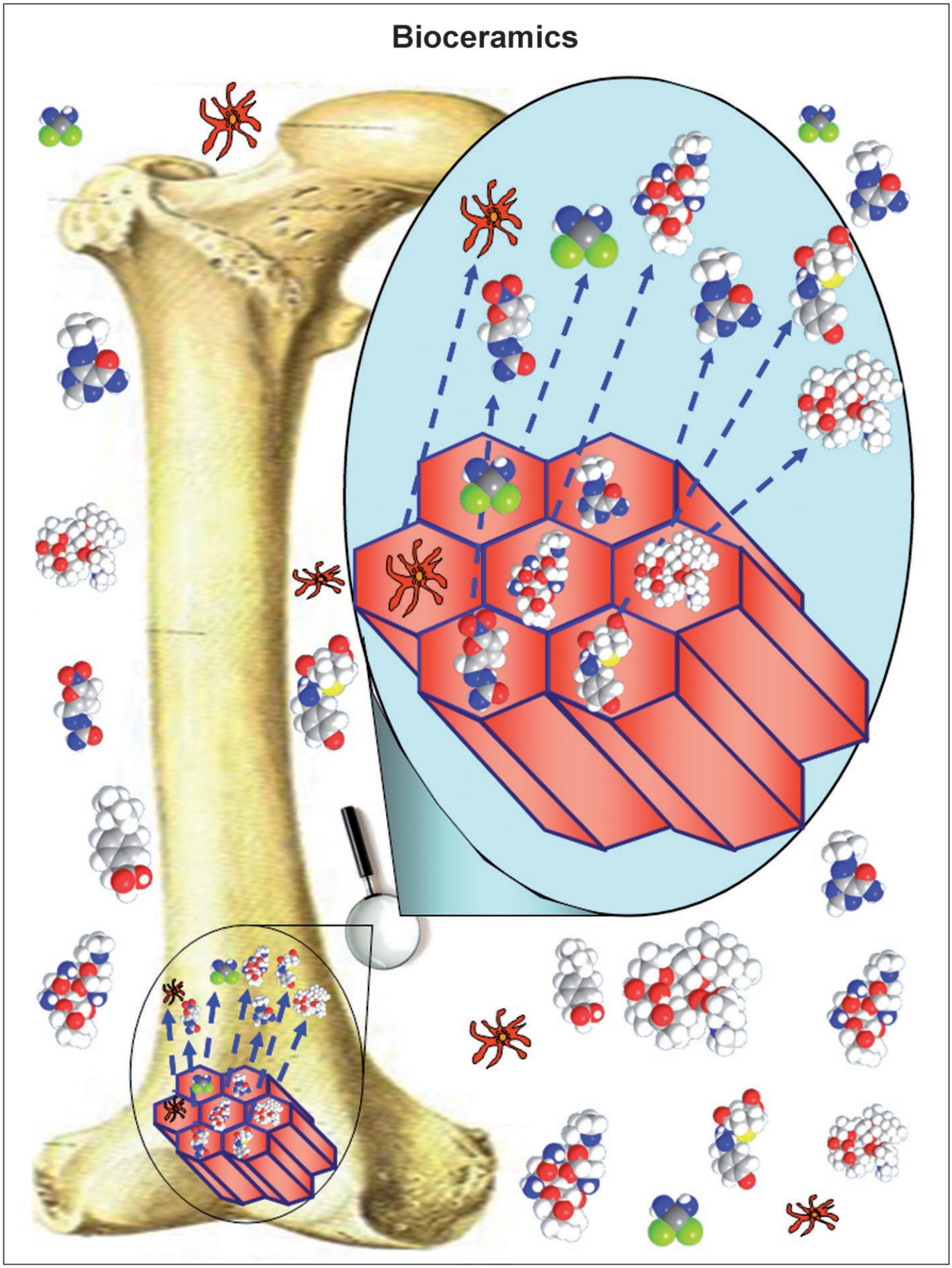
Bioceramics



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Ordered Mesoporous Materials in the Context of Drug Delivery Systems and Bone Tissue Engineering

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Abstract: Chemistry, materials science and medicine are research areas that converge in the field of drug delivery systems and tissue engineering. This paper tries to introduce an example of such an interaction, aimed at solving health issues within the world of biomaterials. Ordered mesoporous materials can be loaded with different organic molecules that would be released afterwards, in a controlled fashion, inside a living body. These materials can also react with the body fluids giving rise to carbonated nanoapatite particles as the products of such a chemical interaction; these particles, equivalent to biological apatites, enable the regeneration of bone tissue.

Keywords: bioceramics · bone tissue regeneration · drug delivery · mesoporous materials

Introduction

The production of nanostructured materials that resemble the complex hierarchical structures of natural hard tissues present in bones and teeth is an extremely attractive field of research, in which remarkable results are beginning to appear. The ability to functionalise nanostructured ceramic surfaces with different molecules, of varying nature and size, grafted to the substrate, allows selective action upon the biological species on a medium term.

The development of drug release systems has experienced a remarkable growth and is now an important market for the industrial sector.[1] Several matrices have been tested so far, such as organic polymers, organic–inorganic hybrid materials, and bioactive glasses and ceramics.[2–4] A pivotal concern in medicine is always to deliver the pharmaceutical product to the patient by using the optimum route from a physiological point of view. Generally speaking, the smaller the size of the drug and the encapsulating material, the better is the absorption of the drug in the body.

Nowadays, the most popular routes for drug intake are oral administration and injection. However, these methods show a lack of efficiency for certain therapies. There are also new therapeutic agents that require new delivery systems, such as unstable or very poorly soluble drugs, proteins or nucleic acids. Among the several innovative approaches applied to these problems, nanotechnology offers the opportunity to investigate materials and their structure at the nanoscale range. Nanotechnology represents a new field of research and includes a wide range of technologies and potential applications. For instance, cell machineries use self-assembly of biological molecules leading to nano-objects that are able continuously be ordered and then return to disorder continuously at the subcellular level. As this example shows, the innovations in the fields of matter and devices are still promising. The development of new drug delivery systems based on these principles requires multidisciplinary inputs. As a brief definition, nanotechnology means to work at the nanoscale under controlled conditions. One approach consists on designing of nano-sized drug delivery systems, using excipients such as polymers, surfactants or lipids. These systems, which can take the final form of, for example, liposomes, nanospheres or nanocapsules, are largely described in the literature and some are already available in the market or under clinical investigations. The other approach consists on obtaining new materials that are structured at the nanoscale. Such materials could be available under different final shapes or morphologies, such as microspheres, monoliths, and so forth.[5] The preparation can be based on diverse methods or mechanisms, following for instance self-assembly or soft chemistry routes. It can be performed in gas or liquid form, but whatever the mechanism is, it requires a precise control of the structuring of the components to obtain a 2D or 3D organisation of the matter.

