Supporting information

Well-Defined Degradable Brush-coil Block Copolymers for Intelligent Release of Insulin at Physiological pH

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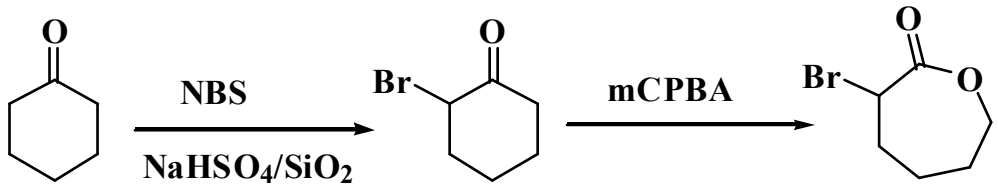
Materials. Cyclohexanone, *N*-bromosuccinimide (NBS), and 3-chloroperoxybenzoic acid (mCPBA) were purchased from Beijing Ouhe Chemical Industry Co. Ltd. (Beijing, China). $NaHSO_4/SiO_2$ catalyst was fabricated according to the reported method.[1]



Scheme S1. Synthesis route of α-BrCL

Synthesis of α-brominated caprolactone (α-BrCL). As shown in Scheme S1, according to the reported methods,[2] the preparation was described in the following. To a mixture of cyclohexanone (2.94 g, 30 mmol) and *N*-bromosuccinimide (4.45 g, 25 mmol) in Et_2O (60 mL), $NaHSO_4/SiO_2$ (2 g) as the catalyst was added. The mixture was stirred at room temperature for 4 h. The filtrate was washed five times with cold water. The collected organic phase was concentrated and purified by column chromatography over silica gel using petroleum ether-EtOAc (v:v = 20:1) as eluent to obtain α-Br-cyclohexanone. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.20 (m, 3H, -COO-CH_2-, -COO-CH(Br)), 3.46-3.79 (m, 2H, -CH_2-CH_2-) , 3.37 (s, 3H, -OCH_3), 2.06 (m, 2H, -CH(Br)-CH_2-), 1.71 (m, 2H, -CH_2- CH_2-OOC-), 1.45-1.58 (m, 2H, -CH_2-) ; ^{13}C NMR (400 MHz, $CDCl_3$) , δ (ppm)：202, 53.41, 38.20, 37.05, 27.03, 22.20.

α-Br-cyclohexanone (4.93 g, 28 mmol) and mCPBA (5.69 g, 33 mmol) was mixed in dried CH_2Cl_2 (40 mL). The mixture was stirred at room temperature for 24 h. After filtration, the filtrate was washed three times with 5% $Na_2S_2O_3$ solution, saturated NaCl solution, cold water, respectively. The organic phase was concentrated and purified by column chromatography over silica gel using petroleum ether-EtOAc (v:v = 5:1) as eluent to afford α-BrCL. ^{1}H NMR (400 MHz, $CDCl_3$), δ (ppm): 4.83 (t, 1H, -COO-CH(Br)), 4.69 (m, 1H, -COO-CH_2-), 4.28 (m, 1H, -COO-CH_2-), 2.13 (m, 2H, -CH(Br)-CH_2-), 1.93-2.04 (m, 2H, -CH_2-), 1.73-1.85 (m, 2H, -CH_2-); ^{13}C NMR (400 MHz, $CDCl_3$), δ (ppm): 169.62, 69.87, 48.22, 32.01, 29.29, 25.24.

