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Drug-Delivery Systems

Mesoporous Materials for Drug Delivery

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Research on mesoporous materials for biomedical purposes has experienced an outstanding increase during recent years. Since 2001, when MCM-41 was first proposed as drug-delivery system, silica-based materials, such as SBA-15 or MCM-48, and some metal–organic frameworks have been discussed as drug carriers and controlled-release systems. Mesoporous materials are intended for both systemic-delivery systems and implantable local-delivery devices. The latter application provides very promising possibilities in the field of bone-tissue repair because of the excellent behavior of these materials as bioceramics. This Minireview deals with the advances in this field by the control of the textural parameters, surface functionalization, and the synthesis of sophisticated stimuli-response systems.

1. Introduction

Controlled drug-delivery systems (DDSs) are one of the most promising applications for human health care and represent an ever-evolving field for biomedical materials science.[1–4] The development of new active molecules and potential treatments, such as gene therapy, is leading to the development of new therapeutic agents and the enhancement of the mechanisms to administer them. Basically, a drug-delivery system can be described as a formulation that controls the rate and period of drug delivery (i.e. time-release dosage) and targets specific areas of the body. Unlike traditional therapies, which show a saw-tooth curve of drug concentration in plasma, DDSs are designed to maintain therapeutic levels during the treatment period.[4]

The field of nanotechnology in recent years has motivated researchers to develop nanostructured materials for biomedical applications. In 2001, the mesoporous material MCM-41 was proposed as a DDS.[5] MCM-41 was synthesized in the 1990s as a member of the M41S family of molecular sieves.[6] In general, mesoporous materials are derived from supramolecular assemblies of surfactants, which template the inorganic component (commonly silica) during synthesis.[6–9] After the surfactant is removed, commonly by pyrolysis or dissolution with the appropriated solvent, the silica mesoporous matrices are potential drug carriers with the following features:

a) *An ordered pore network,* which is very homogeneous in size and allows fine control of the drug load and release kinetics;
b) *A high pore volume* to host the required amount of pharmaceuticals;
c) *A high surface area,* which implies high potential for drug adsorption;
d) *A silanol-containing surface* that can be functionalized to allow better control over drug loading and release.

These unique features make mesoporous materials excellent candidates for controlled drug-delivery systems, and intensive research has been carried out on this topic during recent years. Commercial DDSs—commonly based on polymer technology—are very successful systems that cover several fields, such as implantable, oral, transdermal, and injectable drug reservoirs. These systems also serve in a vast number of medical and pharmaceutical applications, such as in orthopedics and dentistry.[10] However, one of the main and more specific problems of DDSs at present is the loss of activity of several drugs before reaching the target tissue as a result of premature degradation of the active agent. In this context, stimuli-responsive systems that exhibit "zero premature release" could play a fundamental role in enabling this task. Other specific long-term treatments could require an increase or decrease in the rate of drug release, depending on the disease evolution. For this purpose, implantable

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systems able to respond to external stimuli (e.g., magnetic fields) or internal pH changes would be also very interesting, regardless of whether they also exhibit zero premature release behavior.

Implantable drug-delivery systems for local drug release in bone tissue are one of the most promising therapeutic concepts in orthopaedic surgery. Oral administration commonly requires very high, sometimes also low, effective dosages to reach sufficient drug concentrations in the poorly irrigated bone tissue. Antibiotics, growth factors, chemotherapeutic agents, antiestrogens, and anti-inflammatory drugs are good candidates for the most common bone-related therapies.

These different situations cannot be always catered for by conventional drug-delivery devices. The sophisticated and rational design of stimuli-responsive systems often needs well-structured porosity and high surface areas to support the chemical species (frequently polymers) that are to control the drug release. In the case of bone-implantable DDSs the problem is even clearer from the point of view of the clinical practice. After a bone prosthesis setting, the most common antibiotic treatment is the implantation of poly(methyl methacrylate) (PMMA) beads loaded with gentamicin. These systems must be removed in a second surgical procedure, which is a substantial drawback. DDSs exhibiting the properties of biocompatible bioceramics would be highly desirable in these cases, and silica-based mesoporous materials fulfill this condition.

In this Minireview we collect and analyze some of the most relevant milestones in the research of mesoporous materials for controlled drug delivery, mainly those intended as bone implants and for oral administration. To provide a comprehensible and global overview to the reader, this work firstly analyzes biocompatibility aspects, which are inherent to all material intended to interact with biological systems. Secondly, we consider the basic aspects of the textural properties (surface and porosity) that contribute to the understanding of drug-adsorption and controlled-release processes. Finally, more sophisticated stimuli-responsive materials are reviewed, whether they exhibit zero-premature release or not. These systems are very desirable when high-toxicity drugs are involved.

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2. Biocompatibility of DSSs

DDSs have to deal with the physiological environment when performing their functions during oral intake or implantation. Whereas the former situation requires non-toxicity, in the latter these systems have to be considered as biomaterials, that is, nonviable materials that become a part of the body either temporarily or permanently to restore, augment, or replace the natural functions of the living tissues or organs. Therefore, the proper function of the implanted material is restricted by its long-term biocompatibility, which is a dynamic, two-way process that involves the time-dependent effects of the host on the material and of the material on the host. Moreover, the biocompatibility of any implanted material relies on several parameters regarding the site of implantation, the shape and size of the material, as well as its surface chemistry.[11]

The sequence of biological reactions that occur when a material is exposed to blood begins with the rapid adsorption of certain proteins onto the surface of the material. Depending on the type of such proteins, this process is followed by platelet adhesion. Afterwards, immune and inflammatory cells act to protect the body by isolating the foreign material in a fibrous capsule. Encapsulation in this context does not mean a non-biocompatible state and can be considered a normal response. However, the collagen capsule is a barrier for an encapsulated drug to diffuse into the surrounding tissue and for nutrients to supply the encapsulated cells. Also, the activation of adherent platelets leads to the formation of thrombi on the surface. Almost all biomaterials are known to cause surface-induced thrombosis, which, besides the medical complications related to thrombi, affects the drug-release profiles.

