

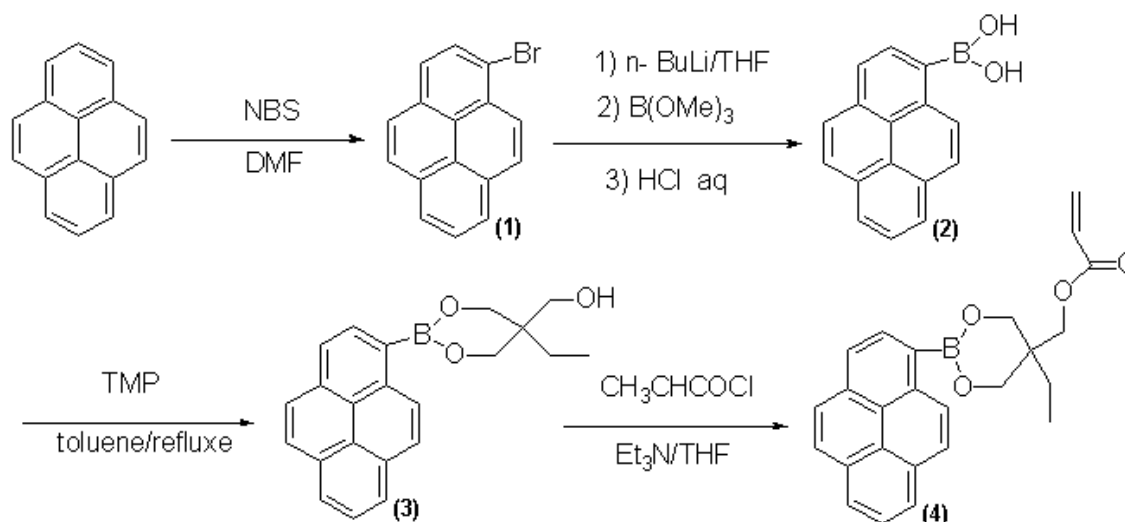
Supporting Information

Smarter Glucose-Sensitivity of Polymeric Micelles
Formed from Phenylborate Ester-*co*-Pyrenylboronic
Ester for Insulin Delivery at Physiological pH

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Scheme S1. Synthesis route of PyBDEMA monomer.

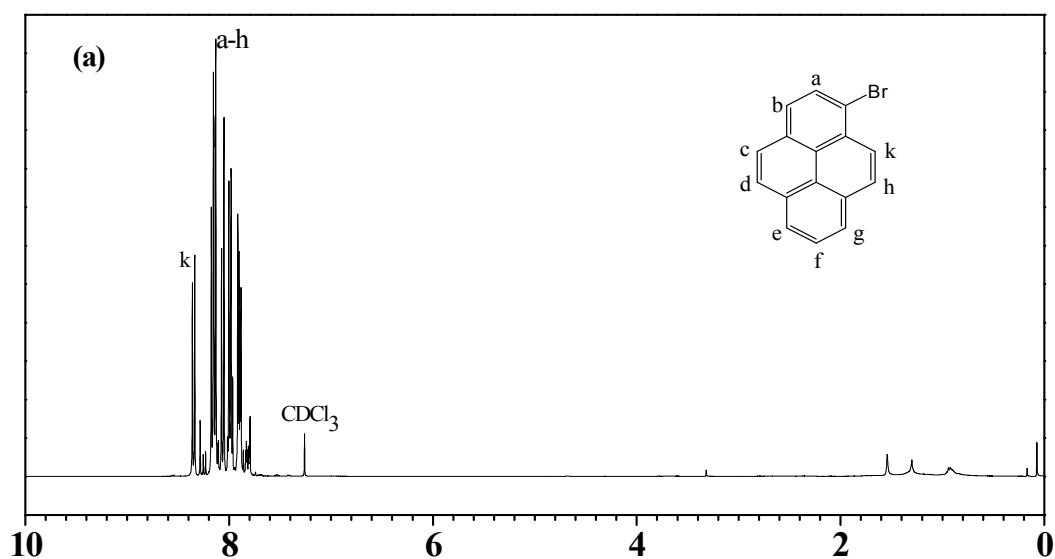
Preparation of 1-bromopyrene. Similar to the reported method.^[1] A mixture of pyrene (9.99 g, 49.4 mmol) and 70 mL DMF was dropwise added into the 250 mL flask containing NBS (8.8 g, 49.5 mmol) and 40 mL DMF at ice bath, and stirred for 24 h. The reaction mixture was diluted with ice water and extracted with ether. After drying with anhydrous Na_2SO_4 , the solution was concentrated and purified with column using hexanes as eluent and obtained white solid in yield of 84.6%. ^1H NMR (400 MHz, CDCl_3) δ (ppm) : 8.41(d, 1H), 8.35-7.76 (m, 8H, $-\text{C}_{16}\text{H}_8\text{Br}$). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 131.87, 129.97, 128.87, 127.61, 126.43, 125.53, 123.98, 119.92.

Preparation of 1-pyrenylboronic acid. According to the reported procedure.^[2] Into one degassed 250 mL three-necked flask containing bromopyrene (9.95 g, 35.5 mmol) and 120 mL THF was dropwise added n-butyllithium (23.9 mL, 53.3 mmol) at -78°C , followed by stirring for 1 h at such cold environment. After trimethylborate (11.0 g, 106.5 mmol) was added into the above mixture, the reaction solution was maintained at -78°C for additional 2 h, and then kept at room temperature for 24 h. pH of the reaction mixture was adjusted to 3~4 using HCl aqueous solution (0.12 M). The solution was washed with distilled water, extracted with ethyl acetate. After the organic phase was dried with anhydrous MgSO_4 and concentrated, the crude product was recrystallized using hexanes and CH_2Cl_2 in yield of 41.2%. ^1H NMR (400 MHz, CDCl_3) δ (ppm): 8.76 (d, 1H), 8.65 (s, 2H, HOBOH), 8.33~7.99 (m, 8H, $-\text{C}_{16}\text{H}_8$). ^{13}C NMR (100 MHz, CDCl_3) δ (ppm): 134.87, 134.30, 132.03, 131.17, 128.89, 127.93, 126.77, 126.26, 125.43, 124.01, 123.97.