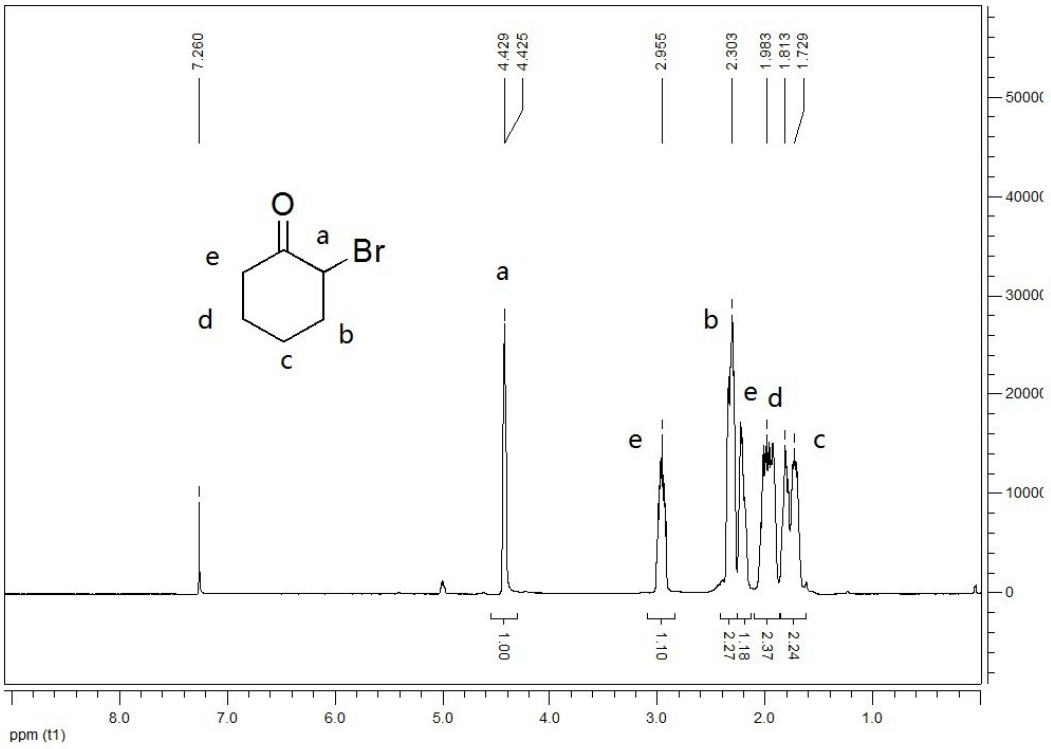


Figure S1. ^{1}H NMR spectrum of α-Br-cyclohexanone.

