Supporting Information

Radical Ring-Opening Polymerization-Induced Self-Assembly for the Synthesis of Degradable Particles Incorporating Ethyl Lipoate

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Experimental Section

Materials

Lipoic acid, 4-(dimethylamino)pyridine (DMAP), poly(ethylene glycol) methyl ether (average M_n 5,000 Da), tris(2-carboxyethyl)phosphine hydrochloride (TCEP), sodium chloride, potassium chloride, sodium phosphate dibasic and potassium phosphate monobasic were purchased from Sigma-Aldrich and used as received. 4-cyano-4-(((dodecylthio)carbonothioyl)thio) pentanoic acid was purchased from Boron Molecular. Phenyl acrylate (PhA, 99.97%) was purchased from BLDpharm. 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) and dithiothreitol (DTT) were purchased from Oakwood Chemical. VA-044 was purchased from Novachem. To obtain 10 mM phosphate buffered saline (PBS), 0.1 M PBS stock solution was prepared using sodium chloride (80 g, 137 mmol), potassium chloride (2 g, 27 mmol), potassium phosphate monobasic (2.4 g, 17 mmol), and sodium phosphate dibasic (14.4 g, 10 mmol) in reverse osmosis water (1.0 L) and the 0.1 M PBS stock was diluted by a factor of 10 to be 10 mM before use.

Characterization

Nuclear Magnetic Resonance Spectroscopy (NMR)

^{1}H NMR, ^{13}C NMR, COSY and HSQC spectroscopy were performed on a Bruker Avance 400 MHz spectrometer operated at 25 ºC, using deuterated chloroform ($CDCl_3$) as the solvent, with NMR spectra calibrated by the residual solvent peaks using MestreNova or TopSpin software.

Size Exclusion Chromatography (SEC)

SEC was performed on a Shimadzu system equipped with a CMB-20A controller system, an SIL-20A HT autosampler, an LC-20AT tandem pump system, a DGU-20A degasser unit, a CTO-20AC column oven, an RDI-10A refractive index detector, and 4 × Waters Styragel columns (HT2, HT3, HT4, and HT5, each 300 mm × 7.8 mm^2, providing an effective molar mass range of 100 - 4 × 10^6 Da). *N,N*-Dimethylacetamide (DMAc) (containing 4.34 g L^{-1} lithium bromide (LiBr)) was used as an eluent with a flow rate of 1 mL/min at 80 °C. Number (M_n) and weight average (M_w) molar masses were evaluated using Shimadzu LC Solution software. The SEC columns were calibrated with low dispersity polystyrene (PSt) standards (Polymer Laboratories) ranging from 575 to 3,242,000 g mol^{-1}, and molar masses are reported as PSt equivalents. A 3rd-order polynomial was used to fit the log M_p *vs*. time calibration curve, which was near linear across the molar mass ranges.

Differential Scanning Calorimetry (DSC)

Nanoparticle samples were purified and freeze dried prior to DSC analysis using a Mettler Toledo DSC-3 connected to a Huber TC100 intracooler. Approximately 10 mg of samples was placed in 40 uL Aluminium crucibles (sealed with pierced lid). Samples were cooled from 25 °C to – 60 °C, heated from – 60 °C to 60 °C, with the cooling and heating cycle repeated and

finally cooled to 25 °C at a heating rate of 10 °C /min under N_2 gas flow (50 mL/min). The mid-point T_g was determined from the second heating cycle using the Mettler Toledo Star-e software (vers 19.00). Exothermic peaks are in the positive y-axis direction on the DSC curve.

Dynamic Light Scattering (DLS)

Nanoparticle intensity-average diameter (D_z) and polydispersity index (PDI_{DLS}) were determined using a Horiba Nanopartica SZ-100 series nanoparticle analyzer (Horiba Scientific, Japan), operating at 25 °C and a fixed scattering angle of 90°. Nanoparticles were diluted to 0.1 % w/w with PBS buffer (pH 7.4) prior to DLS measurements.

Transmission Electron Microscopy (TEM)

The morphology of nanoparticles was observed by TEM. Carbon-coated grids (EMSCF300H-CU-TH, ProSciTech) were glow discharged to render them hydrophilic. A 2 µL drop of sample (diluted to 0.1 % w/w with Milli-Q water) was applied to an upturned grid held in anti-capillary forceps, over moist filter paper, and left to adsorb for 4 minutes. Excess liquid was then removed with Whatman 541 filter paper, a 4 µL drop of 2% phosphotungstic acid (PTA) stain at pH 6.9 was applied for 45 seconds. The excess stain was wicked away with filter paper and allowed to dry before viewing in the microscope. The samples were examined using Tecnai 12 Transmission Electron Microscope (FEI, Eindhoven, The Netherlands) at an operating voltage of 120 kV. Images were recorded using a FEI Eagle 4k × 4k CCD camera and AnalySIS v3.2 camera control software (Olympus).

Cell Culture

Human Embryonic Kidney (HEK) 293 cells (ATCC CRL-1573) were cultured in Dulbecco's modified Eagles medium (DMEM) supplemented with high glucose (GlutaMAX), 10% v/v fetal bovine serum (FBS) and 1% penicillin-streptomycin-amphotericin B. Cells were maintained at 37 °C in a humidified incubator with 5% atmospheric CO_2.

Cell Viability Assay

HEK cells were seeded at 10,000 cells per well in clear-bottom 96-well black plates and incubated overnight at 37 °C with 5% CO_2. The cells were then incubated in culture media with PISA nanoparticles at eight concentrations in triplicates and incubated at 37 °C for 24 h with 5% CO_2. After incubation, the media was removed and a 10% v/v solution of AlamarBlue in DMEM was added. The cells were incubated for a further 3 h at 37 °C. Cell viability was determined by measuring the fluorescence at 590 nm using a fluorescence plate reader (Clariostar, BMG). Control samples were cells incubated with DMEM (without nanoparticles). The viability was calculated using the equation below, where FI = fluorescence intensity. All experiments were performed in triplicate to determine mean fluorescence intensity and SD.

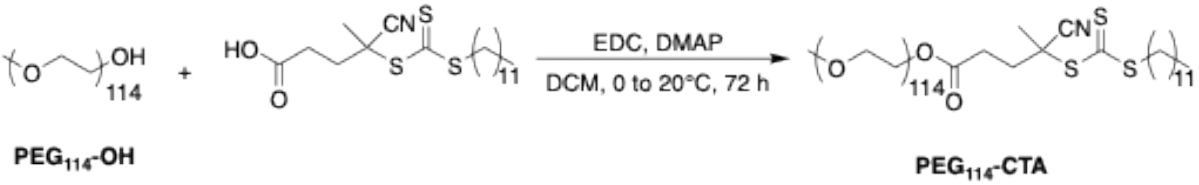
$$\text{Cell viability (\%)} = \frac{(FI\ sample - FI\ blank)}{(FI\ control - FI\ blank)} \times 100\ \%$$

Synthetic Procedures

Synthesis of PEG_{114} Macro-Chain transfer Agent (mCTA).

To a solution of 4-cyano-4-[(dodecyl-sulfanylthiocarbonyl)-sulfanyl]pentanoic acid (807 mg, 2 mmol), poly(ethylene glycol) methyl ether (PEG-OH, 6.0 g, 1.0 mmol), 4-(dimethylamino)pyridine (DMAP, 24.4 mg, 0.2 mmol) in anhydrous dichloromethane (DCM, 15 mL), EDC HCl (383.4 mg, 2 mmol) dissolved in dry DCM (5 mL) was added dropwise at 0 °C using an ice bath. After complete addition, the solution was stirred at room temperature for 3 days to ensure the complete consumption of PEG-OH. The reaction mixture was then washed with 0.1 M HCl (3 × 50 mL), saturated sodium bicarbonate (2 × 50 mL), brine (2 × 50 mL) and dried using magnesium sulfate. The concentrated solution was purified by precipitation in diethyl ether 3 times, filtered off, and then dried under vacuum until constant weight was reached to give a bright yellow solid. The purified PEG_{114} macro-CTA was then analyzed by SEC.

Synthesis of PEG_{114} macro-CTA



PEG_{114}-OH

PEG_{114}-CTA

Scheme S1. Synthesis of PEG_{114} macro-CTA.

