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ARTICLE

Facile Fabrication of Amphiphilic AIE active Glucan via Formation of Dynamic Bonds: Self Assembly, Stimuli Responsiveness and Biological Imaging

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Qing Wan[a,#], Meiying Liu[a,#], Dazhuang Xu[a], Hongye Huang[a], Liucheng Mao[a], Guangjian Zeng[a], Fengjie Deng[a,*], Xiaoyong Zhang[a,*], Yen Wei[b,*]

Fluorescent organic nanoparticles (FONs) with aggregation induced emission (AIE) properties have recently emerged as one of the most promising luminescent nanomaterials for biomedical applications due to their unique AIE feature. In this work, we reported the preparation of AIE active FONs through mixing AIE dye (TPE-CHO), 3-Aminobenzeneboronic acids (ABBA) and Glucan in one-pot. ABBA was acted as molecular "bridge" to conjugate TPE-CHO with Glucan via formation of Schiff base and phenyl borate. The resultant products (Glu-TPE FONs) showed amphiphilic properties and could self-assemble into nanoparticles in aqueous solution. Glu-TPE FONs showed strong luminescence intensity and high water dispersibility because of the AIE properties of TPE-CHO and hydrophilic nature of Glucan. To examine the biomedical application potential of Glucan-AIE FONs, the responsiveness, biocompatibility and cell uptake behavior of Glu-TPE FONs were subsequently examined. We demonstrated that Glu-TPE FONs possess good biocompatibility and can be potentially used for biological imaging applications. More importantly, it is well known that the Schiff base and phenyl borate can response to pH and glucose. Therefore, Glu-TPE FONs can be used for fabrication of multifunctional biomaterials with stimuli responsiveness.

1. Introduction

The development of luminescent nanoparticles with great sensitivity, selectivity and biocompatibility is of critical importance for bioscience and biotechnology application due to their achievement for detecting biological macromolecules and tracking biological activity.[1-5] As compared with the small organic dyes, fluorescent nanoparticles that integrated more fluorescent chromophores into ones possess many advantages for biological and biomedicine applications for their better photophysical properties, amplication of fluorescent signal and multifunctional potential. Over the past few decades, numerous fluorescent nanoprobes based on inorganic components, organic components and the inorganic/organic hybrids have been reported.[6-12] The inroganic nanoparticles (e.g. semiconductor quantum dots,[13-17] carbon quantum dots, Ln ions doped nanomaterials and luminescent silica nanoparticles) have been reported and utilized for bioimaging applications.[7, 18-21] However, the drawbacks of fluorescent inorganic nanomaterials such as poor biodegradable capability, toxicity to living organisms and low quantum yields etc. have largely impeded their bioimaging applications. On the other hand, the fluorescent organic nanoparticles (FONs) based on conventional organic dyes such as fluorescein, Rhodamine and quinine sulfate often suffer from quenching phenomenon when they are dispersed in aqueous solution or interact with biomacromolecules in living cells due to their aggregated state or high concentration in human body. The phenomenon was named as aggregation caused quenching (ACQ) effect, which makes preparation of ultrabright FONs based on conventional organic dyes problematic.

Recently, some organic molecules with unique aggregated induced emission (AIE) feature have drawn increasingly attention and provided effective platform for the research and development of unique fluorescent nanomaterials due to their obvious enhancement fluorescence at aggregated state. Since the first report for facile preparation of AIE active luminophors for biological imaging by research Park group,[22, 23] numerous attention has been attracted by these types of fluorescent materials, which showed unique properties for the practical applications in organic light-emitting diode (OLED),[24] chem-biosensors[25-27] and fluorescent probes.[26, 28] In the past few years, many simple and effective strategies have been developed for fabrication of AIE-active polymeric

[a] Department of Chemistry and Jiangxi Provincial Key Laboratory of New Energy Chemistry, Nanchang University, 999 Xuefu Avenue, Nanchang 330031, China.
[b] Department of Chemistry and the Tsinghua Center for Frontier Polymer Research, Tsinghua University, Beijing, 100084, P. R. China.
[c] # These authors contributed equally to this work

