MESOPOROUS SILICA NANOPARTICLES FOR CONTROLLED DRUG DELIVERY

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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 materials emerged as a promising candidate that can deliver a variety of drug molecules in a controllable and sustainable manner. In particular, mesoporous silica nanoparticles are widely used as a delivery reagent, sol-gel derived mesoporous silica nanoparticles in soft conditions are of main interest due to simplicity in production and modification and the capacity to maintain function of bioactive agents. The properties of mesopores, including pore size and porosity as well as the surface properties, can be altered depending on additives used to fabricate mesoporous silica nanoparticles. This review aims to present the state of knowledge of currently available drug delivery system and identify properties of an ideal drug carrier for specific application, focusing on mesoporous silica nanoparticles.

KEYWORDS: Mesoporous silica nanoparticle, targeted drug delivery, controlled release, sol-gel process, properties.

INTRODUCTION
Nanotechnology is a word used to describe a wide variety of different technologies and materials that share one thing in common-their very small size. We could define the nanotechnology as the creation of functional materials, devices and systems through control of matter on the nanometer length scale (1–100 nanometers), and exploitation of novel...
phenomena and properties (physical, chemical, biological, mechanical and electrical) at that length scale. We also could say nanotechnology is the reason of the development of “applied surface science”. With the prefix “nano” is being carried out a scientific-technological revolution[2]. The development of nanotechnology and nanomedicine in the past decades has facilitated the development of various nano vehicles for experimental and clinical application as drug delivery systems to solve the problems. Nano vehicles can carry a large payload of cargoes and be conveniently modified to perform desirable functions, such as controlling drug release, improving blood circulation half-life, increasing bioavailability, and bypassing multidrug resistance mechanism[1]. Several controlled drug delivery nano vehicles based on organic platforms have been fabricate, discoveries based on inorganic materials have recently opened up new and exciting possibilities in designing controlled drug delivery systems. During the last three decades, various polymeric devices have been fabricated for the delivery of a variety of drugs or bioactive agents. These devices include, for example, parenteral depot systems, microspheres, implants and nanoparticles. Nanoparticles have received considerable attention because of their special physical and chemical properties[15-17]. They are useful, as they represent intracellular drug depots with sustained release profiles and protect the drug against degradation.[9] The controlled release of the drug has been mainly controlled by controlling the molecular weight of the polymeric device and/or the drug loading content. For drug delivery, various nanoparticle designs have been established, mainly based on polymers and liposomes. Among the different types of nanoparticles with applications in nanomedicine, ceramic (inorganic) nanoparticles are receiving huge attention due to their increased mechanical strength, chemical stability, biocompatibility and resistance to microbial attack as compared to their organic (polymeric) equivalents.[12-14] Various methods for the preparation of nanoparticles are employed such as plasma synthesis, chemical vapour deposition, micro emulsion processing, combustion synthesis, sol-gel processing, hydrothermal techniques etc. These materials include gold nanoparticles, magnetic nanoparticles, and silica nanoparticles. Recent efforts for the preparation of nanoparticles are focused to control size, morphology, and surface reactivity of nanoparticles. Development of new drug delivery systems (NDDS) has been observed. Both natural and synthetic materials have been tested and proposed as components of NDDS and many efforts have been made to synthesize materials with biological, technological, and mechanical properties for application in drug delivery.[10] Many types of materials including inorganic silica, carbon materials and layered double hydroxides as well as polymers have been employed as substrates for controlled drug delivery systems. Controlled drug delivery
systems can maintain the concentration of drugs in the precise sites of the body within the optimum range and under the toxicity threshold, which improves the therapeutic efficacy and reduces toxicity. Further, non-toxicity and biocompatibility are the fundamental requirements for the materials used for controlled drug delivery.\textsuperscript{11}