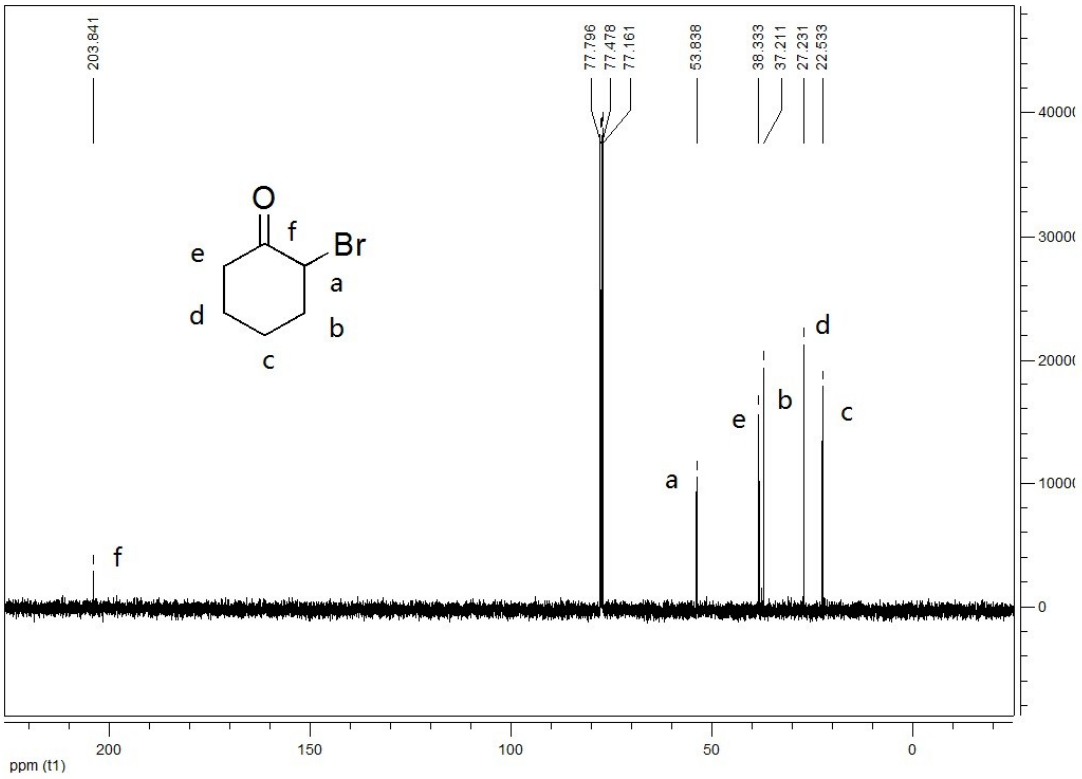


Figure S2. ^{13}C NMR spectrum of α-Br-cyclohexanone.

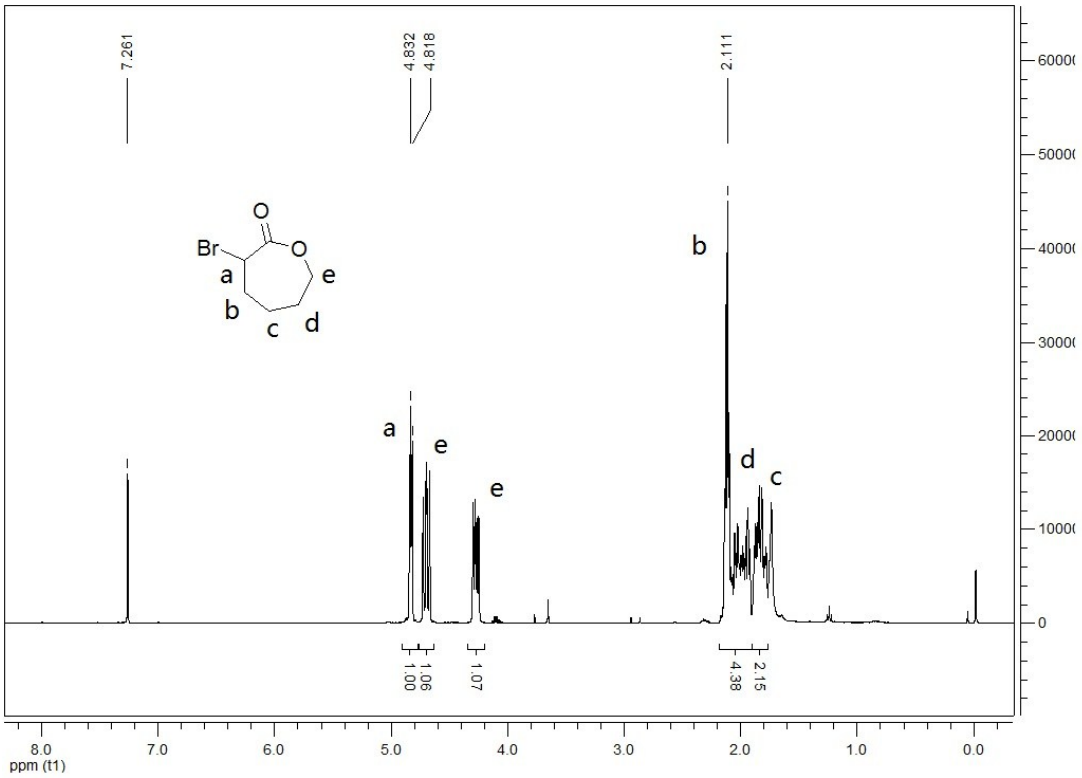


Figure S3. ^{1}H NMR spectrum of α-BrCL.

