Drug release from ordered mesoporous silicas

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Abstract

The state of the art in the investigation of drugs release from Silica-based ordered Mesoporous Materials (SMMs) is reviewed. First, the SMM systems used like host matrixes are described. Then, the model drugs studied until now, including their pharmacological action, structure and the mesoporous matrix employed for each drug, are comprehensively listed. Next, the factors influencing the release of drugs from SMMs and the strategies used to control the drug delivery, specially the chemical functionalization of the silica surface, are discussed. In addition, how all these factors were gathered in a kinetic equation that describes the drug release from the mesoporous matrixes is explained. The new application of molecular modeling and docking in the investigation of the drug delivery mechanisms from SMMs is also presented. Finally, the new approaches under investigation in this field are mentioned including the design of smart stimuli-responsive materials and other recent proposals for a future investigation.

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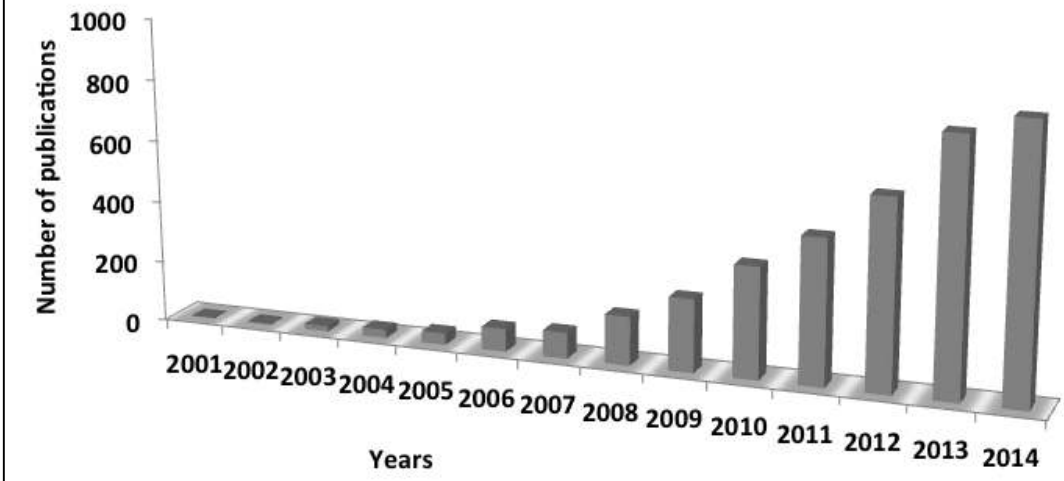
INTRODUCTION

The application of ordered mesoporous materials like matrixes in drug delivery systems began in 2001 with the publication of the first article describing the discovery that ibuprofen could be loaded and released from MCM-41, a Silica-based ordered Mesoporous Material (SMM) [1]. A new class of host-guest system was thus established where the guest (the drug) were loaded into host (the mesoporous matrix) to be afterwards released by dissolution of the drug in an aqueous solvent. The fluid solvent, competing with the inorganic groups of the mesoporous SiO_2 matrix, transported the drug through the mesoporous channels until it is released. The drug can be released as much *in vitro* as *in vivo* to a biological fluid like blood plasma to exert its therapeutic action in the human organism.

From 2001, the scientific interest on this application of the SMMs has been exponentially growing, as it is demonstrated by the high number of publications since then (Fig. **1**). As it can be observed in the figure, from the 2001 to 2014 over 3773 articles and review papers were published using "mesoporous silica" and "drug delivery" or "drug release" as search criteria.



Year	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
n° pub.	2	4	17	27	37	74	84	158	235	359	468	612	818	878

Fig. (1). Evolution in the number of publications regarding the drug administration models from SMMs. Data obtained from ISI Web of Knowledge®.

On the other hand, if we made this search in Google Scholar® more than 27200 results are found and 257000 doing that in Google®. This gives an idea of the interest of this subject for the specialized researchers and also for the whole society.

Much has been advanced in this research field from the beginnings where the drug was released without know neither the adsorption and release kinetics nor the drug-matrix interaction mechanisms and without a control at demand of the release process. Nowadays, we can control the release of the drug, to know the kinetics of release, the interactions, essentially electrostatic, that govern the chemical interaction of the drug and the mesoporous matrix as well as other parameters that affect the release rate of the drug.

Nevertheless, still much work remains to be done with the objective that the mesoporous matrixes release the drug of a selective manner in the human body. That supposes to carry out the drug to the site where its pharmacological action is needed and then release it from the matrix. That way, an intelligent drug delivery system, and not only controlled, would be created.

In general, drugs are administered to human body by the following routes: oral, topical, inhalation, rectal or parenteral [2]. Nevertheless, the first application for the delivery of drugs in the humans with SMMs was not the administration by those routes, but to be included in clinical implants. It must be taken into account that inflammation and infection produce important problems in Orthopedic and Dental surgeries after the implantation [3-5]. For that reason, anti-inflammatory and antibiotics were the first drugs investigated to load SMMs, so that they were released *in situ* [6, 7]. Nowadays, its field of application was extended, with the introduction of new SMMs and drugs with further therapeutic actions as it will be described in this paper.

The selection of the concrete SMM which is going to act like host for a specific the drug guest is essential for its correct therapeutic action. Therefore, it is necessary to know how to combine both factors of the more appropriate way, to establish a SMM-drug system that increased the security and effectiveness in the administration of the drug. With this purpose it is necessary a deep knowledge of the characteristics of the mesoporous matrix and the drug, as well as the factors that regulate the interaction mechanisms of adsorption and release of the drug within the channels of the matrix. The application of *in silico* molecular modeling techniques, together experimental characterization techniques including Transmission Electron Microscopy, TEM, High

Performance Liquid Chromatography, HPLC, Nuclear Magnetic Resonance, NMR, and many others will help us to the understanding all these factors.

This review article gives an outlook of the state-of the-art of the investigation in drugs delivery from SMMs and the future perspectives of research in this field. First, the main types of SMMs investigated for this purpose are described. The second section includes a comprehensive table of the SMM-drug model systems investigated until now classified by its therapeutic action, together another list including representative examples of SMM- biological and food models. This is the core of the paper. Third section comprises the parameters influencing the release of drugs from SMMs including pore diameter, surface, pore volume, electrostatic forces, tortuosity of the channels and others. The fourth section presents the Higuchi model, the most used to adjust the drug release kinetics in these models. The fifth section describes the most common strategies used for control the drug release, like the matrixes functionalization with polar or apolar chains to tailor the drug-matrix interactions and consequently the kinetics of release. The sixth section describes how molecular modeling can be applied as a predictive tool in the release of drugs from SMMs and includes a few molecular models that have been reported. Finally, the main conclusions and future perspectives in this emergent research field are summarized.

1. SILICA BASED ORDERED MESOPOROUS MATERIALS TO HOST DRUGS

In general, SMMs have a structure or superstructure of intermediate complexity (mesostructure) containing pores with diameter ranging from 2 to 50 nm (mesopores). Ordered mesoporous materials can be or disordered and are based structurally on repetitive pores. Typically, they are constituted by silica or alumina exhibiting mesopores of uniform size. Furthermore, they can be also constituted by other oxides for example of niobium, tantalum, titanium, cerium, zirconium or tin [8].

The load and release processes of a drug in a SMM, take place in the interphase fluid medium and porous solid. Thus, the adsorption of the drug by the matrix and the release process fairly depend on the nature of the porous solid.

The synthesis of the SMM is basic to determine its nature. These materials are based on the sol-gel chemistry principles along with those of supramolecular chemistry.

To obtain ordered mesoporous materials, organic tensioactive acting as templates during the condensation of the inorganic precursors are used. During the process, a threshold value is reached, denominated critical micellar concentration, where the tensioactive molecules form molecular aggregates denominated micelles which are also grouped in supramicellar structures. In the synthesis of the SMMs the oligomers of silicate dissolved condense around the micelles that act as templates to form a solid that contains the tensioactive, which is eliminated by extraction with solvents or calcination. This way, and once eliminated the tensioactive agent, diverse geometries, including hexagonal, cubical or the lamellar that typically constitute in channels or cavities separated and supported by amorphous silica walls. The dimensions, topology and the chemical nature of the inorganic skeleton of the cavities determine the physical chemical properties of the mesoporous material. Such properties depend on the nature and concentration of tensioactive and the synthesis conditions including temperature, pH, saline total concentration and others.

The type of the surfactant and the pH of the medium are the key factors affecting to the properties of the SMM obtained. Surfactants can be classified as cationic, anionic, neutral or non-ionic. The type of surfactant has great importance in the synthesis of mesoporous materials, since the nature of the phase is largely influenced by the interaction between the chemical species in solution and the surfactant. Basically, three types of interactions can be established: $I^- S^+$, in which the inorganic species in solution has negative charge (I^-) whereas the surfactant is positively charged (S^+); $I^+ S^-$, the case opposed to the previous one and the type in which both chemical species have not net electrical charge $S^0 (XI)^0$ (being X^- the contra-anion). In all the cases it is necessary to consider that pH determines the charge of the chemical species that are going to form the inorganic skeleton of the material and consequently it controls the mechanism of interaction with the surfactant. Thus, the silica species in solution will be negatively charged at pH $\geq$ 9, whereas at pH neutral or weakly acidic the negative charge is very small, prevailing the Si–OH groups. For that reason, for the synthesis of SMMs, like MCM-41, MCM-48 and others, cationic surfactants (S^+) like alkyltrimethyl ammonium bromide are performed under basic conditions, where silica species are present as anions (I^-).

On the other hand, for the SBA-15 synthesis, a neutral surfactant, such as Pluronic® P123, ($HO(CH_2CH_2O)_{20}(CH_2CH(CH_3)O)_{70}(CH_2CH_2O)_{20}H$) is used at acidic

pH. In this case the synthesis pathway takes place through a double layer hydrogen-bonding interaction that occurs between non-ionic surfactant (S^0) and the X^-I^+ ionic pairs formed in the acidic medium. This synthetic route is used for SBA-n (n= 11, 12, 15 and 16) and FDU-n (n= 1, 5 and 12). Other strategies based in neutral surfactants have also yielded to HMS and MSU families, whereas the S^-I^+ type, failed in the synthesis of SMMs when used acidic conditions, although it can be used to create the AMS-n family by working in basic conditions [9-11].

The great versatility in the synthesis of these materials is a great advantage, since allow its obtaining as discs, powders, microcapsules or nanoparticles, which opens a great number of possibilities for the administration of drugs guests.

The necessity to create these SMMs, arise in the decade of 1990s. Their precursors are the zeolites, a type of silicates that are mainly used as catalysts in the cracking of petroleum to obtain gasoline or diesel combustibles. However, zeolites are microporous materials with pore diameter lower than 1 nm. This limits its applications to the adsorption of very small molecules, and most of drugs and biological molecules are greater than this size. For example, amoxicillin molecule is 1.1 nm lengths, erythromycin of 1.4 nm and there are many others of even bigger sizes.

The necessity to obtain zeolites with greater pore size for the adsorption of molecules of greater dimensions to expand its field of application is what took to a group of scientists of Mobil Oil Company to synthesize a new family of compounds denominated M41S. These synthetic materials have pores of diameter between 2-10 nm, *i.e.* they are mesoporous but, in addition, their pores exhibit an ordered and very homogenous pore size distribution. Other characteristics, like high pore volumes of around 1 cm^3/g and specific surface areas between 500-1000 m^2/g, become these SMMs in very useful for the adsorption of elevated amounts of big molecules, like many drugs are.

The first ordered mesoporous silica material used as drug host system was MCM-41 (Mobil Composite Matter number 41) and later on MCM-48 (Mobil Composite Matter number 48). Other, widely used later, was SBA-15 (Santa Barbara Amorphous number 15). All these structures are amorphous at the atomic scale, but they exhibit ordered mesostructures at the molecular scale and consist of pores in the form of channels [9-20]. MCM-41 has a flat hexagonal structure, whereas the one of MCM-48 is cubical bicontinuous.

