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Drug delivery from ordered mesoporous matrices

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Research interest in silica-based ordered mesoporous materials (SMMs) as drug delivery systems has grown drastically in the last few years owing to the great versatility and stability of these mesoporous matrices. This review aims to resume the work carried out in this area so far and the possible applications in biomedical technologies. The different SMMs can be designed and tailored using different chemical strategies according to the drug and clinical necessity. The available channels of SMMs that can be used to store drugs can be opened and closed by different systems, in the so-called stimuli-responsive release devices. These systems could improve the therapeutic efficacy compared with conventional sustained release systems. SMMs offer such a great versatility that can be used both for oral and for local drug delivery, with huge possible applications in different clinical areas.

Keywords: biomedical applications, drug delivery systems, silica-based ordered mesoporous materials, stimuli-responsive drug delivery systems

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1. Introduction

Drug delivery systems (DDSs) generally aim to maintain the concentration of drugs in the precise sites of the body within the optimum range and under the toxicity threshold, which improves the therapeutic efficacy and reduces toxicity. A large number of organic materials have been investigated as drug delivery vectors, such as polymeric nanoparticles, liposomes and micelles. However, these organic matrices present some drawbacks, such as their limited chemical and mechanic stability, swelling, susceptibility to microbiological contamination and inadequate control over the drug release rate. On the other hand, there are some other inorganic materials, non-toxic and biocompatible, that present a higher chemical and mechanical stability. They also present a porous structure that can be modified to control the release rate of any adsorbed drug or biomolecule.

Silica-based ordered mesoporous materials (SMMs) present unique properties that make them of great interest for application in biotechnology. Their high surface area, high pore volume and narrow mesopore channels allow the adsorption of drugs and biomolecules into their mesostructures to be then locally released. Ordered mesoporous silicates offer the advantage that the available channels that can be used as reservoirs to store drugs and biomolecules can be opened and closed by different systems, in the so-called stimuli-responsive release systems. There are also triggers that can activate the release of the guest molecules, such as heat, pH, light, chemicals, ultrasound or even magnetism.

This review summarises some of the research work carried out in the design of SMMs for controlled drug and biomolecule release applications [1-7]. As mentioned above, the high surface area, tunable pore diameter and uniform mesoporous structure of the mesoporous silicas render the opportunity of loading and releasing large quantities of biomedical agents. Different strategies have been developed to encapsulate guest biomolecules inside the porous matrices, with the subsequent

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utilisation of these surface-functionalised mesoporous silica nanomaterials for stimuli-responsive controlled release *in vitro* and *in vivo*.

2. General properties of ordered mesoporous materials

SMMs were first reported back in the 1990s by the oil industry [8,9]. The synthesis of these mesoporous materials is based on the use of supramolecular assemblies of surfactants in aqueous media that template the silica mesostructure during the synthesis. Then, the directing agents of the mesostructure, normally surfactants, are removed by thermal methods or through dissolution using different solvent extractions [10-16].

The final mesostructure of the silica material would depend on the surfactant template selected, together with the synthesis conditions, that is, concentration, temperature, co-solvents, additives, etc.

The applications of these mesoporous materials have received intense attention because of their properties, such as highly ordered structures (hexagonal and cubic pores), large pore volume (~ 1 cm^3/g) and high surface area (~ 1000 m^2/g). The well-ordered pore distribution in these matrices favours the homogeneity and reproducibility on the drug adsorption and release stages. The high pore volume allows the hosting of a great amount of pharmaceutical drugs into their mesostructure of cavities. The high surface area means a high potential for drug adsorption. Owing to the stable mesostructure and the previously mentioned well-defined surface properties, these mesoporous materials are ideal candidates for encapsulation of pharmaceutical drugs, proteins and other biological active species, as reviewed in this paper.

3. Functionalisation of ordered mesoporous materials

The surface of SMMs presents a high density of silanol groups (SiOH), which brings the possibility of undergoing easy chemical functionalisation of pore walls by grafting different organic alcoxysilanes. Thus, it is possible to tune the chemical properties of the mesoporous surfaces to achieve the desired properties [17-20]. Among them, it is possible to control drug adsorption and release depending on the grafting organic group chosen. There are basically two methods of organically modifying mesoporous matrices described in the literature: *direct functionalisation* [21], which is based on the addition of a trialkoxysilane with the selected functional group to the reaction mixture during the synthetic process; and the *post-synthesis functionalisation* [22], which involves the grafting of the functional group onto the mesoporous material after surfactant removal. The modification of the surface through different organic groups was a cornerstone in the development of silica mesoporous materials as drug delivery systems [1]. The chemical modification of the pore walls is normally selected depending on the molecule to the adsorbed, taking into account the desired load and release kinetics [5]. For every case described in this review, the chosen functionalisation is presented and discussed.

4. Mesoporous materials as drug delivery systems for different therapeutic applications

The outstanding structural and textural properties of SMMs made them excellent choices for use as DDSs of a wide range of pharmaceutical formulations with different therapeutic applications. **Table 1** collects different SMMs proposed so far for diverse pharmaceuticals for the treatment of different pathologies. This section describes the choice of the suitable mesoporous matrix attending to the chemical properties of the targeted drug. Moreover, the different approaches developed so far to tailor the physicochemical properties of the drug carrier according to the chemical nature of the pharmaceutical agent are also reviewed. The effect of increasing host–guest mesoporous matrix–drug interactions in drug adsorption and release is also summarised.

In the case of SMMs, molecule loading is usually performed by impregnation methods by soaking the mesoporous carrier into a concentrated molecule solution. Loading solvent is selected attending to the chemical nature of the guest molecule [23]. Then, the release process is commonly performed by placing the molecule-loaded mesoporous material into SBF solution [24], which has ionic concentrations similar to those in the human plasma, or in physiological serum to make the detection process easy.

4.1 Adsorption and delivery of anti-inflammatory drugs

The confinement of different non-steroidal anti-inflammatory drugs, such as ibuprofen (IBU), naproxen (NX), diflunisal (DF), piroxicam (PX) or aspirin (ASP), into different mesoporous matrices has been described extensively in the literature.

Vallet-Regí *et al.* reported in 2001 for the first time the possibility of using MCM-41 matrices as a delivery system of ibuprofen [25]. In this study, two MCM-41 matrices with different pores sizes, 2.5 nm ($MCM\text{-}41_{16}$) and 1.8 nm ($MCM\text{-}41_{12}$), were chosen. These SMMs were synthesised using cationic surfactants with different hydrocarbon chain lengths. It has been widely reported that the first limiting factor in molecules' adsorption into mesoporous matrices is the pore diameter (D_P), which acts as a size-selective parameter [1,26,27]. Considering that the size of IBU is 1.0 × 0.6 nm, the pore diameter is not the limiting factor in drug adsorption in this case. However, the adsorption of drugs into SMMs is a surface phenomenon that is governed mainly by the chemical interactions between silanol groups and the functional groups of the guest molecule. For this reason, the different IBU amounts adsorbed into $MCM\text{-}41_{16}$ (34 wt%) and $MCM\text{-}41_{12}$ (23 wt%) can be attributed to their different surface areas, which are 1157 and 1099 m^2/g, respectively. High surface areas promote chemical interactions between the functional groups

Table 1. Drugs, pharmacological action and maximum drug load adsorbed into SMMs.

Drug	Pharmacological action	Mesoporous matrix	Max. load (wt%)	Ref.
Ibuprofen	Anti-inflammatory Analgesic Antipyretic	MCM-41$_{12}$*	23	[25]
Ibuprofen		MCM-41$_{16}$‡	34	[25]
Ibuprofen		MCM-41$_{12}$-NH_2*§	23	[30]
Ibuprofen		MCM-41$_{16}$-NH_2‡§	33	[30]
Ibuprofen		MCM-48	28.7	[48]
Ibuprofen		FDU-5¶	20.1	[48]
Ibuprofen		SBA-15	14.6	[31]
Ibuprofen		TDU-1	24.4	[112]
Ibuprofen		MCM-41-MS#	19	[33]
Ibuprofen		MCM-41-DMS**	17	[33]
Ibuprofen		MCM-41-TMS‡‡	22	[34]
Naproxen		MCM-41-Al§§	7.3	[34]
Diflunisal		MCM-41-Al§§	8.7	[35]
Piroxicam		MCM-41	14	[37]
Aspirin		MCM-41	15	[38]
Aspirin		MCM-41-NH_2§	15	[38]
Amoxicillin	Antibiotic	SBA-15	24	[45]
Gentamicin		SBA-15-$C_3N^+Me_2C_{18}$	20	[46]
Gentamicin		PLGA-SiO_2¶¶	22.4	[47]
Gentamicin		PLGA-SiO_2¶¶	45.6	[47]
Erythromycin		MCM-48	28	[48]
Erythromycin		FDU-5¶	28	[48]
Erythromycin		FDU-5-C8¶##	12	[48]
Erythromycin		SBA-15	34	[49]
Erythromycin		SBA-15-C8***	13	[49]
Erythromycin		SBA-15-C18‡‡‡	18	[49]
Erythromycin		MCM-41	29	[49]
Itraconazole	Antifungal	SBA-15	24.6	[50]
ZnNIA	Bactericidal	SBA-16	14.3	[53]
ZnPCB		SBA-16	18.3	[53]
Captopril	Antihypertensive	MCM-41$_{12}$*	23.6	[54]

