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Full Paper

Nanodiamond Based Supermolecular Nanocomposites: Preparation and Biocompatibility Evaluation

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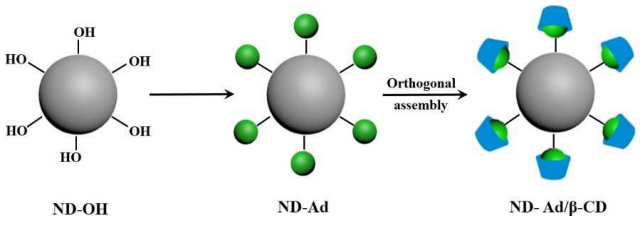
Nanodiamond (ND) is a relative novel carbon nanomaterial that has recently received great research attention for biomedical applications thanks to the small size, unique luminescent properties and good biocompatibility. However, the water dispersibility of such material has significantly impacted its performance. Although considerable advance has been made for the surface modification of ND, facile and efficient strategies are still highly desirable to be developed. In this study, high water dispersible ND based nanocomposites have been fabricated for the first time through host-guest interaction between adamantane and β cyclodextrin (β-CD). Adamantane chloride was first reacted with the hydroxyl group of ND through esterification to obtain ND-Ad. Then β-CD was orthogonally immobilized onto ND-Ad through host-guest interaction. These reactions can be occurred within 30 min under rather mild experimental conditions, including room temperature, air atmosphere, absent of hazardous reagents and expensive equipments. The successful preparation of such ND based supermolecular nanocomposites (ND-Ad/β-CD) was confirmed by a number of characterization techniques. ND-Ad/β-CD showed well water dispersibility and excellent cytocompatibility, making it promising for biomedical applications.

1. Introduction

With the rapid development in nanoscience and nanotechnology, there had been a large variety of nanomaterials with diverse size, compositions and structure characteristics were synthesized and applied.[1-5] Owing to their outstanding properties and great potential applications, a large number of carbon nanoparticles (CNPs) have attracted great interest.[6-15] As a relative novel carbon nanomaterial, nanodiamond (ND) has only just recently taken a place on center stage.[16] Nevertheless, research enthusiasm soared in the past few years fueled and the finding that its unique electrical, optical and mechanical properties make it as a desired candidate for drug delivery, biosensing, cell imaging, polymer composites and so on.[17-23] For example, recent studies have focused on the use of ND for biomedical applications by taking advantages of its small size, high specific surface area, biocompatibility, low toxicity and biological inert.[24-31] Particularly, ND particles possess the alter-natural fluorescence from lattice defects such as N-V center which show red fluorescence that had a promising in fluorescence labels and in vivo molecular imaging.[32-36] Furthermore, the ND which synthesized by detonation process is cheap and has small particle size in narrow distribution. Indeed, for most of these biomedical applications, the efficient dispersion of ND in aqueous solution is one of the prerequisites. Especially, for sufficient study of the unique properties on nanoscale diamond composite materials, it is necessary to make nanoparticles into good dispersion state. Nonetheless, like many other carbon materials, ND is tended to agglomerate into much larger aggregates with size ranging from hundreds of nanometers to tens of microns, and is difficult to form stable colloidal solution. The agglomeration emerged not only related to electrostatic interactions and van der Waals force, but also chemical bonding. Surface functionalization was the fundamental way to improve its solution properties.[19, 37-42] Over the past decade, much effort has been focused on surface modification of ND to improve its colloid stability in aqueous or organic media. For example, covalent surface functionalization of ND aims to introduce applicable functional groups to strengthen ND processibility or endow certain properties.[26, 43-50] Among them, surface modification of ND with polymers via "grafting to" or "grafting from" methods has been widely employed to improve the dispersity of ND in organic and aqueous solutions.[51, 52] Besides, many other surface functionalization methods include ball milling, laser irradiation, click chemistry, fluorination and reduction followed by silanization have been also developed.[45, 53-55] Whereas, most of aforementioned methods were suffered from various limitations, such as time-consuming, inefficiency and complicated experimental procedure. Thus, the development of simple and effective methods to improve the dispersion of ND is still urgently required for its practical applications.