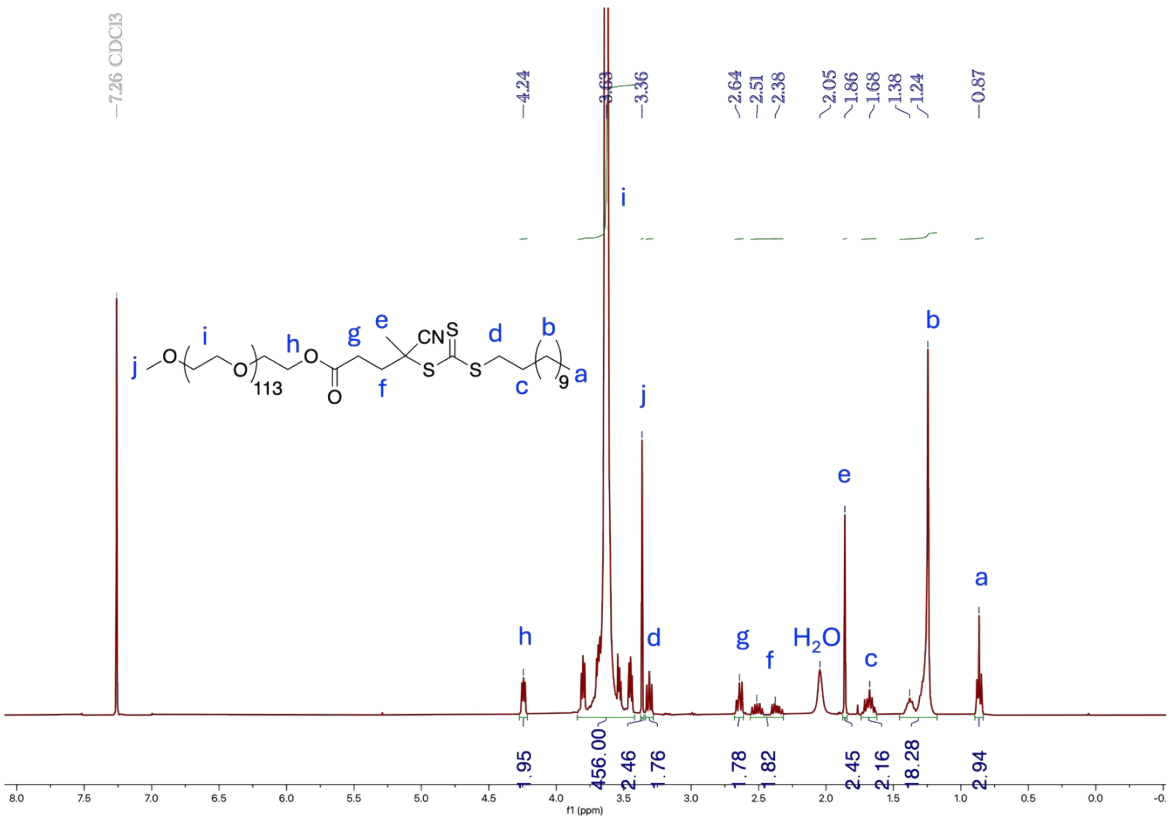


Figure S1. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of **PEG_{114} macro-CTA**.

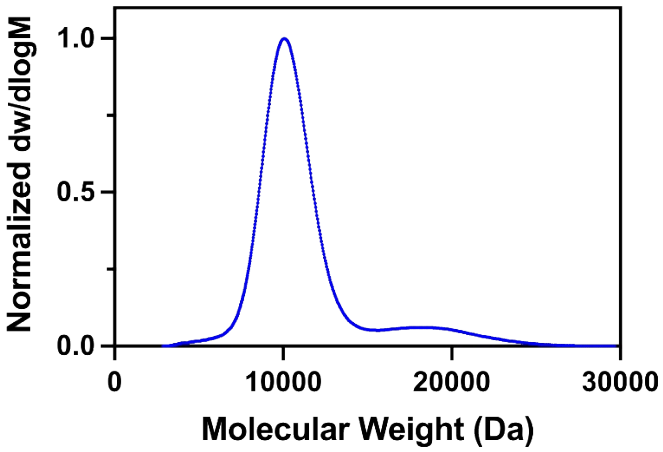
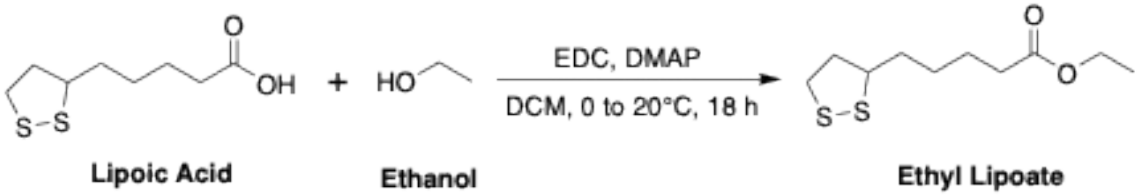


Figure S2. SEC trace of **PEG_{114} macro-CTA**.

Synthesis of Ethyl Lipoate (LpEt).

To a solution of lipoic acid (2 g, 9.7 mmol), ethanol (1.1 mL, molar excess), DMAP (118 mg, 0.97 mmol) in dry DCM (15 mL), EDC HCl (383.4 mg, 2 mmol) dissolved in dry DCM (10 mL) was added dropwise at 0 °C using an ice bath. After complete addition, the reaction was stirred for 30 min at 0 °C and then removed from the ice-bath. The flask was wrapped in aluminium foil to protect from ambient light and was stirred overnight at room temperature (18 h). The reaction mixture was then diluted with 50 mL DCM and washed with 0.1 M HCl (3 × 100 mL), saturated sodium bicarbonate (1 × 100 mL) and brine (1 × 100 mL) before drying over $MgSO_4$. The final mixture was concentrated *in vacuo* to give a yellow oil (yield = 1.84 g, 81%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.13 (q, 2H), 3.57 (m, 1H), 3.13 (m, 2H), 2.47 (m, 1H), 2.31 (t, 2H), 1.92 (m, 1H), 1.67 (m, 4H), 1.48 (m, 2H), 1.25 (t, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.63, 60.41, 56.48, 40.35, 38.62, 34.74, 34.25, 28.89, 24.83, 14.39.



Scheme S2. Synthesis of ethyl lipoate (LpEt).

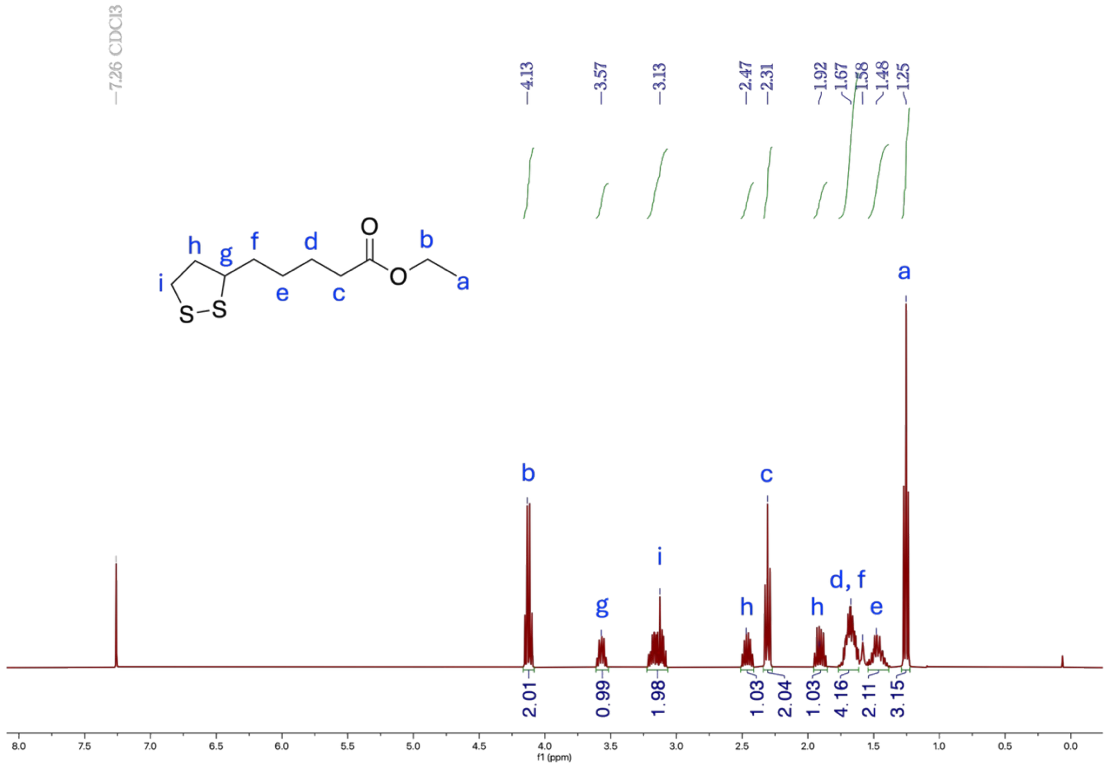


Figure S3. ^{1}H NMR spectrum ($CDCl_3$, 400 MHz) of LpEt.

