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Amine-functionalized mesoporous silica KIT-6 as a controlled release drug delivery carrier

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ABSTRACT

Mesoporous silica KIT-6, has been prepared through the sol-gel method followed by a chemical modification using 3-aminopropyl triethoxysilane (APTS) to obtain KIT-6-NH_2 as a drug delivery carrier. The mesostructure properties was fully characterized by transmission electron microscope (TEM), N_2 sorption isotherm, Fourier transform infrared (FT-IR), low-angel X-ray diffraction (XRD) and small-angel x-ray scattering (SAXS). Loading of ketoprofen (KP) and 5-flurouracil (5-FU) drugs as models into KIT-6 and KIT-6-NH_2 was studied using quartz crystal microbalance (QCM) and UV–visible spectroscopy. The loading uptake and release behaviors of KP and 5-FU were highly dependent on the textural properties of KIT-6 and KIT-6-NH_2. The release of drugs was carefully studied in simulated gastric fluid (pH 2) and in simulated intestinal fluid (pH 7.4). First order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas release kinetic models were applied to the experimental data and the release was found to obey a first-order rate kinetic.

1. Introduction

Mesoporous materials synthesized by the surfactant-templated method, resulting in highly ordered arrays of one-dimensional (1D), two-dimensional (2D) and three-dimensional (3D) channels. One of them, is mesoporous silica, has attracted much attention of scientists because of their outstanding features such as high surface area, high porosity, well-ordered structure, tunable pores, and non-cytotoxic properties [1,2]. Remarkable efforts have been devoted towards the development of mesoporous silica towards their practical applications as advanced catalysts, adsorbents, sensors, optical waveguides, electrochemical battery components/electrode materials and biomedical drug carriers [3–5]. Therefore, mesoporous silica materials with large pore diameters are considered good candidates as drug delivery system (DDS) for carrying high dosages of a variety of drugs in their mesopores by systematic tuning the pore sizes using different templates to improve the accommodation of large sized-drug molecules [6]. In addition, the presence of silanol groups can be further functionalized with different organic groups to modify the surface properties to induce favorable surface-drug interactions, which will in turn result in improved loading capacity for the drug molecules [7].

In 2001, mesoporous silica, MCM-41 was first reported as a DDS of ibuprofen drug [8]. In DDSs, the successful deliver of precise quantities of drugs to the targeted cells or tissues in a controlled release manner to enhance drug efficiency [9,10] have been considered as one of the most promising applications for human health care and represent a field for biomedical materials science [11–13]. Release of different kinds of drugs from mesostructured silica materials has been studied so far. For example, synthesis of mesoporous silica, SBA-15 inside a macroporous bioactive glass-ceramic scaffold of the type SiO_2–CaO–K_2O was reported by Cauda et al. [14] to combine the bioactivity of the latter with the release properties of the former, in view of local drug delivery of ibuprofen. They demonstrated that ibuprofen loading percentage onto SBA-15-scaffold (33%) was found to be almost five times higher than that of the scaffold alone. Vallet-Regí et al. [15] demonstrated the release of ibuprofen, erythromycin [16] and alendronate [17] from SBA-15 by using different strategies to modify the control of drug release. Tamanoi et al. [18] reported the release of camptothecin as anti-cancer drug from mesoporous silica nanoparticles fluorescent mesoporous silica nanoparticles

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(FMSNs) and confirmed the drug release inside of various cancer-cell lines.

Very recently, Wojciech Chrzanowski et al. [19] reported the use of organically functionalized MCM-41 with CdS nanoparticle of surface area 941.0 $m^2 g^{-1}$ and pore diameter 2.3 nm as a DDS for vancomycin drug. They demonstrated that the loading/release mechanism was found to depend on the electrostatic interaction between the drug molecules and the linker derivatized mesopores. In addition, loading of alendronate into MCM-41 and SBA-15 matrices modified with propylamine groups ($PrNH_2$) was carefully studied and it was found to be 14% and 8%, respectively [20]. It was proved that the surface areas and mesopore sizes would have combined effects on the release kinetics. The release of alendronate drug from the MCM-41-modified $PrNH_2$ groups of 3 nm in diameter was found to obey first order rate kinetics, whereas release from SBA-15-modified $PrNH_2$ groups of 9 nm in diameter showed a linear or zero order rate kinetics. The loading/release mechanism of alendronate drug was investigated to be an electrostatic attraction. Furthermore, SBA-15 and SBA-15/poly(*N*-isopropylacrylamide) functional hybrid was employed as a DDS for atenolol drug [21]. The remarkable surface area (326 $m^2 g^{-1}$), pore volume 0.484 ($cm^3 g^{-1}$), and pore diameter (3.76 nm) made the functional hybrid a good candidate for trapping atenolol drug into the porous structures of the silica network with a loading capacity of 60%. They concluded that the efficiency of atenolol DDS is influenced by volumetric contraction of poly(*N*-isopropylacrylamide).

