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Functionalized silica nanoparticles as a carrier for Betamethasone Sodium Phosphate: Drug release study and statistical optimization of drug loading by response surface method

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ABSTRACT

Mesoporous silica nanoparticles with a hexagonal structure (SBA-15) were synthesized and modified with (3-aminopropyl) triethoxysilane (APTES), and their performance as a carrier for drug delivery system was studied. Chemical structure and morphology of the synthesized and modified SBA-15 were characterized by SEM, BET, TEM, FT-IR and CHN technique. Betamethasone Sodium Phosphate (BSP) as a water soluble drug was loaded on the mesoporous silica particle for the first time. The response surface method was employed to obtain the optimum conditions for the drug/silica nanoparticle preparation, by using Design-Expert software. The effect of time, pH of preparative media, and drug/silica ratio on the drug loading efficiency was investigated by the software. The maximum loading (33.69%) was achieved under optimized condition (pH: 1.8, time: 3.54 (h) and drug/silica ratio: 1.7). The in vitro release behavior of drug loaded particles under various pH values was evaluated. Finally, the release kinetic of the drug was investigated using the Higuchi and Korsmeyer–Peppas models. Cell culture and cytotoxicity assays revealed the synthesized product doesn't have any cytotoxicity against human bladder cell line 5637. Accordingly, the produced drug-loaded nanostructures can be applied via different routes, such as implantation and topical or oral administration.

1. Introduction

Controlled drug delivery systems can prevent the side effects of the conventional dosage such as potential degradation and toxic effects of the drug [1]. Further, in this method the drug dosage and its frequency can be adjusted [2]. In drug delivery systems, the physicochemical properties of the drug affect the performance of the release [3]. Controlled drug delivery systems have some potential advantages. The first one is avoiding patient compliance problems, which are based on the psychological and physical condition of the patient. Sometimes patients forget the drug taking at a necessary time interval or do not follow the treatment, and therefore the therapy would be ineffective. The second advantage is a smaller amount of drugs would be used, and so the synthesis and preparation of drugs would be less expensive. Finally, the efficiency of treatment could be improved by controlling the conditions and minimizing the side effects [4,5]. Biocompatibility and capacity of drug loading are important characteristics of drug carriers. In addition, these materials must be properly designed to avoid premature release from the host.

Polymers have been used as carriers in drug delivery systems for many years. However, there are some limitations such as the premature degradation of the therapeutic agent, poor chemical and thermal stability, destruction of the polymeric system, and rapid excretion through the system. Mesoporous silica, such as SBA-15, is solid materials, which are comprised of a honeycomb-like porous structure with hundreds of vacant channels (meso pores) that are capable to adsorb/encapsulate relatively large amounts of bioactive molecules. The distinctive properties, such as high surface area, large pore volume, tunable pore size with a narrow distribution (2–10 nm), plentiful surface silanol groups (around 30 mol%), hexagonal porous channel arrangement and excellent chemical and thermal permanence, of these materials make them potentially appropriate for a variety of controlled release applications [6–9].

The release of the drug molecules depends on the pore size of the silica, which can result in a prolonged or burst release. Moreover, by making alterations to the silica pore size and structure, and chemical modification of the mesoporous silica surface, it is possible to control the drug absorption and release [10–12]. Accordingly a lot of researches

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have been done on the use of rope like SBA-15 in the field of drug delivery systems. A variety of drugs, such as ibuprofen, vitamin B1 and amoxicillin have been used in their studies [10–15]. Application of silica particles with the size of 700 nm to 4 μm by injection method has been reported in the literature previously [16–18]. Accordingly, the synthesized SBA-15 with the particle size of ~1 μm can be used by subcutaneous injection. Furthermore, histopathological studies by researchers proved that impregnated reservoirs of SBA-15 exhibit benign local biocompatibility and macrophages showed little or no toxicity from the SBA-15 particle. Thus, mesoporous silica particles with excellent biocompatibility are the attractive candidates for a wide range of biomedical purposes [19,20].

According to these unique properties SBA-15 [21], in this paper amine functionalized SBA-15 have been synthesized and characterized. To study its drug delivery behavior, Betamethasone Sodium Phosphate an anti-inflammatory synthetic corticosteroid drug that has broad applications in the treatment of disorders ranging from asthma, dermatitis, and musculoskeletal disorders was selected [22]. The influence of various parameters on drug loading process on modified SBA-15 is investigated and the preparative conditions are optimized by the response surface method. A literature review revealed that the loading and optimization of the preparative conditions for this type of drug delivery system of the response surface method is novel and has not been reported previously.

2. Experimental

2.1. Materials

Triblock copolymer Pluronic P123 $[(EO)_{20}(PO)_{70}(EO)_{20}]$ as a template for synthesis of SBA-15 was purchased from Aldrich. Tetraethylorthosilicate (TEOS), 3-aminopropyltriethoxysilane (APTES), toluene, n-hexane and dichloromethane were obtained from Merck. Betamethasone disodium phosphate (BSP) was obtained from DaruPakhsh Company. Toluene and n-hexane were refluxed over sodium with benzophenone as an indicator and distilled under nitrogen atmosphere before use. Distilled water was used during the experiments.

