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A supramolecular curcumin vesicle and its application in controlling curcumin release

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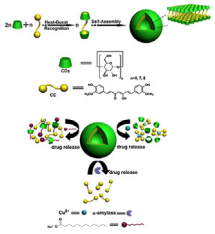
HIGHLIGHTS

- A supramolecular curcumin vesicle, which can greatly enhance curcumin solubility, is prepared by different cyclodextrins and curcumin in aqueous solution.
- The morphologies and sizes of the vesicles were identified by TEM, SEM, AFM and DLS.
- The mechanism of the vesicle formation was studied with various methods.
- Curcumin could be controllably released by the addition of external stimuli into the vesicle solution.

GRAPHICAL ABSTRACT

We designed a supramolecular curcumin vesicle based on different curcumin-cyclodextrin amphiphiles, which could greatly enhance the aqueous solubility of curcumin up to 7000-fold. The vesicles existed for about one month in aqueous solution at around 20 °C, showing a certain colloidal stability. Curcumin vesicles were also prepared when different host molecules were employed as the hydrophilic heads of the supramolecular amphiphiles. Finally, curcumin could be controllably released with the disruption of the vesicles when the external stimuli, including competitive guest molecules, enzymes and copper ions were added into the vesicles system.



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ABSTRACT

Curcumin is a safe and nontoxic natural potential antitumor drug. However, its extremely low aqueous solubility severely limits its clinical application. We designed a supramolecular curcumin vesicle based on different curcumin-cyclodextrin amphiphiles, which could greatly enhance the aqueous solubility of curcumin up to 7000-fold. The vesicles can exist for about one month in aqueous solution at around 20 °C, showing a certain colloidal stability. The curcumin-β-cyclodextrin vesicles were identified by transmission electron microscopy (TEM), scanning electron microscopy (SEM), atomic force microscopy (AFM), and dynamic light scattering (DLS). X-ray diffraction (XRD), Fourier transform infrared spectroscopy (FT-IR), UV–vis spectrum and ^{1}H NMR were further employed to study the formation mechanism of the vesicles. Curcumin vesicles were also prepared when different host molecules were employed as the hydrophilic heads of the supramolecular amphiphiles. Finally, curcumin could be controllably released with the disruption of the vesicles when the external stimuli, including competitive guest molecules, enzymes and copper ions were added into the vesicles system.

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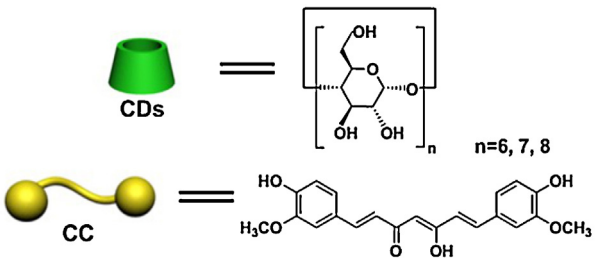
1. Introduction

Curcumin (CC, Scheme 1), which is a yellow natural diphenolic compound derived from turmeric (*Curcuma longa L.*), has been proven to possess potential antitumor activity [1]. Also, it is nontoxic, even when used in a high dose. However, its insolubility in aqueous solution (11 ng/mL) has limited its widespread clinical application [2]. Different CC drug delivery approaches, including nanoparticles, liposomes, microemulsions, and polymer conjugate, were prepared to improve its solubility [3]. Those approaches can enhance the solubility of CC, but the tedious synthesis and preparation process increase the difficulty for practical application and may reduce CC biocompatibility. The solubility should be markedly improved before CC can be applied as an efficient antitumor drug. The strategy of loading CC on supramolecular vesicles may be a good solution to this problem.

Vesicles, which enclose a volume with membranes consisting of bilayers or multilayers, are extremely useful in the fields of cell membrane mimicking [4], nanoreactors [5], template synthesis [6], and gene or drug delivery [7]. The morphologies of vesicles can be tuned through responding to the external stimuli (such as light [8], pH [9], ions [10], electrons [11], and enzymes [12]). This property gives this soft material a promising application in controllable self-assembly and target release. The supramolecular vesicles, which can be constructed through non-covalent interactions, including host guest recognition [13], π–π stacking [14], electrostatic forces [15], and charge transfer [16], can quickly respond to external stimuli. This advantage makes it a unique material in supramolecular chemistry, especially in the field of drug delivery.