Implantable DDS materials should provide an adequate combination of the desired biological response and the release of drugs against the inflammatory and encapsulation processes.[12] Among the biomaterials that display biocompatibility are the silica-based systems.[13–15] The biocompatibility of silica nanospheres that interact with cellular systems has been demonstrated.[16] Also, surface functionalization of

MCM-41 nanoparticles has been shown to regulate the material endocytosis, a key factor for intracellular delivery.[17]

Osteointegration is a fundamental factor for the performance of implantable DDSs intended as permanent bone grafts. During the drug-releasing process, both matrix degradation and tissue ingrowth occur at the implant site. The latter process is accompanied by the deposition of calcium and phosphate ions on the material surface to deposit a poorly crystallized apatite phase similar to the inorganic phase of bones.[18,19] This set of reactions modifies the drug-release kinetics with respect to other "inert" systems, such as PMMA beads. This phenomenon, known as bioactivity, constitutes an advantage over currently used polymer-based devices. All these surface reactions affecting biocompatibility and bioactivity must be taken into account before application of a DDS.

3. The Influence of Textural Properties on Performance

3.1. Pore Size

When considering mesoporous materials for DDSs, an essential question arises: how are drugs to be incorporated into a mesoporous matrix? The drug incorporation is commonly carried out by soaking of the matrix in a highly concentrated drug solution and subsequent drying. Therefore, the process is mainly based on the adsorptive properties of mesoporous materials. The pore size of mesoporous materials determines the size of the molecule that can be adsorbed into the mesopores. Thus, the adsorption of molecules in the mesoporous matrix is governed by size selectivity. Commonly, pore diameters slightly larger than the drug molecule dimensions (pore/drug size ratio >1) are enough to allow the adsorption of drug inside the pores. One of the most important characteristics of mesoporous materials is that the mesopores diameters can be tuned from 1.5 nm to several tens of nanometers by changing the chain length of the surfactant, employing polymeric structure-directing agents, or solubilizing auxiliary substances into micelles.[20,21] These different tools allow mesoporous matrices to be tailored to host either small molecules or macromolecules such as proteins.

Mesoporous materials exhibit molecular-sieve properties for relatively large molecules. Hata et al. reported in 1999 that taxol, an anticancer substance, was adsorbed into FSM-type mesoporous silica when the pore size was larger than 1.8 nm.[22] Although the proposed system was not designed as a DDS, their studies set an important precedent for this field. These authors for the first time considered the molecular-sieve properties of mesoporous silicas and the solvent polarity as fundamental factors for drug loading. However, when mesoporous materials are designed as DDS, the pore size not only exerts a molecular-sieving function but also controls the drug-release rate. When MCM-41 was first tested as DDS,[5] our research group used C_{12}TAB and C_{16}TAB as structure directing agents (C_{12}TAB = dodecyltrimethylammonium bromide, C_{16}TAB = hexadecyltrimethylammonium bromide). The MCM-41 with larger pore size, obtained using C_{16}TAB, released 68% of the loaded ibuprofen (IBU) after 24 h in simulated body fluid (SBF). In contrast, MCM-41 obtained with C_{12}TAB released only 55% of the drug after the same period of time.

Further studies confirmed the role of the pore size as drug-delivery controller.[23] When IBU is incorporated into MCM-41 mesoporous materials with pore diameters between 2.5 and 3.6 nm, an increase in release rate with pore size is evident (Figure 1).

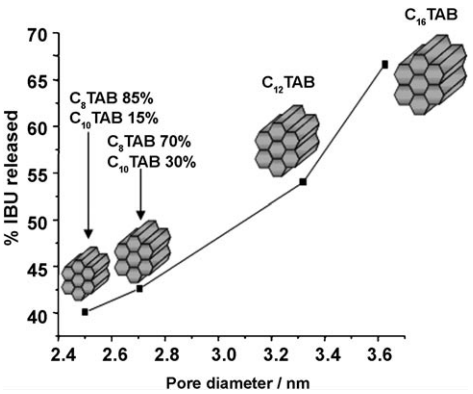

Figure 1. IBU fraction released from MCM-41 after 24 h in SBF. The plot is represented as a function of pore diameter and the surfactants used are indicated for each case. C_8TAB = trimethyloctylammonium bromide; C_{10}TAB = decyltrimethylammonium bromide.

The concept of pore size as a kinetic-release controller is not only applicable to 2D hexagonal structures, such as MCM-41, but also to 3D cubic ones, such as MCM-48 mesoporous materials. Our group has studied incorporation of IBU into MCM-48 molecular sieves, which have a cubic unit cell with *Ia3d* symmetry and a pore size of 3.6 nm, as well as into LP-I*a3d*, which possesses the same symmetry but exhibits a larger pore size of 5.7 nm.[24] After fitting the release plots to a Higuchi model,[25] we determined that IBU released faster from LP-*Ia3d*, which indicates that the pore-size effect is also present in mesoporous DDSs for this symmetry ordering.

Andersson et al. considered additional factors that affect the porosity and the kinetic release.[26] They reported the influence of the pore connectivity, geometry, and matrix degradation in aqueous media, as well as the pore-size effect. The stability of the pore structure varies depending on the thermal treatment (which determines the thickness of the silica wall), and consequently the kinetic release of the drug changes during the drug-delivery process. Structures containing cagelike or corrugated pores (which are essentially equivalent to larger pores connected through smaller windows) seem to be excellent matrices for long-term drug delivery.

Very recently, Qu et al.[27] reported the release of captopril from several 2D hexagonal structures ($MCM\text{-}41_{12}$, $MCM\text{-}41_{16}$, and SBA-15). The authors described the influence of pore size on the kinetic processes: not only on the kinetic release of drug, but also on the kinetic loading (the final amount of drug adsorbed essentially depends on the surface area). They also pointed out that the pore-size effect can be evaluated only if

the morphology is similar at the microstructure level. As an example, when the microstructure of the matrix consists of small spherical particles (120–250 nm), the drug release is faster than that observed in bigger rodlike particles (20 μm in length), independent of the mesopore size. Similarly, our research group reported important differences at the macroscopic level in the kinetic release of amoxicillin from powder and disk-shaped samples.[28]

Adsorption experiments carried out with alendronate[29] (small molecule) and albumin[30] (macromolecule) on SBA-15 indicate that the very high or very low drug molecule/pore size ratios are, in both cases, inadequate for incorporating large amounts of drug.

