Supporting Information for

Controlled synthesis of *β*-sheet polymers based on side-chain amyloidogenic short peptide segments *via* RAFT polymerization

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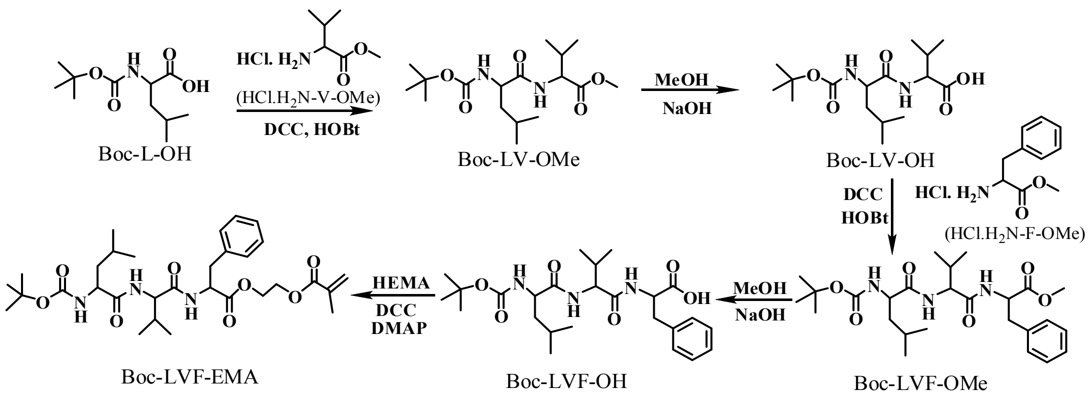
Experimental section

Atomic force microscopy (AFM). The morphology of the polymer was investigated by AFM. The polymer solution were sonicated for 3 h and then an aliquot of the solution were drop casted on a glass cover slip and dried by slow evaporation. The materials were allowed to further dry under vacuum for two days. The micrographs were taken from NT-MDT micro-40 AFM instrument using a semicontact mode at a scan rate of 1 Hz.

Field emission scanning electron microscopy (FE-SEM). The morphology of the polymer was investigated by high resolution FE-SEM. The polymer solution were sonicated for 3 h and then an aliquot of the solution were drop casted on a silicon wafer and dried by slow evaporation. The materials were allowed to further dry under vacuum for two days and were coated with gold:palladium (20:80). The micrographs were taken from Zeiss microscope; SUPRA 55VP-Field Emission Scanning Electron Microscope.

Peptidic monomer synthesis. The tripeptide moiety Boc-LVF-OMe was synthesized by conventional solution-phase methods using condensation strategy mediated by DCC/HOBt. The Boc-group was used for *N*-terminal protection. The *C*-terminus was protected as a methyl ester, which was further deprotected and coupled with HEMA mediated by DCC/DMAP and were subsequently purified by column chromatography using silica gel (100-200 mesh size) as stationary phase and n-hexane-ethyl acetate mixture as eluent, for obtaining final peptidic vinyl monomer Boc-LVF-EMA which was fully characterized by 500MHz ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, mass spectrometry, and FT-IR spectroscopy.



Scheme S1 Synthesis of tripeptide based monomers Boc-LVF-EMA.

Synthesis of Boc-LV-OMe. Initially, H_2N-Val-OMe (H_2N-V-OMe) was isolated from 14.5 g (86.50 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate. This ethyl acetate extract was concentrated and added to the stirring solution of 10 g (43.23 mmol) of Boc-Leu-OH (Boc-L-OH) dissolved in 150 ml dry DCM in an ice-water bath condition, followed by addition of 8.92 g (43.23 mmol) of DCC and 6.62 g (43.23 mmol) of HOBt. The reaction mixture was allowed to come at room temperature and was further stirred for 48 h. After removing insoluble *N*,*N′*-dicyclohexylurea (DCU) by suction filtration, filterate was evaporated and was further dissolved in 100 mL ethyl acetate. Then organic layer was further washed with 1N HCl, saturated $NaHCO_3$ and brine solution and dried over anhydrous Na_2SO_4 and evaporate in vacuum. The product was further purified by silica gel column chromatography using hexane:ethyl acetate (3:1) as eluent, resulting Boc-LV-OMe as a white solid with a yield of 80 %, and were further characterized by ^{1}H NMR and ^{13}C NMR (Fig. S1 and S2, respectively).

Synthesis of Boc-LV-OH. To 8 g (23.23 mmol) of Boc-LV-OMe, 70 mL MeOH and 50 mL of 2M NaOH were added and were stirred at room temperature for 10 h. The progress of saponification was monitored by thin layer chromatography (TLC). Then methanol was removed from reaction mixture under vacuum and the residue was taken in 100 mL of water, washed with diethyl ether. Then pH of the aqueous layer was adjusted to 2 by adding 1M HCl and was extracted with ethyl acetate, dried over anhydrous sodium sulphate and evaporated under vacuum to obtain the compound Boc-LV-OH as a white waxy solid with a yield of 82%, and were further characterized by ^{1}H NMR and ^{13}C NMR (Fig. S3 and S4, respectively).

Synthesis of Boc-LVF-OMe. Initially, H_2N-Phe-OMe (H_2N-F-OMe) was isolated from 6.2 g (28.8 mmol) of the corresponding methyl ester hydrochloride by neutralization and subsequent extraction with ethyl acetate. This ethyl acetate extract was concentrated and added to the stirring solution of 5 g (15.13 mmol) of Boc-LV-OH dissolved in 100 ml dry DCM in an ice-water bath condition, followed by addition of 3.27 g (15.84 mmol) of DCC and 2.41 g (15.84 mmol) of HOBt. The reaction mixture was allowed to come at room temperature and was further stirred for 48 h. After removing insoluble DCU by suction filtration, filterate was evaporated and was further dissolved in 100 mL ethyl acetate. Then organic layer was further washed with 1N HCl, saturated $NaHCO_3$ and brine solution and dried over anhydrous Na_2SO_4 and evaporate in vacuum. The product was further purified by silica gel column chromatography using hexane:ethyl acetate (3:1) as eluent, resulting Boc-LVF-OMe as a white solid with a yield of 78 %, and were further characterized by ^{1}H NMR and ^{13}C NMR (Fig. S5 and S6, respectively).

Synthesis of Boc-LVF-OH. To 4 g (8.14 mmol) of Boc-LVF-OMe, 35 mL MeOH and 25 mL of 2M NaOH were added and were stirred at room temperature for 10 h. The progress of saponification was monitored by thin layer chromatography (TLC). Then methanol was removed from reaction mixture under vacuum and the residue was taken in 60 mL of water, washed with diethyl ether. Then pH of the aqueous layer was adjusted to 2 by adding 1M HCl and was extracted with ethyl acetate, dried over anhydrous sodium sulphate and evaporated under vacuum to obtain the compound Boc-LVF-OH as a white waxy solid with a yield 81%, and were further characterized by ^{1}H NMR (Fig. S7).