The supramolecular vesicles cannot only encapsulate hydrophilic drugs in the cavity of the vesicle but also encapsulate hydrophobic drugs in the membrane of the vesicle. Recently, Wang and his coworkers reported a supramolecular vesicle system based on pillar(6)arene and ferrocene derivatives for drug delivery [17]. They encapsulated hydrophilic mitoxantrone into the cavity of the vesicle. The obtained vesicles can release loaded drugs by responding to the stimulus of low-pH and have more effective anticancer activity than free mitoxantrone. Our team previously reported vesicles prepared from cyclodextrin derivatives [18]. Hydrophobic paclitaxel was embedded in the membrane of the vesicle. The obtained vesicles can be disrupted through responding to pH or copper ions and exhibited a better anticancer effect than natural paclitaxel. However, the above strategies do not make full use of the drug loading space in the building block of the vesicles, since the cavities of host molecules can still load a large number of hydrophobic drug molecules. Recently our team found that cyclodextrin derivatives can directly form amphiphiles with drugs, which can further construct supramolecular vesicles in aqueous solution [19].

Here, we designed a supramolecular CC vesicle prepared by CC with cyclodextrin (CD, Scheme 1). Although there are many reports about CD/CC complexes or CC loaded liposome systems [20], CD/CC supramolecular vesicles are rarely reported. As a class of α-1,4-linked cyclic oligosaccharides, CD can be divided into α-, β-, and γ-CD according to repeating glucose units number, six, seven, and eight respectively [21]. CD, a truncated cone molecule with a hydrophobic cavity and hydrophilic outside surface, is widely used as the host molecule in supramolecular chemistry because of its low price, water-solubility, biocompatibility, and easy functionalization [22]. In this work, CD encapsulated CC to form supramolecular amphiphiles, which further self-assembled into CC vesicles in aqueous solution. This strategy can greatly increase CC aqueous solubility up to 7000-fold, since the solubility of CC in aqueous solution is about 3×10^{-8} mol/L and the strategy of loading CC in β-CD/CC vesicles can increase CC solubility to 2×10^{-4} mol/L. Also, the obtained vesicles can exist for about one month in aqueous solution at around 20 °C, showing a certain colloidal stability. In addition, different host molecules can be employed as the hydrophilic hosts of the supramolecular amphiphiles in constructing the CC vesicles. Finally, the vesicles exhibit multiple stimuli responsiveness. The vesicles morphologies were disrupted with the CC release in the presence of different external stimuli, such as competitive guest molecules, enzymes, and copper ions, thus providing a new possibility for controlling CC release.



Scheme 1. Structure of cyclodextrins (CDs: $n = 6$, α-CD; $n = 7$, β-CD; $n = 8$, γ-CD) and curcumin (CC).

2. Experimental

2.1. Materials

α-Cyclodextrin, β-cyclodextrin, γ-cyclodextrin, mono-(6-O-hydroxypropy)-β-CD, mono-(6-O-paratoluensulfonyl)-β-CD, and mono-(6-dexoy-6-amino)-CD, were triply recrystallized in distilled water and then dried under a vacuum for 12 h at 50 °C before use, They were purchased from Binzhou Zhiyuan Biotechnology Co. Ltd., China. The substitution degrees were all 1. Curcumin and all other organic reagents were of analytical quality without further purification and are all commercially available from Sinopharm Chemical Reagent Co. Ltd., China.

2.2. Analytical instruments and methods

TEM images were carried out on a JEM-100CX electron microscope from JEOL Ltd. SEM pictures were obtained with a Hitachi S-4800 scanning electron microscope. The samples for TEM detection were dropped in a copper wire mesh and stained by phosphotungstic acid. Then the samples were dried under an infrared lamp. The samples of SEM measurement were obtained by dropping the vesicle solution to the copper wire mesh and then dried and sprayed with the gold. AFM testing was conducted with a Veeco Nanoscope Multimode Ⅲ SPM and operated in tapping contact mode at the ambient temperature. The AFM sample was dropped on the smooth silicon wafer and freeze dried for 5 days. The average diameter of vesicles was recorded by DLS measurement with a Wyatt QELS Technology DAWN HELEOS instrument, which used a 12-angle replaced detector in a scintillation vial and a 50 mW solid-state laser. The water for preparation samples of DLS was filtered by a 0.45 μm filter and samples of DLS were also filtered by a 0.45 μm filter before testing. The X-Ray powder Diffraction experiment was performed on a German Bruker/D8 ADVANCE diffractometer with Cu Kα radiation. The supramolecular inclusion of β-CD and CC was prepared in the same way as the FT-IR sample. The physical mixture of host and guest was obtained by quickly mixing the powder of β-CD and CC before testing in order to avoid the formation of supramolecular inclusions. The IR spectrum was obtained on an Avatar 370 FT-IR Spectrometer with the KBr pellet method at room temperature. The solid supramolecular inclusion compound of β-CD and CC was obtained by rapid freeze drying of