Nowadays, supramolecular chemistry is an important branch of chemistry which has attracted great research attentions.[56-60] Based on the intermolecular relative weak non-covalent interactions such as hydrogen bonds, π-π interactions, metal coordination as well as van der waals forces, the research area is mainly focused on the molecular recognition and the self-assembly of

functionalized structures. Among them, the most fascinating one is the host-guest model system for their specific recognition among the host and guest molecules. In this work, we present for the first time that a facile and efficient method for surface modification of ND through host-guest interaction. As shown in **Scheme 1**, 1-Adamantanecarbonyl chloride could introduce on the surface of ND via esterification reaction in anhydrous THF within 30 min. And then, β cyclodextrin (β-CD) was combined with adamantane (Ad) modified ND through host-guest interaction between adamantine structure and β-CD. The obtained ND based supermolecular nanocomposites exhibited enhanced dispersibility in aqueous solution and good biocompatibility.



Scheme 1 Schematic showing the fabrication of ND-Ad/β-CD supermolecular nanocomposites via host-guest interaction.

2. Experiments

2.1 Materials and Characterization

ND with individual diameter ranging from 2 to 10 nm synthesized by detonation techniques were purchased from Beijing Grish Hitech Co. Ltd. The ND was first dissolved in ethanol in a glass tube, and then sonicated for 20 min before irradiation and then subjected to γ irradiation of ^{60}Co source for 48 h to a total dose of 50.0 kGy (dose rate: 17.4 Gy/min). All other chemical reagents were of analytical grade and without any further purification before used. 1-Adamantanecarbonyl chloride (MW = 198.69, 97%) and β-cyclodextrin (β-CD) (MW = 1134.98, 98%) are purchased from Aladdin company (Shanghai China). The obtained functionalized materials were characterized by ^{1}H NMR spectra were recorded on Bruker Avance-400 spectrometer with D_2O and $CDCl_3$ as the solvents. Fourier transform infrared (FT-IR) spectra by using a Nicolet 380 Fourier transform spectrometer with a resolution of 2 cm^{-1} and the samples were squeezed with KBr into pellet before measure its infrared absorption spectra. Thermo-gravimetric analysis (TGA) was conducted on a TA instrument Q50 with a heating rate of 10 °C min^{-1}. All samples were heated from room temperature to 600 °C under air flow (60 mL min^{-1}) and N_2 flow that as the balance gas (40 mL min^{-1}). The X-ray photoelectron spectra (XPS) were performed on a VGESCALAB 220-IXL spectrometer using an Al Kα X-ray source (1486.6 eV). Transmission electron microscopy (TEM) images were recorded on a Hitachi 7650B microscope operated at 80 kV, the TEM specimens were got by putting a drop of the nanoparticle ethanol suspension on a carbon-coated copper grid. The size distribution of ND-Ad/β-CD in water was determined using a zeta Plus apparatus (ZetaPlus, Brookhaven Instruments, Holtsville, NY). Each sample was ultrasonicated for 30 min prior to analysis.

2.2 Fabrication of ND-Ad/β-CD

200 mg of ND was added to anhydrous THF solution and ultrasonic treatment for 5 min to achieve homogeneous dispersion for a short time. And then 30 mg of 1-Adamantanecarbonyl chloride was put into ND suspension. In order to accelerate the thermodynamic balance towards the forward reaction, a drop of triethylamine (TEA) was add. The mixture was further stirred at room temperature for 30 min. Then the ND-Ad was segregated by centrifugation at 8000 rpm for 10 min. The primary product was washed with distilled water and ethanol for three times to remove unreacted agents. Finally, half of ND-Ad and 170 mg of β-CD were mixed together in aqueous for 30 S. The obtained ND-Ad/β-CD was purified by centrifugation and repeatedly washed with deionized water for three times to remove free β-CD.

2.3 Cytotoxicity evaluation of ND-Ad/β-CD

The cell viability of ND-Ad/β-CD toward A549 cells was evaluated using Cell Counting Kit-8 (CCK-8) assay.[61, 62] Cells were seeded in 96-well microplates at a density of 5×10^4 cells per mL in 160 μL of the respective media containing 10% fetal bovine serum (FBS). After 24 h of cell attachment, A549 cells were incubated with 20, 40, 80, 120, 160 μg mL^{-1} of ND-Ad/β-CD for 10 and 24 h. Then the cells were washed with phosphate buffered saline (PBS) for three times to remove the uninternalized nanoparticles. After that, 10 μL of CCK-8 dye and 100 μL of Dulbecco's Modified Eagle's Medium (DMEM) cell culture media was added to each well and incubated for 2 h at 37 °C. Plates were then analyzed with a microplate reader (VictorIII, Perkin-Elmer). Measurements of dye absorbance were carried out at 450 nm, with the reference wavelength at 620 nm. The values were proportional to the number of live cells. The percent reduction of WST was compared to the control (cells not exposed to nanoparticles), which represented 100% WST reduction. Three replicate wells were used for each control and test concentrations per microplate, and the experiment was repeated three times. Cell survival was expressed as absorbance relative to that of untreated controls. Results are presented as mean ± standard deviation (SD).