Synthesis of Boc-LVF-EMA monomer. To the stirring solution of Boc-LVF-OH (3.6 g, 7.54 mmol) and HEMA (1.0 g, 7.73 mmol, 0.94 mL) in dry DCM (60 mL) under dry N_2 atmosphere, a solution of DCC (1.6 g, 7.73 mmol) and DMAP (0.172 g, 1.41 mmol) in 10 mL of dry DCM were added dropwise to the reaction mixture in ice-water bath condition under stirring and was allowed to react at room temperature for 24 h. After removing insoluble *N*,*N′*-dicyclohexylurea (DCU) by suction filtration, the organic layer was further washed with 1N HCl, saturated $NaHCO_3$ and brine solution and dried over anhydrous Na_2SO_4 and evaporate in vacuum. The crude product was purified by silica gel column chromatography using hexane:ethyl acetate (3:1) as mobile phase, to get a white solid compound Boc-LVF-EMA, with a yield of 83%, and were further characterized by ^{1}H NMR, ^{13}C NMR and ESI-MS (Fig. 1, S8 and S9, respectively).

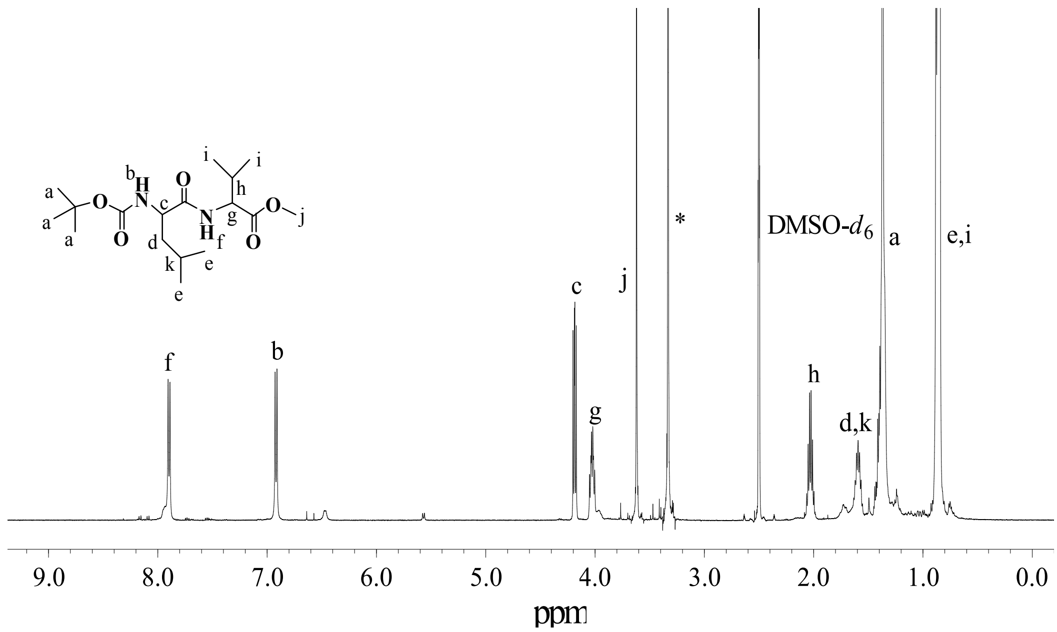


Fig. S1 ^{1}H NMR spectrum of Boc-LV-OMe (* denote the solvent resonance).

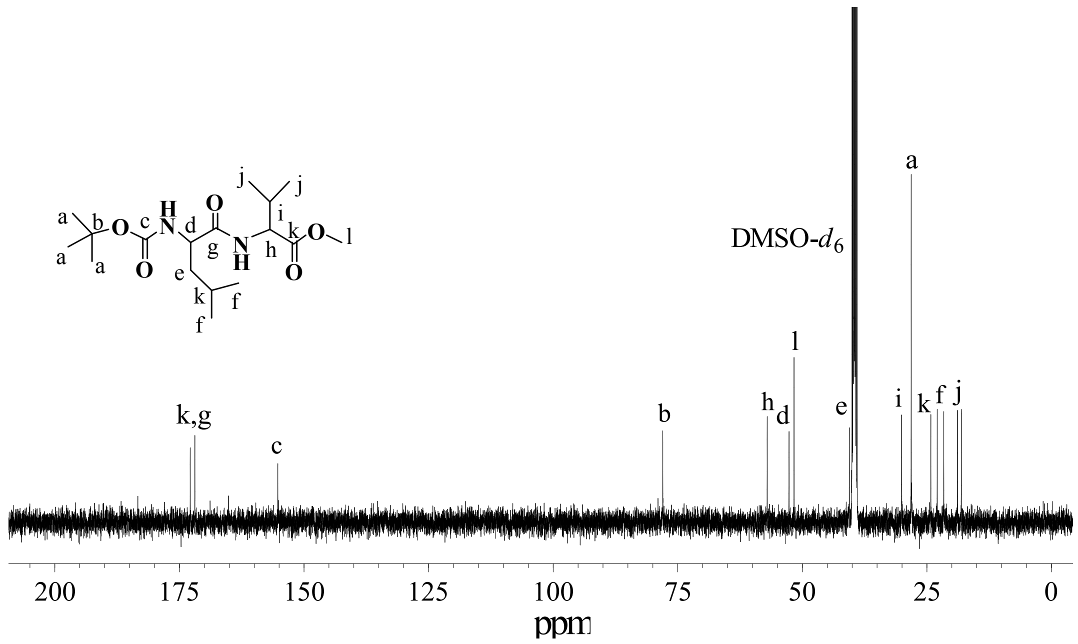


Fig. S2 ^{13}C NMR spectrum of Boc-LV-OMe.