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New functionalities of the materials so obtained can also be tailored through the properties of the excipients used and also by controlling their nanostructure, leading to different delivery patterns, such as sustained or triggered release and/or targeting. Most applications of these technologies concern the areas of tissue engineering, cancer therapy, cardiovascular and infectious diseases, vaccines and imaging.

Since 1991, when Mobil Oil Corporation synthesised the silica-based MCM-41, highly ordered mesoporous materials have attracted the attention of many scientists, mainly due to their potential technological applications.[6–8] Mesoporous materials are characterised by their large surface area, pore volume and pore size, with a narrow pore diameter distribution. For this reason, applications in the fields of catalysis, lasers, sensors, solar cells and so forth have been proposed and/or developed.

Recently, these materials have been proposed for their application in biomaterials science. Due to the outstanding features of surface and porosity, ordered mesoporous materials have shown to be excellent candidates for two biomedical applications: 1) local drug delivery systems and 2) bone tissue regeneration. In fact silica-based mesoporous materials are able to incorporate high dosages of drugs into the mesopores.[9] Moreover, their silanol-containing surface can be functionalised, allowing a better control over the drug release, which depends on the chemical nature of the functional group attached to the surface.[10]

On the other hand, mesoporous materials can be synthesised with similar chemical composition to that of highly bioactive sol–gel glasses. When implanted, bioactive glasses are able to bond to living bone through the formation of a nanometre-sized nonstoichiometric carbonated apatite (CHA).[11–12] This bioactive bond ensures that the implant osteo-integration and its degradation products promote the bone tissue regeneration. Increasing the specific surface and pore volume of bioactive glasses greatly accelerate the CHA formation and therefore enhance the bioactive behaviour. In this sense, highly ordered mesoporous materials provide very promising possibilities in the field of bone tissue regeneration. Moreover, these materials can be loaded with osteogenic agents promoting the new bone formation in vivo and can be also applied as scaffolds for bone tissue engineering.

Drug Delivery Systems

The research on confinement of drug delivery systems in bioceramic matrices presents two distinct sides; one route aims at embedding pharmaceuticals in biomaterials designed for the reconstruction or regeneration of living tissues, in order to counteract inflammatory responses, infections, bone carcinomas and so forth, while the other route deals with their more traditional drug introduction system, that is, oral administration.

The incorporation of pharmaceuticals to bioceramic matrices could be very interesting in clinical practice. It is common these days for an orthopaedic surgeon working in bone reconstruction to use bioceramics in granulated form, or with predefined shapes, in either porous[13] or dense[14] pieces (Figure 1). The demand for bioceramics in injectable

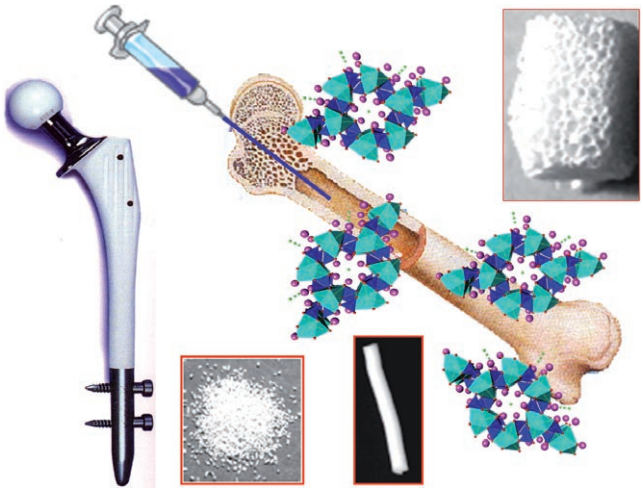

Figure 1. Different bioceramics types employed in bone substitution or regeneration, showed as grains, dense pieces, porous pieces, injectables and thin films.

form is also increasing,[15] since it greatly simplifies the surgical practice, and can even be reclassified as noninvasive. Finally, for those applications that require certain mechanical properties as in the case of metals and alloys, the trend is to coat the metallic prostheses with a ceramic layer[16] to achieve a better and faster osseointegration as well as to reduce the release of ions from the implant alloy to the living body; this procedure also brings a more satisfactory attachment of the prosthesis to the host due to the excellent biological properties of the ceramic, such as atoxicity, lack of inflammatory response and absence of fibrous and immunitary reactions. An added value to the production of these ceramics would be the optional addition of pharmaceuticals such as antibiotics, antiinflammatories, anticarcinogens, and so forth. In this sense, if we take into account the statistics on infections at hip-joint prostheses, the incidence varies between 2 and 4%, reaching up to a 45% in bolts used as external fixation. One of the main problems in these situations is the access to the infected area of the bone, in order to deliver the adequate antibiotic. If the pharmaceutical could be included in the implant itself, the added value would be straightforward.

The controlled drug delivery from polymer matrices has been a widely used and applied tool,[17–19] but what is useful and adequate in oral administration might not be the best option for drug release systems from implants designed for bone regeneration. This is the reason why it is necessary to study in depth the research field of drug inclusion in ceramic matrices, trying to solve first of all a very important issue:

how to proceed with the loading mechanism without using temperature. A thermal treatment is the most common and easy route followed in the world of ceramics, but it is extremely inconvenient when dealing with molecules of pharmaceutical species, which exhibit very low decomposition temperatures.

If we turn back now into the matrices made exclusively from ceramic materials, there is a wide range of options available (Table 1), and radically different drug molecules can be confined in different matrices. What is more, the matrices can accept not only drugs, but also substances that can induce fast bone-growth kinetics, such as certain peptides, proteins and growth factors.

Table 1. Ceramic–drug matrix.