2.4 Reactive oxygen species (ROS) generation

ROS generation was measured to evaluate the oxidative stress induced by ND-Ad/β-CD.[63] The ability of ND-Ad/β-CD to induce intracellular ROS formation was determined using a 2,7-dichlorodihydrofluorescein diacetate (DCFH-DA) assay as reported in our previous work.[61, 62] In brief, A549 cells were cultured in 96 well plates and incubated with different concentrations (20, 40, 80, 120 and 160 μg mL^{-1}) of ND-Ad/β-CD for 24 h. After washed three times with PBS to remove the uninternalized nanoparticles, cells were subsequently incubated in 200 μL of a working solution of DCFH-DA, a fluorogenic probe commonly used to detect intracellular generation of ROS, at 37 °C for 30 min. Fluorescence data of oxidized DCFH-DA were recorded by using a microplate reader (VictorIII, Perkin-Elmer) with the excitation and emission wavelengths set at 485 and 535 nm, respectively. The fluorescence of cells without incubation with dyes was defined as the background (F_0), and cells incubated with 0.5 and 1.0 mg mL^{-1} of Rosup for 30 min served as the positive control. The values were expressed as a percentage of fluorescence intensity relative to control wells. All

the procedures were performed without exposure to light. Three replicate wells were used for each control and test concentrations per microplate, and the experiment was repeated three times. Results are presented as mean ± SD.

3. Results and discussion

ND is a relative novel carbon nanomaterial, that showed relative good biocompatibility as compared with other carbon nanomaterials such as carbon black, carbon nanotubes and graphene.[64, 65] Furthermore, the ND with N-V defect can emit desirable luminescence, which make ND potential candidate for bioimaging applications. It is therefore, ND has been regarded as one of the promising biomaterials, that has been extensively explored for biosensor, bioimaging, tissue enigeering and drug/gene delivery applications.[66, 67] However, these applications are largely limited because of the poor dispersibility of ND in aqueous and organic solvents. Over the past decade, many efforts have been devoted to surface modification of ND. The surface oxidation of ND to introduce functional groups and improve its dispersibility has been commonly adopted previously.[68, 69] These functional groups can also be utilized for conjugation with other components or immobilization of polymer initiator for surface-initiated polymerization.[52] However, to the best of our knowledge, the fabrication of ND based supermolecular nanocomposites has not been reported thus far. In this work, we demonstrated for the first time that ND based nanocomposites with excellent water dispersible can be facilely prepared through supermolecular chemistry. The successful formation of ND based supermolecular nanocomposites was characterized by a series of techniques in detail.

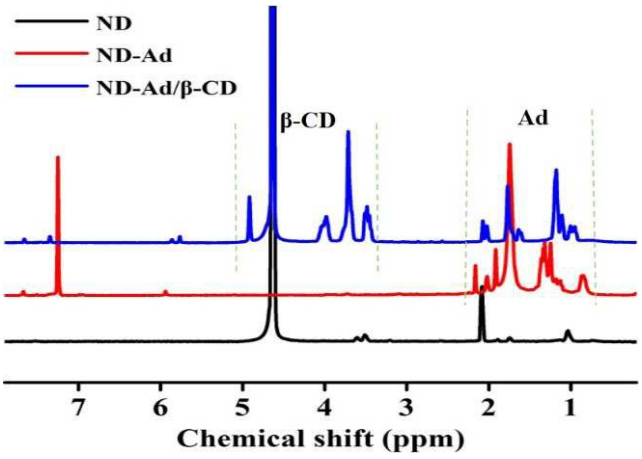


Fig. 1 ^{1}H NMR spectra of ND, ND-Ad and ND- Ad/β-CD. Among them ND and ND-Ad/β-CD were dissolved in D_2O. ND-Ad was dissovled $CDCl_3$.

