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Applications of mesoporous material for drug delivery

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Abstract

In recent years mesoporous silica is gaining attention because of their emerging applications in drug delivery. Since their first appearance in materials science in the 1990s, these inorganic carriers have been successfully used in other areas such as catalysis, purification, and adsorption. The majority of ordered MSNs have two-dimensionally ordered arrays of cylindrical pores of uniform size disposed parallel to each other and separated by thin walls.

Mesoporous silica has stable mesoporous structure, large surface area, good biocompatibility and tailored size of mesopores, all these requisites exhibited promising application as an immediate and controlled drug delivery system. Compared with amorphous colloidal and porous silica, mesoporous silica exhibit higher loading of drugs and provide an immediate release and controlled drug release if modified by functionalization. Different MSNs like MCM-41, SBA-15, TUD, MCM-50, HMS, MSU-H, etc., have many important properties advantageous to drug delivery applications. The importance of these materials as drug carriers is based on the ability of the silanol groups in the mesopore walls to adsorb molecules of pharmacological interest, followed by an immediate or controlled or modified release of active molecules. Silanol groups on the pore walls are also susceptible to undergoing a chemical modification with a large variety of organic groups through a functionalization process.

Opening remarks

Over the past two and a half decades, the distinctions among material science, chemistry, and biology have become increasingly indistinguishable. Since the discovery of organic surfactant templating methods for preparing Mesoporous Silica Materials (MSNs) such as MCM-41 [1], MCM-48 [2] , SBA [3], MSUn [4], KIT [5], and FSM-16 [6] etc, the field of ordered materials has undergone extensive investigation regarding synthesis, characterization, and applications. The most common and well known microporous materials are zeolites [7], which are basically natural or synthetic hydrated aluminium-silicate with an open 3D crystal structure. Because of its active sorbent property zeolites widely used in different filed like petrochemical, nuclear, biogas, heating, and regeneration, detergent, construction, etc [8]. Unfortunately, applications with zeolites are limited by the relatively small pore sizes and thermal instability. In 1992, a research team from Mobil Oil Company synthesized a new family of materials and presented a paper entitled “A new family of mesoporous molecular sieves prepared with liquid crystal templates”. This newly developed M41S family that characterized with homogeneous size range (approximately between 2 nm to 10 nm) ordered and uniform pore distributions. These M41S family also represented by different mesostructured materials like MCM-41 with hexagonal array [9], MCM-48 with cubic [2], and MCM-50 with lamellar arranged structured material [10].

All these materials are presented by uniform and regularly arranged channels, and more importantly, their dimensions can greatly be modified by the selective choice of surfactants, use of organic and inorganic additives and controlling various synthesis conditions. Their potentiality in drug delivery system was scientifically studied and reported in the literature. [11-13]. The important features of these materials are great opportunity to modify the mesoporous characteristics and this can be achieved with proper selection and optimization of various synthesis conditions that ultimately lead to the development of a wide range of materials of different pore geometry with different pore size, surface area, and pore volume [14]. The loading of the molecule of interest within the mesopores can efficiently be changed, controlled and modified according to the intended application (s) and this can be well explained by the concept of host-guest chemistry. This feasibility of material engineering makes them a suitable candidate as gate-keeper for a variety of drug molecules. Nowadays these materials draw great attention as a drug carrier for their ability to accommodate a wide range of molecules of different sizes, as the pore size of these materials are of the same extent as of the majority of drug molecules and if not then effectively tailored to attain the required size.

Classification

Porous materials created by nature or by synthetic design have found great applications in different aspects of human activities. Their pore structure is usually formed in the stages of crystallization or by subsequent treatment like calcination or solvent extraction. The synthetic pathway leads to the formation of interconnected mesopores that may have similar or different shapes and sizes.

Porous materials with small pore diameters are generally used for their molecular sieving properties. In general, IUPAC classified [15] mesoporous materials in three main categories according to their pore size, microporous (< 2 nm), mesoporous (2-50 nm), and macroporous (> 50 nm) materials.

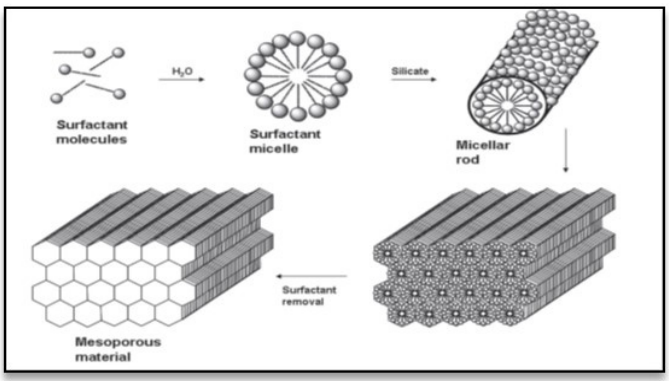

Figure 1: General synthesis scheme for M41S mesoporous family

Table 1: Classification of porous materials

Type of Material	Pore Size (nm)	Examples	Pore Size Range (nm)
Macroporous	> 50	Porous glasses	> 50
Mesoporous	2-50	Pillared layered clays M41S SBA-15 SBA-16 Diatom biosilica Mesoporous alumina	10 2-10 8 - 10 5 2-50 2
Microporous	< 2	Zeolites Activated carbon ZSM-5 Zeolite A Beta and Mordernite-Zeolites Faujasite Cloverite	< 1.42 0.6 0.45-0.6 0.3-0.45 0.6-0.8 0.74 0.6-0.132

Porous materials are also defined and classified according to their adsorption properties. The term adsorption denoted the condensation of inert gas on a free surface as opposed to its entry into the bulk. However, this distinction is commonly not observed and the uptake of gas molecules by porous materials is often referred to sorption, regardless of the physical mechanism involved. Quantity of gas adsorbed by a porous material is frequently referred by adsorption isotherm and the amount of gas adsorbed will be considered at a specified temperature as a function of pressure. Porous materials are frequently characterized with regard to their pore sizes derived from gas sorption data. Hence, IUPAC classifying [15] porous materials on the basis of pore sizes and gas sorption isotherms that reflect the relationship between the porosity of the material and amount of gas adsorbed [15-17]. The IUPAC classification of adsorption isotherms is illustrated in figure 2.

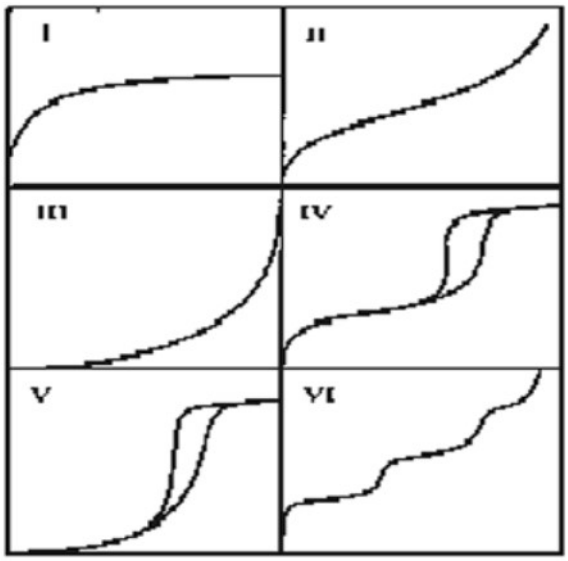

Figure 2: Types of adsorption isotherm according to IUPAC

Mesoporous materials are synthesized by a variety of organic, inorganic or mixture of organic and inorganic compounds [18] and are classified according to the type of framework developed as shown in figure 3.