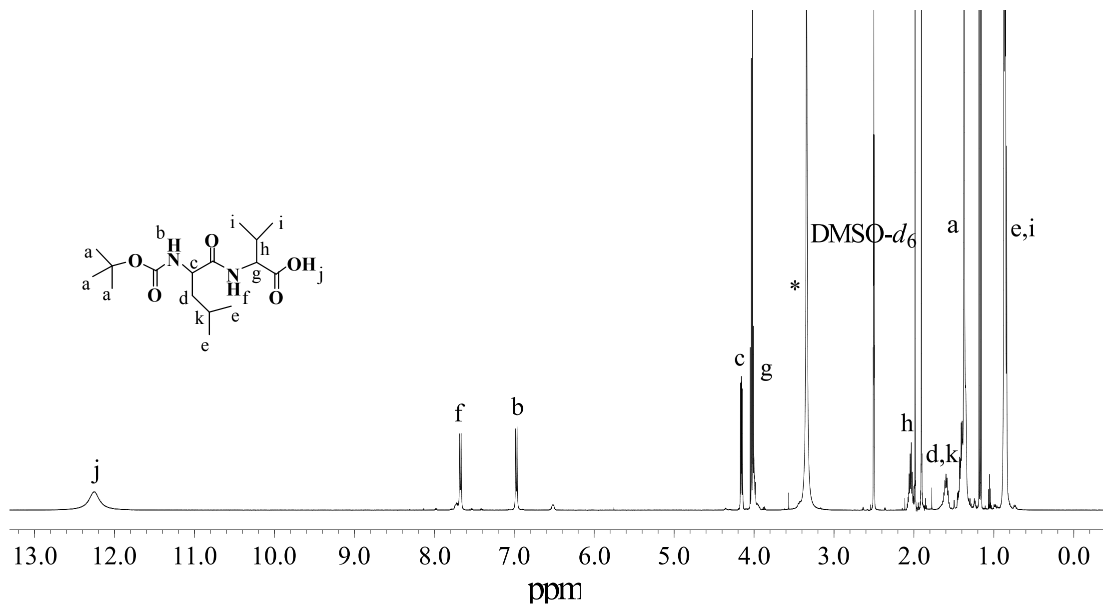


Fig. S3 ^{1}H NMR spectrum of Boc-LV-OH (* denote the solvent resonance).

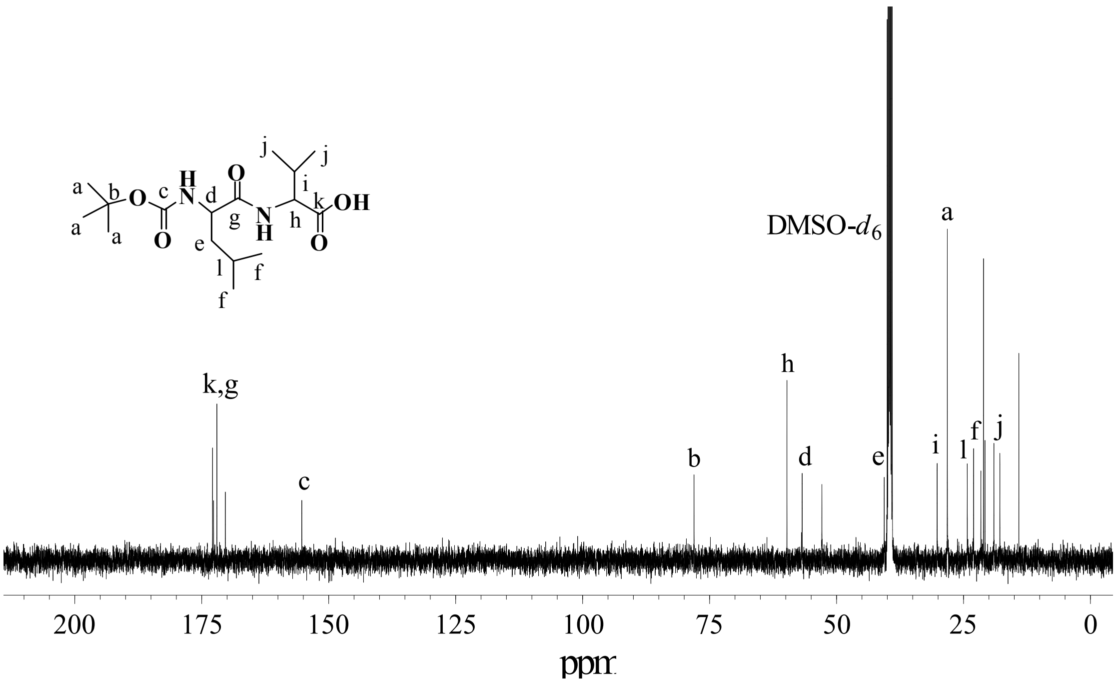


Fig. S4 ^{13}C NMR spectrum of Boc-LV-OH.

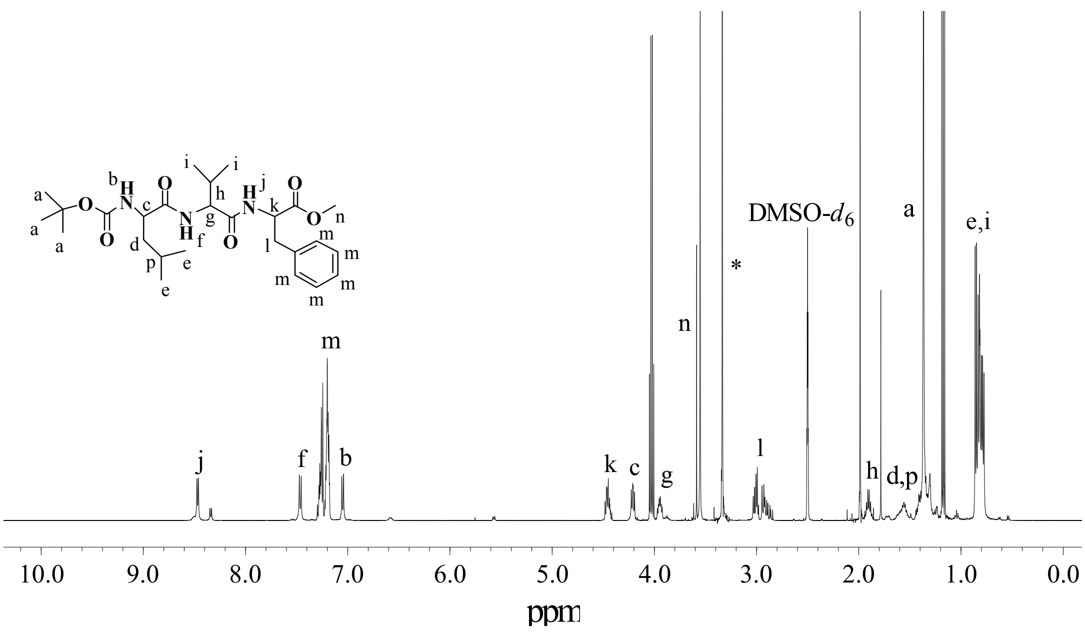


Fig. S5 ^{1}H NMR spectrum of Boc-LVF-OMe (* denote the solvent resonance).

