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Formation of extended probe–cyclodextrin nanotubular supra structures: Endogenous surfactants triggered on-demand release

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ABSTRACT

Steady state absorption, emission, and picosecond time resolved fluorescence and transmission electron microscopic (TEM) techniques have been exploited to substantiate and characterize the formation of a substrate—anchored β-cyclodextrin nanotubular suprastructure in aqueous medium. Experimental results reveal that suprastructure is originated from a purely ground state interaction between a newly developed bisindole based drug molecule namely 3,3′-bis(indolyl)-4-chlorophenylmethane (BICPM) with β-cyclodextrin. The bound drug molecule is susceptible to be released out from the supramolecular complex in a controlled manner by the use of endogenous surfactants and is poised to serve a significant purpose in targeted drug delivery preferably at the intestinal region.

1. Introduction

The design and preparation of supramolecular nanostructures is one of the challenging fields with increasing attention because of their intrinsic scientific interest and technological applications in diverse fields like carrier for targeted drug or gene delivery, biochemical sensor, electronic or photonic material, nanoreactor etc. Self-assembly is a more friendly strategy for the preparation of the suprastructures compared to synthesizing them bond by bond. Spontaneous or induced self-assembly and chemical transformation of biological or organic subunits (molecules, macromolecules, and supramolecules) in a wide range of scientific fields are crucial subjects for the accomplishment of well defined nanostructures and the precise control of the function of supramolecules at the molecular level [1–15]. Under appropriate conditions, different types of cyclodextrin aggregates can be formed, such as catenanes [7], rotaxanes [7], polyrotaxanes [8], and threaded cyclodextrins [9] that do not involve any covalent bonding between the cyclodextrins and the other molecules. Li and his co-workers [10] found that β-CD or γ-CD can form rodlike nanotubes by including a molecule, i.e., all-*trans*-1,6-diphenyl-1,3,5-hexatriene (DPH). Agbaria and Gill [11,12] found that some oxazole molecules, such as PBD, 2,5-diphenyl 1,3-oxazole (PPO), 2,5-diphenyl 1,3,4-oxadiazole (PPD), and 2,5-(4,40-diphenyl) 1,3,4-oxazole (BBOD) can form 2:1 binary inclusion complexes with γ-CD at relatively lower concentrations. At higher concentrations, however, these inclusion complexes can form extended nanotubes [11,12].

In particular, vesicular and tubular assemblies are of much interest because of their unique characteristics as biomimetic systems. With potential applications across the food chain (in pesticides, vaccines, veterinary medicine and nutritionally-enhanced food), these nano- and micro-formulations are being developed day by day. Self-assembly of synthetic building blocks by noncovalent interactions is thus expected to provide a unique methodology for the development of supramolecular functional materials of the new generation [1,2,4,9–13]. The topic demands attention from the medical research considering the prospective application of these nanostructures for selected and targeted drug delivery.

Cyclodextrin (CD) are interesting microvessels capable of embedding appropriately sized molecules and the resulting supramolecules can serve as an excellent miniature models for nano-bio conjugates [1–4]. These conjugates are drawing much attention to the chemists as well as biologists because of its widespread application in the pharmaceutical industry; especially due to their importance as micro vessel for the selective drug delivery. Because of this particular property, CDs are able to complex various organic compounds in aqueous solution and are of special interest in pharmacology and supramolecular chemistry. Some interesting examples include trans-2-[4-(dimethylamino)styryl]benzothiazole (DMASBT), [16,17] and 3-acetyl-4-oxo-6,7-dihydro-12H indolo-[2,3-a] quinolizine (AODIQ) [18,19] which self-assemble to form extended aggregates that are supported together when included inside CD channels. These studies have successfully demonstrated the formation of chromophore-anchored supramolecular aggregates. Numerous CD-based inclusion complexes have been

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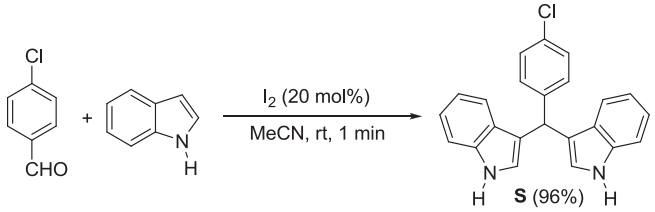
made which exhibit stimuli-responsive properties to external sources, such as heat, light, pH, and chemicals [20–22]. A detailed understanding of such host–guest interaction helps in designing a better drug delivery system coupled with increased therapeutic potential. Therefore, in recent times, supramolecular chemist have devoted considerable effort to develop systems capable of forming the drug delivery vehicle that can deliver the requisite drug to the targeted region and simultaneously to fit an option for extracting the drug in case of overdose [23].