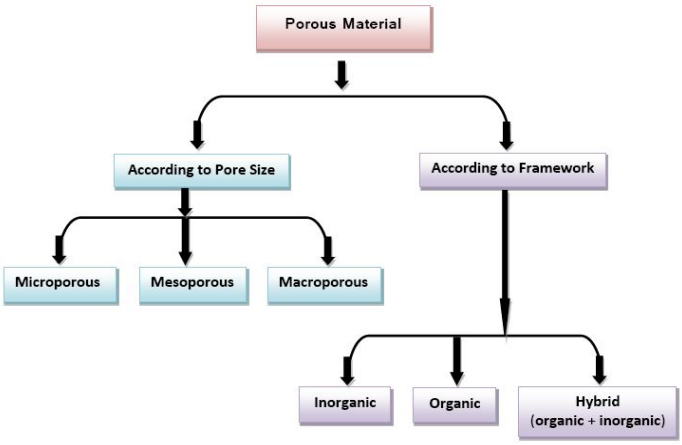

Figure 3: Classification of porous material according to pore size and build-up framework

Synthesis and nomenclature of mesoporous material

The presence of mesopores of controllable dimensions at the atomic, sub-atomic, molecular, micrometer or nano-meter scale makes them of specific and technological and scientific importance. A large diversity of materials with different properties is developed and synthesized over the past decades (Table. 2).

Table 2: Different mesoporous materials

MSNs	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
KIT	Korean Advanced Institute of Technology
AMS	Anionic Surfactant templated Mesoporous silica

New strategies and modification techniques are being continuously explored for the development of mesoporous materials with different characteristics. Some commonly used conventional methods include liquid crystal templating mechanism [19], charge density matching mechanism [20], folded sheet mechanism [21], silica tropic liquid crystal mechanism [22], etc. Different mechanism yield materials with different morphology, some of them are given in table 3.

Table 3: Synthesis mechanism and type of material

Synthesis mechanism	Driving force	Characteristic of material
Liquid crystal	Hydrocarbon chain length of the surfactant	Hexagonal, cubic and lamellar structures
Charge Density- Matching	Electrostatic interaction between the anionic silicates and the cationic surfactant	Hexagonal mesostructure
Folded Sheet- Mechanism	Interaction between cationic surfactant and intercalated silicate phases at higher pH	Highly porous hexagonal structure
Silica tropic Liquid- Crystals	Organization of inorganic and organic molecular species in to 3D structure	3D porous structure
Soft template (endo template)	Use of organic molecule	Mesoporous material with good shape, size and characteristic
Hard template (exo template)	Use of inorganic molecule	Mesoporous material with irregular and non uniform morphology

Generally, surfactant directed self-assembly fabrication is the most commonly used approach towards the synthesis of mesoporous materials with specific chemical composition, structure, and function. The route of self-assembly is mainly governed by different forces like non-covalent weak interactions such as hydrogen bonding, Van-der Waals forces, and electrostatic interaction between the surfactants or their supermolecular structures and the building blocks [23]. Specific surfactant is employed as a structure directing agent for the synthesis of mesoporous materials followed by polycondensation with different silica sources [24]. The fundamental difference among different mesoporous materials governed by the nature of the synthesis conditions employed for their synthesis. These synthesis conditions are responsible for mesoporous material with different physiochemical characteristics like type of mesostructure framework, surface area, wall thickness, pore characteristics like pore distribution, pore diameter, pore volume, etc.

The mesoporosity developed by liquid crystal mechanism depends on the composition and chemical nature of the surfactant, and different parameters such as surfactant concentration, pH, temperature, the presence of additives, etc. In the synthetic process, once the silica source has condensed around the micelles, the surfactant is removed by thermal degradation or solvent extraction. This surfactant removal results in the development of mesostructure framework. The surface area of the developed materials is generally greater than 700 m2/g and have absorption capacities of 0.7 cm3/g and greater. A series of inorganic mesostructures have been synthesized with the different surfactant and different experimental conditions, according to the structural requirement of the material [1,25-28]. These materials are named after the company or research group introducing them or according to the structural characteristics of the developed material, some of them are listed in table 2.

A wide range of ionic and non-ionic surfactants has been used for the synthesis of materials with different mesoporous characteristics. Mesoporous materials like MCM-41, MCM-48 and MCM-50 with hexagonal, cubic and lamellar mesostructures respectively and with different morphologies have been synthesized by alkyl ammonium surfactants and tetraethyl orthosilicate. With the use of cationic surfactants in an acidic medium the first SBA type material [28] with different mesostructures and having identical porous characteristics to the

MCM type materials [1] has been synthesized. Santa Barbara University type mesoporous materials like SBA-15 [27] and SBA-16 [29] with larger pore sizes and thicker walls are prepared by non-ionic surfactants like polypropylene oxide and polyethylene oxide under the acidic medium. Other mesoporous materials named MSU-X [4] were synthesized with neutral pH with the use of non- ionic surfactants, the resultant mesostructure is more unorganized and their pore diameter and wall thickness are around 2-8 nm and 1.5- 4 nm respectively. A fairly new member in the group of the porous silica is TUD-1 [30], which was introduced and the major difference between TUD-1 and the other porous silicas is that the fabrication process for the TUD-1 silica is completely surfactant free. Instead of micelles or large organic compounds, the formation of pores is induced by aggregates of smaller molecules. This makes the process cost-effective. Inclusion of different heteroatoms such as Cu, Zn, Al, B, Ga, Fe, Cr, Ti, V Sn etc.in mesoporous frame structure has been explored for different application needs [31-36]. Methodology to prepare mesoporous silica via the template synthesis is extended to preparation of some mesoporous metal oxides [19,20,37-40]such as TiO2, Ta2O5, Nb2O5, ZrO2, Al2O3, V2O5 etc.

Characterization of mesoporous material

The mesoporous material is characterized for its mesostructure, particle and pore morphology and surface characterization using techniques such as low angle powder X-ray Diffraction (XRD), FT-IR spectroscopy, Nitrogen adsorption/desorption, electron microscopy such as Scanning Electron Microscopy (SEM) and Transmission Electron Microscopy (TEM), Nuclear Magnetic Resonance (NMR), Differential Scanning Calorimetry (DSC) etc.

Adsorption analysis gives information about the porosity and surface area of the materials, while SEM gives particle size and morphology. Diffraction techniques, FTIR and TEM give insight to the degree of structural order and DSC measurements provide details regarding the drug loading into the pores of mesoporous material. Summarized applications with reference to their evaluating parameters of all the instrumental technique are presented in table 4.

Table 4: Characterization techniques and evaluation parameter

Characterization techniques	Evaluation parameter
X-ray powder diffraction	Pore structure topology
Fourier transformed Spectroscopy	Structural details especially silanol group
Nitrogen adsorption/desorption	Pore size, pore volume and surface area
Scanning electron microscopy	Exterior structural morphology
Transmission electron microscopy	Interior structural morphology especially pore geometry
Differential scanning calorimetry	Physical changes as a function of temperature
Elemental analysis	Estimation organic elements especially after functionalization
Thermogravimetry	Evaluation of the mesopore volume and specific surface area

X-Ray diffraction

X-ray diffraction is one of the important techniques for structural characterization. This technique is commonly used for the identification and characterization of crystalline material. It provides information about unit cell dimensions, phase impurity, and crystal structure. All the information is presented as a plot of the intensity of the diffraction beams as a function of 2θ.

This technique used to determine the pore geometry and determine the average pore to pore distance. As the particle size of mesoporous materials ranges from nanometer to micrometer scale, its characterization is commonly performed with powder x-ray diffraction technique. Most of the mesoporous materials are present in a disordered amorphous state and having large unit cell area, the diffraction angles (2θ) selected are very small. In large angle x-ray diffraction, diffraction is measured between 10° and 90° whereas, in small-angle x-ray scattering measurements, scattering is measured in the region in which the angle of scattering (2θ) is 5° or less. This provides measurements that would not be possible with ordinary X-ray diffraction and allows the evaluation of structures in the nm to tens of nm scale. Small angle x-ray scattering is the most rapid method to determine the nature and degree of pore order in the material and employed for characterization of nanoscale structure and structural morphology of mesoporous materials [41].

