



Light-sensitive intelligent drug delivery systems of coumarin-modified mesoporous bioactive glass

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ARTICLE INFO

Article history:

Received 18 September 2009

Received in revised form 20 January 2010

Accepted 5 February 2010

Available online 10 February 2010

Keywords:

Mesoporous bioactive glass

Photo-controlled

Drug delivery system

Light-sensitive intelligent

ABSTRACT

Functionalized mesoporous bioactive glasses (MBG) with photoactive coumarin demonstrates photo-responsive dimerization resulting in reversible gate operation. Coumarin-modified MBG was used as a drug delivery carrier to investigate drug storage/release characteristics using phenanthrene as a model drug. Irradiation with UV light (>310 nm) induced photo-dimerization of the coumarin-modified MBG, which led to the pores' closing with cyclobutane dimers and trapping of the guest phenanthrene in the mesopores. However, irradiating the dimerized-coumarin-modified MBG with shorter wavelength UV light (~250 nm) regenerates the coumarin monomer derivative by the photo-cleavage of cyclobutane dimers, such that trapped guest molecules are released from the mesopores. The structural, morphological, textural and optical properties are well characterized by X-ray diffraction, transmission electron microscopy, N² adsorption/desorption, and UV-visible spectroscopy. The results reveal that the MBG exhibits the typical ordered characteristics of the hexagonal mesostructure. The system demonstrates great potential in light-sensitive intelligent drug delivery systems and disease therapy fields.

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1. Introduction

Since the discovery of bioactive glasses (BG) by Hench et al. [1], various types of BG, ceramics and glass-ceramics have been widely developed and investigated for bone and tooth repair and replacement [2–4], because such materials can chemically bond to and integrate with both living soft and hard tissue in the body by the formation of a biologically active apatite layer at the implant–tissue interface, without inducing toxicity, inflammation or immune response [5,6]. Because of these properties, these biomaterials have been used in a variety of medical applications, such as implants in clinical bone repair and regeneration materials, bioactive coatings of metallic implants in tissue engineering, such as the bioactive coating of metallic implants, clinical tissue regeneration and tissue engineering, drug delivery capabilities, biomimetics, treatments and protein and/or cell activation [1–15]. When implanted in the human body, these bioactive materials can develop an amorphous calcium phosphate layer and then crystallize to hydroxycarbonate apatite on the surface of the tissue [1].

Recently, a new family of biomaterials has been developed, called mesoporous bioactive glasses (MBG), beginning with pioneering

work by Yan et al. [16]. Yan and coworkers successfully synthesized highly well-ordered MBG with higher specific surface area and pore volume compared with conventional BG. This new family of MBG exhibits enhanced bioactive behavior with even faster apatite phase formation than conventional BG [11–18]. Subsequently, Chang et al. reported a drug delivery system (DDS) using well-ordered MBG as the carrier [19].

In recent years, many types of materials, including inorganic silica, carbon materials and layered double hydroxides [20–23] and polymers [24,25], have been employed as DDS. Inorganic mesoporous silica materials have garnered increased interest, with particular attention to drug storage and release of the host. Since 2001, when Vallet-Regi first proposed MCM-41 [20] as a DDS, silica-based materials such as SBA-15 and MCM-48 have been studied as drug carriers and controlled release systems. The advantageous characteristics of mesoporous silica materials for the utilization of controlled release are due to the unique characteristics and structure of the surface, including the stability of the stable ordered pore network, high pore volume and surface area, adjustable pore size and easily functionalized surface modification of specific locations for delivery [13,20]. Modified mesoporous silica material is a well-studied material [26], and the latest research has made much progress [27].