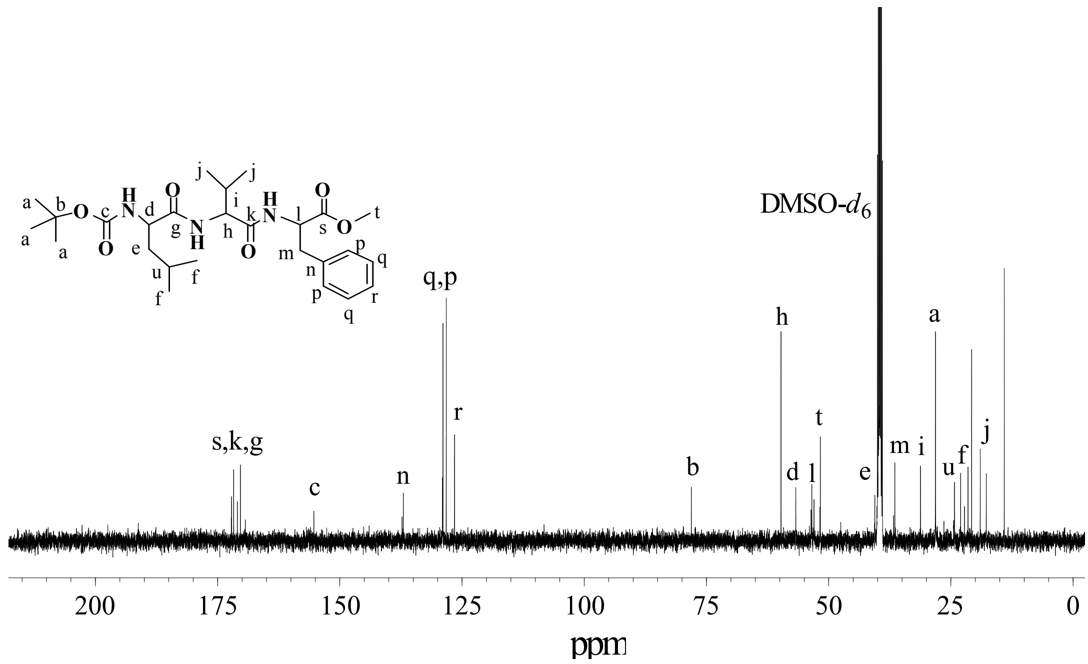


Fig. S6 ^{13}C NMR spectrum of Boc-LVF-OMe.

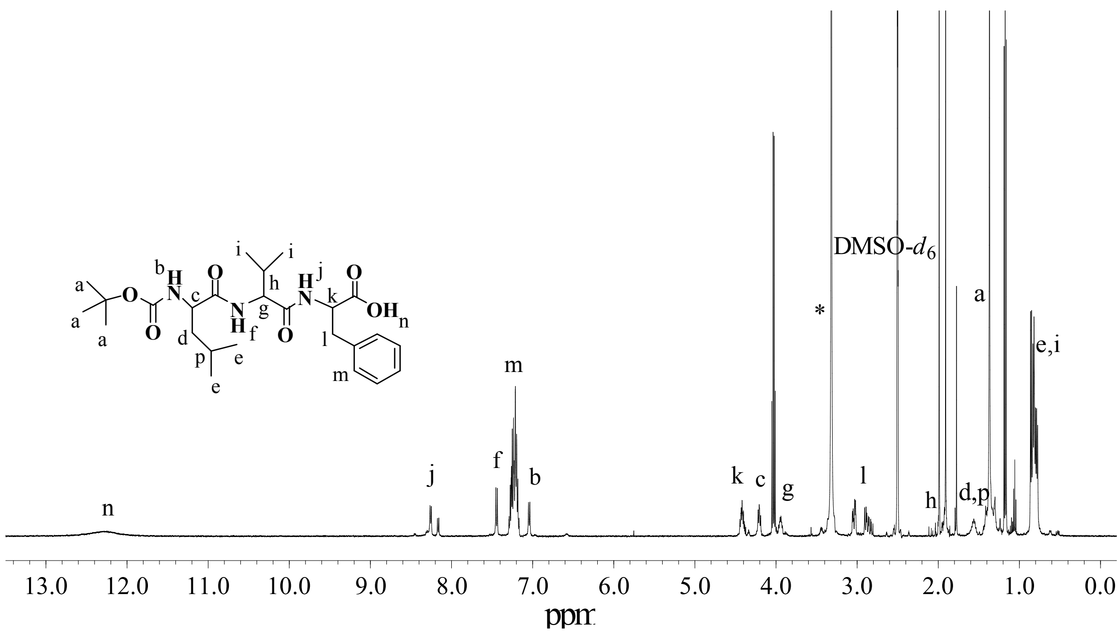


Fig. S7 ^{1}H NMR spectrum of Boc-LVF-OH (* denote the solvent resonance).

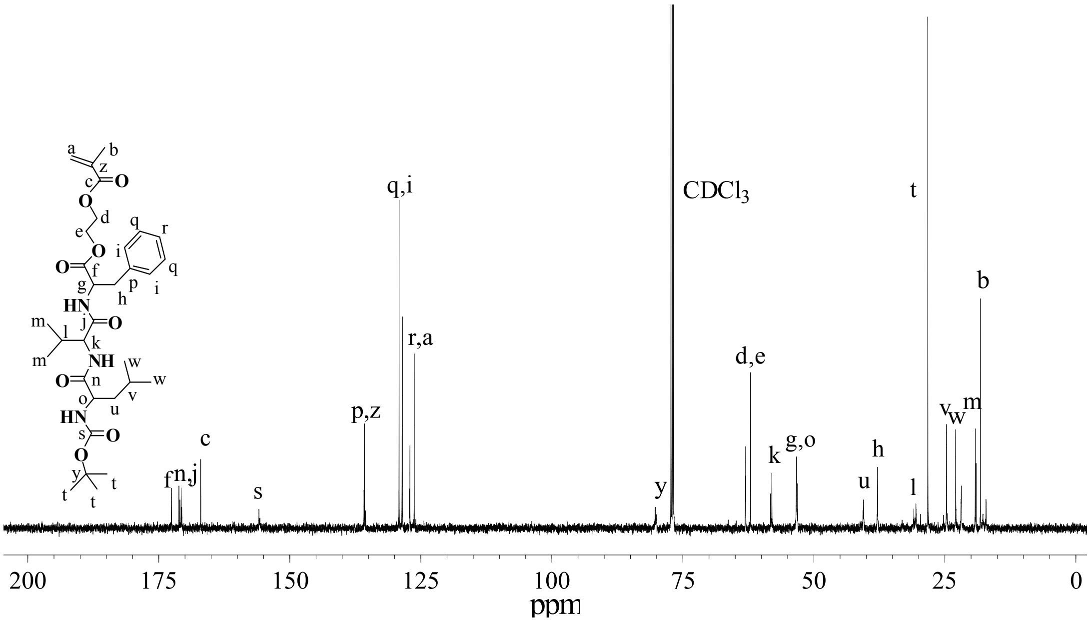


Fig. S8 ^{13}C NMR spectrum of Boc-LVF-EMA.