† Footnotes relating to the title and/or authors should appear here.
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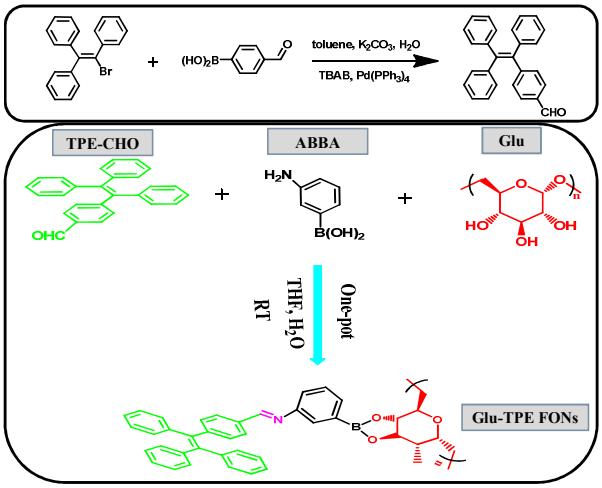
nanoprobes.[29-35] For instance, hydrophobic AIE dyes can be facilely incorporated into amphiphilic macromolecules such as Bovine serum albumin (BSA), commercial available surfactants and synthetic copolymers to increase their biocompatibility and water dispersibility in aqueous solution via noncovalent self assembly procedure.[36] On the other hand, a number of covalent methods such covalent conjugation, ring-opening reaction, Schiff base condensation, free radical polymerization, reversible addition-fragmentation chain transfer polymerization (RAFT)[37] and emulsion polymerization[38] have been also been developed for fabrication of AIE polymeric nanoprobes with well controlled properties and functions.[32, 38-40] Carbohydrate polymers are types of polymers from natural living organisms. Some of them have demonstrated to be potentially utilized for different biomedical applications due to their hydrophilic nature, biological activity and low cost etc. Among them, Glucan have great potential for biomimicry and wide biomedical applications such as therapeutic drugs, drug delivery and bioactive hydrogels.[41, 42] However, to the best of the authors knowledge, only very few studies have reported the fabrication of AIE-active carbohydrate polymers thus far. The fabrication of stimuli responsive AIE-active Glucan through formation of dynamic bonds has not been demonstrated before.

In this contribution, a facile and fast strategy for preparation of amphiphilic AIE active Glucan is developed by one-pot procedure for the first time. 1,1,2-triphenyl-2-(p-formyl)ethylene (TPE-CHO) can be synthesized based on Suzuki reaction. Then TPE-CHO was conjugated with Glucan using 3-Aminobenzeneboronic acids (ABBA) as the molecular "bridge", which can form Schiff base and phenyl borate with TPE-CHO and Glucan, respectively (**Scheme 1**). The method described in this work is especially attractive due to its easy handle, mild reaction conditions (atmosphere and room temperature) and environmentally benign (without catalysis and only water as by-products). More importantly, both Schiff base and phenyl borate can response to pH and glucose.[43] Therefore, this work could provide an important tool for fabrication of stimuli responsive AIE active carbohydrate polymers.



Scheme 1 Schematic showing the synthetic procedure of TPE-CHO and Glu-TPE FONs via a facile one-pot method.

2. Experiment

2.1 measurements and materials

All available starting materials contained reaction materials, reagents and solvents were used from commercially purchased. The raw materials for the synthesis of TPE-CHO were 2-Bromo-1,1,2-triphenylethylene (MW: 335.24 Da, > 98.0%, purchased from Tokyo Chemical Industry Co. LTD.), 4-Acetylphenylboronic acid (MW:163.97 Da, > 98.0%) Bis(triphenylphosphine) palladium(II) diacetate (MW: 749.08, Pd: 14.2%) and Potassium bicarbonate (MW:100.12 Da, 99.7%), were offered from Aladdin. Glucan (MW: 10000 Da) and ABBA monohydrate were also purchased from Aladdin, which was used to fabricate FONs. Other dry solvents were directly used without other purification.

