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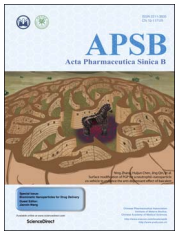

REVIEW

Mesoporous silica nanoparticles for drug and gene delivery

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KEY WORDS

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Abstract Mesoporous silica nanoparticles (MSNs) are attracting increasing interest for potential biomedical applications. With tailored mesoporous structure, huge surface area and pore volume, selective surface functionality, as well as morphology control, MSNs exhibit high loading capacity for therapeutic agents and controlled release properties if modified with stimuli-responsive groups, polymers or proteins. In this review article, the applications of MSNs in pharmaceutics to improve drug bioavailability, reduce drug toxicity, and deliver with cellular targetability are summarized. Particularly,

Abbreviations: AO, acridine orange; APTES, 3-aminopropyltriethoxysilane; APTMS, amino propyl trimethoxysilane; BCL-2, B-cell lymphoma-2; BCS, Biopharmaceutical Classification System; Bio-TEM, biological transmission electron microscopy; C dots, Cornell dots; CMC, critical micelle concentration; CPT, camptothecin; CTAB, cetyltrimethyl ammonium bromide; EPR, enhanced permeability and retention; FDA, Food and Drug Administration; GI, gastrointestinal; GNRs@mSiO$_2$, mesoporous silica-encapsulated gold nanorods; LHRH, luteinising-hormone releasing hormone; MDR, multi-drug resistance; MTT, 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide; MRP1, multidrug resistance protein 1; MSN-Dox-G2, Dox-loaded and G2 PAMAM-modified MSNs; MSNs, mesoporous silica nanoparticles; MSNs@PDA-PEG-FA, poly(ethylene glycol)-folic acid-functionalized polydopamine-modified MSNs; MSNs-HA, hyaluronic acid-conjugated MSNs; MSNs-RGD/TAT, RGD/TAT peptide-modified MSNs; MSNs-TAT, TAT peptide-modified MSNs; NIR, near-infrared; PAMAM, polyamidoamine; PDEAEMA, poly (2-(diethylamino)ethylmethacrylate); PDMAEMA, poly(2-(dimethylamino)ethylmethacrylate); pDNA, plasmid DNA; PEG400, polyethylene glycol 400; PEI, polyethyleneimine; P-gp, P-glycoprotein; PLL, poly-L-lysine; PTX, paclitaxel; Q-MSNs, quercetin encapsulated MSNs; RGD, arginine-glycine-aspartate; TAT, trans-activating transcriptor; TMB, 1,3,5-trimethybenzene

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Multidrug resistance;
Gene delivery

the exciting progress in the development of MSNs-based effective delivery systems for poorly soluble drugs, anticancer agents, and therapeutic genes are highlighted.

1. Introduction

In recent years, there has been a rapid growth in the area of biomedicine, particularly in exploring new drug/gene delivery systems. More recently, nanotechnology emerged as a promising approach which has motivated researchers to develop nanostructured materials. Among various integrated nanostructured materials, mesoporous silica nanoparticles (MSNs) have become a new generation of inorganic platforms for biomedical application.

MSNs with uniform pore size and a long-range ordered mesoporous structure were first introduced by Mobil corporation scientists in 1992[1]. In general, supramolecular assemblies of surfactants are necessary in the synthesis of MSNs. Usually, the surfactant will self-aggregate into micelles at a concentration higher than the critical micelle concentration (CMC). Then, the silica precursors can condense at the surface of the micelles forming an inorganic-organic hybrid material. Finally, the template surfactant can be removed either by calcination or by solvent extraction to generate pores (Fig. 1). The resulting silica-based mesoporous matrices may offer the following unique structural and biomedical properties:

1) *Ordered porous structure*. MSNs have a long-range ordered porous structure without interconnection between individual porous channels, which allows fine control of the drug loading and release kinetics (Fig. 2).
2) *Large pore volume and surface area*. The pore volume and surface area of MSNs are usually above 1 cm^3/g and 700 m^2/g, respectively, showing high potential for molecule loading and dissolution enhancement.
3) *Tunable particle size*. The particle size of MSNs can be controlled from 50 to 300 nm, which is suitable for facile endocytosis by living cells.
4) *Two functional surfaces*. MSNs have two functional surfaces, namely cylindrical pore surface and exterior particle surface. These silanol-contained surfaces can be selectively functionalized to achieve better control over drug loading and release[2]. Moreover, the external surface can be conjugated with targeting ligands for efficient cell-specific drug delivery.
5) *Good biocompatibility*. Silica is "Generally Recognized As Safe" by the United States Food and Drug Administration (FDA). Recently, silica nanoparticles in the form of Cornell dots (C dots) received FDA approval for stage I human clinical trial for targeted molecular imaging[3,4]. It was reported that MSNs exhibited a three-stage degradation behavior in simulated body fluid[5], suggesting that MSNs might degrade after administration, which is favorable for cargo release. Several *in vivo* biodistribution studies of MSNs have been reported recently[6,7]. Liu et al.[6] evaluated the systematic toxicity of MSNs after intravenous injection of single and repeated dose to mice. The results of clinical features, pathological examinations, mortalities, and blood biochemical indexes indicated low *in vivo* toxicity of MSNs. It was also reported that MSNs were mainly excreted through feces and urine following different administration routes[7].

These unique features make MSNs excellent candidate for controlled drug/gene delivery systems. Since the first report using MCM-41 type MSNs as drug delivery system by Vallet-Regi et al.[8] in 2001, the research on biomedical application of MSNs has steadily increased, with an exponential rise in last decade. Various mesoporous materials with different porous structure and functionality have been developed for controlled and targeted drug/gene delivery. Here, we give an overview of the recent research progress and future development of MSNs in biomedical applications, particularly focused on the practical applications of MSNs as delivery systems for poorly soluble drugs, anticancer agents, and therapeutic genes. Based on the review, we have also included our perspectives on the further applications of MSNs.

2. Mesoporous silica-based system for poorly soluble drugs

With the increasing numbers of innovative new drugs in development, almost 70% of new drug candidates exhibit low aqueous solubility, ultimately resulting in poor absorption[9]. In an attempt to overcome this solubility obstacle and to improve the oral bioavailability, a growing number of drug delivery technologies have been developed. Presently, nanotechnology is attracting increasing attention as it can be applied in two aspects[10]: processing the drug itself into nano-sized particles or preparing drug-contained nanoparticles from various materials. With the excellent features including huge surface area and ordered porous interior, mesoporous silica can be used as a perfect drug delivery carrier for improving the solubility of poorly water-soluble drugs[11–14] and subsequently enhancing their oral bioavailability[15–17].

When water-insoluble drug molecules are contained in mesoporous silica, the spatial confinement within the mesopores can reduce the crystallization of the amorphous drug[18]. Compared with the crystalline drug, the amorphous drug can reduce the lattice

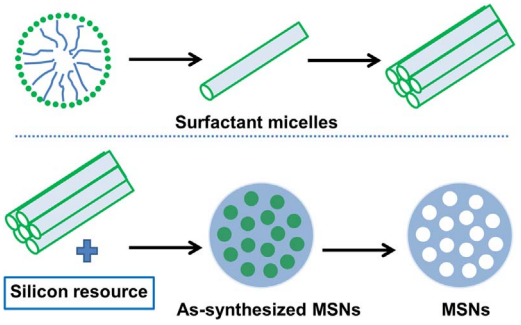

Fig. 1 Schematic diagram showing the preparation of mesoporous silica nanoparticles (MSNs).