Ceramic matrix	Type of drug
calcium phosphates	antibiotics
bioactive glasses	antitumorals
calcium salt cements	anti-inflammatories
biphasic materials	growth factors
bioactive hybrid materials	peptides
zeolites and/or mesoporous materials	proteins

It is feasible to obtain open textures in ceramic matrices with large specific surfaces and high degrees of porosity. These structures can be achieved in traditional ceramics such as phosphates, glasses, cements or in any of their biphasic combinations, by using adequate procedures[13] or by synthesising ordered mesoporous materials with an ordered distribution of channels and cavities with different geometries. In such materials the scaffold is exclusively made of silica, with a large pore volume in the range of mesopores (with pore diameters of $2\,\text{nm} < D_p < 50\,\text{nm}$), and with a very homogeneous and controllable size within a relatively wide range.[6]

Any of these ceramics that exhibit many pores with an adequate size, which can host the molecules of the drug, are good candidates for designing a controlled drug delivery system. First of all, the drug has to fill the empty pores of the ceramic matrix; in a second stage, the controlled release will take place from these occupied pores. Hence, the first step consists of the pore design in the ceramic material, with an adequate control over their number, size, shape, distribution, connectivity and potential functionalisation of their walls, depending on the drug to be introduced. The dimensions of the drug molecules that might be of interest in clinical applications for implants are in the range of one nanometre (Figure 2). Therefore, any material with a pore diameter larger than one nanometre should easily host these molecules. Occasionally, these materials exhibit a very inconvenient heterogeneity between different samples, due to the lack of homogeneity in the distribution at molecular level of the drugs to be encapsulated.

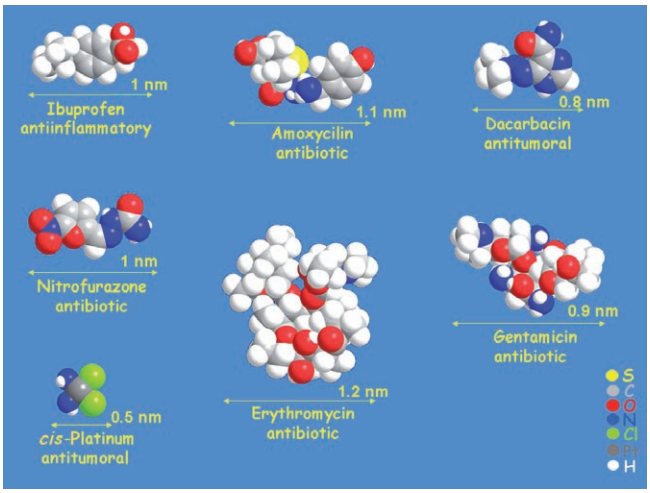

Figure 2. Molecules of several drugs with their sizes.

Ordered Mesoporous Materials as Matrices for Delivery Systems

The porosity of a ceramic matrix can be ordered or disordered. It is clear that a well-ordered pore distribution in a ceramic matrix favours the homogeneity of the adsorption and release stages; thus, ordered silica mesoporous materials are potentially excellent candidates and can play a significant role in the field of controlled drug delivery systems. This fact was evidenced for the first time by the confinement of ibuprofen in two MCM-41 matrices with different pore diameters (1.9 and 2.5 nm).[9] The weight percentage of ibuprofen in MCM-41 reached a value of about 30%; the drug was released from the MCM-41 matrix by immersion of the delivery system in a simulated body fluid. Working under optimum conditions, the full amount of ibuprofen loaded in the MCM-41 matrix was released to the external medium within three days.

The pore morphology and clearance determine the type of molecules that can fit into it and, therefore, those that are eligible for the adsorption process; however, the maximum amount accepted depends on the pore volume, which is generally described in terms of $\text{cm}^3\,\text{g}^{-1}$ of material. In systems that only contain mesopores, the total pore volume is evidently equal to the mesopore total volume, but this is not generally the case. Frequently, there are also micropores or even macropores (pores with diameter larger than 50 nm) present; this last type of pore is usually associated to interparticle porosity, and its contribution to the total pore volume increases with a decreasing particle size in the material. Undoubtedly, the specific surface is a parameter that influences the adsorption properties of the material, since it is a surface phenomenon itself. The concept of surface encompasses not only the outer surface of the material, but also the inner surface of its cavities and channels, provided that the nitrogen-based molecules used in these measurements can pass freely through these inner areas.

It seems reasonable to believe that the pore size must affect the amount of drug readily adsorbed. When comparing MCM-41 type mesoporous materials with different pore diameters (2.5, 1.9, 1.6, 1.5 nm), the amount of ibuprofen adsorbed depends on the matrix pore size, hence allowing the regulation of the amount of drug introduced. Besides, the release rate is directly proportional to the pore size, and it is feasible to predict such rates[20] (Figure 3).

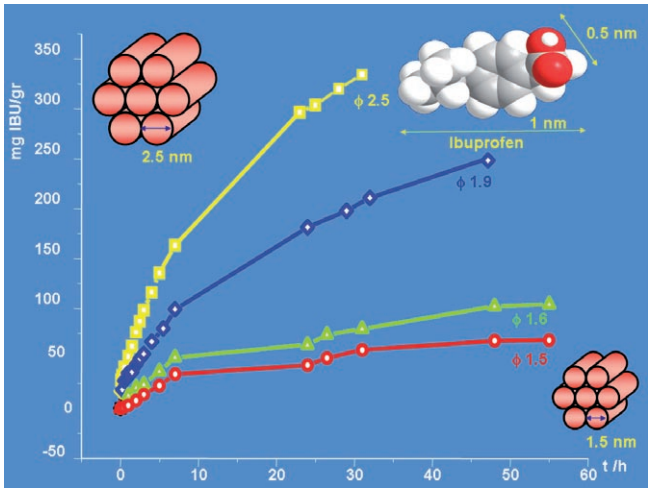

Figure 3. Release patterns of adsorbed ibuprofen in MCM-41 matrices with four different pore sizes.

