High-performance nano-splitters containing aggregation-induced emission luminogens for stereoselective crystallization obtained via polymerization-induced self-assembly

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INTRODUCTION

With the development of modern pharmacy, people have been aware that two enantiomers may have totally different effects in vivo: one could be effective component while the other less effective\(^{[1–2]}\) or even toxic.\(^{[3]}\) In some cases, a pair of enantiomers show synergistic effects in specific proportioning.\(^{[4]}\) Antagonistic effect.\(^{[5–6]}\) or disparate functionality.\(^{[7]}\) Not only from the respect of practical applications, but also the necessity for thorough understanding the pharmacology and pharmacokinetics of two enantiomers, it is highly desired to seek efficient methods to obtain enantiopure compounds.

Although asymmetric synthesis has greatly advanced in recent decades,\(^{[8–11]}\) the majority of chiral drugs and their intermediates are still obtained by chiral resolution of racemates because of low cost, easy operation, and high reliability for mass production. Among chiral resolution methods,\(^{[12–17]}\) stereoselective crystallization is the most convenient and economical one to obtain enantiopure compounds in large scale.\(^{[18,19]}\) For conglomerate-forming racemic compounds, preferential crystallization (PC)\(^{[20]}\) (including heterogeneous nucleation\(^{[21,22]}\)) and reverse crystallization (RC)\(^{[23–25]}\) have been developed to obtain one enantiomorph from a pair of enantiomers. PC utilizes optically pure compounds as the seeds to enhance the nucleation and crystal growth of desired enantiomer, while RC employs “tailor-made additives” to disturb or delay the crystal growth of the undesired enantiomer by stereoselective residence on its specific crystal faces. Other than small molecule and polymeric additives used in RC, some nanoparticles are reported to fulfill the crystallization resolution via enantioselective nucleation effect.\(^{[26–28]}\) However, limited by kinetic resolution nature, only one

Abstract
Collecting both enantiomers with high optical purity and yield in a single crystallization process can be achieved by adding aggregated polymeric “tailor-made” additives, known as nano-splitters. Inefficient preparation and large addition amount have hindered the practical application of such amazing nanoparticles. Herein, we report the first nano-splitters containing aggregation-induced emission luminogens prepared via polymerization-induced self-assembly of block copolymer, poly[(S)-2-(tert-butoxycarbonylamino)-6-(methacrylamido)hexanoic acid]-b-polystyrene, followed by the removal of tert-butoxycarbonyl groups. When added into the super-saturated solution of racemic amino acids (a.a.) with seeds, the fluorescent labeled nano-assemblies enantioselectivity dyed the crystals of S-a.a. and enabled the separation from colorless R-a.a. crystals in terms of fluorescent difference. Both enantiomers were obtained with high optical purity and yield (e.g., R-asparagine monohydrate, >99 ee%; S-asparagine monohydrate, ~94 ee%; 88% total yield). Owing to a low detection limit of fluorescence, the addition amount was reduced to 0.03 wt% without remarkably compromising the ee values of both enantiomers. Due to the low addition amount and efficient synthesis, the output–input ratio was increased greatly.

KEYWORDS
aggregation-induced emission (AIE), chiral, conglomerate, polymerization-induced self-assembly, RAFT, stereoseparation
enantiomer can be obtained in a single unit operation, and the yield is usually quite low (<20%). “Viedma ripening” can provide enantiopure compounds with nearly 100% yield merely by grinding, but only works for the substrates that can be racemized spontaneously under crystallization conditions.[29,30]

Recently, we have prepared dyed or magnetic responsive “tailor-made” additives of polymeric nanoparticles, known as nano-splitters, through self-assembly of graft or block copolymers in dilute solution.[31,32] These functional nanoparticles selectively dye or magnetize one enantiomorph and enable the stereoseparation of both enantiomers with high optical purity and yield in a single crystallization process. Limited to the low sensitivity of color and magnetism, nano-splitters have to be added in a relatively large amount to effectively distinguish two enantiomorphs (>1.5 wt%, functional segments: rac-substrate, w/w). Moreover, the self-assembly of amphiphilic copolymers in solution suffers from low preparation efficiency, which greatly hinders the use of nano-splitters in large-scale production.[33,34]