FT-IR spectroscopy

Infrared spectroscopy is an elegant and very unique technique to determine the surface species and kinetics of surface reactions. Typically one can follow the changes at the surface by examining characteristic vibrations of function group(s). Fourier transform infrared spectroscopy deals with the vibration of chemical bonds in a molecule at various frequencies depending on the elements and types of bonds. After absorbing incident electromagnetic radiation the frequency of vibration of a bond increases leading to transition between the ground state and different excited states. The energy corresponding to these transitions correlates to the infrared region (4000–400 cm^{-1}) of the electromagnetic spectrum. The term Fourier transform refers to a development in the manner in which the data are collected and converted from an interference pattern to an infrared absorption spectrum. In the case of porous silicates, the FTIR spectra are recorded in the frequency range of 300–1500 cm^{-1} that will provide information about the structural details and presence of silanol groups on particular mesoporous material [42].

Nitrogen adsorption/desorption isotherm

Nitrogen adsorption/ desorption is an important technique of material characterizing for pore geometry especially for the determination of pore size, pore volume, and surface area. Stephen Brunauer, P.H. Emmett, and Edward Teller have developed a method in the mid-twentieth century to calculate the surface area [43]. This calculation, known as Brunauer-Emmett-Teller (BET surface area), determines the surface area by measuring the adsorption of non-polar inert gases like nitrogen and argon. In Figure 4, a typical adsorption isotherm for nano-sized mesoporous material with fields for the individual sorption stages is shown.

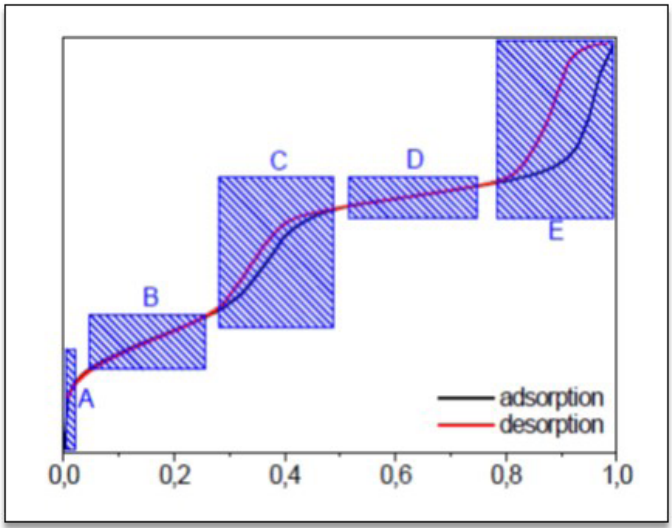

Figure 4: Typical isotherm for a bulk sample of mesoporous material

The steps A to E can be attributed to the different processes as follows: Area- A indicated that at low relative pressures a monolayer of adsorbate molecules is forming on the high inner surface of the material; Area- B: represented multi-layers of adsorbate; Area- C revealed the filling of the mesopores by capillary condensation; Area- D: indicated the remaining outer surface (plateau) and Area- E described condensation of adsorbate in the interparticle pores of mesoporous material.

For the measurement of adsorption isotherm most common sorption method is nitrogen sorption, as it is suitable for its heat of adsorption (5-25 kJ/mol) and provide good access of nitrogen molecules (0.354 nm) into small pores of mesoporous material. Due to the low temperature, the nitrogen is adsorbed on the sample surface, resulting in equilibrium between adsorbed film and gas phase at a constant temperature. The isotherm shows the adsorbed amount of gas as a function of the pressure [44]. As pressure increases, the amount of gas adsorbed rapidly rises due to the capillary condensation in mesopores. The pressure is increased until saturation is reached when all mesopores are filled. The pressure is reduced incrementally, evaporating the condensed gas from the system and on desorption, a hysteresis is commonly observed. The hysteresis between the adsorption and desorption branches of the isotherm reveals information regarding pore size, volume, area, and shape. Hysteresis loops most likely arise from a combination of the thermodynamic and network effects. The thermodynamic hysteresis may be due to capillary condensation and capillary evaporation occurring at higher and lower pressures, respectively. The network effect may be caused by a decrease in pore diameter at the mouths of the pores. Another mathematical equation for calculations for pore diameter and pore volume was developed by Elliot P. Barrett, Leslie G. Joyner, and Paul P. Halenda [45]. This calculation, known as BJH, assumes a similar theory to the BET of the adsorption/desorption process. The BJH calculates a pore diameter distribution, outputs a histogram, and average pore size. This calculation assumes the approximate cylindrical pore geometry and calculated when saturation is reached as all the mesopores are filled with the adsorptive gas molecules.

Scanning and transmission electron microscopy

High energy electrons are used to record an image of the respective samples or specimen. Such images have advantages of higher magnifications and good resolution as compare to light microscopes. This technique is very much useful for studying the structural parameters such as mesoporous structure, pore geometry, particle size and shape, and the presence of different transformation phases.

The high voltage electron beam of transmission electron microscopy allows the electron beam to transmit through specimen carries the information about the structure of the specimen and produces highly resolved two-dimensional images. Whereas secondary electrons in scanning electron microscopy produce images. These high magnifications images are produced due to the excitation by the primary electron beam impinges on the surface of the specimen. Scanning electron microscopy provides three-dimensional images of the samples and thus very much useful for topographic and surface morphological study of the sample of interest.

For the characterization of mesoporous materials, the Scanning and Transmission Electron Microscopy (SEM and TEM, respectively) are used to confirm the information obtained from low angel powder XRD technique. Scanning electron microscopy utilizes a lower voltage electron beam (< 20 kV) and is useful for determining exterior particle morphology to about 50,000x magnification [46]. The shape and size of the mesoporous material are readily observed by SEM. Transmission electron microscopy utilizes a stronger electron beam (about 300 kV) and allows for the visualization of pores. The magnification achievable by TEM is in the order of 300,000x [47].

Nuclear magnetic resonance

The principle of absorption spectroscopy along with the law of spinning nuclei is the basis of, Nuclear Magnetic Resonance (NMR) spectroscopy. The change in absorption energy leads to results in changes in the orientation of the spinning nuclei in a magnetic field. This technique helps in the structural identification of the organic compounds. Solid-state NMR has been widely used in elucidating the structure of both mesoporous silica and zeolites. NMR is a well-established method for characterizing mesoporous materials and for investigating the behavior of adsorbed or loaded drug substances or molecules.

Mesoporous materials are basically built from an amorphous structure and as it contains plenty of silanol groups on its surface and pores it can be effectively characterized with solid-state NMR technique. This technique is very much useful for the study of host-guest chemistry. Since mesoporous materials are widely used as nanoparticles, this technique is useful for the study of the interaction between mesoporous material (silanol group) and drug and/or molecule loaded in mesopores of the materials [48].

Differential scanning calorimetry

Differential Scanning Calorimetry (DSC) is widely used to characterize the thermo-physical properties of a wide variety of substances. DSC can measure important properties such as melting point, the heat of melting, percent crystallinity, softening temperature point, degree of crystallization, presence of recyclates, composition and compatibility studies especially in pharmaceutical formulations.

DSC is a useful tool to check the drug loading in the pores of mesoporous. The absence of a melting peak of the drug is observed when drug molecules get entrapped in pores of mesoporous material [49]. The thermal analytical method, Thermogravimetry (TG) and DSC, were used to measure mass changes and thermal effects in the material, due to evaporation, decom-

position, and interaction with air. In combination with other methods like XRD, thermal methods (DSC/TG and dilatometer) are used to study the phase transformations and their microstructural configurational changes occurred due to entrapment of molecule within the mesopores.

