testing the release mechanism. The differences in the polarity between the silica surface and the bisphosphonate, or between the $PrNH_2$-covered surface and bisphosphonate, induce the weakening of the adsorbed molecules, and the latter are slowly released to the media. Different release kinetics can be found for the mesoporous matrices as a function of both their surface areas and mesopore sizes. For current applications, it is assumed that the alendronate release mechanism is due to diffusive transport through the ordered array of mesopores since the silica matrix is virtually insoluble at pH 7.4. In materials with high surface areas and small mesopores, the diffusion of bisphosphonate molecules to the liquid media is a surface-dependent phenomenon that can be predicted by a first-order kinetics[10] (Figure 3b). It is worth mentioning the deviation from the exponential decay behavior of the bisphosphonate delivery from amino-functionalized MCM41. In this case, the decrease on the mesopore surface area due to functionalization as well as the partial surface dissolution of the amino-modified silica matrix after long periods in the release medium may involve slight changes in the release mechanism to different diffusion processes or even a dissolution−diffusion process.

When the mesoporous silica shows smaller surface area and larger mesopore size than in the previous case, the solvent accessible area does not significantly change along the release period and no equilibrium conditions are achieved. Therefore, the diffusive behavior of the adsorbed molecule through the mesopores can be calculated using a zero-order or lineal model[10] (Figure 3b). It has to be noted that alendronate concentration in the media increases very fast in the initial testing time due to the release of the molecules adsorbed in the outer surface of silica matrices. This burst effect has been taken into account in the kinetic analysis of bisphosphonate desorption in the tested environment. It can be noted that the previously mentioned electrostatic host−guest interaction induces the partial retention of bisphosphonate on the silica walls surrounding the ordered array of mesopores. The presence of microporous connection between adjacent mesopore channels[11] may also account for the partial drug retaining.

In conclusion, bisphosphonates, well-known drugs for inhibiting bone resorption interfering with the action of osteoclasts, have been loaded in siliceous ordered mesoporous materials in an effort to design a controlled drug delivery system to be used for repairing bone defects. Up to date, bisphosphonates have been introduced in the body through oral ingestion, with the drawback of a very poor intestinal absorption. With the system presented here, the drug intake rate can be increased from 1% up to a 40% of bisphosphonate. Moreover, the possibility to use alendronate-loaded mesoporous silica to manufacture implants for bone defect repairing/regeneration represents an added value. This novel feature is important from the point of view of avoiding a drug overdose on the whole body. The amount and delivery rate of bisphosphonate can be modulated through an organic modification on the surface of the pore walls present in the investigated mesoporous materials. When amine groups are being covalently grafted to the silanol groups on the pore surfaces, the bisphosphonate adsorption is increased almost 3-fold, with the subsequent intensification of the drug dosage in the required area.

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Supporting Information Available: Material synthesis and amine functionalization. Additional FTIR, XRD, and N_2 adsorption data. Procedure details for the adsorption and release of alendronate. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Hench, L. L.; Polar, J. M. *Science* **2002**, *295*, 1014−1017.
(2) (a) Russell, R. G. G.; Rogers, M. J. *Bone* **1999**, *25*, 97−106. (b) Erza, A.; Golomb, G. *Adv. Drug Delivery Rev.* **2000**, *42*, 175−195.
(3) (a) Kresge, C. T.; Leonowicz, M. E.; Roth, W. J.; Vartulli, J. C.; Beck, J. S. *Nature* **1992**, *359*, 710−712. (b) Inagaki, S.; Fukushima, Y.; Kuroda, K. *J. Chem. Soc., Chem. Commun.* **1993**, 680−681. (c) Zhao, D. Y.; Feng, J. L.; Huo, Q. S.; Melosh, N.; Fredricksson, G. H.; Chmelka, B. F.; Stucky, G. D. *Science* **1998**, *279*, 548−552. (d) Corma, A. *Chem. Rev.* **1997**, *97*, 2373−2420.
(4) (a) Vallet-Regí, M.; Rámila, A.; del Real, R. P.; Pérez-Pariente, J. *Chem. Mater.* **2001**, *13*, 308−311. (b) Hartmann, M. *Chem. Mater.* **2005**, *17*, 4577−4593.
(5) Vallet-Regí, M.; Ruiz-González, L.; Izquierdo-Barba, I.; González-Calbet, J. M. *J. Mater. Chem.* **2005**, *15*, 1−7.
(6) Thomas, J. M.; Johnson, B. F. G.; Raja, R.; Samkar, G.; Midgley, P. A. *Acc. Chem. Res.* **2003**, *36*, 20−30.
(7) Chong, A. S. M.; Zhao, X. S. *J. Phys. Chem. B* **2003**, *107*, 12650−12657.
(8) Walcarius, A.; Etienne, M.; Lebeau, B. *Chem. Mater.* **2003**, *15*, 2161−2173.
(9) Kruk, M.; Jaroniec, M.; Sayari, A. *Chem. Mater.* **1999**, *11*, 492−500.
(10) (a) Crank, J. *The Mathematics of Diffusion*, 2nd ed.; Oxford University Press: Oxford, 1975. (b) Costa, P.; Sousa-Lobo, J. M. *Eur. J. Pharm. Sci.* **2001**, *13*, 123−133.
(11) Impéror-Clerc, M.; Davidson, P.; Davidson, A. *J. Am. Chem. Soc.* **2000**, *122*, 11925−11933.

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