Polymerization-induced self-assembly (PISA) has become an efficient method to produce categories of nano-objects varying in morphology via simultaneous polymerization and in situ self-assembly.[35–39] Compared to the traditional block copolymer self-assembly method, PISA usually enables a much higher solid content (usually 10–30 wt%), which is quite favored in large scaled preparation of polymeric assemblies. Besides, guest molecules could also be encapsulated into the assemblies in situ to form functional assemblies.[40-43] Among these guests, the introduction of aggregation-induced emission luminogens (AIEgens)[44–48] endows the assemblies with quite sensitive fluorescent property because of avoiding the aggregation-caused quenching.[49–51] Besides, AIEgens are advantageous for wash-free imaging that the discrete luminogens in solution make almost no contribution to the total emission in comparison to the encapsulated luminogens in the assemblies.[52–55]

Herein, we described a strategy for the efficient production of “nano-splitters” with AIE fluorescence probes entrapped into the hydrophobic zones through PISA process in one pot (Figure 1A). The solid content was significantly raised (14%∼22%, Figure 1B) with a good dispersibility. The obtained water-dispersed assemblies were directly used in the resolution of racemic amino acids. Colorless and green fluorescent crystals with over 94 ee% were collected in a unit operation. Owing to the lower detection limit of fluorescence (Figure 1C), the adding amounts of nano-splitters were greatly reduced to 0.03 wt%, which greatly improved the output–input ratio.

RESULTS AND DISCUSSION

Reversible addition-fragmentation transfer (RAFT) dispersion polymerization of styrene (St) was conducted in methanol at 80°C by using azodisobutyronitrile (AIBN) as the initiator and narrowly distributed trithiocarbonate-terminated poly[(S)-2-(tert-butoxycarbonylamino)-6-(methacrylamido)hexanoic acid] (PMALBoc-CDP) as the macromolecular chain transfer reagent. PMALBoc-CDP was prepared by following the previously reported procedures, and its number-averaged degree of polymerization (DP) was fixed to 29 since the polymer of such size was proved to

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**FIGURE 1** (A) Schematic diagram of reversible addition-fragmentation transfer (RAFT) dispersion polymerization of styrene and crystallization resolution process of rac-asparagine monohydrate and rac-threonine. (B) Photos of solutions obtained via polymerization-induced self-assembly (PISA) and block copolymer self-assembly, respectively. Flocculent precipitation occurs at 0.1 wt% solid content in the block copolymer self-assembly experiment (SI method), while the stable dispersion is maintained at 22 wt% solid content in the PISA process. (C) Detection limit of nano-splitters in UV-visible absorption and fluorescence spectrum (FLS). The detection limit is reduced by 82 times.
Methanol was chosen as the copolymerization solvent since it enables PISA of poly(acrylic acid)-b-polystyrene (PAA-b-PS) to form assemblies with diverse morphologies, and the solubility of PMALBoc-CDP is similar with PAA. The molar ratio of St, PMALBoc-CDP, and AIBN was 7500/5/1 (c(PMALBoc-CDP) = 30 mg/ml). 4-Dicyanomethylene-2,6-distyryl-4H-pyran (DCMDSP) was added as AIE lumogen (1 mg/ml), which was encapsulated into the polystyrene cores in situ through the hydrophobic interactions. Block copolymers with different molar masses were obtained by monitoring the polymerization time (5–25 h) with the solid contents of 13%–22%. As shown in Figure 2A, the polymerization mixture was initially transparent owing to the good solubility of PMALBoc29-CDP, St, and DCMDSP in methanol. The solution turned turbid at 5 h implying the occurrence of in situ self-assembly. As the polymerization proceeded further, the polymerization mixture gradually turned translucent and even opaque. After a predetermined reaction time, unreacted styrene and unpacked luminogens were removed by dialyzing against methanol to obtain the dispersion of poly[(S)-2-(tert-butoxycarbonylamino)-6-methacrylamidoheptanoic acid]-block-polystyrene (PMALBoc29-b-PSn, n denotes the DP of polystyrene). A weighted portion of the obtained dispersion was taken out and reacted with trimethylsilyl diazomethane to produce methyl esterified block copolymers, PMALBoc29CH3-b-PSn. Gel permeation chromatography (GPC) and 1H-NMR measurements were conducted to prove the success of RAFT polymerization (SI method, Figures S1 and S2). As summarized in Table 1, five block copolymers were prepared, and the DPs of PS segments estimated by GPC were 295, 385, 463, 478, and 517, separately. The remained PMALBoc29-b-PSn dispersions were deprotected by adding acetic acid/HCl. After dialyzing against water, five water-dispersed fluorescent nano-splitters, FNS-n (n represents the DP of PS segment by GPC), were obtained. The dispersibility of FNS-n in water was quite good. No precipitation was observed after 8 months even with 22% solid content. In a contrast, the dispersion system prepared via block copolymer self-assembly was unstable at a solid content of 0.1% (Figure 1B). It magnified the advantage of PISA in preparing nano-splitters. The morphologies of assemblies were investigated by using transmission electron microscopy (TEM) after the polymerization mixtures were dialyzed against methanol. As shown in Figure 2A, the obtained assemblies showed a morphological transition from micelles to vesicles: When n increased from 295 to 463, uniform spherical micelles were observed, and their average sizes were increased from 25 to 33 nm. Micelles and very small amounts of vesicles coexisted when n came to 478. Only vesicles with a uniform size of 49 nm were observed when n reached to 517, and the membrane thickness was evaluated to be 6.4 nm. Negative-staining TEM further supported this speculation (Figure S6). Its mean square radius of gyration ($R_g$) and the hydrodynamic radius ($R_h$) were measured by using the static and dynamic light scattering to conform its morphology. The results showed that $R_g = 86.5$ nm, $R_{h,0} = 78.4$ nm and $R_g/R_h = 1.10$, which suggested its morphology was vesicle and consistent with TEM tests. To obtain the FNS-n utilized in the crystallization resolution, the N-Boc group of assemblies should be removed (SI method, Figure S7). After being dialyzed against water, the morphological change of these assemblies was neglectable (Figure 2G-K).
### Table 1: Results of polymerization-induced self-assembly (PISA) at different reaction time