However, the adsorption and subsequent release of a drug does not depend on the design of the matrix porosity alone. Once the pharmaceutical molecule to be loaded has been chosen, it is required to calculate the ratio between the matrix pore size and the drug molecule size, to study the drug solubility and its interaction with the pore wall. This last aspect is crucial in order to adjust the drug release to the desired kinetics for the specific application.[21] Figure 4 shows the different amounts of ibuprofen loaded in four MCM-41 matrices with different pore sizes, as well as the release times required. The amount of drug loaded in the porous matrix depends greatly on the solvent used, the pH value during the process and the drug concentration in the solution.[22] Also, the drug release rate will depend on whether the experiment is carried out with the material in powder form or shaped as dense pieces; the release rate will always be higher from powder than from disk-shaped pieces, for instance.[21]

The cubic mesoporous structures with *Ia3d* symmetry, such as MCM-48 and large-pore *Ia3d* material (LP-*Ia3d*), which have different pore sizes (3.6 and 5.7 nm, respectively), are also suitable matrices for the adsorption and in vitro release of ibuprofen, erythromycin and other drugs. It has been found that the release becomes slower as the pore size of the matrix decreases or the molecular size of the drug increases.[23]

Another point to be considered is the matrix structure. Although all mesoporous materials are apparently very diverse, their structural types, in terms of channel and cavity topology, are very few; we can distinguish three large groups: 1) MCM-41[24] or SBA-15[25] both with unidirectional pores and, in the case of SBA-15, sometimes with a secondary micropore system that interconnect the hexagonal channels; 2) MCM-48[26] from the M41S family, which exhibits a three-dimensional pore system, formed by intersected longitudinal pores along the three directions in space; and 3) structures with a porous system basically formed by pseudospherical cavities interconnected by different pore configurations, which could be essentially described as short channels or even "windows" between cavities, with diameters similar to those of micropores.[27]

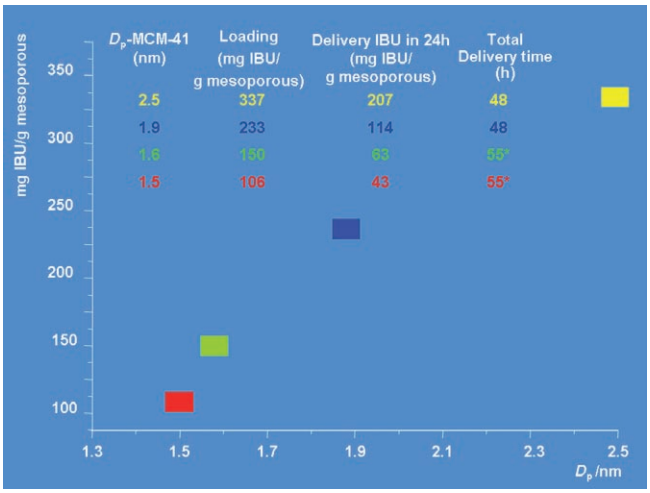

Figure 4. Plot of the maximum load of ibuprofen in four MCM-41 matrices with different pore sizes. The inset table provides data of the ibuprofen load that can be host in every of four matrices together with their release periods. Asterisk (*) indicates incomplete delivery.

Although it also seems logical to believe that the structure must influence the drug adsorption and release in these materials, in which the interconnected pores should at least theoretically facilitate the displacement of molecules if compared with nonconnected, longitudinal pores, the truth is that the effect of these interconnections is rather weak, according to the studies performed.[28]

The pore walls in ceramic matrices can be functionalised with a wide range of chemical species in order to modify their adsorption properties. These features make them suitable to host different pharmaceutical species and to release them in a sustained regime to the external medium, for long time periods, under appropriate conditions. Therefore, the functionalisation of the ceramic walls is another important aspect to consider in these systems. The walls of the glassy matrices of ordered mesoporous materials of silicon oxide contain large amounts of silanol groups, which perhaps could facilitate certain interactions, for example, between the OH group of silanol and the COOH group in ibuprofen (Figure 5). These interactions can be chemically modified, through the adequate functionalisation of the matrix walls; a precise functionalisation performed on the pore walls could enable the control of the adsorption and release rates

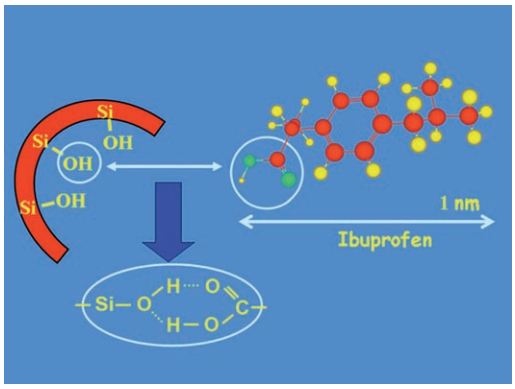

Figure 5. Interaction of OH group in the silanol at the pore wall of silica mesoporous material with the COOH group in the ibuprofen molecule.

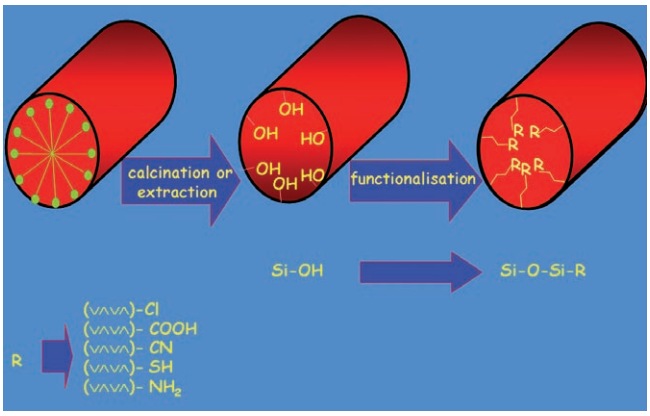

Figure 6. Simplified scheme of the pore wall functionalisation in a silica mesoporous material.

of a given drug. Such intervention requires structural modifications that can be carried out by different methods, using both in situ[29] and ex situ[30–31] techniques to modify the terminal groups on the mesoporous material pore walls, selecting those groups which are better suited for each type of drug.

Presence of Silanol Groups

The lack of order in the space configuration of the tetrahedral lattice that forms the inorganic scaffold is revealed by a very large amount of connectivity defects, that is, not all the tetrahedrons are connected to another four tetrahedrons sharing oxygen atoms. If an oxygen atom positioned at a tetrahedron corner is not shared with a neighbouring tetrahedron, a silanol group is formed. The presence of large amounts of connectivity defects in mesoporous materials is a direct consequence of their formation mechanism. The interaction between the tensoactive agent and the silicate oligomers in dissolution takes place through the silanol groups Si–OH or through the corresponding anion, $Si–O^-$. The concentration of Si–OH groups in the material after eliminating the tensoactive agent depends also on the method chosen for this removal. Usually, calcination reduces the concentration of defects, since it promotes the condensation of Si–OH groups, in particular those that share hydrogen bonds. On the other hand, the solvent extraction of the tensoactive agent does not modify significantly the amount of silanol groups.

The Si–OH groups exert a remarkable influence on the properties of the material. Generally, their affinity for polar molecules increases with the silanol concentration, but these groups can also react with a large variety of chemical products yielding covalent bonds of the Si-O-R type. This fact allows to attach or anchor different chemical species on the material surface, that is, to functionalise their surface (Figure 6).

