IMPACT: International Journal of Research in Engineering and Technology
ISSN (P): 2347–4599; ISSN (E): 2321–8843
Vol. 9, Issue 4, Apr 2021, 27–34

DRUG DELIVERY USING MESOPOROUS SILICA NANOPARTICLES

Saveena Solanki

Research Scholar, Department of Biotechnology and Bioinformatics, Jaypee University of Information Technology, Solan, India

Received: 11 Apr 2021 **Accepted:** 16 Apr 2021 **Published:** 30 Apr 2021

ABSTRACT

Mesoporous silica nanoparticles are one of the versatile nanomaterials; that can be used to target drug delivery and the treatment of various diseases. Their high porosity, biocompatibility, low toxicity, high stability makes them a suitable candidate as nanocarriers. Nano-capping can help in controlled drug release, and their shape and size determine their circulation time. These inorganic based nanomaterials and surface functionalization have gained much of the attention in recent times and provide a promising platform for biomedical applications. MSNs can stay or circulate in the body for a longer time than organic nanoparticles like carbon-based nanotubes, dendrimers, liposomes, etc. This property can help in making clinical procedures short and easy.

KEYWORDS: *Mesoporous Silica Nanoparticles, Properties, Synthesis, Controlled Release Drug Delivery, Targeting Sites, Breast Cancer, Bone Cancer, Bone Infection, Bone Regeneration, Osteoporosis*

INTRODUCTION

The application of silica-based materials is widely accepted in controlled drug delivery systems (CDDS) [7]. Biological profiles that can be manipulated by Drug Delivery Systems (DDS) such as therapeutic index, pharmacodynamics, biodistribution, pharmacokinetics have gained the interest of researchers worldwide [8]. High drug loading efficacy and controlled drug release emphasize various aspects of mesoporous silica nanoparticles [5]. MSNs have been used as an ideal carrier for different biogenic agents [3]. Mesoporous silica nanoparticles (MSNs) drugs have a significant ability to release drugs with fewer side effects than recently used treatment methods[8]. Importantly, the formulation of mesoporous structured silica nanoparticles is simple, cost-effective, and controllable [5]. Cellular uptake of MSN depends on the functional groups present on the surface of MSNs and their charge [2]. The use of quaternary ammonium salts can prepare various M41S, MCM-41, MCM-48, SBA- 1, SBA-2, that can be used for targeted delivery [3].

PREPARATION AND PROPERTIES OF MSNs

MSNs have proven to possess one of the best therapeutic nanoformulations. MSNs are solid materials exhibiting high biocompatibility at concentrations adequate for the pharmacological applications. The structural properties of MSNs are unique and advantageous such as large surface area, large pore volume, which allows high drug loading and delivery [8]. The pore diameter depends upon the surfactant employed during synthesis. The absorption factor is influenced by host-guest interaction, mainly attached covalently to functional groups [1]. The wide range of manipulation of surface properties is often used for biosensing applications [5]. MSNs can protect the pharmaceutical cargoes such as drugs, enzymes, oligonucleotides, antibodies, peptides, degradation, and denaturation by external triggers like change in pH, temperature,

light, and electromagnetic field, ultrasound, unfavourable environment before reaching the designated site [8]. The physical properties of MSNs lead to improved therapeutics' efficiency due to its cell-specific interaction during drug delivery [8]. The characteristics of MSNs are observed by X-ray diffraction and transmission electron microscope; it reveals the 2-D hexagonal structure of MSNs [5].

There are varieties of a method to synthesize MSNs, but the conventional approach to produce silica nanoparticles is a hydrolytic sol-gel method that involves hydrolysis and silica precursor [1]. In the sol-gel process, the addition of surfactant quaternary ammonium salt, cetyltrimethylammonium bromide (CTAB) acts as structure-directing agents and liquid crystal template [9,6]. The silica precursor such as tetraethyl orthosilicate (TEOS) or sodium metasilicate forms an oxide network, leading to a sol. This colloidal solution further evolves towards the formation of gel under specific favourable conditions [9,1]. The positively charged polar heads of surfactant molecules interact with negatively charged silica precursor and further sit self-assembled into rod-like surfactant micelles. The concentration and temperature have a strong influence on the self-assembling process to form mesostructure nanoparticles. The pure MSNs are extracted after the removal of surfactants through the solvent extraction method [6,1]. The morphology of nanoparticles is tailored by surfactant concentration, pH, temperature, and silica precursor [6].MCM 41 type is the most widely used MSNs with modified shapes and sizes ranging from 20 to 500nm and with pore size approximately 2 to 6nm [5].