The ^{1}H NMR spectroscopy was used to characterize the chemical information of ND and ND based nanocomposites. As displayed in **Fig. 1**, distinct difference in chemical shifts was observed between ND, ND-Ad and ND-Ad/β-CD. Compared with ND, there have some novel low field proton shifts emerged at the ranged from 2.1 to 0.8 ppm, which were consistent with Ad protons, Furthermore, the protons peaks at 2.06 ppm in the sample of ND was disappeared. These changes indicated Ad was grafted to surface of ND successfully via esterification reaction. After β-CD was conjugated with Ad through host-guest interactions, a few chemical shifts belong to β-CD protons were occurred that display in the ^{1}H NMR spectra. Such changes confirmed the presence of Ad and β-CD, which indicated the ND-Ad was successfully hitched up by β-CD.

The TGA and DSC results could also provide additional evidence to the surface functionalization of ND via host-guest interaction. Thus, the extent of surface modification was further calculated based on the ratio of weight loss by TGA. As shown in **Fig. 2A**, an obvious amount of weight loss from ND-Ad was appeared in the temperature range of 130-300 °C. Compared with the control experiment on the sample of ND, the weight loss of ND-Ad was owing to the decomposition of the surface grafted Ad. Based on the TGA curves, the weight ratio of grafted Ad was reached 7.8 wt%. In addition, after β-CD was conjugated on the surface of ND-Ad via host-gest interaction, greater weight loss could be observed (**Fig. 2A**). Compared to the weight loss of ND-Ad, it can draw a conclusion that ND-Ad/β-CD was prepared successfully through orthogonal assembly of Ad to exactly formed 1:1 inclusion complexes. Among them, the weight loss of ND-Ad/β-CD nanocomposites up to 37 %. Subtracted the weight loss of Ad, the weight loss of β-CD was approximately 20%. In general, the TGA shows each step successful modification of ND. Furthermore, according to the DSC spectra (**Fig. 2B**), every DSC curve had a slight decrease ranged from 25 to 70 °C which was caused by the evaporation of water. Apart from this, just one endothermic event from 100 to 300 °C during the entire heating process in ND-Ad, which was correspond to TGA results. Compared with ND-Ad, two main endothermic events can be observed. Except the one belong to the decomposition of Ad, another huge exothermic peak located at 283 °C can be obtained. On the basis of the endothermic peak, we affirmed this was resulted in the decomposition of β-CD. Therefore, the TGA and DSC curves had a perfect parallelism, both of them indicated the successful assembly of ND-Ad/β-CD by means of host-guest interaction.

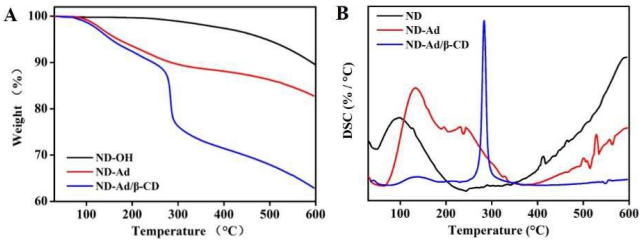


Fig. 2 TGA characterization of weight percentage (A) and DSC curves (B) as a function of temperature for ND, ND-AD and ND-Ad/β-CD.

The successful surface modification of ND was directly evidenced by TEM images. As shown in **Fig. S1**, the diameter of ND was about 2-10 nm, which is well consistent with information of manufacturer. Many of these ND nanoparticles are tended to agrragate into large clusters with size upto several hundreds (**Fig. S1A**). After surface modification of β-CD, the size of ND agglomerates was obviously decreased. Moreover, thin coating on ND nanoparticles with lower contrast was observed, that should be the image of β-CD (**Fig. S1B**). These comparasion implied that β-CD was successfully coated on ND nanoparticles through host-guest interaction. The poor dispersibility of as-received ND particles in solution is an urgent problem to be

