Asian Journal of Pharmaceutical and Clinical Research
Vol. 4, Issue 2, 2011 ISSN - 0974-2441

Review Article

MESOPOROUS MATERIAL, MCM- 41: A NEW DRUG CARRIER

NASIR VADIA*[A] AND SADHANA RAJPUT[B]

[a, b] **Pharmacy Department, M. S. University of Baroda, Centre of Relevance and Excellence in New Drug Delivery System, Government of India, Vadodara 390002, India Email: nasirvadia@rediff.com**

ABSTRACT

Nanotechnology is a fast-growing area, involving the fabrication and use of nano-sized materials and devices. Various nanocomposite materials play a number of important roles in modern science and technology including pharmaceutical science. Among these materials mesoporous materials covers large number of applications in drug delivery system. Mesoporous MCM-41 is one of the mesoporous materials, used now-a-days as a drug carrier. Since this kind of materials consist on a disordered network of siloxane bridges and free silanol groups, these latter could be the reacting sites against appropriate guest chemical species. In this review, the application of mesoporous MCM-41 as drug delivery system has been discuss from the host guest interaction point of view. This article reviews the fabrication and chemistry of mesoporous MCM- 41 for biomedical applications, and also the potential advantages of mesoporous MCM- 41 in drug delivery.

Key words: Mesoporous material MCM-41, Drug delivery, Chemistry, Applications.

INTRODUCTION

Mesoporous materials with regular geometries are generating a lot of attention owing to their great potentials in practical applications such as catalysis, adsorption, sensing, medical usage, ecology, nanotechnology [1-15], Chemical and biological separations, chromatography, photonic and electronic devices, drug delivery, and energy storage[16]. Mesoporous materials are classified under porous material and these porous materials are classified according to their pore diameter [17] (table-1). Researchers had taken great efforts to synthesize mesoporous materials such as silicas [18], transitional aluminas [19] and pillard clays. In fact, in 1990, Yanagisawa and co-workers [20, 21], described the preparation of mesoporous silicas with uniform pore size. However, the pores in these materials were generally irregularly spaced and broadly distributed in size.

Table 1: Classification of porous materials

Types of porous material	Diameter of pores (nm)	Examples
Micrporous	Diameter < 2	Zeolites, $AlPO_4$
Mesoporous	2 < Diameter < 50	HMS,MCM-41,SBA-15
Macroporous	Diameter > 50	Porous gel, Porous glasses

In 1992, a research team from Mobil Oil Company synthesized a new family of materials, the so-called M41S [22-25] that presents ordered pore distributions, with homogeneous sizes ranging between 2 nm -10 nm, including different materials like hexagonal-MCM-41, cubic-MCM-48, and lamellar-MCM-50.The mesoporous materials were basically prepared through silica formation around template micelle [26, 27] assemblies followed by template removal by appropriate methods such as calcination and solvent evaporation. Different mesoporous materials are listed in table. 2.

Table 2: Different mesoporous materials

Mesoporous material	Full name
MSU	Michigan State University
SBA	Santa Barbara Amorphous
MCM	Mobil Crystalline Matter/ Mobil Composite Matter
HMS	Hollow Mesoporous Silica
OMS	Ordered Mesoporous Silica
TUD	Technische Universiteit Delft
MCF	Meso Cellular Form
FSM	Folded Sheet Mesoporous

These pioneering findings were followed by various kinds of mesoporous materials. For example, hexagonal mesoporous silica (HMS) prepared using neutral amine as template possesses slightly disordered hexagonal structure and thicker walls, superior thermal stability upon calcination in air, and a smaller crystallite size, which affords complementary textural mesoporosity for improved access to the framework-confined mesopores[28]. Michigan State University (MSU-1) synthesized by using polyethylene oxide (PEO) as a structure directing agent also has a disordered channel structure [29].

This material possesses large wall thickness and small particle size with considerable textural mesoporosity due to pores formed between the relatively small particles.

The widely used material is Santa Barbara Amorphous-15 (SBA-15), having highly orderd pores with thicker pore walls and two dimensional hexagonal structure, by using amphiphilic triblock-copolymer of poly(ethylene oxide) and poly(propylene oxide) (Pluronic P123) as the structure directing reagent in highly acidic media [30].

In addition to preparation of various mesoporous silica structures, incorporation of heteroatoms such as Cu, Zn, Al, B, Ga, Fe, Cr, Ti, V Sn etc. into mesoporous silica framework has been widely investigated [31-49]. Methodology to prepare mesoporous silica via the template synthesis is extended to preparation of a various mesoporous metal oxides [50-63] such as TiO_2, Ta_2O_5, Nb_2O_5, ZrO_2, Al_2O_3, V_2O_5 etc. as well as synthesis of mesoporous aluminophosphate [64-67].

In recent years, mesoporous materials, which have unique pore size, higher surface area and pore volume, have been widely employed as carriers for drug delivery.

Compared with amorphous colloidal and porous silica, mesoporous silicas exhibit higher loading of drugs and provide a controlled drug release if modified by functionalisation. Numerous interesting drug delivery applications of mesoporous materials have been demonstrated. Different Mesoporous material like MCM- 41, SBA-15, TUD, MCM- 50, HMS, TMS etc have many important properties advantageous to drug delivery applications.

The small size of the pores confines the space of a drug and engages the effects of surface interactions of the drug molecules and the pore wall. The size of the pores and the surface chemistry of the pore walls may be easily changed and controlled. Depending on the size and the surface chemistry of the pores, increased or sustained release of the loaded drug can be obtained. Sensitive therapeutic compounds susceptible to degradation, like peptides and proteins are also effectively loaded with mesoporous material. This article reviews the fabrication and chemistry of mesoporous MCM- 41 for biomedical applications, and also the potential advantages of mesoporous MCM- 41 in drug delivery.

DRUG AND MESOPOROUS MATERIAL

Following oral administration, dissolution of the drug molecule in the gastrointestinal (GI) milieu is a prerequisite for the absorption process. Up to 40 per cent of new chemical entities (NCEs) discovered by the pharmaceutical industry today are poorly soluble or lipophilic compounds. The solubility issues complicating the delivery of these new drugs also affect the delivery of many existing drugs. Low drug solubility often manifests itself in a host of in vivo consequences, including decreased bioavailability, increased chance of food effect, more frequent incomplete release from the dosage form and higher interpatient variability.

Poorly soluble compounds also present many in vitro formulation obstacles, such as severely limited choices of delivery technologies and increasingly complex dissolution testing with limited or poor correlation to the in vivo absorption. These in vivo and in vitro characteristics and the difficulties in achieving predictable and reproducible in vivo/in vitro correlations are often sufficiently formidable to halt development on many newly synthesized compounds due to solubility issues.

Developing strategies to overcome this handicap and to enable oral delivery of these new chemical entities now constitutes one of the greatest challenges to scientists active in pharmaceutical research [68]. Although several formulation approaches including solid dispersions [69], emulsion based systems [70] and nanosizing [71] have led to promising in vitro results, the number of marketed applications of these technologies remains very limited. Together with the growing number of poorly water soluble compounds, this emphasizes the need to explore new types of approaches.

Ordered mesoporous silica materials have recently attracted much attention because of their emerging applications in drug delivery [72]. Since their first appearance in materials science in the 1990s, these inorganic carriers have been successfully used in other research areas such as catalysis, purification [73] and adsorption [74].

The majority of ordered mesoporous materials have a two dimensionally ordered array of cylindrical pores of uniform size disposed parallel to each other and separated by thin walls [26, 27]. MCM-41 (Mobil Composition of Matter number forty one) and SBA-15 (Santa Barbara Amorphous number fifteen) are probably the most investigated materials of this type. Mesoporous materials based on silica are currently a field of intensive activity because of their high potential in a very broad range of applications. A series of inorganic mesostructures, like MCM41, HMS, SBAn etc, have been synthesized with different templating schemes [26, 27], Amongst different such materials some are listed in table.3 with their structural characteristics.

Table 3: Structural Characteristics of mesoporous materials

Types of mesoporous materials	Structural characteristics
MCM-41	Hexagonal 1 D
MC M- 48	Bicontinuous 3 D
SBA- 1	Cubic- 3 D
SBA-3	Hexagonal 2 D
SBA-15	Hexagonal 1 D
SBA- 16	Cage like arrangement
MSU	Hexagonal 2 D
HMS	Hexagonal

The operating tool in mesoporous MCM- 41 is the presence of micropores and these micropores are located in the walls between adjacent mesopores and do not bridge the wall; they constitute dead end pores [75]. Due to their open and well-defined pore system in combination with high surface area, ordered mesoporous MCM-41 is potential carrier for therapeutic molecules [76]. During the last few years, a number of interesting drug delivery applications of mesoporous materials has been demonstrated. Table. 4

CHEMISTRY OF MESOPOROUS MATERIAL MCM- 41

In 1990, Yanagisawa and colleague reported the synthesis of the mesoporous materials which shows the characteristic of MCM-41. Through intercalation of long-chain alkyltrimethylammonium cations into the layered silicate kanemite followed by calcination to remove the organic species, a mesoporous material was obtained. The silicate layers condensed to form a three-dimensional structure with "nanoscale pores".

