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Modulation of release behaviors of methylene blue from degradable silica-methylene blue@octacalcium phosphate powders with different shell structures

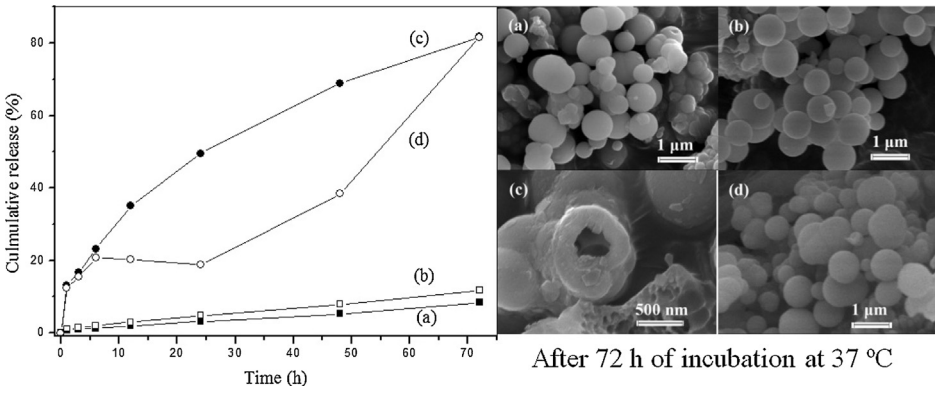
Chengfeng Li[a,*], Xiaolu Ge[b], Yadong Li[a], Jiahai Bai[a], Guochang Li[a], Changhong Su[a], Zanzhong Yang[a]

[a] School of Materials Science and Engineering, Shandong University of Technology, 255049 Shandong, PR China
[b] School of Science, Shandong University of Technology, 255049 Shandong, PR China

HIGHLIGHTS

- The coating of OCP on silica-MB was achieved by a facile sol–gel method.
- The release behavior of MB from samples was sensitive with the pH value.
- The shell structure modulated the release behavior of MB from silica-MB@OCP.
- The structure-destruction of silica-MB was promoted after the deposition of OCP.

GRAPHICAL ABSTRACT



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ABSTRACT

Methylene blue-loaded silica (silica-MB) was coated by a shell of polyethylene glycol (PEG), citrate ions and octacalcium phosphate (OCP) through a facile sol–gel method. The influences of molecular weight of PEG, addition amount of PEG and citric acid on the phase, morphology and chemical composition of samples were characterized by X-ray diffraction, scanning electron microscopy and Fourier transform infrared spectroscopy, respectively. Compared with that of silica-MB, the sustained-release behavior of MB from silica-MB@OCP was sensitive to the shell structure and the pH value of culture solution. At each time interval, the ratio of absorbance of MB monomers over that of MB dimers released from silica-MB@OCP was higher than that from silica-MB, indicating that the significant influence of interaction density among the network of PEG, citrate ions and OCP on the release behavior of MB. Silica-MB and silica-MB@OCP were degraded when MB molecules diffused to the culture solution from solid silica matrix, which would shed light on the self-destruction investigation of drug/drug carrier systems in the biological system.

* Corresponding author. Tel.: +86 533 2782232; fax: +86 533 2781665.
E-mail address: cfli@sdut.edu.cn (C. Li).

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1. Introduction

The essential features of drug/drug carrier systems included effective cellular uptake, controllable release of drug and self-destruction of drug carrier for safe excretion from the biological system [1]. The surfaces of inorganic powders, like silica and calcium phosphate, are hydrophilic and favorable for cellular uptake. Silica is generally accepted as a promising carrier due to its non-toxicity and versatile function after surface modification [1–4]. As the main inorganic component of biological hard tissues, calcium phosphate is currently used for gene delivery (transfection), luminescent labels, or luminescent drug carriers [5–9]. However, drug loading and controlled release are also limited due to the weak interactions between inorganic powders and drug molecules.

As a drug, methylene blue (MB) plays a crucial role to treat methemoglobinemia, urinary tract infections and malaria infection [10,11]. In recent studies, MB is used as an antagonist against heat-shock response gene expression in cancer cells [12] or as a photosensitizer in photochemotherapy for the treatment for tumor tissues [13–17]. Monomers and dimers of MB have distinct photochemical reactions and cancer-killing efficacies [18]. After optical pumping, the monomer in a singlet state generally undergoes intersystem crossing (ISC) to a metastable triplet state with a high quantum yield. Then, exchanged energy is transferred from the triplet MB molecule to oxygen molecule and results in the generation of singlet oxygen molecule ($^1O_2$) to exert an antiproliferative effect. MB monomer is easily reduced and oxidized in the biological media, which makes it cross membranes to treat methemoglobinemia [19–21]. Although larger affinity to negatively charged interfaces and to melanin [22,23], MB monomer was reduced easily and excreted rapidly from biological system, which resulted in its ineffectiveness to stain most of the tumor tissues and the hindrance of the widespread clinical application of MB [24]. Raising the dosage of administrated MB would cause the formation of hardly-reduced MB dimers and the serious influence on the health of normal tissues. A sustained-release of MB monomers from drug carriers could be expected to maintain its circulated concentration in blood, which would effectively improve its accumulation in tumor tissues.

