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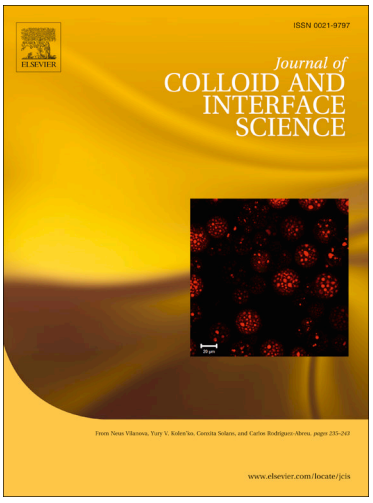

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Multiple dye-doped silica cross-linked micellar nanoparticles for colour-tuneable sensing of cysteine in an aqueous media and living cells

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Abstract: This work demonstrated the design and synthesis of multiple dye-doped silica cross-linked micellar nanoparticles (MD-SCMNPs) by encapsulating three organic dyes (fluorescein derivative (FCD), coumarin derivative (HCE) and Rhodamine b (RhB)) in SCMNPs cores for colour-tuneable sensing of cysteine (Cys) in aqueous media and in living cells. In the presence of Cys, HCE exhibited blue emission, and RhB exhibited purple emission, while FCD reacted with Cys and exhibited green fluorescence "turn-on" in the core of MD-SCMNPs. This green-light-emitting sensing product may cause "step by step" fluorescent resonance energy transfer (FRET) from HCE to the sensing product and then to RhB. Based on the FRET process in the core, MD-SCMNPs can quantitatively detect Cys by a colour change with a low limit of detection (LOD) of 0.3 μM in living cells. Furthermore, MD-SCMNPs exhibited ultrasmall size (~12 nm) and excellent dispersity and biocompatibility, which could potentially be used as a visualized Cys sensor for health monitoring and disease prediction in the human body.

Introduction

Cysteine (Cys) is a vital thiol-containing biomolecule that plays important roles in many living organisms and biological processes.[1-5] The thiol of Cys is able to coordinate with many types of metal ions and metal cofactors in enzymes, which facilitate the detoxification of the human body.[6-8] In the antioxidant system, Cys is an essential structural and functional part of proteins.[5, 9-11] Due to their characteristic redox properties and nucleophilicity, abnormal levels of Cys lead to a series of syndromes and diseases.[12-14] For example, Cys deficiency hinders the production of the tripeptide, which results in many health problems, such as slow growth in children, hair depigmentation, liver damage, muscle and fat loss, skin lesions, edema, lethargy, and weakness.[2, 15-17] Moreover, depressed levels of Cys are associated with the dysfunction of intracellular antioxidant glutathione and disturbance of anti-inflammatory and neuroprotective properties in brain cells,[9, 18] leading to neuropsychiatric disease.[9, 19, 20] Therefore, it is very important to detect Cys in the human body for health monitoring and disease prediction.

A variety of analytical methods including high-performance liquid chromatography (HPLC), capillary electrophoresis, spectrophotometry, voltammetry, and mass spectrometry (MS) have been conducted to address the specific detection of Cys.[21] Compared with various reported analytical methods, fluorescent methods have attracted much more attention due to its fast test speed, low cost, high sensitivity and relative operational simplicity.[22-24] A large number of organic fluorescent probes have been synthesized and designed to detect Cys based on specific chemical reactions between the active groups of probe and the amino or thiol groups of Cys.[1, 25 26, 27] For example, Wu and co-workers synthesized a boron dipyrromethene probe for fluorescent sensing of Cys based on a Michael addition reaction between thiol groups and double bonds.[25] Wang and co-workers induced a classical spirolactone-opening reaction between Cys and the fluorescein-derived probe, which exhibited a fluorescence "turn-on" sensing process.[28] Miao and co-workers reported inter-charge transfer (ICT)-based fluorescent probes, which possessed two potential reaction sites for the discrimination of Cys and GSH by ratiometric quantification.[29] However, most of the above-mentioned organic fluorescent probes exhibited disadvantages including low fluorescence quantum yield, weak resistance to photobleaching, narrow excitation, and especially poor solubility in aqueous solutions, which largely limited their application for in vivo sensing in biological fields.[30, 31]

As one of the most effective strategies to develop Cys fluorescent sensors for biological systems, the method is commonly used to incorporate fluorescent sensing species with inorganic nano-structured scaffolds. For instance, organic probes and upconversion nanoparticles have been encapsulated into core-shell[2] and York-shell nanostructures[32] for the construction of Cys fluorescent nanosensors with excellent selectivity in serum and living cells. Moreover, to make the sensing signal as obvious as possible, two quantum dots have been incorporated into nonporous silica nanoparticles for the visual detection of Cys in serum.[33] However, the above-mentioned nanosensors of Cys possessed relatively large sizes of more than 100 nm, which may lead to biodegradation and elimination after use in the human body. [34-37] Therefore, it is crucial to design and synthesize a Cys nanosensor with ultrasmall size to obtain excellent biocompatibility, water-compatibility and nontoxicity for in vivo sensing. [38-40]

Recently, silica cross-linked micellar nanoparticles (SCMNPs) have been induced as a nanoscaffold to overcome this issue.[41] Compared to the above-mentioned nanostructures, SCMNPs exhibited a diameter of 12 nm, smaller than the aforementioned particles. In addition, SCMNPs exhibited a superior mesostructured hydrophobic core, which could be