Mesoporous materials and drug

Mesoporous silica has stable mesoporous structure, large surface area, tailored size of mesopores, well-defined surface properties, bio-compatibility, makes them ideal as a carrier and act as a host for drug, proteins, a pharmaceutical compound, chemical compound, and other biogenic molecules. Since the discovery of these materials in the 1990s, numerous reports are available in the literature revealed the use of different synthesis condition for specific applications of the materials. Earlier such materials were effectively used in a field of separation science, catalysis, adsorbent, sensors, and devices.

In the year 2001, the first time Vallet-Regi and group introduce the use of mesoporous material as a drug delivery system. In recent years, it has been shown that both micro and macromolecular drugs can be entrapped within the mesopores and effectively employed for immediate, controlled and targeted release system.

The important feature of mesoporous materials is the feasibility to synthesize the mesoporous frameworks with different pore sizes and geometries (figure 5).

The mesoporous drug delivery system can effectively be explained by the host-guest interaction that would take place between the silanol groups located at the surface of the host material and the functional groups from the guest molecules [50]. The type of interaction will decide the quantity to be adsorbed/ entrapped and its release characteristics from the host. In addition to that structural properties and mesoporous geometry has been observed to modulate the adsorption and release properties of the molecule.

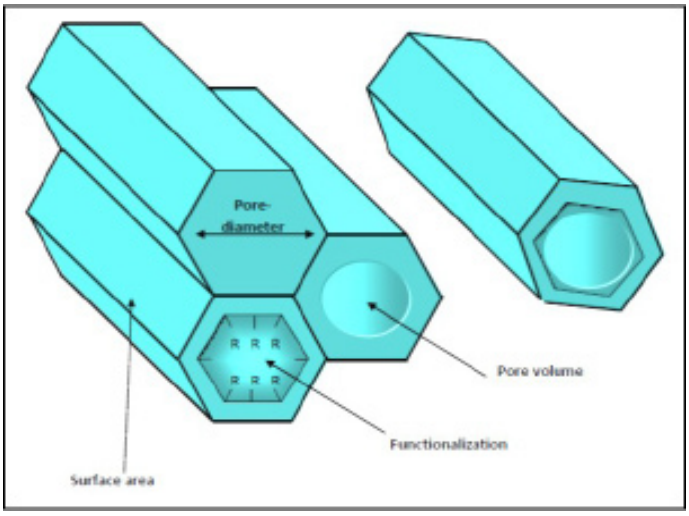

Figure 5: Pore geometry of mesoporous material

The numbers and type of silanol groups on mesoporous materials highly influence their role as a drug carrier. When these materials used for drug delivery, the important aspect is the proper selection of the mesoporous material as large numbers of materials are available or can be synthesized and all are having different surface morphology and pore geometry. The selection of specific mesoporous material depends on the molecule or drug that is to be hosted or entrapped within the mesopores. Same time if the material with required characteristic is not available one can modify or improve the relevant properties by functionalization process. Silanol groups on the pore walls are susceptible to undergoing a chemical modification with a large variety of organic groups through a functionalization 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 [50]. Therefore, if the pore wall surface is covered by amine groups, there would be a larger alendronate loading than in unmodified materials. The results showed that drug loading increased from 14% (unmodified) to 37% (modified) for amine-grafted materials MCM-41.

The mesoporous characteristics of the respective material can be modified either by Co-condensation and Post-synthesis grafting processes. During the synthesis of such material addition of desired functional group is known as the co-condensation method. In this process, all the procedures are carried out in the same reaction vessel so that the organic functionality is incorporated into mesoporous silica directly during the synthesis. Whereas in post-synthesis mesoporous silica is treated with the functionalizing agent in anhydrous conditions to yield organically modified silica mesopores. These methods of modification decide the distribution of functional groups. For uniform distribution of functional group, the co-condensation technique is useful whereas in post-synthesis grafting technique; the functional groups are irregularly distributed. The diffusion rate of the guest molecule is well controlled in post-synthesis methods, as added organosilane acted on the opening of the mesopores. Amount of organosilane also decides an extent and distribution of the functional group. According to required drug loading and release profile, proper chemical modification of the silanol groups of pore walls to be carried out. Several factors influence the final adsorption properties of the mesoporous silicas when intended for drug delivery. Some of the important such factors are discussed as follows.

Significance of textural properties on adsorption/entrapment of drug molecules on/ into the pores of mesoporous material

Pore size

The important tool of a mesoporous material is its pore size as it plays an important role in drug entrapment and can be used as a drug delivery system. The entrapment of drug within the pores is commonly carried out by soaking/impregnation of the mesoporous material in a highly concentrated drug solution (nearly saturated solution). During this process of drug loading several other parameters have to be considered like the type of a solvent, the concentration of drug in a particular solvent, pH of the solution, temperature, type and speed of mixing, duration of agitation, etc. The diameter of the mesopore determines the size of the molecule be hosted hence the size of the molecule to be selected for confined also to be considered for the proper selection of material. When the molecule is smaller than the pore cavity, the drug would be confined in the inner part of the mesopores. However, when the drug molecule is larger than the mesopores diameter, the adsorption would only take place at the external surface of the material. Drug molecules confined in pores behave differently than those in bulk. After their entrapment within the pores, their dynamics and thermodynamic

properties will altered. For effective drug loading, the mesoporous materials with slightly bigger size mesopore as compare to drug molecule size to be considered. Ideally, the ratio of the pore to drug molecule size greater than 1, suit best for easy passage of drug molecules to mesopores. Easy tailoring pore size from unit nano-meter to several tens of nanometers can be achieved by changing and controlling various synthesis conditions such as a proper selection of structure directing agent, the addition of some auxiliary substances and most importantly the chain length of the surfactant. [9,51]. The mesoporous material has plenty of silanol groups that would react with the functional groups of the drug and the strength of interaction will greatly affect the release pattern of the drug. A common example is of ibuprofen, as it contains carboxylic acid group in its chemical structure would form hydrogen bonds with the silanol groups of mesoporous material and consequently ibuprofen molecules would be retained in mesopores and resulted to delayed drug release profile [52].

Surface area

The drug loading process in the mesoporous system is mainly governed by the adsorptive properties of mesoporous material. Hence, the surface property of the mesoporous material is very important parameters for drug adsorption/loading. The surface area of the material facilitates the contact time between the host and guest molecules. Overall surface area is related to size, morphology, texture, and porosity of mesoporous material. Emmett and Edward Teller have developed a method to calculate the surface area. This calculation, known as Brunauer-Emmett-Teller (BET), determines the surface area by measuring the adsorption of non-polar gases like nitrogen or argon. The value of S_{BET} is closely correlated with the maximum load of the matrix surface [43]. Mesoporous materials have an advantage over other drug carrier is that due to its high surface area, drug molecules are not just entrapped in mesopores but they get adsorbed onto the silica surface (figure 6).

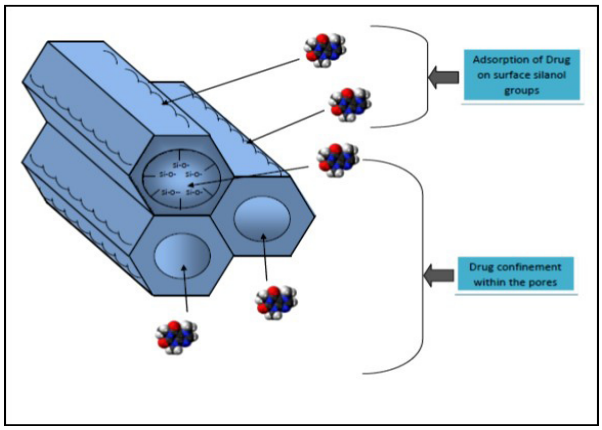

Figure 6: Schematic presentation of the drug loading procedure

A high surface area enables enhanced potential for drug adsorption. As discussed previously, mesoporous material contains large numbers of silanol groups in their structure (within mesopores and on the surface) and are susceptible to chemical modification with a wide range of organic groups through a functionalization process. This functionalization allows better control over drug loading and release and can be utilized for an immediate or controlled release of active molecules. Indeed, the pore and surface silanol group modification would be performed depending on the functional groups of the molecules or substance with pharmacological interest to be adsorbed. It is possible to increase the payload and to modify/control the release pattern of the drug by increasing/reducing the surface area or by modifying the surface–drug affinity.