Preparation of (2-pyrenylboronic esters-1,3-dioxane-5-ethyl) methylacrylate (PyBDEMA)

monomer 4. The following monomer synthesis involving two steps was similar to the preparation method of PBDEMA. For the first step, the mixture of pyrenylboronic acid (5.2 g, 21.0 mmol) and 1,1,1-tris(hydroxymethyl) propane (3.1 g, 21.0 mmol) charged in one three-necked round bottle was stirred in toluene (100 mL) in the presence of a small amount of molecular sieves at 120 °C for 4 h. The reaction solution was filtered, and the crude solid precursor **3** was obtained by toluene removal in vacuum. Yield: 81.3%. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.07 (d, 1H), 8.52 (m, 1H), 8.52~8.07 (m, 7H, -C₁₆H₇), 3.84-4.05 (m, 4H, CH₂OBOCH₂), 3.65 (br, 2H, CH₂OH), 1.53 (m, 2H, CH₂CH₃), 0.89 (m, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 136.0, 133.1, 131.3, 127.91, 125.54, 124.2, 67.1, 66.8, 39.1, 23.5, 7.4.

For the second step, the preparation of monomer **4** (PyBDEMA) was carried out by the reaction of precursor **3** (10.0 g, 29.0 mmol), acryloyl chloride (4.2 g, 46.4 mmol) and triethylamine (2.9 g, 29.0 mmol) in anhydrous CH₂Cl₂ (60 mL) in an ice bath for 8 h. After filtration, the concentrated filtrate was purified by column chromatography with mixture of petroleum ether and ethyl acetate (v/v = 4/1) as eluent to afford slightly yellow solid. Yield: 60.3%. ¹H NMR (400 MHz, CDCl₃) δ (ppm): 9.12 (d, 1H), 8.58 (m, 1H), 8.23~8.05 (m, -C₁₆H₇), 6.40 (d, *J* = 16 Hz, 1H, CH₂=CH), 6.12 (m, 1H, CH₂=CH), 5.84 (d, *J* = 8 Hz, 1H, CH₂=CH), 4.19 (s, 2H, CH₂OOCCH=CH₂), 4.05 (d, *J* = 8 Hz, 2H, CH₂OBOCH₂), 3.92 (d, *J* = 8 Hz, 2H, CH₂OBOCH₂), 1.50 (m, 2H, CH₂CH₃), 0.92 (t, *J* = 8 Hz, 3H, CH₂CH₃); ¹³C NMR (100 MHz, CDCl₃) δ (ppm): 166.1, 136.1, 133.02, 131.87, 128.69, 124.3, 67.3, 64.1, 38.0, 24.1, 7.5.



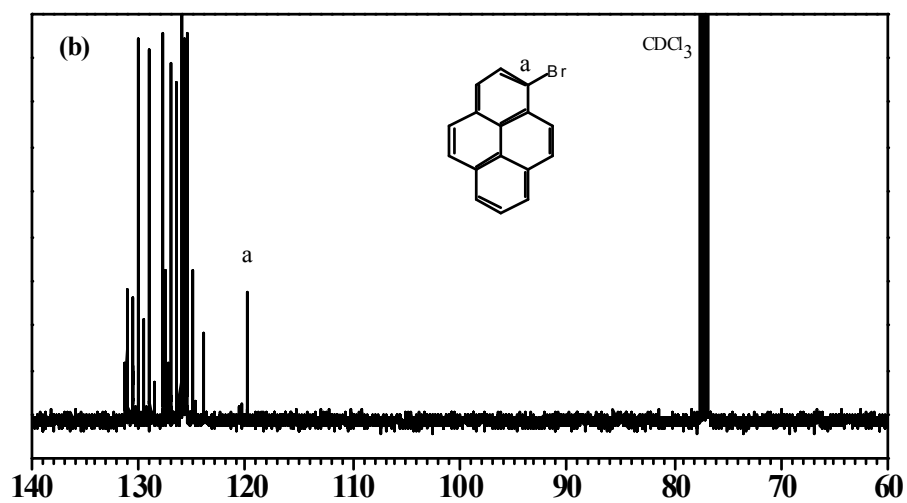


Figure S1. ^1H NMR spectrum (a) and ^{13}C NMR spectrum (b) of bromopyrene

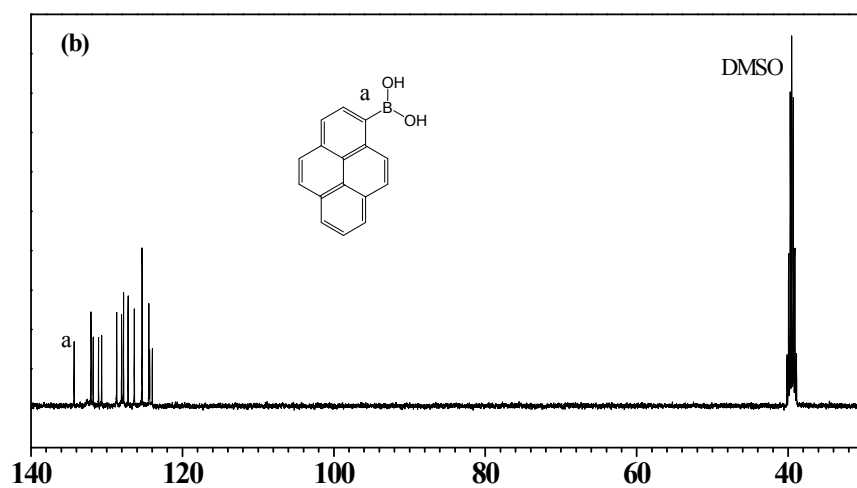
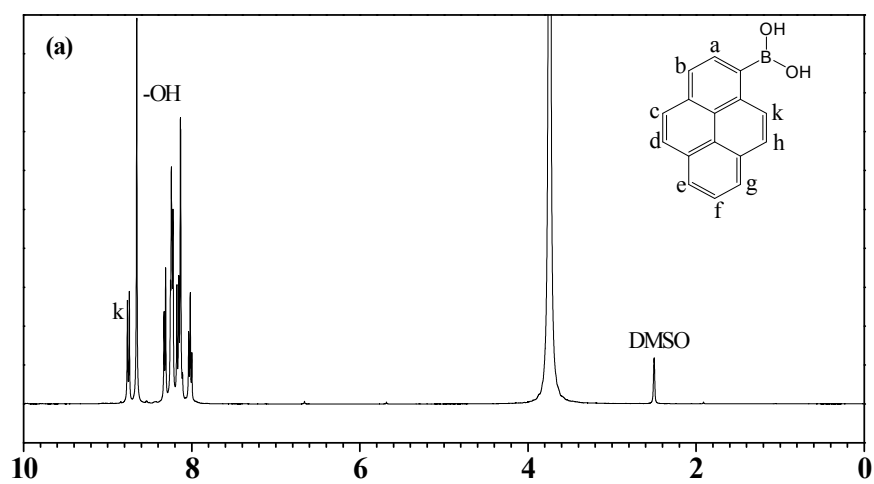