^{1}H NMR spectra were recorded on Bruker Avance-400 spectrometer with D_2O and $CDCl_3$ as the solvents. The synthetic polymers were characterized by Fourier transform infrared spectroscopy (FT-IR) using KBr pellets, FT-IR spectra were supplied from Nicolet5700 (Thermo Nicolet corporation). 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 fluorescence data were obtained from the Fluorescence spectrophotometer (FSP, model: C11367-11), which purchased from Hamamatsu (Japanese). UV-Vis spectra were obtained from a Perkin Elmer LAMBDA 35 UV/Vis system.

2.2 Synthesis of TPE-CHO

The AIE dye (TPE-CHO) was synthesized according the previous report.[44] 2-Bromo-1,1,2-triphenylethylene (1.67 g, 5 mM) and 4-Acetylphenylboronic acid (1.23 g, 7.5 mM) were dissolved in the mixture solution, which contained toluene (50 mL), TBAB (200 mg, 0.7 mM) and 2 M Potassium bicarbonate were dissolved in 20 mL water. The mixture solution was sharply stirring at room temperature for 30 min under nitrogen atmosphere. Afterward, $Pd(PPh_3)_4$ (10 mg) was quickly put into reaction bottle and refluxed at 90 °C for 24 h. When the raw reaction chemical agents were disappeared via evaluation of silica gel column, the mixture was poured into water and extracted three times with ethyl acetate (100 mL). The organic layer was obtained and dried with anhydrous sodium sulfate. After removing the organic solvent by rotary evaporation, the purified products could be obtained via chromatographic separation on a silica gel column with n-hexane/CH_2Cl_2 (2/1) as eluent solvents.

2.3 Preparation of Glu-TPE FONs

Glu-TPE FONs were prepared via a facile one-pot procedure as described follows. TPE-CHO (35.8 mg, 0.1 mM) and ABBA

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(13.7 mg, o.1 mM) were dissolved in the 10 mL THF solution, while Glucan (100 mg, 0.1 mM) was dissolved in a bit of water. Mixing THF solution and water and adding several drops of TEA and stirring at room temperature for 8 h under nitrogen atmosphere. The resulting white solid could be obtained via perticipating using cool diethyl ether and washed with ethyl acetate three times to remove unreacted TPE-CHO. The final products were dried by vacuum oven at 50 °C for 24 h.

2.4 Cytotoxicity evaluation of Glu-TPE FONs

In order to evaluate the toxic effects of Glu-TPE FONs for living cells, the cell viability of Glu-TPE FONs with strong green fluorescence on HeLa cells was evaluated by cell counting kit-8 (CCK-8) assay.[45-48] The experimental procedure could be demonstrated by follows: Cells were put into 96-well microplates at a density of 5×10^4 cells mL^{-1} in 160 μL of respective media containing 10% fetal bovine serum (FBS). After 24 h of cell attachment, the cells were incubated with different concentrations of FONs (10-100 μg mL^{-1}) for 12 and 24 h. Then nanoparticles were removed and cells were washed with PBS three times. 10 μL of CCK-8 dye and 100 μL of DMEM cell culture medium were added to each well and incubated for 2 h at room temperature. Afterward, plates were analyzed using a microplate reader (VictorIII, Perkin-Elmer). Measurements of formazan 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 CCK-8 dye was compared to controls, which represented 100% CCK-8 reduction. Three replicate wells were used per microplate, and the experiment was operated for three times. Cell survival was expressed as absorbance relative to that of untreated controls. Results are presented as mean ± standard deviation (SD).

2.5 Confocal microscopic imaging

HeLa cells were cultured in Dulbecco's modified eagle medium (DMEM) supplemented with 10% heat-inactivated FBS, 2 mM Glucantamine, 100 U mL^{-1} penicillin, and 100 μg mL^{-1} of streptomycin. Cell culture was controlled at 37 °C in a similar humidified condition of 95% air and 5% CO_2 in culture medium. Culture medium should be updated every three days for maintaining the exponential growth of the cells. Before treatment, cells were seeded in a glass bottom dish with a density of 1×10^5 cells per dish. On the day of treatment, the cells were incubated with Glu-TPE FONs at a final concentration of 20 μg mL^{-1} for 3 h at 37 °C. Afterward, the cells were washed three times with PBS to remove the Glu-TPE FONs and then fixed with 4% paraformaldehyde for 10 min at room temperature. Cell images were obtained using a confocal laser scanning microscope (CLSM) Zesis 710 3-channel (Zesis, Germany) with the excitation wavelength of 405 nm.

