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Amine bridges grafted mesoporous silica, as a prolonged/controlled drug release system for the enhanced therapeutic effect of short life drugs

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ABSTRACT

Hybrid mesoporous silica SBA-15, with surface incorporated cross-linked long hydrophobic organic bridges was synthesized using stepwise synthesis. The synthesized materials were characterized by elemental analysis, infrared spectroscopy, nuclear magnetic resonance spectroscopy, nitrogen adsorption, X-rays diffraction, thermogravimetry and scanning and transmission electron microscopy. The functionalized material showed highly ordered mesoporous network with a surface area of 629.0 $m^2 g^{-1}$. The incorporation of long hydrophobic amine chains on silica surface resulted in high drug loading capacity (21% Mass/Mass) and prolonged release of ibuprofen up till 75.5 h. The preliminary investigations suggests that the synthesized materials could be proposed as controlled release devices to prolong the therapeutic effect of short life drugs such as ibuprofen to increase its efficacy and to reduce frequent dosage.

1. Introduction

Among porous materials, mesoporous silica (SiO_2) has attracted much attention in the recent years due to their highly ordered porous network, extremely high surface area 1500 $m^2 g^{-1}$, large pore volume and tunable/uniform pore and particle size. The high surface silanol (Si—OH) density of these materials permits the tailoring of the surface properties such as hydrophilicity, and binding of molecular entities. The surface functionalization of SiO_2 with organic molecules is emerged as one of the most important research areas in the field of advanced functional materials [1]. The versatile nature of mesoporous SiO_2 attracted great deal of attention in various applied fields such as adsorption [2], catalysis [3], drug and gene delivery [4,5], imprinting for molecular recognition [6] *etc.*

Controlled release systems have been devised to enable superior control of drug exposure over time, to assist drug in crossing physiological barriers, to shield drug from premature elimination, and to shepherd drug to the desired site of action while minimizing drug exposure elsewhere in the body. These carriers systems may also increase patient compliance by reducing frequency of administration, and may add commercial value to marketed drugs by extending patent protection. Mesoporous silica materials have been intensively investigated as a carrier for controlled and targeted drug release, gene and enzyme immobilization [7–9], enabling them to retain their activity after reaching to the specific targeted site. These materials have the significant advantage of being free from various biochemical attacks and bioerosions. In addition to their high drug loading capacity and controlled/sustained release pattern, their biocompatible and nontoxic nature has attracted a great deal of research attention for various controlled release systems [10].

The physiochemical properties, such as surface charge, surface topography of biomaterials has great influence on its biocompatibility [11,12]. In mesoporous silica the surface exposed silanol group (about 6% of the total of the particles) can interact with cellular membrane lipids and proteins [13]. Mesoporous silica would rapidly associate with serum opsonin, and then could be removed from circulation by macrophages in reticuloendothelial system (RES) after entering into the blood stream [14]. Some studies also suggest that surface modification plays pivotal role in altering the surface reactivity, improving the biocompatibility and increasing *in vivo* circulation time [15]. The *in vitro* cellular uptake and cytotoxicity, *in vivo* biodistribution and excretion of mesoporous SiO_2 can be regulated by surface modification with functional groups such as amino (—NH_2), carboxyl (—COOH), phenyl (—Ph), and methyl phosphonate (—PO_3^-) groups [14]. Modified mesoporous SiO_2 with amino groups, could manipulate the particle endocytosis [15].

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Among mesoporous silicas, SBA-15 with large surface area up to 1500 $m^2 g^{-1}$, pore volume (~1.5 $cm^3 g^{-1}$) and facile surface modification promise great opportunities to obtain functional biomaterials with improved and tailored properties [16]. The large pore diameter of this silica is also important and beneficial for accommodation of large molecular weight enzymes and proteins. SBA-15 has two-dimension hexagonal pore channels that allow loaded drug molecules to directly diffuse outwards. Moreover, both the opposite potential and the similar hydrophilicity between silica and drug molecules also favor the sustained/prolonged release of drugs. Compared to the negatively charged silica, the positive-charge modified silica materials exhibited remarkably sustained release profiles [17].

Drug loading, generally is a quite complex issue and much efforts were focused on improving drug loading capacity and prolonged therapeutic effect. Surface modification is one of such ways to achieve high drug loading capacity and prolonged/controlled release over an extended time period. Similarly, the diffusion rate of the drug molecules depends on the carrier type [18]. Ibuprofen is an extensively prescribed analgesic and anti-inflammatory drug with a relatively narrow therapeutic range that rapidly eliminate from the body. The efficacy of this drug would be enhanced by protecting it from physiological degradation before absorption. The structure of ibuprofen contains one carboxylic acid group, which can form the stronger bonding with many functional groups such as amines *via* acid base reaction. Ibuprofen has been also reported as a model drug to study the loading and release profiles from porous systems such as mesoporous silica based carriers. The good pharmacological activity and the suitable molecule size of about 1.0 × 0.6 nm [19], ensures its easy diffusion into or out of the mesoporous channels of mesoporous silica. Thus the efficacy of this drug would be enhanced by loading it to mesoporous channels of silica to protect it from physiological degradation before absorption.