Figure S2. ^1H NMR spectrum (a) and ^{13}C NMR spectrum (b) of pyrenylboronic acid

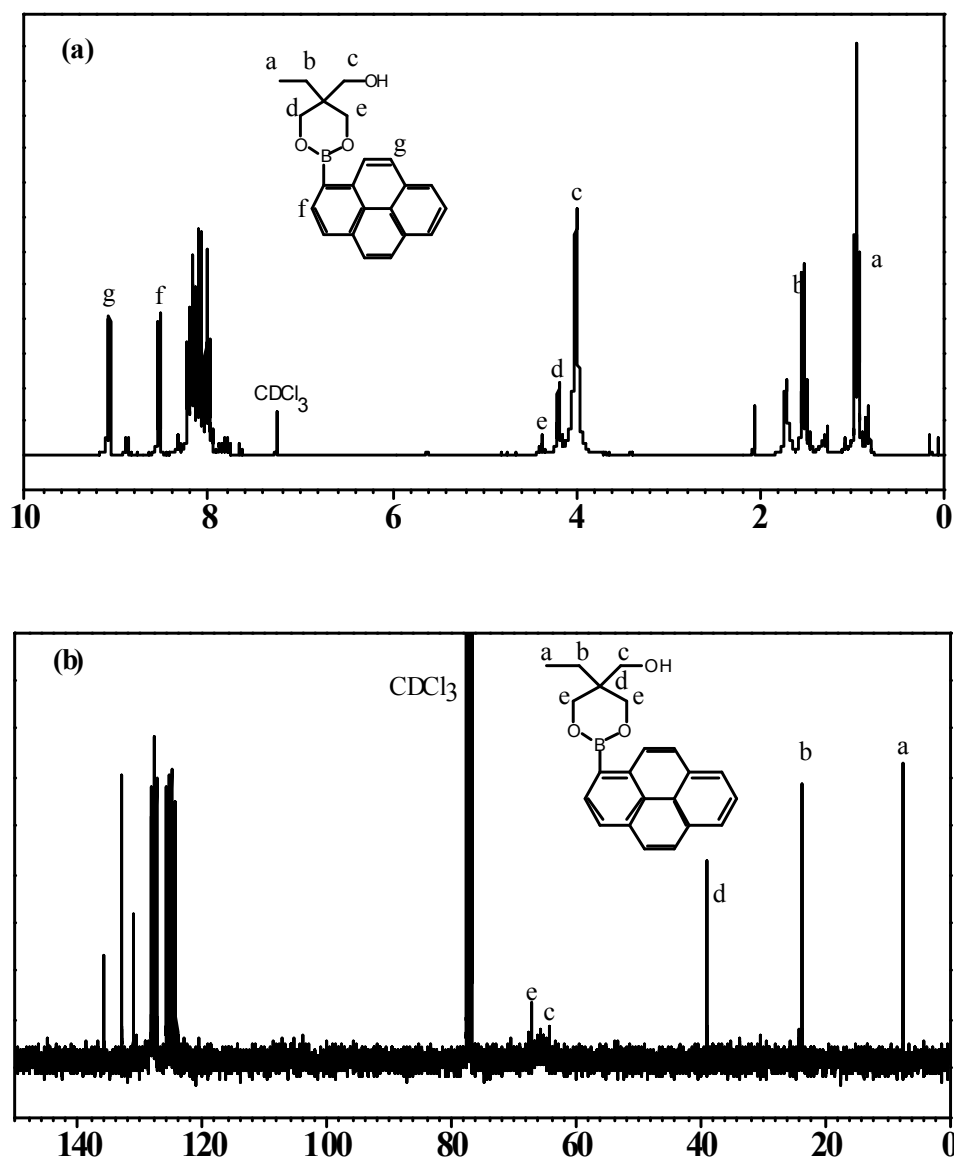


Figure S3. ^1H NMR spectrum (a) and ^{13}C NMR spectrum (b) of precursor 3.