Studies related to MCM-41 began in 1992 when a group of scientists employed by the Mobile Corporation published a paper entitled "A New Family of Mesoporous Molecular Sieves Prepared with Liquid Crystal Templates" [25]. The paper described the synthesis and characterization of a new family of mesoporous molecular sieves to which they gave the name M41S. MCM-41 is a material belonging to this family. The material was an improvement over other mesoporous materials of the time, which were generally amorphous solids with irregularly spaced, non-uniform sized pores[25]. A successful synthesis of MCM-41 produces a pure silica material composed by a hexagonal array of tubular channels of nearly uniform diameter.

Interconnections between the pores of MCM-41 are energetically unfavourable and the pore walls are made of an amorphous arrangement of silica tetrahedral [97]. The mesoporous structure can be controlled by a sophisticated choice of templates (surfactants), adding auxiliary organic chemicals, and changing reaction parameters (e.g., temperature, pressure, crystallization time, water content, pH, compositions).

A notable aspect of MCM-41 is that the diameter of the pores can be controlled through the carbon chain length of the surfactant used during synthesis [98- 100]. Pore size may also be controlled through the addition of auxiliary organic reagents during synthesis [25]. The addition of some auxiliary compound like 1, 3, 5-trimethylbenzene and triisopropylbenzene is effective in increasing the size of micelles [25, 67]. Alkanes such as n-pentane, n-hexane, n-heptane, n-octane and n-dodecane and N,N-dimethylhexadecylamine which can interact with the micelles of cationic surfactants, lead to the enlargement of the mesopores [2, 101]. The specific hydrothermal treatment of mesoporous materials is an another method of obtaining stable and enlarged mesopores [102, 103].

Numerous studies of this novel material have been published since its discovery. However, a multiple review on MCM-41 has never been published except the brief report [104].

This paper is intended to provide a comprehensive overview on synthesis, formation mechanisms, modification, and applications of MCM-41 in order to its potential applications in drug delivery. MCM-41 is a relatively straightforward material to produce under controlled laboratory conditions. Some common reagents used for synthesis of MCM- 41 are given in and table. 5.

Table 5: Reagents for the synthesis of Mcm 41

Common reagent	Chemical formula
Fumed silica	SiO2
Tetramethyl ammonium silicate	(CH3)4NOH.2SiO2
Tetraethyl orthosilicate	Si(OC2H5)4
Cetyl trimethyl ammonium chloride / hydroxide	C16H33N(CH3)3Cl/ OH
Ammonium hydroxide	NH4OH
Sodium silicate	Na2SiO3
Cetyl trimethyl ammonium bromide	C16H33N(CH3)3Br
Dodecyl trimethyl ammonium bromide	C12H25N(CH3)3Br
Tetramethylammonium hydroxide	(CH3)4NOH
Sodium hydroxide	NaOH

Table 4: Different mesoporous materials as drug carrier

Mesoporous material	Drug	Category	Modification	Comment	Ref
MCM- 41	Ibuprofen, Piroxicam	NSAID	--	Faster release of drug and increase dissolution of drug	77
TUD- 1	Ibuprofen	NSAID	--	Faster release of drug and increase dissolution of drug	78
Mesoporous- silica sphere	Gentamicin	Antibiotic	Coating with pH sensitive polyelectrolyte multilayer	Controlled drug release	79
SBA- 15, MCM- 41	Ibuprofen	NSAID	--	Faster release of drug and increase dissolution of drug	80
Mesoporous- silica powder	Gentamicin	Antibiotic	Hybridization with biodegradable polymer	Sustained release of drug	81
Mnesoporous- silica-nanoparticles	Camptothecin, Taxol	Anticancer ,,	Fluorescent nanoparticles	Effectively targeted to human cancer cells	82
Mesoporous- silica-nanoparticles	Hydralazine	Neuroprotector	functionalizing polyethylene glycol	Significant neuroprotection to damage cells	83
Mesostructured-cellular form	Ibuprofen Vancomycin	NSAID Antibiotic	Modified with hydrophobic polyisoprene	Significantly increase dissolution rate	84
Mesoporous- silica-nanoparticles	Gene	Protein	Surface -functionalization	Effective penetration in cell membranes of animal and plant cells	85
SBA- 15	Atenolol	Antihypertensive	Modified synthesis temperature	Sustained delivery of drug	86
SBA- 15, MCM- 41	Sodium-alendronate	Anti-psoriatic	Surface modification by amine group	Enhanced release rate of drug	87
SBA- 15, MCM- 41	Amoxicillin Erythromycin	Antibiotic ,,	Use of aqueous and non-aqueous solvents respectively for drug loading	Significantly increase dissolution rate	88
SBA- 15	Itraconazole	Antifungal	-	Faster release of drug and increase dissolution of drug	89
MCM- 41	Atenolol	Antihypertensive	Prepared with hydroxyapatite	Slow drug release	90
MCM- 41	Ibuprofen	NSAID	With different morphology & variable pore geometry	Controlled release	91
Hybrid mesoporous silica	Folic acid, Cisplatin	Vitamin, Anticancer	Functionalization with amino group	Targeting drug delivery	92
Hollow mesoporous silica	Ibuprofen	NSAID	Prepared with polyvinylpyrolidone	Sustained release	93
MCM- 48	Erythromycin	Antibiotic	--	Delayed release	94
SBA- 15	Bovine serum	Protein	--	Controlled release	95
Mesoporous orgenosilica sphere	Tetracycline	Antibiotic	--	Sustained release	96

Table 6: Synthesis strategies for MCM-41

Characteristic of Synthesized Mesoporous MCM- 41	Molar ratio of different components	Temperature (°C)	Time (h)	Ref
Prepared with liquid crystal mechanism	2.6 OH: 30 SiO2 : Al2O3: 6.3 CTA: 8.4 TMA: 382H2O	150	48	22
Simple preparation	30 SiO2: 0.4 Al2O3: 2.6 CTA: 4.5 TMAOH: 500 H2O	70	24	126
Prepared in acidic médium	26.9 H: 30 SiO2: 3.5 CTA: 3800 H2O	Ambient	05- 24	26
Prepared with primary amine, in acidic medium	0.6 H: 30 SiO2: 192 C2H5OH: 8DA: 1060 H2O	Ambient	18	28
Synthesis of V- MCM-41	5.1 Na2O: 30 SiO2: 0.6 VO2: 15 CTMA: 900 H2O	100	144	127
Prepared in alkali free medium	4 (NH4)2O: 30 SiO2: Al2O3:6 CTA: 700 H2O	100	72	30
Ordered MCM-41 with acetic acid addition	15 OH: 30 SiO2: Al2O3:5 CTMA:1125 H2O	100	72	128
Synthesis of Fe- MCM-41	15 OH: 30 SiO2: 0.3 Fe2O3: 6CTA	150	168-240	129
Synthesis of B- MCM-41	2.5 Na2O: 30 SiO2: x BO2: 4.8 CTA: 1890 H2O	100	24	130
Synthesis of Mn- MCM-41	(4.7 - 14.3) OH: 30 SiO2: (0.01-2.6) MnO:3.5 CTA: 4000 H2O	21-100	72	131

CHEMISTRY OF MESOPOROUS MATERIAL MCM- 41

In 1990, Yanagisawa and colleague reported the synthesis of the mesoporous materials which shows the characteristic of MCM-41. Through intercalation of long-chain alkyltrimethylammonium cations into the layered silicate kanemite followed by calcination to remove the organic species, a mesoporous material was obtained. The silicate layers condensed to form a three-dimensional structure with "nanoscale pores".

Studies related to MCM-41 began in 1992 when a group of scientists employed by the Mobile Corporation published a paper entitled "A New Family of Mesoporous Molecular Sieves Prepared with Liquid Crystal Templates" [25]. The paper described the synthesis and

characterization of a new family of mesoporous molecular sieves to which they gave the name M41S. MCM-41 is a material belonging to this family. The material was an improvement over other mesoporous materials of the time, which were generally amorphous solids with irregularly spaced, non-uniform sized pores [25]. A successful synthesis of MCM-41 produces a pure silica material composed by a hexagonal array of tubular channels of nearly uniform diameter.