The SBA-15 structure is hexagonal plane like MCM-41 [21]. Nevertheless, the pore diameter of SBA-15 of around 9 nm (up to 30 nm with special synthesis conditions) is greater than the one of the approximately 3 nm of MCM-41 (can be up to 10 nm). In addition, the SBA-15 structure also contains a microchannels system of that connect to the mesochannels. On the other hand, the pores of MCM-48, present a typical range size between 1.6 and 3.8 nm.

The pores of MCM-41 and SBA-15 are longitudinal, whose cross-sectional section is similar to a hexagon, whereas MCM-48 has a tridimensional pore system, since the longitudinal pores produce intersections in the three directions of the space.

These three materials, MCM-41, MCM-48 and SBA-15 have been traditionally used like hosts for the drug adsorption and still they are being investigated [22, 23]. This is due to that the inorganic silica, base of these mesoporous materials, has biocompatibility and a low cytotoxicity, which makes safe its administration in the human body.

Fig. **2** shows the structures of MCM-48 and MCM-41 (similar to SBA-15). Later on, other ordered mesoporous silica materials, for that and other applications were investigated including FDU-5 [24], FDU-12 [25] (FDU coming from Fudan University), FSM-16 (Folded Sheet Mesoporous Material) [26], HMM-33 (Hiroshima Mesoporous Material) [27], PLGA-SiO_2 (Poly-Lactic-co-Glycolic Acid) [28], SBA-16 [29] or TDU-1 (Technical Delft University) [30].

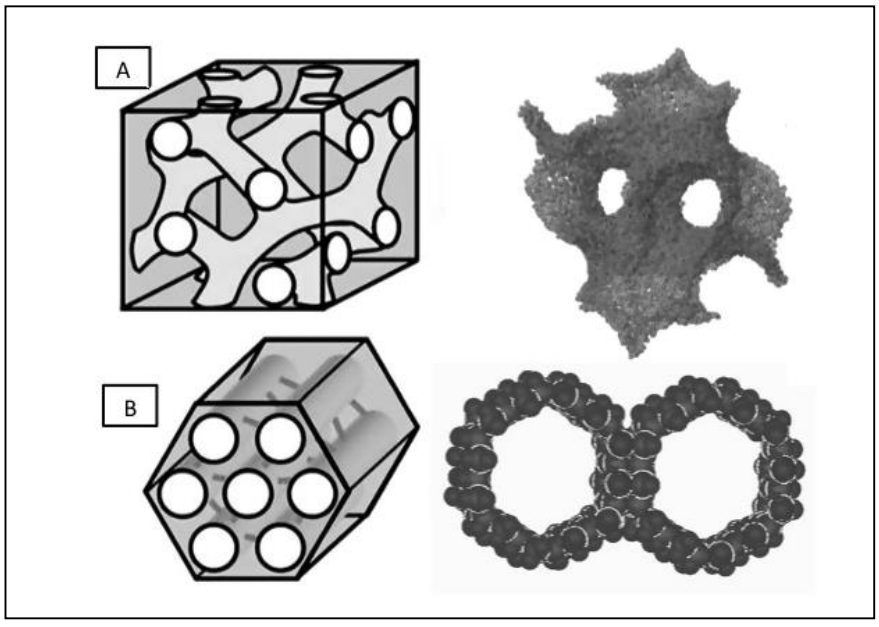


Fig. (2). Porous structures of: A) MCM-48 and B) MCM-41. (Modified from [31-33]).

These SMMs can be functionalized and then they are named adding to the acronym of the material (for example, SBA-15, MCM-41) the number of carbon atoms of the used alkyl chain for the inorganic functionalization (basically C8 and C18), for example, SBA-15-C8, the inorganic (basically - NH_2 and - SH) or organic groups (basically -COOH) used, for example, MCM-41-NH_2 or SBA-15-COOH and also composed like $C_3N^+Me_2C18$ or derivatives of TMS (trimethylsilyl), and others. Furthermore the SMMs can be doped with metals like titanium (Ti-SBA-15, for instance) [34] or zirconium (like Zr-MCM-41) [35] and so on.

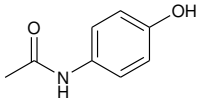
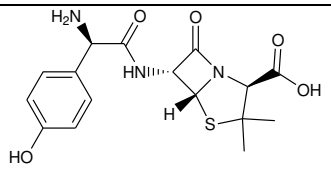
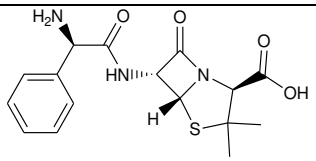
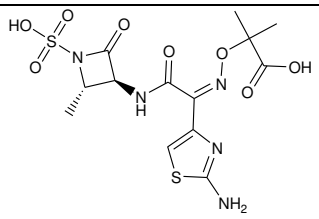
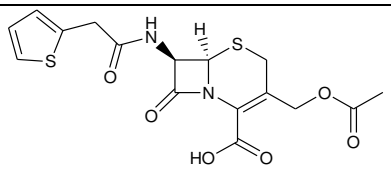
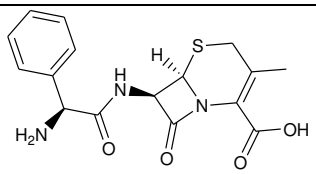
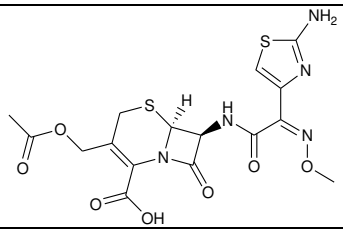
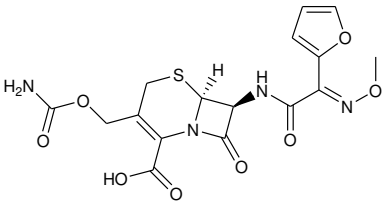
All the properties of the SMMs native, functionalized or doped, especially by their textural properties (high surface area and great internal pore volume) are much appropriated for the drugs adsorption, even of a great size. In addition, the ordered distribution of its pores with linear channels, mainly in SBA-15 and MCM-41, favors the homogeneity in the diffusion of drug molecules, guaranteeing the reproducibility.

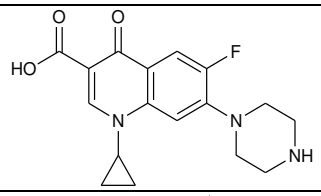
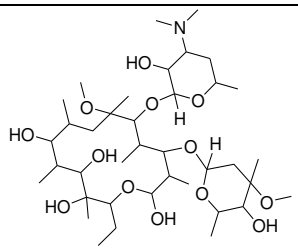
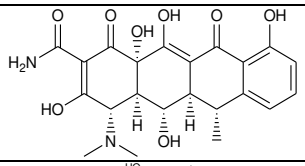
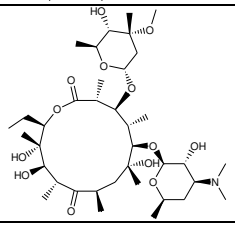
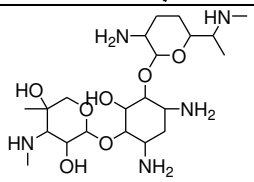
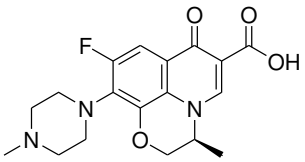
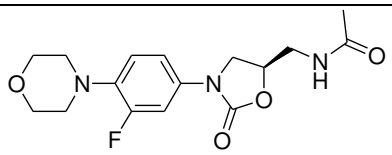
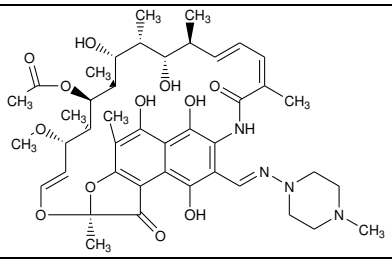
2. HOST DRUG MODELS

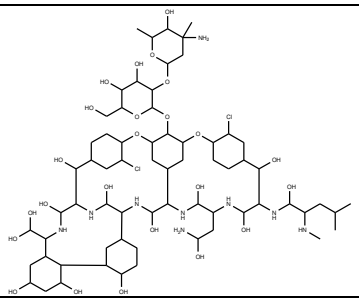
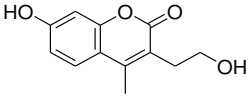
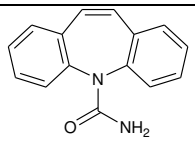
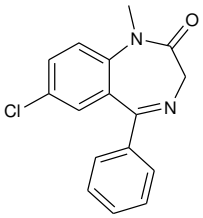
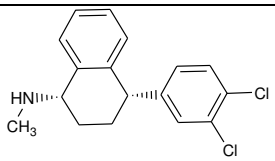
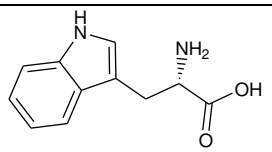
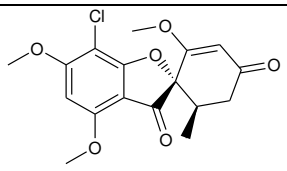
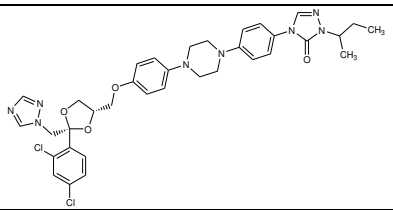
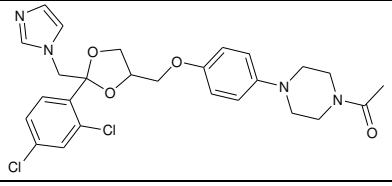
The drug guests are usually loaded in the SMM by impregnation from a solution containing the drug at constant temperature, until reaching the time at which the maximum adsorption of the drug in the mesoporous matrix takes place.

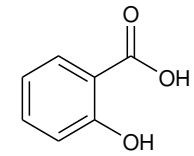
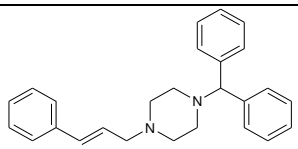
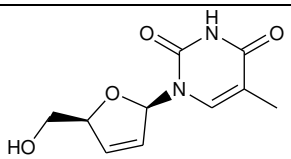
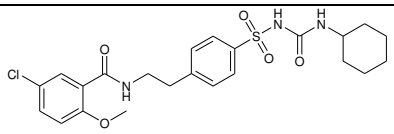
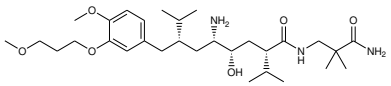
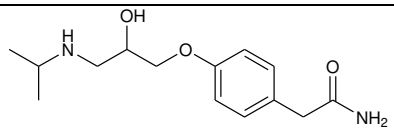
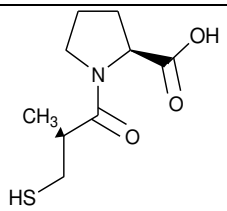
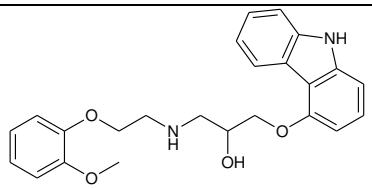
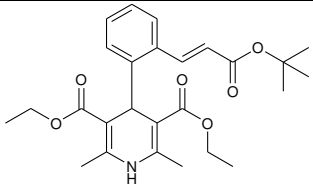
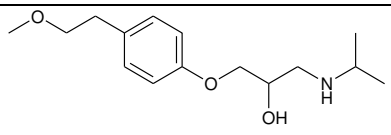
In this stage, to choose the more suitable mesoporous material for the drug between all the available ones is very important [36], but also is the selection of the drug that is going to load in the matrix. We have comprehensively compiled all the host-guest, SMM-drug, models as well as the main biological materials and nutritional complements investigated to date to be released from SMMs (Tables **1** and **2**).

