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APPLICATIONS OF SILICA-BASED MICROPOROUS AND MESOPOROUS MATERIALS FOR DRUG DELIVERY

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1. Introduction:

Porous Materials: Porous material may be defined as material having voids. On the basis of size porous materials may be divided into four types. These are given as follows:

a. **Microporous Materials:** These have pore diameters of less than 2 nm. Examples of microporous materials include zeolite and metal-organic frameworks.

b. **Mesoporous Materials**: These have pore diameters between 2 nm and 50 nm. Some kinds of silica and alumina that have similarly-sized fine mesopores are included in mesoporous materials. Mesoporous oxides of niobium, titanium, and tin have also been reported. According to the IUPAC, a mesoporous material can be disordered or ordered in a mesostructure.

c. **Macro Porous Materials:** These have pore diameters of more than 50 nm. Macro pores may also be described in different way. For example, surface chemists define macropores as cavities that are greater than 50 nm

d. **Nonporous Materials:** These consist of regular organic or inorganic framework supporting a regular, porous structure. The size of the pores is generally 100 nanometer or smaller. Most nanoporous materials can be classified as bulk materials or membranes. Activated carbon and zeolites come under the category of bulk nanoporous materials[1].

2. Advantages of Microporous and Mesoporous Materials:

Major disadvantages of conventional dosage forms are their icapability to control either the rate of drug delivery or the target area of drug administration and provide a rapid and an immediate drug release. As a result, frequent administration is essential in order to maintain a therapeutic level, which in turn may result into peak and valley pattern in plasma drug concentration v/s time curve. Polymeric cross-linked carrier matrices, such as hydrogels and supra-molecular polymer aggregates as well as several kinds of microencapsulation vehicles, are typical examples of common drug delivery devices. Different drug delivery systems may possess different release mechanisms for releasing active component, depending upon the several factors. However, most of the delivery system follows three primary drug release patterns: diffusion, degradation, and swelling followed by diffusion. Any or all of these mechanisms may take place 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 triggered by various modes, including ionic strength, pH and thermal, magnetic or chemical changes. The ability to control over the drug delivery can be a significant 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 hydrophilic drug or a fast release of hydrophobic drugs. Site specific delivery using nanoparticulate system may also be a good option. Two or more agents from the same formulation may also be delivered. Scientists are also interested in the systems based on carriers that can dissolve or degrade and be readily eliminated. The ideal drug delivery system must be inert or biodegradable, biocompatible, mechanically strong, comfortable for the patient, capable of achieving high drug loading, safe from dose dumping, simple to administer and remove, and easy to fabricate and sterilize. Mesoporous silica has many important characteristics helpful to drug delivery applications. Some advantages of mesopororus and microporous materials are as follows:

a. Mesoporous materials with regular geometries are becoming noticeable because of their exceptional potentials in practical applications such as catalysis, adsorption, sensing, medical usage, ecology, nanotechnology, chemical and biological separations, chromatography, photonic and electronic devices, drug delivery, and energy storage.

b. The small size of the pores enclose 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. Sensitive therapeutic compounds prone to degradation, like peptides and proteins may also be effectively loaded with mesoporous material. As the purely siliceous mesoporous materials have been shown to be compatible, 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[2-4]. Amorphous silica is degradable in an aqueous solution, and thus difficulty related to the removal of the material after use can be avoided.

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c. Mesoporous materials can be used as medical devices due to the presence of larger pores and well-defined structure. They present high surface areas, above 1000 m^2/g, and ordered mesopores ranging from 2.0 nm to 10 nm, depending on the conditions of synthesis. It is noticed that mesoporous materials show high drug loading and the amount can be as high as 97 weight %. Several factoring can affect the drug loading such as pore structure, surface functionality, morphology, drug molecule size and solvent for drug loading. Usually, hollow mesoporous silica exhibits the highest loading for various drugs due to their hollowed pore structure.

d. Lower drug loading and slow release rate can be obtained by grafting/ functionalisation of mesoporous silica. This process changes the pore size and the interaction between drug and substrate.

e. In addition, their pore size and environment as well as their size and shape can be easily modified, making them an appropriate choice as intracellular drug carriers[5-8].

3. Functionalized Mesoporous Carriers:

Mesoporous systems are getting greater attention as controlled drug delivery system due to the incorporation into the pores as well as eventual binding between drug and functional groups of functionalized mesoporous carriers. A mesoporous silica surface covered with silanol groups is not selective enough to absorb drug molecules with different functionalities[9-13]. Surface modifiation could enhance the loading degree of drug molecules, and it could also change their release. Silica nanoparticles may be used for sustained drug delivery by functionalizing the unreacted silanol groups using different organic groups (figure 1). This creates favorable surface–drug interactions, which in turn result in improved loading degree and possibilities for sustained drug release[14-20].