**Classification of porous materials**

<table>
<thead>
<tr>
<th>Types of porous materials</th>
<th>Diameter of pores (nm)</th>
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<tbody>
<tr>
<td>Microporous</td>
<td>Diameter &lt; 2</td>
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<tr>
<td>Mesoporous</td>
<td>2&lt; Diameter &lt; 50</td>
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<tr>
<td>Macroporous</td>
<td>Diameter &gt; 50</td>
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Mesoporous materials consist of metal oxides, like titania, iron oxide, silica or alumina. The word *meso* is referred to one specific range of pore size from 2 to 50 nm.\textsuperscript{2} Compared to other metal oxides, silica is considered to have better biocompatibility and can be safely taken up by living cells through endocytosis.\textsuperscript{19, 20} Mesoporous silica material discovered in 1992 in the labs of the Mobil Oil Corporation was the M41S phase having pore diameters from approximately 2 to 10 nm.\textsuperscript{44} Mobil Crystalline Materials developed as an inorganic delivery agent. The materials are often referred to MCM materials, which stands for Mobil Composition of Matter\textsuperscript{7} and most popular MCM materials are MCM-41 and MCM-48 in which MCM-41 material exhibits a 2D hexagonal arrangement of pores, while MCM-48 has a 3D cubic pore system.\textsuperscript{11} Others are SBA 15, TUD, MCM 50, HMS, TMS etc.\textsuperscript{43} It have received considerable attention due to their superior textual properties such as high surface area and large pore volume, tunable particle size (10-1000 nm) and pore diameter (2-30 nm), uniform mesoporosity, flexible morphology, facile surface functionalisation, excellent biocompatibility and biodegradation, tunable and narrow pore size distribution. MSNs were developed as an inorganic delivery agent.\textsuperscript{7} The basic structure of a MSN is- particle 50-500 nm in diameter with pores ranging from 2 to 20 nm in size. These pores are mostly cylindrical in shape.\textsuperscript{8} They have emerged as vehicles and reservoirs in a wide range of fields such as drug delivery, adsorption and heterogeneous catalysis. Administration routes used are oral and parentral routes.\textsuperscript{18} The mesoporous form of silica has unique properties, particularly in loading of therapeutic agents at high quantities and in the subsequent releases.\textsuperscript{45,46} They can be designed as a multifunctional shell structure and functionalization on the surface of mesoporous silica. Among them, the core-shell structured functional MSNs can combine new functions in the platform without blocking the mesoporous channels. Therefore, the core-shell structured functional MSNs are desirable for drug delivery and have been one of the
most active research topics on the applications of MSNs. The advancement of mesoporous silica nanoparticles with unique structural features as non-invasive and biocompatible carriers to deliver drug molecules into animal and plant cells has been well established in pharmaceutical research over the recent decade.

Recently, many efforts have been made in the structure design and functional optimization for the advancement in development of Mesoporous silica-based drug delivery system, such as embedding of functional materials in Mesoporous channels. Chemical modification of MSNs allow incorporation of functional groups to facilitate absorption of target compounds. Modification of the external surface of the MSNs has been done to introduce targeting ligands. In these ways, MSNs can be modified to be taken up by a specific receptor mediated process by target cells to complete controlled release of genes and drugs within the cell.\(^7\)

**MSNs have become uniquely attractive because**

- They are non toxic and biocompatible,
- They can be fabricated to include a ‘tunable’ adjustable pore size, large surface area and a hexagonally ordered and well defined internal structure.
- They possess thermal and chemical stability and controllable degradation rates.

This versatility makes them ideal for adsorption and release of variety of compounds by organically modifying them with the desired functional groups that is attached to and within the walls of the pores.\(^3\)

MSNs are administered through oral and parenteral routes.\(^18\) They hold great promise for a diversity of applications, by suitable modification with various chemicals, successfully demonstrated MSNs as an ideal platform for the following applications

1. **Cell marker:** Through co-condensation process, dye (FITC) functionalized hexagonal crystal-like mesoporous silica nanoparticles were synthesized with high yield and the cell labeling capability was demonstrated. These nanoparticles are about 30-300 nm in size and appear to have no apparent cytotoxic effects. We had demonstrated their application as cell markers in both normal, cancer, and stem cells.