Interconnections between the pores of MCM-41 are energetically unfavourable and the pore walls are made of an amorphous arrangement of silica tetrahedral [97]. The mesoporous structure can be controlled by a sophisticated choice of templates (surfactants), adding auxiliary organic chemicals, and changing reaction parameters (e.g., temperature, pressure, crystallization time, water content, pH, compositions). A notable aspect of MCM-41 is that the diameter of the pores can be controlled through the carbon chain length of the surfactant used during synthesis [98- 100]. Pore size may also be controlled through the addition of auxiliary organic reagents during synthesis [25]. The addition of some auxiliary compound like 1, 3, 5-trimethylbenzene and triisopropylbenzene is effective in increasing the size of micelles [25, 67]. Alkanes such as n-pentane, n-hexane, n-heptane, n-octane and n-dodecane and N,N-dimethylhexadecylamine which can interact with the micelles of cationic surfactants, lead to the enlargement of the mesopores [2, 101]. The specific hydrothermal treatment of mesoporous materials is an another method of obtaining stable and enlarged mesopores [102, 103].

Numerous studies of this novel material have been published since its discovery. However, a multiple review on MCM-41 has never been published except the brief report [104].

This paper is intended to provide a comprehensive overview on synthesis, formation mechanisms, modification, and applications of MCM-41 in order to its potential applications in drug delivery. MCM-41 is a relatively straightforward material to produce under controlled laboratory conditions. Some common reagents used for synthesis of MCM- 41 are given in and table. 5. The morphology of the MCM-41 particles depends on the reagents and synthesis procedure used.

Freshly prepared MCM-41 presents as a loose, agglomerated white powder with low mechanical stability [27]. It is the structure and properties of the material at the nanometer scale which have generated a great deal of interest in it and its many potential applications. The uniform size and shape of pores, large surface areas, and high thermal and hydrothermal stability are advantages of MCM-41 with respect to its potential use as a drug carrier and catalyst support [105].

Various morphologies can be achieved for mesoporous silica using either the templating method or the phase transformation approach. This usually involves order or shape in the micron scale. In addition to the normal particulate form, different shapes are also observed like fibers, gyroids and discoids [106, 107], ropes [108], hollow [109], spheres [110, 111], films supported [112] or free-standing [113], tubular [114], and pillar-within-spheres [115].

The surfaces of MCM-41 particles are dominated by silanol groups. These silanol groups may be classified as being one of three different varieties: single, (SiO) 3Si-OH; geminal, (SiO) 2Si (OH)2; or hydrogen bonded, (SiO) 3Si-OH-OH-Si (SiO)3. The surface density of these groups is approximately 2.5 to 3.0 groups/ nm2 and depends on the surfactant removal technique [116]. Under ambient humidity levels, all silanol groups become involved in hydrogen bonding with drug molecules [117]. If drugs have to be placed into pores, a material with a homogeneous ordered pore distribution should be specially designed. In such material, the drug adsorption and subsequent delivery will be more regular and reproducible than that coming from a disordered pore distribution. A step forward to this type of systems is the transition from nondesigned materials to specially designed porous matrices (ordered mesoporous materials).

The fundamental reasons for such rich morphological behaviors are:

- The silicate ions act as counterions to the cylindrical micelles to organize into soft hexagonal liquid crystalline phase.
- The rich organization of lyotropic surfactant system can be exploited to form many meso- structures.
- Control of higher hierarchical order of size above the nanometer scale can be achieved by fine tuning the interface curvature, either by changing composition or reaction condition.
- Silica condensation reaction can be controlled as in the late stage of the reaction.
- The self- organization and siloxane bond formation processes can be separately controlled.

The composition and pore structures are thoroughly studied with various spectroscopic and microscopic methods such as IR, TGA, SEM, TEM, BET (gas sorption measurements), XRD and solid state NMR. Following synthesis, the materia1s are characterized to determine particle and pore morphology, structure and surface details. The main characterizing techniques used on most mesoporous materials are low angle powder X-ray diffraction (XRD), nitrogen adsorption/desorption, scanning electron microscopy (SEM), transmission electron microscopy (TEM), and, recently induced coupled plasma atomic emission spectroscopy (ICP-AES), diffuse reflectance ultraviolet-visible spectroscopy (DRUVVIS), and fluorescence spectroscopy, solid state nuclear magnetic resonance (NMR). Adsorption analysis gives information about the porosity and surface area of the materials, while SEM gives particle size and morphology. Diffraction techniques and TEM supply insight to the degree of structural order whereas; solid state NMR measurements provide details regarding the surfaces of MCM-41 materials. Chemical composition of mesoporous particles can be examined by energy dispersive spectrometry (EDS). Many a times the obtained materials are characterized by thermal analysis like thermogravimetric (TG) and Differential scanning calorimetry (DSC).

The use of mesoporous materials as drug carrier has been extensively studied in an attempt to make use of their uniform mesopores and large surface areas. The drug loading is performed by direct impregnation methods. The mesoporous matrix is placed either as powder particles with regular sizes or as compacted pieces into the solution of the drug with a given concentration. In this impregnation procedure several factors have to be considered like the solution pH, temperature, drug solubility and polarity and generally its chemical nature. The release process is then carried out placing the drug-loaded mesoporous matrices into a solution and monitoring the drug concentration along the test time. In particular, a good election is a simulated body fluid. The selection of the loading solvent will have an effect on the amount of loaded drug. Thus when polar drug molecules such as amoxicillin [118] or gentamicin [119] are targeted, a polar solvent like water have to be used to enhance the concentration of drug into the pores. Sodium alendronate [120, 121] is a water-soluble salt, so an aqueous saline solution buffered at pH 4.8 was used to load this drug into mesoporous matrices. On the other hand, when a non-polar drug is aimed like ibuprofen, the chosen solvent also needs to be non-polar like hexane. Intermediate cases can also be found like erythromycin [122] that has to be loaded using acetonitrile. The drug loading into the mesoporous matrices is controlled by the chemical nature of the pore walls. The inorganic network of silica-based ordered mesoporous materials is plenty of silanol groups (Si-OH) that would interact with the functional groups of the drug. Depending on the strength of this attracting interaction, the drug retention will be modulated. Thus, ibuprofen that has a carboxylic acid group would form hydrogen bonds with the silanol groups and consequently drug molecules would be retained into the mesopores [123].

The release kinetics of drugs from OMS carriers is dependent on several material characteristics including pore size [100], pore connectivity [124] and the chemical composition of the silica surface [125]. Initially, the focus of mesoporous silica materials has been on the development of slow release formulations; but the applicability has recently been expanded towards dissolution enhancement of poorly water soluble compounds. Numerous research papers have revealed

the use of mesoporous material as drug carrier; some are listed in table. 4.

MECHANISM OF SYNTHESIS OF MESOPOROUS SILICA MCM- 41

The synthesis of mesoporous material is one of the most important subjects in modern pharmaceutical science. The synthesis and applications of mesoporous materials prepared using surfactant as templates have attracted great attention since the discovery of the M41S family of mesoporous molecular sieves by scientists at the Mobil Corporation. The main characteristics of MCM-41 materials are their high thermal stability, large surface area and narrow pore size distribution.

Different synthesis strategies have been proposed and successfully used, some reported synthesis for mesoporous MCM -41 are given in table. 6. However, there is one thing all these procedures have in common next to the obvious presence of a source of silica, viz. a templating agent. A template is a structure-directing agent, which is usually a relatively simple molecule or ion, around which a framework is built up. The most common templates for the synthesis of MCM-41 are quaternary ammonium ions with long alkyl chain, generally a hexadecyl group.

The energetically most favourable form of micelles is spherical, because in this geometry the surface energy is minimised most efficiently. Moreover, this conformation allows the largest number of micelles to be formed out of a certain amount of template, which is attractive considering the entropy of the system.

Nevertheless, it is observed that at increasing amounts of template in water different micelle geometry evolves: the spherical micelles gradually transform into long tubes, often denoted as rod-like micelles. Increasing the template concentration even further results in aggregation of the rod-like micelles into a hexagonal liquid crystalline structure, resembling the MCM-41 structure. If the template concentration is increased further this hexagonal liquid crystalline phase first transforms into a cubic liquid crystalline phase and eventually, at the highest template concentrations, into a lamellar liquid crystalline phase. The cubic liquid crystalline phase resembles the structure of mesoporous MCM-48, whereas the lamellar phase is the structural analogue of MCM-50 (an unstable material, which consists of platelets of amorphous silica). Because of the resemblances between the liquid crystalline phases and the MCM structures it is often assumed that the liquid crystalline structures are the actual templates of MCM-41 and MCM-48.

According to Myers [132], the particular phase present in a surfactant aqueous solution at a given

concentration depends not only on the concentrations but also on the nature of itself (the length of the hydrophobic carbon chain, hydrophilic head group, and counterion) and the environmental parameters (pH, temperature, the ionic strength, effect of stirring, effect of addition of silica source and other additives).

Once MCM-41 has been formed its pores are filled with template and in order to obtain a completely mesoporous support material the micelles must be removed. The most elegant solution to this demand is removal by means of repeated washing with (slightly acidified) mixtures of organic solvent and water, resulting in extraction of the template. The resulting solutions, containing the template, can be evaporated to dryness, which leads to recovery of the template. If the synthesis conditions were relatively mild the template will not have decomposed and can be re-used for a next synthesis. A simpler method for template removal is calcination. During this process template is decomposed into CO2, some NOx and steam.