The elimination of drug carrier from the biologic system is rather difficult after the accomplishment of the diagnostic or therapeutic functions, which remains as one of the major obstacles impeding potential clinical translation of drug/drug carrier systems [1,25,26]. Recently, the degradation of silica aroused great research interesting and was achieved through introducing large pores with thin pore wall and low cross-linking degree in silica matrix. For example, the degradation of silica nanospheres with mesoporous structure was complete in 24 h for samples with high specific surface area of 632 m^2/g and pore size of 10 nm [25]. Through the exposure to the iron chelates, approximately 84% of the iron(III) doped into the silica nanoshell was removed after 3 days in an 80 °C water bath, and silica samples were degraded completely after at least 17 days of culture in physiological conditions [26]. Solid silica with MB-rich nuclei degraded in two weeks after the release of encapsulated MB molecules [1]. Herein, MB molecules were firstly encapsulated in silica particles (silica-MB), followed by a deposition of octacalcium phosphate (OCP) shell on silica-MB (silica-MB@OCP) with the favor of polyethylene glycol (PEG) molecules and citrate ions. The absorbance of the supernatant in phosphate buffered saline (PBS) and lysosome-like buffer was measured and used to investigate the release behaviors of MB from hybrid powders. The occurrence of degradation in a fast rate was expected through the modulation of diffusion behavior of MB from the core–shell structured powders. The degradation of drug carriers would shed light on the self-destruction investigation of drug/drug carrier systems for their potential diagnostic or therapeutic functions to treat tumor issues.

2. Experimental

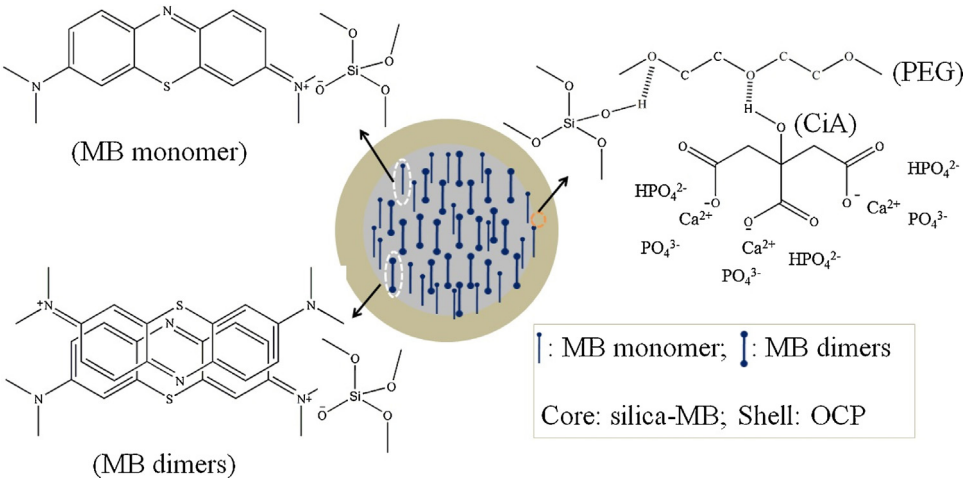
2.1. Synthesis

2.1.1. Silica-MB

Silica-MB was synthesized by a modified Stöber method [27,28]. Typically, 0.10 g of methylene blue (MB) was dissolved in 92 ml of ethanol, 13.8 ml of deionized water and 2.38 ml of aqueous ammonia ($NH_3 \bullet H_2O$) under stirring. After 15 min, 3.44 ml of tetraethyl orthosilicate (TEOS) was added and then the stirring of the reaction mixture was continued for another 4 h. Precipitations of silica-MB were collected by centrifugation, washed with ethanol twice and used to prepare a dispersion of silica-MB in 10 ml of ethanol (with a concentration of 53 mg/ml).

2.1.2. Silica-MB@OCP

The coating of OCP on silica-MB was carried out by a modified Pechini sol–gel process [27,29], which was illustrated in Scheme 1. In a typical reaction, 4.50 g of citric acid monohydrate (CiA), 2.48 g of tetrahydrate calcium nitride and 0.85 g of diammonium hydrogen phosphate were dissolved in 46.1 ml of ethanol and 138.3 ml of deionized water. The pH value of the solution was adjusted to 9 by the addition of $NH_3 \bullet H_2O$, and then 9.22 g of PEG with a



Scheme 1. The schematic illustration of the preparation of silica-MB@OCP.