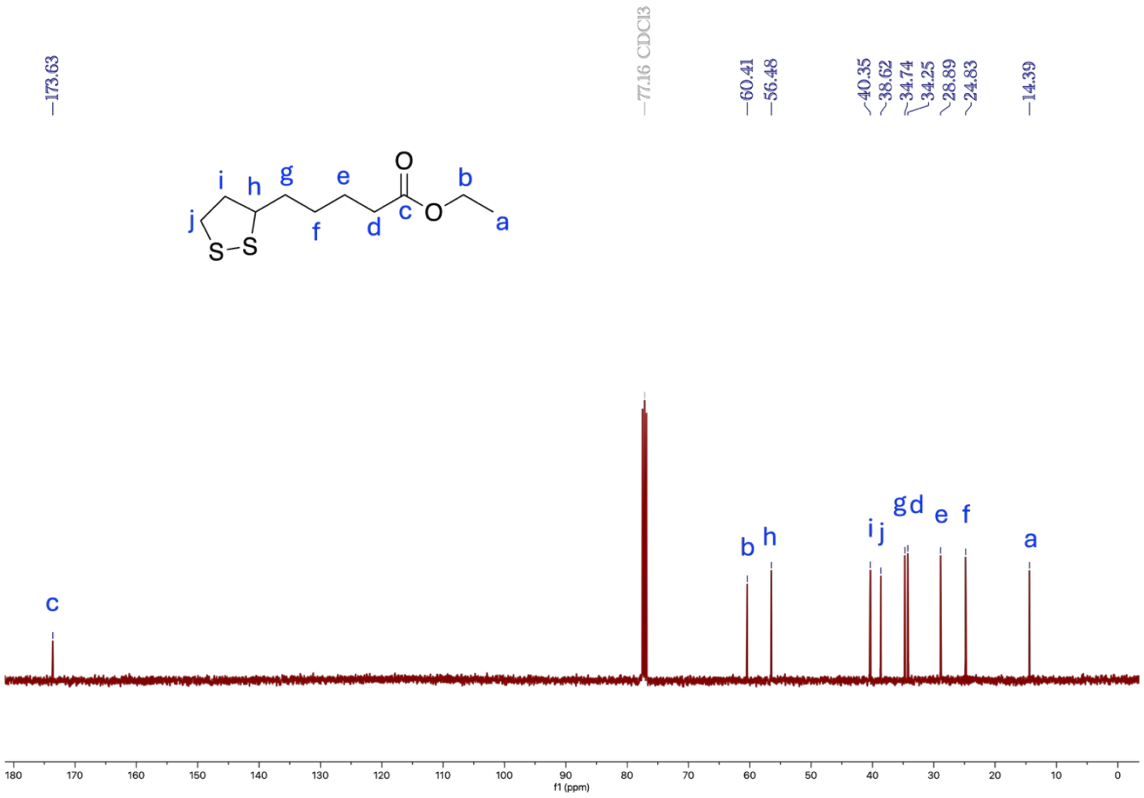


Figure S4. ^{13}C NMR spectrum ($CDCl_3$, 400 MHz) of LpEt.

Synthesis of Poly(ethylene glycol)-*b*-poly(phenyl acrylate-*co*-ethyl lipoate) (PEG_{114}-*b*-$P(PhA_{150}$-*co*-$LpEt_y$) diblock copolymer particles by RAFT PISA.

A typical protocol for the synthesis of PEG_{113}-*b*-$P(PhA_{150}$-*co*-$LpEt_{15})$ was as follows: PEG_{114} macro-CTA (1 eq., 50 mg, 9.3 μmol) was added to a glass vial equipped with a magnetic stirrer bar, followed by PhA monomer (150 eq., 206 mg, 1.39 mmol), LpEt monomer (15 eq., 32.6 mg, 0.139 mmol), ethanol (580 mg) and water (580 mg), corresponding to a 20% w/w solution. VA-044 initiator was then added (0.5 eq., 1.5 mg, 4.7 μmol). The vial was cooled using an ice bath to prevent solvent evaporation and the solution sparged with nitrogen gas for 30 minutes. The vial was then sealed and immersed in a preheated oil bath at 37 °C for 20 h to ensure high monomer conversion (>98% by ^{1}H NMR spectroscopic analysis) and subsequently quenched by cooling followed by exposure to air. The crude materials were placed in a 3.5 kDa SnakeSkin dialysis tubing, dialysed against 50:50 (w/w) ethanol/water for 4 hours, 30:70 (w/w) ethanol/water for 4 hours, 10:90 (w/w) ethanol/water for 4 hours and finally against Milli-Q water for 4 hours (one change of water after 2 hours). The nanoparticle colloidal characteristics (D_z and PDI_{DLS}) were determined by DLS and their morphology was assessed by TEM. The final sample was also freeze dried prior to analysis by ^{1}H NMR in $CDCl_3$ and SEC. ^{1}H NMR indicated near quantitative conversion of PhA and LpEt and DMAc SEC analysis of PEG_{114}-*b*-$P(PhA_{150}$-*co*-$LpEt_{15})$ indicated M_n and M_w/M_n *(Đ)* values of 29,120 g mol^{-1} and 1.28, respectively.

The same procedure was repeated by independently varying the solids content and the input of LpEt (0, 10, 20, 30 mol% relative to PhA).

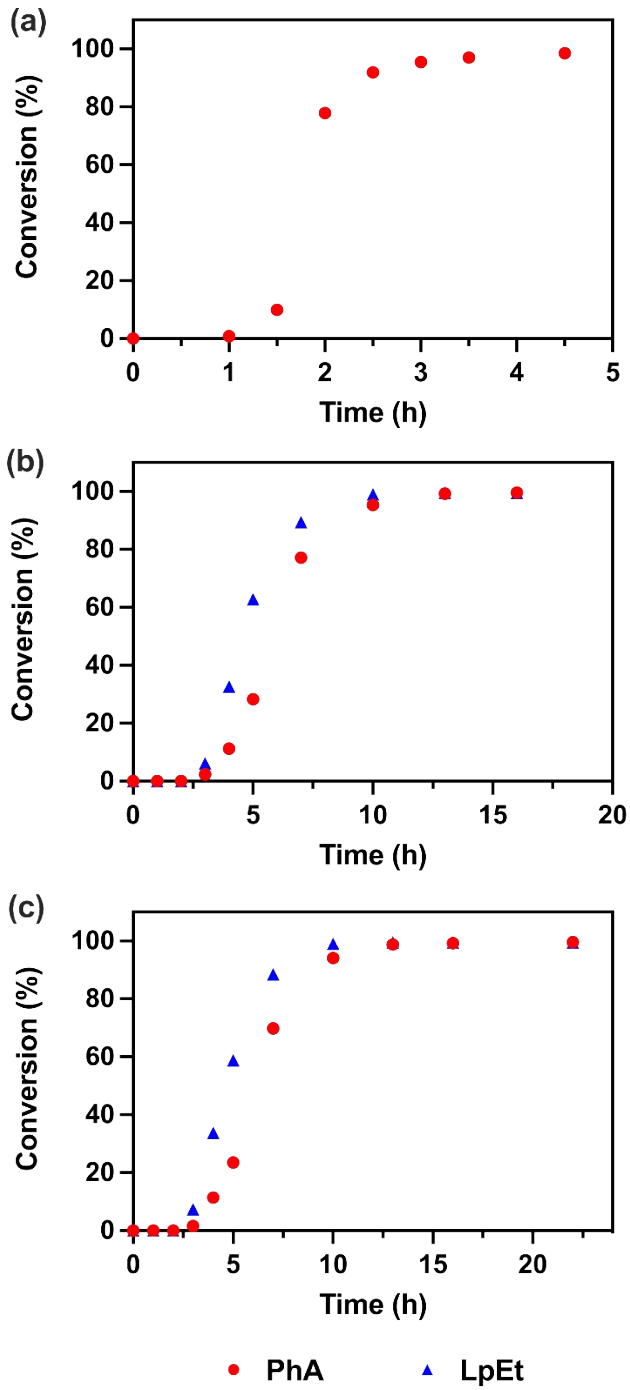


Figure S5. Kinetics study of (a) P_{150}, (b) P_{150}-L_{30} and (c) P_{150}-L_{45} prepared at 20% w/w. PhA and LpEt conversion were plotted against time.

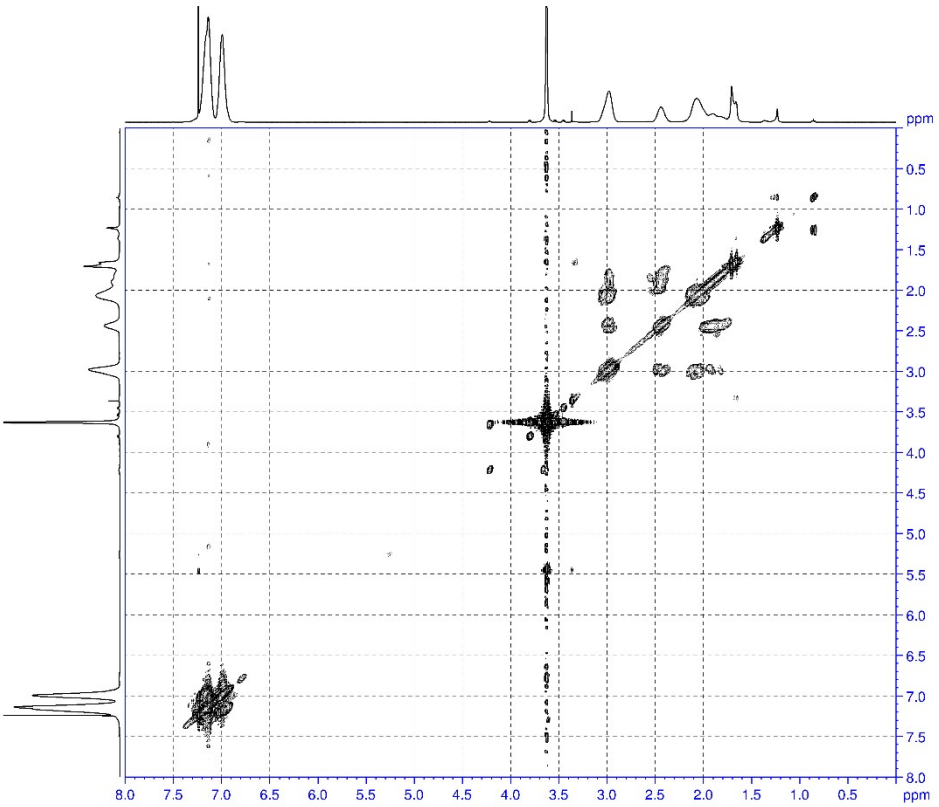


Figure S6. COSY spectrum of P_{150} prepared at 20% w/w.