Certain factors greatly affect the properties and characteristics of mesoporous MCM- 41, some of the factors are discussed below.

The most frequently used template for the synthesis of MCM-41 is hexadecyl (cetyl) trimethyl ammonium bromide (or chloride), i.e. a template with an alkyl chain containing sixteen -CH2 moieties. This template yields MCM-41 with a uniform pore size. Using templates with longer or shorter alkyl chains the pore size of MCM- 41 can be influenced.

Different research articles revealed the use of cationic surfactant for the synthesis of mesoporous silica, though several articles imposed the use of anionic surfactant as well as non ionic surfactant also [133, 134]. The variation in the sizes and shapes of the templates leads to the formation of mesoporous materials with different pore sizes and structures. The mesoporous materials that are prepared using anionic surfactants show chiral properties in their pores, and thus, they attract much attention as adsorbents that are useful in the separation of chiral drug molecules [135, 136]. Cationic surfactants with increased carbon chains length show increase in the size of micelles [137, 138]. Although the increase in the length of the carbon chains of anionic surfactants definitely results in the enlargement of the mesopores, the extent of the enlargement is not sufficient due to the difficulty in the preparation of long chain surfactants. Furthermore, the addition of alkylbenzenes and amines to the synthetic mixtures of mesoporous materials containing anionic surfactants is usually ineffective in enlarging their pore sizes. One research article imparts that, when ordered mesoporous materials have been synthesized using mixture of surfactants such as cationic/nonionic [139] and cationic/anionic surfactants [140], give rise to mesoporous materials with well defined pore sizes and morphologies. Mixtures of surfactants with different charges allow a wide variety of silica sources and synthetic conditions for the preparation of mesoporous materials. The surface properties of the pore walls is also different according to the type of surfactant used.

Silanol groups on the pore walls are also susceptible of undergoing a chemical modification with a large variety of organic groups through a functionalisation process. Indeed, the pore-wall modification would be performed depending on the functional groups of the drug molecules to be adsorbed. For example, sodium alendronate, a drug employed for osteoporosis treatments, has two phosphonate groups that would undergo stronger attracting interactions with amine groups than with silanols [120]. Therefore, if the pore wall surface is covered by amine groups, there would be a larger alendronate loading than in unmodified materials. The result shows that drug loading increased from 14% (unmodified) to 37% (modified) for amine-grafted materials MCM-41.

The pH of the synthesis procedure also has influence on pore size and volume of MCM-41. Cheng and his colleague studied the post-synthesis structural modulation of silica by the treatments with the ammonia solution of NH4OH and the aqueous solution of H2SO4. Their investigation revealed that NH4OH treated silicas generally have smaller unit cell parameters, smaller mesopores sizes and lower pore volumes, while the H2SO4 treatment gave materials with larger mesopores sizes and pore entrances but very low pore volumes [141].

ORDERED MESOPOROUS MATERIALS: IMMEDIATE Vs CONTROL RELEASE

Conventional dosage forms have the disadvantage of not being able to control either the rate of drug delivery or the target area of drug administration and provide a rapid and an immediate drug release. Thus, frequent administration is necessary in order to maintain a therapeutic level, which in turn causes drug concentration in blood and tissues to fluctuate widely. Polymeric cross-linked carrier matrices, such as hydrogels and supra-molecular polymer aggregates as well as different types of microencapsulation vehicles, are typical examples of common drug delivery devices. Depending on the delivery system and the pharmaceutical in use, different release mechanisms are applied. However, there are three primary ways by which active agents can be released from such system: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may occur in a given release system. Diffusion occurs when a drug or other active agent passes through the system (a ceramic or polymer based matrix) that forms the controlled-release device. The diffusion can occur on a macroscopic scale as through pores in the matrix or on a molecular level, by passing between, for instance, polymer chains. The diffusion controlled release could be activated by several means, including ionic strength, pH and thermal, magnetic or chemical changes. The ability to control over the drug delivery can be an important factor especially at times when traditional oral or injectable drug

formulations are difficult to distribute. In some cases there might be a need of a slow release of a water soluble drug or a fast release of low-solubility drugs. It might also be convenient for drug delivery to specific sites, drug delivery using nanoparticulate systems, delivery of two or more agents with the same formulation, and also systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system should be inert or biodegradable, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from accidental release, simple to administer and remove, and easy to fabricate and sterilize.

Mesoporous silica has many important properties advantageous to drug delivery applications. The small size of the pores confines the space of a drug and engages the effects of surface interactions of the drug molecules and the pore wall. The size of the pores and the surface chemistry of the pore walls may be easily changed and controlled. Depending on the size and the surface chemistry of the pores, increased or sustained release of the loaded drug can be obtained. As the purely siliceous mesoporous materials have been shown to be biocompatible, or sometimes even bioactive, there is an increasing interest in this class of materials for applications in the field of bioceramics, especially as bone substitute materials. Furthermore, the highly organized porous silica matrix could be used as a potential controlled drug release system. Another attractive advantage is that amorphous silica is degradable in an aqueous solution, and thus problems related to the removal of the material after use can be avoided.

Numerous articles represent the use of mesoporous materials as pharmaceutical carrier systems for immediate as well as controlled drug release. Mesoporous materials can be used as medical devices because of the presence of larger pores and well-defined structure. They present high surface areas, above 1000 m2/g, and ordered mesopores ranging from 2.0 nm to tens nanometers, depending on the conditions of synthesis. It is observed that mesoporous materials exhibit high drug loading and the amount can be as high as 97 wt%. Several factoring can influence the drug loading such as pore structure, surface functionality, morphology, drug molecule size and solvent for drug loading. Generally, hollow mesoporous silica presents the highest loading for various drugs due to their hollowed pore structure. Higher surface area and pore size will favour the loading of drug. Grafting/ functionalisation of mesoporous silica change the pore size and the interaction between drug and substrate, resulting in lower drug loading and slow release rate.

Vallet-Regi and colleague were one of the first to explore the drug release properties of these materials in an attempt to prolong the release of ibuprofen using MCM-41 as a carrier [85]. Charnay showed a rapid and pH dependent release of ibuprofen from MCM-41 with a pore size of 3.5 nm [142]. Later studies evidenced a high mobility of ibuprofen inside the pore system of MCM-41 at ambient temperature and pointed out the weak interaction of ibuprofen with the silica matrix. Cavallaro have investigated mesoporous silicate as devices for drug delivery. Four anti-inflammatory agents such as diflunisal, naproxen, ibuprofen and its sodium salt have been used. Drug release studies were also performed at pH 1.1 and 6.8 mimicking gastrointestinal fluids. Release data suggest that the matrix impregnated with diflunisal offers good potential as a system for the modified drug release [143]. Qu recently studied a water-soluble drug captopril with mesoporous MCM-41 system [144]. The drug-loading amount is correlated to the Brunauer–Emmett–Teller (BET) surface area and surface hydrophilicity and hydrophobicity of the mesoporous silica material, while drug release profiles could be controlled by tailoring the surface properties and pore size. Trewyn presented an investigation on preparation of mesoporous silica nanoparticle (MSN) materials with various particle morphologies, including spheres, ellipsoids, rods, and tubes, using room-temperature ionic liquid (RTIL). By changing the RTIL template, the pore morphology was tuned from the MCM-41 type of hexagonal mesopores to helical channels, and to wormhole-like porous structures. These materials were then used as controlled-release delivery nanodevices to release antibacterial ionic liquids against Escherichia coli K12. The antibacterial activity was dependent on the rate of diffusional release of the pore encapsulated RTIL, which was governed by the particle and pore morphology of the MSN materials [145].

