Gels

Triterpenoid-Based Self-Healing Supramolecular Polymer Hydrogels Formed by Host–Guest Interactions

Ying Li,[a, d] Jianzuo Li,[a, d] Xia Zhao,[a] Qiang Yan,*[b] Yuxia Gao,[c] Jie Hao,[c] Jun Hu,*[a] and Yong Ju[c]

Abstract: Pentacyclic triterpenoids, a class of naturally bioactive products having multiple functional groups, unique chiral centers, rigid skeletons, and good biocompatibility, are ideal building blocks for fabricating versatile supramolecular structures. In this research, the natural pentacyclic triterpenoid glycyrrhetinic acid (GA) was used as a guest molecule for β-cyclodextrin (β-CD) to form a GA/β-CD (1:1) inclusion complex. By means of GA and β-CD pendant groups in N,N'-dimethylacrylamide copolymers, a supramolecular polymer hydrogel can be physically cross-linked by host–guest interactions between GA and β-CD moieties. Moreover, self-healing of this hydrogel was observed and confirmed by step-strain rheological measurements, whereby the maximum storage modulus occurred at a [GA]/[β-CD] molar ratio of 1:1. Additionally, these polymers displayed outstanding biocompatibility. The introduction of a natural pentacyclic triterpenoid into a hydrogel system not only provides a biocompatible guest–host complementary GA/β-CD pair, but also makes this hydrogel an attractive candidate for tissue engineering.

Introduction

Pentacyclic triterpenoids, as a class of bioactive natural products, are abundant in many plants in the form of free acids or aglycones.[1–5] Generally, they consist of six isoprene units with multiple functional groups, unique chiral centers, rigid skeletons, and good biocompatibility. These features not only endow them with pharmacological properties,[6–9] but also make them ideal building blocks for self-assembling versatile supramolecular structures.[10–13] Since the first supramolecular organogel based on a pentacyclic triterpenoid was reported by Bag and co-workers in 2005,[14] a series of pentacyclic triterpenoid-based small molecules have been designed and synthesized to study their supramolecular gelation behavior.[15–24] For example, Mezzenga et al. reported that the right-handed fibril networks in the hydrogel of glycyrrhizic acid could be utilized as scaffolds for hybrid nanomaterials in heterogeneous catalysis.[15] We found that a pyridinium-tailored glycyrrhetinic acid amphiphile could transfer and magnify its chirality at the supramolecular level, and consequently result in the formation of helical nanofibers.[16] However, these low molecular weight gels have limitations in applications due to the participation of toxic organic solvents or weak mechanical properties. Thus, it is necessary to explore polymeric hydrogels based on pentacyclic triterpenoids, which will may open a new scenario for pentacyclic-triterpenoid-based biomaterials.

Self-healing polymeric hydrogels exhibit improved safety and extended lifetime in comparison with traditional hydrogels. Furthermore, they can restore their initial properties after interior or exterior cracking owing to the dynamic/reversible linkages in the hydrogel networks.[25–28] To date, a variety of self-healing hydrogels have been designed for diverse applications, such as biosensors, drug-delivery systems, wound healing, and shape-memory materials.[29–36] Nonetheless, reports on using abundant biocompatible natural products as building blocks in self-healing hydrogels are still rare.[32] Therefore, designing self-healing polymeric hydrogels based on natural pentacyclic triterpenoids that have good mechanical strength, structural stability, and biocompatibility remains a considerable challenge.