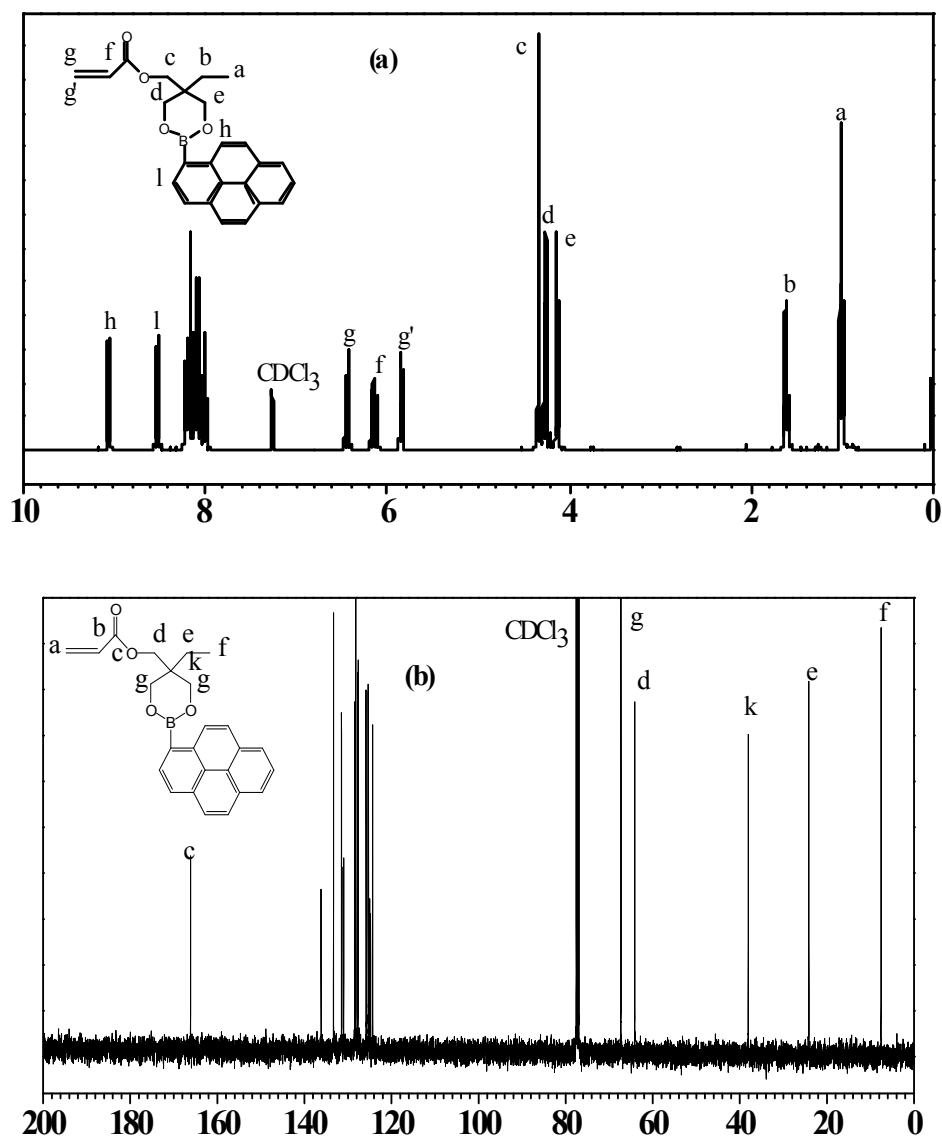


Figure S4. ^1H NMR spectrum (a) and ^{13}C NMR spectrum (b) of monomer PyBDEMA.

References

- [1] Hsu, C.; Lin, H.; Yan, X. *J. Chin. Chem. Soc.*, **2012**, *59*, 89-296.
- [2] Tang, C.; Liu, F.; Xia, Y. *Organic Electronics*, **2006**, *7*, 155–162.

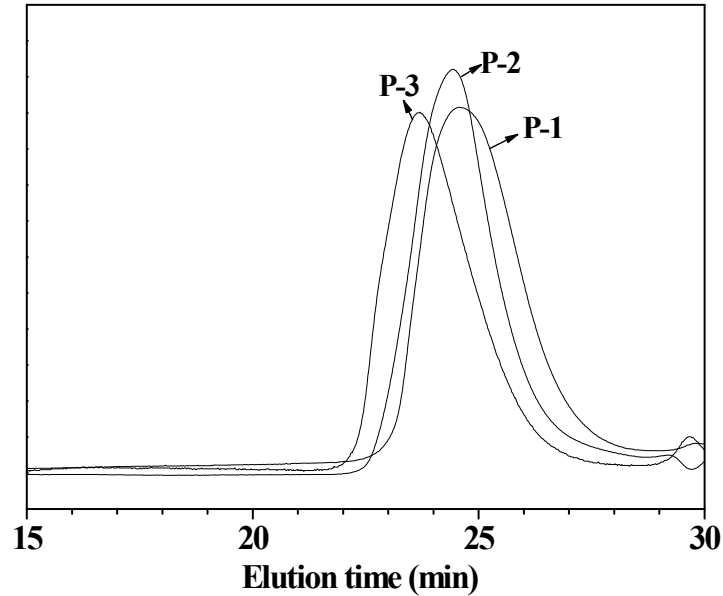
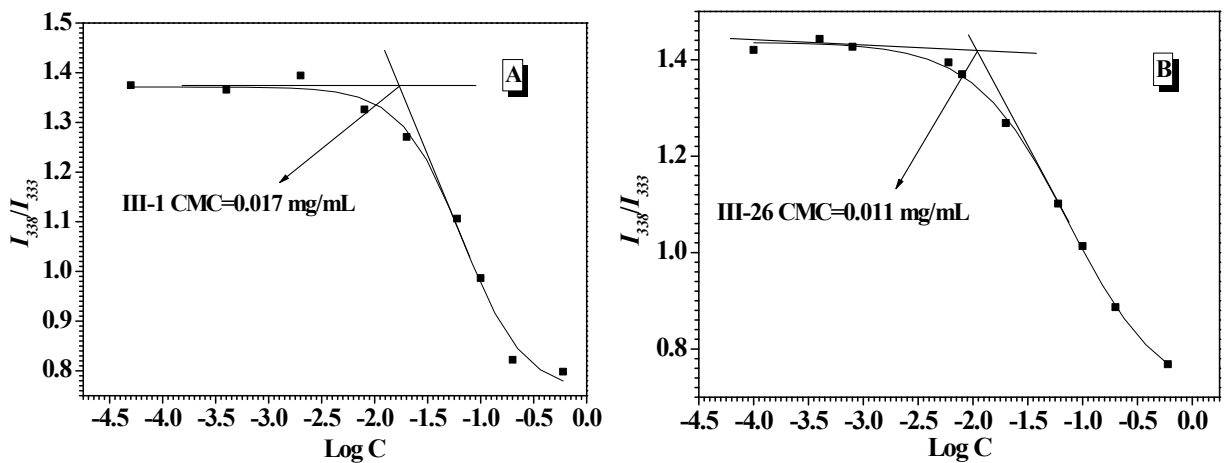


Figure S5. GPC of the copolymers MPEG-*b*-P(PBDEMA-*co*-PyBDEMA).