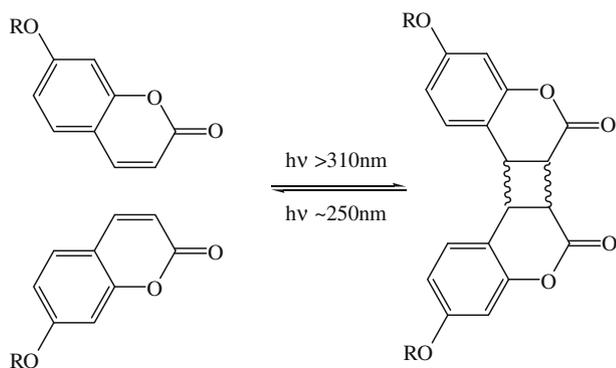
Controlled release from mesopores is an interesting topic. Various stimuli-responsive substrate systems responding to tempera-

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ture, pH, electrical field, chemicals and UV light have been employed to build novel DDS [2,28–31]. DDS that modulate drug release as a function of the specific stimuli intensity are called “intelligent” and can work in open or closed gate [32–34]. Light-sensitive inorganic substrate systems that can help achieve improved control of the loading and release of guest substances have been highlighted recently [35–40]. Light-sensitivity is an attractive phenomenon for developing advanced DDS capable of precise external modulation of the site. Recently, Ferris et al. [41] and Mal et al. [42] demonstrated the photo-responsive pore size control of mesoporous silica by azobenzene and coumarin modification. Azobenzene groups are toxic according to the Federal Drug Administration, and this limits the application of such DDS to topical formulations. Thus, coumarin groups may be better than azobenzene for photo-responsive pore size control of biomaterials. Coumarin (Scheme 1) was first reported and isolated in the 1820s, recognized as the hay-like sweet aroma of the tonka bean [43]. Ciamician and Silber [44] first discovered the photo-dimerization reactions of coumarin in 1902, but the photo-cleavage reaction was not discovered until the 1960s, when Krauch et al. [45] further studied the photo-dimerization reaction. In Scheme 1, under UVA irradiation ($\lambda = 320\text{--}400\text{ nm}$), the [2 + 2] cycloaddition of a couple of coumarin moieties takes place to form a cyclobutane ring. After irradiation by UVC light ($\lambda = 200\text{--}280\text{ nm}$), the coumarin photo-dimers can be cleaved and regenerate the former coumarin moieties. Several studies related to synthesis of the intermolecular reversible photo-dimerization and photo-cleavage of coumarin derivatives have been reported for polymers and MCM-41 [46,47]. However, there has been no report on the drug release properties of well-ordered coumarin-modified MBG.

In the present paper, the synthesis of a novel coumarin functionalized MBG material is reported. This biomaterial may have potential use in a variety of medical applications, such as implants in clinical bone repair and regeneration materials, and bioactive coatings of metallic implants in tissue engineering and so on. It shows a stable mesoporous structure, a large pore volume and pore diameter, and a large specific surface area with a large number of Si–OH groups on the surface, which is suitable for loading drug molecules and possessing high drug sustained release properties. This material with an “open–close door” system can be used in the photo-switched controlled release of included compounds. Irradiation with UV light ($>310\text{ nm}$) induces the photo-dimerization of coumarin to close the pore with a cyclobutane dimer (Scheme 1). Guest molecules such as phenanthrene can neither enter nor escape from the individual pores of the MBG. However, irradiation with shorter wavelength UV light ($\sim 250\text{ nm}$) cleaves the coumarin dimer to regenerate the coumarin monomer, the pores are opened, and the guest molecules can be released. This material with an “open–close double doors” system can be used in the photo-switched controlled release of included compounds.



Scheme 1. The photoreversible dimerization-cleavage reaction of coumarin derivative.

2. Materials and methods

2.1. Preparation of MBG

MBG was prepared by a modified procedure using the following molar composition of the gel in the presence of poly(ethylene glycol)-block-poly(propylene glycol)-block-poly(ethylene glycol) (P123) as a structure directing agent by the sol–gel process [48]. In a typical synthesis, 3.00 g P123 as surfactant (Aldrich) was dissolved in 30 mL distilled H₂O and 90 mL 2 M HCl (37% aqueous, Aldrich) and stirred at 37 °C for ~ 1 h until clear. Then 8.5 g tetraethoxysilane (Acros) (TEOS) and 9.64 g CaNO₃·4H₂O (98.5%, Showa) were added, and the solution was stirred for 24 h. The resultant product was filtered, washed and dried at 110 °C for 12 h. This sample was an as-synthesized MBG sample. Calcined MBG was obtained by the calcination of the as-synthesized MBG at 700 °C for 3 h.

