Host-guest interaction mediated core-shell assemblies as novel versatile nanocarriers for drug delivery

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Statement of Purpose: Polymeric assemblies have attracted great attention in recent years. These organized materials ranging from nanoscale, micro- to macroscale have found wide applications in areas such as biomedicine, materials science and pharmaceutics [1]. Among these diverse assemblies, polymeric micelles are recognized as one of the most promising nanocarrier systems for drug and gene delivery [2]. Generally, polymeric micelles with a core–shell structure are assembled in aqueous solution due to the hydrophobic interaction between core-forming segments. The interaction between core-forming segments of a block copolymer can also be electrostatic interaction, hydrogen-bonding, and metal-ligand coordination. Our aim is to develop assemblies based on an inclusion interaction between a host molecule and a guest substance. β-Cyclodextrin (β-CD) is selected as a host unit to build a host block that is conjugated with another hydrophilic segment, while a hydrophobic substance either a small molecule or a macromolecule is employed as the guest component. Micelle-like assemblies can form by host-guest interaction mediated spontaneous assembly of the β-CD containing hydrophilic copolymer and a hydrophobic substance in an aqueous solution. This type of novel micelles might be used as versatile nanocarriers, considering the excellent inclusion-solubilization performance of β-CD to many hydrophobic drugs.

Methods: The polyethylene glycol-block-poly(β-benzyl L-aspartate) (PEG-b-PBLA) copolymer was synthesized as reported by Harada et al [3]. PEG-b-polyaspartamide containing EDA unit (PEG-PEDA) was prepared through the quantitative aminolysis reaction of PEG-b-PBLA in dry DMF at 40 ºC in the presence of 50-fold molar amount of EDA [4]. β-CD containing copolymer (PEG-b-PCD) was synthesized by a nucleophilic reaction. Briefly, PEG-b-PEDA dissolved in anhydrous DMSO was reacted with excess amount of 6-monotosyl β-CD, and the copolymer was purified by dialysis. After the dialysate was filtered through a 0.22 μm syringe filter, the resultant aqueous solution was lyophilized. All assemblies containing either a hydrophobic small molecule or a polymer were prepared by dialysis method.

Results: The successful synthesis of PEG-b-PCD was confirmed by ^{1}H and ^{13}C NMR spectra. As demonstrated in Figure 1, in the presence of a hydrophobic small molecule, i.e. pyrene or coumarin 102, well-defined nano-assemblies can be formed by PEG-b-PCD. Atomic force microscopy (AFM), dynamic light scattering (DLS), and transmission electron microscopy were used to characterize the nano-assemblies. It was found that these assemblies were spherical in shape with diameters of about 27 nm (pyrene/PEG-b-PCD) and 50 nm (coumarin102/PEG-b-PCD) respectively. Hydrophobic polymers can also be used with PEG-b-PCD to construct nano-assemblies. As illustrated in Figure 2, spherical nanoparticles were assembled by PEG-b-PCD in the presence of poly(β-benzyl L-aspartate) (PBLA), or poly(D,L-lactic acid) (PDLLA). The size of these assemblies, varying from tens to hundreds of nanometers, can be modulated by the content of guest hydrophobic polymer. Furthermore, polyion complex (PIC) assemblies were also successfully produced by PEG-b-PCD in the presence of adamantane-carboxylic acid (ADCA) and polyethyleneimine (PEI) as shown in Figure 2c.

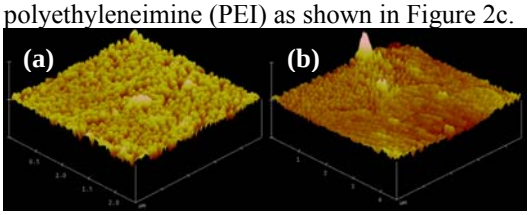

Figure 1. AFM images of PEG-b-PCD based assemblies containing (a) pyrene and (b) coumarin 102.

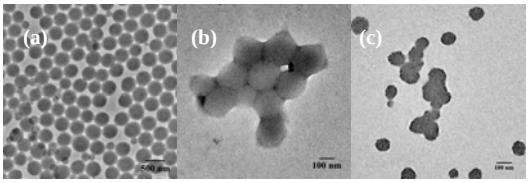

Figure 2. TEM images of assemblies based on PEG-b-PCD containing (a) PBLA, (b) PDLLA, and (c) ADCA and PEI.

Indomethacin (IND), as a model drug, was successfully assembled with PEG-b-PCD to form nanospheres with a high IND loading (12.8 wt.%). Figure 3 shows that the encapsulated IND can be released in a sustained manner.

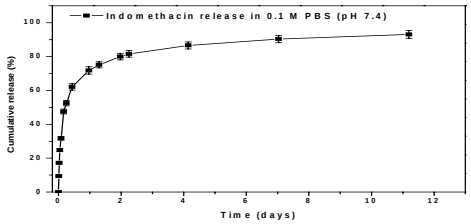

Figure 3. In vitro release profiles of indomethacin (IND) from PEG-b-PCD based assemblies.

Conclusions: A novel hydrophilic-hydrophilic block copolymer has been synthesized. Host-guest recognition mediated nano-assemblies with a hydrophobic core and hydrophilic palisade can be prepared using this copolymer and hydrophobic small molecules or polymers. PIC like assemblies can also be constructed. These novel nano assemblies can be used for drug delivery.

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References:

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