Pore volume

The large surface area and high pore volume enable the encapsulation of drugs with a high payload. Pore volume is an important factor for large volume molecules, such as proteins, antibiotics, amino acid and biomolecules [53]. Barrett-Joyner-Halenda (BJH) method is commonly employed to determine pore size distribution [45]. The BJH method assumes a similar theory to the BET of the adsorption/desorption process. The BJH is calculated when saturation is reached and all mesopores are filled by the adsorptive gas. The BJH calculates a pore diameter distribution, outputs a histogram, and average pore size is reported. It applies only to the mesopores and small macropore size range. This calculation assumes the approximate cylindrical pore geometry [54]. High payload of drug molecules can be achieved by continuous, repeated and consecutive impregnations that would result in complete pore volume filling. The repeated impregnations promoted intermolecular drug-drug interactions, which increased the amount of drug loaded [55].

Functionalization

The cornerstone in the development of mesoporous silica as drug delivery systems is the wide range of possibilities for structural modification and/or chemical functionalization of the silanol groups, present on surface of material by various organic groups [50,56-58]. The feasibility of functionalization makes mesoporous material, a globally accepted material for a variety of applications including drug delivery system. In general, functionalization performed by three methods, most widely accepted and used is co-condensation (one-pot synthesis), grafting (post-synthesis modification) and imprint coating method [59-61].

The co-condensation method is also known as direct synthesis method [62]. In this method mesostructured silica material can be prepared by the co-condensation of tetra alkoxy silanes, with terminal trialkoxyorganosilanes in the presence of structure-directing agents, commonly a surfactant. With the proper selection of structure-directing agents from the synthesis of pure mesoporous silica phases, organically modified silica can be prepared in such a way that the organic functionalities project into the pores (schematically presented in figure 7). Then surfactant is removed by appropriate technique, either solvent extraction or calcination. In direct synthesis the organic units are homogeneously distributed as compare to the grafting process. However, the co-condensation method has some disadvantages like the degree of mesoporosity decreases with increasing concentration of organo-silanes in the reaction mixture, which may results in to totally disordered material. Moreover, higher extent of the incorporated organic groups can lead to a reduction in the pore diameter, pore volume, and specific surface areas of newly formed material.

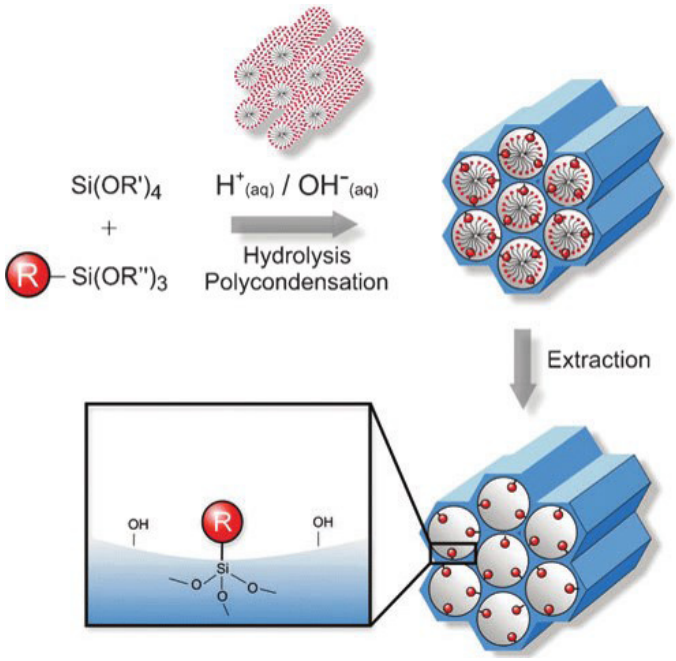

Figure 7: Schematic presentation of co condensation method in mesoporous silica (courtesy from Frank Hoffmann and Michael Fröba" (Article in Chemical Society Reviews 40(2):608-20. February 2011: Vitalising porous inorganic silica networks with organic functions - PMOs and related hybrid materials)

Schematic represen Schematic tation of co-condensation method (direct synthesis) for the organic modification of mesoporous pure silic chematic representation of co-condensation method (direct synthesis) for the organic modification of mesoporous pure silic

The modification by grafting, represents the process for functionalizing various group or atom within the interior pore of mesoporous materials [63]. These type of mesoporous materials are generally synthesized via the post-synthesis grafting method. In this method, mesopore wall surface of the prefabricated inorganic mesoporous materials is modified with organosilane compounds after the surfactant removal. As the mesoporous materials possess silanol (Si-OH) groups they facilitate the attaching of the different organic functional groups to the surface of the mesoporous material. Silylation (Figure 8) and esterification are the most commonly used reactions for the surface modification. Silylation occurs on all surface groups of the silica including the free and/or germinal silanols.

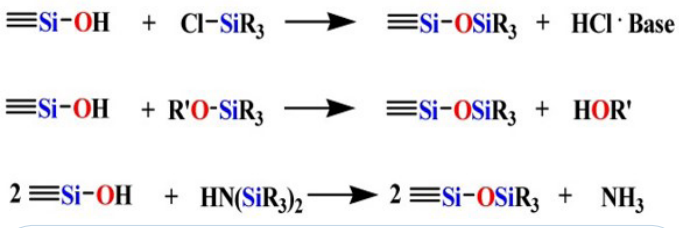

Figure 8: Silylation reaction for the modification of the surface of the mesoporous silica In most advantageous thing is that mesoporous material prepared by this mechanism retains its original structure even after modification of the surface (Figure 9). (courtesy from Frank Hoffmann and Michael Fröba" (Article in Chemical Society Reviews 40(2):608-20. February 2011: Vitalising porous inorganic silica networks with organic functions - PMOs and related hybrid materials)

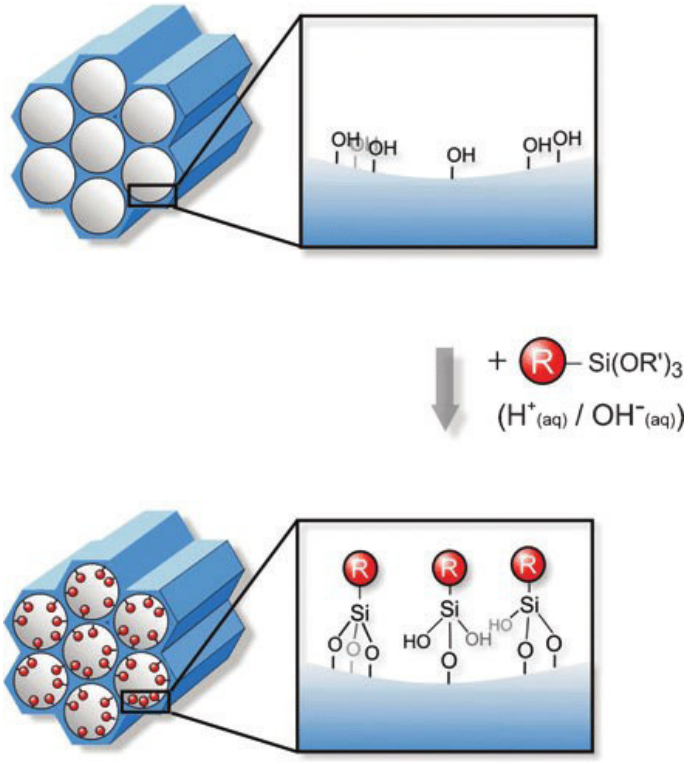

Figure 9: Schematic presentation of post synthesis grafting method (courtesy from Frank Hoffmann and Michael Fröba" (Article in Chemical Society Reviews 40(2):608-20. February 2011: Vitalising porous inorganic silica networks with organic functions - PMOs and related hybrid materials)

However, it was observed that silanol group attached through hydrogen-bond are less accessible for surface modification this may due to the formation of hydrophilic networks. Care should be taken in the post-synthesis grafting method, that before addition of modification precursor, the host materials should be completely dried to avoid self-condensation of the precursors in the presence of water molecule.