CMC measurement.

The CMC of the amphiphilic copolymer was determined using a steady-state fluorescence spectrometer. A stock solution of the copolymer was prepared in ultrapurified water by direct dissolution with vigorous stirring for 48 h, followed by the addition of water affording solution concentrations from 5.0×10^{-8} to 2.5×10^{-3} mg/L. The excitation spectra of the resulting solutions were scanned from 300 to 360 nm at an emission wavelength of 395 nm. The slit width for both excitation and emission was maintained at 2.5 nm. The intensity ratios at wavelengths of 338 and 333 nm (I_{338}/I_{333}) from the excitation spectra were analyzed as a function of the logarithm of polymer concentration.



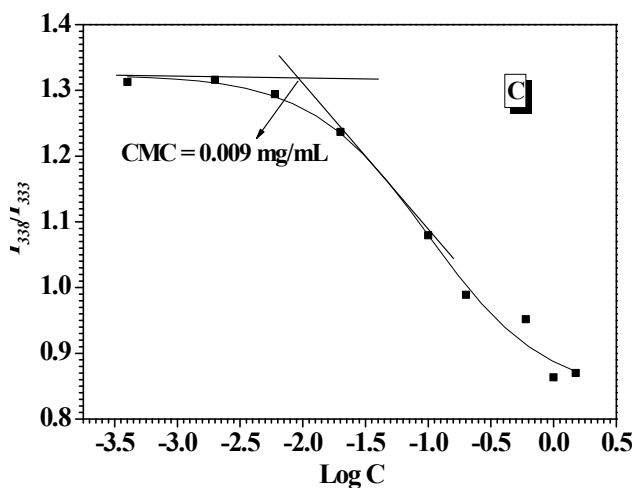


Figure S6. CMC of MPEG-*b*-P(PBDEMA₁₁-*co*-PyBDEMA₈) (A); MPEG-*b*-P(PBDEMA₂₅-*co*-PyBDEMA₈) (B); MPEG-*b*-P(PBDEMA₃₃-*co*-PyBDEMA₈) (C).

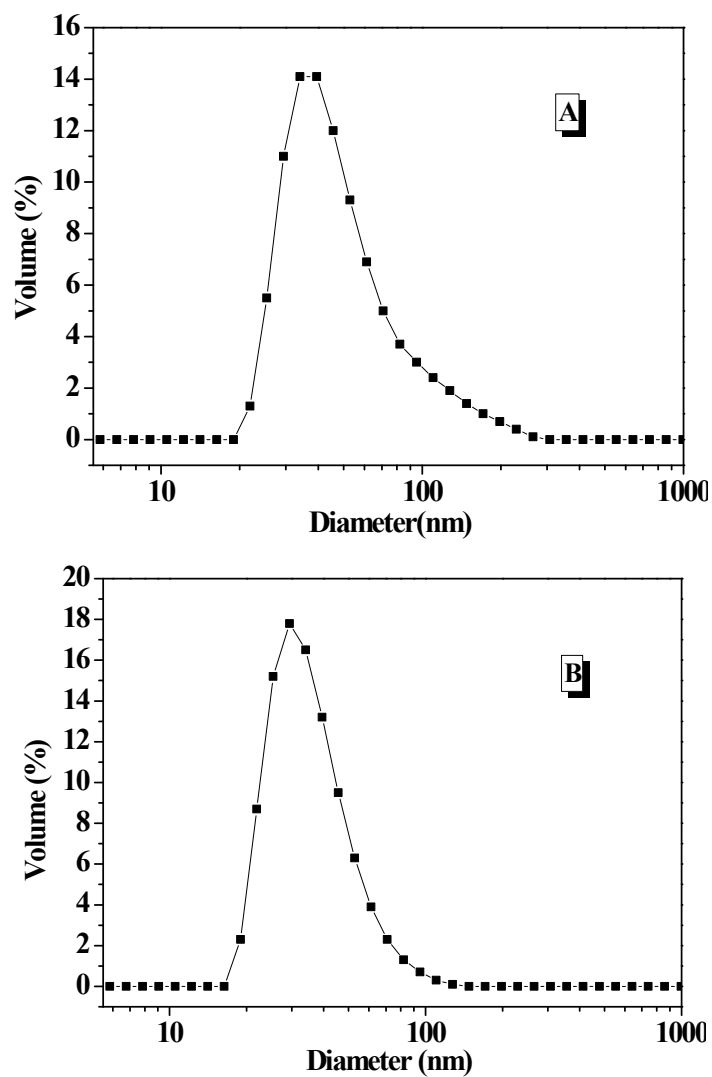


Figure S7. DLS of MPEG-*b*-P(PBDEMA₁₁-*co*-PyBDEMA₈) (A); MPEG-*b*-P(PBDEMA₂₅-*co*-PyBDEMA₈) (B)