Moreover, carboxylic-modified mesoporous silica has been extensively studied as a DDS, as well. In this regard, trimethylsilyl-carboxyl bifunctionalized SBA-15 (TMS/COOH/SBA-15) with high content of carboxyl groups up to 57.2% was synthesized by Yao Xu et al. [22]. The obtained TMS/COOH/SBA-15 exhibited a surface area of 359 $m^2 g^{-1}$, pore diameter 4.2 nm, and total pore volume 0.436 $cm^3 g^{-1}$ was studied as a carrier for controlled release of drug famotidine. By tuning the content of carboxyl groups, the loading capacity for famotidine was reached to about 50%. However, the post-treating drug-loaded COOH/SBA-15 with hexamethyldisilazane, a controlled famotidine release of 80% of loading was achieved. Similar studies were demonstrated by Popova et al. [23]. They synthesized MCM-41 and SBA-15 functionalized with carboxylic groups for a higher degree of loading sulfadiazine drug reached to ~50–52 wt%. They explained that the drug release process was mainly depends on the carboxylic functionalization rather than the pore size. Thus, the pore diameters with the subsequent addition of organic function groups greatly enhance the loading and release of drug molecules and hence its kinetics. It is well known that KIT-6 has pores diameter relatively more than SBA-15. KIT-6 and functionalized KIT-6 have been studied extensively in many interesting applications such as, adsorption [24], sensor [25] and catalyst [26]. However, there is less attention has paid to the use of KIT-6 in DDS, thus our work originally provides a new application of mesoporous silica KIT-6.

Herein, we present synthesis of KIT-6 and KIT-6-NH_2 for controlled drug delivery application of analgesic drugs for the first time to the best of our knowledge. The loading capacity and release of KP and 5-FU as anionic drugs models were studied by QCM and UV–visible spectroscopy. Based on spectroscopic measurements and theoretical calculations, the amine functionalized KIT-6 is very crucial for drug loading/release properties due to the hydrogen bonding interaction with the carboxylic and carbonyl groups of the drug molecules. The release kinetics of KP and 5-FU drugs from functionalized KIT-6 were investigated by applying first order, Higuchi, Hixson–Crowell and Korsmeyer–Peppas release kinetic models.

2. Experimental section

2.1. Chemicals

Tetraethylorthosilicate (TEOS, 98%) (Sigma-Aldrich). Triblock poly(ethylene oxide)-*b*-poly(propyleneoxide)-*b*-poly(ethyleneoxide) copolymer Pluronic® P123 (Sigma-Aldrich), 3-aminopropyl triethoxysilane (APTS, MP biomedicals), butanol (HPLC grade, Fisher), propanol (99%) (ADWIC, Egypt), toluene (HPLC, Tedia), hydrochloric acid (35%) (ADWIC, Egypt), methylene chloride (ADWIC, Egypt), potassium dihydrogen phosphate (ADWIC, Egypt), sodium hydroxide (ADWIC, Egypt), potassium chloride (ADWIC, Egypt), sodium polystyrene sulfonate (PSS, Aldrich), polydiallyldimethylammonium chloride (PDDA, Aldrich), Ketoprofen (Alexandria for chemicals manufacturing, Egypt) and 5-flurouracil (Sigma-Aldrich). All raw chemicals were purchased and used without any further purification.

2.2. Preparation of KIT-6 and KIT-6-NH_2

KIT-6 was synthesized based on sol-gel method according to the previous report [27]. Typically, hydrochloric acid (12 g, 35%) was added to 6.0 g of Pluronic® P123 dissolved in 220 mL distilled water. After the dissolution, the mixture was added in *n*-butanol (6.0 g) and stirred at 35 °C for 1 h until a clear solution was obtained. Then 12.48 g TEOS was added dropwise with stirring into the homogenous clear solution and continue stirring at room temperature for 24 h. After that, the solution was refluxed at 100 °C for 24 h. Finally, KIT-6 was successfully obtained. The sample was then filtered and washed with copious distilled water, and finally dried in air at room temperature and calcined at 550 °C as shown in Scheme 1.

The functionalization of KIT-6 with $PrNH_2$ groups to obtain KIT-6-NH_2 was performed by post-grafting method [28]. In this preparation, 1.00 g of KIT-6 was added to 7 mL of APTS. The mixture was added to a 50 mL dry toluene and refluxed for 6 h as shown in Scheme 1. The mixture was extracted by methylene chloride for 24 h and the KIT-6-NH_2 was then successfully obtained. The sample was dried in an oven under air atmosphere for 24 h. The formation mechanism of KIT-6-NH_2 was proposed according to Scheme 1.

2.3. Preparation of KP and 5-FU solutions

A stock solution of 0.82 mg L^{-1} of KP was prepared by dissolving 0.055 g in a 100 mL of propanol, then complete the flask to 500 mL by phosphate buffer at pH 4. Following the same procedure, a stock solution of 0.96 mg L^{-1} of 5-FU was prepared by dissolving 0.047 g in a 100 mL of propanol/water mixture then complete the flask to 500 mL by phosphate buffer at pH 4. Scheme 2 shows the molecular structure of KP and 5-FU.

2.4. Preparation of different buffer media (pH 7.4, 6.7, 2)

Phosphate buffer solutions (pH 7.4, 6.7 and 2) was prepared by addition 50 mL of 0.2 M potassium dihydrogen phosphate (KH_2PO_4) to 39.5 mL of 0.1 M NaOH, 23.7 mL of 0.1 M NaOH and 1.5 mL of 0.1 M NaOH respectively, followed by the addition of deionized water till 200 mL. A buffer solution of pH 2 was prepared by the addition of 50 mL 0.2 M KCl to 13 mL of 0.2 M HCl and the total volume was completed to 200 mL by deionized water.

2.5. QCM measurements for drugs loading and experimental setup

QCM technique was used to investigate the adsorption behavior of KIT-6-NH_2 sample. The KIT-6-NH_2 film was monitored by mounting a resonating quartz crystal in the cap of the