3. Result and discussion

The TPE-CHO was synthesized based on 2-Bromo-1,1,2-triphenylethylene and 4-Acetylphenylboronic acid as row materials via Suzuki reaction according to our previous report.[44] The structure information of TPE-CHO was confirmed by the ^{1}H NMR、13C NMR and FT-IR spectra (**Fig.S1-3**). The amphipathic Glu-TPE polymers were facilely prepared via a "one-pot" procedure based on TPE-CHO and Glucan using ABBA as "bridge". In order to confirm the successful preparation of Glu-TPE FONs, the ^{1}H NMR spectra of Glucan and Glu-TPE are shown in Fig. 1. After conjugating TPE-CHO with Glucan using ABBA as "bridge", the ^{1}H NMR spectrum of Glu-TPE is found to possess integrated chemical shift from Glucan and TPE-CHO. The chemical shift ranging from 3.0 to 4.0 ppm could be contributed to methylene and methane groups of Glucan. After modification with TPE-CHO via formation of phenyl borate and Schiff base, the signal about the protons of aromatic rings were located between 5.5 to 8.0 ppm. Normally, the chemical shift of benzene ring locat at 6.0 to 8.0 ppm, however, the formation of Schiff base in Glu-TPE FONs results in increasing electron cloud density around bezene rings, which make the chemical shift (δ) of aromatic hydrogens shift to high magnetic field. On the other hand, the peaks of aromatic hydrogens between 5.5 and 8.0 ppm were weaken, which could be explained by the poor solubility of Glu-TPE FONs in D_2O. The resulting Glu-TPE FONs are well dispersed in aqueous solution rather than dissolved in water. All of the above results could demonstrate the successful conjugation between TPE-CHO and Glucan through the one pot strategy. Furthermore, the strong peak at 8.3 ppm can be contributed to CH=N bond, further providing powerful evidence that triumphant preparation of Glu-TPE FONs. Based on above analysis of ^{1}H NMR spectra, we can preliminarily draw a conclusion that successful accomplishment for fabrication of AIE active polymers through dynamic Schiff base and phenyl borate.

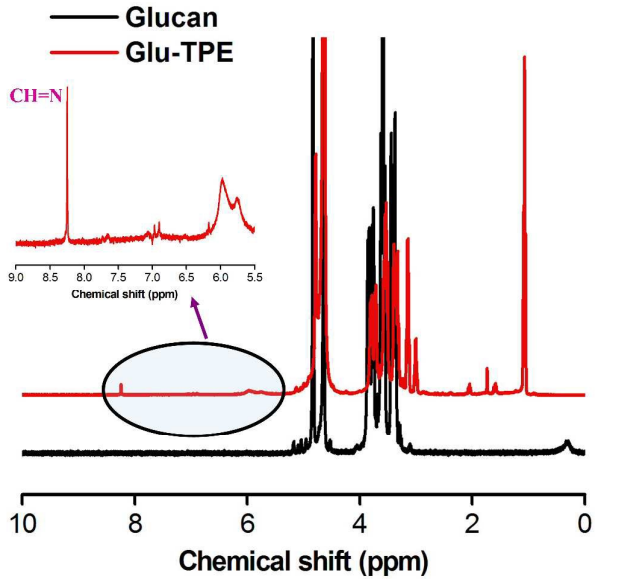

Fig. 1 1H NMR spectra of Glucan and Glu-TPE FONs.The chemical shift ranging from 3.0 to 4.0 ppm can be attributed to the methylene and methane groups, which is derived from Glucan. The amplified 1H NMR spectrum of Glu-TPE ranging from 5.5 to 9.0 ppm can be ascribed to the chemical shift of aromatic rings and formation of Schiff base.