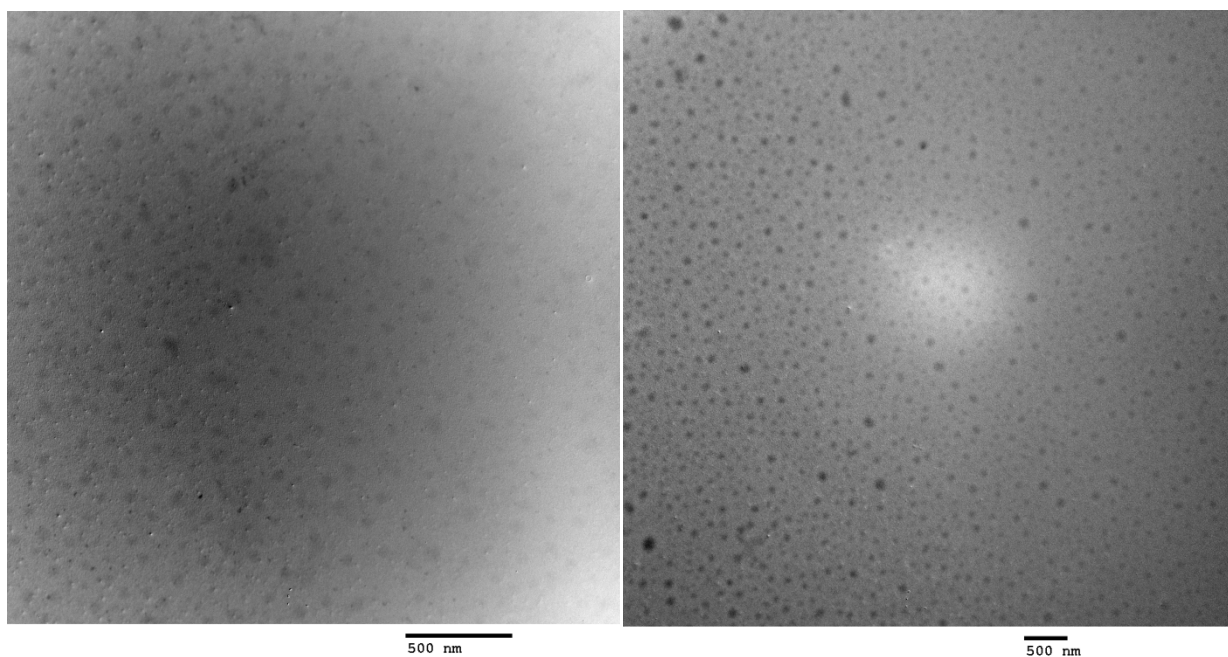


Figure S8. TEM images of MPEG-*b*-P(PBDEMA₁₁-*co*-PyBDEMA₈) (left); MPEG-*b*-P(PBDEMA₂₅-*co*-PyBDEMA₈) (right).

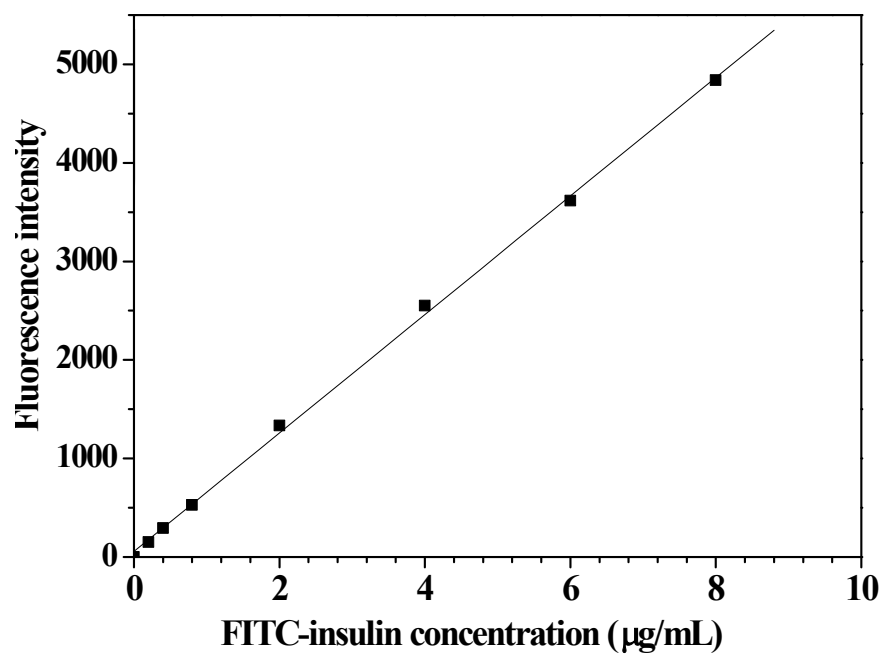
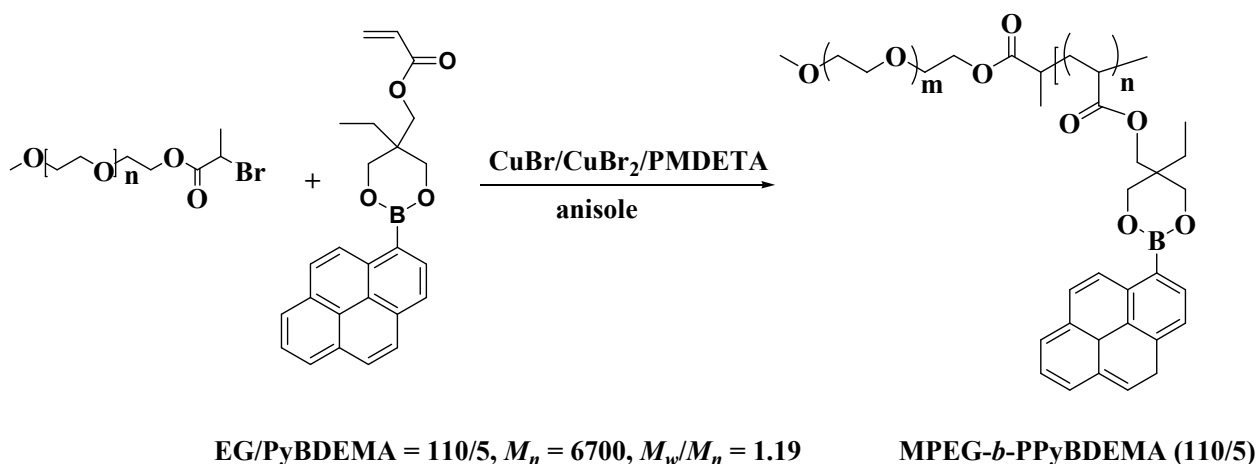


Figure S9. Standard curve of fluorescence intensity at various concentration of FITC-insulin.