*C_{12}TAB used as surfactant.
‡C_{16}TAB used as surfactant.
§Functionalised with amino groups.
¶Large pore three-dimensional cubic *Ia3d* mesoporous materials.
#Functionalised with methylsilyl groups.
**Functionalised with dimethylsilyl groups.
‡‡Functionalised with trimethylsilyl (TMS) groups.
§§Containing 1.04% (w/w) Al.
¶¶Poly(DL-lactide-*co*-glycolide)/mesoporous silica hybrid structure.
##Functionalised with trimethoxyoctylsilane.
***Functionalised trimethoxyoctadecylsilane.
‡‡‡Functionalised with octadecyldimethyl (3-trimethoxysilyl-propyl) ammonium chloride.
§§§Functionalised with carboxyl acid groups.
¶¶¶SBA-15 synthesised using 7 days of hydrothermal treatment.
###Functionalised with *N*-trimethoxysilylpropyl-*N*,*N*,*N*-trimethyl ammonium chloride.
****Functionalised with octadecyldimethyl(3-trimethoxysilylpropyl)ammonium chloride.
‡‡‡‡Functionalised with folic acid.
benz: Benzoate; BSA: Bovine serum albumin; L-Trp: L-tryptophan; nia: Nicotinamide; SMM: Silica-based ordered mesoporous materials; ZnNIA and ZnPCB are, respectively, the $[Zn_3(benz)_6(nia)_2]$ and the $[Zn(benz)_2(3\text{-pymeth})_2]_n$ complexes, where 3-pymeth: 3-pyridinemethanol.

Table 1. Drugs, pharmacological action and maximum drug load adsorbed into SMMs (continued).

Drug	Pharmacological action	Mesoporous matrix	Max. load (wt%)	Ref.
Captopril		MCM-41$_{16}$[‡]	34	[54]
Captopril		SBA-15	22.6	[54]
Captopril		MCM-41-TMS[‡‡]	25.1	[55]
Sertraline	Antidepressant	MCM-41	25	[58]
Famotidine	Antiulcer	MSU-3-COOH[§§§]	20	[59]
Famotidine		SBA-15-COOH[§§§]	25.0	[60]
Famotidine		SBA-15-COOH-TMS[‡‡§§§]	25.0	[60]
Alendronate	Antiosteoporotic	MCM-41	14	[64]
Alendronate		MCM-41-NH$_2$[§]	37	[64]
Alendronate		SBA-15	8	[64]
Alendronate		SBA-15-NH$_2$[§]	22	[64]
BSA	Transport albumin (model protein)	SBA-15	15.1	[26]
BSA		SBA-15-NH$_2$[§]	10.0	[26]
BSA		SBA-15-7d[¶¶¶]	27.0	[26]
BSA		SBA-15-7d-NH$_2$[§¶¶¶]	28.5	[26]
L-Trp	Model amino acid Antidepressant	SBA-15-C$_3$N$^+$Me[###]	4.3	[67]
L-Trp		SBA-15-C$_3$N$^+$Me$_2$C$_{18}$****	8.2	[67]
Pentapeptide	Gastric acid secretion inhibitor Diuretic	MSU-Tween 80	-	[113]
Cisplatin	Anticancer	MCM-41	24.0	[69]
Cisplatin		MCM-41-NH$_2$[§]	37.0	[69]
Cisplatin		MCM-41-NH$_2$-Fol[§‡‡‡‡]	25.0	[69]

*C_{12}TAB used as surfactant.
‡C_{16}TAB used as surfactant.
§Functionalised with amino groups.
¶Large pore three-dimensional cubic *Ia3d* mesoporous materials.
#Functionalised with methylsilyl groups.
**Functionalised with dimethylsilyl groups.
‡‡Functionalised with trimethylsilyl (TMS) groups.
§§Containing 1.04% (w/w) Al.
¶¶Poly(DL-lactide-*co*-glycolide)/mesoporous silica hybrid structure.
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§§§Functionalised with carboxyl acid groups.
¶¶¶SBA-15 synthesised using 7 days of hydrothermal treatment.
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benz: Benzoate; BSA: Bovine serum albumin; L-Trp: L-tryptophan; nia: Nicotinamide; SMM: Silica-based ordered mesoporous materials; ZnNIA and ZnPCB are, respectively, the $[Zn_3(benz)_6(nia)_2]$ and the $[Zn(benz)_2(3\text{-pymeth})_2]_n$ complexes, where 3-pymeth: 3-pyridinemethanol.

of drug and silanol groups of MCM-41. This fact is also evident when comparing different SMMs with similar mesoporous structures (two-dimensional hexagonal *p6mm*), MCM-41 and SBA-15, but different surface areas of 1157 and 602 m^2/g, respectively. The amount of IBU loaded in both matrices was 34 wt% for MCM-41 and 15 wt% for SBA-15.

IBU delivery assays from MCM-41 matrices indicated that the higher the pore size, the faster the drug release. Thus, the percentage of IBU released after 24 h from MCM-41$_{16}$ and MCM-41$_{12}$ was 68 and 55%, respectively. This fact was also confirmed when several MCM-41 matrices with different mesopore sizes, ranging from 2.5 to 3.6 nm, were synthesised and IBU adsorption and release assays were performed [28]. Again, the MCM-41 matrix with the greatest pore diameter had the highest release kinetics. This finding suggests that a certain control over IBU delivery rate can be achieved by choosing the SMM with an appropriate pore size.

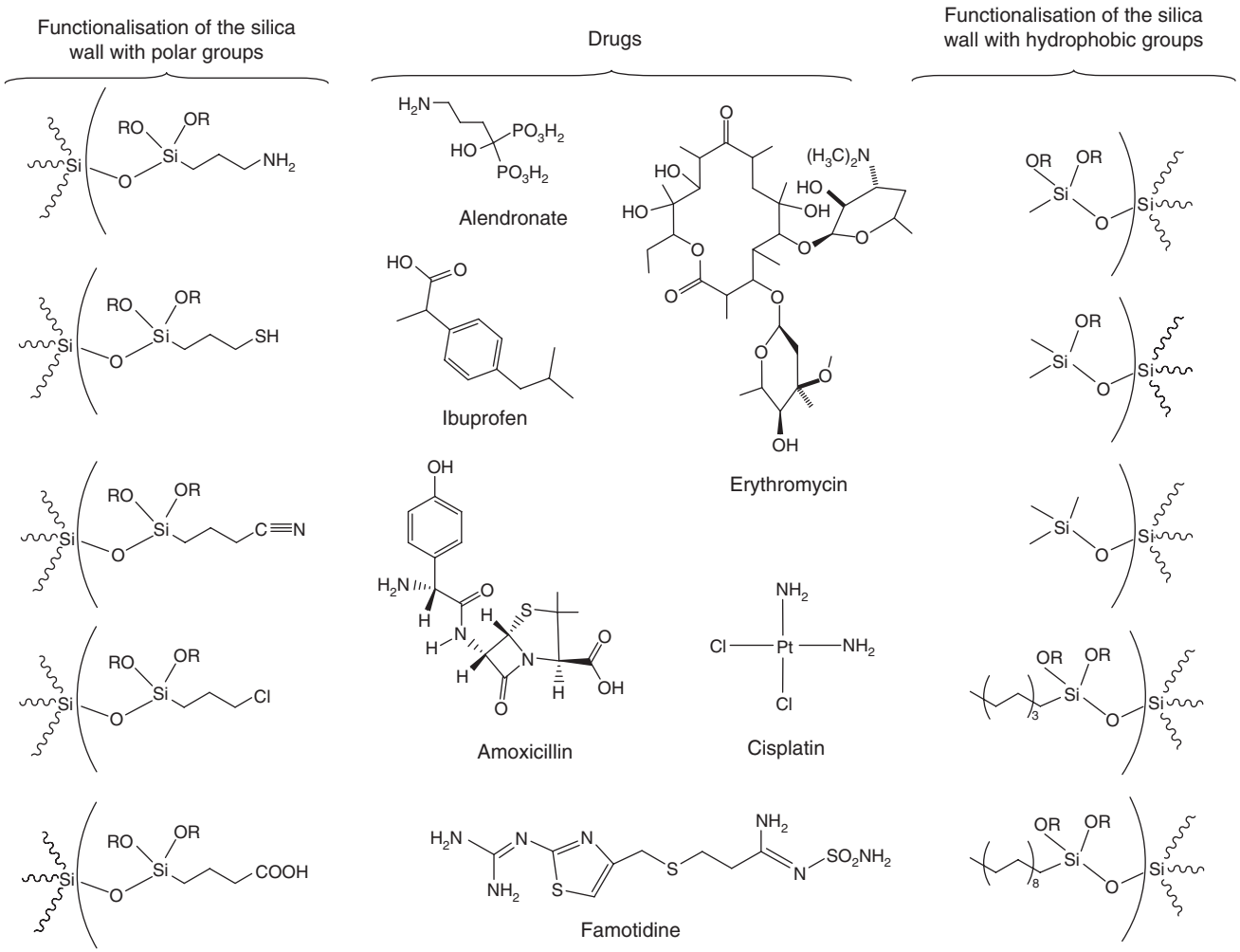

Figure 1. Functionalisation of the mesoporous silica walls and molecular structures of different drugs used in these systems.