resolved. In this work, a simple and efficient method was developed to surface modification of ND through host-guest interaction between the Ad and β-CD. The successful formation of ND-Ad/β-CD was further confirmed by FT-IR spectra. As displayed in **Fig. 3**, an obvious characteristic peak at 3400 cm^{-1} could be assigned to stretching vibration of -OH. After 1-Adamantanecarbonyl chloride was conjugated to the surface of ND, there had some novel characteristic peaks emerged in the sample of ND-Ad. For example, the novel peak at 2900 cm^{-1} represents the vibrational modes of C-H, indicating Ad was successfully conjugated with hydroxyl groups of ND. In addition, increase intensity in C=O stretching vibrational signal (1760 cm^{-1}) was visible, further illustrated the successful formation of ND-Ad via esterification reaction. As compared with ND-Ad, an obvious peak at 1050 cm^{-1} (vibrational modes of C-O-C) can be found in spectrum of ND-Ad/β-CD. At the same time, the intensity of the peak at 1380 cm^{-1} was enhanced distinctly. This may be ascribed to the bending vibration of -OH from the surface modified β-CD. Furthermore, the increase of C-H IR signal should also demonstrate the existence of β-CD on the surface of ND. Therefore, all these results illustrated we had prepared the ND-Ad/β-CD successfully by means of host-guest interaction.

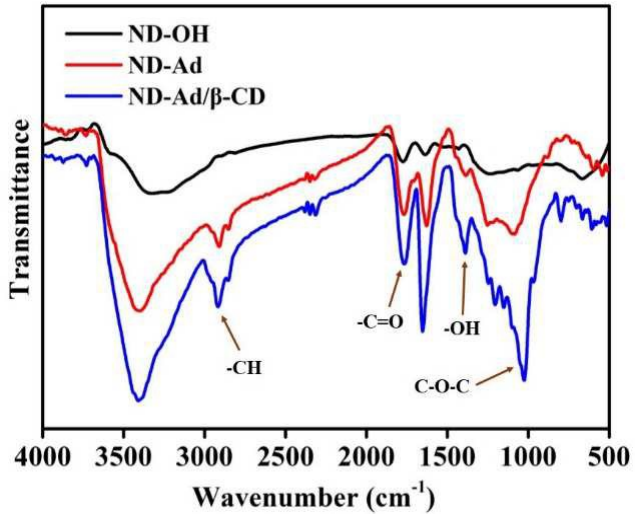


Fig. 3 FT-IR spectra of ND, ND-Ad and ND-Ad/β-CD.

The XPS survey scan ranging from 0 to 1300 eV was carried out to determine the elements present on the surface of different ND samples. As shown in **Fig. 4A**, three characteristic peaks at 284.8, 398.6, 530.9 eV can be observed, that were attributed to elements of C, N and O, respectively. From the XPS spectra, we could find that the major elements of ND samples were C and O. The C1s XPS spectra were displayed in **Fig. 4B**, the intensity of C1s peak for ND-Ad was significantly decreased compared with ND. Furthermore, intensity of C1s peak for ND-Ad/β-CD was increased compared with ND-Ad, indicating the successful formation of ND-Ad/β-CD. In addition, the O1s peak of ND-Ad, corresponding to C-OH and C=O groups, the peak intensity was reduced and shifted to higher binding energy, confirming Ad was conjugated to the surface of ND successfully. Except for this, the oxygen content of ND-Ad/β-CD was increased in some extent compared to ND-Ad (**Fig. 4D**). All these results suggested that successful surface modification of ND via host-guest interaction.

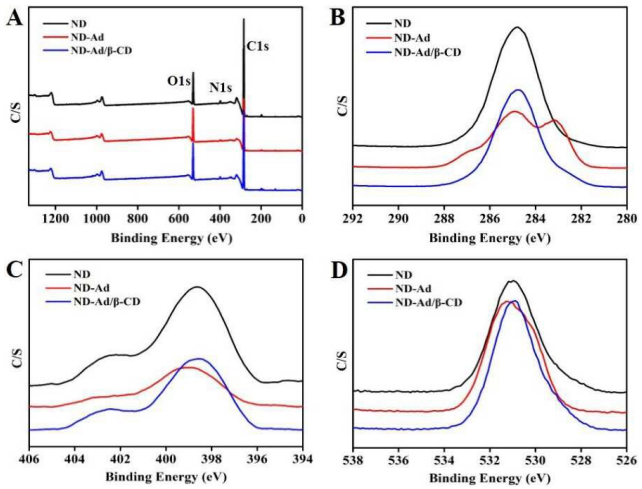


Fig. 4 XPS spectra of ND, ND-Ad and ND-Ad/β-CD. (A) Survey scans the spectral region ranging from 0 to 1300 eV, (B) C1s region, (C) N1s region, (D) O1s region.