Mesoporous silica nanoparticles possess several attractive features such as large surface areas and porous interiors that can be used to store various molecules. In addition, their pore size and environment as well as their size and shape can be easily modified, making them a suitable choice as intracellular drug carriers. Jie prepared biocompatible mesoporous silica nanoparticles, containing the fluorescence dye fluorescein isothiocyanate; provide a promising system to deliver hydrophobic anticancer drugs paclitaxel to cancer cells. In this study, they have shown that fluorescent mesoporous nanoparticles (FMSN) are efficiently taken up by human cancer cells. They have also shown that a hydrophobic anticancer drug paclitaxel can be stored in FMSN and delivered to human cancer cells resulting in the inhibition of proliferation of these cells. These results point to the useful feature of FMSN as a valuable vehicle for anticancer drugs [82]. Another important application of mesoporous nanoparticles also represented by Jie is that it acts as dissolution enhancer for poorly soluble anticancer drug camptothecin (CPT), that was successfully entrapped into the pores of fluorescent mesoporous silica nanoparticles (FMSN) and delivered CPT into a variety of human cancer cells to induce cell death, demonstrating that mesoporous silica nanoparticles are promising in overcoming the insolubility problem of anticancer drugs [82]. Similar findings were mentioned by Wei Sun, when they prepared mesoporous silica nanoparticles (MSN) for lung cancer therapy, It revealed the three-dimensional distribution of the MSN inside the cell. MSNs can be a good drug delivery vector and have lots of applications in controlled drug release systems, as they may be selectively targeted to specific cellular organelles through surface modification. Therefore, drugs can be protected from enzymatic digestion in the cell cytoplasm by capping the channels in MSNs [146]. This approach can be employed to study real-time drug release events in living cells when MSNs or other nanoparticles are used as drug delivery vectors. Shenmin Zhu have explored the use of polymer with mesoporous silica with large pore seize for drug release. They were using hydrophobic polyisoprene (PI) through free radical polymerization in the pores network, and the resulting materials (MCF-PI) were investigated as matrices for drug storage. Ibuprofen (IBU) and vancomycin were selected as model drugs and loaded onto unmodified MCF and modified MCF (MCF-PI). The adsorption capacities of these model drugs on MCF-PI were observed increase as compared to that of on pure MCF, due to the trap effects induced by polyisoprene chains inside the pores. The delivery system of MCF-PI was found to be more favorable for the adsorption of IBU [147]. Kamalakannan have reported the preparation of MCM-41 silica spheres via the pseudomorphic route. Subsequent surface modification of the mesoporous silica spheres was achieved by two silylating agents, n-octadecyltrihydridosilane and noctadecyltrimethoxysilane, which provided different surface morphology and prepared MCM- 41 spheres are highly ordered and having practically uniform mesopores [148]. Some of the research articles have reported the post synthesis treatment which provides important information regarding the surface geometry and morphology of mesopores.

Ordered mesoporous silica has stable mesoporous structure, large surface area, good biocompatibility and tailored size of mesopores, all these requisites exhibited promising application as immediate and controlled drug delivery system. For applications in drug delivery systems , the development of mesoporous materials offer new possibilities for incorporating biological agents and different category of drugs such as anti-inflammatory agents, antibiotics, antifungal, chemotherapeutic drugs, steroids, hormones and vaccines, within a silica sample and for controlling the release kinetics from the matrix because of its well-arranged structure. The delivery of these molecules was once considered impossible because of the difficulty associated with the diffusion of large molecules through the materials of conventional drug delivery systems. These organic substances are normally very large in size, and one can anticipate that mesoporous silica would have a potential for encapsulating bioactive molecules by utilizing ordered mesopores. Plenty of drugs were evaluated for their loading and release characteristics with respect to mesoporous material and all have showed a very potential effect for its controlled and immediate

release pattern. List of such drugs and respective mesoporous materials provided in table. 4

FUTURE POTENTIAL

Nanotechnology is a fast-growing area, involving the fabrication and use of nano-sized materials and devices. Various nanocomposite materials play a number of important roles in modern science and technology. Porous inorganic nanoparticles are of particular importance due to their broad range of potential applications. The synthesis of the mesoporous silicas MCM-41 and MCM-48 in 1992, using a supramolecular surfactant system as a template, provoked a boom in mesoporous materials.

Mesoporous materials (MCM-41), the basis for nano-technologies, are one of the fastest developing fields in pharmaceutical science. It has been shown that ordered mesoporous silica with stable mesoporous structure, large surface area, good biocompatibility and tailored size of mesopores and functionalisation has exhibited promising application as drug delivery system. The mesoporous silica demonstrates higher drug loading followed by controlled sustained release as well as immediate release. The drug release rate is governs by pore size and functional groups on the wall. Functionalisation of MCM-41 leads to cover the walls of silica resulting in pore size decrease and lower drug loading; however, it brings in controlled drug release. In most cases, drug release is a diffusion-controlled process and exhibits a two-stage profile. However, few investigations have been attempted to explore the drug release kinetics and more work should be focused because the understanding of kinetics will help in the achievement of controlled drug release. Surface functionalisation with various groups can change electrostatic, hydrophobic/hydrophilic forces, and the adhesive interactions of drug and matrix, inducing varying drug loading and delivery rate. Moreover, functionalisation with different groups will make the systems attached to cell and biological species such as proteins and enzymes. Future work should be directed to development of non-immunogenic polymer/mesoporous solid as drug carrier, which will show more advantages than glass-polymer systems. There are also many emerging biotechnologies that can benefit from the mesoporous materials-based drug delivery. Bone tissue engineering is an emerging area directed towards the design of materials that will help an organism to improve its ability of regeneration by recovering both the structure and also its function. Biocompatible and bioactive mesoporous materials with controlled drug delivery will favour the cellular growth and bone regeneration. Research should be directed towards finding suitable combination of bioactivity and controlled drug delivery kinetics. For direct drug delivery, nanosize particles have been attracted much attention. These nanoparticle carriers can effectively penetrate or pass through the cell membrane into cells, achieving controlled cellular delivery. Although a lot of inorganic nanoparticles have been produced, little work has been done in synthesis of nanosize mesoporous silica particles. The combination of the mesoporous characteristics and the properties of nanoparticles will provide a fascinating application of nanoparticles for biotechnology and biomedicine and more efforts should be attempted.

Many potential applications of mesoporous MCM-41 have been explored, from catalysis, separation, biology, environmental monitoring, and pharmaceuticals to clinical toxicology, but a gap in real industrial applications still exists. The great challenge facing the mesoporous materials community now is to transfer laboratory studies to industrial applications. Although the potential applications of such materials have been widely studied in many areas, more efforts are still needed for the continuing study of their practical applications to commercialize mesoporous materials in the future. The forthcoming practical applications in fields such as drug delivery, biotechnology, gene & protein therapy, new drug delivery system, catalysis, separation, adsorption, electronic devices, low dielectric constant materials and beyond will stimulate more research interests in this area, and more exciting and useful developments in mesoporous materials will also be delivered.

REFERENCES

1. Raman NK, Anderson MT, Brinker CT. Template-based approaches to the preparation of nanoporous silicas. Chem Mater 1996; 8: 1682- 1701.
2. Sayari A. Aluminosilicate MCM-48 mesostructures assembeled from dried zeolite precursors and gemini surfactant. Chem Mater 1996; 8: 1840- 1852.
3. Corma A. Mesostructured zeolitic materials and methods of making and using the same. Chem Rev 1997; 97: 2373- 2419.
4. Moller K, Bein T. Synthesis and Characterization of Functionalized MCM-41 with copper– and manganese–phenanthroline complexes. Chem Mater 1998; 10: 2950.
5. Causal U, Schu th F. Ordered mesoporous materials. Microporous Mesoporous Mater 1999; 27: 131- 149.
6. Ying JY, Mehnert CP, Wong MS, Angew. Synthesis and applications of supramolecular-templated mesoporous materials. Chem Int Ed 1999; 38- 56.
7. Stein A, Melde BJ, Schroden RC. Hybrid inorganic-organic mesoporous silicates- nanoscopic reactors coming of age. Adv Mater 2000; 12: 1403- 1419.
8. Sanchez C, Soler-Illia GJ de AA, Ribot F, Lalot T, Mayer CR, Cabuil V. Designed hybrid organic–inorganic nanocomposites from functional nanobuilding blocks. Chem Mater 2001; 13: 3061- 3083.
9. Polarz S, Smarsly B. Nanoporous materials (Review). J Nanosci Nanotechnol 2002; 2: 581- 612.
10. Davis ME. Ordered porous materials for emerging applications. Nature 2002; 417: 813- 821.
11. Vinu A, Murugesan V, Hartmann M. Pore size engineering and mechanical stability of cubic mesoporous SBA-1 molecular sieves. Chem Mater 2003; 15: 1385 -1393.
12. Okabe A, Fukushima T, Ariga K, Niki M, Aida T. Tetrafluoroborate salts as site-selective promoters for sol-gel synthesis of mesoporous silica. J Am Chem Soc 2004; 126: 9013- 9016.
13. Ariga K. Template-assisted nano-patterning from submicron-scale to submolecular-level. J Nanosci Nanotechnol 2004; 4: 23-34.
14. Taguchi A, Schu¨ th F, Ordered mesoporous materials in catalysis. Microporous Mesoporous Mater 2005; 77: 1- 45
15. Vinu A, Hossain KZ, Ariga K, Recent Advances in Functionalization of Mesoporous Silica. J Nanosci Nanotechnol 2005; 5: 347- 371
16. Sing KSW, Everett DH, Haul RHW, Moscou L, Pierotti R A, Rouquerol J, Siemieniwska T. Reporting physisorption data for gas/solid systems. Pure Appl Chem 1985; 57: 603- 619.
17. Mal NK, Fujiwara M, Tanaka Y. Photocontrolled reversible release of guest molecules from coumarin-modified mesoporous silica. Nature 2003; 421: 350- 353.
18. Iler RK, The chemistry of silica. Wiley and Sons Inc. 1979; 680-687.
19. Wefers K, Misra C, Alcoa Technical, Paper No 19, Revised. Oxides and hydroxides of aluminum alcoa laboratories. 1987.
20. Yanagisawa T, Schimizu T, Kuroda K, Kato Bull C. The preparation of alkyltriinethyl- aininonium–kaneinite complexes and their conversion to microporous materials. Chem Soc Japan 1990; 988- 992.
21. Pinnavia T. Intercalated Clay. J Catalysts Science 1983; 220: 365- 371.
22. Kresge CT, Leonowicz ME, Roth WJ, Vartuli JC, Beck JS. Ordered mesoporous molecular sieves synthesized by a liquid-crystal template mechanism. Nature 1992; 359: 710- 712.
23. Kresge CT, Leonowicz ME, Roth WJ, Vartuli JC, U S Patent, 1992; US 5,098,684.
24. Beck JS, Chu CT, Johnson ID, Kresge CT, Leonowicz ME, Roth WJ, Vartuli JC, US Patent, 1992 ; 5,145,816.
25. Beck JS, Vertuli JC, Roth WJ, Leonowicz ME, Kresge CT, Schmitt KD, Chu C, Olson DH, Sheppard EW, McCullen SB, Higgins JB, Schlenker JL. A new family of mesoporous molecular sieves prepared with liquid crystal templates. J Am Chem Soc 1992; 114: 10834- 10843.
26. Zhao D, Huo Q, Fena J, Chemelka BF, Stucky GD. Nonionic triblock and mesoporous silica structures. J Amer Chem Soc 1998; 120: 6024- 6036.
27. Hata H. Adsorption of taxol into ordered mesoporous silicas with various pore diameters. Chem Mater 1999; 11: 1110-1119.
28. Tanev PT, Pinnavaia TJ. A neutral templating route to mesoporous molecular sieves. Science 1995; 267: 865- 867.