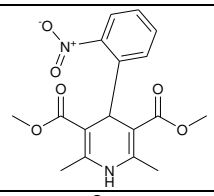
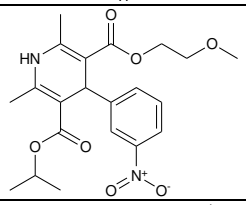
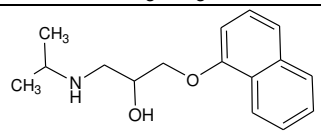
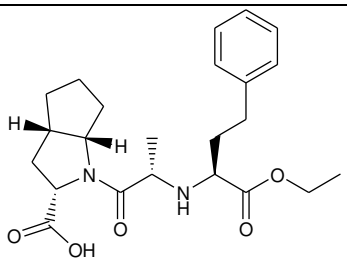
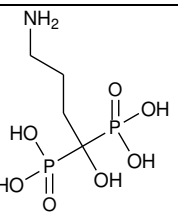
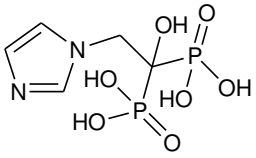
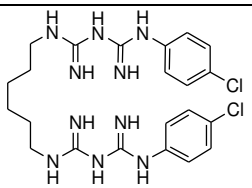
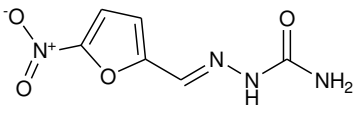
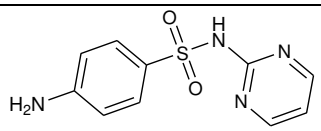
Table 1. Drug models and silica ordered mesoporous matrixes (SMMs) investigated as drug delivery systems, with the pharmacological action and molecular structure.

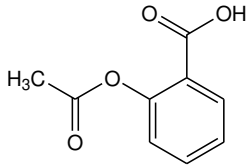
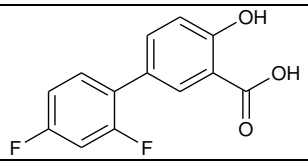
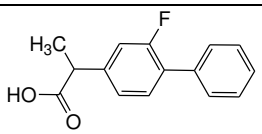
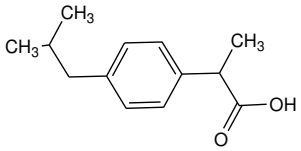
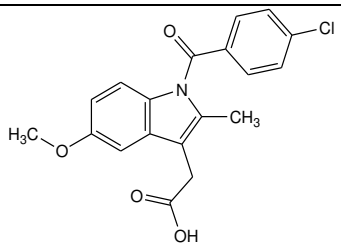
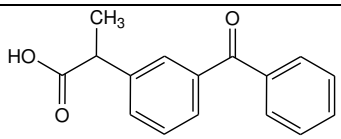
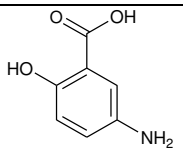
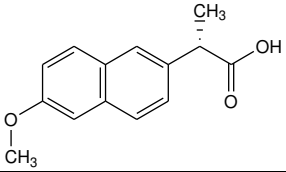
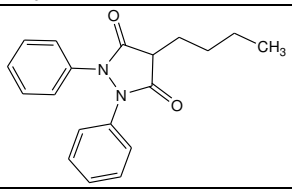
Categorie	Drug –SMM models	Molecular structures	Ref.
Analgesic	**Acetaminophen (Paracetamol)** Analgesics, Non-Narcotic Antipyretics **Matrix:** SBA-15		[37]
Anti-bacterials	**Amoxicillin** Antibiotic semisynthetic Beta-lactam **Matrixes:** SBA-15, MCM-41-APTMS, MCM-41-CPTMS		[38, 39]
	Ampicillin Antibiotic semisynthetic Beta-lactam **Matrix:** MCM-48-HMDS		[40]
	Aztreonam Monobactam antibiotic Gram-negative infections especially of the meninges, bladder and kidneys **Matrix:** MCM-41		[41]
	Cefalotin Cephalosporin first generation Beta-lactam antibiotic **Matrixes:** MCM-41, MCM-41-APTES, MCM-41-VTES		[42]
	Cefalexin Cephalosporin first generation Beta-lactam antibiotic **Matrix**: SBA-15		[43]
	Cefotaxime Cephalosporin third generation Beta-lactam antibiotic Broad-spectrum **Matrixes:** MCM-41, MCM-41-APTES, MCM-41-VTES		[42]
	Cefuroxime Cephalosporin second generation Beta-lactam antibiotic **Matrixes**: SBA-15, SBA-15-MPTES, SBA-15-APMS, FDU-12, FDU-12-MPTES, FDU-12-APMS, MCM-41, MCM-41-APTES, MCM-41-VTES		[42, 44]

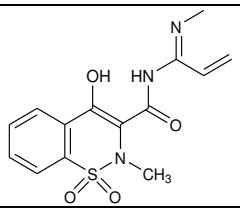
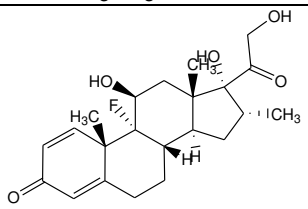
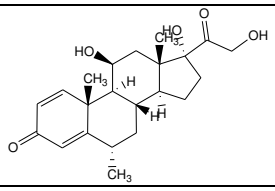
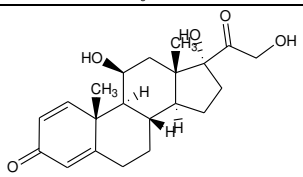
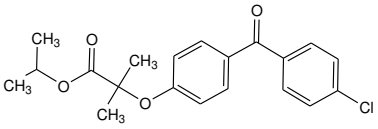
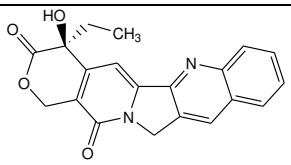
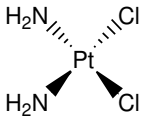
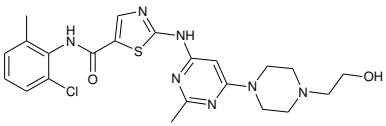
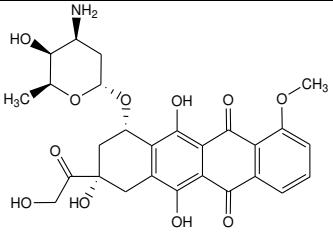
	Ciprofloxacin Fluoroquinolone second-generation Antibiotic **Matrix**: SBA-16-HA		[45]
	Clarithromycin Macrolide antibiotic Respirator and skin infections treatment Lyme disease treatment Helicobacter pylori treatment **Matrixes**: SBA-15, SBA-15-TREN		[46]
	Doxycycline Tetracycline antibiotic Antimalarial **Matrix:** SBA-15		[47]
	Erytromycin Macrolide antibiotic Protein synthesis inhibitor **Matrixes**: MCM-48, FDU-5, FDU-5-C8, SBA-15, SBA-15-C8, SBA-15-C18, MCM-41, LP-Ia3d		[48-50]
	Gentamycin Aminoglycoside antibiotic Broad-spectrum Ototoxic and nephrotoxic **Matrixes**: SBA-15, PLGA-SiO_2		[51, 52]
	Levofloxacin DNA replication inhibitor Synthetic fluoroquinolone antibiotic **Matrix:** MCM-41		[53]
	Linezolid Synthetic oxazolidinone antibiotic Gram-positive bacteria resistant treatment **Matrix**: SBA-15		[54]
	Rifampicin Antibiotic semisynthetic Enzyme Inhibitor Antitubercular agent Nucleic acid synthesis inhibitor Leprostatic agent **Matrix:** SBA-15		[54]

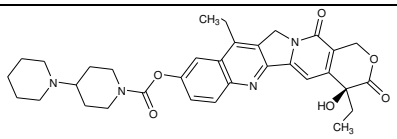
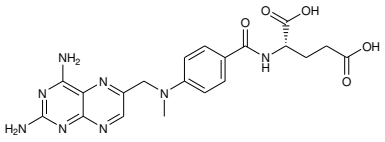
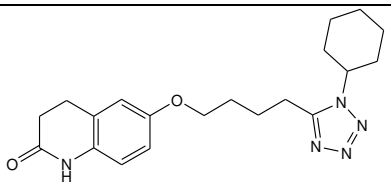
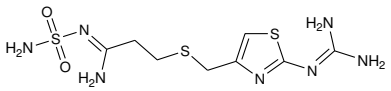
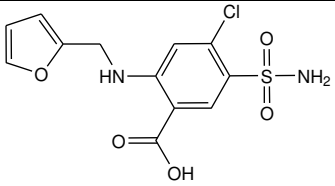
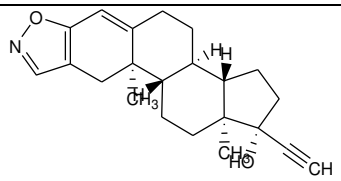
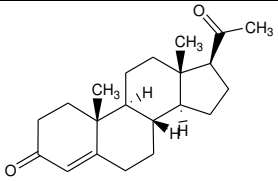
	Vancomycin Glycopeptide antibiotic Gram-positive bacteria effective Penicillin-resistant *Staphylococcus aureus* treatment **Matrixes:** SBA-15, SBA-15-MPTES, SBA-15-APMS, FDU-12, FDU-12-MPTES, FDU-12-APMS		[44, 54, 55]
Anti-coagulant	**Coumarin** Rodenticide **Matrix:** MCM-41		[56]
Anticonvulsant	**Carbamazepine** Antimanic Analgesic non-narcotic **Matrixes:** SBA-15, MCM-41		[57, 58]
	Diazepam Anti-anxiety Hypnotic and sedative Anesthetics intravenous GABA Modulators Muscle Relaxant **Matrix:** SBA-15		[59]
Anti-depressives	**Sertraline** Serotonin uptake inhibitors Major depressive disorder treatment **Matrix:** MCM-41		[60]
	***L*-Tryptophan** Dietary supplement Micronutrient **Matrixes**: SBA-15-C_3N^+Me, SBA-15-$C_3N^+Me_2C_{18}$		[61]
Anti-fungal	**Griseofulvin** Anti-bacterial Skin and nails fungal infections treatment **Matrix:** SBA-15		[59]
	Itraconazole Antiprotozoal 14-alpha demethylase inhibitor Anticancer agent explored **Matrix:** SBA-15		[62]
	Ketoconazole Primarily fungal infections treatment 14-alpha demethylase Inhibitor **Matrix:** SBA-15		[59]

	Salicylic acid Anti-Infective Keratolytic **Matrixes:** SBA-15, SBA-15-NH_2, SBA-15-COOH		[63]
Anti-histaminic	**Cinnarizine** Piperazine derivative Calcium channel blocker **Matrix:** SBA-15		[59]
Anti-HIV	**Stavudine** Antimetabolite Nucleoside analog reverse-transcriptase inhibitor **Matrix:** SBA-15		[37]
Anti-hyperglycemic	**Glyburide (glibenclamide)** Hypoglycemic Anti-arrhythmia Antidiabetic **Matrix:** SBA-15		[64]
Anti-hypertensives	**Aliskiren** Renin inhibitor Essential (primary) hypertension treatment **Matrixes:** SBA-15, SBA-15-MgO		[65]
	Atenolol Adrenergic beta-1 receptor-antagonist Sympatholytic **Matrixes:** MCM-41, SBA-15		[66, 67]
	Captopril Angiotensin-converting enzyme inhibitor **Matrixes**: MCM-41, MCM-41-TMCS, SBA-15, SBA-15-MgO, MCM-48-YVO_4:Eu^{3+}		[65, 68-70]
	Carvedilol Vasodilator Adrenergic alpha-1 receptor antagonist Adrenergic beta-antagonists **Matrixes**: SBA-15, MCM-41		[71, 72]
	Lacidipine Calcium channel blocker Relaxing and opening up the blood vessels **Matrix:** SBA-15		[73]
	Metropolol Adrenergic receptor antagonist Sympatholytic Anti-arrhythmia **Matrix:** SBA-15-MPTMS		[74]