Although ND has demonstrated to be promising candidate for biomedical applications, the poor water dispersibility has largely restricted its performance. In this work, the water dispersibility of ND nanoparticles was preliminarily examined. As shown in **Fig. 5**, the detonation ND could be dispersed in water to form a homogeneous suspension after intense sonication, but sedimentation emerged after standing for about 2 h. Nonetheless, the dispersibility of ND-Ad was attenuated, which could just lasting for about 30 min. This phenomenon occurred due to the decrease of hydroxyl groups indicated adamantanecarbonyl chloride was grafted to ND successfully via esterification reaction. Significant enhanced dispersibility of ND-Ad/β-CD can be found after β-CD conjugated to surface of ND. Even standing for more than 24 h, ND-Ad/β-CD also in uniform dispersion. The Zeta potential of ND-Ad/β-CD in water was determined to be -23.5 ± 4.5 eV. The negative value of Zeta potential implied that ND-Ad/β-CD are stable in water. The hydrodynamic size distribution of ND-Ad/β-CD in water was determined by dynamic light scattering (DLS). Results showed that the size distribution of ND-Ad/β-CD is 210.1 ± 21.7 nm. As compared with the TEM images, the size of ND-Ad/β-CD determined by DLS is some larger than that of TEM characterization. The possible reason may be ascribed to interaction between the ND-Ad/β-CD nanoparticles and the shrinkage of polymers. Given the excellent water dispersibility, the biocompatibility of ND-Ad/β-CD was subsequently investigated.

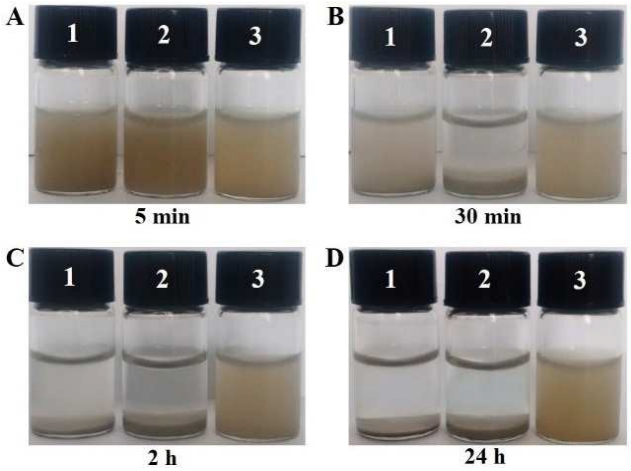


Fig. 5 Dispersibility of ND (1), ND-Ad (2) and ND-Ad/β-CD (3) in aqueous solution at room temperature for different time (A) 5 min, (B) 30 min, (C) 2 h, and (D) 24 h.

The cell viability of ND-Ad/β-CD to A549 cells was further evaluated using CCK-8 assay. **Fig. S2** showed the cell viability values of A549 cells when they were incubated with different concentrations of ND-Ad/β-CD ranged from 20-160 μg mL^{-1}. It can be seen that the cell viability values were gradually decreased when the concentrations of ND-Ad/β-CD were increased. When the concentrations of ND-Ad/β-CD were upto 160 μg mL^{-1}, the cell viability value was still greater than 89% after 24 h incubation. The half maximal inhibitory concentration (IC50) values of ND-Ad/β-CD were calculated based on the cell viability values. The IC50 values of ND-Ad/β-CD to A549 cells at 10 and 24 h are 280.1 and 244.1 μg mL^{-1}, respectively. All of these results implied that β-CD modified ND also possesses excellent biocompatibility. It has been demonstrated ND showed the best biocompatibility as compared with other carbon nanomaterials such as carbon nanotubes, graphene oxide and carbon black et al.[64] Furthermore, the ROS generation was further used to evaluate the biocompatibility of ND-Ad/β-CD. It can be seen that almost no obvious ROS generation can be detected after A549 cells incubated with different concentrations of ND-Ad/β-CD (**Fig. S3**). The ROS level was even decreased as compared with the control group. The decrease of ROS value is likely due to the reduction of cell number. The ROS generation evaluation also suggested that ND-Ad/β-CD possess good biocompatibility. On the other hand, β-CD has also been extensively utilizing for biomedical applications because of its high water solubility, biocompatibility as well as the host-guest interaction with many molecules. More importantly, many other polymers could also be facilely introduced on materials through the strategy developed in this work when we using polymers functionalized β-CD. It is therefore, the method should be a facile, efficient and very interesting strategy for fabrication of multifunctional supermolecular nanocomposites.

