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Hydrophobically modified spherical MCM-41 as nanovalve system for controlled drug delivery

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ABSTRACT

Spherical MCM-41 nanovalve having hydrophobically modified pore channels was synthesized via surfactant assisted sol–gel methodology and post modification process. The spherical MCM-41 has been tailored as a smart pH responsive drug carrier system by the insertion of N-3-(trimethoxysilyl)propyl aniline (TMSPA) at the pore opening before extracting the surfactant and further with phenyltrimethoxysilane (PTMS) to impart hydrophobicity on the inner surfaces of the pore channels. The surfactant extracted MCM-41 exhibits excellent textural properties such as very high specific surface area (1307 $m^2 g^{-1}$), pore diameter (24 Å) and pore volume (0.65 $cm^3 g^{-1}$). The transmission electron microscope (TEM) and scanning electron microscope (SEM) images of mesosphere reflect the highly uniform and mono-dispersed spherical morphology having a particle size of 500 nm. 5-Fluorouracil (5-Fu) and famotidine have been loaded into the hydrophobically modified channels followed with β-cyclodextrin (β-CD) as the gatekeeper to make the material as a pH responsive drug delivery system. The drug delivery has been carried out under *in vitro* condition at pH 4 and the amount of drug released from the nanovalve system was monitored by UV–Vis spectroscopy under regular intervals. The hydrophobically modified nanovalve was found to have delayed drug release of both 5-Fu and famotidine in comparison to the drug delivery from the nanovalve having unmodified pore channels synthesized from spherical MCM-41 under similar experimental conditions. The significance of functionalization as well as capping has been verified by the comparison of drug delivery behaviors among hydrophobically modified, unmodified, β-CD capped and uncapped nanocontainers.

1. Introduction

The exciting discovery of new molecular sieves, generically called M41S [1] in the early 1990s, evoked new windows for the exploration in material research. Cationic surfactant micelles act as templates as well as structure directing agents in mesoporous material synthesis through an electrostatic interaction with the polymerizing silica components. Owing to its convenient synthesis procedure, stupendous mesoporous structure and surface silanol groups, mesoporous silica materials possess exclusive properties such as large surface area, high pore volume, uniform and tunable pore size, low mass density, non-toxic nature, easily modifiable surface properties and good biocompatibility [2–7]. Among the mesoporous materials MCM-41 received much attention due to its tunable nature *i.e.*, its capacity to form different morphologies such as disk, rod, sphere, hexagonal plates, gyroids, crescent-like and worm-shaped particles depending on the various combination of silica precursor/surfactant/water/co-solvent [8]. The spherical morphology has become a passion of modern research in the biomedical field, especially in the drug delivery application. It is possible to tune the size of the sphere and pore diameter by altering synthesis conditions such as amount of silica precursor/water/base or type of surfactant without disturbing the radially aligned mesopores from the center to the surface of the spherical particles for extended applications [9]. Selective functionalization [10–12] of the mesoporous materials play the pivotal role in equipping the modified materials with enhanced hydrothermal stability and cargo loading. Vallet-Regi et al. reported two MCM-41 materials with different pore diameters for the controlled delivery of ibuprofen and found that the release rate of the drug was linearly dependent on the pore size [13]. The study proclaimed that mesoporous silica materials also can fulfill the conditions for homogenous distribution of the drug all over the silica matrix in contrast to the conventionally used polymeric materials. The appropriate

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physicochemical modifications in particle morphology and channel functionalization (hydrophilic/hydrophobic) are essential because the mesoporous silica surface covered with silanol groups is not selective enough to adsorb drug molecules with different functionalities. Even in the presence of such modifications, an immediate or uncontrolled release has been experienced by several researchers, which strengthened the requirement of more advanced and synergic manipulation to attain a perfect drug delivery system. The premature release of drug molecules from the pore channels should result an untargeted drug release that could cause undesirable side effects to normal cells and organs [14]. An overview of the drug delivery studies showed that most of the drug carriers are developed based on the hydrophilically modified inner surfaces since hydrophilic surface favors the high loading and delayed cargo release. But, the drugs utilizing for practical uses generally fall either in hydrophilic or hydrophobic categories. So, it is necessary to investigate the activity of hydrophobically modified surface toward drug delivery from a scientific viewpoint. Unfortunately, only few reports are available under this category. Mesoporous materials with different particle morphology, pore geometry and surface organic composition have been widely investigated as drug delivery system in order to achieve high drug loading capacity and well-defined drug delivery profile. Previous studies revealed that the mesoporous silica carrier modified with special functional groups have great benefits for controlled drug release [15–21]. Several studies pointed out that the release rate of ibuprofen, which has been widely investigated as model drug, could be modulated by varying the density of the surface organic amino groups, changing the chain length of amino groups, or using different species of amino groups, e.g. aminopropyl, aminoethylaminopropyl and so on [15–17]. The drug delivery systems were much professionalized only after the discovery of stimuli-responsive methods for controlling the drug access to and from the nanopores such as pH, temperature, light, magnetism, enzyme, redox agents, etc. These gatekeepers include inorganic nanoparticles, organic molecules, biological macromolecules and supra molecular assemblies, which can keep guest molecules in the pores until they are removed by external stimuli. Grafting suitable gatekeepers onto the surface of mesoporous silica can prevent the premature release of the cargo before reaching the target. These methods range from coating the nanoparticles with polymers to controlling individual nanopores with molecules that undergo large-amplitude motions to the immobilization of small molecules on the pore opening by chemical method. The latter offers the highest degree of control because the "gatekeeper" molecules are bonded covalently inside or at the entrances of the nanopores. When modulating the properties such as morphology, particle size, pore channel functionalization and gatekeeper modifications obviously promise a better candidate for drug delivery application.