	Nifedipine Dihydropyridine Calcium channel blocker Chronic stable angina **Matrix:** SBA-15		[59, 75]
	Nimodipine Dihydropyridine Calcium channel blocker Vasodilator **Matrix:** SBA-15		[76]
	Propanolol Anti-arrhythmia Vasodilator Adrenergic beta-antagonist **Matrix:** MCM-41		[77]
	Ramipril Angiotensin-converting enzyme inhibitor Congestive heart failure treatment Muscle relaxant **Matrix:** SBA-15		[78]
Anti-hypocalcemics	**Alendronate** Bone density conservation agent Antiresorptive **Matrixes**: SBA-15, SBA-15-NH_2, SBA-15-PO_4, MCM-41, MCM-41-NH_2		[79-85]
	Zolendronate Bone density conservation agent Antiresorptive **Matrix**: SBA-15		[86, 87]
Anti-Infectives	**Chlorhexidine** Disinfectant Mouthwashes **Matrix**: MCM-41		[88]
	Nitrofurazone (nitrofural) Bactericidal Antibiotic **Matrix**: MCM-41		[89]
	Sulfadiazine Coccidiostat antiprotozoal **Matrixes**: SBA-15, MCM-41, MCM-41-NH_2, MCM-41-COOH, SBA-15-COOH		[90]

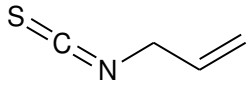
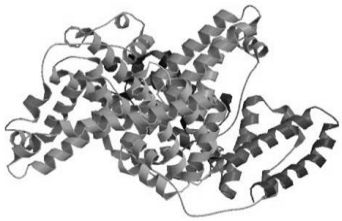
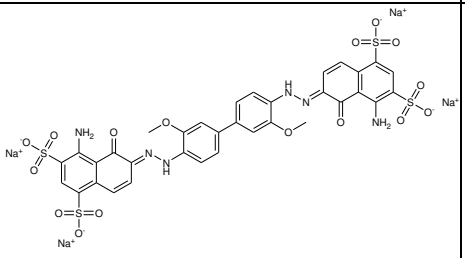
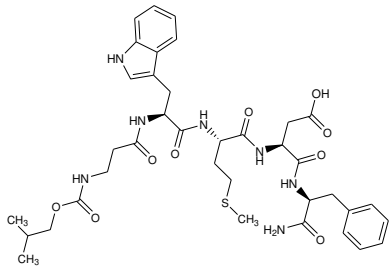
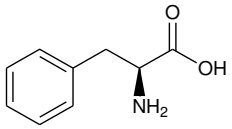
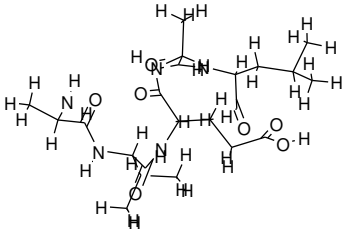
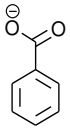
Anti-inflammatory non-steroidal	**Aspirin (Acetylsalicylic acid)** Fibrinolytic Antipyretic Cyclooxygenase Inhibitor **Matrixes:** MCM-41, MCM-41-Al, MCM-41-APTES, SBA-15		[91-94]
	Diflunisal Salicylic acid derivative Analgesic **Matrix:** MCM-41-Al		[95]
	Fluribuprofen Analgesic non-narcotic Cyclooxygenase Inhibitor **Matrix:** FSM-16		[26]
	Ibuprofen Analgesic non-narcotic Cyclooxygenase Inhibitor **Matrixes:** MCM-41, MCM-41-NH_2, MCM-48, LP-Ia3d, FDU-5, SBA-15, TDU-1, MCM-41-HMDS, MCM-41-AEPTMS, MCM-41-APTES, MCM-41-DMS, MCM-41-TMS, Ti-SBA-15, SBA-15-GA		[1, 30, 49, 96-106]
	Indomethacin Cyclooxygenase Inhibitor Cardiovascular Tocolytic Gout Suppressant **Matrixes:** MCM-41, SBA-15, SBA-16		[59, 64, 107, 108]
	Ketoprofen Analgesic Antipyretic Cyclooxygenase inhibitor **Matrix:** SBA-15-APTES		[109]
	Mesalazine Inflammatory bowel disease treatment Ulcerative colitis treatment **Matrixes:** MCM-41, MCM-41-NH_2, MCM-41-COOH		[110]
	Naproxen Analgesic Antipyretic **Matrix:** MCM-41		[111]
	Phenylbutazone Analgesic Antipyretic **Matrix:** SBA-15		[59]

	Piroxicam Oxicam class Arthritis treatment Cyclooxygenase inhibitor **Matrixes:** MCM-41, SBA-15		[112, 113]
Anti-inflammatory steroidal	**Dexamethasone** Glucocorticoid Antineoplastic Antiemetic **Matrixes:** SBA-15, MCM-41		[114]
	Methylprednisolone Glucocorticoid Antineoplastic **Matrixes:** SBA-15, SBA-16, MCM-41, FDU-12		[115]
	Prednisolone Glucocorticoid Antineoplastic **Matrixes:** SBA-15, SBA-3, FDU-12		[116]
Anti-lipemic	**Fenofibrate** Fibrate class Hypolipidemic Reduces LDL and VLD levels increasing HDL levels Reduces triglycerides level **Matrix:** SBA-15		[59]
Anti-neoplastics	**Camptothecin** Phytogenic Topoisomerase I Inhibitor **Matrix:** MCM-41		[117, 118]
	Cisplatin Cross-linking reagent Radiation-sensitizing agent **Matrixes:** MCM-41, SBA-15, MCM-41-APTES, MCM-41-PNTES		[119, 120]
	Desatinib Tyrosine kinase inhibitor Chronic myelogenous leukemia agent **Matrix:** SBA-15		[121]
	Doxorubicin Anthracycline antibiotic Administered only into a vein Isolated from cultures of *Streptomyces peucetius var. caesius* **Matrix:** SBA-15-FA		[122]

	Irinotecan Phytogenic Radiation-sensitizing agent Topoisomerase I inhibitor Prodrug **Matrix**: MCM-41-NH_2		[123]
	Methotrexate Antirheumatic Folic acid antagonist Nucleic acid synthesis inhibitor **Matrix**: MSM-Al		[124]
Anti-thrombotic	**Cilostazol** Fibrinolytic Platelet Aggregation Inhibitor Bronchodilator Phosphodiesterase 3 Inhibitor Vasodilator Neuroprotective **Matrixes:** MCM-41, MCM-48		[125]
Anti-ulcer	**Famotidine** Histamine H2 antagonist **Matrixes**: SBA-15, SBA-15-COOH, SBA-15-COOH-TMS, MCM-41, MSU-1 -2 -3		[126-128]
Diuretic	**Furosemide** Sodium potassium chloride symporter inhibitor **Matrix:** SBA-15		[129]
Endiometriosis treatment	**Danazol** Synthetic steroid ethisterone Gonadotrophins suppressor **Matrix:** SBA-15		[59]
Steroid	**Progesterone** Progestins Contraceptive Agents **Matrix**: SBA-15		[37]

List of abbreviatons: APTMS: 3-aminopropyltrimethoxysilane; **CPTMS:** 3-chloropropyltrimethoxysilane; **HMDS:** hexamethyldisilazine; **APTES**: 3-aminopropyltrietoxysilane; **VTES:** trietoxyvinylsilane; **APMS:** N-(2-aminoethyl)-aminopropyl dimethoxymethylsilane; **MPTES**: 3-mercaptopropyl triethoxysilane; **HA**: Calcium phosphate hydroxyapatite; **TREN:** tris(2-aminoethyl) amine; **TMCS:** trimethylchlorosilane; **MPTMS**: 3-mercaptopropyl trimethoxysilane; **HDMS:** 1,1,1,3,3,3-hexamethyldisilazane; **AEPTMS:** 3-(2-aminoethylamino) propyltrimethoxysilane; **DMS**: dimethyl sulfide; **TMS**: tert-butyl mercaptan; **GA:** glutaraldehyde; **PNTES:** 3-propanonitrile triethoxysilane; **FA**: Folic acid; **MSU:** Michigan State University mesoporous matrix.

Table 2. Biological and food models in SMMs used as delivery systems.

Biological &Food-matrix models	Molecular structures	References
Allyl isothiocyanate Flavouring agent Rubefacient Cancer chemopreventive *in vitro* **Matrix:** SBA-15		[65, 130]
Bovine serum albumin (BSA) Transport protein Biochemical applications including immunohistochemistry and immunoblots **Matrixes**: SBA-15, SBA-15-NH_2		[131, 132]
Chicago Sky Blue 6B Potent L-glutamate inhibitor **Matrix:** SBA-15		[133]
Pentagastrin Pentapeptide synthetic Effects like gastrin Diagnostic agent **Matrix:** MSU-Tween-80		[134]
***L*-Phenylalanine** Intermediate neuriotransmisor Dietary Supplement Micronutrient **Matrixes**: SBA-15, SBA-16		[135]
PTHrp (107-111) osteostatin Bone formation regulator **Matrix:** SBA-15		[136]
Zn(II) benzoate complexes Food preservative Bactericidal Insecticide amd acaricid **Matrix**: SBA-16	 *benzoate ligand*	[137]

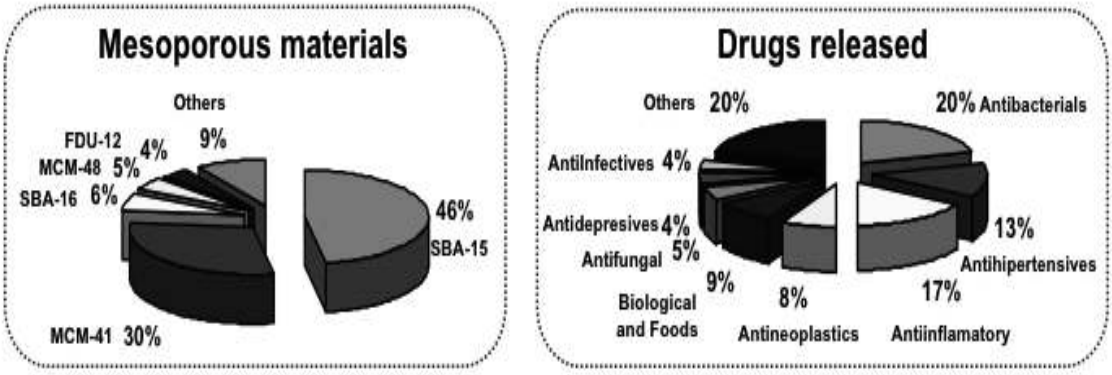


Fig. (3). Summarizing of Tables 1 and 2 to visualize more clearly the main SMMs and families and drugs investigated until now as host-guest systems.

As it can be observed in Fig. **3**, SBA-15 and MCM-41 matrixes are, as much, the more profusely matrixes investigated until now because both together represent 76% of the mesoporous systems studied. Regarding the families of drugs released, the situation is more balanced although three categories: antibacterials, antiinflammatory and hypertensives represent the 50% of total. However, the category of antineoplastics is trending to increase, reaching a great importance in the actual research in mesoporous nanoparticles, which are out of the scope of this article.

Therefore, the selection of the SMMs for a specific drug is not simple if we treat to find a host-guest pair for the optimal release of the drug. In principle, such selection must be randomized in a trial and error strategy with the different SMMs and drugs available. Nevertheless, this task cost time and money and, sometimes, it is not reliable. Initially, the SMM was chosen considering only the size of the drug molecule. With this single parameter, almost any SMM would be valid to host the most part of the drugs investigated. However, although the drug was small enough to penetrate into the pores of the matrix, other factors must be considered. For instance, the lipophilic or hydrophilic nature of the drug can be incompatible with the matrix. Moreover, the SMM and drug can present electrostatic charges repulsion. Anyone of these factors would prevent the use of that matrix for that specific drug.

One of the technological ways to solve this problem of absorption via oral in these drugs is the guest-host system drug-SMM that helps to the drug absorption because it is encapsulated in the matrix. That is an important application of the mesoporous silica matrixes. The resolution of this technical problem can be reached with other materials, but the added value of the SMMs is, in general, that they are able

to adsorb great amounts of water. This ability of SMMs is important for an effective entrance and delivery of the drug. It is necessary to consider that the drug when released it is linked to the matrix in dry conditions and it must be dissolved by the aqueous fluid coming into the SMM channels. Thus, it is established a concentration gradient favored by the fast absorption of the fluid into the pores of the mesoporous material.