The main factor, however, that governs drug loading and release is the functionalisation of SMMs (**Figure 1**). To evaluate the effect of functionalisation on IBU adsorption and release processes, MCM-41 was organically modified with different organic groups, and drug adsorption and release assays were performed. With this purpose two main strategies were used. The first one involves the use of organic groups able to link to the drug molecules mainly through ionic bonds. The choice of the functional groups depends on the targeted molecule. For example, IBU delivery tests from MCM-41 functionalised with several organic groups (chloropropyl, phenyl, benzyl, mercaptopropyl, cyanopropyl and butyl) [29] revealed that polar groups induced greater IBU adsorption than non-polar groups.

In addition, different studies have reported that the functionalisation of MCM-41 [30] and SBA-15 [31] with aminopropyl groups is a good method to control IBU loading and release. The ionic interaction between the carboxyl groups from IBU and the amino groups from the mesoporous surface allows the release rate of IBU from amino-functionalised SMMs to be modulated effectively. This evidence was also supported by NMR analysis, which indicated that IBU molecules are intimately linked at the surface because the drug–surface ionic interactions are stronger than the IBU dimmer hydrogen bonds [32].

The second strategy consists of using hydrophobic species to functionalise the mesoporous silica surfaces. In this case, the drug surface interactions are not necessarily enhanced, but the drug diffusion out of the matrix is difficult because the aqueous medium does not easily penetrate inside the mesopore channels. Thus, Tang *et al.* [33] reported that MCM-41 functionalised with methylsilyl (MS) or dimethylsilyl (DMS) groups led to a slower drug release caused by the difficult penetration of the release medium inside the mesopores. The loading experiments revealed that pure silica MCM-41 loaded a higher amount of IBU (29 wt%) than MCM-41-MS (19 wt %) or MCM-41-DMS (17 wt%). This agrees with the fact that MS or DMS groups prevent the impregnation of IBU. Functionalisation also had a noticeable effect on drug delivery rate from different SMMs. Therefore, the complete release of

IBU was achieved after ~ 10, 20 or 500 h from MCM-41, MCM-41-MS and MCM-41-DMS, respectively.

The same authors also reported the modification of IBU-loaded MCM-41 using trimethylsilyl (TMS) groups [34]. The *in vitro* release tests revealed that the presence of TMS groups greatly retarded the IBU release rate. They also demonstrated that even after 48 h of delivery assay, only 75% of the impregnated IBU could be released from MCM-41-TMS matrix. On the contrary, the release of IBU was completed just after ~ 1 h from the pure silica MCM-41 under the same conditions. These studies demonstrated that the release rate of IBU can be appropriately modulated by choosing the most adequate organic groups to functionalise the SMMs. These findings are extensible to other drugs, as discussed below.

Diflunixal was adsorbed into MCM-41 containing 1 wt% Al, and *in vitro* release studies at pH 1.1 and 6.8 were performed [35]. The amount of drug loaded, which would be interacting with the silanol groups of MCM-41, was 8.7 wt%. *In vitro* release test revealed that DF delivery rate was low at pH 1.1 (simulated gastric fluid), being only 20% the amount of drug released after 2 h of assay. Subsequently, when the pH was increased up to 6.8 (simulated intestinal fluid), the rest of the drug was quickly released to the delivery medium. These *in vitro* assays evidenced that this SMM (silica mesoporous material) could act as a good delivery system of DF. In this sense, only 20% of the loaded drug would be released at the gastric level, allowing the reduction of side effects related to oral administration of DF and the release of most of the drug in the intestinal tract.

Piroxicam is used as analgesic and in acute or long-term treatment of osteoarthritis, rheumatoid arthritis and in a variety of other acute and chronic musculoskeletal diseases. When orally administrated, PX is slowly and gradually absorbed through the gastrointestinal tract, reaching maximum haematic concentrations after 2 – 4 h [36]. As this drug is vaguely soluble in biological fluids, PX dissolution rate turns out to be the absorption rate-limiting step and consequently it critically affects the onset of the analgesic effect. This is an important drawback in the treatment of different diseases that need a fast analgesic effect, such as dysmenorrhoea, migraine, renal colic or postoperative pain. One strategy aimed at improving the PX dissolution rate and obtaining formulations with fast analgesic effect onset consists of confining PX into the mesopore channels of MCM-41 [37]. MCM-41 had a drug loading of ~ 14 wt%. Moreover, PX was not arranged in crystalline form into the mesopores and there were weak hydrogen bond interactions between the silanol groups of MCM-41 and the drug. *In vitro* test revealed that the PX dissolution rate improved compared with the crystalline drug in all tested solutions. In fact, these studies demonstrated that the PX dissolution profile at pH 1.2 (simulated gastric fluid) was comparable to that of some commercial formulations with rapid analgesic effect onset. The improvement of PX dissolution rate is attributed to both the lack of drug in the crystalline form and to the extremely large surface area of MCM-41. This great improvement of dissolution rate at acidic pH is very useful because it allows a fast drug release in the stomach where adsorption can happen, preventing drug contact with the intestinal mucosa.

Zeng *et al.* [38] studied MCM-41 before and after functionalisation with amino groups as controlled delivery system for aspirin. ASP molecules are rich in carboxyl groups and consequently they are expected to interact with free silanol groups or the amino groups on the pore wall. The results revealed that the amount of ASP loaded was similar for both MCM-41 and MCM-41-NH_2 matrices. However, the stronger attracting electrostatic interactions existing between amino groups of MCM-41-NH_2 and carboxyl groups of ASP led to a slower delivery rate compared with MCM-41 in which hydrogen bonds between silanol groups and carboxyl groups exist. Therefore, MCM-41-NH_2 needs 7 h to release 50% of drug, whereas MCM-41 needs only ~ 2 h.

4.2 Adsorption and delivery of antibiotic drugs

Controlled antibiotic delivery systems based on different materials, such as calcium phosphate cements [39,40], polymers [41,42] and composites [43], have been investigated intensively in the last few years. The influence of both the chemical composition and porosity of the carriers on the drug release patterns has been reported [44]. The drawback of heterogeneity of conventional matrices can be overruled by SMMs, which are good candidates as host matrices of antibiotic drugs. In this sense, different ordered mesoporous materials have been tested as controlled delivery systems of several antibiotics such as amoxicillin (AMX), gentamicin (GEN) or erythromycin (ERY).

SBA-15 mesoporous matrix has been proposed as host carrier of amoxicillin [45]. This work reveals that the AMX adsorption from aqueous solutions into SBA-15 is very much dependent on the pH of the solution. AMX is weakly adsorbed (~ 2 – 5 wt%) into the mesoporous matrix in pure water. On the contrary, if the pH of the solution is raised to 7 on NaOH addition, the adsorption of the drug is greatly enhanced, reaching values of 24 wt%. It is interesting to highlight that this is the maximum amount of drug that can be incorporated into SBA-15, despite the large excess of AMX present in the aqueous solution. Release studies were performed into SBF solution from powder and disk-shaped materials, which indicated that the AMX delivery rate in powder was quicker than in disk-shaped materials. This is in agreement with previous results reported for IBU release from MCM-41 materials [25]. These studies revealed that *in vitro* controlled release of AMX in SBA-15 material shows advantages when compared with traditional administration forms (capsules, tablets and suspension), where the AMX liberation is faster and not controlled.

SBA-15 material has been also evaluated as a delivery system of gentamicin [46]. The studies carried out using SBA-15 in powder and in disk forms evidenced that a GEN controlled

release was observed in both cases, with similar delivery patterns. Moreover, the solubility factor is correlated with an acceptable GEN absorption *in vivo*.