2.2. Preparation of 7-[(3-triethoxysilyl)pentyl]oxy]coumarin

5-Bromo-1-pentene (Acros) (8.23 mL, 66 mmol) was added dropwise under dry nitrogen to a stirred mixture of 7-hydroxycoumarin (Sigma) (5.0 g, 30 mmol) and anhydrous potassium carbonate (5.8 g, 41 mmol) in dry acetone (150 mL). The resulting mixture was then boiled under reflux for 5 h, after which it was allowed to cool. The potassium carbonate was filtered off and washed with fresh acetone. The solvent was removed *in vacuo* and the resulting product was purified by recrystallization from ethanol. The yield was $>90\%$ 7-pentenyloxy coumarin (1) (Scheme 2) according to ¹H and ¹³C NMR spectra: δ_{H} (400 MHz, CDCl₃) 1.86 (2H, d, 3'-CH₂), 2.21 (2H, d, 2'-CH₂), 3.96 (2H, d, 1'-CH₂), 4.98 (1H, dd, 5' = CH₂) and 5.04 (1H, dd, 5' = CH₂), 5.83 (1H, ddt, 4'-H), 6.20 (1H, d, 3-H), 6.73 (1H, d, 8-H), 6.88 (1H, dd, 6-H), 7.33 (1H, d, 5-H) and 7.61 (1H, d, 4-H); δ_{C} (400 MHz, CDCl₃) 27.9 (C-3'), 29.8 (C-2'), 67.6 (C-1'), 101.2 (C-8), 112.2 (C-4a), 112.72 (C-3), 112.84 (C-6), 115.4 (C-5'), 128.6 (C-5), 137.2 (C-4'), 143.5 (C-4), 155.7 (C-8a), 161.2 (C-7) and 162.2 (C-2).

7-[(3-Triethoxysilyl)pentyl]oxy]coumarin (2) (Scheme 2) was prepared as follows. After bubbling of dry nitrogen through the toluene solution (100 mL) of 7-pentenyloxy coumarin (3.68 g, 16 mmol) and triethoxysilane (2.94 g, 17.6 mmol) for 10 min, 0.8 mL of the toluene solution (2 mM) of Pt (dvs) (platinum(0)-1,3-divinyl-1,1,3,3-tetramethyldisiloxane complex) (Aldrich) was added, and the resulting solution was stirred for 12 h at room temperature. After removal of the solvent under reduced pressure, the product obtained was used directly in the modification of MBG. This product was successfully identified as 7-[(3-triethoxysilyl)pentyl]oxy]coumarin (2) (Scheme 2) by ¹H and ¹³C NMR spectra: δ_{H} (400 MHz, CDCl₃) 1.62 (2H, d, 5'-CH₂), 1.62 (2H, d, 6'-CH₂), 1.87 (2H, d, 3'-CH₂), 2.22 (2H, d, 2'-CH₂), 4.00 (2H, d, 1'-CH₂), 5.84 (1H, ddt, 4'-H), 6.21 (1H, d, 3-H), 6.78 (1H, d, 8-H), 6.83 (1H, dd, 6-H), 7.24 (1H, d, 5-H) and 7.63 (1H, d, 4-H); δ_{C} (400 MHz, CDCl₃) 14.3 (C-7'), 18.6 (C-6'), 28.2 (C-3'), 29.9 (C-2'), 38.3 (C-5'), 67.9 (C-1'), 101.5 (C-8), 112.6 (C-4a), 113.1 (C-3), 113.4 (C-6), 128.9 (C-5), 137.6 (C-4'), 113.7 (C-4), 156.1 (C-8a), 161.6 (C-7) and 162.5 (C-2). The synthesis of these procedures is shown in Scheme 2.

2.3. Preparation of coumarin-modified MBG

Two grams of as-synthesized MBG was suspended in a solution containing 20 mL of *n*-hexane and 0.30 g of 7-[(3-triethoxysilyl)pentyl]oxy]coumarin (2) under stirring at ambient temperature for 15 min. *n*-Hexane was evaporated by a rotary evaporator at reduced pressure and 100 °C for 14 h. Then, 2 g of coumarin-modified as-synthesized MBG with surfactant was refluxed in 100 mL of ethanol containing 4 mL of conc. HCl at 80 °C for 4 h. The solid

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