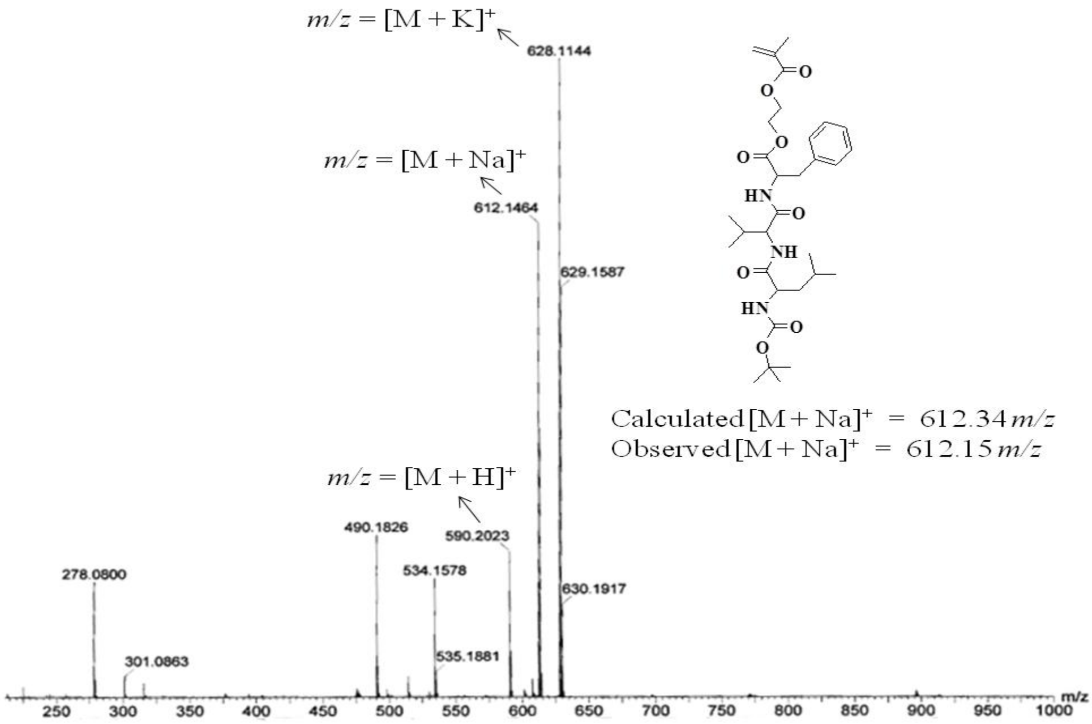


Fig. S9 ESI-MS spectrum of Boc-LVF-EMA monomer.

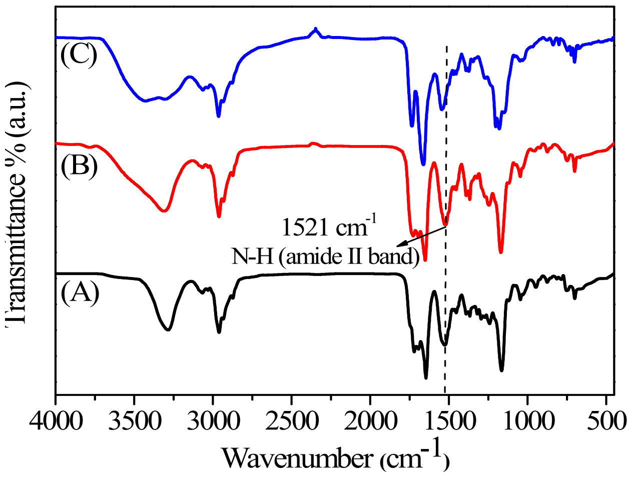


Fig. S10 FT-IR spectra of (A) Boc-LVF-EMA monomer, (B) P(Boc-LVF-EMA) homopolymer, and (C) P(H_3N^+-LVF-EMA) homopolymer.

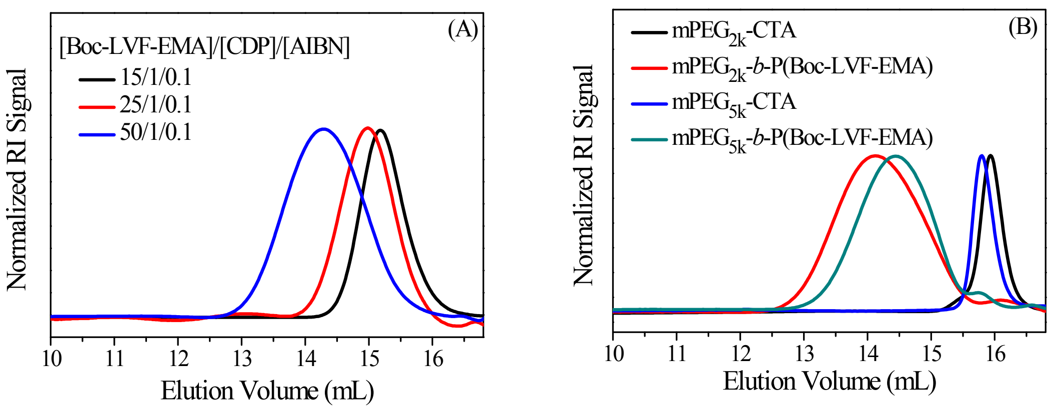


Fig. S11 (A) GPC RI traces of P(Boc-LVF-EMA) obtained at different [Boc-LVF-EMA]/[CDP] ratios varying from 15:1 to 50:1 keeping [CDP]/[AIBN] ratio 1:0.1 constant in DMF at 70 °C, and (B) GPC traces of the $mPEG_n$-CTAs and corresponding block copolymers with Boc-LVF-EMA.

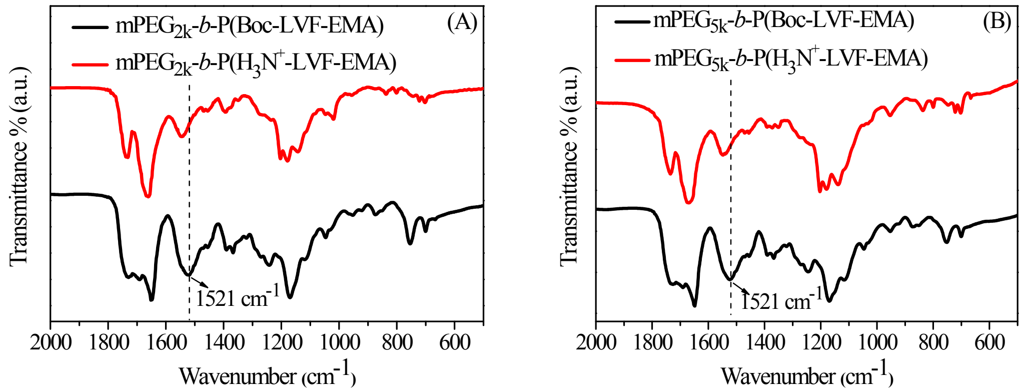


Fig. S12 FT-IR spectra of block copolymer, (A) mPEG$_{2k}$-b-P(Boc-LVF-EMA) and mPEG$_{2k}$-b-P(H_3N^+-LVF-EMA), and (B) mPEG$_{5k}$-b-P(Boc-LVF-EMA) and mPEG$_{5k}$-b-P(H_3N^+-LVF-EMA).

