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Controlling the binding of hydrophobic drugs with supramolecular assemblies of β-cyclodextrin

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ABSTRACT

Supramolecular assemblies generated from self-assembling β-cyclodextrin were evaluated as hydrophobic drug carriers in vitro in aqueous conditions. The native β-cyclodextrin macrocycle was used to develop the novel host-guest assemblies with antitumor drug 2,2′-bibenzimidazole and its new derivate with n-nonyl groups at the nitrogen atoms. The morphology and sizes of these assemblies were characterized by NMR spectroscopy, DLS and TEM techniques. The interaction of the two bibenzimidazole guests with the carrier and their releasing properties under action of exogenous surfactant were investigated by means of UV–vis and fluorescence spectroscopy, DLS and TEM. The study of effect of a cationic surfactant, cetyltrimethylammonium bromide, on the stability of β-cyclodextrin–guest assemblies revealed the higher affinity of β-cyclodextrin for guest with n-nonyl groups and the higher stability of the resulting assemblies compared to those in the case of non-alkylated guest. The non-alkylated guest-rich carrier was disrupted rapidly when mixed with a surfactant trigger. The disruption of β-cyclodextrin–guest assemblies was accompanied by competitive inclusion of surfactant in β-cyclodextrin cavity which resulted in drug release from β-cyclodextrin carrier. The results of this study demonstrate the feasibility and usefulness of a trigger-responsive delivery of hydrophobic drugs using soft β-cyclodextrin assemblies.

1. Introduction

One of the major challenges in hydrophobic drug delivery is to guarantee the bioavailability of the active compounds, especially when they are poorly soluble. To increase aqueous solubility and thus therapeutic effectiveness of such drugs, various formulation techniques by application of pH adjustment, cosolvency, emulsification, micellization, preparation of liposomes and solid lipid nanoparticles, are usually used [1–7]. Currently, the drug solubility enhancement techniques by formation of an inclusion complex are also well established in the pharmaceutical industry [8–10]. In this respect, macrocyclic oligosaccharides, cyclodextrins (CDs), have attractive applications due to their ability to form inclusion complexes selectively with appropriately sized guest compounds in water with high affinity through supramolecular interactions like van der Waals forces, hydrophobic interaction, and hydrogen bonding [11–13].

The CD hosts are made up of α-1,4-linked D-glucopyranosyl units with an inner tridimensional hydrophobic cavity which is able to accommodate a variety of biologically important substances within macrocycle's interior cavity. Native α-, β- and γ-CDs have the advantages of being relatively inexpensive and reveal negligible toxicity and bioadaptability [14]. Thanks to ability to interact with cellular membranes, CDs can be explored in drug delivery. Hence, the formation of inclusion complexes enhances bioavailability and bioactivity of bounded drugs thereby indicating great promise for enhancing targeted drug delivery.

The CD cavity can incorporate one or more guests depending on the relative macrocycle cavity and guest sizes [15,16]. A long slim guest molecule is threaded through the CD molecule [17,18]. The CDs in the presence of some organic molecules (guests) can form various types of supramolecular structures such as inclusion complexes and their aggregates, rotaxanes, nanotubes, nanospheres and network aggregates [19–31]. The formation of these species depends on many factors, including concentration of macrocycle, chemical structure of guest, processing conditions (temperature, ultrasound exposure, etc.). Some of them can be obtained supramolecular self-assembly exhausting synthesis procedures and exhibit potential applications in drug delivery.

Among the three native CDs, β-CD is the most useful due to its less

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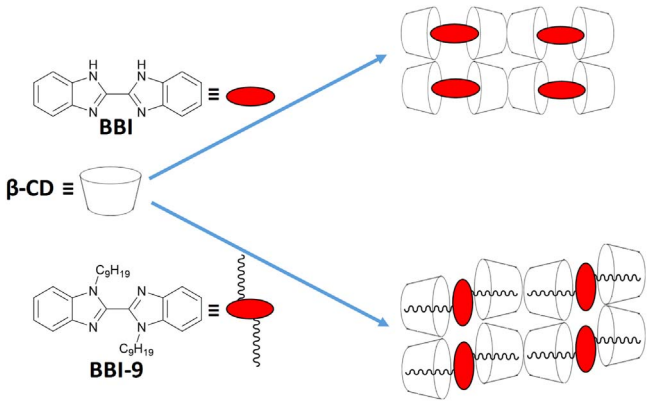

Scheme 1. Graphical illustration of the chemical structures of BBI and BBI-9 and their host–guest complexations induced self-assembly.

solubility in water and suitable molecular dimensions of cavity (diameter 0.60–0.65 nm and height 0.78 nm) which provides a mean to stabilize intramolecular complexes with a wide variety of guests, including drugs and hydrocarbon amphiphiles [32–35]. Although the interaction of β-CD with a wide range of hydrophobic substances and amphiphilic molecules is well explored, there is no study of the effect of amphiphiles on the binding of lipophilic long-chain guest molecule to supramolecular CD assemblies. The aim of this study was to investigate whether supramolecular assemblies, fabricated using a mixture of β-CD and antitumor drug 2,2′-bibenzimidazole (BBI, NCS-322921) [36] and its new derivate with n-nonyl groups at the nitrogen atoms (BBI-9) (Scheme 1), could be formed into the trigger-response system. Benzimidazole and its derivatives are highly lipophilic compounds and recognized as fungicides and anthelmintic drugs [37–39]. They also revealed significant activity against number of human cancer cell lines [40,41]. The water solubility of benzimidazole derivatives in the presence of α- and β-CDs were determined by fluorescence emission experiments [42]. Furthermore, the ability of CD molecules to include guests within their hydrophobic cavities improves notably the pharmaceutical and physicochemical properties of poorly soluble drugs, such as albendazole [43,44]. Under physiological conditions the CD complexes remained stable, and the incorporated hydrophobic drug was slowly released [45]. Therefore, this study is designed to investigate the ability of surfactant to induce morphological changes in the β-CD–guest assemblies with concomitant release of guest.