3.2. Surface Area

As mentioned in Section 3.1, the drug-loading process is mainly based on the adsorptive properties of mesoporous materials. Therefore, the surface becomes the most determining factor for the amount of adsorbed drug. In general terms, it is convenient to host large amounts of pharmaceuticals or, at least, to have the choice of incorporating high or low doses of a drug into the matrix. This challenge can be tackled by two different approaches: by increasing/reducing the surface area or by modifying the surface–drug affinity. The first approach involves the amount of surface available for the drug molecules. So long as the pore size allows the drug to get into the matrix, the higher the surface area the higher the amount of drug adsorbed. The final drug content can be very sensitive to the surface area S_{BET}. We synthesized MCM-41 and SBA-15 (both 2D hexagonal structures) with S_{BET} values of 1157 and 719 $m^2 g^{-1}$, respectively. When both matrices were loaded with alendronate under the same conditions, the maximum loads of alendronate obtained were 139 and 83 $mg g^{-1}$ for MCM-41 and SBA-15, respectively.[29] Thus, the value of S_{BET} is closely correlated with the maximum load of the matrix surface.

A hybrid route, which consists of combining the high and regular porosity of mesoporous materials with the presence of organic groups within the framework, was recently reported for DDSs.[31] The final compounds are metal–organic frameworks (MOFs) that exhibit large S_{BET} values as well as high drug loading and controlled release. These materials are denoted MIL (Materials Institute Lavoisier); the structures of MIL-100 and MIL-101 are shown in Figure 2a.

MIL-100 and MIL-101 have surface areas of 3340 and 5510 $m^2 g^{-1}$, respectively, which are 3 and 5 times larger than the S_{BET} values measured for the MCM-41 inorganic mesoporous materials alone. Moreover, MIL-100 is able to adsorb 350 $mg g^{-1}$ IBU, and MIL-101 loads 1400 $mg g^{-1}$ under the same conditions. These differences were attributed to the pore sizes and structural effects, particularly the accessible dimensions of the windows of the cages in the solids, which are larger in MIL-101. The behavior of these materials has been also compared with that of silica-based MCM-41 with $S_{BET} = 1157\ m^2 g^{-1}$. MCM-41 and MIL-100 materials showed very similar IBU dosage and kinetics, whereas the drug content of MIL-101 is 4 times larger than in MCM-41.

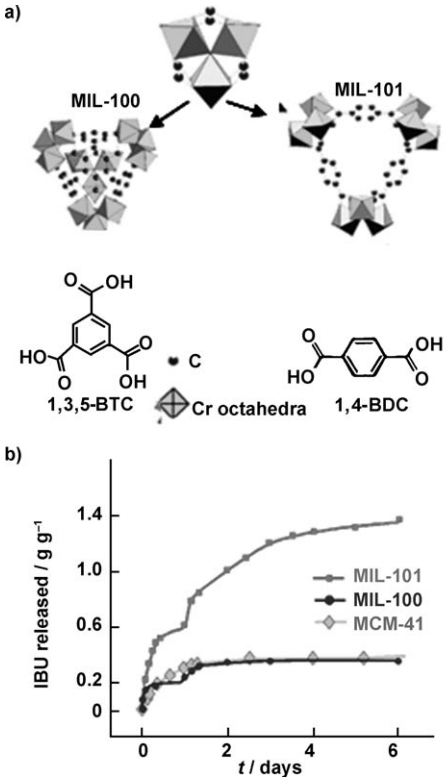

Figure 2. a) Structures of MIL-100 and MIL-101 built up from trimers of chromium octahedra as well as 1,3,5-BTC (benzene-1,3,5-tricarboxylic acid) and 1,4-BDC (benzene-1,4-dicarboxylic acid), respectively. b) IBU release as a function of time for MIL-101, MIL-100, and MCM-41.

However, it must be taken into account that these drug adsorption levels are a consequence of the high surface area provided by the external micropores, as the IBU molecules are mainly retained outside the zeotype architecture. This adsorption mechanism differs from that of silica-based mesoporous materials, which show lower S_{BET} values but possess accessible mesopores for drug storage and release.

The IBU release profiles are compared in Figure 2b for both the MIL materials and MCM-41. As it is speculated that most of the drug is adsorbed in the outermost micropores of MIL materials and only a small amount is retained in the closed mesopore cavities, the drug release should follow different delivery kinetics from that of MCM-41. Two sections can be observed in the release profiles of the MIL materials, corresponding to the release from micropores and from mesopores. In MCM-41, as the drug is essentially loaded into the mesopore channels, the release profile only shows one exponential profile.

The release from MCM-41 and MIL-100 is very similar even though the total surface area is different, whereas the release for MIL-101, with more open mesopores, is larger (Figure 2b). This difference is mainly due to the interaction of IBU molecules with the terephthalic units inside the cavities, which may retain the drug molecules and release them when the micropore windows are clear, that is, when the drug adsorbed in the outer surface has been already delivered.

Although the release profile of IBU from this kind of material could be of interest owing to the special nature of MOF matrices, chromium-containing MIL materials are not biocompatible; iron-based MOFs within the same structure are currently under development.