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The successful formation of Glu-TPE FONs was also confirmed by TEM characterization. Due to their amphiphilic properties, Glu-TPE could self assemble into nanoparticles, in which the hydrophobic TPE-CHO was encapsulated in the core while the hydrophilic Glucan was coated on the hydrophobic core and as shell. As shown in **Fig. S4**, many spherical nanoparticles with diameter between 80 and 250 nm could be clearly observed, giving powerful and direct evidence for the self assembly of Glu-TPE polymers in aqueous solution. Self assembly of amphiphilic polymers in aqueous solution is a very important route for fabrication of nanomaterials for biomedical applications. And the self assembly of AIE dyes contained amphiphilic polymers is of particular interest for fabrication of luminescent nanoparticles because AIE active dyes could effectively overcome the notorious ACQ effect of conventional organic dyes. Moreover, successful preparation of Glu-TPE FONs are further confirmed by FT-IR spectra. As shown in **Fig. 2**, a new incisive peak at 1690 cm^{-1} is emerged in the samples of Glu-TPE FONs as compared the spectrum of Glucan. This peak can be ascribed to the stretching viration of –CH=N- bond, indicating the successful formation of Schiff base between the ABBA and TPE-CHO. Furthermore, another peak at 1350 cm^{-1} was also emerged in the sample of Glu-TPE FONs. This peak can be attributed to the stretching viration of B-O bond. Moreover, many peaks between 500-1000 cm^{-1} and 1300-1600^{-1} were observed in Glu-TPE FONs. These peaks should be ascribed to deformaton vibration of aromatic rings from TPE-CHO and ABBA. Finally, a number of characteristic peaks of Glucan were also found in Glu-TPE FONs. Therefore, we can conclude that Glu-TPE FONs have truly botained via formation of dynamic Schiff base and phenyl borate based on the FT-IR spectra.

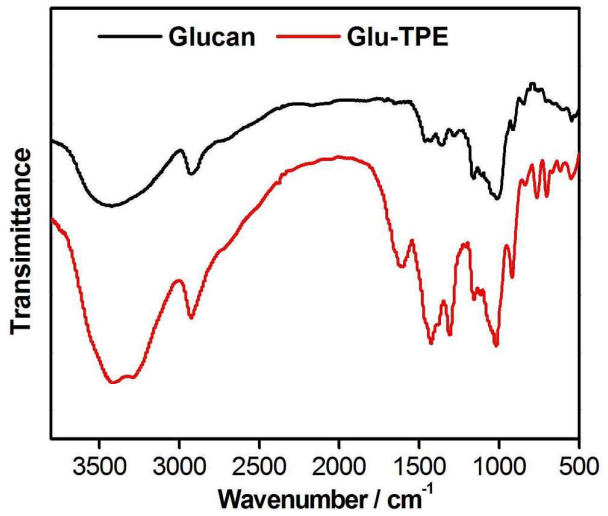

Fig. 2 The FT-IR spectra of Glucan and Glu-TPE FONs, which is used to evidence successful preparation of Glu-TPE FONs. The incisive peak at 1690 cm^{-1} in the sample of Glu-TPE FONs is first appeared, which indicates the formation of –CH=N- bond. The peak at 1350 cm^{-1} is caused by stretching vibration of B-O bond, which is formed by the dehydration reaction of Glucan and ABBA.