The combination of SMMs with polymers to achieve higher control over GEN release has also been reported [47]. A poly (DL-lactide-*co*-glycolide) (PLGA) mesoporous silica hybrid structure (PS hybrid structure) was synthesised by means of a sol-gel route assisted by single emulsion solvent evaporation. The *in vitro* GEN release behaviour of both pure SMM and PS hybrid structure was carried out. These studies showed that mesoporous silica had an initial burst effect for 1 day followed by a slow release over a period of 3 weeks. Such burst release was dependent on the amount of GEN loaded. Therefore, the initial burst was reduced from 77 to 54% when the drug loading decreased from 46 to 22 wt%. On the other hand, the PS hybrid structures showed three distinct drug release stages, an initial burst, a plateau stage with a slow release rate, followed by a sustained release stage that was governed by the degradation of PLGA encapsulating agent. It should be highlighted that the initial burst release was significantly reduced to 27% compared with that of mesoporous silica. Moreover, the hybrid structure can deliver during release periods for as long as 5 weeks. This research demonstrates that the combination of SMMs and polymers could represent a remarkable synergy for the release of drugs.

Other studies were based on the use of cubic mesoporous structures with *Ia3d* symmetry such as MCM-48 and large pore *Ia3d* material (FDU-5) [48] as erythromycin delivery systems. The delivery rate of ERY decreased with the pore size of the matrix. This fact was commented on previously for IBU delivered from MCM-41 matrices with different pore diameters. Therefore, ERY was released faster from FDU-5 (D_P ~ 5.7 nm) than from MCM-48 (D_P ~ 3.6 nm). To achieve higher control over drug release, the FDU-5 surface was made hydrophobic by using octyl hydrocarbon moieties (C8). The delivery assays indicated that the release rate decreased by a factor of nearly six compared with unmodified FDU-5 matrix.

The effect of functionalisation of hexagonal mesoporous structures with hydrophobic groups in drug delivery was also evaluated. Therefore, SBA-15 was functionalised with octyl (C8) and octadecyl (C18) groups and ERY release tests were carried out [49]. The decrease in the textural properties resulting from the functionalisation led to a decrease in the amount of ERY loaded (13 and 18 wt% for SBA-15-C8 and SBA-15-C18, respectively) compared with unmodified SBA-15 (34 wt%), but there was a remarkable effect in the delivery rate. This fact is ascribed to the decrease in the wettability of the functionalised surfaces, which made difficult the penetration of aqueous release medium inside the mesopores and induced slower drug delivery kinetics.

4.3 Adsorption and delivery of antifungal and bactericidal drugs

Some of the emerging innovative drugs display poor water solubility, resulting in poor oral bioavailability owing to insufficient dissolution throughout the gastrointestinal tract. The use of SMMs could help to overcome this drawback. This is the case of itraconazole (ITCZ), an antifungal triazole compound with an estimated aqueous solubility of ~ 1 ng/ml at neutral pH and ~ 4 μg/ml at pH 1. Mellaerts *et al.* [50] reported the use of SBA-15 of different pore diameters as an ITCZ controlled delivery system. The *in vitro* results demonstrated that the release of this hydrophobic drug was enhanced from SBA-15 and that the presence of a sufficiently wide pore diameter is the key factor to accelerate the release rate of ITCZ. These authors also reported the ITCZ loading into SBA-15 and the release studies in an aqueous environment simulating gastric fluid. They used three different loading processes: i) adsorption from solution; ii) incipient wetness impregnation; and iii) heating of a mixture of drug and SBA-15 powder [51]. These studies demonstrated that the effectiveness of the loading method was found to be strongly compound dependent. ITCZ was successfully incorporated into the pores of SBA-15 by using incipient wetness impregnation and via adsorption from dichloromethane. At a loading of ~ 20 wt%, the ITCZ molecules are molecularly deposited over micro- and mesopores. At higher loadings, an adsorbed layer is formed in which ITCZ molecules interact in a way similar to the glassy state. The incipient wetness impregnation method favours the location of ITCZ molecules in the micropores, whereas the solvent method favours their location on the mesopore walls. Samples prepared by means of the solvent method showed the fastest release rates. The melt method was inappropriate for ITCZ incorporation in SBA-15 because of the high viscosity of molten ITCZ.

The next step consisted of the evaluation of the *in vivo* performance of SBA-15 as carrier of ITCZ [52]. This research showed that the release of ITCZ from SBA-15 in aqueous environment took place faster than the dissolution of the pure drug, avoiding its slow dissolution kinetics. When non-sink conditions were established, mesoporous matrix was able to set up a supersaturated solution. The *in vivo* performance of such an SBA-15-ITCZ system in rabbits and dogs showed that the systemic availability of ITCZ was significantly enhanced. Moreover, all results obtained with such systems were comparable to other products existing in the market, such as Sporanox® (Itraconazol, Janssen-Cilag). These findings indicate that SMMs are promising carriers for improving the oral bioavailability of drugs with extremely low water solubility.

The use of SMMs as host systems of bactericidal compounds has also been proposed. The incorporation of two types of zinc(II) complex, namely $[Zn_3(benz)_6(nia)_2]$ (denoted ZnNIA) and $[Zn(benz)_2(3\text{-pymeth})_2]_n$ (denoted ZnPCB) (where benz is benzoate, nia is nicotinamide, and 3-pymeth is 3-pyridinemethanol) into mesoporous silica has been investigated [53]. Loading assays into SMM demonstrated that the load is greater for the ZnPCB complex than for the ZnNIA complex. This can be explained by the difference of structure of the two zinc complexes and by the difference of interactions with the silica pore walls. The release of the complexes from

the mesoporous matrix in deionised water as a function of time revealed that ~ 50 – 60% of the loaded complexes were released after 10 h. However, owing to strong immobilisation of the complexes in the porous structure, part of the complexes was still present in the silica matrix even after 80 h of assay. This was explained by considering the structure of the incorporated species and the more complex pore structure (presence of micropores and mesopores).

4.4 Adsorption and delivery of other drugs (antihypertensive, antidepressant and antiulcer)

SMMs have also been proposed as carriers of different drugs with diverse pharmacological actions. This is the case of the water-soluble drug captopril (CAP), an orally active inhibitor of the angiotensin-converting enzyme, which has been used widely for the treatment of hypertension and congestive heart failure. However, there are some drawbacks concerning the oral administration, such as the instability of the drug caused by the key functional group of thiol and the duration of drug *in vivo* requiring a long drug activity. Some efforts have been committed to designing a long-acting preparation to this problem to sustain or control release of this drug. The oral control release formulation of CAP is rather difficult because the drug is subjected to dose dumping, owing to its solubility in water (125 – 160 mg/ml). For this reason, the confinement of CAP into SMMs has been proposed as a good controlled delivery system. Hence, Qu *et al.* [54] proposed the use of three hexagonal mesoporous silica materials, SBA-15, MCM-41_{16} and MCM-41_{12}, with diverse pore sizes and morphologies as controlled CAP delivery systems. Such studies revealed that CAP could be successfully loaded into the mesopore silica channels. The amount of CAP loaded was directly related to the surface area. Accordingly, MCM-41_{16}, with the highest surface area, adsorbed the greatest amounts of drug (~ 34 wt%). Moreover, the drug release kinetics was tightly related to the morphologies and pore sizes of mesoporous silica. The delivery profiles showed that the CAP delivery rates could be modulated by regulating the pore sizes and morphologies of mesoporous silica. In this sense, SBA-15, with the largest pore diameter (7.4 nm), had the fastest release rate. Moreover, the CAP release from the MCM-41_{12} system, with the smallest pore diameter (1.65 nm) and sphere morphology (120 – 250 nm in size), was faster than from MCM-41_{16}, with 2.17 nm of pore diameter and rod-like morphology (~ 250μm in length). Thus, well-controlled CAP delivery could be achieved by tailoring appropriate pore sizes and suitable morphologies of SMMs.

A step forward towards the controlled release of CAP consisted of silylation of MCM-41 by using trimethylsilyl (TMS) groups [55]. In such work, trimethylchlorosilane (TMCS) was used as the silylanising agent. The grafting density was adjusted by controlling the initial concentration of TMCS, leading to SMMs with different surface properties. These studies showed that the amount of CAP loaded into MCM-41-TMS matrices decreased as the degree of silylation increased. This was ascribed mainly to the variations in the surface area and the hydrophobicity of silylated MCM-41 materials. The surface area gradually decreased as the degree of the silylation increased, which resulted in a decrease in the amount of CAP loaded, in agreement with previous reports [56]. Furthermore, increasing the hydrophobicity of the environment was unfavourable for the loading of hydrophilic drugs such as CAP. *In vitro* delivery tests revealed that the drug release rate decreased significantly after silylation of MCM-41. This is attributed to the decrease in the pore size and the increase in the diffusion resistance caused by the silylation. Moreover, the release rate becomes slow when the degree of silylation decreases. This can be explained by attending to the hydrophobicity of MCM-41. As the silylation degree increases, hydrophobicity also increases and the interactions between the mesoporous surface and the hydrophilic CAP molecules decrease, leading to an increase in the drug release rate. This research shows that a sustained CAP release can be achieved by tailoring the surface chemical properties of SMMs by regulating the degree of silylation.