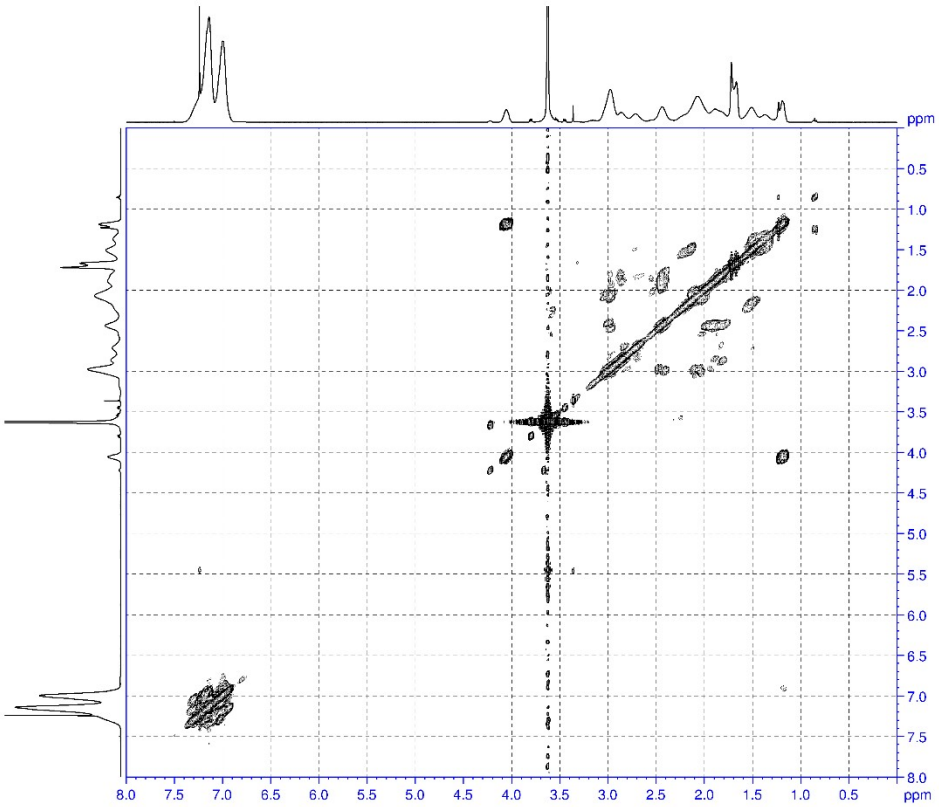


Figure S7. COSY spectrum of P_{150}-L_{15} prepared at 20% w/w.

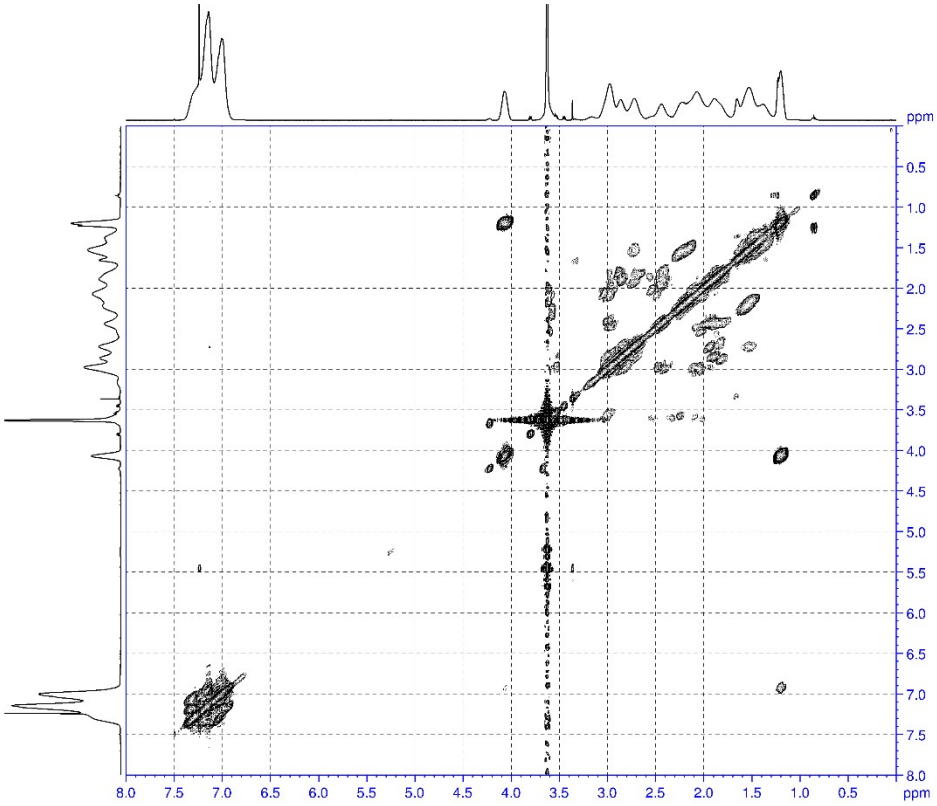


Figure S8. COSY spectrum of P_{150}-L_{30} prepared at 20% w/w.

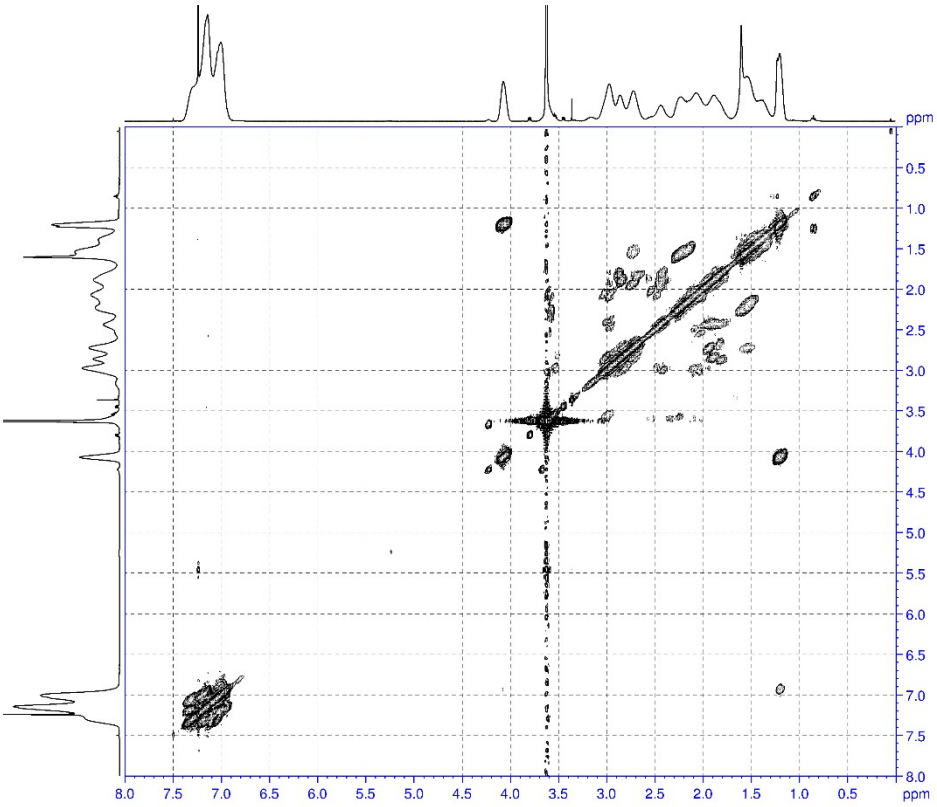


Figure S9. COSY spectrum of P_{150}-L_{45} prepared at 20% w/w.