29. Bagshaw SA, Prouset E, Pinnavaia TJ. Templating of mesoporous molecular sieves by nonionic polyethylene oxide surfactants. Science 1995; 269: 1242- 1244.
30. Zhao D, Feng J, Huo Q, Melosh N, Fredickson GH, Chmelka BF, Stucky GD. Triblock copolymer syntheses of mesoporous silica with periodic 50 to 300 angstrom pores. Science 1998; 279: 548- 552.
31. Morey MS, Davidson A, Stucky GD. Silica-based, cubic mesostructures: synthesis, characterization, and relevance for catalysis. J Porous Mater 1998; 5: 195–204.
32. Khushalani D, Hasenzahl S, Mann S. Synthesis of mesoporous silica monoliths with embedded nanoparticles. J Nanosci Nanotechnol 2001; 1: 129- 132.
33. Hartmann M, Vinu A, Elangovan SP, Murugesan V, Bohlmann W. Direct synthesis and catalytic evaluation of Al-SBA-1. Chem Commun 2002; 1238- 1239.
34. Leite ER, Carreno NLV, Longo E, Valentini A, Probst LFD. Synthesis of mesoporous silica with embedded nickel nanoparticles for catalyst applications. J Nanosci Nanotechnol 2002; 2: 89- 94.
35. Vinu A, Dedeeek J, Murugesan V, Hartmann M. Synthesis and characterization of cosba-1 cubic mesoporous molecular sieves. Chem Mater 2002; 14: 2433- 2435.
36. Vinu A, Hartmann M. Direct synthesis and spectroscopic evidence of framework co(ii) ions in sba-15 mesoporous molecular sieves. Chem Lett 2004; 33: 588- 589.
37. Vinu A, Ariga K, Saravanamurugan S, Hartmann M, Murugesan V. Synthesis of highly acidic and well ordered mgal-mcm-41 and its catalytic performance on isopropylation of m-cresol reaction. Microporous Mesoporous Mater 2004; 76: 91- 98.
38. Wu S, Han Y, Zou YC, Song JW, Zhao L, Di Y, Liu SZ, Xiao FS. Synthesis of heteroatom substituted SBA-15 by the pH-adjusting method. Chem Mater 2004; 16: 486- 492.
39. Vinu A, Krithiga T, Murugesan V, Hartmann M. Direct synthesis of novel Fe-SBA-1 cubic mesoporous catalyst and its high activity in the *tert*-butylation of phenol. Adv Mater 2004; 16: 1817- 1821.
40. Vinu A, Devassy BM, Halligudi SB, Bohlmann W, Hartmann M. highly active and selective Al-SBA-15 catalysts for the vapor phase *tert*-butylation of phenol. Appl Catal A-Gen 2005; 281: 207- 213.
41. Vinu A, Karthik M, Miyahara M, Murugesan V, Ariga K, Ortho selective ethylation of phenol with ethanol catalyzed by bimetallic mesoporous catalyst, coal-MCM-41. J Mol Catal A-Chem 2005; 230: 151- 157.
42. Vinu A, Sawant DP, Ariga K, Hartmann M, Halligudi SB. Benzylation of benzene and other aromatics by benzyl chloride over mesoporous Al-SBA-15 catalysts. Microporous Mesoporous Mater 2005; 80: 195- 203.
43. Vinu A, Kumar GS, Ariga K, Murugesan V. Preparation of highly ordered mesoporous
alsba-15 and its application to isopropylation of m-cresol. J Mol Catal A-Chem 2005; 235: 57- 66.
44. Krithiga T, Vinu A, Ariga K, Arabindoo B, Palanichamy M, Murugesan V. Selective formation 2,6-diisopropyl naphthalene over mesoporous Al-MCM-48 catalysts. J Mol Catal A-Chem 2005; 237: 238- 245.
45. Vinu A, Sawant DP, Ariga K, Hossain KZ, Halligudi SB, Hartmann M, Nomura M. Preparation and characterization of well ordered hexagonal mesoporous carbon nitride. Chem Mater 2005; 17: 5339- 5345.
46. Sawant DP, Vinu A, Jacob NE, Lefebvre F, Halligudi SB. Formation of nano-sized zirconia supported 12-tungstophosphoric acid for benzylation of phenol mesoporous silica SBA-15: a stable and versatile solid acid catalyst. J Catal 2005; 235: 341- 352.
47. Vinu A, Krithiga T, Balasubramanian VV, Asthana A, Srinivasu P, Mori T, Ariga K, Ramanath G, Ganesan PG. Characterization and catalytic performances of three dimensional mesoporous Fe-SBA-1 catalysts. J Phys Chem B 2006; 110: 11924- 11931.
48. Vinu A, Srinivasu P, Miyahara M, Ariga K. Preparation and catalytic performances of ultra large-pore Ti-SBA-15 mesoporous molecular sieves with very high ti content. J Phys Chem B 2006; 110: 801- 806.
49. Umamaheswari V, Bohlmann W, Poppl A, Vinu A, Hartmann M. Spectroscopic characterization of iron-containing MCM-58 framework. Microporous Mesoporous Mater 2006; 89: 47- 57.
50. Antonelli DM, Ying JY, Angew. Synthesis of hexagonally-packed mesoporous TiO2 by a modified sol-gel method. Chem Int Ed Engl 1995; 34: 2014- 2017.
51. Bagshaw SA, Pinnavaia TJ, Angew. Mesoporous alumina molecular sieves. Chem Int Ed Engl 1996; 35: 1102- 1105.
52. Antonelli DM, Ying JY, Angew. Synthesis of Hexagonally-Packed Mesoporous TiO2 by a Modified Sol-Gel Method. Chem Int Ed Engl 1996; 35: 426- 430.
53. Antonelli DM, Nakahira A, Ying JY. Ligand-assisted liquid crystal templating in mesoporous niobium oxide molecular sieves. Inorg Chem 1996; 35: 3126- 3136.
54. Antonelli DM, Ying JY. Synthesis and characterization of hexagonally-packed mesoporous tantalum oxide molecular sieves. Chem Mater 1996; 8: 874- 881.
55. Liu P, Moudrakovski IL, Liu J, Sayari A. Mesostructured vanadium oxide containing dodecylamine. Chem Mater 1997; 9: 2513- 2520.
56. Bach U, Lupo D, Comte P, Moser JE, Weisso rtle F, Salbeck J, Spreitzer H, Gratzel M. Solid-state dye-sensitized mesoporous TiO_2 solar cells with high photon-to-electron conversion efficiencies. Nature 1998; 395: 583- 585.
57. Wong MS, Ying JY. Amphiphilic templating of mesostructured zirconium oxide. Chem Mater 1998; 10: 2067- 2077.
58. Kondo JN, Lu L, Takahara Y, Maruya K, Domen K, Igarashi N, Tatsumi T. Characterization of mesoporous tantalum oxide. Bull Chem Soc Jpn 2000; 73: 1123- 1129.
59. Schu th F. Non-siliceous mesostructured and mesoporous materials. Chem Mater 2001; 13: 3184- 3195.
60. Subramanian V, Jiang JC, Smith PH, Rambabu B. Mesoporous Sno_2 synthesized with non-ionic surfactants as an anode material for lithium batteries. J Nanosci Nanotechnol 2004; 4: 125- 131.
61. Kartini I, Meredith P, Zhao XS, Diniz da Costa JC, Lu GQ. A two-step sol gel method for synthesis of nanoporous TiO_2. J Nanosci Nanotechnol 2004; 4: 270- 274.
62. Hayward RC, Chmelka BF, Kramer EJ. Crosslinked poly(styrene)-*block*-poly(2-vinylpyridine) thin films as swellable templates for mesostructured silica and titania. Adv Mater 2005; 17: 2591- 2595.
63. Shibata H, Ogura T, Mukai T, Ohkubo T, Sakai H, Abe M. Direct synthesis of mesoporous titania particles having a crystalline wall. J Am Chem Soc 2005; 127: 16396- 16397.
64. Chakraborty B, Pulikottil AC, Das S, Viswanathan B. Synthesis and characterization of mesoporous SAPO. Chem Commun 1997; 911- 912.
65. Zhao D, Luan Z, Kevan L. Synthesis of thermally stable mesoporous hexagonal aluminophosphate molecular sieves. Chem Commun 1997; 1009- 1010.
66. Holland BT, Isbester PK, Blanford CF, Munson EJ, Stein A. Synthesis and characterization of a reactive vinyl-functionalized MCM-41: probing the internal pore structure by a bromination reaction. J Am Chem Soc 1997; 119: 6796- 6803.
67. Kimura T, Sugahara Y, Kuroda K. Synthesis and characterization of lamellar and hexagonal mesostructured aluminophosphates using alkyltrimethylammonium cations as structure directing agents. Chem Mater 1999; 11: 508- 518.
68. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev 1997; 23: 3–25.
69. Leuner C, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm 2000; 50: 47–60.
70. Hong JY, Kim JK, Song YK, Park JS, Kim CK. A new selfemulsifying formulation of itroconazole with improved dissolution and oral absorption. J Control Release 2006; 110: 332–338.
71. Rabinow BE. Nanosuspensions in *drug* delivery. Nat Rev Drug Discov 2004; 3: 785–796.
72. Vallet-Regi M. Ordered mesoporous materials in the context of drug delivery systems and bone tissue engineering. Chem Eur J 2006; 12: 5934–5943.