Due to the amphiphilic properties of Glu-TPE, the Glu-TPE are tended to self assemble into nanoparticles with great water dispersibility and strong luminescence. Therefore, the water dispersibility and optical properties of Glu-TPE FONs were further examined. As shown in the inset of **Fig. 3A**, homogeneous suspension was observed when Glu-TPE polymers were dispersed in pure aqueous solution. The "AIE" marker with high transparency could be intuitively observed. The Glu-TPE solution can suspend more than 24 h. The water dispersibility provided powerful evidence for the formation of amphiphilic polymers. The UV-Vis spectrum was utilized to prove the formation of nanoparticles of Glu-TPE in water. As shown in **Fig. 3A**, two peaks at 407 and 337 nm were found in the UV-Vis spectrum. The adsorption peak at 337 nm should be ascribed to the n→π* transition of TPE conjugation structure, while the adsorption peak at 407 nm can be attributed to the formation of –CH=N- on the conjugated structure. The Schiff base will lead to the red shift of conjugated structure.[26] Furthermore, it could notice that whole absorption curve of Glu-TPE was started to increase ranging from 800 to 200 nm, which is ascribed to the Mie effect, indicating that successful formation of Glu-TPE nanoparticles in water. The AIE properties of TPE-CHO were evaluated by FL spectrometer. As shown in **Fig. S5**, the fluorescent intensity was gradually increased when the volume ratio of water to THF increase from 10% to 90%. However, the maximum emission wavelength has not significantly changed (about 496 nm). It is well known that the polarity of solvents will in turn influence the dispersibility of TPE-CHO. When the ratio of water to THF increased, the dispersibility of TPE-CHO is poor, resulting in strong emission. In this case, the fluorescence intensity of TPE-CHO in 90% water is 47 folds to in 10% water. These results suggested that TPE-CHO possess remarkable AIE properties. The PL spectra of Glu-TPE water suspension were displayed in **Fig. 3B**. It can be seen that the maximum emission wavelength of Glu-TPE FONs was located at 516 nm. The emission wavelength is obviously longer than that of TPE-CHO in water. The red shift phenomenon also indicated that the formation of Schiff base between TPE-CHO and ABBA. Well consistent with the fluorescent spectra, bright and uniform green fluorescence can be observed after Glu-TPE FONs were irradiated with UV lamp at 365 nm (Inset of **Fig. 4A**). The fluorescence picture was also implied that Glu-TPE FONs have dispersibility in aqueous solution. Furthermore, the excitation spectrum of Glu-TPE FONs is rather broad with maximum peak at 417 nm when the emission wavelength was set at 516 nm. As compared with typical TPE based AIE dyes, the optimal excitation wavelength was also remarkable red shift.[26] Based on the optical properties of Glu-TPE, we could draw a conclusion that indeed formation of amphiphilic AIE active Glucan through formation of dynamic bonds.

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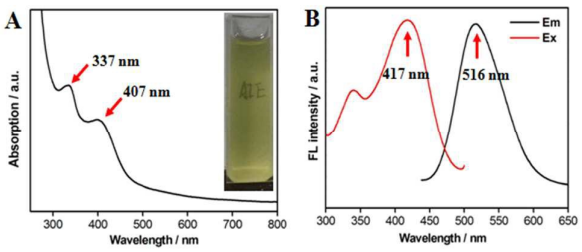

Fig. 3 The representative fluorescence and UV-Vis spectra of Glu-TPE FONs. (A) UV-Vis spectrum of Glu-TPE FONs. The absorption peak was located at 337 and 407 nm, evidencing the formation of Schiff base between TPE-CHO and ABBA. The inset is the water dispersion of Glu-TPE FONs. Good dispersibility and stability can be found, indicating the amphiphilicity of Glu-TPE. (B) Fluorescent excitation and emission spectra of Glu-TPE dispersed in aqueous solution. The excitation wavelength of Glu-TPE is 417 nm, while the emission wavelength was located at 516 nm.

The photostability of FONs play an important role for their biomedical applications. It has been demonstrated that the fluorescent nanoparitcles showed much better photostability as compared with the organic dyes.[49] Herein, the photostability of Glu-TPE FONs was examined via continuous irradiation water suspension of Glu-TPE for 1 h using UV lamp at 365 nm. And the fluorescent spectra of the water suspension of Glu-TPE before and after irradiation were determined. As shown in **Fig. 4A**, it can be seen that the fluorescent intensity of Glu-TPE was decreased from 201 to 186 a.u., demonstrating excellent photostability of Glu-TPE FONs. As reported from previous articles, pH-responsive property of fluorescent nanomaterials based on Schiff-based bind has important potential for biomedical application. For example, Liu *et al* described a novel salicylaldehyde Schiff-based sensor with aggregation induced emission performance for detection of Cu^{2+} and Al^{3+}. The colorimetric and fluorescence variations of salicylaldehyde Schiff-based sensor were happened after addition of Cu^{2+} and Al^{3+}.[50] On the other hand, Tang's group synthesized a pH-responsive fluorogen consisting of tetraphenylethene (TPE) and cyanine (Cy) units with AIE feature, which shows obvious pH variation of strong-to-medium red emission at pH 5-7, weak-to-nil red emission at pH 7-10 and nil-to-strong blue emission at 10-14. This unique pH-responsive performance makes it potential biomedical applications in cancer diagnosis and drug screening.[51] Therefore, the pH responsiveness of Glu-TPE FONs was also evaluated using fluorescent spectroscopy. As shown in **Fig. 4B**, the emission peaks of Glu-TPE FONs were located at 513, 516, 500 and 501 nm when the pH values were 10.8, 7.4, 5.6 and 3.2. The blue shift of emission of Glu-TPE FONs is due to the decomposition of Schiff base. On the other hand, significant decrease of fluorescent intensity of Glu-TPE FONs is likely ascribed to the precipitation of TPE-CHO during measurement.