| Samples  | Reaction time | Solid content | $M_n \times 10^{-4}$ | $D$  | DP of PS$^b$ | FLC$^c$ | Morphology | Diameter$^f$ (nm) |
|----------|---------------|---------------|-----------------------|------|--------------|---------|------------|------------------|
| FNS-295  | 5 h           | 13%           | 4.06                  | 1.17 | 295          | 0.27    | M.$^d$     | 25 ± 2.0         |
| FNS-385  | 10 h          | 16%           | 5.00                  | 1.23 | 385          | 0.34    | M.         | 28 ± 2.2         |
| FNS-463  | 15 h          | 19%           | 5.80                  | 1.33 | 463          | 0.34    | M.         | 32 ± 1.2         |
| FNS-478  | 20 h          | 20%           | 5.96                  | 1.22 | 478          | 0.33    | M. and V.$^e$ | 35 ± 2.1 and 45 ± 2.3$^g$ |
| FNS-517  | 25 h          | 22%           | 6.37                  | 1.38 | 517          | 0.24    | V.         | 49 ± 1.9         |

Abbreviations: FNS, fluorescent nano-spliters; DP, degree of polymerization; FLC, fluorochrome loading content; PS, polystyrene.

$^a$Number-averaged molar mass ($M_n$), weight-averaged molar mass ($M_w$), and molar mass polydispersity ($D = M_w/M_n$) of PMALBoc$_2$CH$_3$-b-PS$_n$ were obtained by gel permeation chromatography (GPC) in tetrahydrofuran (THF).

$^b$Degree of polymerization (DPs) of polystyrene (PS) segments calculated by gel permeation chromatography (GPC) (the values by $^1$H NMR were put in Figure S4).

$^c$Fluorochrome loading content (FLC) can be calculated using the formula, $[w(\text{AIEgen})/w(\text{assemblies})] \times 100\%$. Weights of AIEgens packed in the assemblies were calculated by analyzing their absorbance in ultraviolet-visible (UV-vis) spectra (Test method was shown in the support information. The spectra and standard curve were shown in Figure S5).

$^d$Spherical micelle.

$^e$Vesicle.

$^f$Diameters were measured and counted from transmission electron microscopy (TEM) images.

$^g$Average diameters of micelle and vesicle are 35 nm and 45 nm, respectively.

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**Figure 3** The fluorescent properties of FNS-n. (A) Fluorescence spectra of mixtures containing AIEgens and polymer before and after the polymerization-induced self-assembly (PISA) process (20 h). $c$(PMALBoc-CDP) = 30 mg/ml, $c$(DCMDSP) = 1 mg/ml, wavelength of excitation light: 400 nm. (B) Fluorescence emission and excitation spectra of FNS-n, $c$(FNS-n) = 0.5 mg/ml, wavelength of excitation light in emission spectra is 400 nm, wavelength of emission light in excitation spectra is 533 nm. (C) Fluorescence spectra of nano-splitter (FNS-478) in different concentration (0.5–0.07 mg/ml). Wavelength of excitation light: 400 nm. Insert: The curve of fluorescence intensity varying with concentration. (D) Normalized fluorescence spectra of nano-splitter (FNS-478) in solid state and water dispersion system (0.5 mg/ml), wavelength of excitation light: 400 nm. Insert: Digital photos of nano-splitter (FNS-478) in solid state (right) and water dispersion system (left).