Functionalisation of the Pore Wall

The structure of the mesoporous materials exhibits a very high incidence of structural defects, in form of silanol groups.[32] If the H atom in silanol is replaced by chemical species R, which can be linked to the oxygen atom by a covalent bond, a whole family of hybrid materials can be obtained in which the chemical composition of the R group differs from the inorganic scaffold. The most common cases are those in which R is an organic functional group, that is, chemical species of the type of Si-O-Si-R. Besides, this organic group may contain one or more reactive atoms, which can in turn be chemically modified, as depicted in Figure 7.

The functional groups can be attached or anchored to the scaffold of the mesoporous material during the material synthesis, in a one-pot method, but also during a later post-synthesis stage. The main difference between both methods is the addition stage of the functionalising precursor In the former the alcoxy groups are hydrolysed and condensed with the silica scaffold precursors, which are usually also silicon alkoxydes; in the latter, the condensation reaction takes place between the functionalising precursor and the silanol groups present in the pore walls. In one-pot methods the organic groups R are linked to silicon atoms in the walls and to the inner part of the silica wall; therefore the functionalisation degree is reduced. Post-synthesis methods ensures that the modifying agents are in the outer surface of the pores, leading to a larger functionalisation degree.[33]

It has been shown the feasibility of controlling the delivery rate of drugs occluded in MCM-41 matrices by functionalising the pore wall with silane derivatives. In the case of ibuprofen, which contains an acid group, the functionalisation of well-ordered MCM-41 matrices with aminopropyl moieties lead to a decrease in the delivery rate (Table 2). For ibuprofen loads in the same order of magnitude, the release time is almost five times higher for the functionalised sample. It has been shown that the functionalisation procedure is important for both the adsorption of the drug and its release profile, which is also affected by the pore-filling

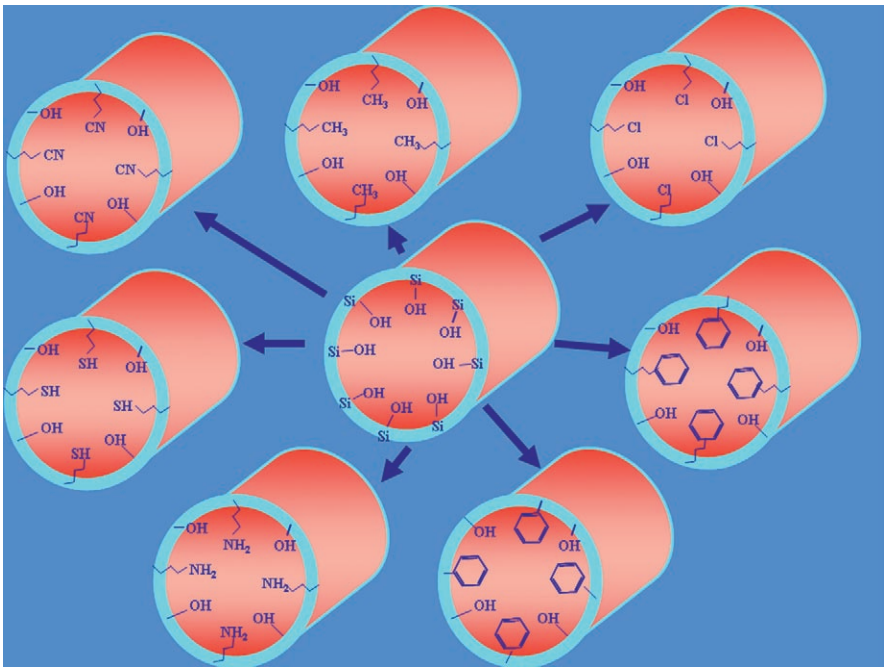

Figure 7. The pore wall functionalisation in a silica mesoporous material is produced through the reaction Si-OH + X_3Si-R-Y → Si-O-SiX_{3-n}-R-Y + nHX, in which X = halogen atom, usually Cl, or an alkoxy group such as ethoxy or methoxy; R = alkyl chain; Y = OH, SH, NH_2, SO_3H, Cl, F, CH_3, Ph, etc. In the figure, the organic chain radicals have been simplified for the sake of image clarity.

Table 2. Decrease of pore diameter and release rate of ibuprofen from MCM-41 functionalised with aminopropyl, compared with MCM-41.

	D_p [nm]	Ibuprofen load [mg g^{-1}]	total release time [h]
MCM-41	2.5	337	48
MCM-41 functionalised with aminopropyl	1.7	270	213

degree of the hybrid organic/inorganic matrix by ibuprofen.[33,34]

Ibuprofen molecules adsorbed in MCM-41 silica with and without amino group functionalisation have been characterised by ^{13}C NMR spectroscopy. They exhibit a completely different behaviour in both silica matrices. The ^{13}C MAS single-pulse or cross-polarisation NMR spectra, as well as the ^{1}H MAS NMR spectra show an extremely high mobility of the ibuprofen molecules when the matrix is not modified. It suggests the absence of any interactions between the ibuprofen molecules and the silica surface, despite the presence of a COOH function. This might be explained by the association of ibuprofen molecules by the carboxylic functions into cyclic hydrogen-bonded dimmers. Such dimers are indeed present in the crystallographic structure of the crystalline *S*-ibuprofen isomer.[35] In contrast, when the silica matrix is functionalised by amino groups, the ^{13}C NMR experiments indicated a more restricted mobility of the ibuprofen molecules, suggesting possible interactions between the amino groups and the carboxylic groups. Similar behaviour was found for encapsulated benzoic acid, and this opens the possibility to develop heteronuclear correlation NMR methods (e.g., ^{29}Si,^{13}C) through using ^{13}C-labeled benzoic acid to better characterise the possible interactions of the encapsulated molecules with silica surfaces with and without modification.[36–37]

The surface of MCM-41 material has been modified by reaction with the organosilanes Cl-Pr, NH_2-Pr, Ph, Bz, SH-Pr, CN-Pr and Bu. This modification allows the selection of the appropriate group depending on the drug and its application. In the case of ibuprofen, which has an acid group, different drug adsorption and delivery rates have been found depending on the functional groups. Thus, MCM-41 modified with polar groups show higher ibuprofen adsorption than that with nonpolar groups. Besides, the ibuprofen release is slowed down with SH-Pr and NH_2-Pr groups. This study evidenced the possibility to design the matrices, according to the functional groups of the pharmacological molecule which will be inserted, allowing to choose the dosage and the release kinetics.[10]