73. Chang JS, Hwang JS, Park SE, Preparation and application of mesoporous materials. Res Chem Intermed 2003; 29: 921–938.
74. Yiu HHP, Wright PA. Enzymes supported on ordered mesoporous solids: a special case of an inorganic-organic hybrid. J Mater Chem 2005; 15: 3690– 3700.
75. Kruk M, Jaroniec M, Ko CH, Ryoo R, Characterization of the porous structure of SBA-15. Chem Mater 2000; 12: 1961–1968.
76. Vallet-Regi MA, Ruiz-Gonzalez L, Izquierdo-Barba I, Gonzalez-Calbet JM. Revisiting silica based ordered mesoporous materials: medical applications. J Mater Chem 2006;16: 26–31.
77. AmbrogiaV, PerioliaL, MarmottinibF, Giovagnolia S, EspositoaM, Rossi C. Improvement of dissolution rate of piroxicam by inclusion into MCM-41 mesoporous silicate. Eur J Pharm Sci, 2007; 32: 216-222.
78. HeikkiläaT,, Salonena J, Tuuraa J, Hamdyb MS, Mulb G, Kumarc N, Salmic T, Murzinc DYu, Laitinend L, Kaukonend AM, Hirvonene J, Lehto V P. Mesoporous silica material TUD-1 as a drug delivery system. Int J Pharm, 2007; 331: 133-138.
79. Zhua Y, Jianlin S. A mesoporous core-shell structure for pH-controlled storage and release of water-soluble drug. Microporous Mesoporous Mater, 2007; 103 : 243-249.
80. Thierry A, Corine T, Fabien A, Niki B, Cristina C , Jean-Marie D, Florence B, Solid-state NMR study of ibuprofen confined in MCM-41 material. Chem Mater, 2006 ; 18: 6382-6390.
81. Xue JM, Tan CH, Lukito D. Biodegradable polymer-silica xerogel composite microspheres for controlled release of gentamicin. J Biomed Mater Res, Part B, 2006 ; 78 : 417 –422.
82. Jie L, Monty L, Sean S, Tian X, Michael K, Andre N, Jeffrey Zink FT, Mesoporous silica nanoparticles for cancer therapy: energy-dependent cellular uptake and delivery of paclitaxel to cancer cells. NanoBioTechnology 2007; 3: 89-95.
83. Cho Y Shi, Borgens RB , Ivanisevic A. The functionalized mesoporous silica nanoparticles (MSNS) based drug delivery system to rescue acrolein-mediated cell death. Nanomedicine 2008; 3: 507-519.
84. Shenmin Z, Di Z, Yang N. Hydrophobic polymers modification of mesoporous silica with large pore size for drug release. J Nano Res 2009; 11: 561-568.
85. Young P, Yong K, Kyong Y, Jaie C, Haing C, Chong Su C. Mannosylated polyethylenimine coupled mesoporous silica nanoparticles for receptor-mediated gene delivery. Int J Pharm 2008; 359: 280-287.
86. FagundesaLB, Sousab TGF, SousacA, Silvac VV, Sousa EMB. SBA-15-collagen hybrid material for drug delivery applications. J Non-Cryst Solids 2006; 352: 3496-3501.
87. Vallet-Regí M, Balasa F, Colillaa M, Manzano M. Bioceramics and pharmaceuticals: A remarkable synergy. Solid State Sci, 2007; 9: 768-776.
88. Wang S. Ordered mesoporous materials for drug delivery. Microporous Mesoporous Mater 2009 ; 117 : 1-9.
89. Mellaerts R, Caroline, Aerts A, Humbeeck J, Augustijns P, Mooter G, Martens J. Enhanced release of itraconazole from ordered mesoporous SBA-15 silica materials. Chem Commun, 2007; 1375 – 1377.
90. Sousa A, Souza KC, Sousa EMB. Mesoporous silica/apatite nanocomposite: Special synthesis route to control local drug delivery. Acta Biomaterialia 2008; 4: 671-679.
91. Xua W, Gaoa Q, Xua Y, Wua D, Suna Y, Shenb W, Deng F. Controllable release of ibuprofen from size-adjustable and surface hydrophobic mesoporous silica spheres. Powder Technol 2009; 191: 13-20.
92. Pasquaa L, Testaa F, Aielloa R, Cundaria S, Nagy J B. Preparation of bifuctional hybrid mesoporous silica potentially for drug targetting. Microporous Mesoporous Mater 2007;103: 166-173.
93. ZhuaY, ChenaJ S H, Shena W, Dong X. A facile method to synthesize novel hollow mesoporous silica spheres and advanced storage property. Microporous Mesoporous Mater 2005; 84: 218-222.
94. Barba II, Martinez Á, Doadrio AL, Pariente JP, Vallet-Regí M. Release evaluation of drugs from ordered three-dimensional silica structures. Eur J Pharm Sci 2005; 26: 365-373.
95. Nguyen T, Wook LJ, Shim WG, Hee M. Synthesis of functionalized SBA-15 with ordered large pore size and its adsorption properties. Microporous Mesoporous Mater 2008; 110: 560-569.
96. Lin C X, Qiao S Z, Yu C Z, Suryadi I, Lu G Q. Periodic mesoporous silica and organosilica with controlled morphologies as carriers for drug release. Microporous Mesoporous Mater 2009; 117: 213-219.
97. Kleestorfer K, Vinek H, Jentys A. Structure simulation of MCM-41 type materials. J Mol Catal A-Chem 2001; 116: 53-57.
98. Letellier F J, Blanchard K, Fajerwerg C, Louis M, Breysse D, Guillaume, Uzio D. Search for confinement effects in mesoporous supports: hydrogenation of o-xylene on Pt degrees/MCM-41. Catal Lett 2006; 110: 115-124.
99. Kruk M, Jaroniec M, Sayari A. Adsorption study of surface and structural properties of MCM-41 materials of different pore sizes. J Phy Chem B 1997; 110: 583-589.
100. Horcajada P, Ramila A, Perez-Pariente J, Vallet-Regi M. Influence of pore size of MCM-41 matrices on drug delivery rate. Microporous Mesoporous Mater 2004; 68: 105- 109.
101. Blin JL, Otjacques C, Herrier G, Su B L. Pore size engineering of mesoporous silicas using alkanes as swelling agents. Stud Surf Sci Catal 2000; 129: 75- 84.
102. Huo Q, Margolez DI, Stucky GD. Surfactant control of phases in the synthesis of mesoporous silica-based materials. Chem Mater 1996; 8: 1147- 1160.
103. Sayar A, Liu P, Kruk M, Jaroniec M. Characterization of large-pore MCM-41 molecular sieves obtained via hydrothermal restructuring. Chem Mater 1997; 9: 2499- 2506.
104. Casci JL. The preparation and potential applications of ultra-large pore molecular sieves: a review. Stud Surf Sci Catal 1994; 85: 329- 356.
105. Koh CA, Nooney R, Tahir S. Characterisation and catalytic properties of MCM-41 and Pd/MCM-41 materials. Catal Lett 1997; 47: 199-203.
106. Yang H, Coombs N, Ozin GA. Morphogenesis of shapes and surface patterns in mesoporous silica. Nature 1997; 386: 692-695.
107. Ozin GA, Yang H, Sokolov I, Coombs N. Shell mimetics. Adv Mater 1997; 9: 662- 667.
108. Huo Q, Zhao D, Feng J, Weston K, Buratto SK, Stucky GD, Schacht S, Schuth F. Room temperature growth of mesoporous silica fibers: A new high-surface-area optical waveguide. Adv Mater 1997; 9: 974- 978.
109. Schacht S, Hou Q, Voigt-Martin I G, Stucky G D, Schüth F. Oil-water interface templating of mesoporous macroscale structures. Science 1996; 273: 768- 771.
110. Huo Q, Feng J, Schüth F, Stucky G D. Preparation of mesoporous silica spheres. Chem Mater 1997; 9: 14- 17.
111. Yang H, Vovk G, Coombs N, Sokolov I, Ozin GA. Synthesis of micron size spherical mesoporous silica under quiescent acidic condition. J Mater Chem 1998; 8: 743- 750.
112. Ogawa M. Overview of silicon-based materials. J Am Chem Soc 1994; 116: 7941- 7942.
113. Yang H, Coombs N, Sokolov I, Ozin GA. Free-standing and oriented mesoporous silica films grown at the air-water interface. Nature 1996; 381: 589- 592.
114. Lin HP, Mou CY. Tubules-within-a-tubule hierarchical order of mesoporous molecular sieves in MCM-1. Science 1996; 273: 765- 768.
115. Lin HP, Cheng YR, Mou CY. Hierarchical order in hollow spheres of mesoporous silicates. Chem Mater 1998; 10: 3772-3776.
116. Zhao XS, Lu GQ, Whittaker AK, Millar GJ, Zhu HY. Comprehensive study of surface chemistry of MCM-41 using ^{29}Si CP/MAS NMR, FTIR, pyridine-TPD, and TGA. J Phys Chem B 1997; 101: 6525- 6531.
117. Trebosc J, Wiench W, Huh S, Lin VSY, Pruski M. Solid-state NMR study of MCM-41-type mesoporous silica nanoparticles. J Amr Chem Soc 2005; 127: 3057-3068.
118. Vallet-Regí M, Doadrio Doadrio JC, Doadrio AL, Izquierdo-Barba I, Pérez-Pariente. Hexagonal ordered mesoporous materials as a matrix for the controlled release of amoxicillin. J Solid State Ionics 2004; 172: 435- 439.
119. Doadrio AL, Sousa EMB, Doadrio JC, Pérez-Pariente J, Izquierdo-Barba I, Vallet-Regí M. Mesoporous SBA-15 HPLC