The assembling process was accompanied by yellow-green-colored suspension visible to naked eyes, which suggested the loading of AIEgens into the hydrophobic cores (Figure 2A). To confirm the loading of AIEgens, the fluorescence emission spectra before and after the PISA processes were tested. Taking FNS-478 as an example, as shown in the Figure 3A, the fluorescence intensity before polymerization was quite weak but was greatly enhanced after the PISA process, because the mobility of DCMDSP encapsulated into the PS core was limited.$^{[56]}$ The discrete AIEgens in solution with the quite weak emission had no effect on the fluorescence of assembly-encapsulated AIEgens, even if both types of emissive species coexisted in the polymerization solution. All the FNS-n showed similar fluorescence emission and excitation spectra (Figure 3B), indicating there was no significant change of molecular conformation of AIEgens in the hydrophobic domain of different assemblies.$^{[58]}$ However, when the DP of PS segment increased from 295 to 517, the intensity of fluorescence slightly decreased, owing to the fewer number of nano-assemblies at the fixed weight.
FIGURE 4  (A) Photos under UV light and fluorescence spectra excited at 400 nm of colorless R-Asn-H₂O crystals and green S-Asn-H₂O crystals, c(Asn-H₂O) = 10 mg/ml. (B) Structural influence of nano-splitters on chiral resolution performance. (C) The fluorescence intensity ratio of green/colorless crystals at 533 nm. Insert: Digital photos of two kinds of crystals in different addition amounts of nano-splitters under UV light. (D) 3D image of the green crystal reconstituted by recording the laser scanning confocal microscope photos of different focal planes. The green pixels mean that there are some AIEgens at these positions.

concentrations of FNS-n, considering the slight increase of the encapsulated amounts of AIEgens in the assemblies with the increase of the molecular weight of copolymers (Table 1). Fluorescence intensity of FNS-478 increased linearly with the increased concentration (Figure 3C), which meant the fluorescence of AIEgens packed in the assemblies showed the classic variation with mass concentration. After lyophilization, these nano-splitters also showed strong yellow–green fluorescence in the solid state, so that when they were entrapped into the enantiomeric crystals, it was easy to be recognized even by naked eyes (Figure 3D). The powders can be redispersed in the water and thus can be conveniently weighted and utilized in the crystallization resolution.

Rac-asparagine monohydrate (rac-Asn-H₂O) was used to demonstrate the selective crystallization process induced by FNS-n. A predetermined amount of FNS-n powders was added into the hot supersaturated solution of rac-Asn-H₂O. After ultrasonic dispersion, the mixture was cooled down to 25°C slowly and seeded with R-Asn-H₂O. It was found that colorless crystals precipitated first, and then green fluorescent crystals appeared (2 h later). The crystal yields reached maximum (about 40%) after the solution was stored for 72 h at 25°C without evaporating solvent. The green fluorescent crystals (several millimeters) were larger than the colorless crystals (hundreds of micrometers). Figure 4A showed the photos under UV light and fluorescence spectra excited at 400 nm of two types of crystals. In terms of size and photoluminescence difference, these crystals were easily separated by manual picking. Since the fluorescence detector is often used in the flotation process of fluorite from gangue particles,[59] it holds the potential to turn hand-pick up method into automated selection in practical production. As expected, the green crystals consisted of S-a.a. with over 85 ee%, while the colorless ones were R-a.a. with over 99 ee% according to the chiral HPLC results (Figure 4B and Figure S9).

The successive formation of colorless and green fluorescent crystals was attributed to the acceleration effect of R-seeds and the multiple functions of nano-splitters.[31,32] The addition of R-seeds decreased the nucleation barrier of R-Asn-H₂O and promoted its crystallization. The nano-splitters consisted of achiral hydrophobic polystyrene core and chiral hydrophilic PMAL shell (S-configuration). PMAL segments could stereoselectively reside on the specific faces of S-Asn-H₂O clusters, that were smaller than the critical nucleus, and delayed the nucleation and crystal growth of S-Asn-H₂O. On the other hand, these clusters were entrapped around the nano-splitters by PMAL segments and became bigger through Ostwald ripening. Once the clusters were larger than the size of critical nucleus, the crystallization of S-Asn-H₂O was triggered.

