



## Fabrication and biological imaging of hydrazine hydrate cross-linked AIE-active fluorescent polymeric nanoparticles



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### ABSTRACT

Amphiphilic copolymers play a paramount role in the fabrication of fluorescent polymeric nanoparticles (FPNs) through the self-assembly procedure. In this work, novel hydrazine hydrate cross-linked amphiphilic poly(PEG-co-FHMA) copolymers were constructed via reversible addition-fragmentation chain transfer (RAFT) polymerization, containing an aggregation-induced emission (AIE) active hydrophobic moiety and a hydrophilic poly(ethylene glycol) (PEG) group. Different characterization techniques have been employed to confirm their successful synthesis. Due to their amphiphilic property, the resulting poly(PEG-co-FHMA) copolymers can self-assemble into FPNs in aqueous solution and form poly(PEG-co-FHMA) FPNs with size ranging from 100 to 200 nm. The investigation of photophysical properties demonstrated poly(PEG-co-FHMA) FPNs possess strong fluorescence, large Stokes shift, excellent AIE characteristic, low critical micelle concentration and remarkable photostability. Biological assay results suggested that these cross-linked AIE-active FPNs are of low toxicity and excellent cell dyeing performances. All of these features make them promising candidates for biomedical applications. As compared with typical AIE-active FPNs based on the synthetic AIE-active compounds, the novel cross-linked AIE-active FPNs based on the Schiff base is rather simple, good designable and universal. More importantly, this strategy could also be adopted for preparation of a large number of AIE-active FPNs because of the well designability of copolymers and salicylaldehyde derivatives. Thus this work will provide a novel route for preparation of multifunctional AIE-active FPNs in a rather facile manner.

### 1. Introduction

Fluorescent polymeric nanoparticles (FPNs) play a significant role in biological imaging, cancer diagnosis and therapy owing to their high luminescence, superior photo-bleaching resistance, excellent physiological stability, good cellular retention and excellent biocompatibility [1–4]. The pervasive FPNs, which contain both hydrophilic and hydrophobic segments, could be constructed through a self-assembly strategy [5,6]. By virtue of the amphiphilic feature, the hydrophobic fluorophores are clustered as the core whereas the hydrophilic moieties are exposed to aqueous solution forming a uniform shell. The shell not only protects the fluorophores against the biological environment, but also endows the FPNs with good water dispersibility and stability [6–8]. Nevertheless, traditional organic small molecular dyes such as fluorescein and perylene usually suffer from aggregation-caused quenching

(ACQ) due to strong intermolecular  $\pi$ - $\pi$  interactions, which seriously restricted their potential applications in FPNs [9]. In sharp contrast, a class of unusual aggregation-induced emission (AIE) dyes, which are induced to emit efficiently by the aggregate formation, have been applied in constructing FPNs for circumventing the interference of ACQ phenomenon [10–12]. So far, a series of typical AIE fluorophores including siloles [13], tetraphenylethylene (TPE) [14–17], distyrylanthracene [18], cyano-substituted diarylethene derivatives [19–21] and Schiff base based molecules [22–26] have been widely researched and developed for fabricating AIE-active FPNs for potential biomedical applications.

Recently, various strategies mainly including non-covalent and covalent methods for the construction of AIE-active FPNs have been extensively exploited [27–36]. For instance, our group employed commercial available surfactant and synthesized controllable

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amphiphilic block copolymers for encapsulating AIE dyes to construct water soluble and biocompatible FPNs [37,38]. Although the physical encapsulation is relatively simple and efficient, some drawbacks such as the leakage of dyes and instability on dilute solution could not be avoided. Therefore, so many covalent strategies, which include various polymerization methods [6], Schiff-base reaction [39] and multi-component reactions (MCRs) [40], have been continuously reported to prepare AIE-active FPNs. For example, we designed many functionalized AIE molecules that have been utilized to produce AIE-active FPNs based on different chemical methods. Chen et al. [41] developed a novel AIE active zwitterionic copolymer via combine reversible addition-fragmentation chain transfer (RAFT) polymerization with Schiff-base reaction for cancer theranostics. However, such non cross-linked self-assembled system is often unstable in dilute solution below the critical micelle concentration (CMC) [42]. Thus, it is important to be aware of the development of cross-linked FPNs with low CMC. Xie et al. [20] reported chitosan-based cross-linked AIE-active FPNs with low CMC ( $0.063 \text{ mg mL}^{-1}$ ) for cell imaging application through ring-opening polymerization. Despite the significant advances in fabrication of AIE-active FPNs with high brightness, high water dispersibility, low CMC and excellent biocompatibility, more new construction methodologies are still highly desirable.