SMMs are also interesting as controlled delivery systems of drugs with unpleasant effects in the gastric tract. This is the case of sertraline hydrochloride (SER), a new antidepressant drug that is administered orally. It is not chemically related to tricyclic, tetracyclic, or other available antidepressant agents and has fewer cardiovascular and anticholinergic adverse effects than these, but it is known for causing adverse secondary effects in the gastric tract [57]. Nunes *et al.* [58] proposed the use of MCM-41 as a host matrix of SER. The amount of SER loaded into MCM-41 was 25 wt%. Moreover, *in vitro* release tests in SBF indicated that ~ 90% of SER was released after 60 h of assay. The authors attribute this incomplete delivery to the existence of hydrogen bonding interactions between SER and the silanol groups covering the SMM surface.

SMMs have been also proposed as host matrices of other drugs in which the direct oral administration presents different drawbacks. This is the case of famotidine (FAMO), a histamine H2-receptor antagonist for treating ulcers in the stomach and intestine. The pharmacokinetics of FAMO indicated that its half-life of elimination was only 2.6 h in normal subjects. Moreover, it was found that the bioavailability of oral FAMO reached 43% and the blood concentration of FAMO showed a severe peak-to-trough fluctuation. With the aim of minimising such disadvantages, different controlled FAMO delivery systems were developed. Recently, the controlled release of FAMO from MSU and carboxylic-modified MSU (MSU-COOH) materials was evaluated [59]. It was found that FAMO could not be adsorbed into unmodified MSU, but significant drug adsorption was observed in MSU-COOH material. Thus, the functionalisation level of carboxylic groups has been found to be the key factor affecting the adsorption capacities of the modified MSU materials for FAMO. Three kinds of release fluid, including simulated gastric medium, simulated intestinal medium and simulated body fluid, were used to test the FAMO release rate from MSU-COOH material. Such delivery assays

show obvious delayed effect when compared with FAMO dissolution under the same conditions.

Later on, trimethylsilyl-carboxyl bifunctionalised SBA-15 (SBA-15-COOH-TMS) was studied as a carrier for controlled release of FAMO [60]. The results obtained were compared with those resulting from SBA-15-COOH mesoporous matrix. SBA-15-COOH matrices were synthesised by one-pot synthesis and the ordered mesostructure was maintained even though the content of carboxyl groups was up to 57%. The increase in the carboxyl content resulted in an enhanced FAMO loading capacity. Compared with pure SBA-15, in which FAMO could hardly be adsorbed, the largest drug loading capacity of SBA-15-COOH was 40 wt%. The release of FAMO from SMM was studied in simulated intestine fluid, indicating that for SBA-15-COOH the FAMO release rate decreased with narrowing pore size. The grafting of TMS groups on the surface of SBA-15-COOH led to a great delay in the FAMO release kinetics. Moreover, the higher the TMS group's content, the slower the drug release rate.

4.5 Adsorption and delivery of antiosteoporotic drugs

Bisphosphonates are one of the most widely used drugs for the treatment of those diseases associated with increased bone resorption or bone metastasis, among other pathologies, and they act by inhibiting bone resorption by osteoclasts [61]. Chemically, bisphosphonates are analogous to pyrophosphates, which have been shown to be naturally occurring modulators of bone metabolism, although the former are very resistant to hydrolysis owing to the presence of P–C–P bonds [62]. This leads to a poor intestinal absorption when orally administered, typically < 1% [63]. To overcome these drawbacks, the confinement of the bisphosphonate alendronate (AL) in the pores of SMMs for a local and controlled drug delivery system was proposed [64]. For this reason, two types of hexagonal SMM, MCM-41 (D_P = 3.8 nm) and SBA-15 (D_P = 9.0 nm), with two-dimensional hexagonal and *p6mm* symmetry, were selected. There was a dependence of the AL loading on the surface area of the SMM, that is, the highest surface areas promoted the greatest amounts of drug loaded. Therefore, MCM-41 and SBA-15 matrices, with surface areas of 1157 and 719 m^2/g, respectively, had AL loads of 14 and 8.3 wt%, respectively. AL loading increased when these SMMs were organically modified with aminopropyl groups. Thus, MCM-41-NH_2 and SBA-15-NH_2 had AL loadings of 37 and 22 wt%, respectively (**Figure 2C**). This fact can be attributed to the strong attracting interactions existing between the phosphonate groups in AL and the amino groups covering the silica surface (**Figure 2A**). This leads to a higher drug loading of modified materials compared with pure silica matrices, in which there are weak hydrogen bonds between the phosphonate groups of AL and the silanol groups covering the silica surface (**Figure 2A**).

Regarding AL release, it should be highlighted that in all cases an initial burst effect was observed. This fast release of the drug could be due to several reasons: AL that could be adsorbed in the outer surface of the matrix or by the existing alendronate gradient between mesoporous matrix and delivery medium. Therefore, after 24 h of assay, 28% of the total amount of AL adsorbed was delivered from MCM-41-NH_2, whereas at the same time this percentage was 58% for unmodified MCM-41. On the other hand, 11% of the total AL loaded was released after 24 h of assay from SBA-15-NH_2 matrix, whereas 55% of AL loaded was delivered after this time from SBA-15. After such a burst effect, the AL was released to the medium in a sustained manner following first-order kinetics for unmodified and modified MCM-41 materials and zero-order or linear kinetics for unmodified and modified SBA-15 materials. Moreover, the increase in the total drug delivery time in functionalised materials compared with unmodified matrices (**Figure 2D**) can be ascribed to the stronger interactions between phosphonate groups from AL and amino groups covering the pore walls (**Figure 2A**). This interaction led to a decrease in the AL delivery rate. This study reveals that it is possible to increase the AL intake rate from 1% up to a 40% when this drug is confined into mesoporous silica materials to be used as implants for bone defect repairing/regeneration. This new feature is important to avoid drug overdose on the whole body or undesirable side effects resulting from high dose administration. The amount and delivery rate of AL can be modulated by organically modifying the mesoporous silica walls. When amine groups are covalently grafted to the silanol groups on the pore surfaces, the bisphosphonate adsorption is increased almost threefold, with the subsequent intensification of drug dosage in the required area.

Recently, the amino modification of SBA-15 mesoporous materials using different functionalisation degrees has been revealed as key factor for modulating AL dosage [65]. The amino-modification method was improved by adding a catalyst during the functionalisation process. The amount of AL loaded linearly increased as the functionalisation degree increased, ranging from 8.8 wt% for the lowest functionalisation degree (0%) to 12 wt%, for the highest functionalisation degree (47%). Moreover, functionalisation degree also allowed a better control over AL release, that is, the higher the functionalisation degree, the smaller the percentage of AL released. This work shows the possibility of modulating drug dosage by varying the functionalisation degree of mesoporous matrix, which is particularly interesting when using bisphosphonates because the high potency of these drugs implies that only small local doses are needed.