Hence the aim of this work is to synthesize mesoporous silica SBA-15 with hydrophobic organic functionality for controlled release of ibuprofen. For this purpose modified silica, SBA-15TPA with long hydrophobic chains of tetraethylenepentamine (TPA) was synthesized and tested for the *in vitro* controlled release of ibuprofen. The sustained/controlled release capacities of the ibuprofen-loaded materials were investigated. The structure and synthesis route of functionalized silica is illustrated in Scheme 1.

2. Experimental

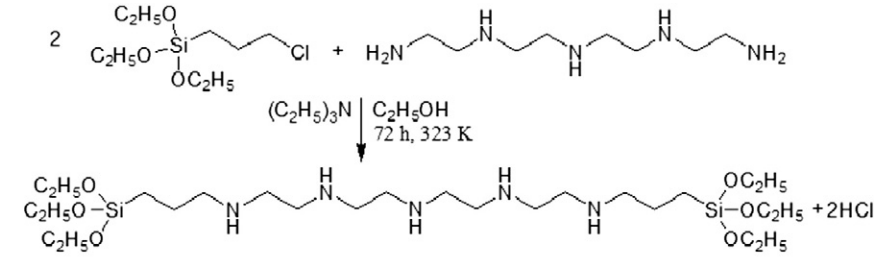
2.1. Reagents

All reagents and solvents were of analytical grade and used as received. Tetraethylorthosilicate (TEOS), 3-chlropropyltriethoxysilane, tetraethylenepentamine (TPA), co–block polymer Pluronic $P_{123,}$ sodium hydroxide (NaOH), sodium chloride (NaCl), sodium bicarbonate ($NaHCO_3$), sodium carbonate (Na_2CO_3), potassium chloride (KCl), potassium phosphate dibasic trihydrate ($K_2HPO_4 \cdot 3H_2O$), magnesium chloride hexahydrate ($MgCl_2 \cdot 6H_2O$), calcium chloride ($CaCl_2$), sodium sulphate (Na_2SO_4), and tris(hydroxymethyl)aminomethane ($NH_2C(CH_2OH)_{3,}$ were Sigma Aldrich products. Ethanol, Xylene and HCl were Synth products. Ibuprofen (IBU) was donated by Galena Pharma Campinas-Brazil and deionized water was used throughout the experiment.

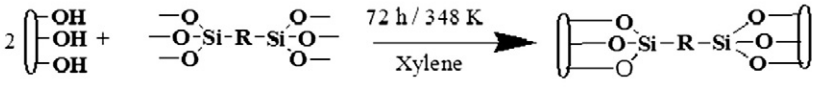
2.2. Synthesis of mesoporous silica

Mesoporous silica SBA-15 was synthesized according to a reported method [20]. Briefly, for the synthesis of 1.0 g of SBA-15, 2.0 g of surfactant polymer Pluronic P_{123} was dissolved in 12.0 cm^3 of deionized water at 313 K, followed by the addition of 60.0 cm^3 of hydrochloric acid (2.0 mol dm^{-3}) and the solution was stirred for 4 h. After this step, 4.0 g of TEOS was added drop wise on stirring and the resulted white suspension was kept in an autoclave for crystallization, under static conditions in a polypropylene bottle for 24 h at 373 K. The white suspended SBA-15 silica was then filtered, washed several times with deionized water and dried at room temperature and calcined in air at 873 K for 6 h to remove the template.

To obtain amine grafted SBA-15TPA silica, 36.0 mmol (5.4 cm^3) of 3-chloropropyltriethoxysilane was reacted with 18.0 mmol (3.4 cm^3) of tetraethylenepentamine in 50.0 cm^3 of ethanol. This mixture was stirred for 72 h at 323 K under anhydrous nitrogen atmosphere. The resultant bridged silylating agent (Scheme 1) was then transferred to a three-necked round bottom flask, containing 1.0 g of the prepared SBA-15 (calcined), suspended in xylene. The reaction mixture was kept on stirring under dry nitrogen for another 72 h at 348 K and the



Step 1



SBA-15 Bridged monomer (R) SBA-15TPA

Step 2

Scheme 1. Step 1; Synthesis of amine bridges and step 2: immobilization of the synthesized amine bridges on silica surface.