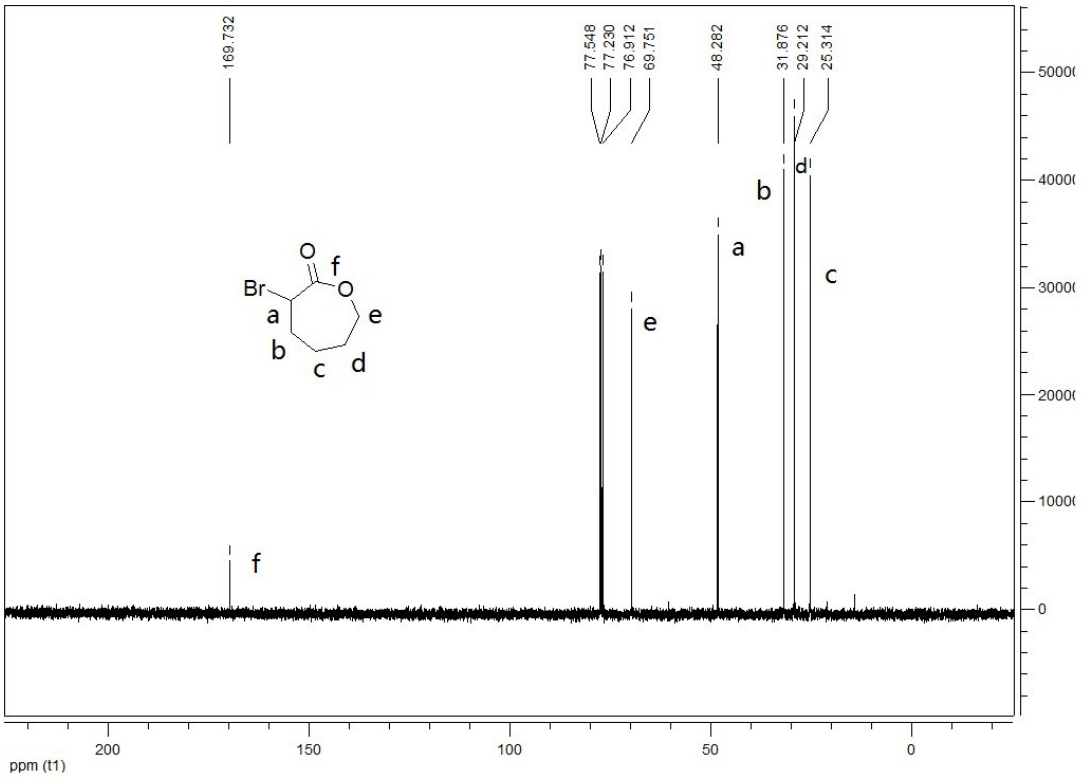


Figure S4. ^{13}C NMR spectrum of α-BrCL.

