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Nanostructures formed by cyclodextrin covered procainamide through supramolecular self assembly – Spectral and molecular modeling study

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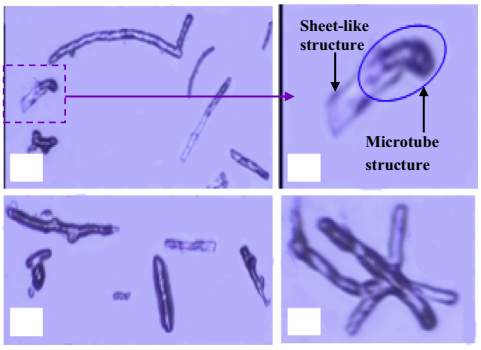
HIGHLIGHTS

- PCA forms 1:2 inclusion complex with CDs.
- Phenyl ring of the PCA drug is entrapped in the CD cavity.
- PCA/α-CD complex self-assembled to form nano particles.
- PCA/β-CD complex self-assembled to form micro tubular structure.
- Shape-shifting of 2D nanosheets into 1D microtube by simple rolling mechanism.

GRAPHICAL ABSTRACT



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ABSTRACT

Inclusion complexation behavior of procainamide (PCA) with two cyclodextrins (α-CD and β-CD) were analyzed by absorption, fluorescence, scanning electron microscope (SEM), transmission electron microscope (TEM), Raman image, FT-IR, differential scanning colorimeter (DSC), Powder X ray diffraction (XRD) and ^{1}H NMR. Blue shift was observed in β-CD whereas no significant spectral shift observed in α-CD. The inclusion complex formation results suggest that water molecules also present in the inside of the CD cavity. The present study revealed that the phenyl ring of the PCA drug is entrapped in the CD cavity. Cyclodextrin studies show that PCA forms 1:2 inclusion complex with α-CD and β-CD. PCA:α-CD complex form nano-sized particles (46 nm) and PCA:β-CD complex form self-assembled to micro-sized tubular structures. The shape-shifting of 2D nanosheets into 1D microtubes by simple rolling mechanism were analysed by micro-Raman and TEM images. Thermodynamic parameters (ΔH, ΔG and ΔS) of inclusion process were determined from semiempirical PM3 calculations.

Introduction

One-dimensional (1D) supramolecular aggregates from the self-assembly of functional, organic and π-conjugated molecules is fascinating because of their novel properties and potential uses in chemical and biological systems [1–6]. A drug delivery system is expected to deliver the required amount of drug to the targeted site for the necessary period of time, both efficiently and precisely. Different carrier materials are being constantly developed to overcome the undesirable properties of drug molecules. Amongst them, cyclodextrins (CDs) have been found to alter physical, chemical and biological properties of guest molecules through the formation of inclusion complexes [7,8]. CDs have mainly been used as complexing agents to increase the aqueous solubility of poorly water-soluble drugs and to increase their bioavailability and stability. In addition, CDs have been used to reduce or prevent gastrointestinal or ocular irritation, reduce or eliminate unpleasant smells or tastes,

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prevent drug or drug additive interactions, or even to convert oils and liquid drugs into microcrystalline or amorphous powders.

CDs are class of cyclic oligosaccharides with six to eight D-glucose units linked by α-(1 → 4)-glucose bonds, have been extensively investigated in molecular recognition and construction of versatile supramolecular architectures [9]. 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 [10].

Only very few shape-shifting molecular level layer sheet-like nanostructures into tubular structure were reported. Harada et al. [11] reported a cyclodextrin derivative which has a cinnamoyl group as a guest part on the 6-position of cyclodextrins forms an oligomeric supramolecular structure in aqueous solution. Mandal et al. [12] observed that the nanotubular aggregates of γ-CD in the presence of guest molecules like coumarin153. Stoddart et al. also prepared some CD-threaded polyrotaxanes (PRs) and reviewed a number of CD-containing polyrotaxanes using various molecules as stoppers, which exhibited important chemical and biological functions [13,14]. Park et al. [15] 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. Further, Li et al. [16] reported the formation of rigid molecular nanotube aggregates of β-CD and γ-CD through linkages by the rodlike molecules of all-trans-1,6-diphenyl-1,3,5-hexatriene using a STM under ambient conditions.

Medicinal chemistry is concerned with the understanding of chemical and biological mechanism by which the action of drug molecules can be explained. It also tries to establish relations between chemical structure and biological activity and to link the latter to the physical properties of the drug molecules. The discovery of a new and biologically important active compound usually gives rise to an extended search for closely related compounds of similar more effective, more specific or even opposite activity. In many cases, substitution of one atom or group of atoms in the parent compound (drug) results to surprising actions.