2. Materials and methods

2.1. Materials

CTAB and β-CD were procured from Acros Organics. Syntheses of 2,2′-bibenzimidazole (BBI) was described elsewhere [46]. The deionized water used for the preparation of all solutions was provided by the Millipore Direct-Q 5 UV system.

2.2. Synthesis of BBI-9

2,2′-bibenzimidazole with n-nonyl groups at the nitrogen atoms (BBI-9) was synthesized by adding of 1 M NaOH aqueous solution (10 mL) to a suspension of BBI (5 mM) in EtOH (5 mL). The mixture was stirred for 1 h at room temperature, and then nonyl iodide (10.8 mM) was added and refluxed with stirring for 21 h. The reaction mixture was triturated with hexane (100 mL), and undissolved part was filtered. The solvent was evaporated, and the residue was chromatographed on silica gel (eluent hexane/EtOAc, 100:1 → 5:1). 0.75 g (32%) of orange-brown powder was obtained. Rf = 0.66 (hexane/EtOAc, 1:1); m.p. 61–62 °C; ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C, TMS): δ 0.85 (dd, 6H, J = 7.2, 6.9 Hz), 1.18–1.30 (m, 24H), 1.82–1.87 (m, 4H), 4.88 (dd, 4H, J = 7.6, 7.6 Hz), 7.34 (dd, 2H, J = 7.7, 7.2), 7.39 (dd, 2H, J = 7.8, 7.2), 7.50 (d, 2H, J = 7.9), 7.86 (d, 2H, J = 7.8); IR (KBr, cm^{-1}): ν 2955, 2922, 2852, 1468, 1408, 1344, 1328, 743, 725; elemental analysis calcd (%) for $C_{30}H_{42}N_4$: C 78.96, H 9.53, N 11.51, found: C 79.05, H 9.61, N 11.48.

2.3. Methods

All NMR experiments were performed on Avance-600 (Bruker, Germany) spectrometer equipped with a pulsed gradient unit capable of producing magnetic field pulse gradients in the z-direction of about 56 G cm^{-1}. Chemical shifts were reported relative to HDO (4.7 ppm) as an internal standard.

The absorbance was measured on a Specord 250 Plus spectrophotometer (Analytic Jena, Germany) equipped with WinAspect software at 25 ± 0.1 °C in a 1 cm path-length quartz cell. Absorbance for each sample was obtained by subtraction of the contribution of components to the summary spectrum. Reproducibility was checked for selected samples and no significant differences were observed.

Fluorescence emission spectra were done on a Cary Eclipse fluorescence spectrophotometer (USA). A quartz cell of 1 cm path length was used for all fluorescence measurements. Temperature of 25 °C was maintained. The excitation and emission slit widths were 1.5 for BBI and 2.5 nm for BBI-9 fluorescence measurements.

DLS studies were conducted at 25 °C using a Zetasizer Nano instrument (Malvern, UK) equipped with a 4 mW He-Ne laser operating at 633 nm. Correlation data were fitted using the method of cumulants to the logarithm of the correlation function, yielding the diffusion coefficient. Backscattered light was detected at 173°, and the intensity-average hydrodynamic diameter was calculated using the Stokes-Einstein equation. All DLS scattering data were processed using Malvern Zetasizer Software.

Transmission electron microscopy (TEM) images were recorded on a Hitachi HT7700 TEM instrument (Japan) operated at 110 kV accelerating voltage. The samples were ultrasonicated in water for 10 min and then dispersed on 300 mesh carbon-coated copper grid.

3. Results and discussion

3.1. Host–guest complexation

^{1}H NMR spectroscopy has been used widely to provide information on the host–guest interaction between β-CD and a variety of aromatic compounds. We investigated the changes of the chemical shifts of β-CD protons in the aqueous solutions with BBI and BBI-9 as compared to the shifts in the single β-CD solution. Strong evidence of the formation of inclusion complex between β-CD and BBI is clearly provided by large chemical shift changes of resonances in β-CD–BBI system as compared to those of single β-CD solution. Fig. 1 for ^{1}H NMR region with β-CD chemical shifts shown that all macrocycle resonances were shifted upfield and broadened, identifying the presence of new structures formed through self-assembly of β-CD. The upfield chemical shifts of H-3, H-5, and H-6 protons lying on inner surface of β-CD confirm that BBI was included in the β-CD cavity. The protons outside the cavity (H-1, H-2 and H-4) show the changes probably due to self-aggregation between β-CD molecules [21,22,47,48]. The underlying assumption here is that the formation of assemblies by CDs in the presence of some other organic compounds is observed due to supramolecular interactions [49].

The addition of BBI-9 to the 10 mM β-CD aqueous solution leads to lower changes of β-CD proton chemical shifts as in the case of addition of non-alkylated derivative BBI (Fig. 1). Interestingly, in the presence of BBI-9 H-6 proton positioned at narrow mouth showed splitting. The possible reason for this is slight destruction of β-CD aggregates in the presence of BBI-9. It is known that H-6 protons in β-CD are nonequivalent, but they do not resonate as separate signals as a result of