4.6 Adsorption and delivery of proteins and amino acids

When the confinement of proteins into SMMs is targeted, the pore diameter is a limiting factor in molecule adsorption. The first report demonstrating the good properties of mesoporous silicas for use as protein adsorbents was performed in 1999 by Han *et al.* [18]. Yiu *et al.* [66] investigated the influence of protein dimensions on the adsorption into SBA-15, whose silica walls were functionalised with thiol groups. Then, a series of proteins

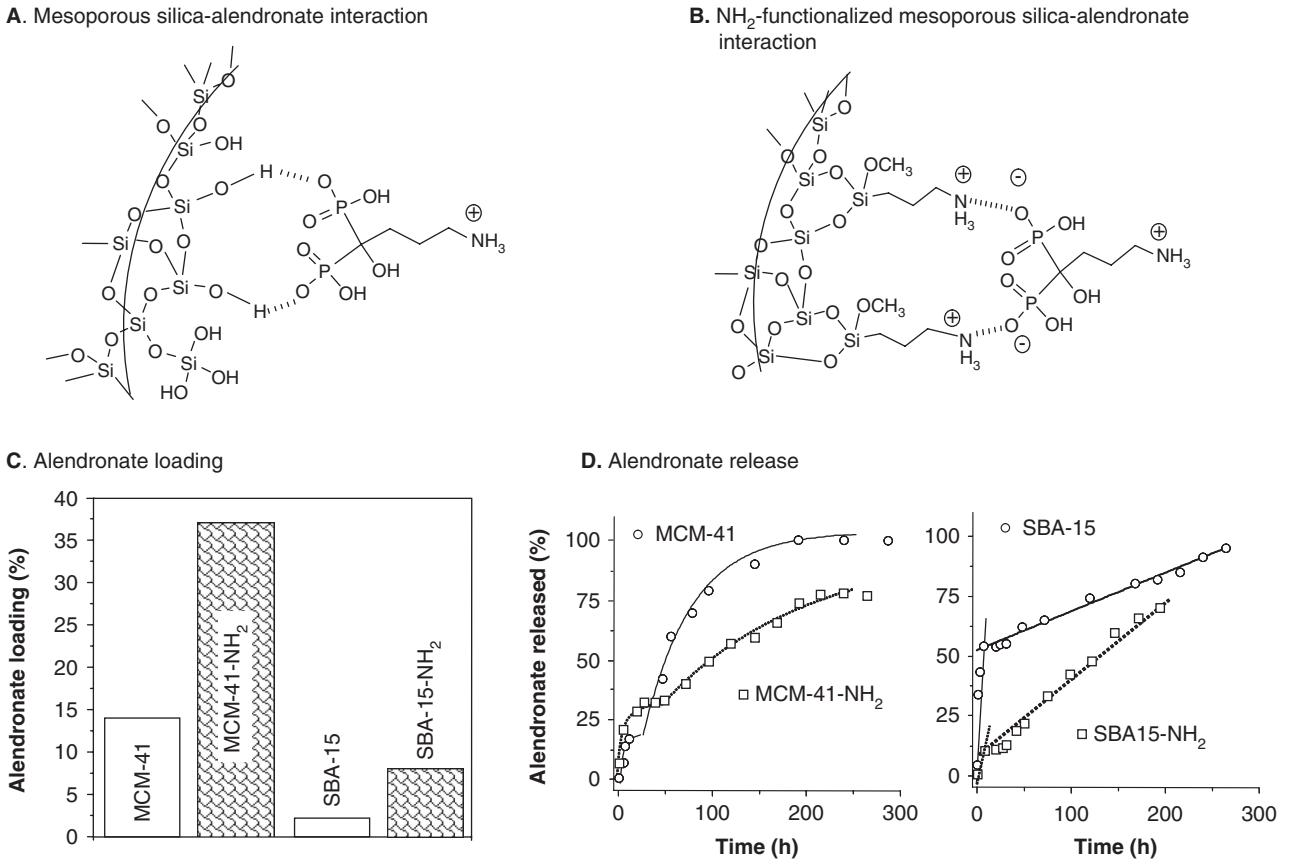

Figure 2. Schematic representation of the interaction of alendronate with (A) pure mesoporous silica and (B) amino-modified mesoporous silica, (C) Alendronate loads in different mesoporous materials and (D) Alendronate release profiles from different silica mesoporous materials.

with molecular masses ranging from 12,000 to 76,000 Da were used to investigate adsorption on SBA-15-SH materials. Further adsorption studies revealed that the proteins with the smallest sizes, such as cytochrome *c*, lysozyme, myoglobin and β-lactoglobulin, showed significant adsorption. On the contrary, the proteins with the largest sizes, such as conalbumin, serum albumin and ovalbumin were excluded from the internal surfaces of SBA-15-SH. This fact agrees with the sieving expected from the 5.1 nm pore size of SBA-15-SH matrix when compared with the proteins' dimensions. Moreover, the exclusion of ovalbumin (4.0 × 5.0 × 7.0 nm), with dimensions quite close to SBA-15-SH matrix, indicates that this size selectivity is rigorous and that there are very few pores appreciably larger than the average pore size.

From the above results it can be deduced that when the confinement of large proteins is aimed for, large pore mesoporous matrices are needed. This fact inspired the idea of using SBA-15 as a mesoporous carrier using different hydrothermal treatments during the synthesis to widen the pore diameter of SBA-15 [26]. Hence, pore diameters ranging from 8.2 to 11.4 nm were obtained for SBA-15 materials submitted to hydrothermal treatments periods ranging from 1 to 7 days. These pore dimensions seem suitable for hosting large proteins. Moreover, bovine serum albumin (BSA) loading dependence on SBA-15 diameter was observed. The amount of BSA loaded was 15, 23, 24 and 27 wt% for SBA-15 having pore diameters of 8.2, 9.5, 10.5 and 11.4 nm, respectively. To promote host–guest SBA-15-protein interactions, SMM was functionalised with aminopropyl groups by the post-synthesis method [26]. Thus, the amino groups of SBA-15-modified materials would undergo attracting electrostatic interactions with the carboxylic fraction of amide groups from the protein. As mentioned before, organic functionalisation always leads to a decrease in the mesopore diameter. The BSA molecule is just on the limit of the mesopore dimensions, and thus after amino functionalisation the amount of BSA loaded decreased compared with unmodified matrices. However, the BSA loading on amino-modified SBA-15 matrices underwent behaviour comparable to unmodified matrices in terms of loading increment as the pore size increased (**Table 2**). The amino functionalisation of SBA-15 had a noticeable influence on BSA delivery kinetics. The BSA release from pure silica mesopore surfaces essentially showed a burst profile, where > 90% of the adsorbed protein was released within

Table 2. BSA loading on functionalised matrices with different pore diameters synthesised by using different hydrothermal treatments (1, 3, 5 or 7 days).

Sample	D_P (nm)	BSA loaded (wt%)
SBA15-NH_2	7.5	10.0
SBA15-3d-NH_2	8.4	15.3
SBA15-5d-NH_2	9.2	18.5
SBA15-7d-NH_2	9.8	28.5

the initial 24 h of tests. The rest of the adsorbed protein was linearly released up to complete delivery in 192 h in all tested materials, regardless of the hydrothermal treatment carried out for synthesis. However, amino-modified SBA-15 materials showed an incomplete release of the protein from the mesopores in all cases. This partial protein retention was attributed to the strong attracting interaction of silica wall amine groups with the protein. After 192 h, the released protein ranged from 25% (SBA-15-7d-NH_2) up to 60% (SBA-15-3d-NH_2) of the initially loaded amount of protein.

Recently, functionalised SBA-15 has been proposed as a delivery system of L-tryptophan (*L*-Trp) [67], a hydrophobic amino acid present in the three-dimensional structure of many peptides, proteins and growth factors of interest in bone tissue regeneration technologies [68]. *L*-Trp presents an aromatic indol ring that makes it necessary to modify the silanol-rich walls of SBA-15. In fact, unmodified SBA-15 loaded < 5 mg/g of *L*-Trp, probably because of the extremely different chemical nature of hydrophobic amino acid and hydrophilic SBA-15. The small amount of *L*-Trp adsorbed into SBA-15 could be due to weak hydrogen bonds interactions between deprotonated carboxylic group of amino acid and silanol groups covering the silica walls. For this reason, SBA-15 matrix was organically modified using quaternary amines with different alkyl lengths (~ $C_3N^+Me_3$ and ~ $C_3N^+Me_2C_{18}$) [67]. Functionalisation with short alkyl chains (~ $C_3N^+Me_3$) allowed electrostatic attracting interactions between deprotonated carboxylic groups of amino acid ($-COO^-$) and protonated quaternary amines ($-N^+R_4$) covering the mesoporous surface. In this case, the amount of L-Trp loaded into SBA-15-$C_3N^+Me_3$ matrix was higher (4.3 wt%) than in unmodified SBA-15 (< 0.5 wt%). On the other hand, using long hydrocarbon chains (~ $C_3N^+Me_2C_{18}$), two-thirds of the silica surface was functionalised. This high degree of functionalisation with hydrophobic chains promoted interaction of mesoporous surface with the indol group of L-Trp and, consequently, the amount of amino acid loaded increased to 8.2 wt%. In both cases, there is an initial burst effect, where most of the *L*-Trp loaded is quickly released to the delivery medium. After such a burst effect, the rest of the amino acid is released in a controlled fashion, following first-order and zero-order or linear kinetics from SBA-15-$C_3N^+Me_3$ and SBA-15-$C_3N^+Me_2C_{18}$ matrices, respectively.