Scheme S2. The synthesis route of amphiphilic block polymer MPEG-*b*-PPyBDEMA.

Preparation of amphiphilic block polymer MPEG-*b*-PPyBDEMA. A Schlenk flask charged with CuBr (5.2 mg, 0.036 mmol), CuBr₂ (0.2 mg, 0.0009 mmol) and macroinitiator MPEG-Br (154 mg, 0.03 mmol) was degassed using three vacuum–nitrogen cycles. The degassed materials including ligand PMDETA (6.3 mg, 0.036 mmol), monomers PyBDEMA (0.715 g, 1.8 mmol) and anisole (1.0 mL) were introduced into the reaction flask using syringes under nitrogen atmosphere. The reaction system was further degassed using three freeze–pump–thaw cycles, and then immersed in an oil bath at 95 °C under thermostat control. After 24 h, the cooled reaction solution was diluted with CHCl₃ (3 mL) and passed through a neutral alumina column to remove the catalyst. The concentrated reaction solution was dropwise added into the mixed solvent of hexane/diethyl ether (v/v = 4/1). ¹H NMR (400 MHz, CDCl₃) δ (ppm): 8.98 (br, 1H, *o*-pyrenyl), 8.43 (br, 1H, from pyrenyl), 8.08 (br, 7H, other hydrogens from pyrenyl), 3.76-3.99 (m, 6H, CH₂OOC, CH₂OBOCH₂ and CH₂OBOCH₂), 2.29 (br, 1H, CHCH₂), 1.60-1.91 (br, 2H, CHCH₂), 1.35 (m, 2H, CH₂CH₃), 0.79 (m, 3H, CH₂CH₃); for MPEG block: 3.64 (s, 4H, CH₂CH₂O), 3.38 (s, 3H, CH₃O).

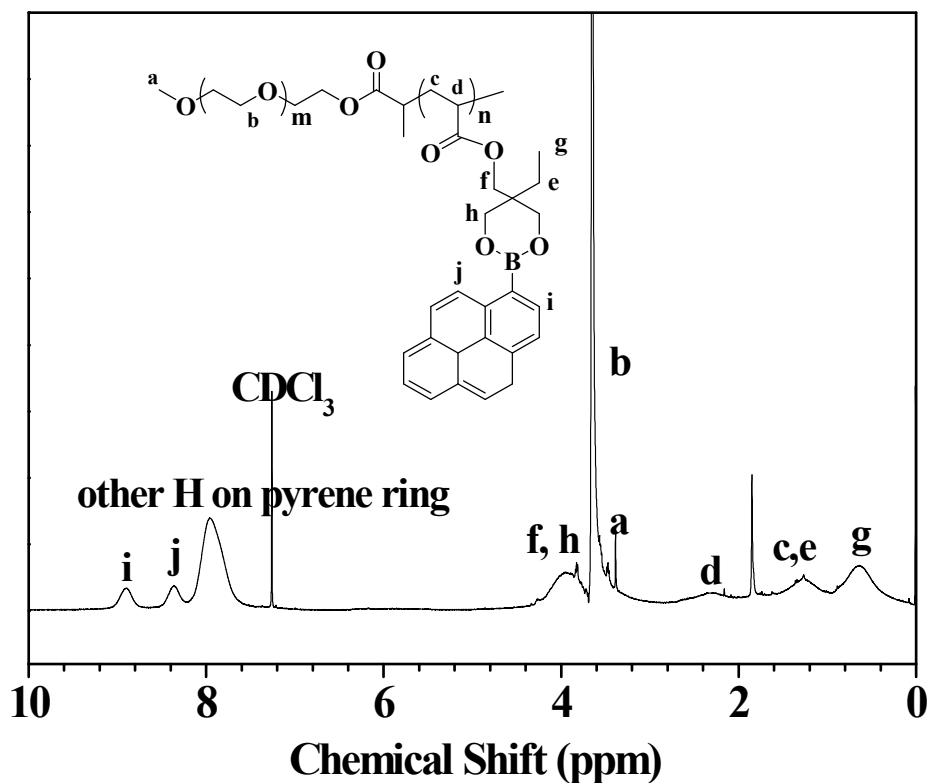


Figure S10. ^1H NMR spectrum of MPEG-*b*-PPyBDEMA.