3.3. Pore Volume

The surface area and pore diameter are critical factors for drug adsorption and release in implantable ceramic-based drug-delivery systems. The outermost mesopore surface of virtually insoluble porous frameworks is responsible for the interaction with the loaded drug. As the pore size is usually less than 15 nm and surface areas are roughly 1000 $m^2 g^{-1}$, the pore volumes are generally in the range of 2.0 $cm^3 g^{-1}$. The drug–mesopore interaction is a surface phenomenon; however, weak drug–drug interactions can result under loading conditions and could lead to the pore filling. In this case, the pore volume is a key factor in determining the amount of drug adsorbed. It was recently reported that several consecutive loadings of drug in ordered mesoporous materials leads to larger filling of the mesopores, which was attributed to the increased drug intermolecular interactions within the pore voids, whereby larger pore volumes may result in greater drug loading.[32]

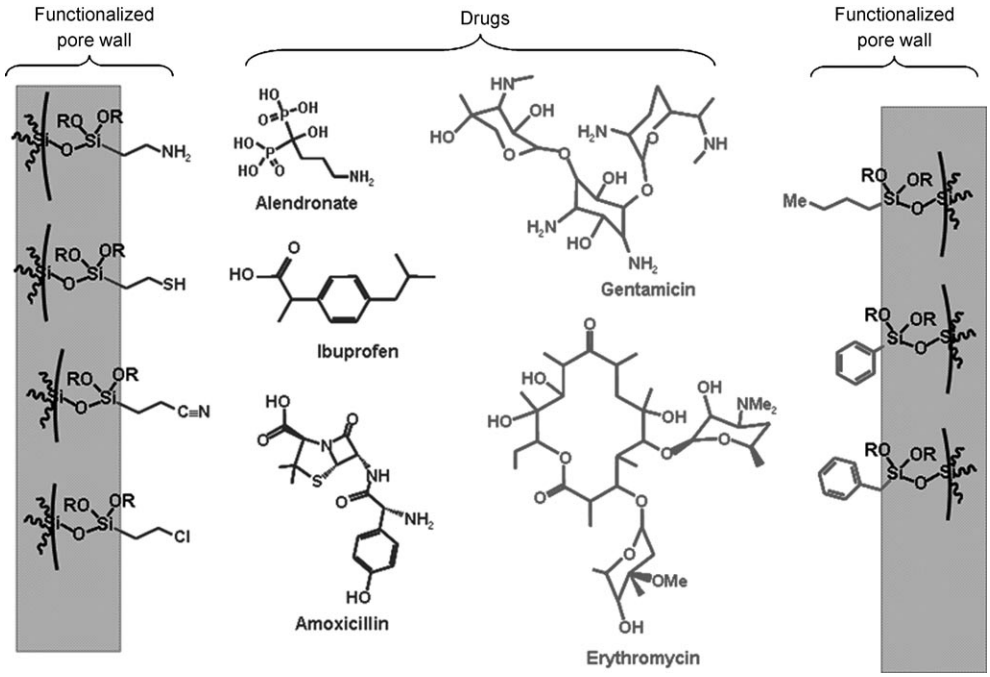

Figure 3. Pore-wall functionalization in silica mesoporous materials and structures of several drugs used in these systems.

4. Functionalization of Mesoporous Drug-Delivery Systems

The keystone in the development of silica mesoporous materials as DDSs is the modification or functionalization of the surface through organic groups.[33,34,56,58] This process provides numerous possibilities to control drug adsorption and release. Mesoporous silica shows a high density of silanol groups, which can be used to obtain functionalized surfaces by grafting organic silanes ($(RO)_3SiR'$). Figure 3 collects some of the most-used functional groups together with several drugs employed in these systems so far.

The drug release can be effectively controlled by different methods, the most developed of which is increasing the drug–surface interaction. For this purpose the surface is functionalized with chemical groups that are able to link to the drug molecules through ionic bonds or through ester groups.[35] One of the most studied cases is the adsorption of IBU on functionalized matrices. IBU was incorporated in these systems on the assumption that its carboxy group links the silanol groups at the surface (Figure 4). However, this situation is not exclusive in nonfunctionalized matrices, as

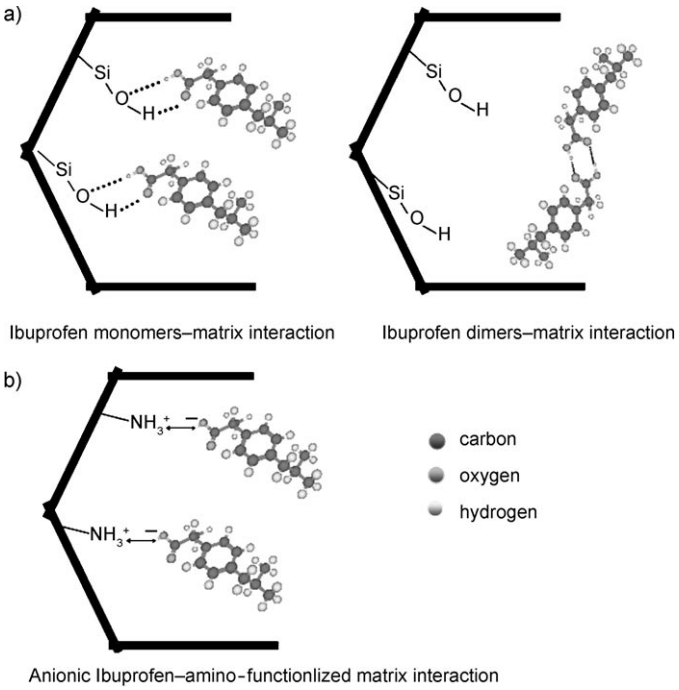

Figure 4. IBU linkage to a silica mesoporous material. a) Nonfunctionalized matrix: IBU can be linked through weak hydrogen bonds between its carboxylic acid group and the silanol groups (left) and is also found as a physisorbed dimer molecule at the surface (right). b) Amino-functionalized matrix: IBU is linked to the pore wall through stronger ionic bonds between carboxylate and ammonium groups.

drug–drug interactions are also present and lead to the formation of IBU dimers.[36] This dimer configuration is formed by an intermolecular hydrogen bond through the carboxy groups. Babonneau et al.[37,38] showed by NMR studies that the IBU molecules exhibit high mobility, which is incompatible with the behavior of molecules linked at the pore wall of mesoporous silica. On the contrary, this mobility agrees with dimers physisorbed on the surface and also explains the predominant initial burst effect observed for these systems.

The IBU linkage is quite different when the surface is functionalized. Our research group[39] and thereafter Song et al.[40] reported the functionalization of MCM-41 and SBA-15, respectively, with amino groups as an effective method to control IBU release. The ionic interaction between the carboxy groups in IBU and the amino groups on the matrix surface allows the release rate of IBU from amino-functionalized SMMs to be effectively controlled (SMM = silica mesoporous material). This evidence is also supported by NMR analysis,[37,38] which revealed that IBU molecules are tightly linked at the surface because the drug–surface ionic interactions are stronger than the IBU dimer hydrogen bonds.