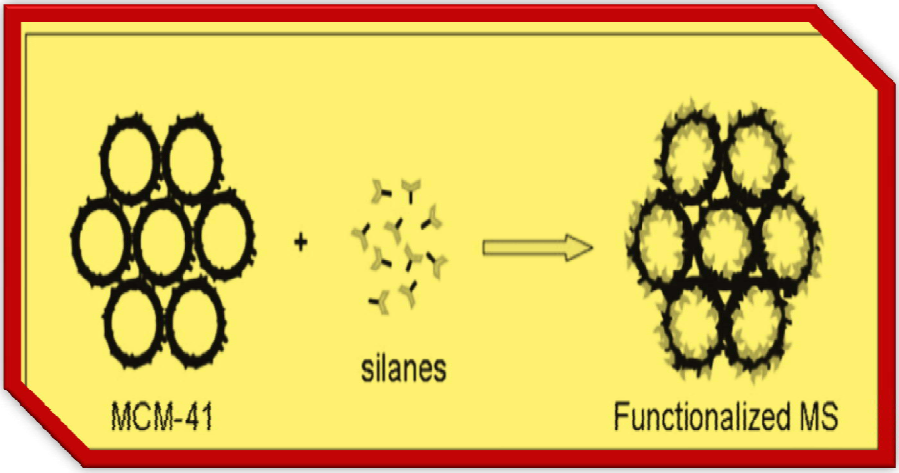

Figure 1: Functionalization of Mesoporous Silica by different Organic groups

Functionalization at specific sites within mesoporous material could be conducted by different methods (figure 2). The control was attained by a partial cleavage of P123 surfactant in the mesopores of SBA-15, leaving the micropores unextracted. Subsequent functionalization with trimethylchlorosilane and further template removal allowed the deposition of metals selectively in the micropore volume of SBA-15. A selective functionalization of the outer surface was achieved by the addition of (3-mercaptopropyl) trimethoxysilane to radially growing mesoporous silica microspheres.

The obtained material exhibited a hydrophilic/hydrophobic core/shell structure, characterized by the reductive deposition of aqueous platinum precursors to the inner core of the silica sphere. By adding only a fractional amount of grafting agent compared to the present silanols, a preferential functionalization on the outer surface takes place[21-22].

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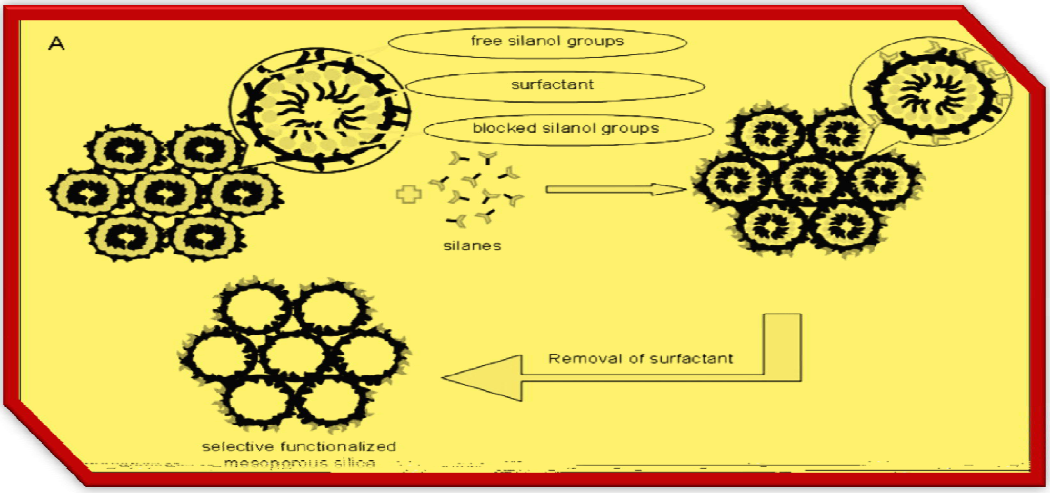

Figure 2: Site-selective functionalization of Mesoporous Silica

4. Pharmaceutical Applications of Microporous and Mesoporous Materials

Microporous and mesoporous materials have been used as drug carrier successfully for the delivery of different categories of drugs. Some important applications are as follows:

4.1 For Analgesic Drugs: The workability of four mesoporous materials composed of biocompatible Si (TCPSi) or SiO (2) (MCM-41, SBA-15, and TUD-1) were evaluated for oral drug delivery of ibuprofen. The main focus was to study the effect of the materials having different pore systems (unidirectional/2D/3D) and their pore diameters, pore size distributions, pore volumes on the maximal drug load capacity and release profiles of a drug. SBA-15 reached a very high drug load of 1:1 in weight due to its high pore volume. The total pore volume of the mesoporous solid was the main factor limiting the maximum drug load capacity. At pH 5.5 the dissolution rate of ibuprofen released from the mesoporous carriers was significantly faster compared with the standard bulk ibuprofen (86-63% versus 25% released at 45 min), with the fastest release observed from the 3D pore network of TUD-1 carrier. The utilization of mesoporous carriers diminished the pH dependency of ibuprofen dissolution (pK(a) = 4.42), providing an interesting prospect for the formulation of poorly soluble drug compounds[23].

4.2 For Anticancer Drugs: Mesoporous silica Nanoparticles (MSNs) have several attractive properties as a drug delivery system, such as ordered porous structure, large surface area, controllable particle size as well as interior and exterior dual-functional surfaces. Novel lactosaminated mesoporous silica nanoparticles (Lac-MSNs) were developed for a sialo glycoprotein receptor (ASGPR) targeted anticancer drug delivery. Model drug docetaxel (DTX) was loaded in the mesopores of Lac-MSNs by wetness impregnation method. In vitro cytotoxicity assay showed that DTX transported by Lac-MSNs effectively inhibited the growth of HepG2 and SMMC7721 cells in a time- and concentration- dependent manner[24-25].

4.3 Delivery of water insoluble drugs: Cilostazol (CLT) a water insoluble drug was loaded into synthesized MCM-48 (Mobil Composition of Matter number forty-eight) and commercial MCM-41. It was found that solvent evaporation method was preferred according to the drug loading efficiency and the maximum percent cumulative drug dissolution. MCM-48 with 3D cubic pore structure and MCM-41 with 2D long tubular structure are nearly spherical particles in 300-500 nm. The maximum percent cumulative drug release of the two CLT/silica solid dispersion (CLT-MCM-48 and CLT-MCM-41) was 63.41% and 85.78% within 60 min, respectively; while in the subsequent 12 h release experiment, almost 100% cumulative drug release were both obtained[26].

4.4 For Anti-hypertensive drugs: Unfunctionalized and functionalized mesoporous silica matrices were used successfully for the entrapment of Captopril, an angiotensin converting enzyme inhibitor. Plasma concentration of the released captopril was determined using UV-Vis and HPLC method. Pharmacokinetic parameters such as time to the maximum concentration (Tmax), maximum value of plasma concentration, Cmax (µg/mL), half life (T1/2, h), area under curve AUC0-72 (µgh/mL) were also evaluated. Temperature conditions for drug loading and chemical nature of silica surface were found to directly influence the overall pharmacokinetics. The silica-captopril formulations may be considered

attractive controlled release systems, potentially offering better bioavailability and other advantages, compared to the commercial formulation[27].

4.5 For Anti-convulsant drugs: SBA-15 ordered mesoporous silica functionalized with (3-aminopropyl)triethoxysilane (APTES) was employed as the carrier for anticonvulsant drug 2-propylpentanoic acid (valproic acid). The surface of SBA-15 containing free silanol groups was modified with 3-aminopropyltriethoxysilane via postsynthetic reaction. Functionalization resulted in an ionic interaction with acidic valproic acid. Techniques like elemental analysis, N_2 adsorption, FTIR and UV spectroscopy were used to characterize samples of carriers and carrier-drug complexes. The adsorption of valproic acid on modified mesoporous matrix was proportional to the amount of introduced aminopropyl groups. A thermodynamic study with isothermal titration calorimetry (ITC) was made to characterize the modification and encapsulation of SBA-15 with APTES and valproic acid, respectively[28.]

4.6 For Insulin delivery: Silica has also been used for the coating of Liposomes. Silica coated liposomes were explored as protein delivery vehicles for their enhanced stability and improved encapsulation efficiency. Insulin was encapsulated within the fluidic phosphatidylcholine lipid vesicles by thin film hydration at pH 2.5, and layer of silica was formed above lipid bilayer by acid catalysis. Silica coat enhances the stability of insulin-loaded delivery vehicles. Literature shows that these silica coated formulations were biologically active in reducing glucose levels[29].

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