2. **Magnetic Resonance Contrast agent:** Functionalized MSNs (Gd-EDTA and Fe2O3) were used as contrast agents to track cells. These nanoparticles showed high cellular uptake efficiency and can be used in tracking the distribution of stem cells.
3. **Targeting and Therapeutic platforms:** In the ongoing research projects, we try to incorporate various biologically important groups onto MSNs. For example, by modification with suitable antibodies or short chain peptides, MSNs might be used to target specific cell. Similarly, MSNs should be an ideal platform for drug- or enzyme-released systems. We will focus on the design and synthesis of multifunctional MSNs-based materials for the field of biomedicine.[21]

In this paper, we review the present state of knowledge focused on Mesoporous silica nanoparticles emphasizing on their synthesis and properties which have effect on them including size, surface area, pH etc.

**SYNTHESIS**

**Materials:** In general, four ingredients are necessary to form a mesoporous silica materials: a surfactant, silica source, an acid or base catalyst and a solvent like ethanol or water. Surfactants are used in coatings, according to different chemical structure of surfactants, it can be divided into four categories- nonionic, anionic, cationic, zwitterionics.[42] Nonionic surfactants which are a group of chemical compounds are useful in surface activity, wetting, emulsification, solubilization, spreading, detergency and permeability enhancement[34-36], however, they have many advantages over cationic, anionic and amphoteric surfactants as a result of their intrinsic electrical neutrality.[37-40] Out of other nonionic surfactants, PEG is used most where surface activity is required, also wetting, emulsification, spreading, solubilization, detergency, permeability enhancement.[41] Quarternary ammonium surfactants are used as structure-directing agents under a wide range of pH and temperature conditions.[48]

Silica Mesoporous Materials are synthesized using amphiphilic molecules as a template for their internal structure. Varying the conditions of the syntheses we could obtain two different types of internal structures: two-dimensional hexagonal structure also known as MCM-41[49,50]; tridimensional cubic structure, known as MCM-48.[2] silica precursors which are commonly used and accordingly will be discussed in this review include glycerol-derived polyol-based silanes, orthosilicic acid, sodium metasilicate, tetraethyl ortho silicate (TEOS) or tetramethoxysilane (TMOS) and tetrakis(2-hydroxyethyl)orthosilicate(THEOS)[61], Vinyltrihydroxysilane (VTOS) [24-26], methacryloxypropyltriethoxysilane[27], methyltrimethoxy silane[28], γ-glycidyloxypropyltrimethoxysilane[29] are examples of modifier molecules or coupling agents which have been used for surface modification or
reaction modification of the silica nanoparticles for preparation of polymer/silica nanocomposites, modifier molecules which have been also used for surface modification are epichlorohydrin, tolylene-2,4-diisocynate, oleic acid, stearic acid.

The formation of mesoporous materials such as MCM 41 family is of organic surfactants and inorganic species, silica precursors like tetraethyl ortho silicate (TEOS) or sodium metasilicate with alkali as catalyst in basic media, cetyltrimethylammonium bromide (CTAB) used as template, deionised water and ammonia. MCM 48 use triblock copolymer pluronic F127 as surfactant. Another very prominent type of mesoporous silica materials, in particular the SBA materials (Santa Barbara materials) in which triblock copolymers of the Pluronic family used as template, the structure of the template consists of poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) units with variable chain lengths of PEO and PPO,TMOS (tetraethoxysilicane) as silica precursor, the synthesis environment is strongly acidic.

**Methods:** Essentially all the synthesis has the same principle, the addition of one silica source into a surfactant template in water solution.