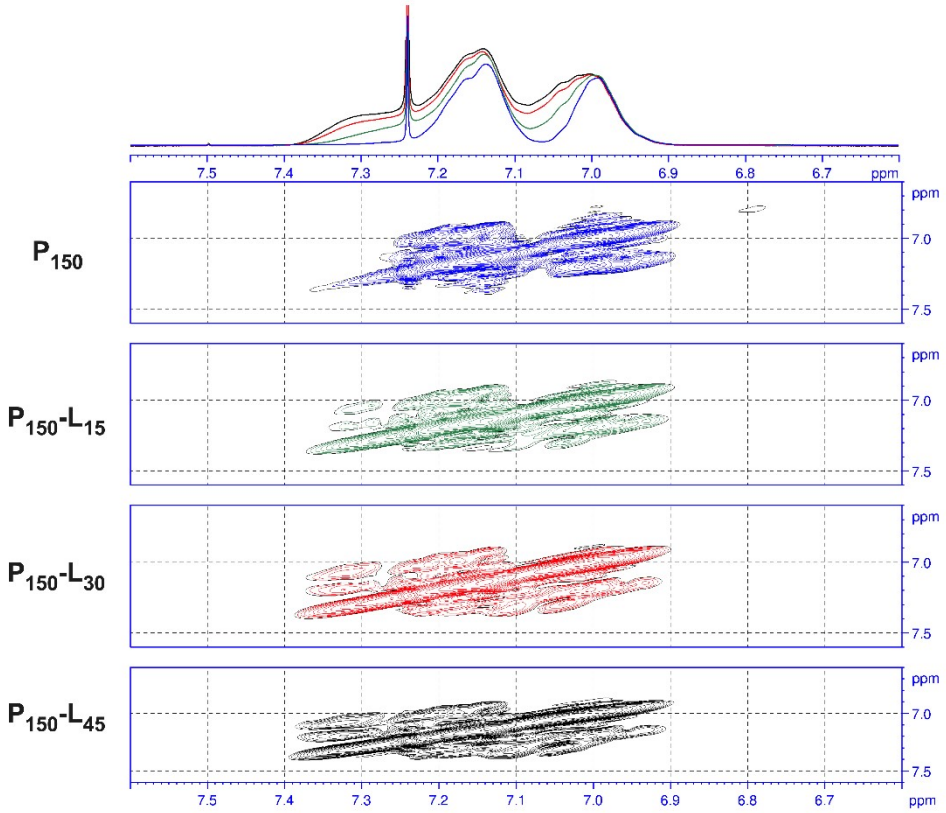


Figure S10. Overlay of COSY spectra of P_{150}, P_{150}-L_{15}, P_{150}-L_{30}, and P_{150}-L_{45} prepared at 20% w/w.

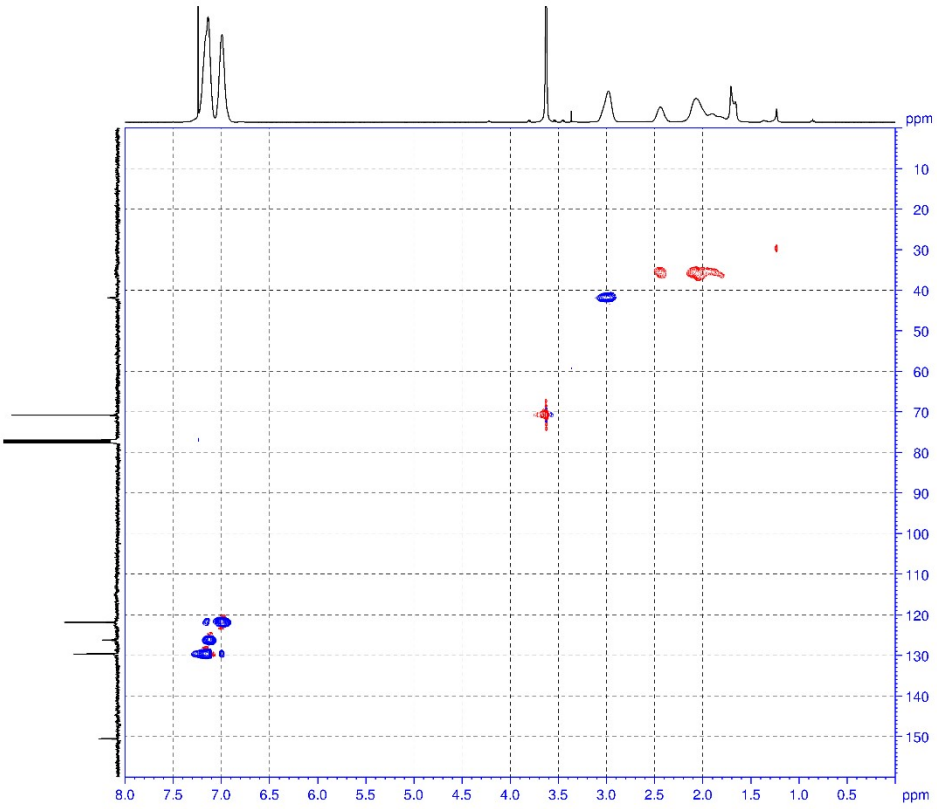


Figure S11. HSQC spectrum of P_{150} prepared at 20% w/w.

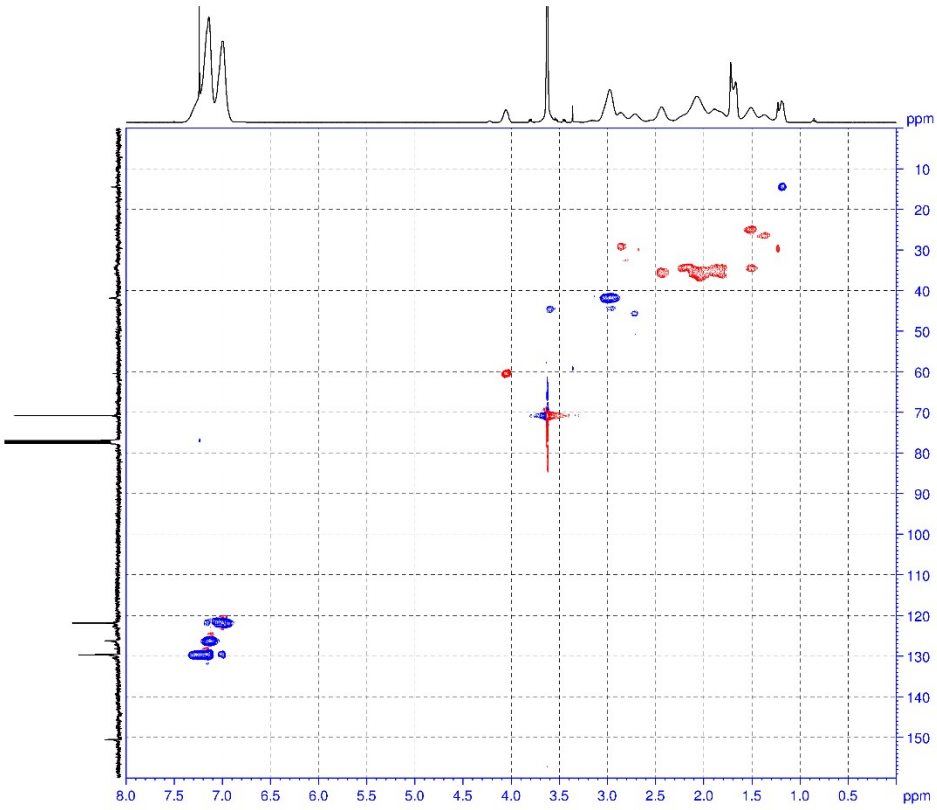


Figure S12. HSQC spectrum of P_{150}-L_{15} prepared at 20% w/w.

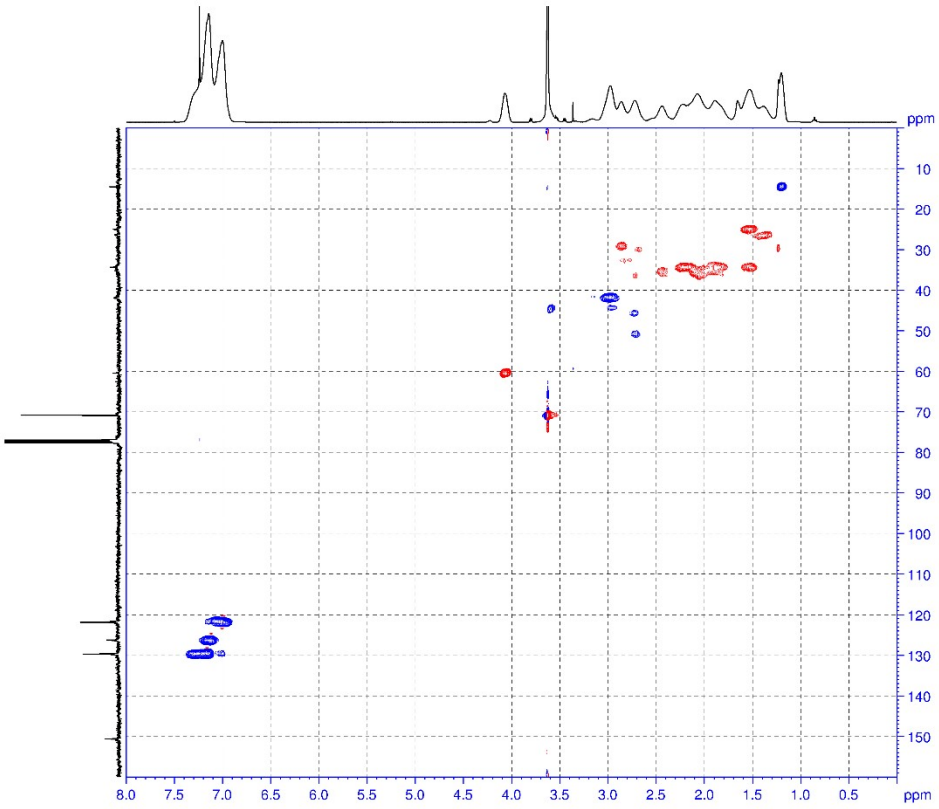


Figure S13. HSQC spectrum of P_{150}-L_{30} prepared at 20% w/w.