In imprint coating method, polymerization of metal alkoxides is carried out in the presence of structure directing agent and that would results in the formation of mesoporous materials with relatively large surface areas and uniform mesostructure [9]. These large surface area materials are extensively used in a field of catalysis and in preparation of chromatographic resins. Imprinting processes governed by different steps like selection of a target molecule as a template, incorporation of the template into rigid solid networks through in situ copolymerization, and removal of the template, to leave cavities with a predetermined number and arrangement of ligands that on later stage selectively rebind to the target molecule. This imprinted mesoporous materials extensively useful for the separation of racemic mixture and mixtures of metal cations. Due to unfavourable kinetics of sorption/desorption process this technique has some limitation as compare to other established method. Moreover, this technique is practically more explored in disordered polymers matrices which reduces the selectivity of the final imprinted materials due to the inhomogeneity of the cavities produced. Such issues of molecular imprinting are overcome by development of surface imprinting. In this approach, the functional group of interest is introduced onto the mesopore surface of mesoporous material through imprint coating. The important feature of this technique is to perform the coat of mesopore surface with complexes of the ligands. In this technique the target is the metal ions rather than just the free ligands [64].

Functionalization can change the different physicochemical properties of the host (mesoporous material) like hydrophobicity; hence greatly affect the adsorption properties of the guest molecule. The organic modification should be selected depending on the drug or biomolecule to be adsorbed, and more especially, the functional groups of the guest molecule. The drug release from the mesopores can be controlled by different methods. The method of choice is to increase the drug surface interaction and can be achieved by surface functionalization with some chemical groups that are able to link to the drug molecules through ionic bonds or through ester bond [13]. Another widely used strategy for the development of controlled release drug formulation is functionalization of the surface silanol groups by some hydrophobic species. This mechanism hindered the drug release by preventing the contact between drug molecules and aqueous medium. Thus penetration of aqueous phase is prevented that leads to poor wettability which in turn prevents the diffusion from the carrier. [65]. Nowadays the process of functionalization provides a great platform for targeted delivery systems, interactions with biomolecules, cells, and tissues enable controlled drug release and shift the safety profile of the drug molecules. Surface functionalization, particle type, and size might influence internalization routes which might have an impact on cytotoxicity. Furthermore, surface functionalized mesoporous material has a great impact on biological interactions, bioavailability issues, cellular migration, and autoimmune surveillance. Considering all together this will open up for customized pharmacokinetic release profiles, enhanced dissolution and bioavailability, target delivery and thereby enhanced therapeutic efficacy with least possible side effects.

Bioavailability and toxicity of MSNs

Chemically, mesoporous silica is an oxide of silicon, viz., silicon dioxide, and is generally colorless to white and insoluble in water. When associated with metals or minerals the family of silicates is formed. There are several water-soluble forms of silica referred collectively to as silicic acid (ortho, meta, di, and trisilicates). Orthosilicic acid is the form predominantly absorbed by humans and is found in numerous tissues including bone, tendons, aorta, liver, and kidney [66]. Silicon is a non-metallic element with an atomic weight of 28 and belongs to group IV of the periodic table along with carbon, germanium, tin, and lead. It is tetravalent and the atom is structurally rigid. Apart from extensive industrial uses, silica has been used in a nutritional context as a food additive, i.e., an anti-caking agent in foods, as a means to clarify beverages and control viscosity, as an antifoaming agent, dough modifier, and as excipients in drugs and vitamins. Silica is used biologically by diatoms as a structural component of cell walls [67]. Clearly, silica is omnipresent in the human environment and has a diverse multitude of uses. Silica also appears in the food chain with concentrations tending to be much higher in plant-based foods. Beverages, however, are the major contributor to dietary silica, or silicon, and include water, beer (due to barley, hops, etc.), and coffee [68]. Silica is prevalent in municipal water supplies but is particularly high in bottled spring and artesian waters depending on the geological source. In fact, beverages alone contribute to 55% of the total dietary intake of silicon as silica. Grains and grain products as part of food contribute around 14% and vegetables contribute 8% [66]. It is noteworthy that refinement of grains removes silicon during the process but silica-derived food additives can replace the stripped silicon and increase the content. Basically, silica has been considered as biocompatible [69]. Biocompatibility is the ability of a material to easily accept by the biological system without any side effect, toxic effect or immunological rejection. It is commonly observed that every biological system including the human body responds to any synthetic or natural material when it comes in contact with the immune system [70]. Those materials which are accepted or tolerated by the biological system are commonly referred to as 'Bio-inert'. Once mesoporous materials used as drug delivery system it will be acted upon the human immune system. Scientifically silicon is considered as a biodegradable material, thus materials which are made from such materials are also considered to be biocompatible. However several issues need to re-address, some of them are, pharmacokinetic properties of selected materials, their degradation pathways within the body, the mechanical integrity and disposition of the material, possible local and systemic interactions with various tissues and organs, etc. Silicon is considered an essential ion in human body however greater picture is needed when it is used as a drug delivery system. It is obvious that any essential ion used beyond their daily need by human body lead to toxicity and this is also true for silicon [71]. Numerous reports have been found in literature about the toxicity studies on these materials, very few of them revealed the toxicity criteria of the stated materials. Various research reports indicated in-vivo and in-vitro studies also, one such report revealed that when a thick layer of high porosity silicon was exposed to simulated body fluids in in-vitro conditions, it was completely dissolved and removed within a 24 h [72]. The same conclusion was later confirmed by Bowditch and group when they conducted the study in a guinea pig model, by injecting mesoporous nanoparticles via the subcutaneous route to test toxicity behavior of material [73]. The dissolved silica prone to cause the toxicity to the living system hence needs to be evaluated for biomedical applications of silica-containing materials. Biodegradation of silica leads to the formation of monomeric silicic acid within the human body, and this natural form of silica is abundantly present in the environment. Healthy adult consumes 20–50 mg/day and study revealed that the silicic concentration within the blood is about 1 mg/l [69]. The ingested silicic having very good water solubility and hence efficiently excreted via urine. It is also found that the degradant (orthosilicic acid) of mesoporous materials in healthy adult was quite low, about 10 µM [70,74]. The scientific study revealed that degradant product of silica material i.e., orthosilicic acid (pKa of 9.5) and which is the bioavailable form of dietary silicon and having good solubility in an aqueous phase and hence easily removed from the body [75]. De-protonation of silicic acid within the body may take place at physiological pH and this may results loss of some biological activity. It was found that the concentration of silicic acid was quite low when tested via in-vitro study and this can be effectively maintained by controlling mesoporosity of materials [76]. The results of cell culture tests indicated that mesoporous materials do not affect the living mammalian cells [77]. Little acute or chronic data exist on oral toxicity in humans generally due to the lack of any observed toxicity. Limited studies, however, have been conducted in rodents to determine a No Observed Adverse Effects Level (NOAEL). The NOAEL for dietary silica was determined to be 50,000 ppm (mg/L) demonstrating a huge margin of safety. In fact, this is equivalent to 2,500 mg/kg body weight/day for a rodent with the appropriately incorporated safety factors in the experimental design (100 fold). From this, the safe upper level for humans is calculated as 1,750 mg/day for a typical adult male (70 kg). In conclusion, many forms of silica exist in nature. Inhalation of crystalline silica is toxic, but consumption of water-soluble silica as orthosilicic acid is not toxic even at very high levels.