It should be noted that the absence of chiral seeds would not reduce the stereoseparation performance of nano-splitters but remarkably increase operation time. When FNS-478 was added alone into the supersaturated solution of rac-Asn-H₂O, crystals would not be observed until 1 week. But finally, two kinds of crystals with different colors can still be obtained by extending crystallization time (Figure S10 and S11A, colorless R-crystals: ee > 99%, green S-crystals: ee ~95%). It might be rationalized by the inhibiting effect of nano-splitters, that delayed the nucleation and crystal growth of both enantiomers.

The morphology of FNS-n slightly influenced the resolution performance. The best resolution results (R-a.a.: > 99.9 ee%, S-a.a.: ~95.6 ee%, yield: 40%) were obtained when 0.3 wt% of FNS-478 was used as the additives (Figure 4B).
The relative poorer resolution performance of vesicles than the micelles was properly due to the PMAL segments in the internal water phase of vesicle, that could not tune the crystallization.

To further improve the crystal yields, solvent evaporation was adopted to maintain continual oversaturated state after the crystallization reached equilibrium. In order to avoid crystal adhesion, the evaporation was stopped when water content was reduced by roughly 80%. The final total yield of the crystals reached 88%, without reducing the ee values of both green and colorless crystals significantly ($R$-a.a.: $> 99.9$ ee%, $S$-a.a.: $\sim 94$ ee%) (Figure S12).

Besides, 3D fluorescent image of the green crystals revealed that these fluorescent nanoparticles gathered on both the body and the surface of the crystal (Figure 4D, Figure S13), indicating that the polymeric assemblies were entrapped in the crystal at the very beginning of the crystallization process and re-adsorbed onto the surface when the crystallization stopped. More importantly, owing to the strong fluorescence of the $S$-crystals and the high sensitivity of fluorescence detectors, the adding amounts of nano-splitters were further reduced to $\sim 0.03$ wt%. At this limit, the two kinds of crystals were still discriminated from each other (Figure 4C inserted picture, Figure S14) without reducing the ee values of both enantiomorphs too much (green crystals: 88 ee%, colorless crystals: 98 ee%). When the adding amounts of nano-splitters were further reduced, due to the extremely low concentration of nano-splitters, the probability of $S$-crystals without nano-splitters would be improved, and as a result, the ee values of colorless crystals would decrease dramatically. In our previous work $^{[11,32]}$ by using nano-splitters powder containing 1 mg PMAL can only obtain 26 mg enantiomeric crystals due to low sensitivity of color and magnetism. But in this work, by using nano-splitters powder containing 1 mg PMAL, 1.3 g of crystals can be obtained, the input–output ratio greatly went down by two orders of magnitude herein.

The nano-splitters were also utilized to separate other conglomerate forming amino acids, that is, threonine (Thr). Under similar crystallization condition, FNS-478 yielded colorless $R$-Thr crystals (67 ee%) and green fluorescent $S$-Thr crystals (78 ee%). The relatively lower optical purities of $R$- and $S$-Thr than those of Asn-$\text{H}_2\text{O}$ enantiomers were due to their distinct crystal habits. Thr formed fragile laminar crystals and the difference in fluorescence intensity between two types of crystals were small (Figure S15). It was difficult to separate two enantiomorphs by manual selection. This result suggested that the crystal habit was an important factor determining the application scope of nano-splitters thereof.

In summary, a kind of fluorescent “nano-splitters” were prepared through a polymerization-induced assembly process by using PMAL-Boc-CDP as the macromolecular chain transfer agent, St as the monomer, and DCMDS as the fluorescent dyes followed by deprotection of N-Boc groups. The DCMDS was encapsulated into the hydrophobic cores of the nano-assemblies in situ through the polymerization, and its aggregation triggered its strong fluorescence. The spherical micelles and vesicles were obtained in succession as the polymerization proceeded. The solid content can be improved by 220 folds compared with the block copolymer self-assembly. When used to control the crystallization of conglomerates, two enantiomorphs with different color, morphologies, and fluorescent properties were obtained in a single crystallization process with a total yield of 88% and over 94 ee% for both enantiomers. This strategy not only allowed stable dispersions of nano-splitters with high concentration (up to 22 wt%), but also reduced the adding amount to 0.03 wt% due to the lower detection limit of fluorescence. Thus, a quite low input–output ratio can be achieved, which is 50 folds lower than our previous work. We believe that this strategy can pave the way for the practical use of nano-splitters in large scales.

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**CONFLICT OF INTEREST**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

**DATA AVAILABILITY STATEMENT**

The data that support the findings of this study are available from the corresponding author upon request.

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