One efficient approach is to utilize a noncovalent system to construct self-healing hydrogels, since they can autonomously restore their initial properties.[37–39] Among these approaches, host–guest systems are crucial, as they combine multiple dy-
namic interactions and form dynamic reversible inclusion complexes, which play an important role in constructing self-healing hydrogels.\textsuperscript{[40–46]} In these works, azobenzene, ferrocene, and adamantyl groups were utilized as guest groups attached to different functional main chains, and thus resulted in self-healing hydrogels by complexation with β-cyclodextrin (β-CD). To explore biocompatible compounds as guests, we chose glycerol–rhetinic acid (GA, a natural pentacyclic triterpenoid) and β-CD as the guest and host, respectively, both of which are biocompatible compounds. They were copolymerized with N,N-dimethylacrylamide (DMA) to afford the copolymers poly(DMA-GA) and poly(DMA-CD) with different GA and β-CD contents (Figure 1). Due to the dynamic host–guest interactions between GA and β-CD units, this supramolecular hydrogel exhibited good self-healing properties. Moreover, these polymers displayed outstanding biocompatibility, which makes them attractive candidates for tissue engineering.

### Results and Discussion

#### Polymer design and characteristics

Statistical copolymers with GA or β-CD pendants were synthesized by free-radical polymerization (Figure 1 and Scheme S1 of the Supporting Information). The copolymerization of DMA with GA-based methacrylate provided water-soluble copolymer poly(DMA-GA) bearing 1–4\% GA pendant groups. A GA moiety was linked with a short spacer by an esterification reaction to give a flexible GA species to interact with a host molecule. The characteristic methyl proton peaks of GA moieties at 0.73, 0.92, 1.05, 1.06, 1.07, and 1.32 ppm were clearly observed in the $^1$H NMR spectrum, and the molar fractions of GA units in copolymers were calculated by integration (Supporting Information, Figure S1). For poly(DMA-CD), precursor polymer poly(DMA-NPA) was obtained by copolymerization of DMA with an active ester monomer (NPA). Then, amino-CD substitution of NPA moieties on poly(DMA-NPA) resulted in poly(DMA-CD). The extent of CD substitution was estimated to be about 93\% from the $^1$H NMR integration ratio of aromatic protons of NPA moieties and backbone protons at 1.0–2.0 ppm (Supporting Information, Figure S2). Moreover, FTIR spectra of poly(DMA-NPA), poly(DMA-CD), and amino-CD showed that the peak at 1758 cm\(^{-1}\) decreased sharply after amino-CD substitution (Supporting Information, Figure S3), as a further indication that most of the active ester groups (NPA moieties) were substituted, consistent with the $^1$H NMR results shown in Figure S2 of the Supporting Information. The characteristics of these copolymers are summarized in Table 1.

#### Formation and mechanical properties of supramolecular polymer hydrogels

In a typical procedure for hydrogel formation, solutions of poly(DMA-GA) and poly(DMA-CD) in deionized water were mixed in different GA/CD molar ratios (3:1, 2:1, 1:1, 1:2, and 1:3) at different polymer concentrations to form hydrogels.

To clarify the network formation induced by inclusion complexation of GA and CD moieties, $^1$H NMR, 2D $^1$H NOESY NMR, theoretical computation, XRD, and isothermal titration calorimetry (ITC) were performed. In the $^1$H NMR spectrum of poly(DMA-GA-2\%), no signal of methyl groups on GA moieties was observable in D$_2$O (Figure 2a, bottom), and this indicated formation of aggregates by sequestration of hydrophobic GA moieties within hydrophilic polydimethylacrylamide. On addition of β-CD, signals for the methyl protons (positions 23–28) appeared and shifted downfield (Figure 2a, top), because the polymer became more hydrophilic due to the complexation of GA with β-CD. Continuous downfield shift of the GA methyl protons occurred until the [CD]/[GA] ratio reached 1:1 (Supporting Information, Figure S4). This may be caused by the random distribution of GA pendants on the polymer chain. Thus, restricted access to GA units limited the formation of complexes in comparison to free GA as guest.\textsuperscript{[47]} Clearly, adding more β-CD could shift the equilibrium in the direction of complexation, and led to a gradual increase in chemical shift of the methyl groups of GA.

Cross-correlation peaks between GA methyl protons and β-CD protons were observed in the 2D $^1$H NOESY NMR spectrum.