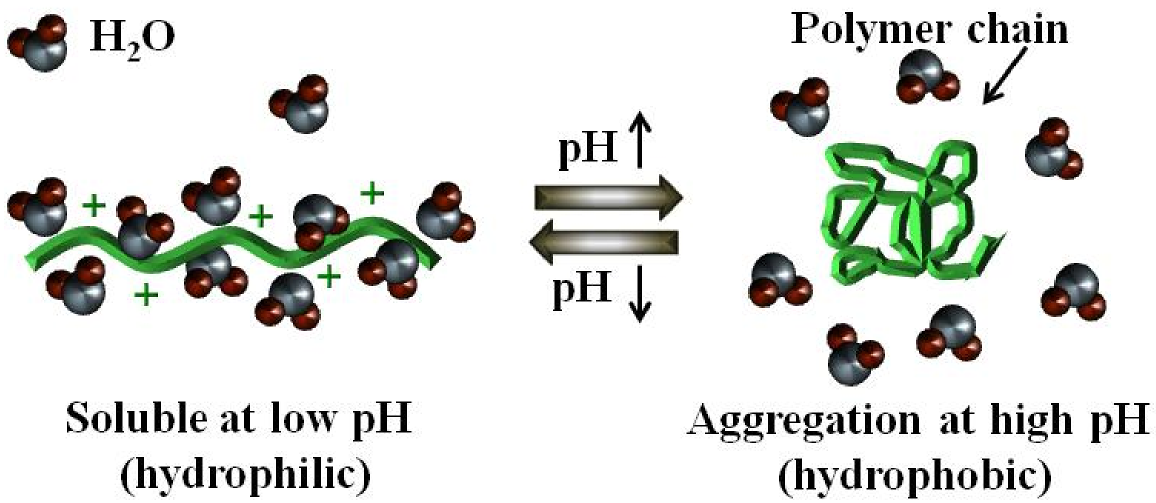


Fig. S13 Schematic illustration for pH responsiveness of tripeptidic polymer P(H_3N^+-LVF-EMA) in aqueous medium.

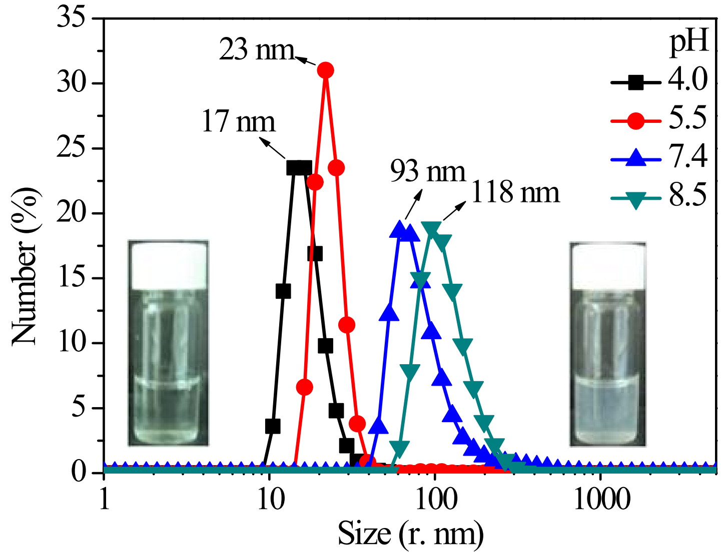


Fig. S14 Size distribution plot for pH dependence of 0.1 mg mL^{-1} aqueous solution of block copolymer $mPEG_{2k}$-*b*-P(H_3N^+-LVF-EMA).

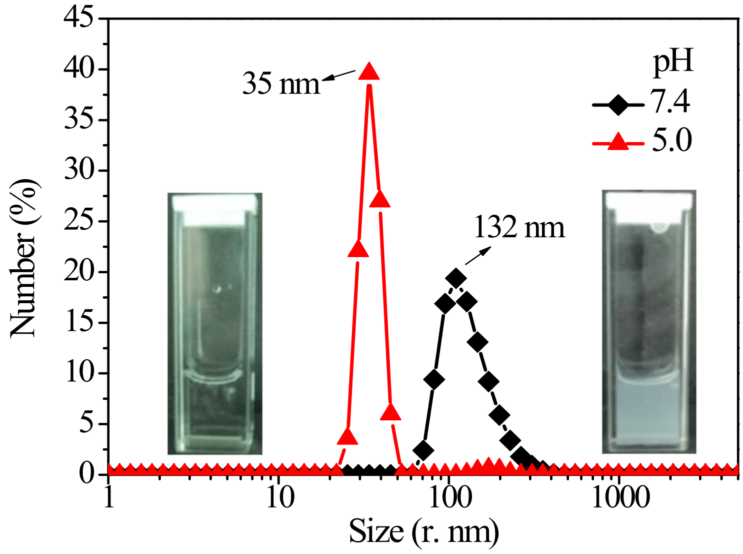


Fig. S15 Size distribution plot for pH dependence of 0.1 mg mL^{-1} phosphate buffer saline (PBS) solution of block copolymer $mPEG_{2k}$-*b*-P(H_3N^+-LVF-EMA).

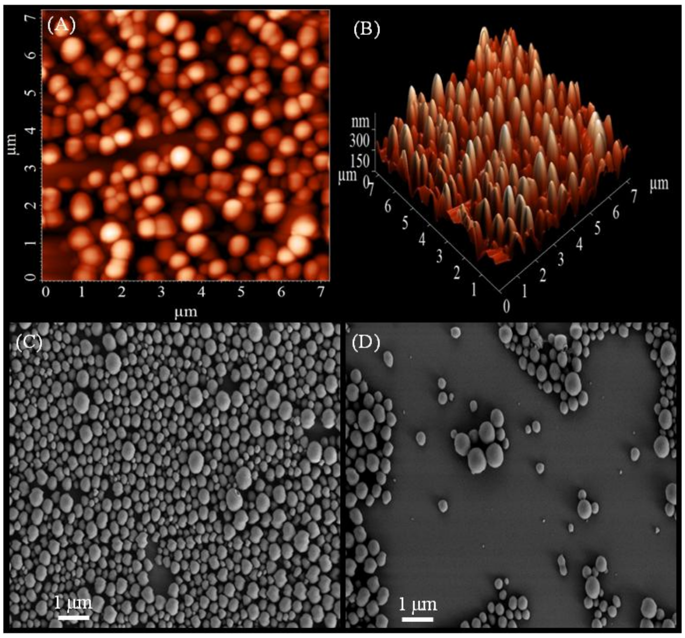


Fig. S16 AFM height (A), and 3D (B) image, and SEM image (C and D) of homopolymer P(Boc-LVF-EMA) (prepared from 1 mg mL^{-1} mathanol solution).

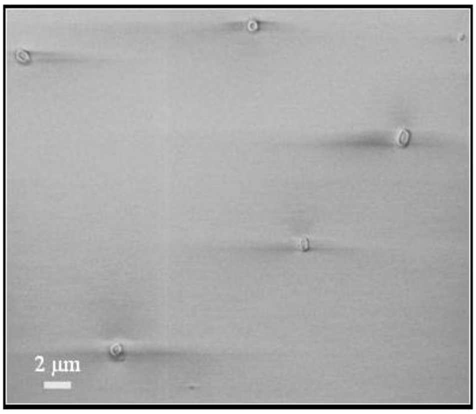


Figure S17. FE-SEM image of homopolymer P(H_3N^+-LVF-EMA), (prepared from 1 mg mL^{-1} methanol solution).