The biomedical applications of ND based nanocomposites have extensively investigated recently considered its good biocompatibility and luminescent properties. Although a number of strategies have been adopted for surface modification of ND nanoparticles for biomedical applications.[52] The surface modification of ND nanoparticles has seldom been reported. As compared with previous methods, the supermolecular method described in this work should be of some advantages. It has been demonstrated that supermolecular chemistry has been widely utilized for surface modification of mesoporous silica nanoparticles to construct controlled drug delivery systems.[70, 71] For example, Zhao et al have demonstrated the mesoporous silica nanoparticles can be facilely modified with β-CD through different responsive routes.[70, 71] These β-CD can be detached from mesoporous silica nanoparticles, thus the release of cargos from these drug delivery systems can be well controlled. On the other hand, the individual ND nanoparticles with diameter ranged from 2-10 nm can pile up into porous agglomerates, which can be used for loading drugs high efficient and controlled release of these cargos for cancer treatment.[50] Therefore we expect that these ND based supermolecular nanocomposites can also be used for controlled drug release when the responsive units were incorporated into them. This should be of great importance for fabrication of multifunctional ND based controlled drug delivery systems.

Conclusion

In conclusion, we have reported for the first time that high water dispersible ND nanocomposites can be prepared via host-guest interaction of which β-CD orthogonal assembly with Ad to form an exactly 1:1 inclusion complexes. The successful preparation of ND based supermolecular nanocomposites were evidenced by a number of characterization techniques. These functionalized ND (ND-Ad/β-CD) showed superb dispersibility in aqueous solution and excellent biocompatibility, which is very important for their biomedical applications. Compared with previous methods, this strategy has the advantages such as easy operation, mild reaction conditions and high efficiency. For example, the surface modification reaction can occur under air atmosphere, low temperature and absent of toxic metal catalysts within short reaction time. More importantly, many functional polymers can also be introduced onto ND through the host-guest interaction when polymers functionalized β-CD derivates were adopted. Therefore, this strategy can be largely extended for fabrication of various multifunctional supermolecular nanocomposites for different applications.

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Notes

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† Electronic Supplementary Information (ESI) available: [The TEM images of ND and ND-Ad/β-CD, the biocompatibility evaluation of ND-Ad/β-CD was provided in supplementary information]. See DOI: 10.1039/b000000x/

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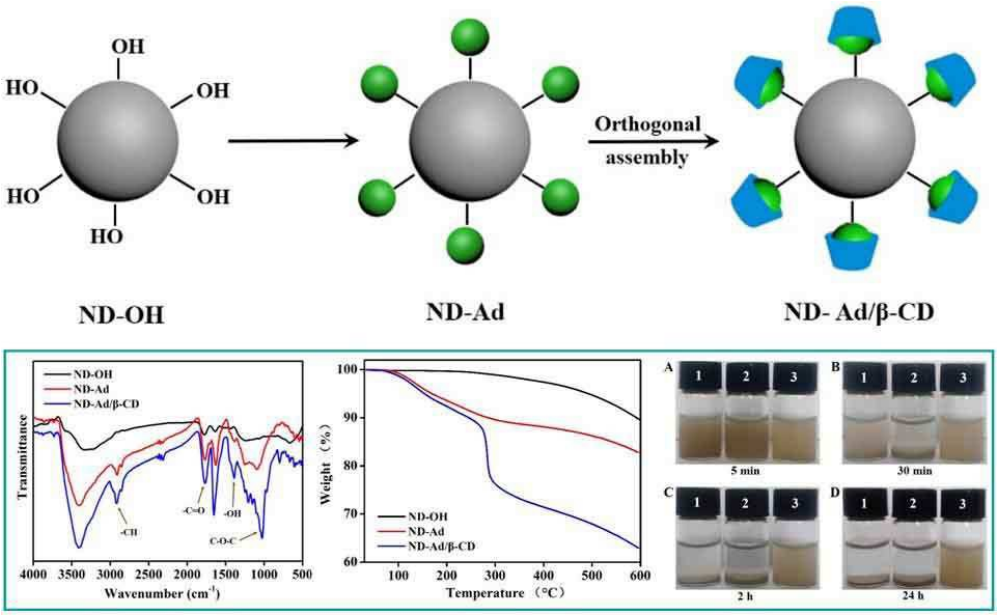

We reported for the first time that water dispersible and biocompatible ND based supermolecular nanocomposites can be facilely and efficiently fabricated via host-guest interaction.