![Figure 1. Preparation and self-healing process of supramolecular hydrogels cross-linked by poly(DMA-GA) and poly(DMA-CD) on the basis of host-guest interactions between GA and β-CD units.](image)

![Table 1. Characteristics of poly(DMA-GA) and poly(DMA-NPA).](table)\[a\] Molar ratio of DMA to GA/NPA monomer in the feed. \[b\] Actual ratio calculated by $^1$H NMR integration. \[c\] Yield calculated from the insoluble fraction in diethyl ether. \[d\] Determined by GPC.

<table>
<thead>
<tr>
<th>Polymers</th>
<th>Feed ratio$^\text{[b]}$</th>
<th>Ratio$^\text{[b]}$</th>
<th>Yield$^\text{[c]}$</th>
<th>$M_n$$^\text{[d]}$</th>
<th>$M_w$$^\text{[d]}$</th>
<th>$M_w/M_n$$^\text{[d]}$</th>
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<td>poly(DMA-GA-1%)</td>
<td>100:1</td>
<td>91:1</td>
<td>96</td>
<td>9600</td>
<td>1.95</td>
<td></td>
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<tr>
<td>poly(DMA-GA-2%)</td>
<td>50:1</td>
<td>54:1</td>
<td>87</td>
<td>13000</td>
<td>1.32</td>
<td></td>
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<tr>
<td>poly(DMA-GA-4%)</td>
<td>25:1</td>
<td>26:1</td>
<td>92</td>
<td>8300</td>
<td>1.83</td>
<td></td>
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<tr>
<td>poly(DMA-NPA)</td>
<td>10:1</td>
<td>10:1</td>
<td>89</td>
<td>7900</td>
<td>1.93</td>
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Moreover, because the molecular breadth of GA is 0.58–0.60 nm, which is smaller than the diameter of the β-CD cavity (0.60–0.65 nm). This size match enables GA units to enter the cavity of β-CD.\(^{[46]}\) However, because the molecular length of GA (1.27 nm) is larger than the height of β-CD (0.79 nm), only part of the GA unit can enter the cavity of β-CD when the host–guest complex forms, which is consistent with the results of \(^1\)H NMR titration. Apparently, the synergistic effect of size matching, hydrophobic interactions, and van der Waals forces between GA and β-CD units primarily promoted dynamic host–guest complexation, and consequently resulted in the formation of a supramolecular polymer hydrogel.

Figure 2. a) \(^1\)H NMR spectra of poly(DMA-GA-2\%) in D\(_2\)O (bottom) and poly(DMA-GA-2\%) mixed with [β-CD] in D\(_2\)O (25°C, 10 mg mL\(^{-1}\)) ([CD]/[GA] = 3:1) (top). b) Calorimetric titration curve of GANa with β-CD in deionized water at 25°C. Raw data for sequential 10 μL injections of a solution of β-CD (4.48 mm) into a 0.25 mm solution of GANa (top); heats of reactions obtained by integration of the calorimetric traces (bottom). c) Theoretical optimized structure of GA. Carbon atoms, hydrogen atoms, and oxygen atoms are shown in gray, light gray, and red, respectively.

More evidence for the complexation of GA and β-CD moieties was obtained by XRD. As shown in Figure S6 (Supporting Information), poly(DMA-GA-2\%) was found to be amorphous, and a certain degree of crystallinity of poly(DMA-CD) was demonstrated by two broad peaks at 2θ = 11.6 and 18.1° in the diffractogram. Conversely, the diffractogram of poly(DMA-GA-2\%)/poly(DMA-CD) hydrogel ([GA]/[CD] = 1:1, 15 wt\%) did not show a peak at 2θ = 18.1°, whereas a broad diffraction peak in the range of 7–30° was detected. This revealed that host–guest complexation between poly(DMA-GA-2\%) and poly(DMA-CD) occurred.\(^{[50]}\)