However, there are more aspects that must be taken into consideration. For instance, a drug can be essentially lipophilic, like ibuprofen, or essentially hydrophilic, like vancomycin [138]. This fact not only influences its absorption in the organism, but it is also an important parameter to consider in the delivery of a drug from a hydrophilic silica matrix that does not dissolve in aqueous fluids.

Therefore, in the election of a drug model for its delivery from SMM, besides the size of the molecule, it is necessary to consider other factors related with the diffusion or the interactions with the matrix, as it will be detailed in the next section.

On the other hand, to know if a drug was loaded in a SMM, indirect methods were used, for instance determining the reduction of the surface area and pore volume of the matrix. This changed when for the first time Vallet-Regi *et al* [139] in 2010 used the Scanning Transmission Electron Microscopy (STEM) to visualize with atomic resolution the SBA-15 and SBA-15-NH_2 SMMs. STEM equipped with aberration corrector is able to determine the distribution of silicon, oxygen, nitrogen and carbon, through the mesoporous silica network. This way, the presence of zolendronate inside the channels of the mesoporous matrix was confirmed.

Nevertheless, to obtain the total amount of drug adsorbed in a SMM it is necessary to use indirect methods like thermogravimetry, porosimetry and other methods of chemical analysis [140-146].

3. FACTORS INFLUENCING THE DRUG RELEASE FROM SILICA ORDERED MESOPOROUS MATRIXES

In this section, the main factors that take part in the process of release of a drug from SMM, in their great majority common and related to the process of adsorption of the drug in the matrix, are described.

3A. Pore diameter

As we previously established, the diameter pore that acts like selective sieve, determines if a drug, by size, can penetrate into the pore channels [131]. This way, and considering only the sieve effect of pores, although any SMM would be suitable to adsorb small size drugs, MCM-41 usually is used due to its great stability. In addition, MCM-41, as MCM-48 and SBA-15, presents the advantage to be easily functionalized, which has great importance in the controlled release of drugs guests, as we will see later.

As an example and due to its small size, ibuprofen can be loaded in any SMM. For other drugs of greater size like the glycopeptide vancomycin ($C_{66}H_{75}C_{l2}N_9O_{24}$) or others of similar size, it is preferable to use SBA-15 as first option to be sure that these drugs will be able to be included within its pores [54, 147-150].

In any case, it is necessary to notice that the fact that a drug can penetrate by size within pores does not guarantee that this will happen, because there are other factors that influence, as we will see ahead in an example of application of molecular models. Such factors can produce a rejection of the drug molecules by the inorganic or organic components of the channels of the mesoporous matrix.

3B. Surface

When the drug to be loaded is of a size much smaller than the pores of the matrix, most of the drug molecules are not adsorbed to the pores surface. This is due that only a few of them can directly interact with the matrix surface and the remaining molecules do not interact with the surface and they are not retained. This is a relevant fact that was investigated by Vallet-Regi *et al.* in a model of alendronate from MCM-41 and SBA-15 matrixes [131]. Experimental results of Vallet-Regí *et al* indicate that MCM-41 is able to load more alendronate than SBA-15 (surface area= 719 m^2/g) because in MCM-41 (surface area= 1157 m^2/g) the contact surface with alendronate is higher than that of SBA-15.

The molecules are confined inside the pores through the attractive interaction with the internal mesopore walls. It is rational to consider the opposite process, that is the release of the adsorbed drug, will also depend on the material surface area. In fact, different experiments have shown that when the surface area of a SMM is very high, there is a great molecular retention and as a result a slower drug release in comparison with materials exhibiting smaller surface areas. The extra interactions of the drug

molecules with a higher surface available are responsible of retard in the kinetics of release of the drug [131].

3C. Pore volume

Pore volume is an important parameter for great size molecules. The pore volume determines the available space to load molecules of drug. Whichever greater is the pore volume, greater will be the load [151], which also influence the drug release. In case of small volume of pores, the channel of the matrix could be occluded with the drug molecules.

3D. Electrostatic forces

When the drug contacts with the mesoporous matrix, interactions by electrostatic forces of the partial charges produced by the movement of the electrons are established. The native silica in normal conditions has negative electrostatic charges with uniform zones of a great electron density. However, the drug molecule can be exclusively charged by positive charges, with deficit of electrons, negative, rich in electrons, or, the most habitual case, to exhibit zones of partial charges positive and negative in different positions of the molecule. It is understood that if the charges are of equal sign, they will be repulsed. Therefore if the drug is highly charged of negative electronic density, cannot penetrate into the pores, although it could be possible if size were the only criterion.

Nevertheless, when electrostatic forces of different sign between the guest and the mesoporous host are established, they must influence the drug retention in the matrix channels. We will come back to it when we will study the application of the molecular modeling to the drug release from SMMs.

3E. Tortuosity of the channel

In the diffusion of the drug through a porous matrix, a factor to consider is the tortuosity of the channel. Nevertheless, and due to the property of SMMs to adsorb great amount of fluid as a sponge and the homogeneity and linearity of its channels, tortuosity is not a significant factor in the release of the drug from a SMM even in *a priori* more winding materials like MCM-48.

The fact that the material tortuosity does not significantly affect the kinetic of release was shown in a model with ibuprofen and MCM-48 and SBA-15 like matrixes.

Izquierdo-Barba *et al* [152] experimentally demonstrated that there are no significant differences in the velocity of delivery of ibuprofen from MCM-48 and SBA-15, according to the obtained values using the Noyes-Whitney equation and the application of the first Fick´s law [153].

3F. Other factors

Another factor to be considered is the lipophilic or hydrophilic nature of the guest-host system. In principle, the mesoporous silica matrix is hydrophilic and does not dissolve in water, but that can change if the material is modified after be functionalized. This parameter influences both the adsorption of the drug and its delivery.

Other factors that influence the delivery of a drug, like pH, temperature or pressure, usually are kept constants in the trials. Being thus, they cannot influence in the kinetic of release of the drug. But if they are modified those three parameters exert their influence in the release process. For instance, Rosenholm *et al* [154] demonstrated that the interface chemistry of SBA-15 is pH dependent and it is controlled by the type of silanol groups (Q^2 ($Si(OH)_2(OSi)$), Q^3 ($Si(OH)(OSi)_3$) and Q^4 (($Si(OSi)_4$)).

Finally, is necessary to consider that the singular SBA-15 micropores that connect the mesoporous channels are too small so that the drugs commonly used as models are introduced into them. For this reason they do not influence the delivery of the drug and they are not considered as a factor that takes part in the drug release.

The challenge consists in the evaluation of the specific participation of each factor that govern the drug delivery, to be able to find out how it works their mechanism of action and to act consequently, to release the drug in a controlled way.

4. RELEASE KINETICS OF THE DRUG

Once established the main factors that take part in the release of a drug from SMMs it is necessary to establish the type of kinetic that is going to govern that process. In the materials that we are reviewing, the objective is that the drug was released *in vivo* from the matrix by a biological fluid. Due to it, in the kinetic tests of drug delivery a common alternative is the use of solutions mimicking plasma, like the Simulated Body Fluid (SBF) proposed by Kokubo *et al* [155], isotonic serum or just a buffer at pH 7. In addition, to simulate better the *in vivo* conditions of plasma temperature usually is about 37ºC at atmospheric pressure and all under stirring.

Like in the process of adsorption of the drug in the mesoporous matrix, the drug can be adsorbed in the outer or in the inner part of the channels. Thus, two delivery stages are observed. The molecules of drug adsorbed in the outer part of the matrix are quickly released, whereas the adsorbed ones within the channel exhibit a slower kinetic, since the diffusion of the drug is faster on the surface that within the pores.

The fact that it is not possible in principle, to establish a traditional kinetics of order, zero, one or two, in the kinetics of administration, delivery and degradation of a drug, it is difficult to compare different kinetic models mesoporous matrix-drug. To solve this problem made the mesoporous models comparable to each other, Higuchi [156] established being based initially on the Fick´s law, one kinetic equation: $a = kt^{1/2}$ to calculate the constant observed of the reaction of release (k), that makes it dependent on the square root of the time ($t^{1/2}$) and the concentration of the drug (a). This equation, adapted for the first mesoporous material-drug model, is suitable for a model of release of the drug from the matrix when the diffusion takes place through pores full of dissolvent. Then, it establishes that the equation is: $k= f (D, \varepsilon, \tau, C, A)$, reuniting the main factors that take part in the release of a drug since D is the diffusion of the drug in the dissolvent, τ the tortuosity factor of the system, ε the porosity of the matrix, A the total amount of drug in the matrix and C the solubility of the drug in the solvent used.

Thus, the release of the drug can be experimentally evaluated by the calculation of the kinetic constant observed for the drug release from the matrix for concentrations or percentages of release of the drug determined by using analytical techniques such as UV spectrometry or HPLC. In addition, the percentage (or milligrams) of drug released with time can be represented by a straight line. A typical profile of kinetic of release in a SMM - drug model in which a first stage of quick release is observed and later a sustained release (Fig. **4)**.

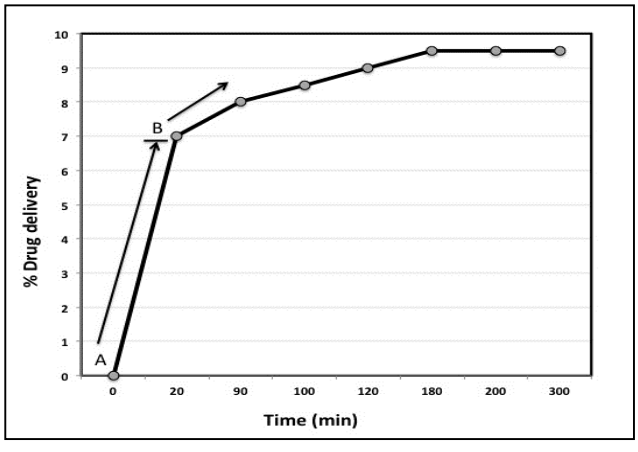


Fig. (4). Release of a drug from a SMM. A) Quick stage. B) Sustained step. (Unpublished results)

Higuchi equation that is applied in these models was modified by several authors, for example Dash *et al* [157], introducing new factors, to make it more effective.

5. CONTROLLED RELEASE OF DRUG: FUNCTIONALIZATION

In the initial works of drug release from SMMs of MCM-41 and SBA-15, it was still not had knowledge sufficient to obtain a really controlled delivery of the drug. For example, in the pioneering work of Doadrio *et al* [52] they demonstrated that it is possible to load and release a drug of greater size than ibuprofen used like first model from a SMM with pore diameter greater than that MCM-41, also used till then like a model, without collapse the matrix channels. It was an important first step. But the model of gentamicin-SBA-15 used, like other contemporary ones, although very reproducible does not control at demand the delivery of the drug.

In that work, it is demonstrated that the kinetic of release is time dependent and that it is similar as much in the material as powders or as pellets. In the plot of gentamicin release (Fig. **4**) the two stages described in the previous section are observed. In the first one, a fast delivery (60%) of the drug takes place in the first hour, attributed to its weak interaction in the surface of the matrix. In the second, a slower delivery of gentamicin (up to 100%) takes place until 24 h, due to the progressive release of the drug from the interior of the pores of the matrix [49]. This will be confirmed later with the application of molecular modeling and docking techniques.

Results of similar profiles of release following the kinetics of Higuchi with other drugs, like the amoxicillin, were obtained [38]. Nevertheless, in this case, the drug release from the SBA-15 is more sustained. Indeed, there are not two identical models, reason why in the interpretation mechanism of release of a drug, we only have the security that is valid for the considered drug-matrix model, but in another model it could

be different. However in this review paper of computer-assisted mechanical-quantum models has not been considered yet.

A considerable advance in the effective control of the drug release from SMMs, took place when the silica base of the matrix was functionalized. This functionalization allows an effective control on the kinetics of release of the drug, through several factors. In the first place, since the size and tortuosity of pores are inherent to the internal structure of the matrix, if they are modified, is carried out an alteration of the flow and therefore, also of the kinetic of delivery of the drug, that can be slowed down. The functionalization involves a decrease in the diameter and volume of pores, by the interaction of new groups to the silica matrix, which increases the tortuosity of the channel. Second, the hydrophilic capacity of the silica is modified, which can diminish until be converted into a lipophilic matrix, if we introduce sufficient number of carbon atoms, or conversely it can be increased if including new highly hydrophilic groups. Finally, new electrostatic drug-matrix interactions will be established, which will diminish or increase the negative electron density of silica surface.

