

Enhanced photodynamic efficiency of methylene blue with controlled aggregation state in silica-methylene blue-acetate@tannic acid-iron(III) ions complexes



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ABSTRACT

Photodynamic therapy (PDT) is a promising alternative to traditional chemotherapy for cancer treatment. The photodynamic efficiency of PDT is closely related to the generation of singlet oxygen, which is greatly dependent on the aggregation state of photosensitizer (PS). Herein, methylene blue (MB) molecules as PSs were loaded in silica-MB via electrostatic interactions, and silica-MB was subsequently incubated in acetate (Ac) buffer solution to obtain silica-MB-Ac. Silica-MB-Ac@TA with a core-shell structure was finally prepared with an assembly of coordination complexes of tannic acid (TA) and Fe(III) ions. Compared with those values for silica-MB, cumulative amount and absorbance ratio of monomer versus dimer of MB released from both silica-MB-Ac and silica-MB-Ac@TA increased remarkably as a result of significant decrease of MB self-aggregations with aromatic-aromatic interactions. Sustained and pH-dependent release behaviors of monomeric MB were well simulated by the theoretical Higuchi model based on the Fickian diffusion. The generation of singlet oxygen, photodynamic efficiency and stability against *in vitro* reduction of monomeric MB released from silica-MB-Ac@TA were significantly higher than those for silica-MB-Ac, due to the effective control of aggregation state of MB molecules during outward diffusion through the complexes of TA and Fe(III) ions. The present investigation demonstrated a facile route to obtain high photodynamic efficiency by finely controlling the aggregation state of MB molecules.

1. Introduction

Photodynamic therapy (PDT) is emerging as a very promising alternative to traditional chemotherapy for cancer treatment, due to its ability to avoid multidrug resistance and cancer recurrence by directly damaging proteins of the pathological cells [1–4]. The PDT efficiency is highly related to light source, oxygen concentration and photosensitizer (PS) characteristics [5,6]. Methylene blue (MB) as a cost-effective PS is soluble in water and able to generate high ratio of singlet oxygen ($\Phi_{\Delta} \sim 0.5$) with strong electrophilic activation of oxidizing electron-rich double bonds in biological molecules and macromolecules [7]. Singlet oxygen is generally produced in a type II photochemical pathway of MB monomer with the excitation light in the “optical window” of 600–900 nm and the decay of its triplet state in ~ 370 ps [8–15]. With aromatic-aromatic interaction, self-aggregation reactions of MB dimers, trimers or higher-order aggregates in aqueous solution are always caused by an increase of concentration (higher than ~ 20 μM) and/or the presence of negatively charged surfaces [7,16,17]. With the

decrease of the ratio of monomer versus dimer, the production of singlet oxygen decreases extremely [15] due to a fast nonradiative decay (3–4 ps) of the excited dimer population [18].

Thus, many efforts have been devoted to control the aggregation state of MB by confining dyes inside drug vehicles through conjugation of aromatic-aromatic interaction [7,19], electrostatic interaction [12–15,20] or covalent bond with associated economic and environmental costs [11,20]. Charged aromatic MB molecules are prone to undergo short-distance aromatic-aromatic interactions with aromatic groups of polymer vehicles [7,19], depending on linear aromatic density, flexibility and amphiphilia [21–24]. Although the fraction of monomeric MB is able to be tuned through aromatic-aromatic interaction, π - π^* couples of MB and aromatic polymer would form a hydrophobic environment, which seriously reduces the efficiency of triplet energy transfer to molecular oxygen and the transfer of singlet oxygen to bulk solution, especially at a high molar ratio of MB molecule over aromatic polymer [7]. For long-range electrostatic interactions, MB molecules with positive charges are bound to negative-charged sites

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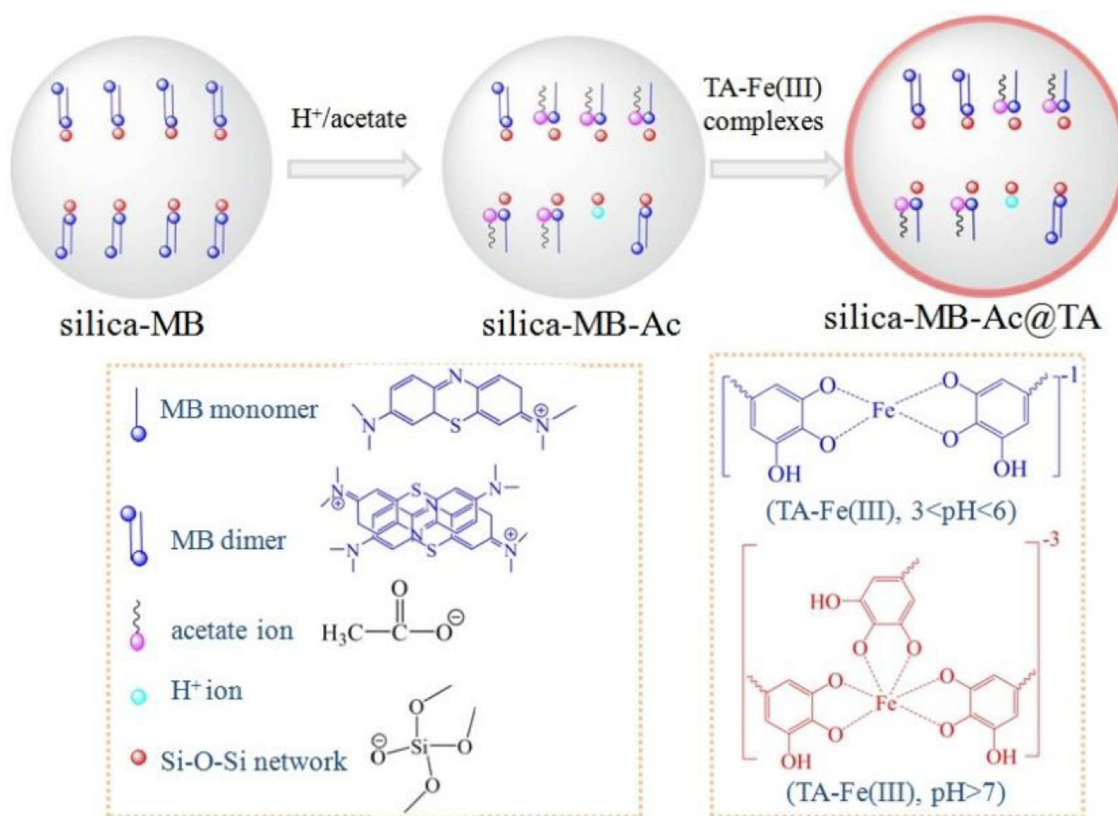
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Scheme 1. Schematic illustration of synthesis process of silica-MB-Ac@TA.