4.7 Adsorption and delivery of anticancer drugs

SMMs would be of great relevance for the confinement of anticancer drugs, which usually show high toxicity. Pasqua *et al.* [69] reported the use of bifunctional hybrid mesoporous silicas for drug targeting using cisplatin (CisPt) as an anticancer agent. A receptor-specific ligand folic acid (Fol) was covalently coupled on the external function of as-synthesised MCM-41 thanks to the presence of aminopropyl groups. Then, a series of hybrid materials useful for investigating the complex structure of folate-derivatised materials were developed starting from a silica gel substrate derivatised with aminopropyl functionality and successively coupled to folic or heptanoic acid. CisPt loading was 25, 37 and 24 wt%, for MCM-41-Fol, MCM-41-NH_2 and MCM-41, respectively. Probably, and despite the surface area available in the three materials, the interaction between folic acid and amino groups with the Pt atom in CisPt is the driving force for the adsorption of the drug. In fact, MCM-41-Fol (~ 250 m^2/g) and MCM-41 (~ 600 m^2/g) load the same amount of drug, whereas MCM-41-NH_2 (~ 400 m^2/g) adsorbs 50% CisPt more. *In vitro* delivery test of CisPt showed that the drug release is faster from pure silica MCM-41 than from MCM-41-NH_2 or MCM-41-Fol materials. This work showed that multifunctional hybrid mesoporous materials conceptually open new perspectives in developing new therapeutics.

5. Mesoporous materials as stimuli-responsive drug delivery systems

A stimuli-responsive controlled release system can achieve a site-selective controlled release pattern, which can improve the therapeutic efficacy compared with a standard sustained release system (**Figure 3**). An original idea consisted of capping the mesoporous channels of MCM-41-type matrix with cadmium sulphide nanoparticles to physically block the drug molecules from leaching out [70]. Lin and co-workers developed this approach to study the stimuli-responsive release of vancomycin and adenosine triphosphate (ATP) by adding certain releasing triggers. Thus, drugs can be encapsulated inside the porous framework and then released when desired.

The same approach of capping the mesoporous channels as mentioned above was used by Radu *et al.* for gene transfection [71]. Second-generation polyamidoamine (PAMAM) dendrimers were covalently attached to the surface of an MCM-41-type mesoporous silica nanosphere material, and this hybrid material was complexed with a plasmid DNA to favour transfection. Thus, this system allows the introduction of membrane-impermeable molecules, such as certain drugs, into the inner part of eukaryotic cells, which could be of interest in cancer therapies.

5.1 pH

A change in the pH is a stimulus that has been widely used in this kind of system. Certain tissues of the body have a pH slightly more acidic than blood and normal tissue. Thus, a

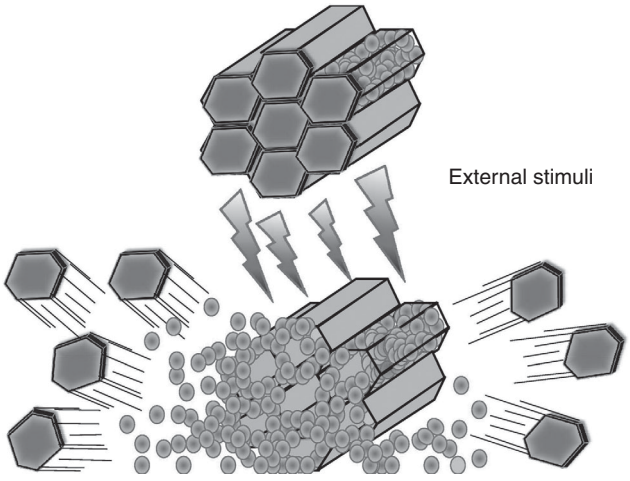

Figure 3. Schematic representation of stimuli-responsive drug delivery from silica-based ordered mesoporous materials.

delivery system based on acid pH means an efficient way of drug release targeting specific sites in the body, such as tumour and inflammatory tissues. Huddersman *et al.* showed how the pH value influenced the release of a model drug fluorescein from an Al-MCM-41 matrix [72]. A similar approach, a pH-responsive carrier system but using different matrix, SBA-15, was presented by Yang *et al.* [73]. They modified the pore entrances of the mesoporous matrix using carboxylic acid. Then, polycations were adsorbed to the anionic SBA-15 by oppositely charged ionic interaction closing the gates of the pores with the drug inside. When changing the pH value, the ionised carboxylic species (COO^-) were transformed to protonated groups (COOH) and polycations were moved away, leading to opening of the gates for releasing the drugs from mesopores. Vancomycin was released at different pHs (2.0, 4.5 and 6.5), showing very different release patterns depending on that pH value. Zink and co-workers reported a different system where the openings of functional MCM-41 were regulated by supramolecules that were controlled by pH and competitive binding [74,75].

The storage capacity of conventional mesoporous silica materials can be enhanced by synthesising hollow mesoporous silica spheres with pore channels penetrating from the outside to the inner hollow core. Shi and co-workers designed a stimuli-responsive controlled drug-release system using these spheres and coating them with polyelectrolyte multilayer composed of sodium polystyrene sulphonate and poly(allylamine hydrochloride) [76]. These multilayers cap the mesopore openings and the release rate can be controlled by changing the pH value of the release medium, so it can be used to release certain drugs into the stomach rather than the intestine. Aiming for this type of oral release system, coating the surface of drug-loaded SBA-15 tablets with a pH-sensitive polymer such as hydroxypropyl methylcellulose phthalate would allow certain control to release the drug where desired, whether in the stomach or in the intestine [77]. A pH-sensitive drug delivery system can also be prepared encapsulating amine-functionalised mesoporous SBA-15 loaded with BSA with a thin layer of poly(acrylic acid) [78]. The authors reported that BSA was released more quickly at pH 7.4 than at pH 1.2, which means that the system has potential application in the release to certain proteins to a site with a higher pH value, such as the small intestine or colon. Another example of a pH-controlled release system, reported by Chiyoung *et al.*, was based on grafting to the external surface of mesoporous silica a pH-responsive polyethyleneimine/cyclodextrin (PEI/CD) polypseudorotaxane [79]. The mesopores of PEI-modified silica were filled with calcein (guest molecule) and then blocked with CD at pH 11. At pH 5.5, the guest molecules were released from the pores by the reversible dethreading of CDs from the PEI chain.

5.2 Temperature

Following a similar approach, but using a thermosensitive polymer rather than pH-responsive, Chang *et al.* designed a bicontinuous, thermosensitive silica nanocomposite system [80]. A well-known thermosensitive polymer, poly(*N*-isopropylacryl amide) (PNIPA) was integrated with L-3 phase silicates at the nanoscale level, and highly controlled drug delivery was successfully demonstrated. The same thermosensitive polymer, PNIPA, was grafted into a mesocellular silica foam (MCF) via atom transfer radical polymerisation (ATRP). The control of drug adsorption and release through the porous network was performed using rhodamine 6G [81] and IBU as model drug [82].

5.3 Photoactive derivates

Fujiwara and co-workers determined, for the first time, that the uptake, storage and release of organic molecules in MCM-41 could be regulated through the photocontrolled and reversible intermolecular dimerisation of coumarin derivates attached to the pore outlets [83]. Other photoresponsive release systems have used azobenzene molecules to produce movement [84] and to deliver a drug to cancer cells [85].

5.4 Ultrasounds

A different stimulus that has been used by Honma and co-workers is the use of ultrasound as an external trigger for the pulsatile release of IBU [86]. Mesoporous silica was modified with poly(dimethylsiloxane) and IBU was released under the stimulus of ultrasounds.

5.5 Nanovalves

Hernández *et al.* developed an efficient reversibly operated nanovalve that can be turned on and off by redox chemistry [87]. The mesopores were loaded with the fluorescent molecule tris(2-phenylpyridine) iridium and capped with a pseudorotaxane. The opening of the nanovalve was stimulated by the addition of an external reducing agent, which causes the pseudorotaxane to disassemble and the fluorescent molecule to

be released. The same researchers have been working with the same approach of redox-controllable systems to open and close the pores of mesoporous release systems [88,89]. Nanovalves have also been prepared using a pH-sensitive macromolecule to cap the mesoporous channels of MCM-41 [90]. The release system relies on the ion–dipole interaction of the capping molecule when increasing the pH.

5.6 Light

Light is an external stimulus that can cause a chemical change and, therefore, a system that responds to this external stimulus can be developed. Ferris *et al.* reported light-operated mechanised MCM-41 nanoparticles modified with two azobenzene derivates that were able to retain dye molecules and then release them on exposure to light [91]. The ability of these systems to release stored drug molecules in response to an external light source makes these delivery systems applicable to light-operated intracellular drug delivery systems.

6. Mesoporous silica spheres

Control of the particle morphology of the mesoporous material leads to more reliable and reproducible drug delivery systems. This control can be achieved using an aerosol-assisted synthesis to produce different mesoporous structures in the form of spheres of a micrometric size to produce a triclosan release system [92]. In fact, morphology and aggregation of the mesoporous particles seem to affect the delivery rate from these matrices, as has been observed with IBU from MCM-41 matrices [93,94].