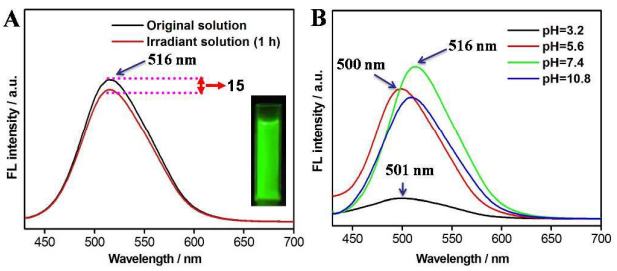

Fig. 4 (A) the representative fluorescent curves of Glu-TPE FONs dispersed in aqueous solution before and after UV lamp irradiation. The results demonstrated the great photostability of Glu-TPE FONs. (B) pH-responsive PL spectrum of Glu-TPE FONs dispersed in water with different pH values, which is used to demonstrate that existence of Schiff base (-CH=N-) in Glu-TPE FONs.

The great biocompatibility of fluorescent nanoparticles is of great importance for their application prospect in biomedical fields. Therefore, the cell viability of Glu-TPE FONs was detected to evaluate their potential biomedical application prospects. As shown in **Fig. S6**, no obvious decrease of cell viability could be observed after HeLa cells were incubated with 10-100 μg mL $^{-1}$ of Glu-TPE FONs for different time. The cell viability is still greater than 90% even the concentrations of Glu-TPE FONs were arrived to 100 μg mL^{-1}. The preliminary results indicated that Glu-TPE FONs possess desirable cytocompatibility. On the other hand, cell uptake behavior of Glu-TPE FONs was determined using CLSM. As shown in **Fig. 5A**, the fluorescent signal can be clearly observed when cells were irradiated with 405 nm laser. Furthermore, many dark areas were surrounded by the areas with fluorescent signal. Combined with the bright field image of cells, we could find that the areas with fluorescent signal were overlapped with the location of cells (**Fig. 5C**). The CLSM results clearly confirmed that Glu-TPE FONs can be internalized by cells. Moreover, the dark areas at the center of cells should be the location of cell nucleus. It is therefore we could conclude that Glu-TPE FONs are mainly distributed in the cytoplasm and cannot enter the cell nucleus. Taken advantages of the good biocompatibility, fluorescent properties and stimuli responsiveness, Glu-TPE FONs should be promising candidates for bioimaging, biosensing and drug delivery applications.

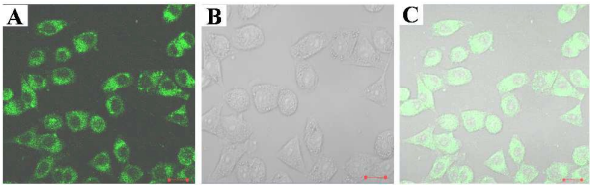

Fig. 5 CLSM images of HeLa cells incubated with 20 μg mL -1 of Glu-TPE FONs for 3 h. (A) fluorescent image after excitation with 405 nm laser. (B) Bright field. (C) Merged image. Scale bar = 20 μm