The binding affinity between GA and β-CD moieties was determined by ITC. Glycyrrhetinic acid sodium salt (GANa) and β-CD were used as model guest and host molecules, respectively. As shown in Figure 2b, a typical titration curve of 1:1 complex formation was observed with a stoichiometric ratio of \(N = 0.96\) from the curve-fitting results. Moreover, a binding constant of \(K_b = 1.59 \times 10^4\) M\(^{-1}\), as well as thermodynamic parameters of \(\Delta H = -21.10\) kJ mol\(^{-1}\) and \(\Delta S = -9.47\) mol\(^{-1}\) K\(^{-1}\), were determined. Thermodynamically, the binding of β-CD with GANa is entirely driven by favorable enthalpic changes accompanied by unfavorable entropic changes (\(\Delta H^0 < 0; \Delta S^0 < 0\)).\(^{[50]}\)

Oscillatory rheology was used to measure the mechanical properties of the hydrogels. As shown in Figure 3a, the highest

\(G^'\) value was obtained when poly(DMA-GA-2\%) and poly(DMA-CD) were mixed in a molar ratio of [GA]/[CD] = 1.0 (corresponding to a weight ratio of 55/22 for the two polymers), ascribed to the highest cross-linking density at 1:1 ratio. When either GA or CD units were present in excess, a decrease in \(G^'\) was observed, indicating effective formation of complementary inclusion complex, consistent with the behavior of the cholic acid/β-CD complexation hydrogel system.\(^{[32]}\) An increase in polymer concentration led to an increase in \(G^'\) at [GA]/[CD] = 1.0, and consequently a tougher hydrogel (Figure 3b). Moreover, lower \(G^'\) values were obtained with decreasing GA fraction of poly(DMA-GA) at the same polymer concentration (Figure 3c), which demonstrates the effect of cross-linking density on the strength of hydrogels. From the above results, it is apparent that the mechanical properties of the complex hydrogel are greatly influenced by the [GA]/[CD] molar ratio, concentra-

Figure 3. \(G^'\) and \(G^\prime\) (time sweep at 25°C) of poly(DMA-GA-2\%)/poly(DMA-CD) hydrogel in relationship to a) the molar ratio of GA to CD units (15 wt\%) and b) the concentration of the polymer complex ([CD]/[GA] = 1). c) \(G^'\) and \(G^\prime\) (frequency sweep at 25°C, 15 wt\%, [CD]/[GA] = 1) of poly(DMA-GA-1\%)/poly(DMA-CD), poly(DMA-GA-2\%)/poly(DMA-CD), and poly(DMA-GA-4\%)/poly(DMA-CD). d) SEM image of poly(DMA-GA-2\%)/poly(DMA-CD) hydrogel (15 wt\%, [CD]/[GA] = 1).
tion of polymers, and GA fraction of poly(DMA-GA), which primarily determine the cross-linking density of these two components. Figure 3d shows the native morphology of poly(DMA-GA-2 %)/poly(DMA-CD) hydrogel at a concentration of 15 wt%. The hydrogel exhibits a porous and interconnected structure with a pore diameter of about 40 μm, which offers a comfortable environment for mass delivery and cell growth in tissue engineering.

Self-healing ability

To demonstrate the self-healing behavior of poly(DMA-GA)/poly(DMA-CD) hydrogels at room temperature, two cylindrical hydrogels stained with erioglaucine disodium salt (EDS) and tartrazine (TAR; Figure 4a) were cut into two pieces (Figure 4b) and then put back together. After 60 s, the two pieces of hydrogel healed (Figure 4c). Optical micrographs showed that EDS and TAR, which were used to stain the hydrogels, interpenetrated quickly with each other to give a green color (Figure 4d). The above results showed that the hydrogels have good self-healing ability and appropriate permeability for delivery of bioactive agents.