in vehicle matrix, such as polymer [7,12,15,20], zeolite [10] and silica [13,25]. However, the efficiency of triplet energy transfer is greatly minimized by self-aggregation of MB [18]. The cleavage of ion pair of MB and vehicle matrix is also extremely sensitive with ionic strength in surroundings [7]. Before these obstacles of MB molecules with electrostatic attraction in drug vehicles are adequately overcome, the aggregation state of MB can not be finely control, and thus, the efficiency of single oxygen generation will not be significantly improved.

Herein, MB molecules were firstly bound to silica vehicles through an electrostatic interaction during the precipitation of silica-MB, and then, incubation of silica-MB in acetate (Ac) buffer solution (pH = 3.6) was performed to prepare silica-MB-Ac. Encapsulation of tannic acid (TA) and Fe(III) ions complexes [26] was finally assembled on silica-MB-Ac to synthesize silica-MB-Ac@TA (Scheme 1). Immersing of silica-MB in acetate buffer solution was purposed to tune the fraction of monomeric MB in silica-MB-Ac through the influence of penetrated H⁺ and acetate ions on cooperative self-aggregation tendency of MB to increase the generation ratio of singlet oxygen [25]. The facile assembly of TA and Fe(III) ions coordination complexes on silica-MB-Ac was intended to control the aggregation state and pH-sensitized release behavior of MB from silica-MB-Ac@TA. The sustained release behaviors, absorbance ratios of monomer versus dimer, stabilities against *in vitro* reduction by ascorbic acid, generation of singlet oxygen and photodynamic efficiency for MB released from different silica vehicles were systematically compared and discussed in detail.

2. Materials and methods

All chemical reagents with analysis purity were purchased from Sinopharm. Chemical Reagent Co. Ltd. (China) and used without any further purification. All aqueous solutions were prepared with doubly-distilled and de-ionized water.

2.1. Synthesis of silica-MB, silica-MB-Ac and silica-MB@Ac

A modified Stöber method was employed to synthesis silica-MB [27,28]. Typically, a mixture solution containing 92 ml of ethanol, 17.20 ml of water, 2.48 ml of NH₃·H₂O and 0.10 g of MB was prepared under stirring for 15 min. 3.44 ml of tetraethoxysilane (TEOS) was subsequently added to the mixture solution and stirred for another 4 h. Precipitations of silica-MB were collected by centrifuge, and washed with 100 ml of ethanol twice. Colloidal solution of silica-MB or silica-MB-Ac was prepared by dispersing washed silica-MB precipitations in 20 ml of water or acetate buffer solution, respectively. After incubating for 1 min, sedimentations were collected by centrifuge and dried at 70 °C for 24 h to obtain silica-MB or silica-MB-Ac powders. In addition, 20 ml of aqueous suspension of silica-MB-Ac was also prepared by dispersing final product collected by centrifuge of colloidal solution of silica-MB-Ac. Acetate buffer solution containing 3.2 mM of acetic acid and 2.8 mM of sodium acetate was used to prepare colloidal solution of silica-MB-Ac.

TA and Fe(III) ions complexes were assembled on the surface of silica-MB-Ac by a one-step assembly method [26]. Firstly, FeCl₃·6H₂O solution (Fe(III) ions solution, 10 mg/ml) was prepared and its pH value was then adjusted to 2.80 by addition of NH₃·H₂O. Then, 0.90 ml of Fe(III) ions solution was mixed with 5 ml of aqueous suspension of silica-MB-Ac prepared as mentioned above. After 1 min, 0.90 ml of TA solution (40 mg/ml) was added and the mixture was stirred for another 4 min. Finally, 100 ml of phosphate buffer saline (PBS, pH = 7.2–7.4) was added and the stirring was continued for 5 min. The products were collected by centrifuge, and washed with ethanol and water twice to remove excess TA and Fe(III) ions. The remaining powders were dried at 70 °C for 24 h to obtain silica-MB-Ac@TA powders.

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