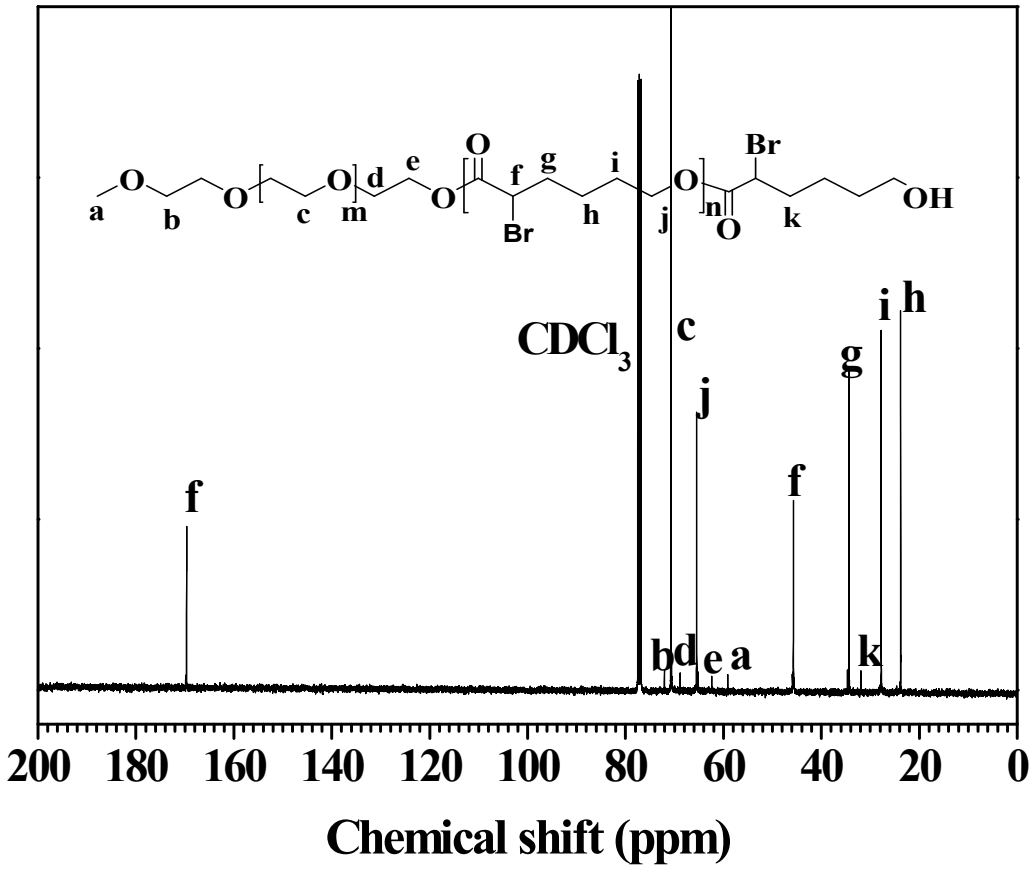


Figure S5. ^{13}C NMR spectrum of macroinitiator MPEG-*b*-PBrCL

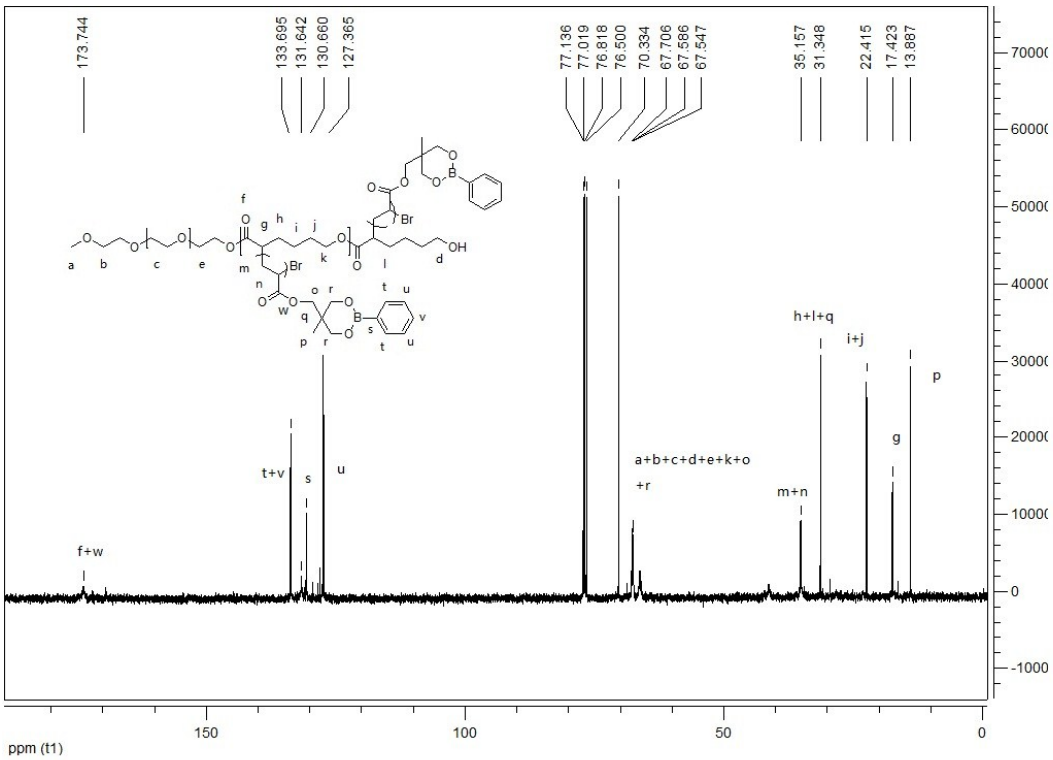


Figure S6. ^{13}C NMR spectrum of brush polymer MPEG-*b*-P(CL-*g*-PPBDMMA)

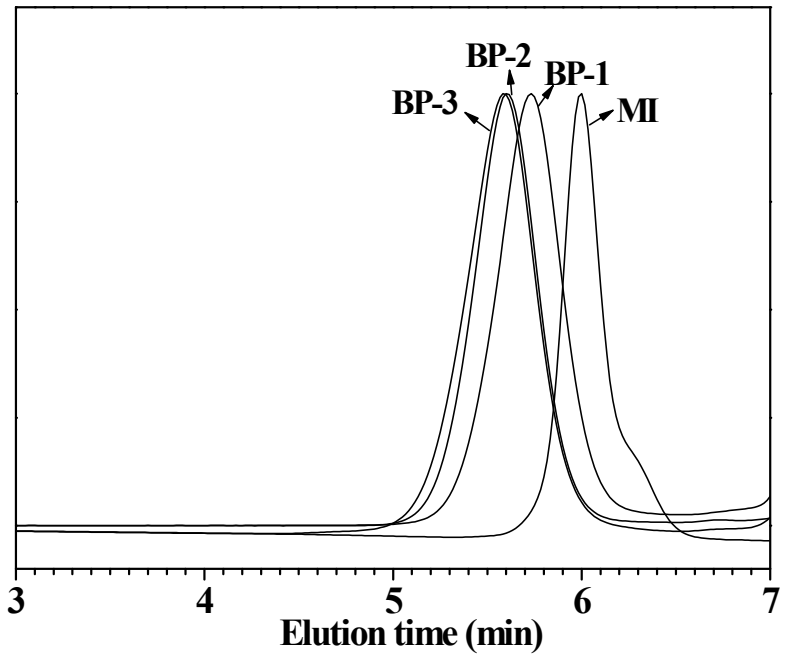


Figure S7. GPC curves of the brush polymers MPEG-*b*-P(CL-*g*-PPBDMMA) (BP-1~BP-3) and macroinitiator MPEG5000-*b*-PBrCL.

The measurement of critical micellar concentration. To estimate the CMCs of the brush polymers, pyrene was used as the fluorescence probe[3]. A predetermined amount of pyrene in acetone was added into a series of volumetric flasks, and the acetone was then evaporated completely. A predetermined volume of MPEG-*b*-P(CL-*g*-PPBDMMA) polymer solutions and ultrapurified water were added into the volumetric flasks consecutively to get solutions of different micelle concentrations ranging from 5.0×10^{-8} to 2.5×10^{-3} mg/L, while the concentration of pyrene in each flask was fixed at 2.0×10^{-6} mol/L. Fluorescence spectra were recorded on a Hitachi F-4600 fluorescence instrument (Hitachi High-Technologies Corporation, Tokyo Japan) at 395 nm excitation wavelength and 5 nm slit width.