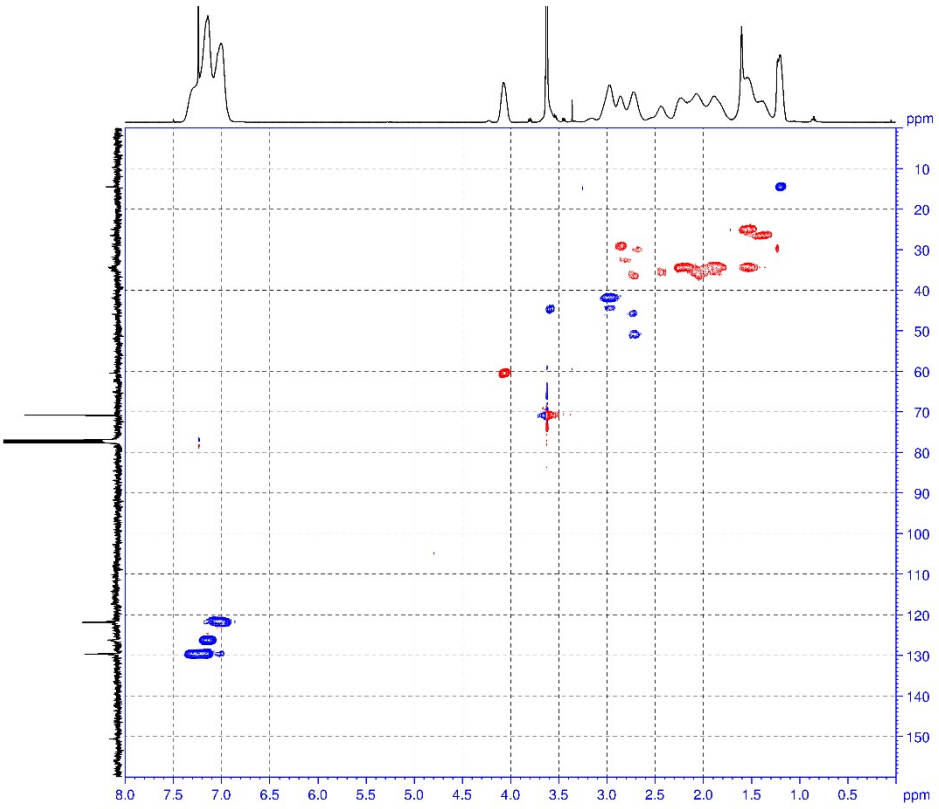


Figure S14. HSQC spectrum of P_{150}-L_{45} prepared at 20% w/w.

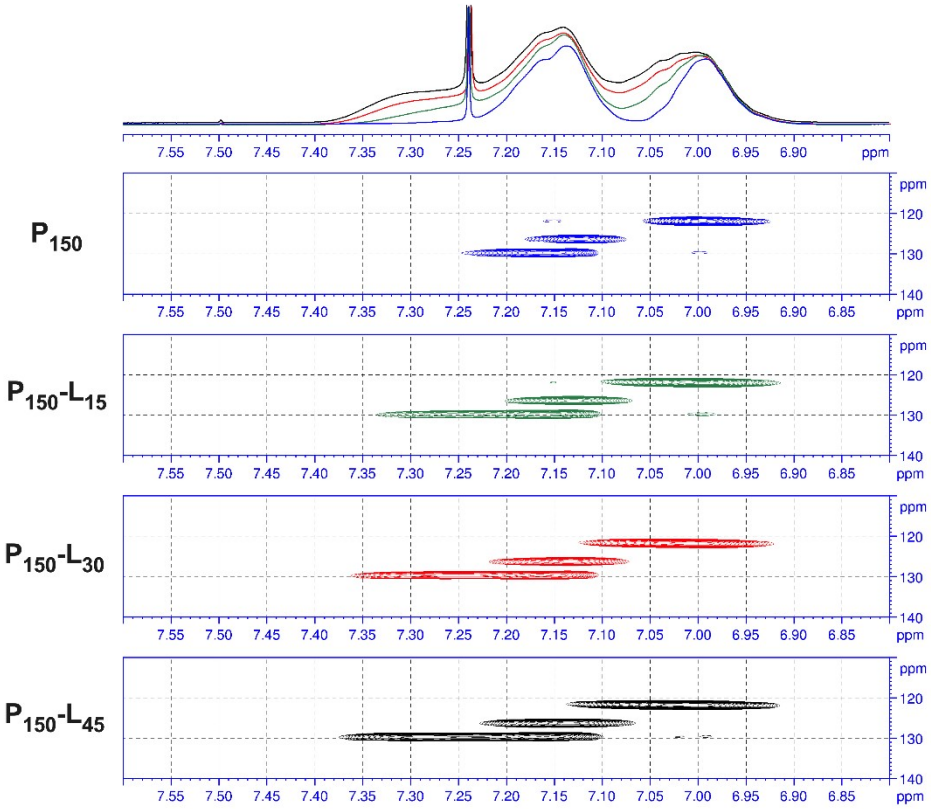


Figure S15. Overlay of HSQC spectra of P_{150}, P_{150}-L_{15}, P_{150}-L_{30}, and P_{150}-L_{45} prepared at 20% w/w.

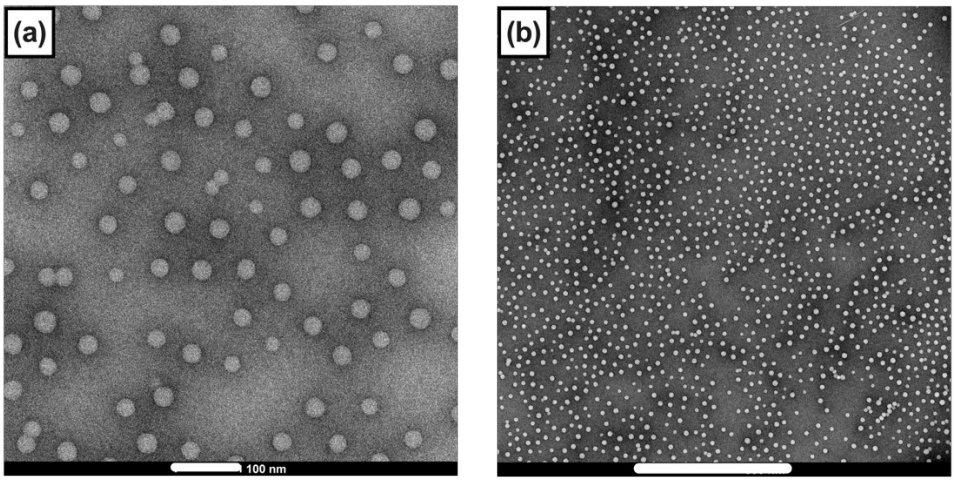


Figure S16. Representative TEM images of P_{150} nanoparticles. (a) Scale bar = 100 nm, (b) scale bar = 500 nm. Particle solution was diluted to 0.1% w/w prior to imaging.

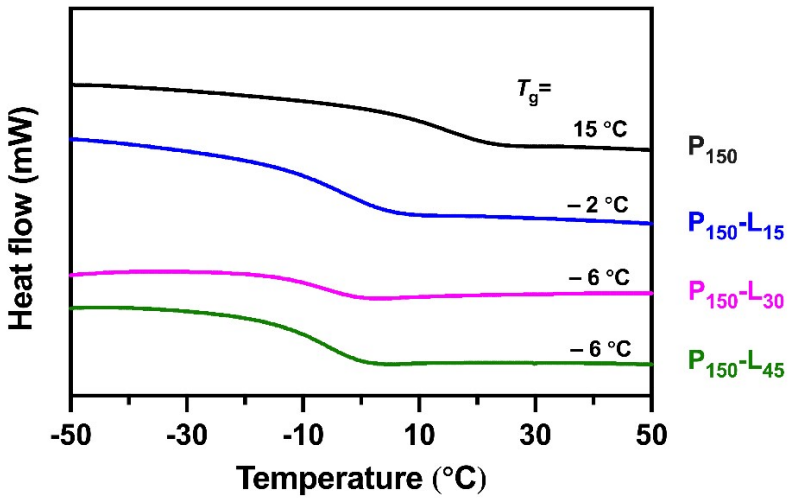


Figure S17. DSC curves recorded at 10 °C/min for copolymers P_{150}, P_{150}-L_{15}, P_{150}-L_{30}, and P_{150}-L_{45}.

