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Fabrication of cyclodextrins-procainamide supramolecular self-assembly: Shape-shifting of nanosheet into microtubular structure

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ABSTRACT

Encapsulation behavior of α- and β-cyclodextrins (α-CD, β-CD) with procainamide hydrochloride (PCA) has been investigated by absorption, fluorescence, time-resolved fluorescence, proton nuclear magnetic resonance spectroscopy, scanning electron microscope, Fourier transform-infrared spectroscopy, differential scanning calorimetry, and powder X-ray diffraction techniques. Spectral results revealed that PCA forms 1:2 drug–CD_2 inclusion complexes with CDs. Novel supramolecular self-assemblies have been fabricated by inclusion complexation of PCA with α-CD/β-CD and characterized by transmission electron microscope and micro-Raman imaging. The obtained results from transmission electron microscope indicated that PCA/α-CD complex could form nano-sized particles. However, when the macrocyclic ring with six glucose units was switched into seven glucose units, the resultant PCA/β-CD complex could be self-assembled to micro-sized tubular structures. Shape-shifting of 2D nanosheet into 1D microtube by simple rolling mechanism was analyzed. Thermodynamic parameters of inclusion process were determined by Parameter Method 3 calculations.

1. Introduction

One-dimensional (1D) supramolecular aggregates from the self-assembly of functional, organic and π-conjugated molecules are fascinating because of their novel properties and potential uses in chemical and biological systems (Chandini, Klyatskaya, Ruben, Wernsdorfer, & Affronte, 2011; Chen et al., 2011; Ke, Zhan, Li, Yao, 2011; Liu, Yang, Chen, Song, & Shao, 2008; Prasanthkumar, Gopal, & Ajayaghosh, 2010; Yagai et al., 2008). Recently, tremendous research efforts have been paid at the achievement of well-defined nanostructures of supramolecules at molecular level. Naturally a multitude of biological and chemical assemblies including vesicle, tubule, fibril and viral helical coats performs numerous biochemical operations. Among them, vesicular and tubular assemblies from cyclodextrin-based building blocks have attracted many scientific and technological attentions in material sciences and medicinal chemistry (Bellomo, Wyrsta, Pakstis, Pochan, & Deming, 2004; Martin & Kohli, 2003). Cyclodextrins (CDs), a class of cyclic oligosaccharides with six to eight D-glucose units linked by α-(1→4)-glucosidic bonds, have extensively been investigated in molecular recognition and construction of versatile supramolecular architectures (Szejtli, 1998). More promising applications are possible if the CD cavities can function as independent host sites for molecular recognition when they are confined to the nanostructure. The recognition process is also a useful model of the ligands and receptors on the surface of cell membranes (Liu, Wang, Guo, & Jiang, 2009).

Recently, Hoshino, Miyauchi, Kawaguchi, Yamaguchi, & Harada (2000) reported that cyclodextrin derivative which has a cinnamoyl group as a guest part on the 6-position of cyclodextrin forms an oligomeric supramolecular structure in aqueous solution. Mandal, Das, Das, Sen Mojumdar, and Bhattacharyya (2011) observed the nanotubular aggregates of γ-CD in the presence of guest molecules like coumarin 153. Stoddart also prepared some CD-threaded polyrotaxanes and reviewed a number of CD-containing polyrotaxanes using various molecules as stoppers, which exhibited important chemical and biological functions (Nelson et al., 2004; Tseng, Vignon, & Stoddart, 2003). Park, Im, Lee, Lim, & Kim (2008) demonstrated that CD-covered dendron nanotubes can be obtained by a hierarchical self-assembly process derived from host–guest complexation between the amide dendrons with the focal pyrene moiety and functionalized CDs. However, Li and

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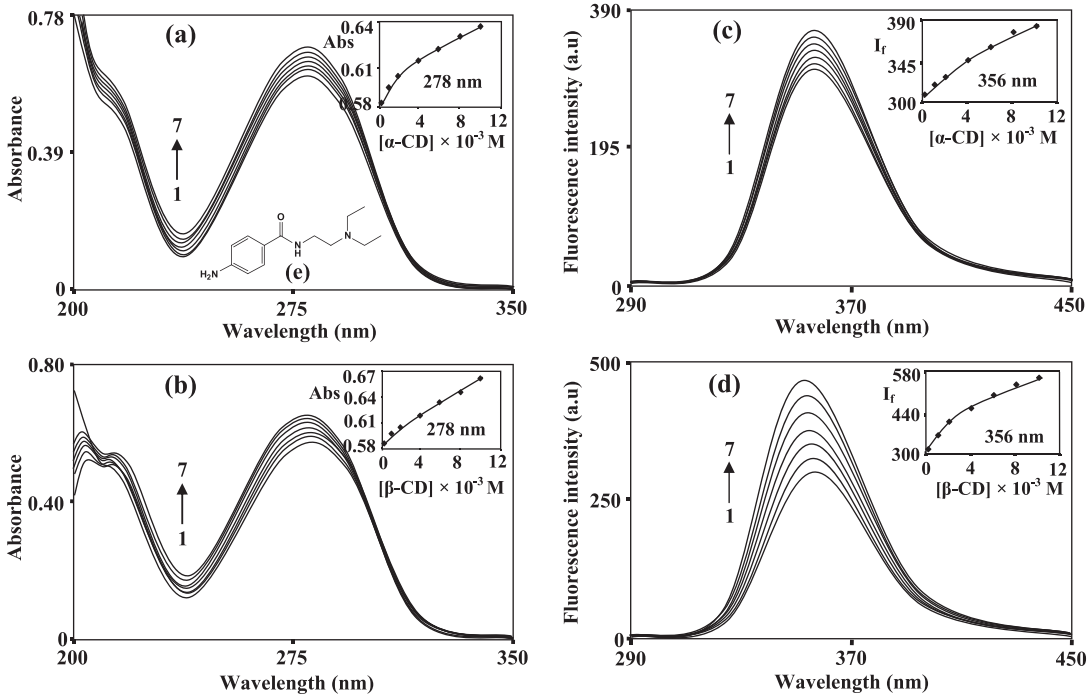