An effective control of the release rate of the macrolide antibiotic erythromycin has been also achieved by modification the surface of SBA-15 with hydrophobic long-chain hydrocarbon moieties of different lengths. For the sample containing the largest amount of $-CH_2-$ groups, the release rate decreases by a factor of nearly one order of magnitude compared to that of unfunctionalised SBA-15.[38]

The polarity of the surface of the SBA-15 material has been modified by anchoring hydrophobic long-chain hydrocarbons (C_{18}) on the surface. This treatment decreases the interaction of ibuprofen with the modified surface, which results in a very fast delivery of ibuprofen from this system. ^{13}C and ^{1}H NMR experiments evidence differences in the mobility of ibuprofen molecules adsorbed into the matrices, but they are not reflected in the overall release pattern, which obeys a diffusion model.[28]

The results obtained in these studies of controlled delivery of different drugs show the influence of aspects such as pore size, structure and functionalisation on the delivery kinetics. However, it seems clear that functionalisation is the main controlling factor on the drug adsorption and release rates; it is very important to carefully choose the type of functionalisation of the pore wall in agreement with the specific drug to be adsorbed and subsequently released. There are additional factors that might also affect these phenom-

ena, such as the wall thickness and the particle morphology and size, all of which are currently under investigation.

More than 80 references have been published referring to this new property of MCM-41, that is, controlled drug delivery,[9] since the first publication in 2001. Hence, Fujiwara et al. prepared MCM-41 functionalised with a photosensitive derivative of cumarine that exhibited an already known reversible dimerisation upon photonic irradiation.[39–40] To control efficiently the drug release, cumarine was introduced into the mesoporous material with the surfactant.

Many other contributions have appeared after this initial idea regarding the use of mesoporous materials as controlled delivery systems for drugs and other chemical species.[41–70]

Tissue Engineering

The silanol groups located on the walls of silica mesoporous materials are not only useful to functionalise the walls for drug delivery purposes; they are also able to react with physiological fluids to produce nanometre-sized carbonated apatite. In 2005, a new application of mesoporous materials as bone regenerators was described.[71] In vitro bioactivity studies by soaking three different mesoporous materials, SBA-15, MCM-48 and MCM-41, in simulated body fluid were carried out, revealing that an apatite-like layer is formed on the surface of SBA-15 and MCM-48 materials after 30 and 60 days, respectively, allowing their use in biomedical engineering for tissue regeneration. MCM-41 also exhibits a bioactive behaviour when its walls are doped with phosphorus[72] or when small amounts of bioactive glasses are added.[73]

The role that the textural and structural properties of the mesoporous materials play on their bioactive behaviour is extremely important. Alternatively, it is shown how the kinetics of the apatite formation can be modified and improved.[74] The possibility to control the periods of time needed for a positive response, together with the ability to functionalise the surface and the introduction of osteogenic substances inside the pores, open new expectations for designing novel mesoporous materials directed to specific medical applications (Figure 8).

The inorganic scaffold in ordered silica mesoporous materials and in bioactive glasses contains silanol groups that can be functionalised with an enormous variety of organic molecules, as mentioned throughout this paper. Taking into account the ability to introduce different species in the mesoporous matrices that can be subsequently released in a controlled fashion, combining this property with their inherent bioactivity could open new fields of application for these materials in tissue engineering, in which they can act as cellular scaffolds with embedded proteins, peptides or growth factors, that would be released to the medium promoting cell proliferation and differentiation.

The use of such bioactive porous ceramics as scaffolds for tissue engineering is still at a very preliminary stage of research; however, it can be foreseen that their use will be a routine procedure in perhaps a few years.

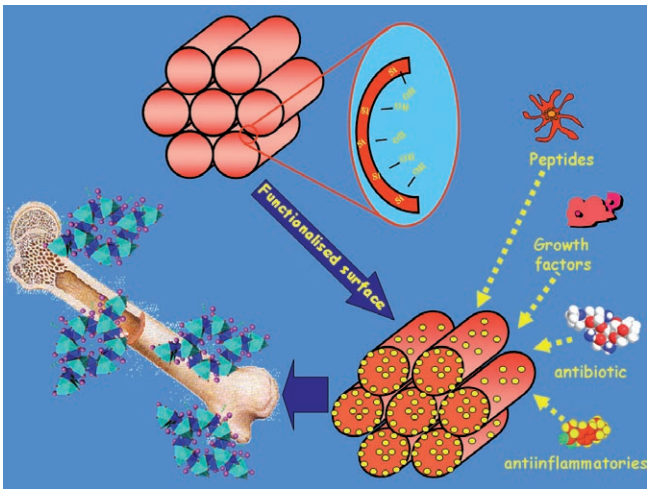

Figure 8. Scheme of the possible bone regeneration from a silica mesoporous material.

Conclusion

The application of well-established knowledge from the field of mesoporous materials,[75–80] combined with the current experience gathered in the areas of controlled drug delivery and biomaterials, is allowing the design of new applications[9,74] aimed at the clinical field. And this is just the beginning.

Once again, we are facing a fine example of multidisciplinary research, in which the so-called transversal supply of knowledge from and between the domains of chemistry, biology, materials science and medicine will empower the know-how and applications that shall, undoubtedly, give rise to new advances in science and technology.

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[1] "Biomaterials in Mesoporous Media: From Open Space to Confined Space": K. Ariga, K. Z. Hossain, A. Vinu, M. Hartmann in *Handbook of Nanostructured Biomaterials and Their Applications in Nanobiotechnology, Vol. 1* (Ed.: H. S. Nalwa), American Scientific, **2005** p. 343.
[2] R. Langer, *Nature* **1998**, *392*, 5.
[3] R. Yoshida, K. Sakai, T. Okano, Y. Sakurai, *Adv. Drug Delivery Rev.* **1993**, *11*, 85.
[4] K. Kataoka, A. Harada, Y. Nagasaki, *Adv. Drug Delivery Rev.* **2001**, *47*, 113.
[5] S. Bégu, C. Charnay, C. Tourne-Peteilh, R. Durand, D. A. Lerner, J. M. Devoisselle, *Chem. Commun.* **2003**, *5*, 640.

