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Mesoporous silica as a support for poorly soluble drug: Influence of pH and amino group on the drug release

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ABSTRACT

Two different structures of mesoporous silica materials (MSMs), MCM-41 and MCM-41-NH_2, were studied to investigate their suitability for drug delivery systems (DDS). The synthesized mesoporous materials were used as hosts for encapsulation of artesunate (ART) drug. The artesunate, an experimental anticancer drug, was incorporated in both hosts by two methods, mixing and high pressure methods. These new drug delivery systems were characterized by scanning electron microscope (SEM), N_2 sorption isotherm, X-ray diffraction (XRD) and Fourier transform infrared (FT-IR). Loading of ART as models into MCM-41 and MCM-41-NH_2 was studied using thermogravimetric analysis (TGA) and UV-visible spectroscopy (UV-Vis). The loading uptake and release behaviors of ART were dependent on the textural properties of MCM-41 and MCM-41-NH_2. The release of drug was carefully studied in different pH (7and7.4). The effect of the synthesized hosts and ART@mesoporousdrug deliveries on MCF-7 human breast cancer cell line viability was evaluated. Both hosts alone revealed no toxicity to MCF-7 cancer cells. But, ART@MSMs indicated an inhibition of cell livability, when compared to the non-encapsulated drug. These results indicate the application of the MCM-41 mesoporous material for drug loading, and delivery into cancer cells to impel cell death.

1. Introduction

Drug delivery by means of controlled release technology began in the 1970s and has continued to expand so that nowadays numerous products, both on the market and in development [1]. Majority of the failures in new drug development have been attributed to poor water solubility of the drug. Issues associated with poor solubility can lead to low bioavailability resulting in suboptimal drug delivery. With the advent of various insoluble drug delivery technologies, the challenge to formulate poorly water soluble drugs could be achieved. In traditional pharmaceutical formulations, large doses are generally administered to the patients to reach therapeutic levels of the drug. In contrast, new formulation approaches based on drug delivery systems (DDS) with an engineered biodistribution profile may be exploited to overcome problems related to side effects, insufficient drug concentration at targeted sites, rapid metabolization or drug degradation [2,3]. Current technology for controlled drug delivery is mainly based on the use of micron or submicron matrices of polymers, nanoparticles, Liposomes, dendrimers and quantum dots that they contained problems related to aggregation of lipophilic polymeric nanoparticles upon its intravenous administration causing embolism or local toxicity, low stability under thermal and chemical conditions [4]. These problems could be overcome by materials such as porous materials, such as mesoporous silica [5,6], zeolites [7,8] and metal organic frameworks [9].

Among porous materials, one system that can adjust such extensive multifunctionality is mesoporous silica materials (MSMs) due to their high surface area, large pore volume, stable and tunable pore size, and easy functionalization [10]. The surfactant-templated synthesis of MCM-41 (Mobil Composition of Matter No. 41) material was first synthesized at Mobil in 1992 [11], but MCM-41 was not considered in biomedical studies until 2001 when it was first used as a support for DDS [12]. The control of drug loading and its release properties in MSMs depend on pore diameters, pore volumes, particles morphology and surface modifications [13]. Modification of MSMs with organic functional groups is an important method.

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Two different methods were used for functionalizing of MSMs: co-condensation and post synthesis grafting [14].

The ideal drug delivery system should be biodegradable, biocompatible, mechanically strong and capable of achieving high drug dosage form. Many examples of drug molecules loaded into MSMs have been reported in the literature [15–17]. In recently years, MCM-41 was used for loading of Ibuprofen, Piroxicam, Atenolol, Sodium-alendronate, Rythromycin and Aspirin [13,18,19]. In addition, many anticancer drugs, such as Doxorubicin and Camptothecin, have also been studied for controlling release using MSMs [20]. Various drug loading methods use stirring in drug solution or suspension, immersion for long times till equilibrium is reached, using vacuum, emulsion formation, gravimetric method [21], passive or mixing method [22], pressure method [1] and solvent evaporation to contain drug within the carrier [21]. Usually, pressure method was used for drugs with poor water solubility and the simple mixing method is a general method for all drugs. This drude material interaction is responsible for the adsorption and delivery of the drug. Therefore, modifications of the pore wall of the support or changes of the drug will affect drug adsorption and delivery [23].

The drug release rate for such mesoporous systems depends on a large number of parameters, such as: support structural properties, drug features, properties of the simulated biological fluid interacting with the drug-linker-support system, release conditions and modify the support surface properties by binding functional organic groups. However, there are some primary ways for releasing drug in the system: diffusion, degradation and swelling followed by diffusion. There are several mathematical and mechanistic models available in the literature to describe the drug release profile [24–26]. In the rigid mesoporous systems, the diffusion and possible chemical control of the release process dynamics is reported. The reports indicated that the loading/release mechanism depend on the electrostatic interaction between the drug molecules and the linker derivatized mesopores. On the other hand, the surface areas and mesopore sizes have combined effects on the release kinetics [25,26]. The solubility of the drug and its dissolution in the solvent media, both influence the drug release kinetics. A first order release kinetics are generally obtained from a porous matrix [27,28].