Fig. 1. (a,b) Absorption and (c,d) fluorescence spectra of SDMO in different α-CD and β-CD concentrations (M): (1) 0, (2) 0.001, (3) 0.002, (4) 0.004, (5) 0.006, (6) 0.008 and (7) 0.01. Inset Figs.: Intensity versus concentration of CD. (e) Chemical structure of PCA.

McGown (1994) reported that the rigid molecular nanotube aggregates of β-CD and γ-CD form through linkages by the rodlike molecules of all-trans-1,6-diphenyl-1,3,5-hexatriene under ambient conditions. The fabrications of shape-shifting molecular level layer sheet-like nanostructures into tubular structure have been reported (Chandrasekhar & Chandrasekar, 2012). In addition, the shape-shifting between 2D nanosheet and 1D nanotube might be reversible.

CDs are commonly used in drug formulations to improve solubility, dissolution rate, stability and bioavailability by means of the formation of inclusion complexes (Loftsson & Duchene, 2007). These CD inclusion complexes can serve as miniature models for studying the mode of action of enzymes (Villalonga, Cao, & Fragoso, 2007), targeted delivery of drugs (Victor & Sharma, 2011), mimicking the reactions in biosystems (Ukeama, Hirayama, & Irie, 1998), and so on. CD-based nanostructures have recently been developed and the useful technological advantages of CD-based nanostructures as drug carrier are; (i) high stability and improved oral bioavailability, (ii) high carrier capacity, and delivery to site specific, (iii) reduced toxicity with increase in drug efficacy, (iv) Delivery of the drug to brain and CNS overcoming blood brain barrier, and (v) feasibility of incorporation of both hydrophobic and hydrophilic substances (Dubes et al., 2003; Duchene, Ponchel, & Wouassindjewe, 1999; McCormack & Gregoriadis, 1998). In this article, we report the fabrication the supramolecular micro structures in aqueous solution by the secondary self-assembly of β-CD nanotube induced by procainamide hydrochloride drug. The self-assembled morphology was observed using transmission electron microscope (TEM) and micro-Raman imaging. We proposed a reasonable formation mechanism for the formation of the 1D microtube based on molecular modeling studies. The inclusion complexes were subsequently characterized by proton nuclear magnetic resonance spectroscopy (^{1}H NMR), scanning electron microscope (SEM), Fourier transform-infrared spectroscopy (FT-IR), differential scanning calorimetry (DSC) powder X-ray diffractometry (XRD), absorption, fluorescence emission and time-resolved fluorescence spectroscopy techniques. Procainamide hydrochloride (*p*-amino-*N*-(2-(diethylaminoethyl)benzamide hydrochloride, PCA) is a Class Ia antiarrhythmic agents (Fig. 1e), finds use in pharmaceutics as a cardiac depressant (Bigger & Heissenbuttel, 1969; Perry, 1973).

In this study, the rhombus-shaped nanosheets were fabricated through self-assembly of PCA with β-CD using water as solvent. The shape-shifting of 2D nanosheet into 1D microtube by 1:2 inclusion complexes were characterized by micro-Raman and TEM analysis. The effect of pH on nanotubes and their secondary self-assembly was also studied. Further studies on the inclusion complexes of CDs with PCA in solid state have been performed to obtain direct evidence for the formation of inclusion complex, such as ^{1}H NMR, SEM, FT-IR, DSC and XRD methods. The obtained results indicated that the solid structures of these inclusion complexes are designable by appropriately selecting type, length and functional substituent group in the guest. Parameter Method 3 (PM3) calculations were also performed for the stable inclusion complexes with least energy.

2. Materials and methods

2.1. Materials

PCA (98%), α-CD (98%) and β-CD (98%) were purchased from Sigma–Aldrich chemical company and used as received. All other chemicals and solvents used were of the spectrograde commercially available. Triply distilled water was used for the preparation of aqueous solutions.

2.2. Sample preparation

The concentration of stock solution of the drug was 2×10^{-3} M. The stock solution (0.2 ml) was pipetted out into 10 ml volumetric flasks. To this, varying concentration of CD solutions (0, 1, 2, 4, 6, 8 and 10×10^{-3} M) were added and made up to 10 ml with triply distilled water. Then the solution was kept for 6 h to bring it to a