In addition, drug-matrix hydrogen bonds can be established and even between two groups of matrix when is functionalized with - NH_2 groups, that also must be considered. Functionalization of the matrix with apolar groups can be obtained (*i.e.* C18, C8) or with polar groups (like -NH_2, -SH, -COOH). For example, the functionalization with C8 and C18 chains are made introducing octyldimethylchlorosilane molecules ($CH_3(CH_2)_7Si(CH_3)_2Cl$) or octadecyldimethyl chlorosilane ($CH_3(CH_2)_{17}Si(CH_3)_2Cl$), respectively, over the silica surface, which will react to interact the carbon chains and the silanol groups. In this way the lipidic character of the material is increased.

The question is what percentage of silanol groups is functionalized. In the case of the functionalization with C18 chains, very voluminous alkyl silane chains are created that are randomly arranged, reason why all cannot react with the silanol groups by steric effect. That way, approximately the 2.5% of -OH groups in the silica surface remains unreacted [158]. Thus, if the functionalization is made in the suitable conditions, the channels of the mesoporous material would not be occluded. Nevertheless, the functionalization can lead in some cases, an obstruction of the mesoporous material pores. For example, Izquierdo-Barba *et al.* [49] discovered that the

functionalization of MCM-48 with C18 chains covers all the pores of the mesoporous material and prevents the access of the drug to the inner of the channel.

The release is generally slower from the functionalized matrix, with respect to not functionalized. A comparative example of the modification of the vancomycin kinetic release when SBA-15 is functionalized with C8 is shown in Fig. **5**. In the figure, a smaller velocity of release in the functionalized material (k= 0.068 $min^{-1/2}$) with respect to not functionalized is observed (k= 0.89 $min^{-1/2}$) [55]. In analogous studies differences between the functionalized and non-functionalized matrixes regarding the drug delivery were also observed [159].

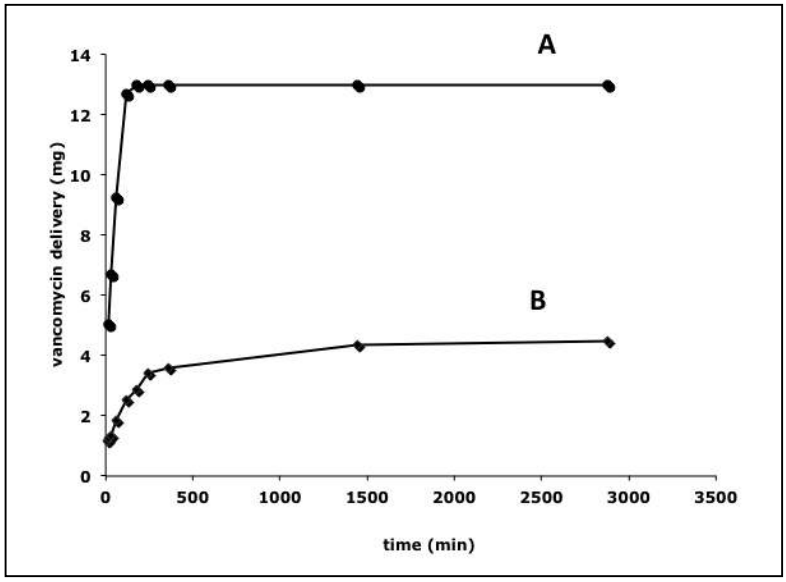


Fig. (5). Profiles of the delivery plots of a model of vancomycin in: A) SBA-15 and B) SBA-15-C8 (Modified form [55]).

In a study about the influence of the matrix functionalization in the drug delivery, functionalizing SBA-15 with C8 and C18 chains and using erythromycin as model drug, it was demonstrated that the release rate diminishes when the number of hydrophobic $–CH_2-$ groups – increased [48].

Therefore, it has been demonstrated that, with the suitable functionalization, the release of a drug from a SMM can be controlled. Nevertheless, with the data described until now all the factors that govern the adsorption and delivery of the drug in the mesoporous matrix are not completely described. This situation changes when molecular modeling analysis is combined together with the experimental data that we will describe in the following section.

6. MOLECULAR MODELING APPLICATION TO SILICA ORDERED MESOPOROUS MATERIALS – DRUG SYSTEMS

The recent introduction of the *in silico* molecular modeling analysis in the the drug release investigation from SMMs, supposes a significant advance in the interpretation of the drug-delivery mechanism from mesoporous matrixes, since it allows establishing the interactions by electrostatic charges and hydrogen bonds in the guest-host models.

The importance of using these models in chemistry was recognized in 2013 with the concession of the Nobel Prize in Chemistry to Karplu, Levitt and Warshel by the development of multiscale models of complex chemical systems [160]. These advanced models are tools mainly predictive, that allows approaching reality and can to establish if a reaction is going to happen or no, to design new materials or drugs, to know how certain proteins respond to polluting agents or drugs, to determine the interactions drug-receptor and more applications. At the moment, these models have such predictive power that Chemistry experiments can be done in computer instead of in the conventional laboratory, which saves time and money.

Appling this techniques to the silica-based ordered mesoporous materials and with appropriate software, it can be constructed the structure of a mesoporous material, such as MCM-41 and SB-15 in a 3D representation. Then, the minimum energy configuration, the electrostatic potential map, and other parameters of this structure can be calculated by semiempirical or *ab initio* mechanical-quantum methods. These calculations facilitate the comprehension of the mechanism of release of the drugs because the power of the computer calculations of the theoretical models provides the necessary information to understand these processes. For that reason, they must become in essential tools for experimentalist chemical, in general, and specifically for the study of the SMMs.

For instance, it could be constructed the electrostatic potentials maps of the drugs included in Table **1**, that could be used, among other applications, to predict what functional group of the drug molecule interacts with the matrix of silica, native or functionalized. This can be visualized by a representation in a gradient of molecular electrostatic potentials map that has been obtained from the mechanical-quantum calculations. In these map the atom zones rich in electrons are usually represented in red

and the deficit in electrons in blue. Other colors (green and yellow) usually are uniform and representative of covalent bonds or electron delocalization of pi bonds.

Next a representative example of the application of these electrostatic potential maps the SMM-drug system based ibuprofen is presented. If we observed at detail this electrostatic potential map optimized by an *ab initio* method (Fig. **6**), zones of negative charges rich in electrons and others of positive charge can be observed. Nevertheless, zones of positive charge predominate in the molecule. The figure also shows that the positive charges are mainly oriented towards the outer part of the molecule. This way, and because ibuprofen molecule is small enough to penetrate into the porous channels of the matrix it will be more probable that this molecule interact with the negatively charged silica matrix (dark grey contrast in Fig. 7).

Another example is the vancomycin molecule, whose electrostatic potential map (Fig. **8**) displays also two parts of different sign like ibuprofen. In this case predominate the zones with great electron density (negatively charged) but vancomycin molecule also exhibit a well differentiated part positively charged that is susceptible to establish electrostatic interactions with the negatively charged silica matrix.

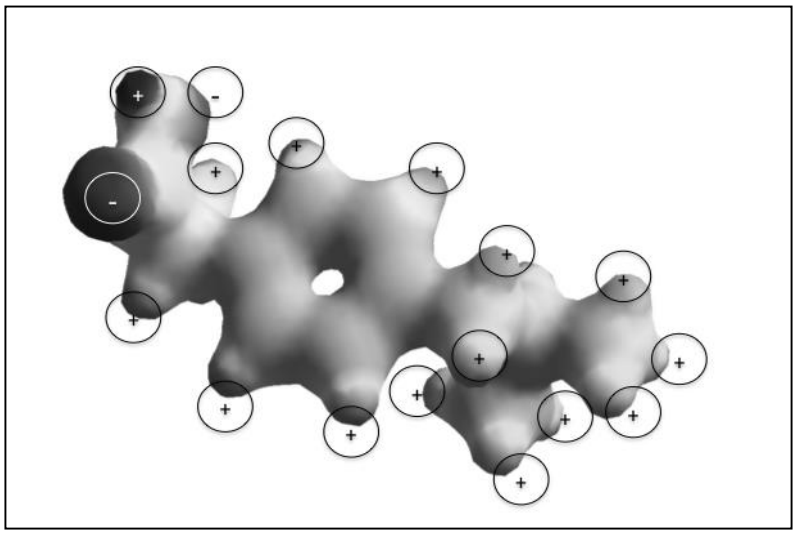


Fig. (6). Map of electrostatic potential of ibuprofen. (Unpublished results).

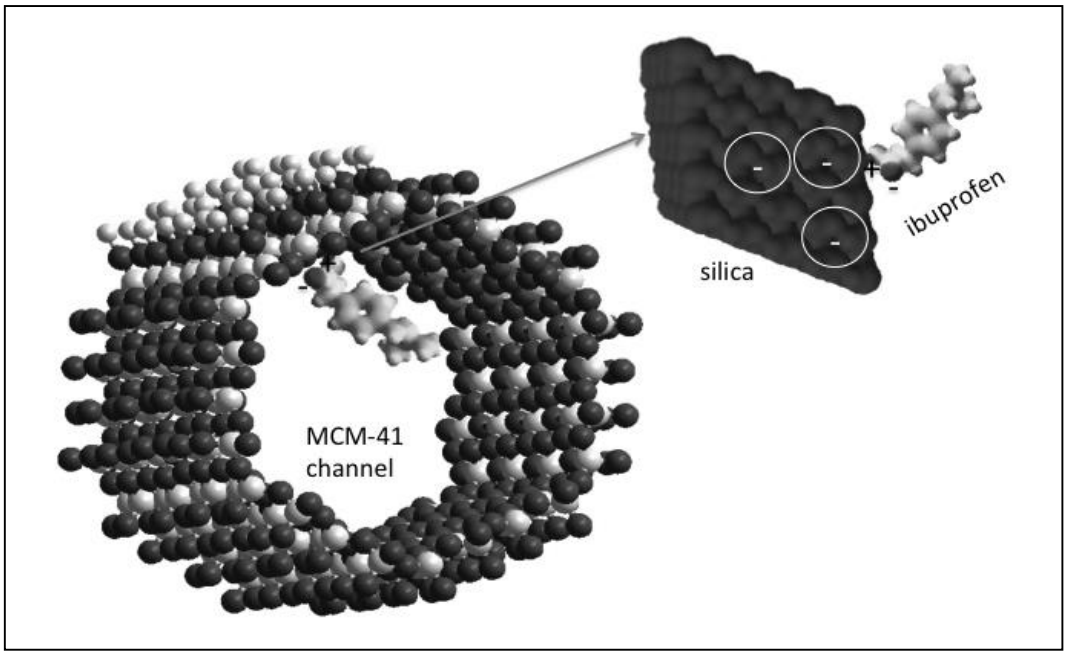


Fig. (7). Adsorption of a molecule of ibuprofen within the MCM-41 channels by electrostatic interactions. (Unpublished results).

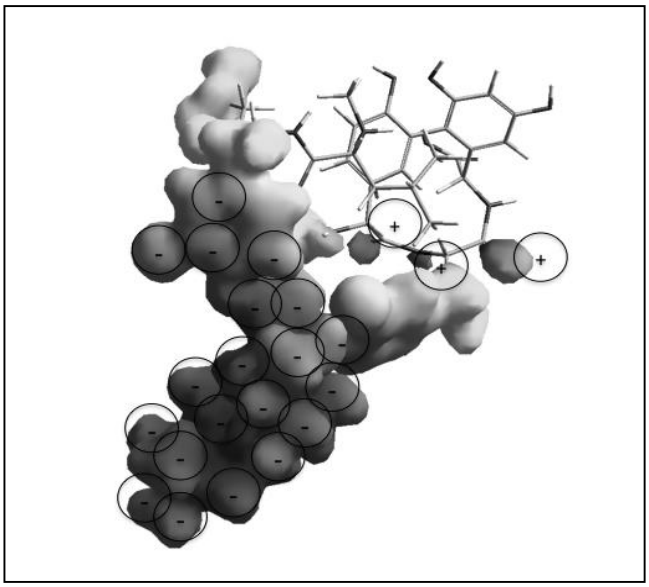


Fig. (8). Map of electrostatic potential of vancomycin. (Unpublished results).