At one hand, we should create a template for the meso structure, by dissolving a surfactant. At the other hand, we have to prepare a silica solution, it could be from an inorganic source, as sodium silicate solution, or from an organic source as TEOS. In both cases we should reach a low pH value. Low pH values also help to reach more ordered materials. Since all the conditions for the synthesis are reached, mix both solutions under vigorous stirring during X hours. After that the mixture has to be aged in autoclaves. This process allows to
control the pore diameter. The last step for the basic synthesis is the collection of the particles and the calcinations in order to remove of the surfactant template to get finally the mesoporous material.\[^2\] To overcome impediments such as reduction in pore size, particle agglomeration, removal of organic moieties, or low degree of condensation of the silica network, a new approach which combines the advantages of both aforementioned methods for template removal\[^5\]\[^4\], where, a liquid-phase high temperature “calcination” of MSNs is performed in a high-boiling organic solvent leading to a higher degree of silica condensation while maintaining the colloidal nature of the nanoparticles.

In particular, there are four main steps in the preparation of SBA. The first step is the synthesis of the mesoporous structure using a block copolymer and a silica precursor. The second step is the hydrothermal treatment at a higher temperature. Filtration and washing the samples are the third step and the fourth step is removing the polymer by calcinations.\[^5\]

Within a MSN there are two distinct surfaces including the external and internal surfaces, both of these surfaces can be further functionalized with active groups. There are two processes to functionalize the surfaces of MSN; the first process is called grafting. Grafting can be completed with post-synthesis nanoparticles to selectively functionalizing the exterior surface of the MSN. The organosilanes, organotrialkoxysilanes or organotrichlorosilanes, are reacted with the MSN in a non-polar anhydrous solvent. This method usually leads to most of the organosilanes binding to the exterior of the MSN or in the openings of the pores.\[^45\] The second method for functionalizing the MSN is called the co-condensation method. In this direct synthesis method, a co-condensing agent is added to the aqueous CTAB and TEOS solution during condensation to control the shape of the MSN. The condensing agent will allow for control of the morphology of the particles along with the type and degree of functionality. The characteristics of the co-condensing agent that should be considered include concentration, molecular size, and hydrophobicity or hydrophilicity. These properties will determine the ability of the co-condenser to influence the stabilization of the micelles during the formation of MSN.\[^7\]

There are few methods to synthesize silica nanoparticles, are reverse microemulsion and flame synthesis and commonly sol-gel process.

In reverse microemulsion, the nanoparticles can be grown inside the microcavities by carefully controlling the addition of silicon alkoxides and catalyst into the medium containing
reverse micelles, reverse micelles are formed by dissolving surfactant molecules in organic solvents which forms spherical micelles and in presence of water, the polar head groups organize themselves to form microcavities contained water. High cost and difficulty in removal of surfactant in the final products are drawbacks and successfully applied for the coating of nanoparticles with different functional groups for various applications.\textsuperscript{[55,56]}

In flame synthesis, silica nanoparticles are produced through high temperature flame decomposition of metal-organic precursor, this process also referred as CVC (chemical vapour condensation)\textsuperscript{[57]}, in this typical process, silica nanoparticles are produced by reacting silicon tetrachloride with oxygen and hydrogen.\textsuperscript{[58]} Difficulty in controlling the particle size, morphology, phase composition are main disadvantages\textsuperscript{[59]} and prominent for commercially producing silica nanoparticles in powder form.\textsuperscript{[60]}

Sol-gel process is widely applied to produce silica, glass and ceramic materials due to its ability to form pure and homogenous products at mild conditions.\textsuperscript{[60]} Some polymer/mesoporous silica composites can be synthesized by this method.\textsuperscript{[62]} In this method, hydrolysis and condensation of metal alkoxides such as TEOS etc or inorganic salts such as sodium silicate etc in presence of mineral acid or base as catalyst. The hydrolysis of TEOS molecules forms silanol groups. The condensation/polymerization between the silanol groups or silanol group s and ethoxy groups creates siloxane bridges (Si-O-Si) that form entire silica structure. Formation of silica particles can be divided into two stages: nucleation and growth. For growth two models were proposed which are monomer addition\textsuperscript{[63,64]} (in which after an initial burst of nucleation , the growth of particle occur through addition of hydrolyzed monomers ) and controlled aggregation\textsuperscript{[65,66]} (elaborates that the nucleation occurs continuously throughout the reaction will aggregate together to form dimmer, trimmer and large particles).