Ionic interactions also form when drug molecules that contain amino groups are linked to carboxylic acid functionalized mesoporous silica. Very recently, Tang et al. reported the adsorption of famotidine on carboxylic acid functionalized MSU materials (MSU = Michigan State University).[41] The carboxylation was carried out by the acid-catalyzed hydrolysis of cyano to carboxylic acid groups, and the results obtained by these authors demonstrate that the adsorption of famotidine depends mainly on the degree of functionalization.

The studies reported so far indicate that the postsynthesis functionalization method (i.e., functionalization after the removal of surfactant) leads to better results than the co-condensation method.[39,40] Recently Zeng et al. introduced some controversy in this topic. They stated that owing to a higher degree of order and the uniform distribution of functional groups, a better drug-delivery rate could be obtained by using the co-condensation method, rather than postsynthesis or solvothermal processes.[42,43]

Our research group recently reported amino-functionalized MCM-41 and SBA-15 mesoporous silica-based materials containing alendronate for bone repair or regeneration.[44] Alendronate belongs to the bisphosphonate family, which inhibit bone resorption by osteoclasts (Figure 5). In both systems, the surfaces of the pore walls were organically modified with amino groups. After 24 h in an aqueous alendronate solution, the amino-modified materials showed a drug loading almost 3 times higher than that of the unmodified materials. 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 the unmodified materials and with the amino groups covering the surface of the mesopore walls of the modified materials.

Under the loading conditions (pH 4.8), the interaction between the silanol group in the substrate and the phosphonate group of the adsorbed drug is weaker than that between

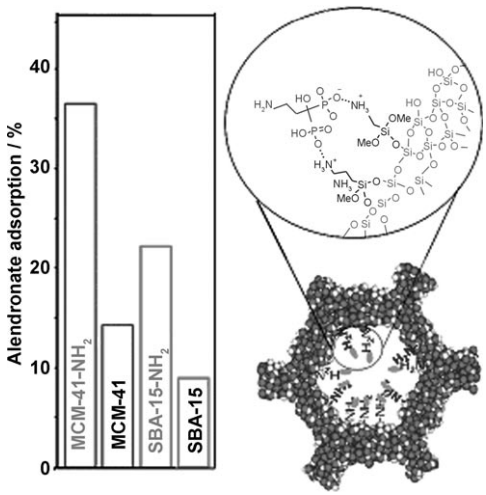

Figure 5. Left: Maximum load of alendronate in ordered mesoporous materials. Right: Chemical bonding between alendronate and amino-functionalized mesoporous materials.

the amino and the phosphonate groups. The adsorption of alendronate molecules on the amino-modified materials was 22 and 37 % in SBA-15-NH_2 and MCM-41-NH_2, respectively. These alendronate loads are significantly larger than those obtained for the unmodified materials: 8 % in SBA-15 and 14 % in MCM-41. This work demonstrated that the amount as well as the delivery rate of adsorbed bisphosphonate can be modulated through modification of the surface of the pore walls through organic molecules. At physiological pH (pH 7.4), the differences in polarity between the silica surface and the bisphosphonate, or between the $PrNH_2$-covered surface and the bisphosphonate, induce weakening of the adsorbed molecules, which are then slowly released to the media.

A second strategy for effective control of drug release is functionalization of the surface with hydrophobic species. In this case, the drug–surface interactions are not necessarily increased, but the drug transport out of the matrix is seriously impeded as the aqueous medium does not easily penetrate inside the pores. This strategy has been recently developed by several authors. Our group reported the controlled release of erythromycin, an antibiotic that belongs to the macrolide family, from functionalized SBA-15.[45] The surface was modified with octyl and octadecyl moieties by treating the mesoporous matrix with trimethoxyoctylsilane and trimethoxyoctadecylsilane, respectively. The consequences on the mesoporous SBA-15 were a decrease of the effective pore size and a decrease of the wettability of the surface by aqueous solutions. We could effectively control the release rate of erythromycin. For example, the octadecyl-functionalized sample exhibited a release rate one order of magnitude lower than that of nonfunctionalized SBA-15.

Similar results were obtained by other authors with mesoporous materials modified by silylation. Captopril[46] and ibuprofen[47] have been incorporated and both cases showed a lower drug loading when silylation is carried out. However, well-defined controlled drug release can be achieved by tailoring the surface properties of mesoporous silica

Table 1: Drugs, adsorption conditions, and maximum drug load adsorbed into SiO_2-based mesoporous materials.

Drug	Mesoporous matrix	Solvent	Max. load [%]	Ref.
taxol	FSM	CH_2Cl_2	6	[22]
ibuprofen	MCM-41_{12}[a]	hexane	23	[5]
ibuprofen	MCM-41_{16}[b]	hexane	34	[5]
ibuprofen	MCM-41_{12}-NH_2[a,c]	hexane	23	[39]
ibuprofen	MCM-41_{16}- NH_2[b,c]	hexane	33	[39]
ibuprofen	MCM-48	hexane	28.7	[24]
ibuprofen	LP-*Ia3d*[d]	hexane	20.1	[24]
gentamicin	SBA-15	water	20	[75]
gentamicin	PLGA-SiO_2[e]	water	22.4	[76]
gentamicin	PLGA-SiO_2[e]	water	45.6	[76]
erythromycin	MCM-48	acetonitrile	28	[24]
erythromycin	LP-*Ia3d*[d]	acetonitrile	28	[24]
erythromycin	LP-*Ia3d*-C8[d,f]	acetonitrile	12	[24]
erythromycin	SBA-15	acetonitrile	34	[45]
erythromycin	SBA-15-C8[f]	acetonitrile	13	[45]
erythromycin	SBA-15-C18[g]	acetonitrile	18	[45]
erythromycin	MCM-41	acetonitrile	29	[45]
alendronate	MCM-41	water	14	[44]
alendronate	MCM-41-NH_2[c]	water	37	[44]
alendronate	SBA-15	water	8	[44]
alendronate	SBA-15-NH_2[c]	water	22	[44]
aspirin	MCM-41	water	15	[43]
aspirin	MCM-41-NH_2[c]	water	15	[43]
amoxicillin	SBA-15	water	24	[28]
captopril	MCM-41_{12}[a]	water	23.6	[27]
captopril	MCM-41_{16}[b]	water	34	[27]
captopril	SBA-15	water	22.6	[27]
famotidine	MSU-3[h]	methanol	20	[47]

[a] C_{12}TAB used as surfactant. [b] C_{16}TAB used as surfactant. [c] Organically modified with amino groups. [d] Large pore 3D cubic *Ia3d* mesoporous material. [e] Poly(D,L-lactide-*co*-glycolide)/mesoporous silica hybrid structure. [f] Organically modified with trimethoxyoctylsilane. [g] Organically modified with trimethoxyoctadecylsilane. [h] Organically modified with carboxylic acid groups.

materials by regulating the degree of silylation. Table 1 collects some the matrix–drug systems reported so far as well as the drug load reached for these systems.

