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Composite smart mesoporous silica nanoparticles as promising therapeutic and diagnostic candidates: Recent trends and applications

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ABSTRACT

Theranostics is an emerging field which involves application of a single formulation for both diagnosis as well as therapeutics. The present manuscript describes various applications of hybrid mesoporous silica nanoparticles in therapeutics, diagnostics and in theranostics. In spite of advancement in medicine, early diagnosis and complete treatment of various diseases like cancers, HIV and diabetes still remains a daunting task. The answer to the treatment of these deadly diseases lies in the vast research done on smart functionally modified mesoporous silica nanoparticles. The promising results given by MSNs in various in vitro and in vivo studies, accounts for the overwhelming attention they are receiving in the field of drug delivery and diagnostics. Their effect on immune system has also been outlined. Applications are also being reported in the field of gene delivery. Due to wide applications, these multifunctional Nano carriers are befitted for the job of drug delivery and cell tracking. Their role as contrast agents in the field of diagnostics is also described. The manuscript focusses on construction strategies, applications, challenges and opportunities associated with this emerging Nano drug delivery technology. Though Mesoporous silica nanoparticles have already entered pre-clinical development stage, their testing in clinical trials on a large scale needs to be accomplished to establish their efficacy and safety in humans. The ultimate goal of these astute composite mesoporous carriers is to utilize diagnostic information for controlling their therapeutic function. Smart multifunctional MSNs have a great potential ahead and can be the answer to cure of various deadly diseases.

1. Introduction

The unfolding of Nanotechnology has proffered an opportunity to haul diagnostics and therapeutics closer. There have been lots of investigations on nanoparticle based therapy and imaging separately and now their thorough understanding has led to the emergence of Nano particle (NP) based theranostics which are defined as Nano platforms which can co-deliver therapeutic as well as imaging agents. Controlled synthesis of mesoporous silica nanoparticles has been attained and surface modification has been done with various moieties based on silane coupling chemistries. The main underlying principle involved here is that both imaging as well as therapeutic agents requires accumulation in the diseased area. This common targeting necessity brings the two research domains closer and vague the thin boundary of distinction between them.

Amid the nanomaterials studied, mesoporous silica nanoparticle (MSN) has been one of the most beguiling developments in biomedical practice. Since their astonishing discovery in early 1990's by Mobil scientists, MSN's have allured great interest in most disciplines of science and engineering due to their anomalous physiochemical properties, like its docile particle size [1], large surface area [2], tunable pore size [3], structure [4,5]and morphology [6,7]. These properties furnish them to serve as a multifunctional Nano vessel [8,9] to carry drugs, probes, and biomolecules for therapeutic and diagnostic applications [10,11], with outstanding water dispersibility and biocompatibility [11].

Nanomedicine is an amalgamation of nanotechnology and biomedicine and presents propitious.Therapeutic prospective for number of diseases, including diabetes, tissue engineering and cancer theranostics. The newer advances in nanomaterials provide the dual advantage of preliminary stage diagnosis of cancer and also avoiding chemotherapeutic side-effects. The foremost Food and Drug Administration (FDA)-approved Nanomedicine, Doxil® is an archetypal example, where drug Doxorubicin (DOX) is encapsulated in liposomes to achieve prolonged circulation time and enhanced bioavailability of DOX, and reduced side-effects to heart muscles and other normal tissues [12].

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Theranostic Nanomedicine is emerging as a promising therapeutic prototype. It takes benefit of the high potential of Nano platforms to ferry cargo and imparts them both imaging and therapeutic functions. The term “Theranostics” was conceived to define ongoing efforts in the medical and pharmaceutical domain to develop more specific, distinctive therapies for various diseases, and to combine diagnostic and therapeutic capabilities into a single solitary agent. The rationale emerged from the fact that diseases, such as cancers, are extremely heterogeneous, and all existing therapies are effective for only restricted patient populations and at a few selected stages of disease development. The hope was that a close wedlock of diagnosis and therapeutics could provide therapeutic etiquettes that are more specific to individuals and, therefore, more likely to offer improved prognoses [13]. Mesoporous Silica Nanoparticles, Iron oxide nanoparticles, quantum dots, carbon nanotubes, gold nanoparticles have been previously satisfactorily explored in the imaging milieu and are potential Nano platforms in mushrooming nanoparticle-based theranostics.

All the mesoporous silica nanoparticles possess three basic components 1) solid support, 2) a payload for cargo delivery and 3) external enginery. MCM-41 are widely used as a solid support for mesoporous silica nanoparticles due to their rigidness, robustness, chemical inertness and ease of fabrication [14,15]. The cargo is either drug or imaging agents which are loaded into the pores of mesoporous silica nanoparticles. It is preferable to use fluorescent materials as cargo, since its release can be traced by fluorescent microscopy.

1.1. Various categories of mesoporous silica nanoparticles

Mesoporous silica nanoparticles have pore diameter ranging from 2 to 50 nm [16]. MSNs can be classified as MCM 41S Type MSN Family, Organically modified Silica (ORMOSIL) nanoparticles and Hollow/Rattle type MSN.