Rheology measurements were performed to confirm the self-healing ability of hydrogels. A strain amplitude sweep was employed to monitor $G'$ and $G''$ of poly(DMA-GA-2 %)/poly(DMA-CD) hydrogel. As shown in Figure 4e, under 0.1–80% strain, $G'$ was larger than $G''$, which suggests that the hydrogel networks were stiff and the cross-links remained undamaged under relatively large deformations. Where the $G'$ and $G''$ curves crossed, a gel–sol transition occurred at a strain of 110%, which implied the beginning of destruction of the hydrogel networks due to the disruption of the GA/CD interaction at such a strain. The fact that $G'$ was smaller than $G''$ and $G'$ dramatically decreased to 63 Pa at a high strain of 650% suggests that the cross-linked networks completely collapsed. The self-repairing capacity of poly(DMA-GA-2 %)/poly(DMA-CD) hydrogels was verified by an alternating step-strain test (strain = 3 and 250 %), as shown in Figure 4f. On switching the strain from a large value of 250 % to a small value of 3 % at a fixed angular frequency (10 rad s⁻¹), $G'$ and $G''$ recovered to the initial values without a significant decrease in each cycle of the recovery. The above studies showed that poly(DMA-GA-2 %)/poly(DMA-CD) hydrogels recovered their original properties rapidly after being sheared. Therefore, the self-healing mechanism for this supramolecular hydrogel was inferred to be reversible host–guest inclusion complexion between GA and CD units. When the host–guest complexes disassembled, the hydrogel broke. At rest, the complexes formed again, and self-healing occurred. It is noteworthy that the self-healing behavior of the supramolecular polymer hydrogel occurred autonomously without any external intervention, which is advantageous in comparison to gels that need external treatment.

Cell viability

Fibroblast 3T3L1 cells were co-cultured with polymers to investigate their cytotoxicity. On account of the natural origin of GA and β-CD, these polymers showed outstanding biocompatibility even at concentrations up to 5.0 mg mL⁻¹ in a CellTiter-Blue cell viability assay (Promega; Figure 5a). Figure 5b and c, in which live cells are stained green and dead cells are red, indicate that the majority of 3T3L1 cells survived in the presence of these polymers (5 mg mL⁻¹) for 24 h. However, cell viability and morphology were the only parameters examined in this study as preliminary indicators of the suitability of poly(DMA-GA)/poly(DMA-CD) hydrogel for tissue engineering applications. Future studies will include the construction of cell-contained self-healing multilayer structures to join different materials in hybrid tissue engineering, with the aim of overcoming the disadvantages of current suturing and gluing methods.
such as the formation of voids and the introduction of adhesive materials between discrete layer compartments.

Conclusion

We utilized natural triterpenoid GA as a guest for β-CD (1:1), and thus obtained the GA/β-CD inclusion complex. On this basis, a supramolecular polymer hydrogel was formed by mixing N,N-dimethylacrylamide copolymers with GA or β-CD pendant groups. The highest storage modulus was found for a [GA]/[β-CD] molar ratio of 1:1. Moreover, the supramolecular hydrogels exhibited good self-healing properties, which not only could be seen visually, but also confirmed by step-strain rheological measurements. Additionally, these polymers displayed outstanding biocompatibility. This work has not only provided new guest–host complex GA/β-CD, but also a hydrogel that is an attractive candidate for tissue engineering.

Experimental Section

Materials

Acryloyl chloride, methacryloyl chloride, β-CD, p-nitrophenol, p-toluensulfonyl chloride, ethylenediamine, GA, erioglaucine disodium salt (EDS), tartrazine (TAR), and other reagents were local commercial products and used as received. 2,2-Azobisobutyronitrile (AIBN) was recrystallized twice from ethanol. DMA was distilled before use. Amino-CD, p-nitrophenyl acrylate (NPA), and glycyrrhetinic acid sodium salt (GANa) were synthesized according to the literature (Supporting Information, Scheme S1).