A pioneer work on synthesis of spherical and monodispersed silica particles reported by Stöber et al. called as Stöber method in which silica particles of range 5 to 2000 nm are produced from aqueous alcohol solutions of silica alkoxides in presence of ammonia as catalyst (basic condition).Another approach is Aerosol assisted synthesis, not only cationic, but also anionic and non ionic surfactants.\textsuperscript{[67-75]}
PROPERTIES

Size dependent: Size is very important in nanomaterials. Five parameters play an important role in the size and size distribution of silica nanoparticles: i) concentration of TEOS, ii) concentration of ammonia, iii) concentration of water, iv) effect of alcohol and v) reaction temperature, the temperature effect related to the saturation concentration of ammonia which decreases with increasing temperature. The size of nanoparticles has an influence on biodistribution and might therefore also have an influence on toxicity. In the field of MSN, the effect of size on the cytotoxicity in vitro. The particle order, size of MSNs can be tuned by varying the concentration of the reagents in a typical reaction mixture. As the chain length of the surfactants increases, the particle size decreases. The non ionic surfactants results in improved particles and tunable particle size. Particle size dependent upon pH of the reaction system, i.e., at high pH the particle size increases. Rate of silica dissolution is dependent on particle size. Silica nanoparticles are widely studied owing to several interesting optical phenomena caused by point defects generated from any defect imperfect SiO4 continuous network, including oxygen and silicon vacancies and several others, these point defects can be divided into: i) Paramagnetic defects which have optical absorption representing half occupied energy level in the optical band gap, thus, electron transition to valence band is possible and ii) Diamagnetic defects have absorption band associated with electron transition to the conduction band. The width of UV-Vis absorption peak at ~525 nm varies with particle size. The amount of atoms residing on the surface increases with decrease in particle size. It is measured by dynamic-light scattering (DLS). The optical emission properties of different size of silica nanoparticles have been characterized by using PL (photoluminescence) spectroscopy.

Temperature

Traditionally, MSNs are produced at high temperature, and there are some problems associated with it. High temperature (≥100°C) in calcination or spray drying can alter the textural properties of MSN and damage biomolecules. Spray drying after sol-gel process can drastically change the properties of sol-gels, which can even result in non-porous structure. At high temperatures, the shrinkage of mesopores is significant, which results in inability to control morphology of MSN and the template cannot be recovered or reused, which results in economic disadvantages. Optimal temperature range is 65-80°C.
Surface area
The concentration of silanol groups increases with the decrease in the particle size which is interrelated to the specific surface area. The unique adsorption property is directly related to the increase in surface area at nanoscale.[85,86] The surface area of mesoporous silica nanoparticles is determined by N2 adsorption-desorption isotherms and calculated by Brunauer-Emmett-Teller (BET) method.[84]

pH
pH plays another important role. Low pH is easy to achieve and has become the focus of numerous investigations in oncology especially. pH is that factor that not only affect the morphology but the size and shape of MSNs. At high pH the particle size of MSNs increases. In recent, few pH responsive MSNs are formed in which pH-sensitive linkers, such as acetal bond, hydrazine bond, and ester bond can be cleaved with decreasing pH value, thus providing opportunities for designing pH-responsive MSNs. On one hand, the pH-sensitive linkers modified over the pore entrances of MSNs can induce bulky groups as nanogates to block the pores and control drug release. On the other hand, the pH-sensitive linkers can also be modified in the nanotunnels to bond with drugs covalently. These drugs will then be released with the cleavage effects of linkers between drugs and MSNs under acidic conditions.[1]

SUMMARY
Mesoporous silica nanoparticles are the particles which are used widely now for their properties and size. Mesoporous silica nanoparticles are just one decade earlier addition to the wide applications of the nanotechnology. The uniqueness of silica makes it desirable to incorporate in mesoporous nanoparticles in comparison to other metal oxides. The most popular method of synthesis is Sol-gel method, now Stöber method and its modifications are also been utilized for the preparation of MSNs. Properties like size, surface area, temperature and most important pH are very prominent out of other properties.

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