In this study, we present the results obtained with two different synthetic structures of mesoporous silica materials, MCM-41 and MCM-41 modified with aminopropyltriethoxysilane (APTES) functional groups (MCM-41-NH_2), and their suitability as drug delivery systems for the anticancer drug artesunate. One of the insoluble drugs is artesunate that is a semi-synthetic derivative of artemisinin. In addition to the efficacy of ART in malaria treatment, it is cytotoxic to cancer cells and multidrug resistant tumor cells. More than 70 cell lines from different tumor types like breast cancer have been reported to be prevented by artesunate and its related compound artemisinin [29]. The artesunate was chosen as a model drug due to its small molecular size, good pharmacological activity [30]. In addition, it has a carboxyl group that can interact with surface silanol groups or amino groups on the pore walls from MCM-41 and MCM-41-NH_2, respectively. Two methods, pressure and simple mixing methods, was used for loading drug in mesoporous silica materials. The effect of the artesunate concentration in both mesoporous silica materials was studied. These new DDS was characterized by different methods (FTIR, XRD, BET, UV–Vis, SEM, and elemental analysis). The effect of the mesoporous silica materials and artesunate@mesoporous DDS was evaluated on MCF-7 human breast cancer cell viability.

2. Experimental section

2.1. Materials

3- Aminopropyltriethoxysilane (APTES, Sigma-Aldrich), tetraethoxysilane (TEOS, Sigma-Aldrich), hexadecyltrimethylammoniumbromide (CTAB, Sigma-Aldrich), NaOH (Merck) and artesunate (sigma) were used as received.

2.2. Synthesis of MCM-41and MCM-41-NH_2

The MCM-41 material was synthesized by a room temperature method with some modification in the described procedure in the literature [20]. We used tetraethylorthosilicate (TEOS:Merck, 800,658) as a source of silicon and hexadecyltrimethylammoniumbromide (HDTMABr; BOH, 103,912) as a surfactant template for preparation of the mesoporous material. The molar composition of the reactant mixture is as follows:

1CTAB:7.564TEOS:2.551NaOH:4652H_2O

The solution was stirred for 2 h until a white product formed. The product was filtered and washed with deionized water. It was then dried at room temperature for at least 72 h. The dried product was heated with air to 550 °C for 6 h to decompose of surfactant. The prepared sample is called MCM-41. The MCM-41-NH_2 was prepared by post synthesis grafting of the APTES on MCM-41. The post synthesis grafting method involved mixing 1 g of calcined MCM-41and 1.6 g APTES in 50 ml toluene at 60 °C for 1 h. The resulting sample was filtered, washed with dichloromethane and dried in an oven at 80 °C for 2 h [31]. MCM-41 surfactant-free and MCM-41-NH_2 was used for loading the drug. The formation mechanism of MCM-41-NH2 was proposed according to Scheme 1.

2.3. Artesunate loading and release

Artesunate was loaded in MCM-41 and MCM-41-NH_2 matrices at a weight ratio of 1.5:10, by the following two ways. The amount of drug loading in the mesoporous silica matrices was performed by TGA. In simple mixing method, the artesunate drug was dissolved in DMSO and then the silica matrices was added with magnetic stirring for 24 h at 25 °C. Prepared sample was maintained for 1 h at room temperature then was dried for 12 h at 60 °C. In the drug loading under high pressure method, artesunate and MCM-41 matrices were mixed and put into a high-pressure adsorption equipment at 30 MPa and 298 K for a period over 24 h. After being washed with deionized water to remove the unentrapped drug, the powders were dried in a vacuum oven at 65 °C for 6 h. The prepared sample with simple mixing method, is called ART@MCM-41/SM and ART@MCM-41-NH_2/SM. The prepared sample with high pressure method, is called ART@MCM-41/HP and ART@MCM-41-NH_2/HP. The formation mechanism of ART@MCM-41-NH2/HP and ART@MCM-41/HP was proposed according to Scheme 1.

For release profiles, the loaded hosts that included 300 μg artesunate, were placed in 2 mL phosphate buffer solution with pH = 7 and 7.4 at 37.4 °C, separately. The contents were shaken, and centrifuged with 3000 rpm for 4 min and solution were removed at regular intervals of time. The aliquots were analyzed for artesunate with UV–visspectroscopy at λ = 235 nm. The amount of released aetesunate was calculated using equation (1):

$$C_{t,corr} = C_t + \frac{v}{V}\sum_{0}^{t-1} C_t \quad (1)$$