evaluation for controlled gentamicin drug delivery. J Control Rel 2004; 97: 125- 132.
120. Balas F, Manzano M, Horcajada P, Vallet-Regí M. Confinement and controlled release of bisphosphonates on ordered mesoporous silica-based materials. J Am Chem Soc 2006; 128: 8116- 8117.
121. Vallet-Regí M. Revisiting ceramics for medical applications. Dalton Trans 2006; 5211- 5220.
122. Doadrio JC, Sousa EMB, Izquierdo-Barba I, Doadrio AL, Pérez-Pariente J, Vallet-Regí M. Functionalization of mesoporous materials with long alkyl chains as a strategy for controlling drug delivery pattern. J Mater Chem 2006; 16: 462- 466.
123. Vallet-Regí M, Rámila A, del Real RP, Pérez-Pariente J. A new property of MCM-41: drug delivery system. J Chem Mater 2001; 13: 308- 311.
124. Andersson J, Rosenholm J, Areva S, Linden M. Influences of material characteristics on ibuprofen drug loading and release profiles from ordered micro- and mesoporous silica matrices. Chem Mater 2004; 16: 4160–4167.
125. Munoz B, Ramila A, Perez-Pariente J, Diaz I, Vallet-Regi M. MCM-41 Organic modification as drug delivery rate regulator. Chem Mater 2003; 15: 500–503.
126. Chen CY, Davis ME. Synthesis and characterization of MCM-41. Microporous Mesoporous Mater 1993 ; 2 : 17-26.
127. Reddy RM, Moudrakovski I, Sayari A. Synthesis of mesoporous vanadium silicate molecular sieves. J Chem Soc Chem Commun 1994; 1059-1060.
128. Ryoo R, Kim J M. Structural order in MCM-41 controlled by shifting silicate polymerization equilibrium. J Chem Soc Chem Commun 1995; 711-712.
129. Yan JY, Liu SU, Chen TH, Wang JZ, H Li X. Synthesis of iron containing MCM-41, J Chem Soc Chem Commun 1995; 973-974.
130. Sayari A, Danumah C, Moudrakovski I. Synthesis characterization and modification of MCM - 41 molecular sieves. Res Soc Symp Proc 1995; 371: 81-92.
131. Zhao DY, Goldfarb D. Synthesis of manganese containing mesoporous molecular sieve Mn-MCM-41, Mn-MCM-48 and Mn-MCM. J Chem Soc Chem Commun 1995; 875-876.
132. Myers D. Surfaces, interfaces, and colloids, principles and applications. Surf Sci Tech; VCH: New York, 1992.
133. Kim JM, Kim SK, Ryoo R. Synthesis of MCM-48 single crystals. Chem Commun 1998; 259- 260.
134. Ryoo R, Joo SH, Kim JM. Energetically favored formation of MCM-48 from cationic-neutral surfactant mixtures. J Phys Chem B 1999; 103: 7435- 7440.
135. Garcia-Bennett AE, Terasaki O, Che S, Tatsumi T. Structural investigations of AMS-n mesoporous materials by transmission electron microscopy. Chem Mater 2004; 16: 813- 821.
136. Che S, Liu Z, Ohsuna T, Sakamoto K, Terasaki O, Tatsumi T. Synthesis and characterization *of* chiral mesoporous silica. Nature 2004; 429: 281- 284.
137. Namba S, Mochizuki A, Kito M. Fine control of pore size of highly ordered MCM-41 by using template mixtures of dodecyltrimethylammonium bromide/ hexadecyl trimethyl-ammonium bromide with various molar ratios. Chem Lett 1998; 569- 570.
138. Namba S, Mochizuki A, Kito M. Preparation of highly ordered MCM-41 with docosyltrimethylammonium chloride (C_{22}TMAC1) as a template and fine control of its pore size. Stud Surf Sci Catal 1998; 117: 257- 264.
139. Suzuki K, Kenichi K, Imai H. Synthesis of silica nanoparticles having a well-ordered mesostructure using a double surfactant system. J Am Chem Soc 2004; 126: 462- 463.
140. Ohkubo T, Ogura T, Sakai H, Abe M. Phase behaviour of cationiv and anionic mixed surfactant. J Colloid Interf Sci 2007; 312: 42.
141. Cheng YW, Hsu YT, Yang CM. Structural modulation of cage-like mesoporous KIT-5 silica by post-synthesis treatments with ammonia and/or sulfuric acid. Microporous Mesoporous Mater 2009 ; 117 : 249–256.
142. Charnay C , Bégu S, Tourné-Péteilh C, Nicole, DA Lerner L, Devoisselle JM. Inclucion of ibuprofen in mesoporous templated silica: Drug loading and release property. Eur J Pharm Biopharm 2004; 57: 533-540.
143. Aiello R, Cavallaro G, Giammona G, Pasqua L, Pierro P, Testa F. Nanostructured materials to porosity 'controlled applications for innovative technology. Surf Sci Cat 2002; 142: 1165-1172.
144. Zhu QF, Shougui SHL, Qiu. Effective controlled release of captopril by silylation of mesoporous MCM-41. Chem Phys Chem 2006; 7: 400 – 406.
145. Trewyn, Brian G, Nieweg, Jennifer A, Zhao, Yannan L. Biocompatible mesoporous silica nanoparticles with different morphologies for animal cell membrane penetration. J Chem Eng 2007; 137: 23–29.
146. Sun W, Fang N, Trewyn BG, Tsunoda, M. Endocytosis of a single mesoporous silica nanoparticle into a human lung cancer cell observed by differential interference contrast microscopy. Anal Bioanal Chem 2008; 391: 2119-2125.
147. Zhou Z, Zhu S, Zhang D, Zhou Z. Evolutionary trace annotation server: automated enzyme function prediction in protein structures using 3D templates, Chem Lett 2006; 35: 1426-1427.
148. Kamalakannan K, Klaus M. Physicochemical characterization of MCM-41 silica sphere made by the psudomorphic route and grafted with octadecyl chain. J Chromatogr Sci 2008; 1191: 125-135.