5. Dosage in Mesoporous Materials

A very important issue for drug-delivery systems is the actual amount of drugs that can be delivered to the targeted sites, that is, the dosages. Questions such as "what dosage has to be achieved when mesoporous materials are formulated as tablets or as bone implants?" arise when a DDS is under development. Obviously, there are many factors that determine the appropriated dosage, including patient characteristics, bioavailability (in the case of oral delivery), and treatment duration.

For oral DDSs, it is desirable to develop matrices for "once-daily" formulations. If it is assumed that all the drug is released according to zero-order kinetics, the amount of drug incorporated should be that indicated for each daily treatment. For famotidine loaded in MSU materials, between 40 and 500 mg of drug could be adsorbed in and released from a 1.5-g mesoporous tablet. The indicated dose of famotidine is 40 mg per day for the treatment gastric ulcers and 500 mg per day for the treatment of Zollinger–Ellison syndrome.[41] Another example is captopril-loaded MCM-41;[46] captopril is an orally active inhibitor of the angiotensin-converting enzyme and is used for the treatment of hypertension and congestive heart failure. The recommended daily dosage for captopril ranges between 50 and 100 mg per day. Up to 32% of captopril was incorporated into MCM-41 matrices, indicating that a 300-mg tablet could contain the maximum daily dosage, and drug release was complete within 24 h in simulated stomach fluid.

The scenario is quite different for long-term implantable drug-delivery systems, and new factors must be considered in the design of these DDSs. Drug bioavailability is generally much higher than for oral administration and the drug release must extend over several days or weeks. Table 2 lists some of the implantable DDSs intended as bone grafts, together with

Table 2: Mesoporous matrices proposed for implantable (bone) drug-delivery systems together with the suitable drug, its daily dose when administered differently, and the recommended dosage.

Mesoporous matrix	Drug	Daily Dose	Dosage [g][c]
SBA-15	gentamicin	150–300 mg[a]	2
SBA15/PLGA	gentamicin	150–300 mg[a]	4.50
SBA-15	erythromycin	1.5–3 g[b]	3.4
SBA-15	amoxicillin	1.5–2 g[b]	2.50
SBA-15-NH_2	alendronate	5–10 mg[b]	2
MCM-41-NH_2	alendronate	5–10 mg[b]	2.5
MCM-41	ibuprofen	0.9–1.2 g[b]	7.0

[a] Dose for gentamicin recommended for intravenous administration. [b] Doses orally administered. These doses take into account the bioavailability of the drugs, which are 60, 80, 0.7, and 92% for erythromycin, amoxicillin, alendronate, and ibuprofen, respectively. [c] Dosages contained into 10 g mesoporous silica, which is the approximate amount of silica-based material to graft a bone defect in a femur fracture. Smaller periodontal defects usually require 3–5 g silica-based glass graft.

the amounts of drugs (dosages) that can be incorporated into 10 g of mesoporous material. This amount would be appropriate for grafting to a bone defect resulting from, for example, a femur fracture. The dosages per implant are calculated from the maximum load percentages previously reported (Table 1). In view of the daily dosage needed for a 60-kg patient and the load capacity of the mesoporous materials (dosage per implant), these mesoporous DDSs could release their drug content over several days or even weeks to provide effective doses at the bone tissue. This assumption would be valid only if the kinetic release is adequate, since the working life of the system depends not only on the amount of drug incorporated, but also on the release rate.

The most common release profiles for mesoporous materials are shown in Figure 6. Profile a is commonly observed for nonfunctionalized matrices, which initially display a burst effect followed by a very slow drug release.[5] This kind of profile can be useful when an immediate high dose is required, for example, for acute infections or inflammations. Profile b is associated with diffusion or

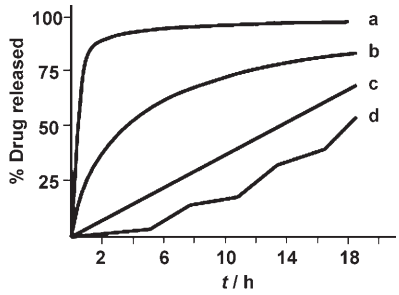

Figure 6. Drug delivery profiles of mesoporous materials. See text for descriptions of plots a–d.

dissolution processes, and generally follows first-order kinetics with respect to drug concentration. A clear example of this profile is the alendronate/MCM-41 system.[44] Profile c corresponds to zero-order kinetics; that is, the release process is only dependent on time. This kind of profile is highly desirable for long-term drug-delivery systems, for which the alendronate/amino-functionalized SBA-15 system is a clear example.[44] Finally, profile d represents a more sophisticated stimulus-responsive system. In these systems the release rate can be controlled by external changes (e.g., pH value, temperature, magnetic field), which opens up a wide range of possible smart DDSs. This kind of matrix is discussed in the following section.

6. Stimuli-Responsive Mesoporous Materials Systems

Together with the development of mesoporous silica for drug-delivery systems, the interest in controlling the release of drug molecules has also grown. In conventional mesoporous systems, as described above, the release of adsorbed molecules usually follows a sustained kinetic mechanism that can be expressed in terms of diffusion of adsorbed molecules throughout the mesopore channels in the silica matrix. Release kinetics, therefore, can be interpreted in terms of the Fickian diffusion coefficients, which depend on the characteristics of both the molecule and the silica matrix. However, for certain applications, the delivery of adsorbed molecules needs to be modulated by environmental stimuli such as pH and temperature changes or light. Furthermore, many site-selective delivery systems, such as those for highly toxic antitumor drugs, require zero release before the targeted cells or tissues are reached.