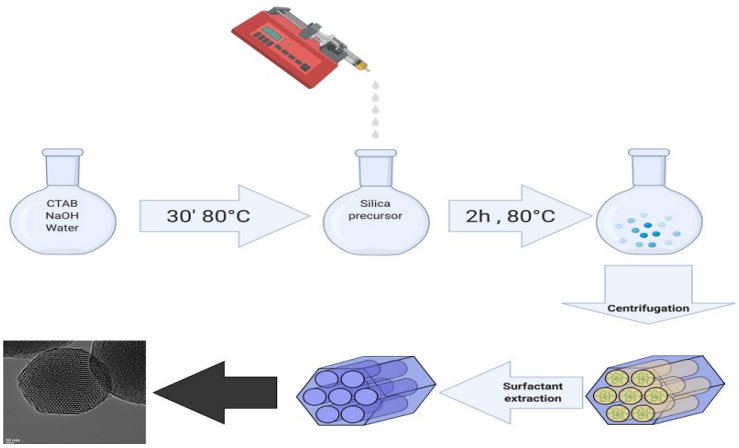

Figure 1: Synthesis of MCM – 41 MSNs using a Modification of the Stober Method.

The inorganic pores were modified with the introduction of aluminium into the template to increase the acidity. These materials could act as an acid catalyst in various reactions such as Friedel crafts acylation, condensation. X-ray pattern results show that after Al's introduction, the surface area and pore volume decrease, whereas pore volume increases by changing the pore wall's thickness [3].

pH-responsive MSN- controlled drug delivery systems (CDDSs) have also attracted extensive research because of its better efficacy for anticancer drug delivery. The pH-responsive MSN -CDDSs are prepared by the amidation reaction of the homopolymer of polyacrylic acid with amino group modified MSNs. The cancerous cells are more acidic than normal cells; thus, pH-responsive MSNs are more suitable to control the drug behaviour by pH stimuli [4].

MESOPOROUS SILICA

pH, concentration, and temperature of the system in which it would solubilize. The Accumulation of these nanoparticles depends on the shape, size, and the route of their introduction into the system. [1]

MSNs received much attention because of its efficient biocompatibility, chemical and thermal stability, and versatile functionalization Direct release as soon as the drug introduced in the body can be harmful to the normal functioning cells, so the Controlled Drug Delivery System (CDDSs) is one of the primary focus. Quantum dots, dendrimers, iron oxide nanoparticles were used as gatekeepers by Lin et al. to cap these nanoparticles. [4]

The release of loaded cargo at the target site is crucial to achieve maximum efficiency. Capping of the guest molecules is done to prevent the pre-release of mesoporous silica nanoparticles.

NANOPARTICLES AS DRUG DELIVERY SYSTEM

MSMs (mesoporous silica materials) having properties like high surface area and pore volume along with bio-active nature due to silanol groups on their surface make them a potential candidate for the drug delivery system, firstly proposed by Vallet–Regi group. MSMs can be used for various medical conditions like bone disease, cancer, for hair dye. For any system, the activity of the material is based on the bio-kinetics. MSNs (mesoporous silica nanoparticles) can be utilized if it is adequately monitored according to its safety and biodegradation perspective as the characteristics of liquid media also play an important role other than Figure : 2 Different types of capping for MSNs

This image of mesoporous silica nanoparticles is taken from shutterstock.com. The diagram shows different capping mechanisms to protect loaded cargo. [5]

As soon as MSNs are introduced in the body, these nanoparticles are required to cross the cell membrane. It has been observed that MSNs cross the cell barrier by endocytosis and sometimes pinocytosis depending on the size and shape of these nanoparticles. In-plant cells, this endocytosis process becomes more complicated due to a rigid cell wall consisting of pectin, cellulose, and hemicellulose. Numerous mechanisms that support endocytic routes to deliver the MSNs through cytoplasm: clathrin-dependent, receptor-mediated, caveolin-dependent, clathrin- and caveolin-independent endocytosis. Once MSNs cross the cell membrane, these nanoparticles pass through primary and secondary endosomes to reach the cytoplasm for cargo release. Negatively charged MSNs are more compatible with escaping endosomes in comparison to positively charged MSNs. MSNs undergo surface charge reversal in acidic conditions due to the transfer of protons to the material's surface from bulk solution, called the proton sponge effect. [8]

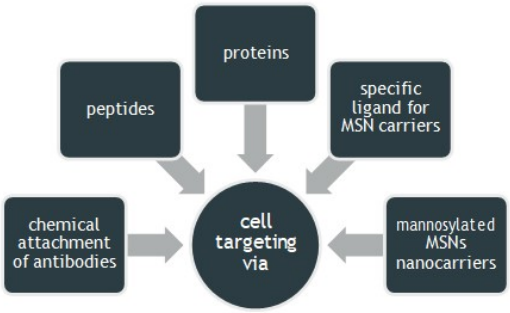

Figure 2: Cell Targeting by Different Modes.