Herein, we have synthesized hydrophobically modified spherical MCM-41 nanovalve system in a multi-step synthesis strategy. The conventional sol–gel synthesis method was adopted for the synthesis of mesoporous spherical MCM-41 and the pore openings have been modified using TMSPA in dry toluene. Further the pore channels were hydrophobically tailored using PTMS after the surfactant removal. 5-Fu and famotidine were loaded into the modified channels and the drug delivery was carried out under *in vitro* condition at pH 4. We have compared the results obtained from hydrophobically modified drug delivery system with the nanovalve having unmodified pore channels synthesized from spherical MCM-41 under similar experimental conditions. To the best of our knowledge there are no studies regarding hydrophobically modified MCM-41 nanovalve systems for controlled drug delivery applications.

2. Experimental

2.1. Reagents and materials

Tetramethylorthosilicate (TMOS), cetyltrimethylammonium bromide (CTABr), N-[3-(trimethoxysilyl)propyl]aniline (TMSPA), phenyltrimethoxysilane (PTMS), 5-fluorouracil (5-Fu), famotidine, β-cyclodextrin (β-CD) and anhydrous toluene were purchased from Sigma–Aldrich. All chemicals were used as received without further purification.

2.2. Synthesis of spherical MCM-41

The spherical MCM-41 has been synthesized using an earlier procedure with suitable adaptation [9]. In a typical synthesis, CTABr (3.52 g, 9.65 mmol) was dissolved in 800 g of methanol/water (50/50∼w/w) mixture containing 4 g of 1 M sodium hydroxide solution. After stirring for 1 h, TMOS (1.32 g, 8.68 mmol) was added to the homogenous solution with constant stirring. Immediately a white precipitate was formed and was allowed to stir for 8 h at room temperature, subsequently aged for overnight at static condition. The white precipitate was filtered off, washed several time with water, and ethanol then dried at 50 °C for 24 h.

2.3. Surface functionalization of spherical MCM-41

Functionalization process was carried out using previously reported procedure [12,14]. As-synthesized spherical MCM-41 (1 g) was functionalized with TMSPA (0.135 g, 0.53 mmol) in dry toluene at reflux temperature for 24 h under inert atmosphere. The functionalized material was filtered and washed with toluene and dichloromethane, then dried under vacuum for overnight at 60 °C. The surfactant extraction was carried out [22] using conc. HCl (3 g, 36%) in 100 ml ethanol per gram of spherical MCM-41. The mixture was stirred at 60 °C for 24 h. The surfactant removed spherical MCM-41 was filtered, washed with water and ethanol, further dried under vacuum at 60 °C for overnight. The TMSPA functionalized and surfactant removed spherical MCM-41 was named as P-MCM-41. PTMS functionalization on the inner surface of P-MCM-41 was carried out in a similar way as discussed previously. 1 g of dried P-MCM-41 was taken in 100 ml of toluene and 1 ml of PTMS was injected and further refluxed for 24 h. After the surface treatment, the solid was filtered, washed and dried overnight in vacuum at 60 °C and named as PP-MCM-41.

2.4. Drug loading and release

5-Fu loading was carried out as per our previous reports [12,14]. A stock solution was made by dissolving a known amount of 5-Fu in water (10 mg/ml). 100 mg of P-MCM-41/PP-MCM-41 nanocontainer was mixed with 12 ml of drug solution. The suspension was stirred for 24 h at room temperature and the pH of the solution was adjusted to 7 before the addition of β-CD (220 mg). The mixture was allowed to stir for another 72 h after that the β-CD capped nanocontainer was filtered off, washed with water and absolute ethanol, dried overnight at 60 °C under vacuum. The β-CD capped systems were named as PA-MCM-41 and PPA-MCM-41, respectively for P-MCM-41 and PP-MCM-41. The above procedure was followed for loading of famotidine except a methanolic stock solution was used instead of water (methanol/water, 50/50∼w/w). The amount of drug loading was determined by UV–Visible spectroscopic analysis. *In vitro* drug release experiments were carried out by placing 100 mg of drug loaded material in a dialysis membrane bag (molecular weight cut-off 5000 KDa) and immersed it into 20 ml of water (pH adjusted to 4 with aqueous solution of