4. Conclusions

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In summary, a facile and high-efficient method for the fabrication of AIE active FONs with pH responsiveness has been developed in a one-pot strategy, which combined the hydrophobic TPE-CHO and hydrophilic carbohydrate polymers (Glucan) using ABBA as the bridge. The dynamic bonds (e. g. Schiff base and phenyl borate) were contained in Glu-TPE FONs. It is therefore Glu-TPE FONs can be potentially responded to the pH and glucose. On the other hand, the Glu-TPE polymers can self assemble into water dispersible nanoparticles because of their amphiphilicity. The hydrophobic AIE dye (TPE-CHO) was encapsulated in the core of FONs, which result in strong fluorescence emission for the AIE properties of TPE-CHO. However, the hydrophilic Glucan was covered on the surface of hydrophobic core, which leads to good water dispersibility of Glu-TPE FONs. As compared with the FONs based on conventional organic dyes, Glu-TPE FONs should possess better optical properties because AIE active dyes could effective overcome the ACQ effect. Furthermore, the strategy described in this work is rather simple and effective, which can occur under room temperature, air atmosphere and absent of toxic metal catalysts. Finally, the stimuli responsiveness of Glu-TPE FONs makes them more promising for various biomedical applications, such as pH sensors and pH/ glucose controlled drug delivery.

Acknowledgements

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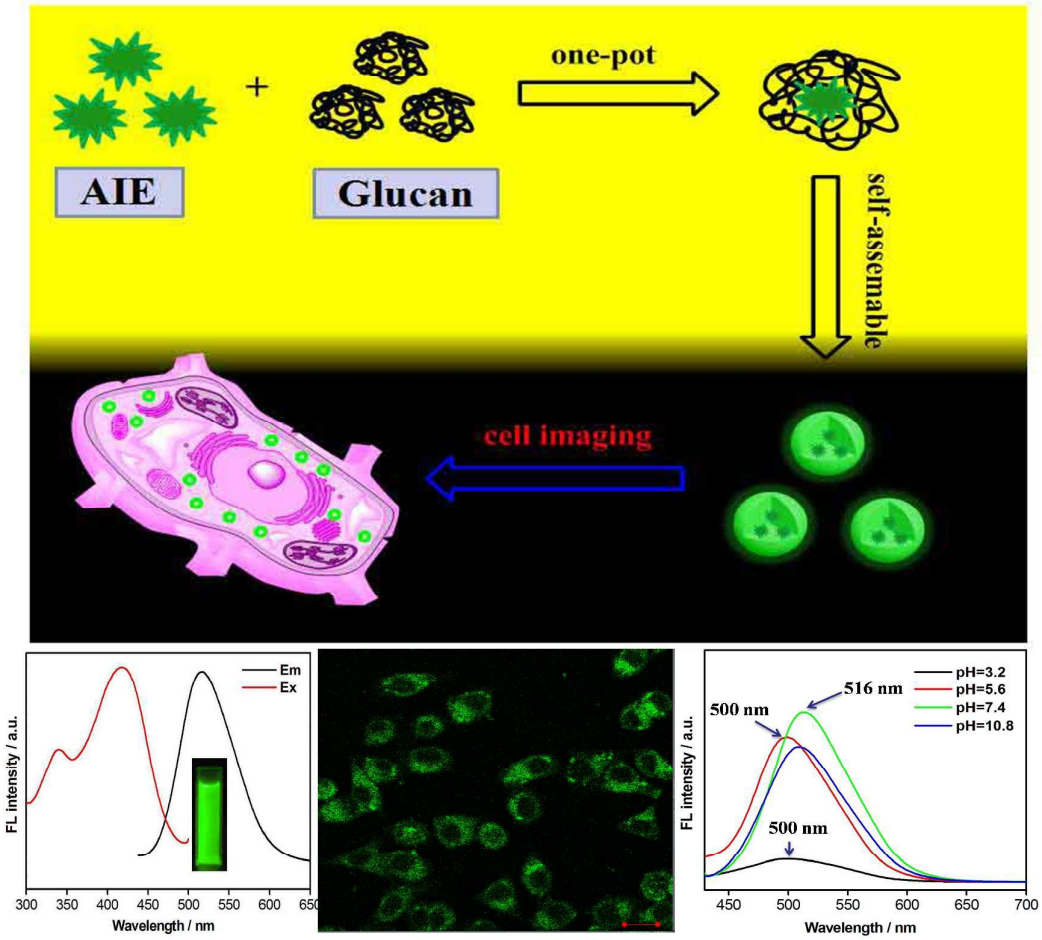

A one-pot strategy has been developed for preparation of stimuli responsive AIE active glucan through formation of dynamic Schiff base and phenyl borate