In general, foreign materials invade a living system through three pathways, namely the respiratory tract, the gastrointestinal tract, or by skin contact. Generally, colloidal silica being accepted as a nontoxic material [78,79]. When living systems come into direct contact with amorphous silica nano-materials, a number of negative results may occur including chronic pulmonary changes during inflammation, generation of reactive oxygen species, and damage to intracellular DNA, RNA and proteins [80-86]. However, when mesoporous silica employed as a drug delivery system, toxicity of this material is a critical concern for their applications in biological samples. As already discussed, the silica is generally treated as nontoxic and is considered to be biocompatible and degradable in living tissues. It has been found that there are some parameters that govern the behavior of these materials when tested in vitro, such as concentration, particle size, shape, surface area, surface modification [86-88], etc. (Figure 10).

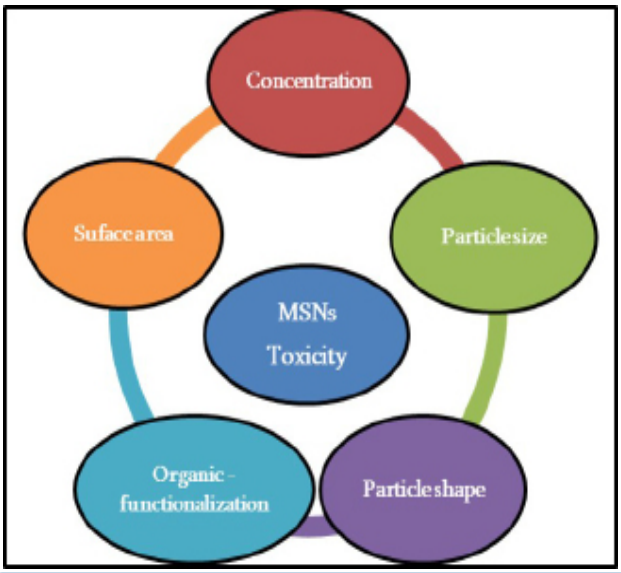

Figure 10: Factors governing cellular toxicity of Mesoporous material

The size of the nano-material greatly influences its toxicity; particularly as the decrease in size of nano-material changes certain parameters [89-91]. Many studies have shown that variations in the size of nano-materials account for the different toxicity levels between nano-sized and micrometer-sized materials [79,92,93]. It is known that a reduction in size can increase the rate of uptake and translocation of silica nano-materials *in vitro* and *in vivo*, thereby inducing more severe and transient toxicity [91]. However, independently of the factors influencing the toxicity and biocompatibility commented on above, the administration route to the living body has been found as the governing factor in the toxicity of these materials. It was found that when proceeding to subcutaneous injections of diverse mesoporous silicas, such as MCM-41, MCM-48, and MCF, at the static nerve in rats, and attending to histology, a non- toxicity was observed at all tested conditions [91]. However, intraperitoneal and intravenous injections in mice resulted in death or euthanasia.

Currently, available information suggests that the shape of silica nano-materials can affect their toxicity in two ways. First, the shape has an effect on the rate of its cellular uptake; and second, it can affect the extent of nano-material aggregation, altering its cytotoxic properties [94]. An *in vitro* toxicity study showed spherical nano-materials to be more toxic than rods [95]. It was also shown to be more difficult for elliptical nano-materials to penetrate the skin layer than spherical nano-materials [96]. The toxicity of surface-modified silica nano-materials is largely determined by their surface functional groups. As an example, Kreuter reported that an apolipo protein coating on silica material aided their endocytosis in brain capillaries through the LDL receptor [97,98].

Overall, silica nano-materials are low-toxicity materials, although their toxicity can be altered by surface modifications. Dose-dependent toxicity has frequently been observed in the study of nano-materials [80,81,84,85], with increasing doses of silica nano-materials invariably worsening their toxicity. Both, cell proliferation and viability were greatly hampered at higher doses observed in *in-vitro* studies [81,83,85]. The toxicity is not only based on the amount or size of silica material, but also on the type of cell line [87]. Cancer cell lines (A 549, MKN-28) had higher viability and resistance to silica material than did normal cell lines [85]. Similarly, a study showed that A549 cells were more resistant to the treatment of silica material than were macrophages [99].

Conventional therapeutic approaches of mesoporous materials as a drug delivery system

Due to their variable and controlled pore sizes, high surface areas and large pore volumes, these materials are widely accepted and play as versatile host for plenty of chemicals, pharmaceuticals, biologically active molecules, diagnostic agent and adsorbent. Furthermore highly ordered mesoporous structures, large surface areas and ease of surface functionalization make them ideal for entrapping, adsorbing and holding of different molecules.

Mesoporous material and fast/immediate drug delivery systems

The tunable pore size, large surface area, and high pore volume empower the encapsulation of drugs and pharmaceuticals with a high payload. The mesoporous channels keep drugs in the amorphous or non-crystalline state within the pores, which enable drug dissolution. Moreover, the marked chemical stability and inert behavior allow for better control of drug loading and release. The function is based on two factors: increasing the active surface area and reducing the crystallinity of the pharmaceutical substance. Once molecules are confined in mesopores have very different kinetic behavior than the molecules in a crystal lattice [100]. The decrease in crystallinity often leads to problems with stability, as the non-crystalline, disordered form has a high chemical potential which tends to transform to a crystalline form of a lower energy state. Therefore, the interaction between the drug molecules and carrier should be sufficiently stable, so that molecules are not altered chemically or physically [101]. The porous carrier prevents these transformations by physically protecting the amorphous drug. Furthermore, the loading of the drug molecule into porous particles has been observed to enhance permeation [55]. It has been reported that small pore size is an important factor in the stabilization of the disordered drug [102]. The pores are usually small enough to restrict the formation of an organized crystal structure inside them, and thus the loaded compound is forced to stay in the amorphous form and the phase transitions upon storage are prevented. The structure of the carrier may also protect the loaded compound from external attacks by causing a steric hindrance. This kind of protection is especially needed for peptides which are vulnerable to enzymatic degradation in the body [103]. The mesopores are usually small enough to pro-

vide satisfactory protection of the loaded drug, but adequate mass transfer rates can be, however, achieved, which is quite important in both dissolution and drug loading. As the diameter of the mesopores is typically several times bigger than the size of the drug molecule, the crystallization inside the pores is not totally impossible. Even though the drug typically is in its amorphous form, it may appear as small, nano-sized crystals as well. The solubility of the nanocrystals is much higher than that of the bulk material. Therefore, this form is also advantageous considering drug absorption, and the stability of the product is better than in the case of the amorphous drug. In order to obtain drug loading in a nanocrystal form, extremely careful optimization and control of the loading process is required.

Mesoporous material and sustained drug delivery systems

Any pharmaceutical dosage form offering sustained release will have a significant advantage due to the maintenance of steady blood concentration for a prolonged period of time. Sustained drug delivery system can be achieved with mesoporous materials by two different techniques. Sustained drug release using unmodified silica can be achieved by regulating and controlling the pore size, pore diameter and particle structure of the intended material. Whereas for modified silica materials, they are conjugated to different chemical functional groups for example organosilanes [104]. Due to the interaction between the drug molecules and the functional groups of modified silica materials, sustained drug release would be possible for the required duration of time.