Current research is focused on the design of ordered mesoporous materials with certain functional groups that respond to environmental changes and thus modify the adsorption and release characteristics. In recent years, several ordered mesoporous materials have been developed with stimuli-responsive ability. For example, Xiao and co-workers designed pH-responsive carriers in which polycations are grafted to anionic, carboxylic acid modified SBA-15 by ionic interactions.[48] The polycations act as closed gates to store the drug within the mesopores (Figure 7). When the ionized carboxylic acid groups are protonated in response to a change

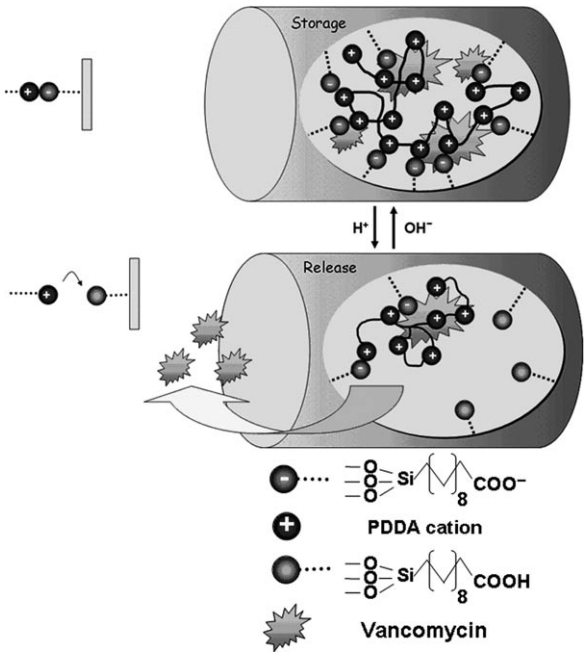

Figure 7. pH-responsive storage–release drug-delivery system based on the interaction between negative carboxylic acid modified SBA-15 silica rods with polycations (PDDA).

in pH value, the polycations are detached from the surface and the drug is released from the mesopores.

Thermoresponsive mesoporous materials have been developed as hybrid systems that combine the silica inorganic phase with thermally active polymers, such as poly(*N*-isopropylacryl amide) (PNIPAm), to produce spongelike phases.[49] The sponge phases are formed by self-assembly of amphiphilic templates during the formation of mesoporous inorganic materials. They consist of a three-dimensional random packing of a multiply connected bilayer of surfactant and cosurfactant, which divides the space into two subspaces filled with solvent, and are similar to the liposome structure. The pore size and distance between adjacent silicate layers in the porous structure were controlled by changing the hydrophilic domain, for example, by varying the amount of water. Drugs could be loaded into the spongelike mesoporous domains, which serve as reservoirs, and drug release could be controlled by cyclic thermally induced polymer shrinkage, which regulates the aperture of the pores.

Ordered mesoporous drug-delivery systems that respond to external magnetic fields on the other hand were obtained by direct encapsulation of magnetic nanoparticles into the mesoporous silica. Such an approach yields materials that can be employed as magnetic nanovectors, and are usually based on magnetite or even iron, covered with mesoporous silica.[50] Another interesting approach involves capping mesopores with magnetic nanoparticles that can be alternately placed and removed. The mesoporous materials for these systems were synthesized by cocondensation with mercaptopropyl silanes and subsequent linkage through the SH groups with 2-carboxyethyl-2-pyridyl disulfide to yield acid-functionalized mesoporous silica. The mesopore entrances of the MCM-41 materials were then closed with magnetic Fe_3O_4 nanoparticles

by placing the acid-functionalized silica in a suspension with magnetite nanoparticles and the drug whose incorporation should be tested. When the capped materials were subjected to adequate magnetic fields to remove the magnetite nanoparticles, the adsorbed drug was released. The controlled-release mechanism of the system is based on the reduction of the disulfide linkage between magnetic Fe_3O_4 nanoparticles and the thiol-functionalized silica mesoporous material by reducing agents such as dihydrolipoic acid or dithiothreitol.[51]

Pore-entrance modification by capping has also been achieved with nonmagnetic nanoparticles, such as CdS, which are linked through disulfide bonds to thiol-functionalized silica.[16] Lin and co-workers have also reported pore capping with polyamidoamine (PAMAM) dendrimers.[52] The PAMAM caps served as a nonviral gene transfection reagent to enable plasmid DNA of an enhanced green fluorescence protein (*Aequorea victoria*) to cross a cell membrane through endocytosis and then be released. The released plasmid DNA is sent to the nucleus to produce green fluorescent proteins.

Pore modification with large organic molecules through a supramolecular route employing rotaxane molecules has been reported.[53,54] These systems act as nanovalves and are operated by a selective redox process that modifies the structure of the linked rotaxane molecules to "open" and "close" the mesopore access. Mesopore entrances can also be modified by other types of organic functionalities to develop supramolecular mesoporous materials that respond to several chemical signals.[55]

Light of a suitable wavelength can be employed for triggering the drug release or even molecular recognition in modified mesoporous silica materials. Lin and co-workers combined the size-sieving efficiency of the mesoporous silica matrix with the possibility of modifying the pore surface with appropriate photosensitive organic groups to allow only small molecules with certain groups to diffuse through the mesopores and react with the modified pore walls.[56] With this system, molecules are adsorbed onto pore walls as a function of their fluorescence characteristics and retained regardless of their release from the matrix. Fujiwara and co-workers have developed a photocontrolled release system for direct-drug-release applications based on pore-entrance modification with coumarin groups. These groups undergo reversible dimerization upon irradiation with UV light at wavelengths longer than 310 nm and return to the monomer form by subsequent irradiation at shorter wavelengths (ca. 250 nm). The dimer form of the coumarin, when grafted on the surface of mesoporous silica systems, such as MCM-41, reduces the effective pore size of the matrix and subsequently hinders the adsorption of molecules into the pore voids as well as their release from them. Adequate irradiation of the material "opens" the entrance to the pores and the adsorbed drugs can be released.[57,58]

7. Mesoporous Silica Nanoparticles as DDSs

As well as the nature of the pore system and the size, shape, and connectivity of mesoporous materials, the morphology of the mesophase may be particularly important. Simple morphologies with short, unhindered path lengths, such as small spheres and crystallike particles, as well as short, straight rods are beneficial for applications that are limited by intraparticle diffusion processes, such as catalysis, separation, guest-molecule encapsulation, and internal-surface modification. Thus, not surprisingly, extensive work has been devoted to the control of the morphology of mesoporous silica[59–63] and organosilicates.[64] Most approaches are based on changes in synthesis conditions, including the silica source, the nature of the surfactants, cosurfactants, cosolvents, and additives, as well as the overall composition of the synthesis mixture.