In this contribution, encouraged by these previous research studies, we herein innovatively designed a cross-linked strategy that hydrazine hydrate as the cross-linking agent for conjugating salicylaldehyde (SA)-functionalized amphiphilic copolymers to obtain AIE-active cross-linking copolymers (poly(PEG-co-FHMA)) (Scheme 1). As-prepared poly(PEG-co-FHMA) tended to self-assemble into FPNs in aqueous solution in which AIE moiety aggregate in core while poly(ethylene

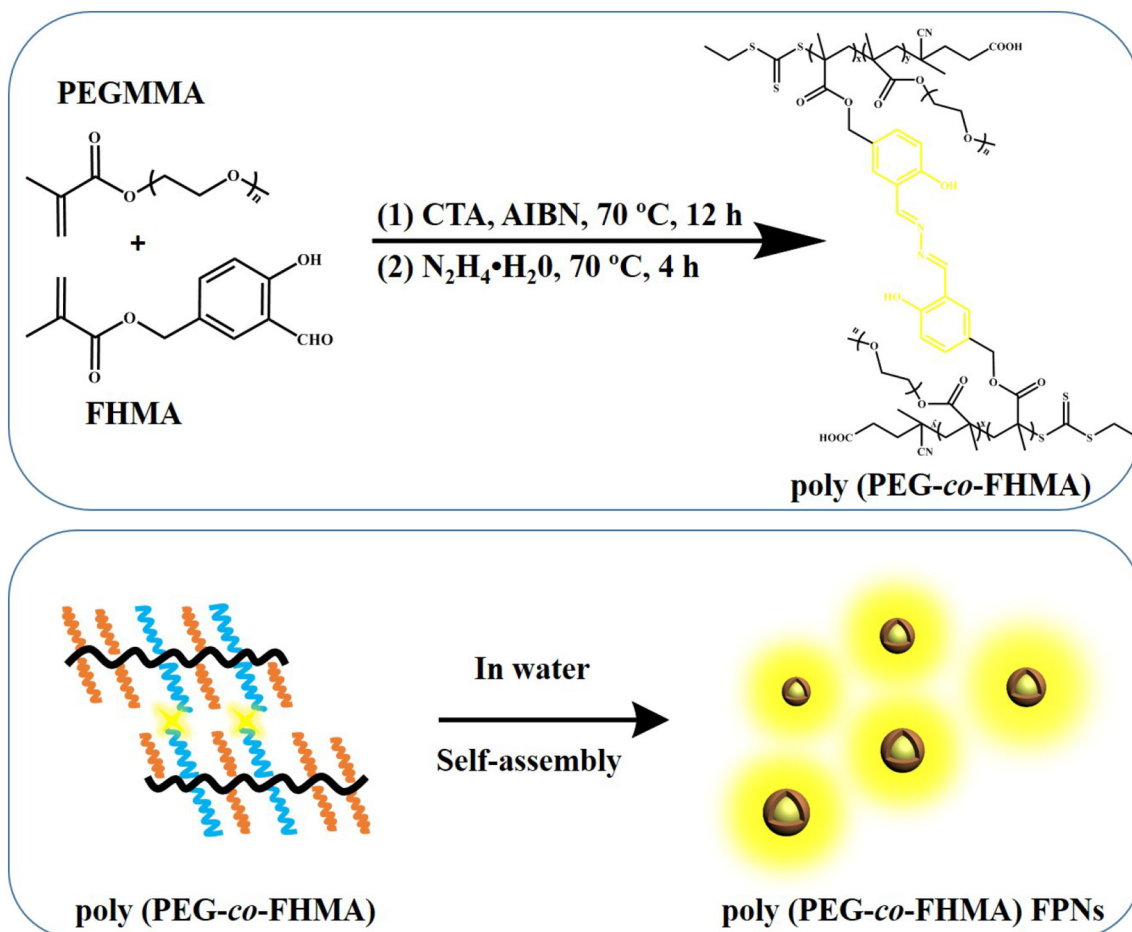
glycol) (PEG) group form a protective shell. The chemical structure of poly(PEG-co-FHMA) FPNs were characterized by  $^1\text{H}$  nuclear magnetic resonance (NMR) spectra, fourier transform infrared (FT-IR) spectroscopy. Furthermore, the photophysical and material properties of poly(PEG-co-FHMA) FPNs were determined by ultraviolet (UV)-visible absorption spectra, fluorescence spectra, transmission electron microscopy (TEM) and dynamic light scattering (DLS). More importantly, the cytotoxicity evaluation of the poly(PEG-co-FHMA) FPNs displayed excellent biocompatibility and can be effective cell dyeing performance. All of the above results endow these poly(PEG-co-FHMA) FPNs great potential for biomedical applications.

## 2. Experimental sections

### 2.1. Materials and characterization

Salicylaldehyde (SA, Heowns, 99%), methacrylic acid (Heowns, 99%) and poly(ethylene glycol) methyl ether methacrylate (PEGMMA,  $M_n \sim 950 \text{ g mol}^{-1}$ , Aladdin) were used as purchased. 2, 2'-Azobis(isobutyronitrile) (AIBN, Sinopharm Chemical Reagent, 99%) was purified by recrystallization from ethanol. 4-Cyano-4-(ethylthiocarbonothioylthio) pentanoic acid was synthesized according to the literature methods and used as the chain transfer agent (CTA). Anhydrous 1,4-dioxane was distilled from sodium benzophenone ketyl under dry nitrogen and stored under a nitrogen atmosphere before use. Deionized water was used in throughout the experiments. All other reagents and solvents, which are analytical grade, were purchased from commercial sources and used directly without further purification.

$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectroscopy was performed in a Bruker



**Scheme 1.** Top: synthetic route to the poly(PEG-co-FHMA) amphiphilic copolymer. Bottom: scheme showed the fabrication of poly(PEG-co-FHMA) FPNs.

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