Numerous bis(indolyl) methanes and their derivates, a new kind of aza-heterocycles, have been isolated from various terrestrial and marine natural sources. These natural products have novel structures and exhibit important biological activities [24,25]. Therefore, there is a great interest in the synthesis of the bisindole compounds, occurring naturally or not. The fluorophore, BICPM, used in the present experiment belongs to the group of such bioactive bisindole family and serving as a proper model drug. The indole nucleus seems to be a promising basis for design and synthesis of new derivatives able to fight against many health disorders including the nervous system. Very recently Yan et al. reported the potent activity of indoloquinones against the human pancreatic cancer [26]. Since most of the drug molecules are hydrophobic in character, they always look for a hydrophobic shelter. β-cyclodextrin (β-CD) bears the responsibility in the present case. Release of the drug molecules from their preferred shelter of hydrophobic CD cavity to the desired location in vivo is primary requirement to heal the sick organ. We have proposed here a simple strategy to tackle this problem by use of BICPM, a small model molecule in this experiment.

Bile salts are important naturally occurring biosurfactants with steroidal structures that play a significant role in the metabolism and excretion of cholesterol in mammals [27]. Deoxycholic acids (DCA) is one of the secondary bile acids, which are metabolic byproducts of intestinal bacteria and are transported in our enterohepatic circulation. DCA bears the responsibility of emulsification of fats for absorption in intestinal region of human body. Current research findings establishing that DCA is a immunity stimulator in our body system which can boost the so called unspecific immune system. The sodium salt of deoxycholic acid, sodium deoxycholate (NaDC) is often used as a biological detergent to lyse cells and solubilise cellular and membrane components. In the present study NaDC has been proven to be an efficient candidate for controlled release of BICPM from β-CD cavity. We believe the concept of the letter will input some novel idea for enhanced drug delivery preferably at the intestinal region.

2. Experimental section

3,3′-Bis(indolyl)-4-chlorophenylmethane (BICPM) (Scheme 1) was synthesized in the laboratory simply by condensation of 4-chlorobenzaldehyde and indole using the method mentioned elsewhere [28]. It was purified by column chromatography and the purity of the compound was checked by thin layer chromatography (TLC). The compound was further vacuum sublimed before use. β-Cyclodextrins (Fluka) were used as received without further purification. Triply distilled water was used for making the experimental solutions.



Scheme 1. Schematic representation of preparation of BICPM.

Shimadzu U3500 absorption spectrophotometer was used for the absorption spectral studies. Fluorescence lifetimes were determined from time resolved intensity decay by the method of time correlated single-photon counting (TCSPC). The pulse duration of the excitation source response is 40 ps. The decay curves were analyzed using IBH decay analysis software. Goodness of fits was judged by the visual inspection of the residuals of the fitted function to the data. The lifetimes were measured in degassed solution of the probe at ambient temperature.

TEM measurement was performed using JEOL, JEM 2010 transmission electron microscope operated at an accelerating voltage ranging from 100 kV to 200 kV. Samples for TEM were prepared by directly dropping the dispersion onto the carbon coated copper grid followed by air-drying. We performed a blank TEM by taking image of β-CD solution only. 0.0283 g of β-CD was dissolved in 2.5 ml double distilled water (Millipore milli q water) for the blank test. Nearly 3 mg of BICPM was dissolved in 10 ml dioxane. This solution was so made that when it was mixed with 2.5 ml distilled water the solution showed the O.D. at the λ_{max} = 290 nm as 0.2. Equal amount of β-CD solution (1st one) and BICPM solution (2nd one) were mixed and sonicated. The dispersion was used for another TEM.

3. Results and discussion

3.1. Steady state and time resolved measurements

Figure 1 displays an excellent spectroscopic response (both in UV–Vis absorption and fluorescence) of BICPM upon addition of gradual amount of β-CD indicating the interaction between the drug and cyclodextrin.

Gradual addition of β-cyclodextrin to the aqueous solution of BICPM leads to the decrease in absorbance and emission intensity. Similar type of observation was noticed by Kondo et. al. [29]. This interesting observation may remain unexplained unless and until we determine in which state (ground or excited state?) The interaction between two partners are taking place actually? In getting answer, we have to consider the following options. One obvious possibility is that the interaction occurs at the excited state, resulting from the diffusive encounter between quencher and fluorophore during the lifetime of the excited state. Had this proposition been correct, the fluorescence lifetime of the fluorophore must alter during interaction. The indifference in fluorescence lifetime on addition of β-CD directly rules out the possibility of dynamic quenching [30]. Another possible explanation behind the suppression of fluorescence may be originated from the formation of a nonfluorescent ground-state complex (fluorophore – quencher) [30]. The mode of quenching of fluorescence of BICPM can be well established employing the time-resolved fluorescence data (Figure 2) and consequently it confirms the occurrence of pure static quenching i.e. formation of complexes solely in ground state.

The ground state formation of this type of supramolecules meets with an additional advantage i.e. effortless preparation of drug delivery material bypassing the exhaustive, frightening synthetic efforts.

Safe arrival of medicine to the affected cell is always a challenging task to the present day chemist and biologist because before doing that one has to ensure that the drug is well protected during its transportation and delivery. Supramolecular assemblies can provide such opportunities to the drug molecules [31–33]. In order to find the drug protective mode of 1:2 stoichiometric binding compositions of the inclusion complexes, the dependence of the