In some cases, the administration of these particles can lead to the formation of protein corona surrounding them, which explains their biological entity and can be removed by the mononuclear phagocyte system and reducing their

therapeutic efficiency. It can be overcome by modifying the nanoparticles with hydrophilic polymers, like polyethene glycol (PEG), which forms a hydrophilic layer improving their colloidal stability and enhancing their circulating half-life. [6]

The unique characteristics of mesoporous silica nanoparticles in controlled drug delivery and cell targeting mark their prominent spot in various diseases.

MSNs for the Treatment of Cancer

Cancer therapy has been a promising research area based on new drug molecule carriers, like nanotubes, liposomes, dendrimers, microcapsules, and hydrogel. Recently, mesoporous silica nanoparticles as nanocarriers in the Controlled drug release have gained much of the attention. MCM- 41, SBA-15, hollow, and bimodal mesoporous sphere are the conventional MSNs for target drug delivery. Polyelectrolyte multilayers (PEM) as drug carriers and DNA-aptamer, sgc8, as target recognition molecules can be selected to detect cancer cells. [10]

Bone Cancer

Anticancer treatments like chemotherapy and radiotherapy lack tumour tissue selectivity, which leads to side effects and non-target specific distribution. Nanoparticles can be engineered to particular target release and Enhanced Permeability and Retention Effect (EPR effect) observed by Maeda et al. some tumour homing peptides, such as iRGD, iNGR induce spontaneous Accumulation of nanomaterials and improve their diffusion in tumours. The nanomedicines can act on bone tissue by:

- Bone targeting agents (alendronate) can support nanomedicines to accumulate on the bone tumour.
- Then the cathepsin K would cleave the sequence of peptides.
- RGD motif exposure can promote the uptake of nanomedicine by the sarcoma cells possessing a tumour.

Accumulation of these nanoparticles on tumour mass can also be enhanced by designing them as glucose analogue because of the high energy requirements of continuously dividing cells. Once the nanomedicine reaches the target site, the cargo can be released by pH-responsive stimuli, alkaline phosphatase enzyme, esterase enzyme for the degradation of the nanocaps. [6]

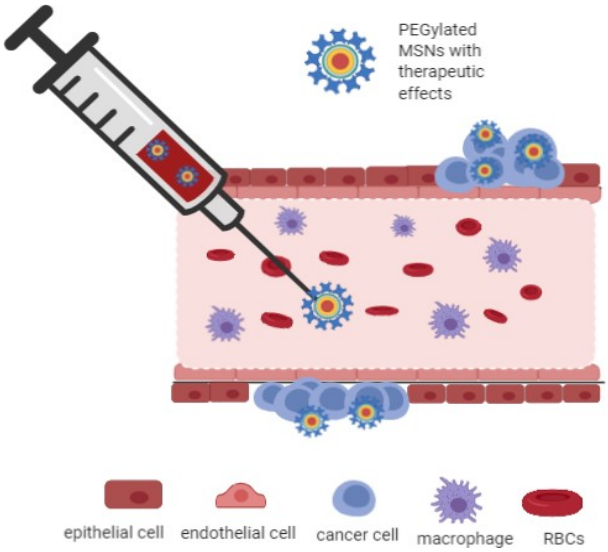

Figure 3: ERP Effect of Msns. Msns Accumulate on the Targeted Cancer Cells and Initiate the Drug Release.

Tumour mass is a combination of cancer cells, extracellular matrix, and blood vessels, which creates a barrier for the nanocarriers to penetrate deeply. This can be overcome by using proteolytic enzymes, which can degrade the tumour matrix so these enzymes can be grafted as protected enzymes on their surface. When these enzymes are exposed to cancer cells' acidic nature, they degrade, penetrating deep into the mass. [1]

Breast Cancer

Ultrasound is currently used to detect breast cancer, but its low specificity and noisiness do not make it a suitable diagnostic tool. These limitations can be reduced by the use of an ultrasound contrast agent. Present clinically approved UCAs are gas microbubbles that are encapsulated in protein or liposomal carriers, but their half-life is extremely poor and becomes unstable during insonication. MSNs can stay up to 4 weeks in the body, which may simplify clinical procedures. They can be endocytosed by the cells and can significantly control cargo loading and release because of its unique properties. [13]