Methods

The molecular weight and polydispersity index (PDI) of the polymers were determined by gel permeation chromatography (GPC) with a Waters system equipped with an HPLC pump (Waters 2414) and a refractive-index detector (Waters 2424). THF was used as the eluent at a flow rate of 1.0 mL/min at 30°C, and polystyrene standards were employed for the GPC calibration. 1H and 13C NMR experiments were carried out in CDCl3 or D2O with a Bruker AVANCE III HD 400 spectrometer at 25°C. 1H NOESY spectra were recorded with a JEOL JNM-ECA 400 instrument in D2O. FTIR spectra were obtained on KBr pellets between 4000 and 500 cm⁻¹ by using a VERTEX 70 spectrometer. ITC was performed with a NANO ITC-SVH from TA Instruments. Solutions were degassed and thermostated by using a TA Vac accessory before each titration. An aqueous solution of β-CD in a 250 μL syringe was sequentially injected into the calorimeter sample cell (1.42 mL) containing an aqueous solution of GANa at a stirring speed of 250 rpm. Each titration experiment was composed of 25 successive injections (10 μL per injection). XRD was conducted with a D8 Discover diffractometer from Bruker by using CuKα radiation, and scanning was performed from 2 to 45° at a scanning rate of 2° min⁻¹. Rheological experiments were performed with an AR 2000 rheometer from TA Instruments with 25 mm-diameter parallel plates. Rheological characteristics of gels were monitored by oscillatory time sweep, frequency–sweep, and strain–sweep experiments. During time–sweep experiments G’ (storage modulus) and G″ (loss modulus) were measured at 25°C for a period of 5 min with a constant strain of 3% and a frequency of 10 rad s⁻¹. Quantum chemical computations were performed with the B3LYP DFT in the framework of the Gaussian 09 suite of programs. The structure was optimized by employing the 6-31G(d,p) basis set in the gas phase.

Cytotoxicity study

Fibroblast cell line 3T3L1 was provided by Norman Bethune Health Science Center of Jilin University and grown in Dulbecco’s Modified Eagle’s Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) in an atmosphere of 5% CO₂ at 37°C. The cells were seeded in 96-well culture plate with a density of 1 × 10⁴ cells per well. After overnight incubation, the medium was replaced by fresh DMEM containing poly(DMA-GA) and poly(DMA-CD) at certain concentrations and incubated for 24 h. Then, 20 μL of CellTitert-Blue reagent was added to each well and incubation continued for a further 3 h to perform the cell viability assay. The fluorescence intensity was measured at 560/590 nm (E/E₄) by using a BioTek Synergy H1 microplate reader.

Cell imaging

The 3T3L1 cells were seeded in 12-well culture plate with a seeding density of 4 × 10⁴ cells per well. After overnight incubation, the cells were treated with DMEM containing poly(DMA-GA) and poly(DMA-CD) at a concentration of 5 mg mL⁻¹, and then co-cultured at 37°C. After 24 h, the samples were stained with 5 μg mL⁻¹ FDA and 10 μg mL⁻¹ PI solution. Cells were imaged with an LSM 700 confocal laser scanning microscope imaging system (Carl Zeiss). FDA was excited with a 488 nm laser to emit 500–600 nm fluorescence, and PI with 555 nm laser to emit 560–700 nm fluorescence.

Synthesis of GA-based hexanol (GAH)

GA (5.00 g, 10.62 mmol), 6-bromo-1-hexanol (1.67 mL, 12.75 mmol), and K₂CO₃ (1.75 g, 12.75 mmol) were dissolved in dry DMF (30 mL). After stirring at room temperature for 5 h, a mixture was stirred at room temperature for 5 h. Then, the mixture was stirred at room temperature for 5 h. After the addition, the reaction mixture was stirred at room temperature for 5 h. The reaction was quenched with dilute hydrochloric acid (1 N) and extracted with ethyl acetate. The organic layer was washed with water and brine, and dried with anhydrous Na₂SO₄. After removing the solvent under reduced pressure, the crude product was further purified by chromatography (hexane/ethyl acetate = 2:1, v/v) to afford GAH as a white powder (5.60 g, 93%). ESI-MS (+): m/z = 571 [M+H]+; 1H NMR (400 MHz, CDCl3): δ = 5.63 (s, H, 12-CH=), 4.10 (m, 2H, J = 6.48 Hz, HOCH₂), 3.21 (m, 1H, 3H), 1.36, 1.14, 1.11, 0.99, 0.80, 0.79 ppm (s, 7 × 3H, 7 × CH₃); 13C NMR (100 MHz, CDCl3): δ = 200.76 (O=C–CH=), 176.65 (CO₂CH₃), 170.00 (O=C–CH=), 128.40 (O=C–CH=), 78.87, 64.58, 62.66, 62.40, 55.07, 48.73, 45.59, 44.15, 43.41, 41.22, 39.26, 37.81, 37.24, 32.90, 32.81, 31.99, 31.25, 28.95, 28.72, 26.83, 26.23, 24.73, 26.54, 26.23, 25.54, 23.52, 18.82, 17.80, 16.49, 15.71 ppm.