Hence, in this paper, we report the different interaction patterns of procainamide hydrochloride (PCA, 4-amino-n-[2′-(diethylamino)ethyl]benzamide HCl) with α-CD and β-CD. The rhombus-shaped nanosheets were fabricated through the self-assembly of PCA with aqueous CD solution. The shape-shifting of 2D nanosheets into 1D microtube by 1:2 inclusion complexes were characterized by micro-Raman and TEM analysis. The effect of pH on nanotubes and secondary assembly was also studied. The complexation behavior of PCA drug with CDs has been performed to obtain evidence for the formation of the inclusion complexes, such as FT-IR, DSC, powder XRD, ^{1}H NMR, SEM and TEM. PM3 method also performed for the stable inclusion complexes with least energy.

Experimental methods

Chemicals

PCA, α-CD and β-CD were purchased from Sigma and Aldrich chemical company and used as such. All other chemicals and solvents used were of the highest grade (spectrograde) commercially available.

Sample preparation

The concentration of stock solution of the PCA drug was 2×10^{-3} mol dm^{-3}. The stock solution (0.2 mL) was transferred into 10 mL volumetric flasks. To this, varying concentration of α-CD or β-CD solution (from 1.0×10^{-3} mol dm^{-3} to 1.2×10^{-2} mol dm^{-3}) was added. Solutions in the pH range 2.5–12.0 were prepared by adding appropriate amount of phosphate buffer (NaOH and H_3PO_4). Hammett acidity function values are used for below pH ∼ 1 solution (i.e., 0.1 mol/L H_2SO_4 are used). The mixed solution was diluted to 10 mL with triply distilled water of appropriate phosphate buffer solution and shaken thoroughly. The final concentration of the PCA drug in all the flasks was 4×10^{-5} mol dm^{-3}. Triply distilled water was used for the preparation of aqueous solutions.

Preparation of the solid inclusion complexes

The inclusion complex was prepared by co precipitation method. α-CD/β-CD (0.973/1.14 g) was dissolved in 40 mL distilled water at 50 °C in a water bath. PCA drug (0.25 g) dissolved in 10 mL methanol and it was slowly added to α-CD or β-CD solution with continuous agitation. The reaction vessel covered with aluminium foil and stirred continuously by magnetic stirrer for 24 h. Then the final solution was refrigerated overnight at 5 °C. The inclusion complex precipitate was recovered by filtration and washed with small amount of methanol and water to remove uncomplexed PCA drug and CDs, respectively. This precipitate was dried in vacuum at room temperature for two days and stored in an airtight bottle. The percentage yield is 70%.

Instruments

Absorption and fluorescence spectral measurements were carried out with Shimadzu UV–visible spectrophotometer (model UV 1601 PC) and Shimadzu spectrofluorimeter (model RF-5301) respectively. SEM photographs were collected on a Hitachi S3400N scanning electron microscope. The morphology of complexed PCA with α-CD/β-CD investigated by TEM using a TECNAI G^4 microscope with accelerating voltage 200 kV. Carbon coated copper TEM grids (200 mesh) was used for the TEM analysis. FT-IR spectra of the PCA drug, CD and the inclusion complexes were measured from 4000 cm^{-1} to 400 cm^{-1} on JASCO FT/IR-5300 spectrometer by using KBr pellets with 256 scans at a resolution of 4 cm^{-1}. ^{1}H NMR spectra for PCA and its inclusion complexes were recorded on a Bruker AVANCE 500 MHz spectrometer (Germany) using an inverse broadband (BBI) probe at room temperature. Samples were dissolved in DMSO-d_6 (99.98%) and were equilibrated for at least 1 h. Thermal characteristics of the solid inclusion complexes were measured using Mettler Toledo DSC1 fitted with STR^e software (Mettler Toledo, Switzerland), temperature scanning range was from 25 to 185 °C with a heating rate of 10 °C/min. PXRD patterns were recorded with a BRUKER D8 Advance diffractometer (Bruker AXS GmbH, Karlsruhe, Germany) with Cu KαI radiation (λ = 1.5406 Å), a voltage of 40 kV and a 20 mA current.

Molecular modeling studies

Theoretical calculations were carried out with Gaussian 03 software, on a Pentium microcomputer. PCA, α-CD and β-CD were constructed with the aid of Spartan 08 and then the ground state geometry optimized at PM3 level of theory. Moreover, CDs were placed on to the XY plane and the primary −OH groups were placed pointing toward the positive *Z*-axis. Inclusion complex was constructed from the PM3 optimized CDs and PCA molecules. The position of the PCA was defined by its *Z* coordinate. Inclusion complexation was evaluated by entering the substrate from one end of the CD and then letting it pass through the CDs by steps. At each step, the geometry of the complex was optimized with PM3 without any restriction. The semiempirical PM3 method has been proved to be a powerful tool in the conformational study of