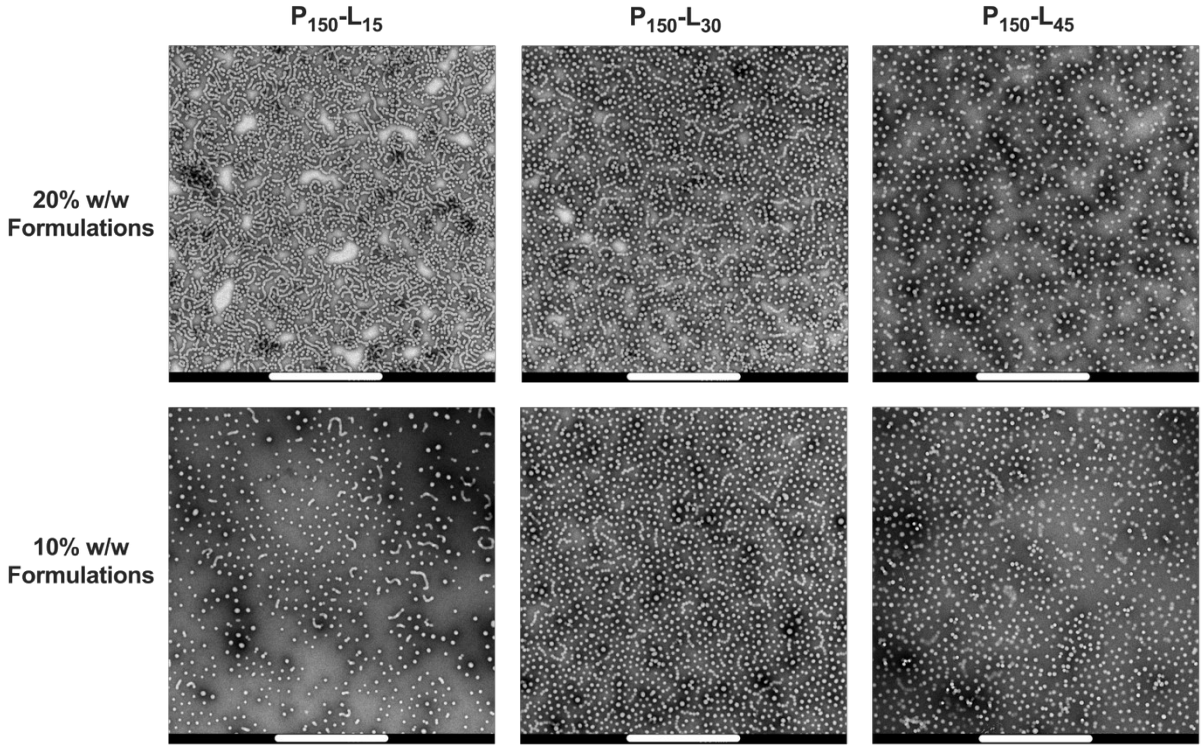


Figure S18. Representative TEM images of P_{150}-L_n (n = 15, 30, 45) copolymer nanoparticles prepared at 10% or 20% w/w. All particle solutions were diluted to 0.1% w/w prior to imaging. Scale bar = 500 nm.

Degradation procedure and analysis

Polymer degradation using tris(2-carboxyethyl)phosphine (TCEP) in DMAc

To verify the presence of disulfide bonds along the polymer backbone, dry extracts of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_n$) copolymers were degraded using tris(2-carboxyethyl)phosphine (TCEP), a mild reducing agent commonly used in biomedical applications. A stock solution of TCEP (100 mg) was prepared by firstly dissolving TCEP in Milli-Q water (200 µL) and subsequently diluting with DMAc (200 µL). Five milligrams of dried polymer from each formulation were solubilised in 1 mL DMAc and a portion of the TCEP stock solution (5 eq. to thiol) was added. The mixture was incubated at 37 °C for 24 h prior to SEC analysis. At the same time, control experiments were conducted on samples incubated without TCEP addition at 37 °C for 24 h. All degradation experiments were conducted three times for each formulation, and the three independent experimental repeats were indicated by R1, R2 and R3.

Table S1. TCEP polymer degradation of PEG_{114}-*b*-$PPhA_{150}$ prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	25.2	32.1	1.27	-	-
37 °C R1	23.8	29.7	1.25	5.6	**3.5 ± 2.0**
37 °C R2	24.4	30.7	1.26	3.3	
37 °C R3	24.8	31.7	1.27	1.6	
TCEP R1	25.5	31.6	1.24	~ 0	**2.5 ± 0.1**
TCEP R2	24.6	30.8	1.25	2.4	
TCEP R3	24.6	30.7	1.25	2.5	

Table S2. TCEP polymer degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{15}$) prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	29.1	37.3	1.28	-	-
37 °C R1	27.9	36.9	1.32	4.2	**3.8 ± 1.0**
37 °C R2	27.8	37.3	1.34	4.5	
37 °C R3	28.4	37.3	1.31	2.6	
TCEP R1	19.8	27.5	1.39	32.1	**29.5 ± 2.5**
TCEP R2	21.2	27.9	1.32	27.1	
TCEP R3	20.6	26.8	1.30	29.3	

Table S3. TCEP polymer degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{15}$) prepared at 10% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	30.6	42.7	1.40	-	-
37 °C R1	29.5	38.8	1.31	3.6	**6.1 ± 4.7**
37 °C R2	27.4	36.3	1.32	10.2	
37 °C R3	29.2	38.9	1.33	4.6	
TCEP R1	19.0	28.8	1.51	37.7	**34.4 ± 3.5**
TCEP R2	21.2	28.9	1.37	30.7	
TCEP R3	20.0	30.4	1.52	34.6	

Table S4. TCEP polymer degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{30}$) prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	37.5	52.9	1.41	-	-
37 °C R1	31.0	43.3	1.40	17.4	**23.3 ± 5.3**
37 °C R2	28.2	38.9	1.38	24.9	
37 °C R3	27.2	39.2	1.44	27.5	
TCEP R1	10.4	21.9	2.11	72.3	**73.6 ± 1.3**
TCEP R2	9.4	18.6	1.97	74.8	
TCEP R3	9.8	18.9	1.92	73.8	

Table S5. TCEP polymer degradation of PEG_{114}-b-P(PhA_{150}-co-$LpEt_{30}$) prepared at 10% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	37.4	53.4	1.43	-	-
37 °C R1	30.2	43.4	1.44	19.2	**23.3 ± 3.7**
37 °C R2	28.3	41.1	1.45	24.3	
37 °C R3	27.5	38.8	1.41	26.4	
TCEP R1	9.5	19.1	2.02	74.7 %	**73.4 ± 2.3**
TCEP R2	9.5	19.1	2.01	74.7 %	
TCEP R3	11.0	23.5	2.15	70.6 %	

Table S6. TCEP polymer degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{45}$) prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	41.5	59.2	1.43	-	-
37 °C R1	30.2	44.4	1.47	27.2	**29.6 ± 4.1**
37 °C R2	30.1	43.5	1.44	27.2	
37 °C R3	27.2	40.4	1.48	34.3	
TCEP R1	6.7	14.8	2.21	83.8 %	**82.7 ± 1.3**
TCEP R2	7.0	16.4	2.33	83.0 %	
TCEP R3	7.8	16.8	2.15	81.2 %	

Table S7. TCEP polymer degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{45}$) prepared at 10% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	39.3	60.3	1.53	-	-
37 °C R1	28.3	41.8	1.48	28.0	**25.9 ± 6.9**
37 °C R2	32.2	47.6	1.48	18.2	
37 °C R3	27.0	42.7	1.59	31.5	
TCEP R1	6.7	13.0	1.92	82.8	**81.2 ± 4.7**
TCEP R2	6.0	11.2	1.87	84.8	
TCEP R3	9.5	18.4	1.94	75.9	

Particle degradation using dithiothreitol (DTT) in buffer

A 100 mM stock solution of DTT was prepared by dissolving 15.4 mg DTT in 1 mL of PBS buffer (pH 7.4). Nanoparticles were diluted to 0.1% w/w in 0.9 mL of PBS buffer (pH 7.4) and 100 µL of the 100 mM DTT stock solution was added to each nanoparticle solution to reach a final 10 mM DTT concentration. The particle solutions were then incubated at 37 °C for 24 h prior to SEC analysis. At the same time, control experiments were conducted on samples incubated without DTT at 37 °C for 24 h. All degradation experiments were conducted three times for each formulation, and the three independent experimental repeats were indicated by R1, R2 and R3.