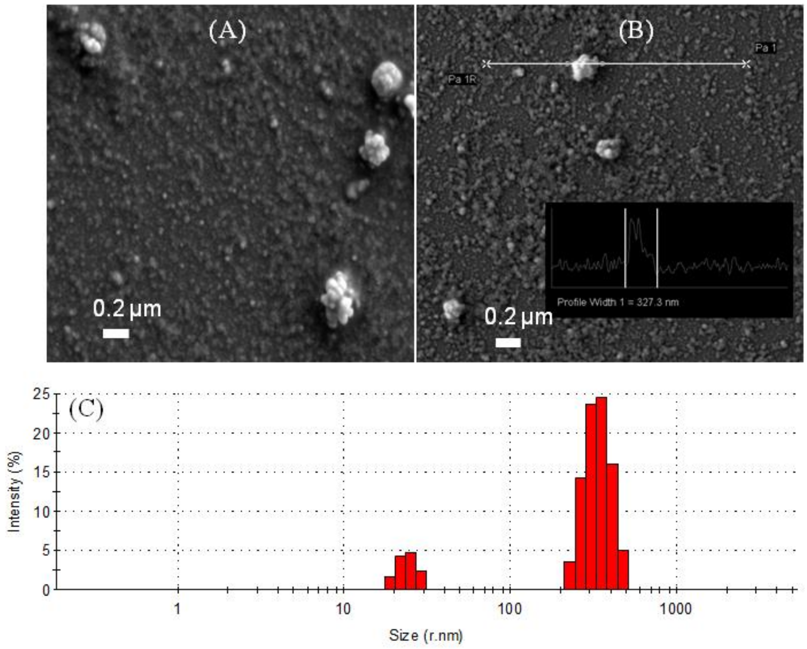


Fig. S18 FE-SEM image (A and B) and size distribution plot by DLS study (C) for 0.1 mg mL^{-1} aqueous solution of homopolymer $P(H_3N^+$-LVF-EMA).

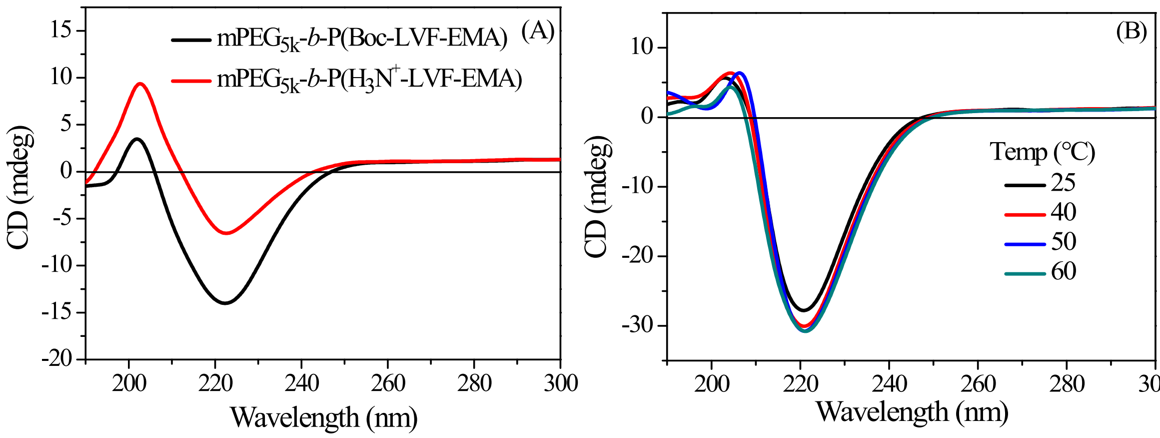


Fig. S19 (A) CD spectra of $mPEG_{5k}$-CTA derived block copolymers in methanol solution, and (B) temperature dependence of CD spectra of block copolymer $mPEG_{2k}$-*b*-$P(H_3N^+$-LVF-EMA) in aqueous solution.

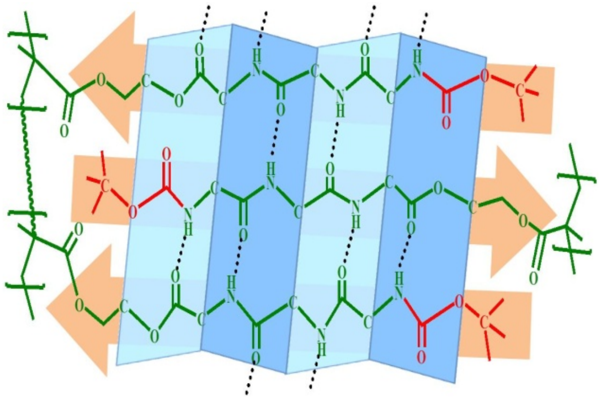


Fig. S20 A proposed cartoon showing the β-sheet motifs of tripeptidic homopolymer.

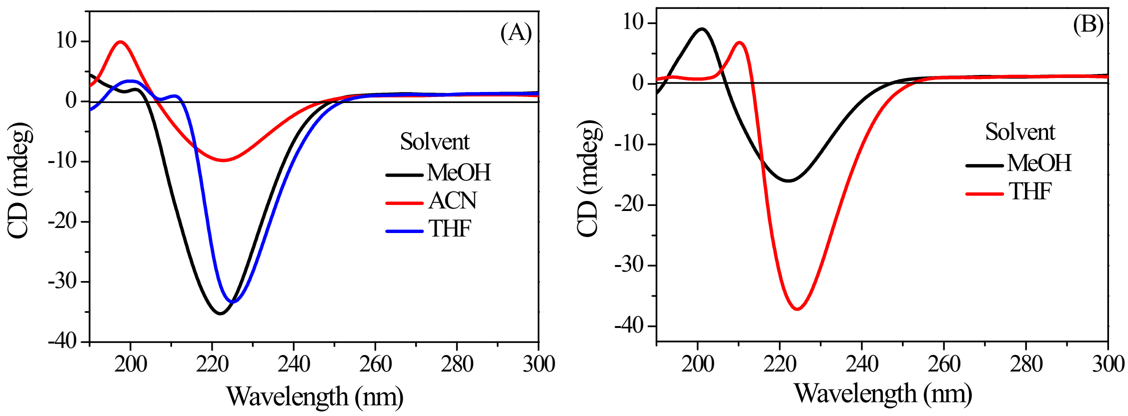


Fig. S21 Solvent dependence of CD spectra of (A) homopolymer P(Boc-LVF-EMA) and (B) block copolymer mPEG$_{2k}$-*b*-P(Boc-LVF-EMA). (MeOH: methanol, ACN: acetonitrile, THF: tetrahydrofuran).