2.2. Synthesis of SBA-15

SBA-15 material was prepared according to our previous work [13] using Pluronic 123 as a structure-directing agent and TEOS as the silica source.

First, 4.0 g of Pluronic was dissolved in a mixture of 30 g of water and 120 g of 2 M HCl aqueous solution at 35 °C. Then 8.50 g of TEOS was added into the solution at 35 °C and the mixture was stirred for 20 h. The suspension was kept for 24 h at 80 °C without stirring. The white precipitate was filtrated, washed repeatedly and air-dried at room temperature. The resultant sample is denoted as SBA-15(SY). The template was removed from the as-made SBA-15 by calcination at 550 °C for 6 h. This sample is denoted as SBA-15.

2.3. Physico-chemical characterization

UV–vis spectroscopy measurements were done by Helios Alpha Double-beam UV–vis scanning spectrophotometer for drug release. The FT-IR spectra of the samples were recorded with FT-IR (Perkin-Elmer, 580 B) in the range of 400 to 4000 cm^{-1} at room temperature from KBr pellets. The morphology of the samples was recorded using a scanning electron microscope (Cambridge S-360). Transmission electron microscopy (TEM) images were obtained with a Philips EM 208. Carbon, hydrogen and nitrogen contents of the samples were determined (CHN techniques) using a Vario EL III elemental analyzer. Nitrogen adsorption–desorption isotherms were obtained at 77 K and vapor pressure of 88.51 kPa using an OMNISORP (TM) 100CX VER 1 G adsorption apparatus; Samples were out gassed at 393 K for at least 8 h in vacuum prior to measurements.

2.4. Modification of SBA-15 by APTES

In order to prepare functionalized SBA-15 type mesoporous silica with amine groups, 3.0 g of dry SBA-15 (dried at 110 °C for 24 h) was introduced into 50 mL of a solution containing 2.4 g of (3-aminopropyl) triethoxysilane (APTES) in dried toluene, under magnetic stirring. The mixture was refluxed at 110 °C for 48 h under nitrogen protection. After 48 h the product was washed with toluene, n-hexane and dichloromethane. Afterwards, the samples were dried at 25 °C for 24 h. This material is denoted as SBA-15-NH_2. The surface modification of SBA-15 is schematically shown in Fig. 1A.

2.5. Preparation of drug loaded silica nanoparticles

2.5.1. General procedure

Silica particles were loaded with drug by soaking them into an acidic buffer solution containing BSP, under continuous magnetic stirring at room temperature (28 °C). Subsequently, BSP loaded samples were centrifuged (4000 rpm, 10 min) and the residue was washed with distilled water before drying for 3 h at 50 °C in an oven. The drug loading efficiency (DL%) was calculated by Eq. (1):

$$DL\% = \frac{m_2 - m_1}{m_3} \times 100 \quad (1)$$

where m_1 is the weight of the drug in the solution after loading, m_2 is the initial weight of the drug in the solution and m_3 is the initial weight of SBA-15. The adsorption of BSP on SBA-15-NH_2 is schematically shown in Fig. 1B.

2.6. Drug loading optimization via response surface method

Response surface method (RSM), as a generic means of optimization, was applied to optimize the drug loading on SBA-15-NH_2 through a decreased number of the experiments. The optimization was designed based on three factors with a total of 28 experimental runs that involved 5 factorial points. Based on the previous studies, three parameters, pH, time, and drug/silica weight ratio, were identified as key factors affecting the drug loading. Further, based on the preliminary experiment we concluded that the adsorption of betamethasone occurred only in acidic pH ($pH < 5$). The drug dissolution experiments showed that in the concentration range of drug loading process (5–20 mg/mL), the betamethasone dissolved in water at pH higher than 1.8. Accordingly the loadings have been done in the pH range between 1.8 and 4.2. The results were analyzed using Design-Expert software (Version 8.0.7.1, 2011; Stat-Ease, Minneapolis, MN). The significance of the model and the regression coefficients were estimated by analysis of variance (ANOVA) combined with the application of Fisher's F-test as well as Student's T-test at a probability P value of 0.05.

2.7. In vitro release experiments

In order to study the release of BSP from SBA-15, 30 mg of the drug loaded silica particles was put in an interpenetrating membrane and immersed in 70 mL buffer solutions under magnetic stirring. The following buffer solutions were used: PBS (pH 7.2–7.4), acetate buffer (pH 4.8) and hydrochloric acid/potassium chloride buffer (pH 1.2). At predetermined time intervals, 4 mL of each extracted solution was analyzed by UV–vis spectroscopy at a wavelength of 242 nm. This amount of the solutions was immediately replaced with an equal volume of the dissolution medium to keep the volume constant.