These theoretical models must be compared with the experimental data as it was reported by Doadrio *et al* in a vancomycin/SBA-15 model [55]. In that work, a MCM-41 channel, similar to SBA-15 but with somewhat smaller pore diameter, was modeled to simulate the electrostatic interactions that take place with the vancomycin. That way, it was demonstrated that in that case the electrostatic attractions between the matrix and

the drug influences decisively the kinetic of delivery of the drug. Fig. **9** shows the channel simulations of MCM-41 (Figs. **9A** and 9**B**) and the optimized structure of vancomycin (Fig. **9C**). This last one shows that the molecule optimized of vancomycin is folded and by dimensions (1.77 nm) could penetrate into the pores of the MCM-41 model (Fig. **9A**) of 2.01 nm of diameter (MCM-$41_{2.01}$) and consequently in the bigger ones of SBA-15. Moreover, the vancomycin molecule can be located in the outer part of the channel as is shown in Fig. **9B.**

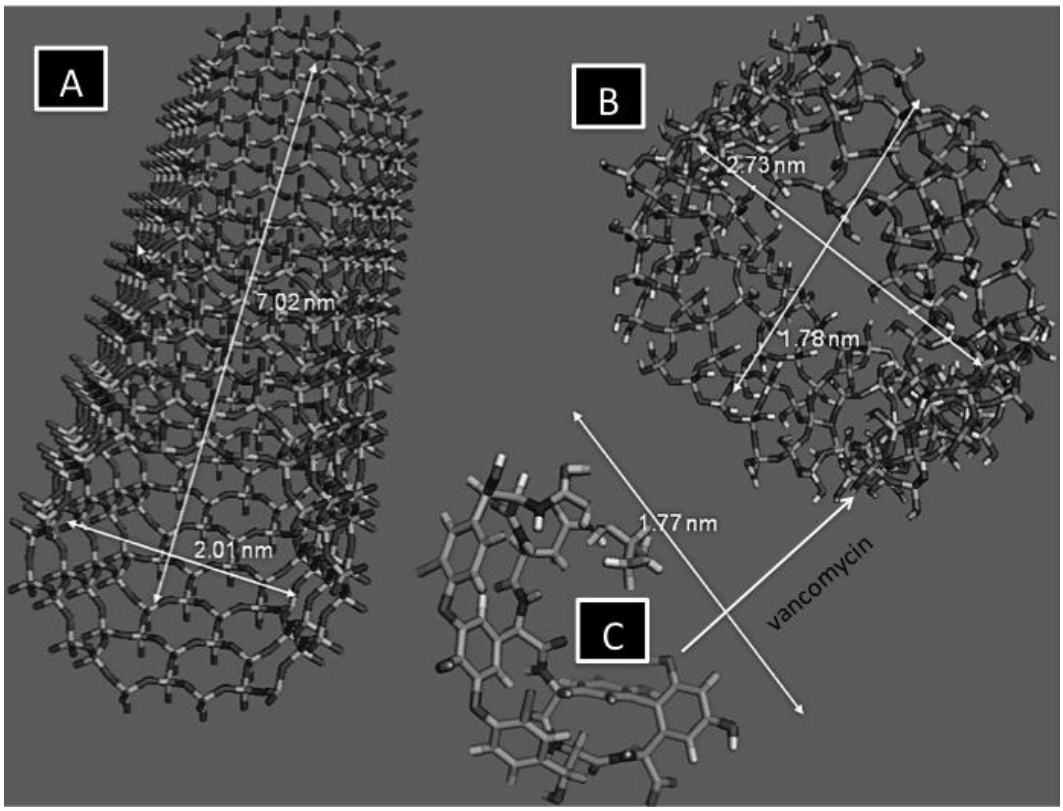


Fig. (9). Molecular modeling of: A) Complete MCM-41 optimized channel. B) Shorter MCM-41 channel to short the simulations time when vancomycin molecule is included. C) Molecule of vancomycin optimized by quantum-mechanical semiempirical calculations. Modified from [55].

In addition, the interaction of the C8 chains functionalizing the silica matrix can also be simulated as well as to calculate its electrostatic potential (Fig. 10). As it can be observed in the figure, the charge density of pure silica is modified when introducing -CH_2- groups with positive partial charge density, in such a way that the silica matrix, now displays a electrostatic potential gradient ranging from +1.34 to +0.005, unlike the native silica which exhibited only negative electron density.

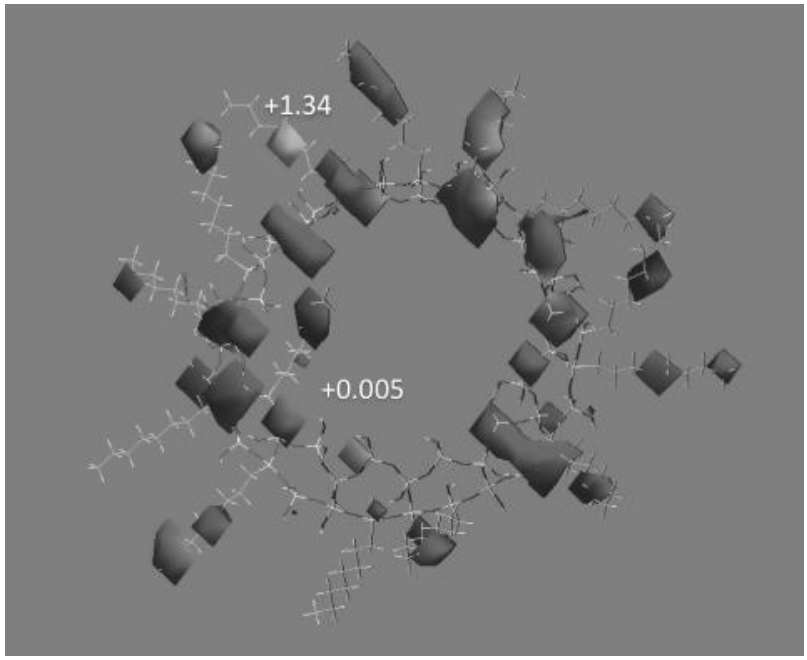


Fig. (10). Optimized molecular model of a MCM-41$_{2.01}$ pore functionalized with random distributed C8 chains. Modified from [55].

These simulations allowed us explaining an experimental fact already mentioned: the kinetic of delivery of the vancomycin in SBA-15 is fairly retarded when SBA15 is functionalized with C8 chains. As it was told, the kinetic constants were 0.890 $min^{-1/2}$ in SBA-15 and 0.068 $min^{-1/2}$ in SBA-15-C8, that is to say, decrease in an order of magnitude with the functionalization. The theoretical molecular model calculations demonstrated that the electrostatic interactions were more intense in the SBA-15-C8 that in native SBA-15. This study demonstrated that modifying the matrix characteristics it can be controlled the delivery kinetic of vancomycin, which would suppose in this case, a clear advantage for its pharmacological applications in implants exposed to infections.

However, when docking technique was applied, the theoretical model also demonstrated that although vancomycin could enters by size into the MCM-41$_{2.01}$ and also in the bigger size channels of SBA-15, the molecule is rejected by the matrix and only the small head of positive charge of vancomycin molecule can interact with the matrix (Fig. **11**). Thus, the guest-host interaction is essentially of adsorption in the pores surface, where the hydrophobic C8 chains positively charged are able to exert a greater retention of the vancomycin molecules which contain a great proportion of negative charge (Fig. **8**) with respect to non functionalized silica.

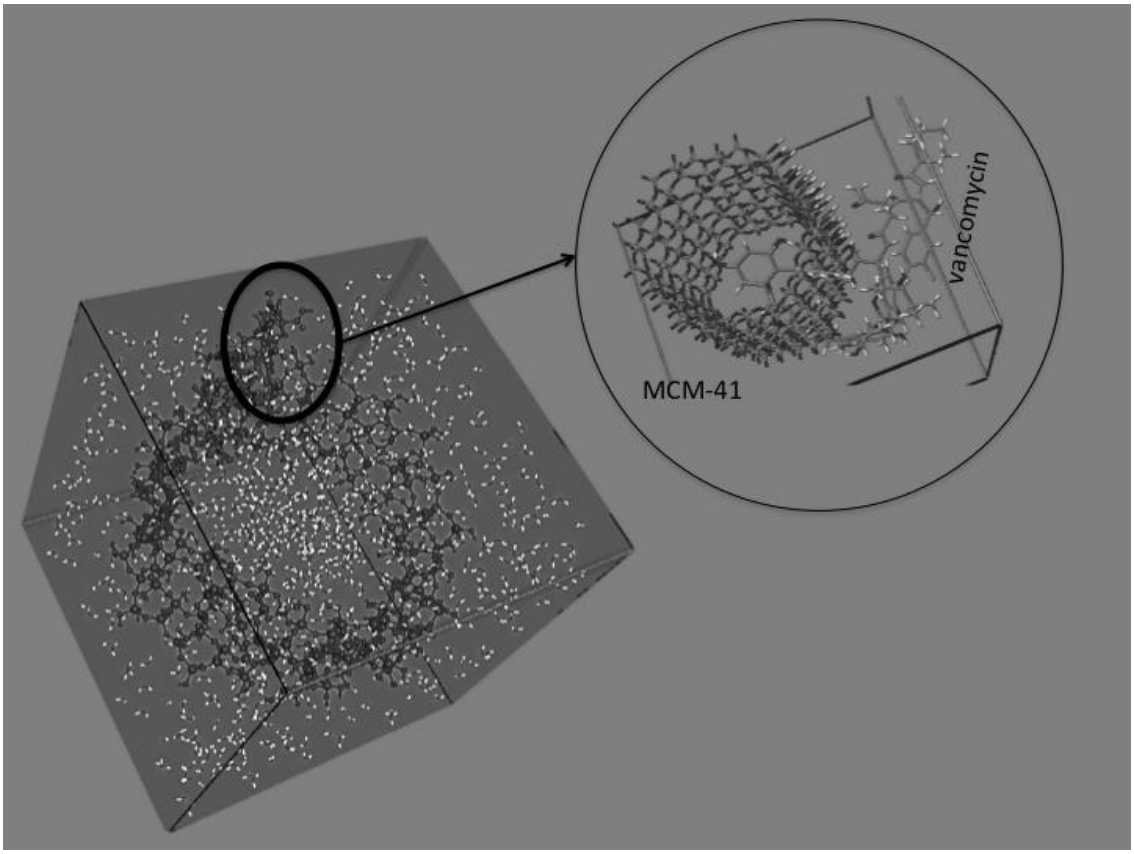


Fig. (11). Simulation by docking in aqueous medium of the entry of a vancomycin molecule into a MCM-41 channel. Modified from [55].

Furthermore it is possible to know by molecular modeling if take place hydrogen bond interactions between the functionalized chains (for example with - NH_2 groups) and the silica matrix. This would be an additional feature to modify the drug release because the channels structures could be altered with functionalizing. In a recent study using SBA-15 functionalized with 3-aminopropyl-triethoxy-silane (APTES) as host and Chicago Sky Blue 6B (CSB) as guest molecule, Doadrio *et al* [133] detected an unusual decrease of two orders of magnitude of the release constant of CSB from SBA-15-APTES (34.7 $min^{-1/2}$) with respect to SBA-15 (7.7 $h^{1/2}$) [161]. This effect could be explained with the construction of an optimized molecular model of SBA-15 with the pore diameter of 5.45 nm ($SBA\text{-}15_{5.45}$). The mentioned decrease was explained watching that the functionalization with APTES forces the channel torsion by the formation of hydrogen bonds between Si-OH groups of $SBA\text{-}15_{5.45}$ and -NH_2 groups of APTES (Fig. **12**).