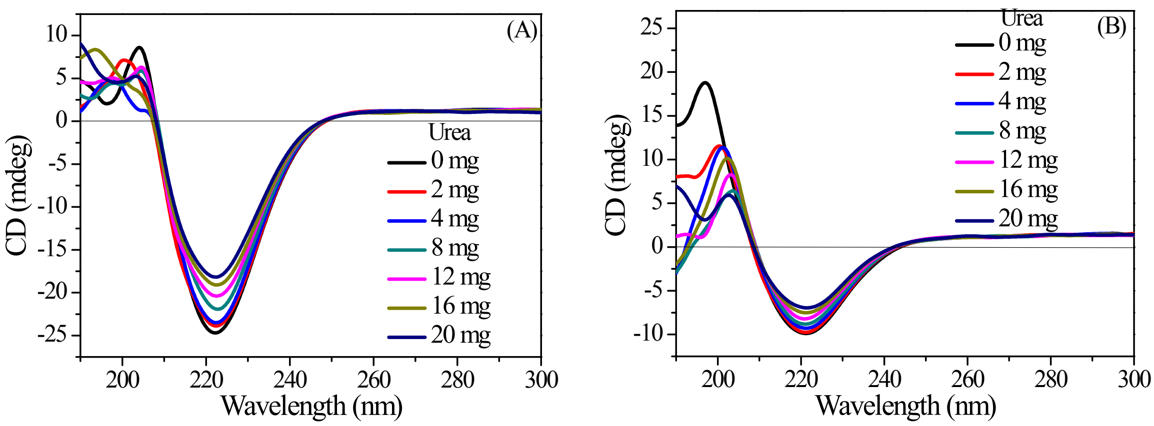


Fig. S22 Effect of urea addition on CD spectra of homopolymer (A) P(Boc-LVF-EMA) in methanol, and (B) P(H_3N^+-LVF-EMA) in aqueous solution. Concentration of polymer = 0.15 mg/mL and urea = 20 mg/mL.

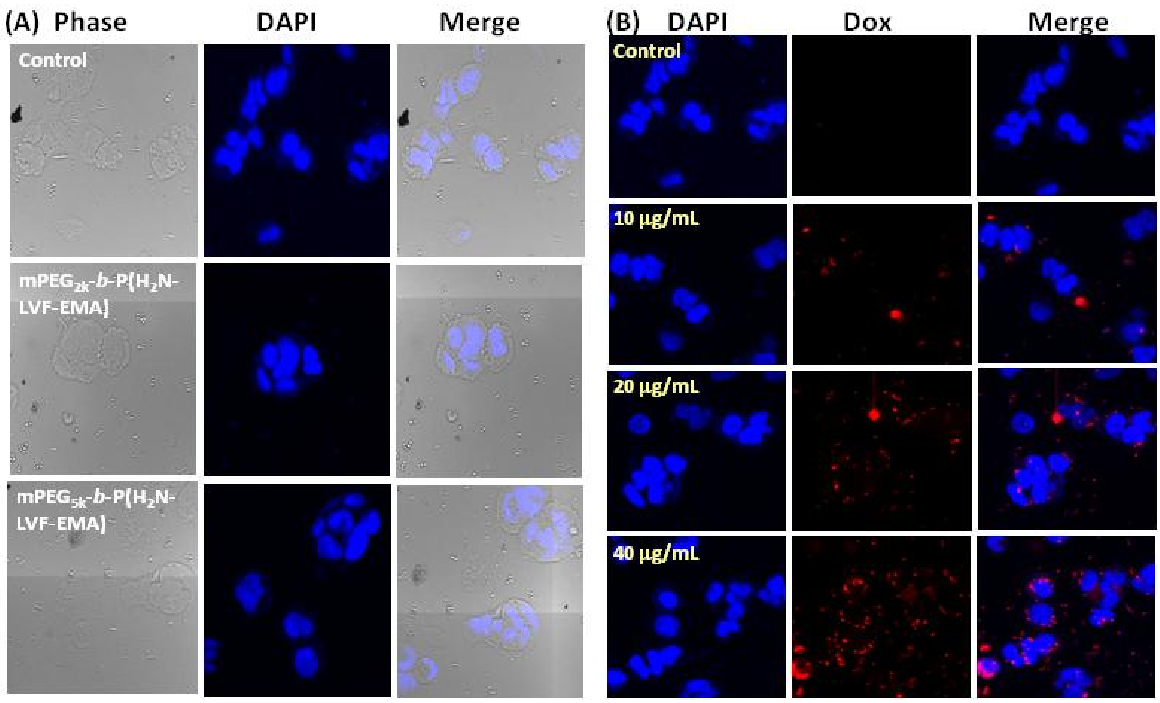


Fig. S23 Fluorescence microscopy image of MCF-7 cells (A) treated with polymer mPEG$_{2k}$-*b*-P(H_3N^+-LVF-EMA), and mPEG$_{5k}$-*b*-P(H_3N^+-LVF-EMA) (polymer concentration: 20 µg/mL), and (B) treated with mPEG$_{5k}$-*b*-P(Boc-LVF-EMA)-Dox for the uptake studies at different concentrations for 24 h.

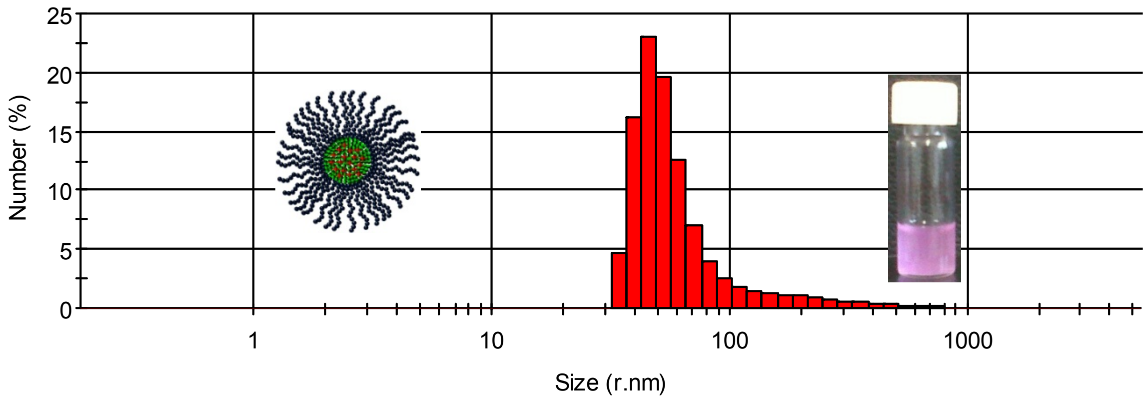


Fig. S24 DLS study of mPEG$_{2k}$-*b*-P(Boc-LVF-EMA) derived micelle encapsulating nile red dye, at a concentration 1 mg mL^{-1} (PDI = 0.398, hydrodynamic radius = 71 nm).