[6] J. S. Beck, C. T. W. Chu, I. D. Johnson, C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, WO Patent 91-11390, **1991**.
[7] C. T. Kresge, M. E. Leonowicz, W. J. Roth, J. C. Vartuli, J. S. Beck, *Nature* **1992**, *359*, 710.
[8] J. S. Beck, J. C. Vartuli, W. J. Roth, M. E. Leonowicz, C. T. Kresge, K. D. Schmitt, C. T. W. Chu, D. H. Olson, E. W. Sheppard, *J. Am. Chem. Soc.* **1992**, *114*, 10834.
[9] M. Vallet-Regi, A Ramila, R. P. del Real, J. Perez-Pariente, *Chem. Mater.* **2001**, *13*, 308.
[10] P. Horcajada, A. Rámila, G. Ferey, M. Vallet-Regí, *Solid State Sci.*, in press.
[11] M. Vallet-Regí, *J. Chem. Soc. Dalton Trans.* **2001**, 97.
[12] L. L. Hench, R. J. Splinter, W. C. Allen, T. K. Greenlee, *J. Biomed. Mater. Res.* **1971**, *2*, 117.
[13] R. P. del Real, J. G. C. Wolke, M. Vallet-Regí, J. A. Jansen, *Biomaterials* **2002**, *23*, 3673–3680.
[14] L. Meseguer-Olmo, M. J. Ros-Nicolás, M. Clavel-Sainz, V. Vicente-Ortega, M. Alcaraz Baños, A. Lax-Pérez, D. Arcos, C. V. Ragel, M. Vallet-Regí, *J. Biomed. Mater. Res.* **2002**, *61*, 458.
[15] B. R. Constantz, I. C. Ison, M. T. Fulmer, R. D. Poser, S. T. Smith, M. VanWagoner, J. Ross, S. A. Goldstein, J. B. Jupiter, D. I. Rosenthal, *Science* **1995**, *267*, 1796.
[16] N. Hijón, M. V. Cabañas, I. Izquierdo-Barba, M. Vallet-Regí, *Chem. Mater.* **2004**, *16*, 1451.
[17] S. Padilla, R. P. del Real, M. Vallet-Regí, *J. Controlled Release* **2002**, *83*, 343.
[18] A. Rámila, R. P. del Real, R. Marcos, P. Horcajada, M. Vallet-Regí, *J. Sol–Gel Sci. Technol.* **2003**, *26*, 1195.
[19] K.-D. Kühn, *Bone Cements*, Springer, Berlin, **2000**.
[20] P. Horcajada, A. Rámila, J. Pérez-Pariente, M. Vallet-Regí, *Micropor. Mesopor. Mater.* **2004**, *68*, 105.
[21] 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.
[22] M. Vallet-Regí, J. C. Doadrio, A. L. Doadrio, I. Izquierdo-Barba, J. Pérez-Pariente, *Solid State Ionics* **2004**, *172*, 435.
[23] I. Izquierdo-Barba, A. Martínez, A. L. Doadrio, J. Pérez-Pariente, M. Vallet-Regí, *Eur. J. Pharm. Sci.* **2005**, *26*, 365.
[24] A. Firouzi, F. Atef, A. G. Oertly, G. D. Stucky, B. Chmelka, *J. Am. Chem. Soc.* **1997**, *119*, 3596.
[25] D. Zhao, J. P. Feng, Q. S. Huo, N. Melosh, G. H. Fredrickson, B. F. Chemelka, G. D. Stucky, *Science* **1998**, *279*, 548.
[26] M. Kaneda, T. Tsubakiyama, A. Carlsson, Y. Sakamoto, T. Ohsuna, O. Terasaki, S. H. Joo, R. Ryoo, *J. Phys. Chem. B* **2002**, *106*, 1256.
[27] Y. Sakamoto, M. Kaneda, O. Terasaki, D. Y. Zhao, J. M. Kim, G. Stucky, H. J. Shin, R. Ryoo, *Nature* **2000**, *408*, 449.
[28] I. Izquierdo-Barba, E. M. B. Sousa, J. C. Doadrio, A. L. Doadrio, J. Pérez-Pariente, A. Martínez, F. Babonneau, M.Vallet-Regí, *Micropor. Mesopor. Mater.*, in press.
[29] A. Stein, B. J. Melde, R. C. Schroden, *Adv. Mater.* **2000**, *12*, 1403.
[30] X. Song Zhao, G. Q. Lu, X. Hu, *Chem. Commun.* **1999**, 1391.
[31] P. K. Jal, S. Patel, B. K. Mishra, *Talanta* **2004**, *62*, 1005.
[32] J. Liu, X. Fena, G. E. Fryxell, L.-Q. Wang, A. Y. Kim, M. Gong, *Adv. Mater.* **1998**, *10*, 161.
[33] B. Muñoz, A. Rámila, J. Pérez-Pariente, M. Vallet-Regí, *Chem. Mater.* **2003**, *15*, 500.
[34] A. Rámila, B. Muñoz, J. Pérez-Pariente, M. Vallet-Regí, *J. Sol–Gel Sci. Technol.* **2003**, *26*, 1199.
[35] N. Shankland, C. C. Wilson, A. J. Florence, P. J. Cox, *Acta Crystallogr. Sect. C* **1997**, *53*, 951.
[36] F. Babonneau, L. Camus, N. Steunou, A. Ramila, M. Vallet-Regí, *Mater. Res. Soc.* **2003**, *775*, 3261.
[37] F. Babonneau, L. Yeung, N. Steunou, C. Gervais, A. Ramila, M. Vallet-Regí, *J. Sol–Gel Sci. Technol* **2004**, *31*, 219.
[38] J. C. Doadrio, E. M. B. Sousa, I. Izquierdo-Barba, A. L. Doadrio, J. Pérez-Pariente, M. Vallet-Regí, *J. Mater. Chem.* **2006**, *16*, 462.
[39] N. K. Mal, M. Fujiwara, Y. Tanaka, *Nature* **2003**, *421*, 350.
[40] N. K. Mal, M. Fujiwara, Y. Tanaka, T. Taguchi, M. Matsukata, *Chem. Mater.* **2003**, *15*, 3385.
[41] T. Czuryszkiewicz, J. Ahvenlammi, P. Kortesuo, M. Ahola, F. Kleitz, M. Jokinen, M. Lindén, J. B. Rosenholm, *J. Non-Cryst. Solids* **2002**, *306*, 1.
[42] H. Y. Zhang, Y. Kim, P. K. Dutta, *Microporous Mesoporous Mater.* **2006**, *88*, 312.