In 25-30% of malignant breast cancer, HER2 /neu glycoproteins are overexpressed. Monoclonal antibody (mAb), Herceptin can be functionalized with MSNs that are loaded with the green fluorescent dye, on the external surface can identify antigens linked with an active cellular oncogene—simultaneously grafting fluorescein isothiocyanate (FITC), a green fluorescent agent on the inner side of MSNs, to precisely identify HER2 receptors. Herceptin is pre-linked to PEG spacer to avoid binding with non-targeted cells. This the approach can minimize the side-effects of the anticancer drug. [2] MSN can target 90% BT-474 cells (human breast cancer, HER2/neu over-expressed) with high Herceptin within 6-hour incubation. [2]

MSNs for the Treatment of Bone Infection

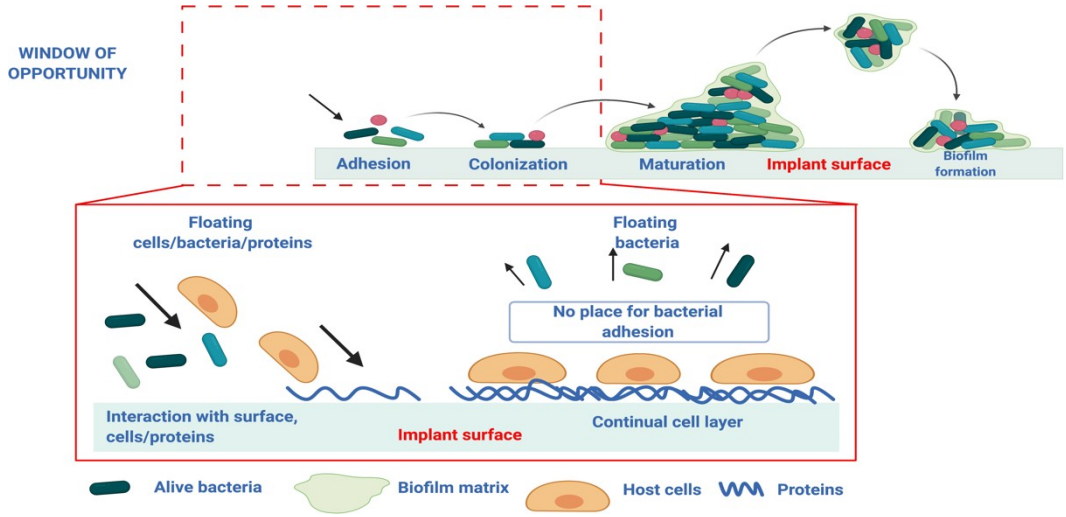

Figure 4: Schematic Biofilm formation.

The application of silica-based materials in the biomedical sector is immensely expanded [7]. Bone infection is a potentially dangerous infection that is directly related to ageing [11]. This infection is triggered by Staphylococcus aureus, Staphylococcus epidermis, Escherichia coli, and Pseudomonas aeruginosa [11, 6]. In this case, the main limitations of antibiotics are progressively leading to more drug resistance cases with a high rate of side effects [6].

This bacteria adhere to the polysaccharide matrix and then form colonies, leading to the formation of biofilm and induced infection. This biofilm acts as a shield and becomes antibiotic resistance. The nanomaterials are prepared to avoid the appearance of biofilm, bacterial adhesion, and protein adsorption [6]. Amine functionalization provides these mesoporous silica nanoparticles, a positive charge that improves the intracellular uptake by gram-positive bacteria and increases pharmacokinetics [11]. The modification of mesoporous silica nanoparticle with a phosphorylcholine group reduces the protein adsorption and provides sustained drug release even in response to an increase or decrease in pH [6]. Besides, silica-based mesoporous bioactive glasses (MBG) were designed with high potential to reduced bacterial adhesion and biofilm formation [7].

The elimination of infection is necessary besides preventing biofilm formation. Thus multifunctional, modified mesoporous silica nanoparticles are synthesized to target infected bone tissue [6]. Silica-based mesoporous glasses are associated with porous collagen gelation for vancomycin's controlled release at the target site [7]. In the presence of positive charges on the surface of MSNs increases the affinity towards negatively charged biofilm to diffuse quickly and exert their therapeutic effect [11]. The silica xerogels, silica ceramics, silica hybrids, and bioactive silica glasses helped achieve higher drug loads with better silica carriers' compatibility. These silica materials have been extensively explored for bone regeneration and bone infection treatments [7].

MSNs for the Treatment of Osteoporosis

Osteoporosis is a degenerative bone disease that is directly related to progressively ageing. Silica-based nanomaterials can serve as the osteoconductive agent for the treatment of osteoporosis [12].