On the other hand, using hollow mesoporous silica spheres brings the possibility of storing much more guest molecules than conventional mesoporous silicates. It is also well known that hollow spheres with mesoporous shells have more advantages in mass diffusion and transportation compared with conventional hollow spheres of solid shells. Within this porous shell, it is important that porous channels penetrate across the shell for drug storage and delivery systems. These penetrating pore channels can be achieved using poly(vinylpyrrolidone) (PVP) and cetyltrimethylammonium bromide (CTAB) as co-templates during the synthesis [95]. They stored IBU in the hollow spheres by impregnation, leading to a storage capacity three times higher than that of conventional mesoporous materials reported previously [96]. The fact that the shell is made of ordered mesoporous silica offers the possibility of producing it with different mesostructure and grafting several organic groups to modify the release patterns of different drugs adsorbed [97,98].

7. Magnetic mesoporous nanoparticles

The introduction of a site-directing capability of silica-based ordered mesoporous delivery systems was an important advance in the application of these matrices as biomedical devices [99]. Magnetic nanoparticles have been shown to target selectively the desired organs or tissues inside the body. The introduction of superparamagnetic iron oxide (Fe_3O_4) nanoparticles capping mesoporous silica nanorods allowed the materials to be attracted to specific sites of interest under a magnetic field [100]. Drug molecules, fluorescein, were encapsulated and released from the system in the presence of an external magnetic field.

A different approach is the encapsulation of magnetic nanoparticles with mesoporous silica microspheres [101]. An aerosol-assisted route was used to obtain stable and homogeneous particles formed of a γ-Fe_2O_3 core and encapsulated by ordered mesoporous silica. This approach allows loading the mesoporous silica with a desired drug, and then the material could be directed with an external magnetic field to release the drug to the specific target [102]. Also, the silica encapsulating the magnetic particles can be developed with different mesostructure, which would lead to different drug release patterns depending on the requirements of the disease [103].

It is also possible to introduce magnetic nanoparticles into the mesoporous channels of MCM materials and hollow silica spheres by impregnation, oxidation and reduction procedures [104]. The advantage of this synthetic method is that it can be repeated to increase the iron content in the particles and microcapsules and, thus, directed with an external magnetic field. The high volume of the internal cavities of both MCM and hollow spheres can be filled with drugs, which would be targeted where needed.

8. Mesoporous materials as cell markers

SMMs have been shown so far in this review as versatile controlled release systems. However, their great internal surface could be used for carrying non-releasing molecular imaging agents, such as fluorophore or magnetic resonance imaging contrast agents [105], which is also important for the biomedical industry. Thus, functionalising the internal surface of mesoporous silicas with fluorophores would allow them to be used as fluorescence cell tags, with the advantage of being stable against enzymatic digestion and therefore good for long time cell marking [106].

A similar approach for cellular labelling with vector composed of mesoporous silica nanoparticles conjugated with fluorescein isothiocyanate in human bone marrow mesenchymal stem cells and 3T3-L1 cells was reported by Huang and co-workers [107]. It should be highlighted that the internalisation of these fluorescein mesoporous silica did not affect the cell viability, proliferation, immunophenotype and differentiation potential of mesenchymal stem cells and 3T3-L1 cells.

9. Toxicity and/or biocompatibility of mesoporous materials

Amorphous silica has generally been considered as non-toxic, and it is known to be biocompatible and degradable in living tissue [108]. In fact, amorphous colloidal and porous silica are

used as adjuvant in pharmaceutical technology. However, there are few research works reporting the inherent cytotoxycity and biocompatibility of SMMs. The concentration of ordered mesoporous silicas has been found to be a key factor in their *in vitro* toxicity; they showed low toxicity at low concentrations and, on the other hand, high toxicity at high concentrations [109]. Also, the possible residual fragments of surfactant coming from the thermal treatment might be cytotoxic. For this reason extracting the surfactant rather than thermal removal is normally preferred for the use of SMMs in biomedical applications. In the biological use of mesoporous silica it is vital to minimise to the nanometre range the particle size if intracellular delivery is the aim. It has been reported that fluorescein-functionalised mesoporous silica nanoparticles with sizes ~ 110 nm have been internalised in 3T3-L1 fibroblast cells and accumulated in cytoplasm with no apparent cytotoxic effects in fibroblast cells [106]. The surface area has also been reported to be an important factor in causing cell death. Di Pasqua *et al.* have been researching the cytotoxicity of MCM-41 materials, unmodified and organically modified with aminopropyl (AP-T) and mercaptopropyl groups (MP-T), and spherical silica nanoparticles towards human neuroblastoma [110]. They related the cytotoxicity to the number of particles required to inhibit normal cell growth by 50% (Q_{50}), and found that this value increased in the order MCM-41 < MP-T < AP-T ≈ SiO_2. Thus, MCM-41 was the most cytotoxic material of all of them. This cytotoxicy was apparently related to the adsorptive surface area of the particle, although the nature of the functional group could not be ruled out.

In vivo toxicity of ordered mesoporous materials was observed at high concentrations with mesothelial cells [111]. When proceeding to subcutaneous injections of diverse mesoporous silicas, such as MCM-41, MCM-48 and MCF, at the static nerve in rats, and attending to histology, a good biocompatibility was observed at all time points [111]. However, intraperitoneal and intravenous injections in mice resulted in death or euthanasia. The fact that no toxicity was observed with subcutaneous injection of the same particles in mice means that toxicity of these types of mesoporous silicate depends strongly on the way that they are supplied to the living body.

10. Expert opinion

This paper has reviewed a wide range of the different research works developed so far aimed at using SMMs as DDSs. The first part of this review summarises the basic investigation carried out by many research groups, which allowed the emergence of this new line of research. The length of this part is intended to facilitate knowledge of the key factors of SMMs that can be used as DDSs.

The research of these materials confining ibuprofen, a common anti-inflammatory drug, as a model drug started back in 2001, and it became the first of many works that were important for acquiring the necessary knowledge of these systems. However, ibuprofen has fulfilled its role as a model drug, and, nowadays, with the properties and perspectives of mesoporous silica, it does not make sense to use this anti-inflammatory drug. Interest should be focused on selecting the drug depending on the application of the material. This DDS should be designed taking into consideration the dosage required for any specific disease.

The possible toxicity of ordered mesoporous silica, which has been commented on throughout this review, has been the subject of many scientific discussions. There are enough data in the literature to assess that when these mesoporous silica are used *in vitro* with the correct concentration and with the proper particle size, they are not toxic. They can even be used as cytoplasm drug delivery systems with no apparent cytotoxic effects in fibroblast cells. When used *in vivo*, the toxicity of these mesoporous silica would depend on the way that they are supplied to the living body: whereas subcutaneous injections presented good biocompatibility, intraperitoneal and intravenous injections resulted in mice dead. Also, the dosage represents a key factor, together with the possible organic modification of the surface of the materials with biocompatible and non-toxic groups that cannot be recognised as foreign by the body's defence mechanisms.

The great majority of researchers aim for oral delivery systems with mesoporous silica, as has been shown throughout this review. However, the authors' research group aimed at local delivery for bone technologies from the very first paper published on this topic. From *in vivo* research experiments, it was found that when the mesoporous material is in contact with bone marrow a haematoma is formed during the first week of implantation. This is precisely the period of time when the release is taking place, and after that first week the haematoma normally evolves to a fibrous tissue or new bone, living the mesoporous material in the inner part of this newly formed structure. Thus, mesoporous materials are good release matrices for delivering pharmacological drugs or biologically active species to the place where needed, the targeted bone tissue, at the time needed, during the first week of formation.

Thus, the research on SMMs opens the gates to an important biomedical application, such as the treatment of infected bones. When bone tissue is infected, there are adverse reactions that require the administration of antibiotics. The main challenge in this situation is to reach the infected tissue with pharmaceutical drugs, which is not possible with conventional therapies. The medical strategies that are being applied nowadays to solve this problem are not very effective when the affected tissue has not been irrigated enough. In this particular situation, it is important to deliver the antibiotics locally to the precise infected area. This task could be achieved with the implantation of SMMs in the infected tissue. There would be a local release of the drug where it had not been possible to reach with conventional therapies. Also, the antibiotic release would take place during a period of time long enough to neutralise the bacteria action,

and before the new bone was formed surrounding the implanted material.

The use of SMMs as local DDSs for the treatment of osseous pathologies and complex diseases gives rise to promising expectations in the clinical field. The properties of SMMs can be designed, as has been shown throughout this review, to adapt the matrix to a proper response and delivery dosage according to the clinical needs of the patient pathology. Thus, the treatment of difficult unsolved clinical situations could be achieved, such as the case of bone tissue infection, which would be of great importance for the biomedical research community.

Declaration of interest

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