[43] Q. Yang, S. H. Wang, P. W. Fan, L. Wang, Y. Di, K. Lin, F.-S. Xiao, *Chem. Mater.* **2005**, *17*, 5999.
[44] D. Huang, Y. Hung, B. Ko, S. Hsu, W. Chen, C. Chien, *FASEB J.* **2005**, *19*, 12.
[45] Y. S. Lin, C. P. Tsai, H. Y. Huang, C. T. Kuo, Y. Hung, *Chem. Mater.* **2005**, *17*, 4570.
[46] C. Gerardin, A. Kostadinova, N. Sanson, D. Francova, *Stud. Surf. Sci. Catal.* **2005**, *156*, 221.
[47] Q. L. Tang, N. Y. Yu, Z. J. Li, D. Wu, Y. H. Sun, *Stud. Surf. Sci. Catal.* **2005**, *156*, 649.
[48] S. Giri, B. G. Trewyn, M. P. Stellmaker, V. S.-Y. Lin, *Angew. Chem.* **2005**, *117*, 5166; *Angew. Chem. Int. Ed.* **2005**, *44*, 5038.
[49] Y. F. Zhu, J. L. Shi, W. H. Shen, X. P. Dong, J. W. Feng, M. L. Ruan, Y. S. Li, *Angew. Chem.* **2005**, *117*, 5213; *Angew. Chem. Int. Ed.* **2005**, *44*, 5083.
[50] J. Liu, Q. H. Yang, M. P. Kapoor, N. Setoyama, *J. Phys. Chem. B* **2005**, *109*, 12250.
[51] W. Zeng, X. F. Qian, Y. B. Zhang, J. Yin, Z. K. Zhu, *Mater. Res. Bull.* **2005**, *40*, 766.
[52] Y. F. Zhu, J. L. Shi, Y. S. Li, H. Chen, W. Shen, X. Dong, *J. Mater. Res.* **2005**, *20*, 54.
[53] S. J. Son, J. Reichel, B. He, M. Schuchmann, S. B. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 7316.
[54] V. P. Lehto, K. Vaha-Heikkila, J. Paski, J. Salonen, *J. Therm. Anal. Calorim.* **2005**, *80*, 393.
[55] C. R. Gordijo, C. A. S. Barbosa, A. M. Da Costa Ferreira, *J. Pharm. Sci.* **2005**, *94*, 1135.
[56] A. Vinu, K. Z. Hossain, K. Ariga, *J. Nanosci. Nanotechnol.* **2005**, *5*, 347.
[57] J. A. Gruenhagen, C. Y. Lai, D. R. Radu, V. S. Y. Lin, E. S. Yeung, *Appl. Spectrosc.* **2005**, *59*, 424.
[58] T. Czuryszkiewicz, S. Areva, M. Honkanen, M. Linden, *Colloids Surf. A* **2005**, *254*, 69–74.
[59] J. L. Blin, C. Gerardin, L. Rodehuser, C. Selve, M. J. Stebe, *Chem. Mater.* **2004**, *16*, 5071.
[60] B. G. Trewyn, C. M. Whitman, V. S. Y. Lin, *Nano Lett.* **2004**, 4, 2139.
[61] J. Andersson, J. Rosenholm, S. Areva, M. Linden, *Chem. Mater.* **2004**, *16*, 4160.
[62] S. Y. Kwak, W. M. Kriven, M. A. Wallig, J. H. Choy, *Biomaterials* **2004**, *25*, 5995.
[63] M. Xue, M. Shi, *J. Controlled Release* **2004**, *98*, 209.
[64] C. Charnay, S. Begu, C. Tourne-Peteilh, L. Nicole, D. A. Lerner, *Eur. J. Pharm. Biopharm.* **2004**, *57*, 533.
[65] G. Cavallaro, P. Pierro, F. S. Palumbo, F. Testa, L. Pasqua, *Drug Delivery* **2004**, *11*, 41.
[66] K. A. Fisher, K. D. Huddersman, M. J. Taylor, *Chem. Eur. J.* **2003**, *9*, 5873.
[67] C. Tourne-Peteilh, D. Brunel, S. Begu, B. Chiche, F. Fajula, *New J. Chem.* **2003**, *27*, 1415.
[68] S. Willemin, G. Arrachart, L. Lecren, J. Larionova, T. Coradin, *New J. Chem.* **2003**, *27*, 1533.
[69] R. Aiello, G. Cavallaro, G. Giammona, L. Pasqua, P. Pierro, *Stud. Surf. Sci. Catal.* **2002**, *142*, 1165.
[70] C. Y. Lai, B. G. Trewyn, D. M. Jeftinija, K. Jeftinija, S. Xu, S. Jeftinija, V. S.-Y. Lin, *J. Am. Chem. Soc.* **2003**, *125*, 4451.
[71] I. Izquierdo-Barba, L. Ruiz-González, J. C. Doadrio, J. M. González-Calbet, M. Vallet-Regí, *Solid State Sci.* **2005**, *7*, 983.
[72] M. Vallet-Regí, I. Izquierdo-Barba, A. Rámila, J. Pérez-Pariente, F. Babonneau, J. González-Calbet, *Solid State Sci.* **2005**, *7*, 233.
[73] P. Horcajada, A. Rámila, K. Boulahya, J. González-Calbet, M. Vallet-Regí, *Solid State Sci.* **2004**, *6*, 1295.
[74] M. Vallet-Regí, L. Ruiz-González, I. Izquierdo-Barba, J. M. Gonzalez-Calbet, *J. Mater. Chem.* **2006**, *16*, 26.

[75] J. M. Thomas, *Angew. Chem.* **1988**, *100*, 1735; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1673.
[76] J. M. Thomas, *Angew. Chem.* **1999**, *111*, 3800; *Angew. Chem. Int. Ed.* **1999**, *38*, 3588.
[77] J. M. Thomas, *Nature* **1994**, *368*, 289.
[78] Y. Sakamoto, M. Kaneda, O. Terasaki, D. Y. Zhao, J. M. Kim, G. Stucky, H. J. Shin, R. Ryoo, *Nature* **2000**, *408*, 449.
[79] A. Corma, *Chem. Rev.* **1997**, *97*, 2373.
[80] G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé, I. Margiolaki, *Science* **2005**, *309*, 2040; corrigendum: G. Férey, C. Mellot-Draznieks, C. Serre, F. Millange, J. Dutour, S. Surblé, I. Margiolaki, *Science* **2005**, *310*, 1119.

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