The modification in SBA-15 type of mesoporous silica nanoparticle, by adding phosphorous groups, enhances the

loading of alendronate and induces apatite formation for osteoporosis [6]. Moreover, the loading of beta-estradiol into mesoporous silica nanoparticles enhances osteoconductivity, which stimulates osteoblast function and actively inhibits osteoclasts' proliferation [6,12]. Furthermore, the bone morphogenic protein-2 (BMP-2) is considered the best growth factor to induce osteoblast and bone regeneration differentiation.

The MSNs are useful for delivering dexamethasone and BMP-2 at the target site to induce osteogenesis and promote bone mesenchymal cells' internalization and facilitate new bone formation [7].

Some metal ion species promotes the differentiation of osteoblasts. For instance, Copper ions incorporated in mesoporous silica nanoparticles enhance bone density and stimulate the differentiation of bone mesenchymal stem cells. Furthermore, gallium and zinc ions are impregnated with mesoporous bioactive glasses, promoting apatite formation and disruption of osteoclasts and stimulates osteogenesis and bone regeneration [6].

CONCLUSIONS

From these studies, it can be concluded that MSNs prove to be very stable nanomaterials that can be used as biosensors and target specific cells involved in severe medical conditions because of controlled drug delivery systems and stability. Importantly, these nanocomposites respond to particular stimuli and exhibit high selectivity for the detection of diseases. Bone diseases and cancer constitute a significant concern for modern societies. These mesoporous silica nanoparticles can be explicitly engineered with biochemical cues to address the affected tissue drug for tumour and bone diseases. From a general perspective, it is evident that there has been vast progress in the structure design and development of inorganic silica nanoparticles in biomedical applications. The synthesis of new nanoparticles and better clinical implementation of this nanotechnology will be developed.

REFERENCES

1. *Manzano, Miguel, and María Vallet-Regí. "Mesoporous silica nanoparticles for drug delivery." Advanced Functional Materials 30.2 (2020):1902634.*
2. *Tsai, Chih-Pin, et al. "Monoclonal antibody- functionalized mesoporous silica nanoparticles (MSN) for selective targeting breast cancer cells." Journal of Materials Chemistry 19.32 (2009): 5737-5743.*
3. *Keshavarz, Meysam, and Norhayati Ahmad. "Characterization and modification of mesoporous silica nanoparticles prepared by sol-gel." Journal of Nanoparticles 2013 (2013).*
4. *Yuan, Li, et al. "Preparation of pH-responsive mesoporous silica nanoparticles and their application in controlled drug delivery." The Journal of Physical Chemistry C 115.20 (2011): 9926-9932.*
5. *Slowing, Igor I. et al. "Mesoporous silica nanoparticles for drug delivery and biosensing applications." Advanced Functional Materials 17.8 (2007): 1225-1236.*
6. *Gisbert-Garzarán, Miguel, Miguel Manzano, and María Vallet-Regí. "Mesoporous silica nanoparticles for the treatment of complex bone diseases: Bone cancer, bone infection, and osteoporosis." Pharmaceutics 12.1 (2020): 83.*

7. *Chowdhury, Mohammad A. "The Silica-based Formulations for Drug Delivery, Bone Treatment, and Bone Regeneration." Chem Bio Eng Reviews 3.5 (2016): 229-246.*
8. *Vivero-Escoto, Juan L., et al. "Mesoporous silica nanoparticles for intracellular controlled drug delivery." Small 6.18 (2010): 1952-1967.*
9. *Tang, Fangqiong, Linlin Li, and Dong Chen. "Mesoporous silica nanoparticles: synthesis, biocompatibility, and drug delivery." Advanced Materials 24.12 (2012): 1504-1534.*
10. *Zhu, Chun-Ling, et al. "An efficient cell-targeting and intracellular controlled-release drug delivery system based on MSN-PEM-aptamer conjugates." Journal of Materials Chemistry 19.41 (2009): 7765-7770.*
11. *Pedraza, Daniel, et al. "Amine-functionalized mesoporous silica nanoparticles: A new nanoantibiotic for bone infection treatment." Biomedical Glasses 4.1 (2018): 1-12.*
12. *Barry, Mikayla, et al. "Advances in Nanotechnology for the Treatment of Osteoporosis." Current osteoporosis reports 14.3 (2016): 87-94.*
13. *Milgroom, Andrew, et al. "Mesoporous silica nanoparticles as a breast-cancer targeting ultrasound contrast agent." Colloids and Surfaces B:Biointerfaces 116 (2014): 652-657.*