Table S8. DTT particle degradation of PEG_{114}-*b*-$PPhA_{150}$ prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	25.2	32.1	1.27	-	
37 °C R1	24.8	31.7	1.28	1.6	**2.2 ± 0.4**
37 °C R2	24.5	31.2	1.27	2.8	
37 °C R3	24.7	30.9	1.25	2.2	
DTT R1	27.7	39.4	1.42	~ 0	**0**
DTT R2	27.0	41.0	1.52	~ 0	
DTT R3	25.4	39.0	1.53	~ 0	

Table S9. DTT particle degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{15}$) prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Initial	29.1	37.3	1.28	-	-
37 °C R1	28.2	40.2	1.42	3.0	**3.0 ± 0.2**
37 °C R2	28.3	39.1	1.38	2.8	
37 °C R3	28.2	38.6	1.37	3.3	
DTT R1	23.6	31.0	1.32	19.1 %	**21.2 ± 3.5**
DTT R2	23.5	35.8	1.53	19.4 %	
DTT R3	21.8	31.5	1.45	25.2 %	

Table S10. DTT particle degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{15}$) prepared at 10% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	30.6	42.7	1.40	-	-
37 °C R1	29.0	41.0	1.42	5.2	**5.2 ± 1.4**
37 °C R2	28.6	40.0	1.40	6.6	
37 °C R3	29.4	39.2	1.33	3.8	
DTT R1	25.3	37.4	1.48	17.3 %	**28.1 ± 11.4**
DTT R2	18.4	26.5	1.44	40.0 %	
DTT R3	22.3	32.7	1.47	27.1 %	

Table S11. DTT particle degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{30}$) prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	37.5	52.9	1.41	-	-
37 °C R1	37.4	51.7	1.38	0.3	**3.5 ± 2.9**
37 °C R2	35.2	49.8	1.41	6.0	
37 °C R3	35.9	49.1	1.36	4.1	
DTT R1	15.0	23.9	1.60	60.1	**59.7 ± 4.5**
DTT R2	16.9	24.9	1.47	55.0	
DTT R3	13.5	21.3	1.58	64.0	

Table S12. DTT particle degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{30}$) prepared at 10% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	37.4	53.4	1.43	-	-
37 °C R1	36.1	50.8	1.41	3.6	**5.7 ± 2.9**
37 °C R2	35.8	50.5	1.41	4.5	
37 °C R3	34.1	47.9	1.41	9.0	
DTT R1	19.4	28.9	1.49	48.1	**55.9 ± 7.0**
DTT R2	14.4	21.7	1.51	61.5	
DTT R3	15.7	24.0	1.53	58.0	

Table S13. DTT particle degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{45}$) prepared at 20% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	41.5	59.2	1.43	-	-
37 °C R1	38.1	54.7	1.44	8.3	**7.8 ± 1.0**
37 °C R2	37.9	58.5	1.54	8.6	
37 °C R3	38.7	57.9	1.50	6.7	
DTT R1	8.9	15.6	1.75	78.5 %	**75.4 ± 3.5**
DTT R2	9.9	16.5	1.66	76.0 %	
DTT R3	11.8	18.1	1.54	71.6 %	

Table S14. DTT particle degradation of PEG_{114}-*b*-P(PhA_{150}-*co*-$LpEt_{45}$) prepared at 10% w/w.

	M_n (kDa)	M_w (kDa)	$Đ$	Degradation (% M_n loss)	Average Degradation (% M_n loss)
Control	39.3	60.3	1.53	-	-
37 °C R1	37.4	55.3	1.48	4.7	**5.0 ± 2.1**
37 °C R2	38.1	58.9	1.55	3.0	
37 °C R3	36.5	55.5	1.52	7.1	
DTT R1	14.5	19.5	1.35	63.2	**64.7 ± 3.3**
DTT R2	13.1	17.0	1.30	68.5	
DTT R3	14.8	20.0	1.35	62.5	

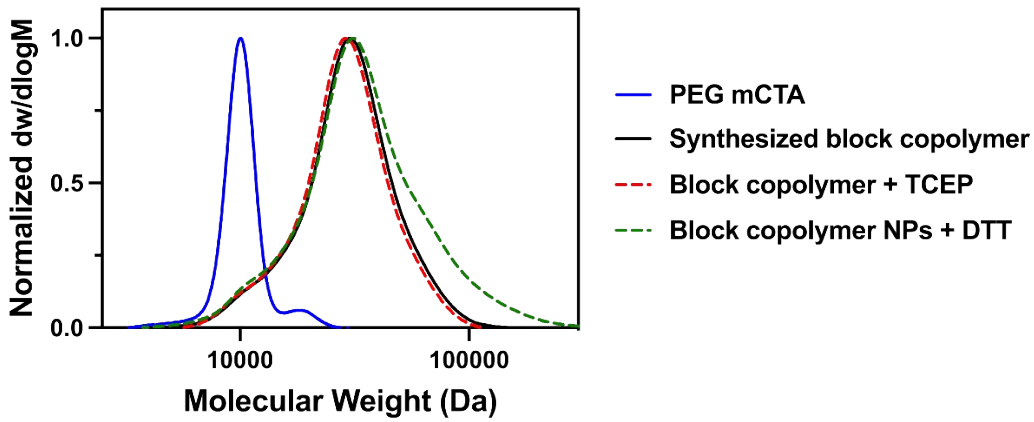


Figure S19. Molecular weight distribution obtained from SEC-DMAc analysis of PEG_{114} mCTA (blue line), dried particle solutions of P_{150} formulation as synthesized (black line), block copolymer after TCEP treatment (red dashed line) and block copolymer nanoparticle after 10 mM DTT treatment (green dashed line).

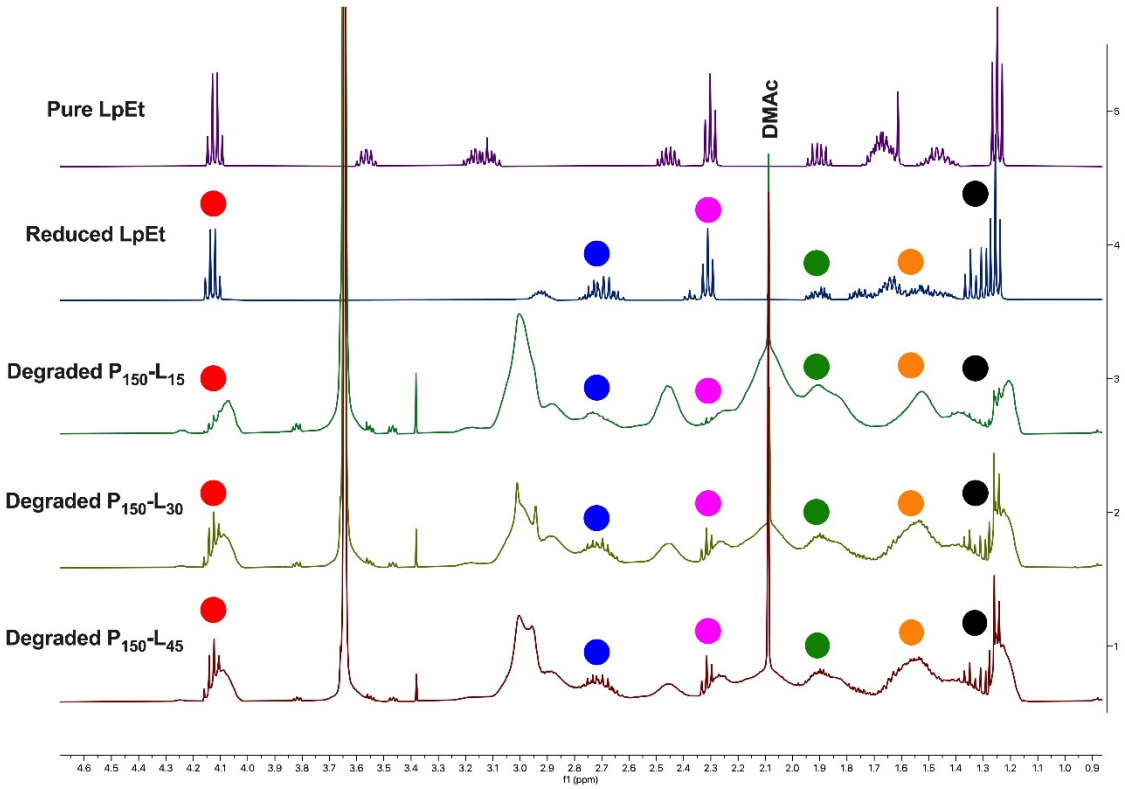


Figure S20. ^{1}H NMR spectra ($CDCl_3$, 400 MHz) of pure LpEt, reduced LpEt, degraded copolymers P_{150}-L_{15}, P_{150}-L_{30}, and P_{150}-L_{45} following TCEP treatment in DMAc at 37 °C for 24 h.