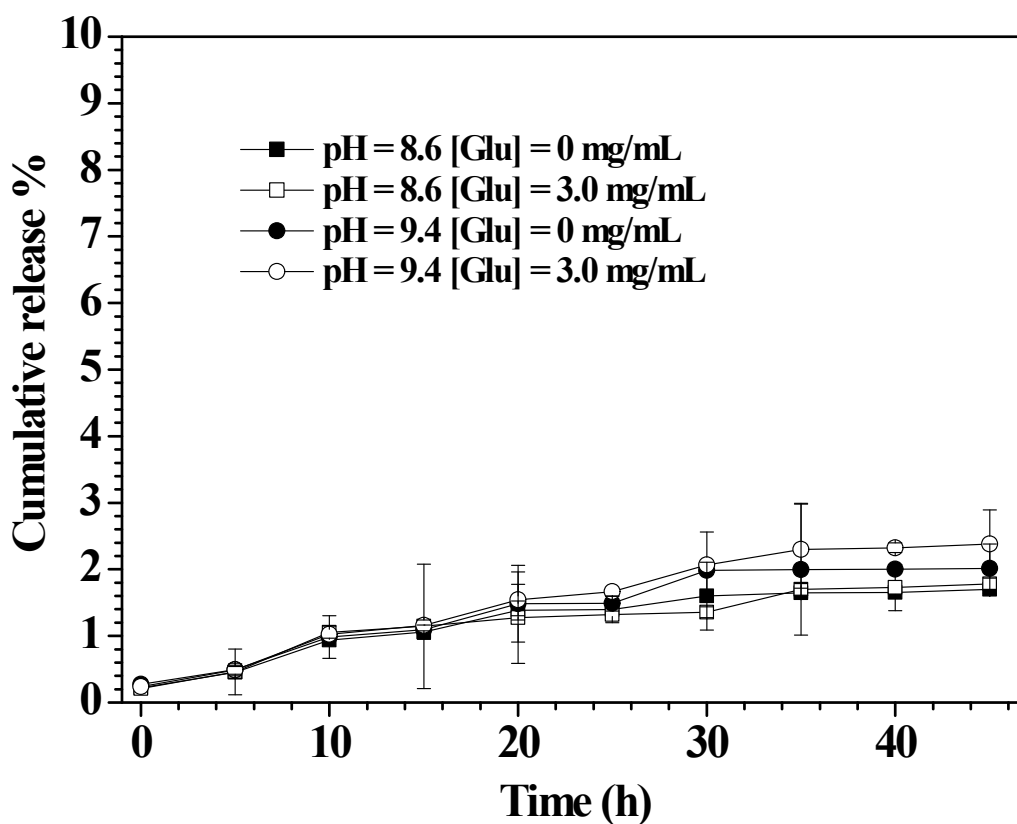


Figure S11. Glucose-responsive behavior of MPEG-*b*-PPyBDEMA (110/5) dependence of environmental pH.

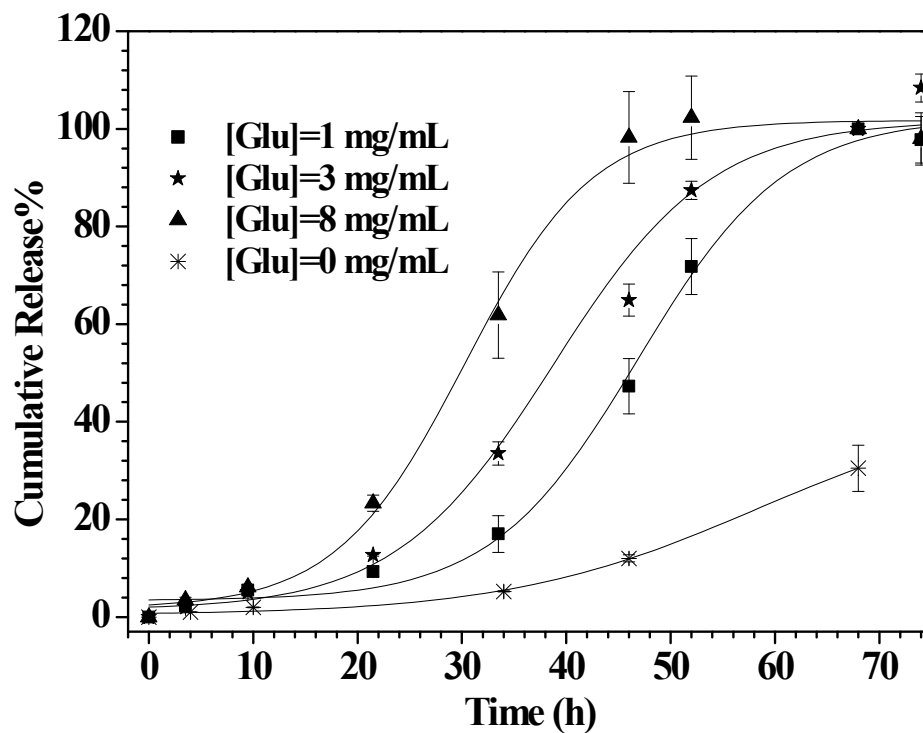


Figure S12. Insulin release behavior of MPEG-*b*-PPBDEMA (110/45) without and with different concentration of glucose.

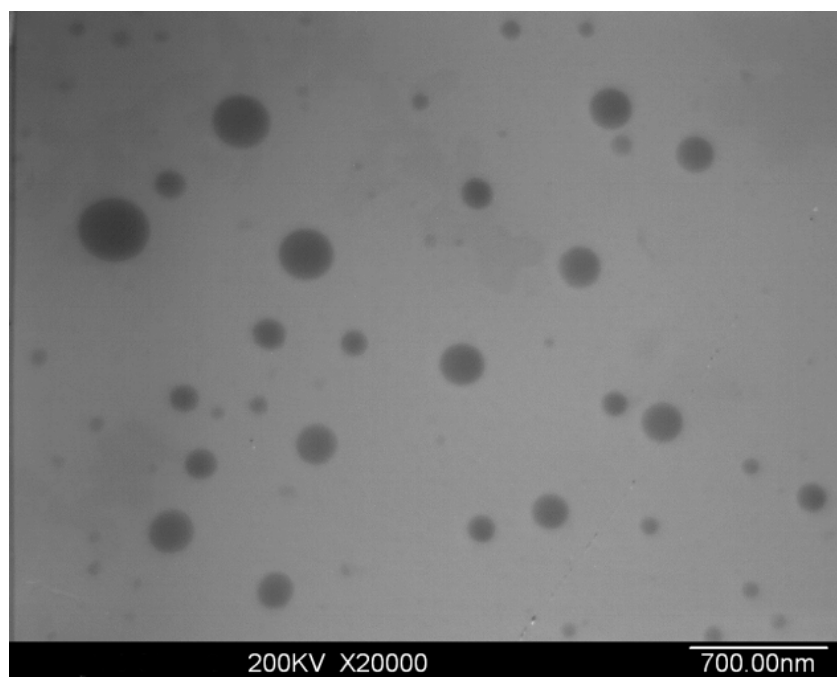


Figure S13. TEM image of MPEG-*b*-P(PBDEMA₃₃-*co*-PyBDEMA₈) after glucose response at 3.0 mg/mL, pH 7.4 and 37 °C.