Regular morphologies provide several advantages for drug-adsorption and -delivery applications. In fact, ordered mesoporous materials with irregular bulk morphology exhibit sustained-release properties, but their drug-storage capacity is relatively low and the drug delivery is erratic. One strategy to overcome these disadvantages is the synthesis of nanosized hollow mesoporous silica spheres with pore channels penetrating from the outside to the inner hollow core.[65,66] Such materials can be also synthesized in the presence of organic molecules during the templating stage to produce ordered mesoporous nanospheres with wormlike pores that can be employed as drug-delivery systems,[67] although the most important procedure to take into account is the control of the outer-sphere morphology. In this respect, organic polymers such as polystyrene, poly(methyl methacrylate)[68] and poly(vinyl pyrrolidone) have been employed to direct the hollow structure of the nanospheres.[69] Thus-obtained hollow nanospheres generally show larger storage capacity than that observed in irregular bulk particles with similar mesoporous structures. Moreover, Lin and co-workers have combined the regular spheroidal morphology of nanoparticles with some stimuli-responsive systems to produce tunable-release mesoporous nanospheres.[70] Finally, hybrid silica-micelle nanospheres have been recently developed as nanovectors for drugs or other biological molecules.[71]

In addition to hollow nanospheres, bulk spherical mesoporous particles have also been synthesized by fluorocarbon surfactant templating. The weakly acidic conditions needed for these materials promote slow hydrolysis of the silica precursors, which coassemble with triblock copolymer templates to yield well-defined mesophases. The structures and pore sizes of such templated mesoporous nanospheres depend on the type of copolymer and the amount of organic additives. Simultaneously, fluorocarbon surfactants surround the silica nanoparticles through $S^+X^-I^+$ (S^+ = surfactant) interactions, thereby limiting the growth of the mesoporous silica spheres.[72] Moreover, control of drug adsorption and release has been tested even with pure silicon mesoporous particles[73] obtained by anodization in HF solutions, although the absence of pore ordering reduces both the molecular selectivity and therefore the drug-delivery performance.

8. Summary and Outlook

During the past five years, there has been an increasing number of research groups involved in the synthesis of mesoporous materials as drug-delivery systems. This field is

currently one of the most evident examples of the transfer of knowledge among materials science and biomedical applications, and its development offers promising possibilities for better medical treatments. Mesoporous materials exhibiting zero premature release seem to be an excellent alternative to conventional systems for the oral administration of highly toxic drugs. Moreover, several stimuli-reponsive materials that have been considered herein allow the drug-release kinetics to be sped up or slowed down, regardless of a potential zero-premature-release effect. The possibility to control the kinetic release of drug through external stimuli opens a wide field of possibilities for long-term therapies.

This Minireview also collects those SMMs intended as implantable drug-delivery systems for hard tissues. The bioceramic character of these materials allows their use in the repair of bone defects with the added value of releasing adequate drugs to help the bone-repair process. These delivery systems, therefore, increase the bioavailability of drugs in the bone tissue relative to oral formulations and fill a gap where conventional polymeric systems cannot be used.

We have reviewed the evolution of mesoporous DDSs since 2001—when MCM-41 was proposed as a DDS. This evolution has two different scopes: firstly, better understanding of the parameters involved in drug adsorption and release, and, secondly, the development of new DDSs through surface functionalization and, in some cases, smart stimuli-responsive systems. Following the premise that by understanding the parameters that govern drug adsorption and release we can tailor more specific matrices for each drug, important efforts have been carried out to control the porosity and surface of mesoporous materials. The role of the decrease in pore diameter in functionalized materials is also a subject for further discussion. Several authors have functionalized the surface with nonpolar species in an attempt to decrease the drug-delivery rate. However, it must be taken into account that the functionalization involves a pore-size decrease. This decrease should be also considered as a factor that controls the drug release. The drug release kinetics can be sensitive to the pore size, especially for those drugs with a similar size to pore diameter.

Many efforts have been aimed to design different pore structures. Currently, large macromolecules can be entrapped into cavities suitable for their adsorption and release. The development of cagelike or "plumber's nightmare" pore structures will play an important role in this respect. A second porosity-related parameter that should be addressed for drug adsorption and delivery is the pore inlet. Studies carried out by Zhao's research group have shown that the immobilization of enzymes is facilitated in materials with cagelike structures and large entrance sites.[21]

Pharmaceutical companies and device manufactures are actively seeking for new products that combine drug and device and utilize their existing drug and device products. However, in the next years we will be witnessing the expansion of biological therapy, which will involve the development of numerous active therapeutic agents (e.g. monoclonal antibodies, peptide and protein-based drugs, gene therapy). Currently, the development of biological therapies based on biotechnology-treated proteins has resulted in more than 60 drugs approved by the US Food and Drug Administration in the last 20 years, and it is estimated that around 360 candidates to treat more than 200 illnesses are currently under clinical testing.

General pharmacokinetic and pharmacodynamic principles are just as applicable to biotech agents as they are to traditional small-molecule drugs. However, the macromolecular nature of biotech drugs and the fact that most of them are identical or similar to endogenous molecules lead to new pharmacokinetics-related problems that subsequently result in bioavailability problems.[74] New mesoporous carriers able to host, protect, and target these kind of products at the appropriate site could play an essential role in these new therapies.

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