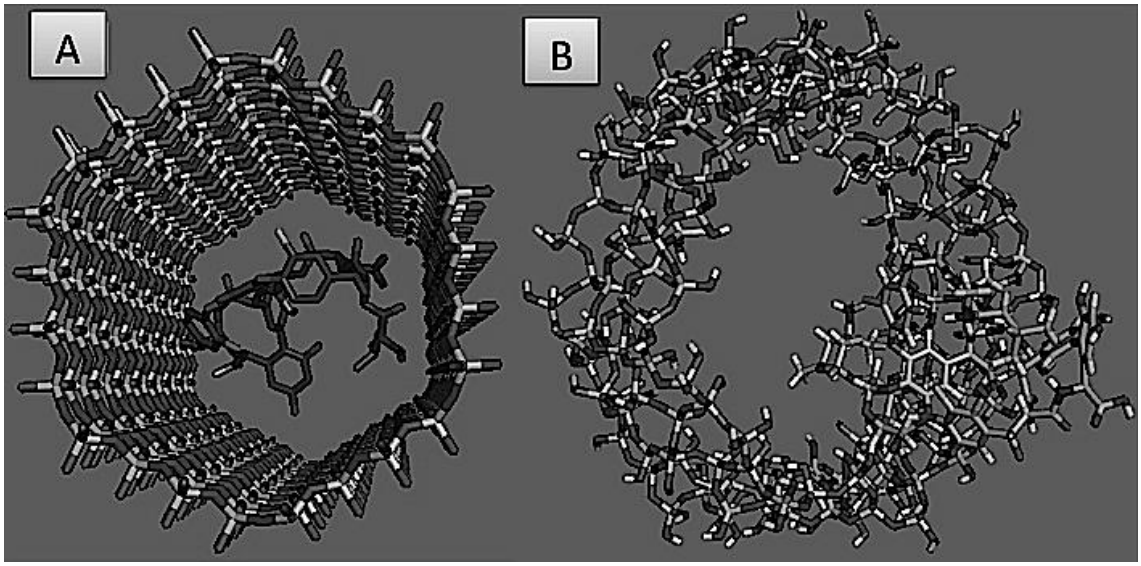


Fig. (12). Molecular modelling of a CSB-SBA-15-APTES system. A) Non optimized model. B) Optimized model. It is observed as the pore of the matrix is deformed and folded. In transparency the original pore model of SBA-15 without optimizing shown in A. Modified from [133].

The folding of the pore caused by the $–NH_2$ group decreasing the pore diameter more than that that takes place after an organic functionalization. Thus, a diameter 8.6 nm was obtained for SBA-15-APTES when in the original native SBA-15 was 10.1 nm. For this reason a huge increase of the tortuosity channel takes place, slowing down the CSB release. This study also demonstrated the importance and relation that exists between both factors: pore size and tortuosity.

In addition, in this case it is possible to establish by molecular modeling and docking, that the CSB molecule penetrates within the matrix channels establishing hydrogen bonds with silanol groups in both functionalized and not functionalized materials (Fig. **13**). Moreover, as it is known, electrostatic interactions will be formed in both the outer part of the wall of the channels and inside the pores.

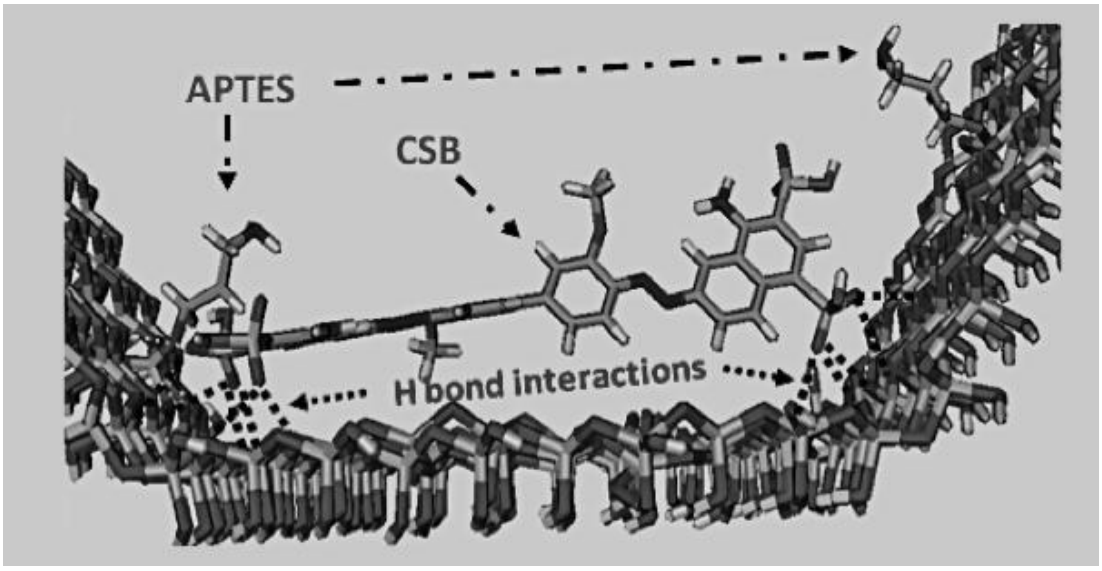


Fig. (13). Molecular model of CSB-SBA-15 system (in vacuum) showing the hydrogen bonds established between the silanol groups of the matrix, functionalised and not functionalised, and the CSB molecule. Modified from [133].

Previous results show that molecular modeling is a powerful tool for the rational explanation of how it works the adsorption and release mechanisms of a drug from a SMM. In addition, these calculations are potent tools to predict if a specific drug can or cannot be retained within the SMM channels. This fact is what actually will determine if the delivery is going to be controlled or not.

CONCLUSIONS AND FUTURE PERSPECTIVES

As we have review in this article, the great advantage of the SMMs in drug administration comes from its pores structure forming cavities where the drug molecules can be hosted. With the functionalization of the mesoporous matrix, controlled release of the drug can be reached. However, we can go a step ahead if we took advantage of the possibilities to close the pore and to open it when is need to release the drug. That is to say, that the mesoporous material serves like an *on off* device. In addition, if we release the confined drug in the place where it is going to product its pharmacological action, in a denominated stimulus-response process, we would have a complete system of controlled and effective release of the drug. In this way, we can be able to reduce the dose of drug to high security levels, since we will release only the necessary amount of drug.

As an example of stimuli-response system, our group used a driving mechanism based on the heat generated by an alternating magnetic field (AMF) in a system that encapsulates the drug on the base of complementary DNA strands [162]. Another example, now using a chemical stimulus, was the MCM-41-vancomycin-ATP system [163]. There the MCM-41 pores were blocked with nanoparticles able to form disulphur bonds. After the disulphur bridges reduction, the vancomycin and ATP molecules in the matrix were released.

Other authors investigated other stimuli including thermosensible polymers to control the release of the drug from the matrix [164, 165]; pH changes [166-168], optical luminescence [56], magnetic stimuli [169] or ultrasounds [170]. A paper of Mura *et al* in [171] and two of our group [172, 173] review the state of the art of these stimuli-response systems for the drug administration from nanocarriers.

Whereas the stimuli-response systems of controlled release continue its advance, the therapy with SMM-drug systems reviewed in the present article will come more effective and safe. As is well known in the progress of a new drug this two objectives mentioned are key factors, in I, II and III phases of development as well as in phase IV, once be commercialized. To this advance molecular modeling and docking techniques will play an important role, trough the development of more powerful computers and software.

But perhaps, the field with more promising future is the one of the galenic formulation of the drug, that is to say, its correct presentation for the administration in an effective, safe and convenient way for the patient. In this sense, the elaboration of SMMs nanoparticles has the advantages that we have already seen in the administration of the drug, with respect to conventional ones, in concrete the possibility of transporting the drug to a determined place of release. In addition nanoparticles present an important advantage with respect the traditional ones as powders or tablets: the nanoparticles can be administered easily by oral route and by a parenteral route which is not possible for the traditional. Nevertheless, it is important to take into consideration the problems that can arise from the use of nanoparticles in the human body, ones originated by the reproducibility of the particles and others by their interaction with the biological fluids and organs, like are biocompatibility, immune response and others that can affect to their security and effectiveness.

In spite of these concerns, Nanotechnology is already beginning to change the way to design the systems for the administration and transport of drugs. As much be applied, and in the SMMs-drug are being already made, it will be able to advance enormously in the development of new therapies to cure diseases like cancer. In these therapies unloading the drug in the place of the tumor is crucial since not only increases the effectiveness, but that also makes the security. That way, it is possible to administer minor doses of a drug that is cytotoxic and besides the drug is coated inside the SMM matrix during the transport until the tumor avoiding that exerts its toxic effect in healthy cells.

Great advances are also reached in related fields with future in the therapy of cancer. For example, the study of cellular lines with the anti-carcinogenic agent bleomycin conjugated with disaccharide, has demonstrated that bleomycin can be targeted to cultivated cancer cells [174, 175]. Moreover, relevant investigations in Nanomedicine were carried out with materials like liposomes or gold nanoparticles [176-178]. Of special relevance in this area, are the studies with Si-RNA that is a powerful approach silencing genes associated with a variety of pathologic conditions [179].

Polymer or peptide based systems (organic), for instance, 3D fibrillar peptide hydrogels can achieve sustained antibody release [180-181]. The main drawback of these models is its foreseeable immunogenic character, a feature not exhibited by the SMMs.

A still unexplored field is the one of polypill based on SMMs. Polypill is a formulation composed of several drugs that are used for the arterial hypertension treatment. That way the patients, in a single daily administration, take his complete medication, instead of the habitual 4-5 daily takings of individual drugs. The SMM of big pore size as SBA-15 would allow to adsorb great amount of molecules of several antihypertensive drugs simultaneously and to release them of a controlled form throughout the day. This would suppose a great advantage for the patients, since it would be more difficult that they forgot to take his medication when ingesting a single daily dose.

CONFLICTS OF INTEREST

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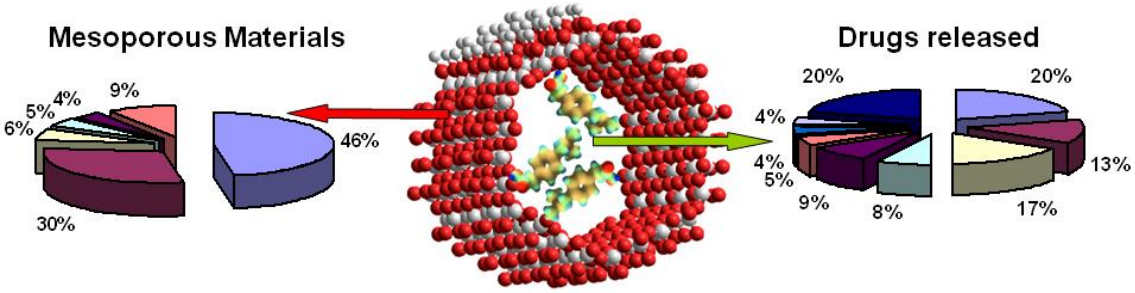
GRAPHICAL ABSTRACT

This article comprehensively reviews the host-guest systems for release drugs from ordered mesoporous silicas together possible future strategies to control demand the kinetics of delivery of drugs from these matrixes.



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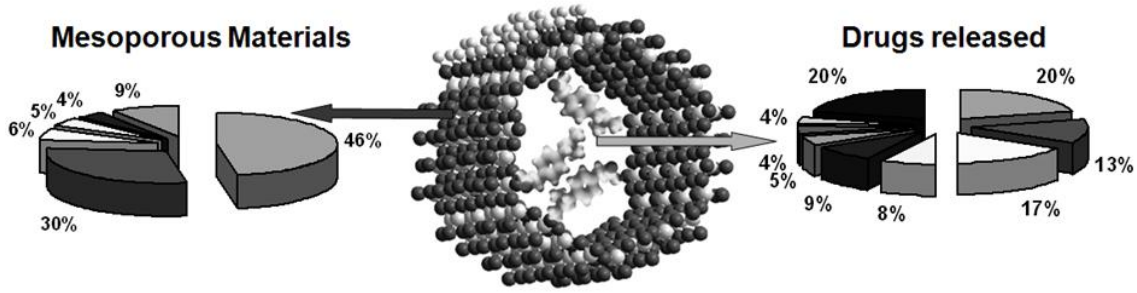
Mesoporous Materials
9%
4%
5%
6%
30%
46%
Drugs released
20%
4%
4%
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