Synthesis of GA-based methacrylate (GAM)

Methacryloyl chloride (340 μL, 3.50 mmol) was added dropwise to a dry dichloromethane solution of GAH (2.00 g, 3.50 mmol) and triethylamine (583 μL, 4.21 mmol) at 0°C. After the addition, the reaction mixture was stirred at room temperature for 5 h. The mixture was quenched with dilute hydrochloric acid (1 N) and then extracted with ethyl acetate. The organic layer was washed with water and brine, and dried with anhydrous Na₂SO₄. After removing the solvent under reduced pressure, the crude product was purified by chromatography (hexane/ethyl acetate = 6:1, v/v) to give GAM as a white powder (1.96 g, 88%). ESI-MS (+): m/z = 639 [M+H]+; 1H NMR (400 MHz, CDCl3): δ = 6.06 (m, 1H, C=CH₂), 5.61 (s, H, 12-CH=), 5.52 (m, 1H, C=CH₂), 4.10 (t, 2H, J = 6.56 Hz, CO₂CH₃),

Synthesis of poly(DMA-GA-2%)  

DMA (2.08 g, 20.99 mmol), GAM (0.27 g, 0.42 mmol), and AIBN (20 mg, 0.12 mmol) were dissolved in dry DMF (5 mL), and then the mixture was frozen in liquid N2. After removing the system air under vacuum, the mixture was purged with N2, prior to its immersion in a preheated oil bath at 70 °C. The reaction was allowed to proceed for 18 h at 70 °C before being quenched by immersion in ice-water. DMF was removed under reduced pressure, and THF was added to redissolve the copolymer. After pouring the reaction mixture into diethyl ether, the precipitate was collected. The copolymer was dried in vacuum to yield poly(DMA-GA-2%) (2.18 g, 94%). poly(DMA-GA-1%) and poly(DMA-GA-4%) with different feed ratios of GA and DMA units were synthesized in a similar fashion to poly(DMA-GA-2%).

Synthesis of poly(DMA-NPA)  

DMA (1.70 mL, 16.82 mmol), NPA (0.32 g, 1.64 mmol), and AIBN (29 mg, 0.16 mmol) were dissolved in dry DMF (15 mL), and then the mixture was frozen in liquid N2. After removing the system air under vacuum, the mixture was purged with N2, prior to its immersion in a preheated oil bath at 70 °C. The reaction was allowed to proceed for 18 h at 70 °C before being quenched by immersion in ice-water. The copolymer was precipitated from diethyl ether after removing most of the DMF, and poly(DMA-NPA) was obtained after drying in vacuum (1.73 g, 89%).

Synthesis of poly(DMA-CD)  

Amino-β-CD (644 mg, 0.55 mmol) and poly(DMA-NPA) (1.00 g) were dissolved in dry DMF (10 mL), and then the reaction was carried out at 50 °C for 2 d. After evaporation most of the DMF, the copolymer was precipitated from diethyl ether and further purified through dialysis against deionized water for 5 d. By removing the water under reduced pressure, poly(DMA-CD) was obtained (1.12 g, 71%).

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