Traditional mesoporous materials effectively employed as sustained drug delivery systems modifying and or controlling their physical-textural properties. The main features of mesoporous material as a controlled drug delivery system are unconnected pore volume, relatively small pore size, length of pore channel and shape of the material. Apart from the pore morphology polarity also influence the loading and release of drug molecules from the mesopores. Additionally, the amount of drug entrapped within the pores also influences the release rate. It was found that the drug release rate decreased with increasing drug content this is due to the solvent molecules are inefficient to penetrate into the pore channels, thus preventing drug release. The literature revealed the controlled release of drug molecules such as ibuprofen [104], doxorubicin [105], camptothecin [106] and aspirin [107] was achieved either by surface modification or by changing the polarity of the system. By changing the physicochemical properties of the selected mesoporous materials one can change the nature of interactions of the drug of interest. As a result, the development of better drug formulation is possible by modification of drug release pattern. [49,52]. Another common approach is the functionalization of mesoporous material. The functionalization with appropriate functional groups as it retards the drug release from the mesopores. This retardation is mainly governed by the diffusion resistance [13]. The use of different organic groups enhances the attraction between drug and host molecule and lead to a decrease in drug release. The extent of drug release depends on the electrostatic force prevailing between the host and guest molecule. In general, this effect observed in all cases as the functionalization is specifically selected to interact with the chemical groups of the drug lead to retention within mesopores. Therefore, it is very much significant to choose appropriate functionalization group depending on the chemical nature of the drug or biologically active agent to be entrapped in mesopores [104].

Mesoporous material and targeted drug delivery system

Mesoporous materials acquire many advantages, such as great physicochemical and biochemical stabilities, good biocompatibility, and complete degradability [108]. These materials are capable to maintain chemical properties of drug intact in unfavorable conditions and would have been released them with appropriate conditions or at the site of action, makes them suitable carrier for targeted drug delivery system. Apart from various characteristics features, functionalization facilitates their role in targeted drug delivery system. The functionalization of these materials is performed by acknowledging the various parameters such as the size of the drug molecule, payload required, chemical nature of the drug, hydrophilic or lipophilic property, etc. lead to the development of too smart and site-specific/ targeted drug delivery system.

In recent years the application of porous silica materials in cancer therapy has been greatly emerged. Targeted cancer therapies may be more effective than other types of treatment, including chemotherapy and radiotherapy and considered comparatively safe to normal cells. Targeting strategies have been utilized for specific receptors on the cell surface of interest provide smooth passage of nano-carrier for binding and subsequent internalization. Mesoporous nanoparticles have effectively employed in targeted drug delivery system on the basis of their vast possibilities of surface functionalization or modification. The selectivity of mesoporous nanoparticles achieved by conjugation various target sites via covalent bonding. Generally, organic molecules are used for targeting of a particular agent as organic moiety already exists in the bio-system, provides complete biodegradability, stability and no toxicity [109]. Targeted Mesoporous material therapies are used to impede the growth and spread of cancerous cells by interfering directly with specific molecules involved in tumor growth and indirectly by stimulating the immune system [110].

Advanced approaches of mesoporous material in clinical and medicinal field

In the last decade, mesoporous materials have been employed for a variety of drug delivery and biomedical applications. Till date fair quantity of reports is available for better understanding of the mesoporous material including their physicochemical properties, pharmacokinetics, biocompatibility, systemic toxicity, mechanism of cellular uptake, etc. Research groups are now focusing on and exploring the new horizon for their clinical, pharmaceutical, biotechnological, and biological applications. These materials open a new avenue for drug delivery due to their unique mesoporous characteristics. Some of the major area where mesoporous materials are used as an advanced tool for drug delivery systems are the stimuli-responsive release systems, protein delivery, gene delivery, antibody delivery, enzyme delivery, carrier for bio-similar, vaccine delivery, bio-imaging, hyperthermia based therapy, biosensing, theranostic nanomedicine, bone/ dental tissue regeneration, bio-ceramics, etc (figure 11).

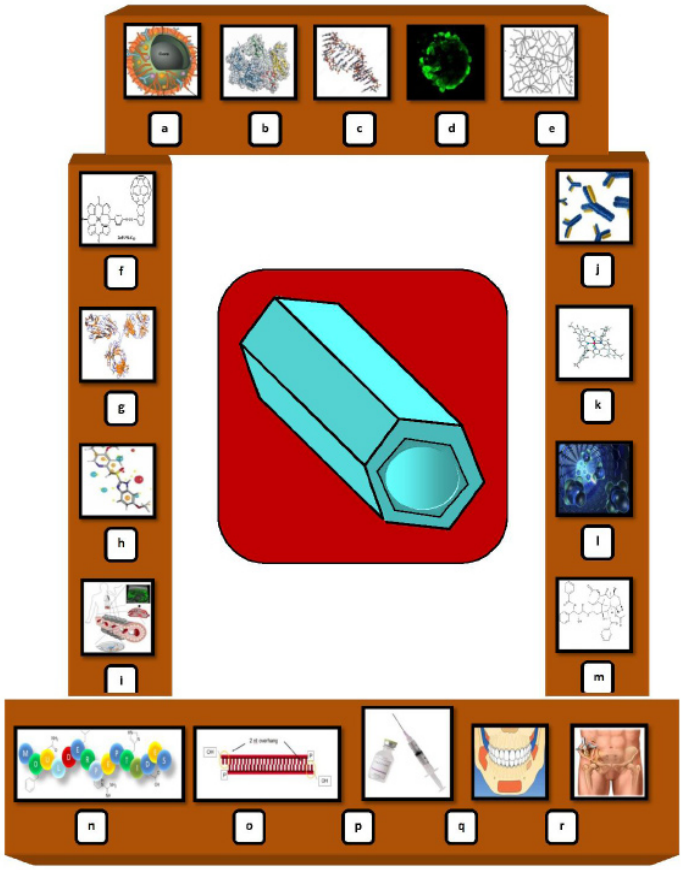

Figure 11: Poly-pharmaceutics approach of mesoporous material

a) Targeted drug delivery; b) Protein delivery; c) DNA/ Gene delivery; d) Bio imaging dye; e) Polymer; f) Photosensitizer; g) Biosimilar; h) Active pharmaceutical ingredient; i) Theranostic agent; j) Antibody; k) Catalysis; l) Adsorbent m) Anticancer/antiviral agent; n) Peptide; o) RNA; p) Vaccine; q) Dental grafting; r) Bone grafting.

The application of silica-based mesoporous materials as drug delivery systems has gained much attention of researchers in drug delivery and in a field of applied sciences due to the tunable designing of the mesoporosity. Additionally, a variety of molecules can be efficiently encapsulated within the pores and released when desired.

Two pharmaceutical companies namely Grace and Formac collaboratively worked on mesoporous based drug delivery system. In 2011, Formac Pharmaceuticals and Grace entered collectively developed a mesoporous silica materials based drug delivery system for the poorly soluble compounds. In 2012 they have the first time presented potentiality of mesoporous based drug delivery on the basis of positive results on human subjects. The data of clinical trials performed by open-label, randomized, single-dose, two-way crossover study on twelve fasted healthy volunteers. They all given with a capsule formulation containing 33.5 mg of fenofibrate as an active pharmaceutical ingredient (API) with mesoporous silica (FP 250 formulation). The study was compared with a marketed capsule containing the same API (67 mg). The data of pharmacokinetic and bioequivalence studies revealed significant higher systemic (54% increase in dose-normalized $AUC_{0\text{-}24h}$), and higher plasma concentrations (77% increase in dose-normalized C_{max}) of fenofibric acid which is an active metabolite of fenofibrate as compared to the marketed formulation. During the study, no adverse events were reported after administration of the mesoporous based drug formulation i.e. FP 250 formulation.

The results of the preclinical study, conducted by Grace and Formac Company, confirmed that these materials are having promising properties for drug delivery system and provide novel, and economical alternative to the existed delivery system. Very recently they have introduced SilSol 6 as first excipient mesoporous silica for drug delivery in the "Grace Silica-based Drug Delivery Platform". The SilSol 6 is developed for optimum pore size and pore size-distribution towards amorphization, supersaturation and stability improvement for BCS class- 2 pharmaceutical compounds. The launch of this new material will complement Formac Ordered Mesoporous Materials and offer to pharmaceutical development scientists a panel of options in the field of silica drug delivery.

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