1.1.1. MCM-41 and similar genre MSNPs

The revelation of MCM 41 type MSN formed the basis of application of MSNs in Therapeutics for drug delivery [17,18]. MCM-41 is a fundamental prototype in mesoporous carriers, and has a hexagonal porous structure and is one of the most widely studied material amongst MSN family, having numerous applications in biomedicine and Nano therapeutics. The advantages that they offer over other mesoporous materials are large surface area, good thermal stability and narrow distribution of pore size [19,20]. Modification in the shape of these MCM-41 like tubular or spherical shaped MCM 41 further enhances their biomedical applications, affecting the drug delivery traits due to their high surface area and smaller diameter of the pores [21]. The temperature at which synthesis of MCM-41 is carried out plays a vital role as it directly affects its physical characteristics like its pore size [22]. Another vital property of MCM is their tendency or capability to form metal-ion complexes by conjugating with the metal ions like Al-MCM-41 [23], Fe-MCM41 [24], Au-MCM41 [25] and Mn-MCM-41 [26]. Aforementioned metal-ion complexes enhance the utility of MCM-41 nanoparticles by providing enhanced catalytic efficiency, increased therapeutic potential in drug delivery and also aid their application in diagnostics.

The MCM-41 family extends to 3-D cubic MCM-48 and lamellar MCM-50 as well. Each of them possessing unique and useful properties for disease treatment, much of which still remains to be explored. MCM- 48 has a distinctive branched 3- dimensional pore system [27]. MCM-48 is the cubic associate of MCM 41S family of ordered mesoporous materials [14,19] and its 3-D pore structure consists of the interlaced pore system divided by a continuous pore wall [28,29]. This characteristic structure is probably more beneficial for catalytic operations as compared to unidirectional pore systems like that of MCM-41, since the active sites are more available to the reactants, it aids the diffusion of reactants and products through the pores, and is less inclined towards deactivation [30,31]. MCM-48 have been reported to provide surface area almost double to that provided by MCM-41 [32]. MCM-50 have layered lamellar structure with wide application as sorbents and in catalysis. Very few applications of MCM-50 have been explored.

1.1.2. Santa Barbara Amorphous-15 (SBA-15) MSNPs

Santa Barbara Amorphous (SBA-15) is also one of the type of MSNs which has been widely researched for use as a drug delivery system. SBA-15 has been widely used for enhancement of bioavailability of poorly soluble BCS class 2 and 4 drugs like ketoprofen [33] and furosemide [34] via stabilization of its amorphous state. Amphiphilic triblock copolymers which possess mesostructured ordering properties serve as a template for synthesis of SBA-15 [35]. The synthesis of SBA-15 is highly dependent on pH and hence it is necessary that pH levels are taken care of when synthesizing SBA-15 [36].

Wide structural differences exist between MCM-41 and SBA-15. The latter possesses thicker pore walls, which provide more mechanical and hydrothermal stability and additionally, controlled micropores in its walls [35]. Due to its wide pore size, higher internal surface area and large particle diameter, SBA-15 finds large number of applications in catalysis [37,38], optics [39,40], adsorption and separation [41] and theranostics [42].

However, SBA-15 has a largest pore diameter of 5–30 nm and is rougher morphologically when compared to MCM-41 which has a smoother wall surface and lesser pore diameter [43]. Hence, research thrust nowadays is on synthesizing smaller SBA -15 nanoparticles with particle size less than 200 nm to improve their applications an increase their usefulness in the field of drug delivery of anticancer agents.

1.1.3. Organically modified silica (ORMOSIL) GENRE of MSNPs clan

Organically modified silica (ORMOSIL) nanoparticles are hybrid nanoparticles actively used for encapsulating or conjugating various agents for use in gene therapy, Photodynamic therapy (PDT) and diagnostics. Compared to their counterparts like gold nanoparticles, nanorods, nanotubes, quantum dots etc., ORMOSIL offer a couple of advantages, like the ease of embodiment of various bio targeting molecules, which are essentially non-toxic and additionally ease of adding fluorescent moieties for tagging. These combined make fluorescent ORMOSIL nanoparticles an effective candidate for functioning as probes for optical Bioimaging in diagnostics both in vitro and in vivo [44]. These ORMOSIL nanoparticles catch the eye in their versatileness and adaptability as a prototype for building multimodal theranostic nanoparticles. They are inert and optically transparent, incorporated with desired fluorophore (NIR/UV) as necessary giving robust and fluorescent nanoparticles [45–48]. Various bioactive molecules like enzymes, genetic materials and drugs, etc. having a specific biological function can be incorporated with ease [49–51]. Successful optical imaging of tumor cells in vitro by incorporation of probes for MRI imaging in conjugation with fluorophores and targeting moieties has been achieved [46,52,53]. The other major advantages it has to offer over conventional silica nanoparticles include ease of synthesis, as these can be synthesized with size as low as ∼∼20 nm in simple aqueous phase, i.e. o/w micro emulsion wherein complex purification steps and corrosive non polar solvents can be avoided [54]. Due to their smaller sizes, they are more suitable for in vivo applications as they are expected to infiltrate to a tumor in a more efficient manner. The rigid silica matrix also gets a high degree of flexibility in presence of certain organic groups. As desired required surface charge can be introduced on the organic part of ORMOSIL which serves as a platform for conjugation with other therapeutic/diagnostic moieties. Kumar et al. have synthesized ORMOSIL nanoparticles covalently conjugated to Rhodamine (RORM) with a variety of active groups (hydroxyl/amine/thiol/carboxyl) anchored on its surface using oil-in-water microemulsion method. Covalent conjugation when compared to simple encapsulation eliminates the chances of fluorophore being leached out of ORMOSIL matrix in body fluids. Additionally bioactive molecules like transferrin,