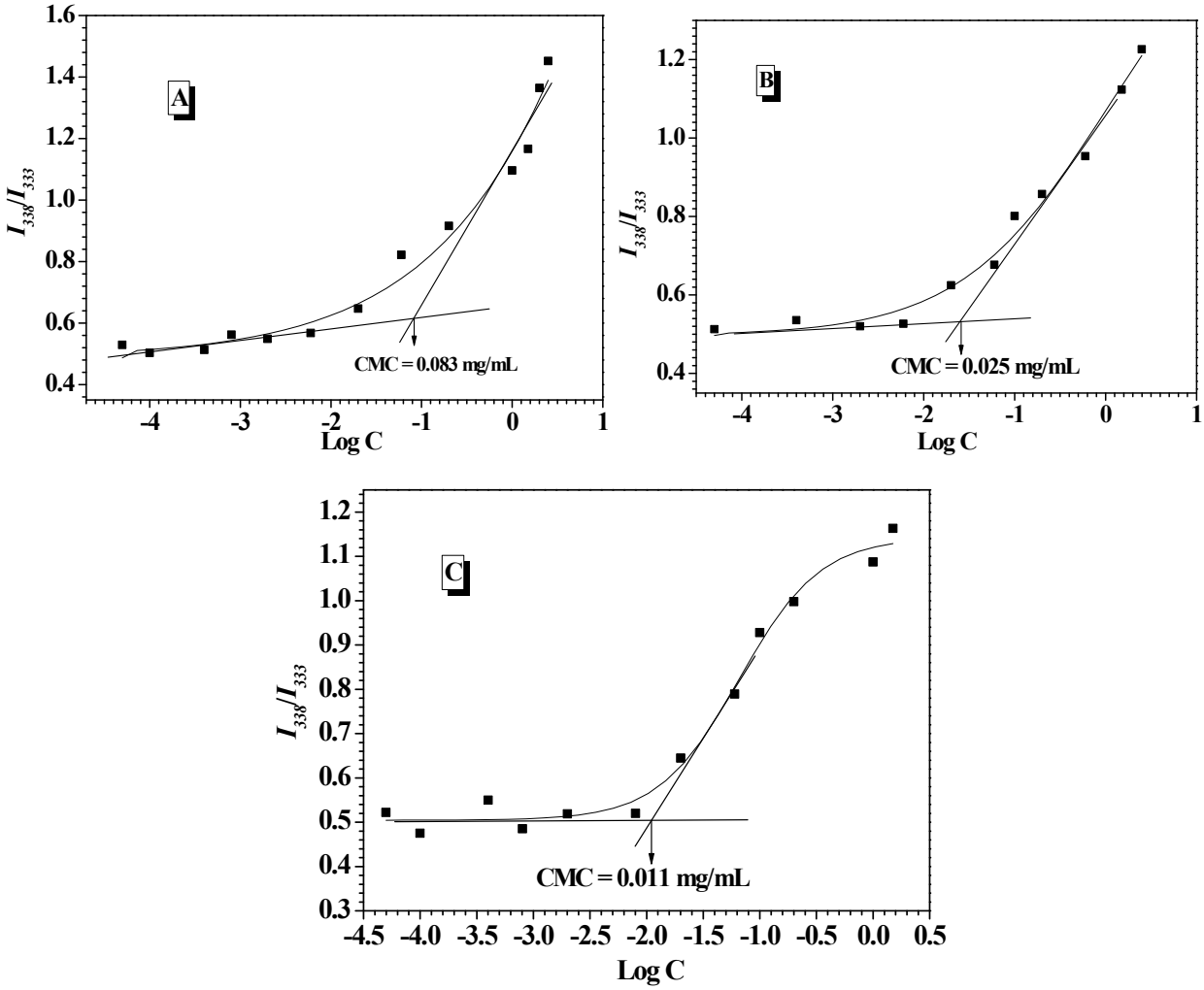


Figure S8. CMC curves of BP-1(A); BP-2 (B); BP-3 (C).

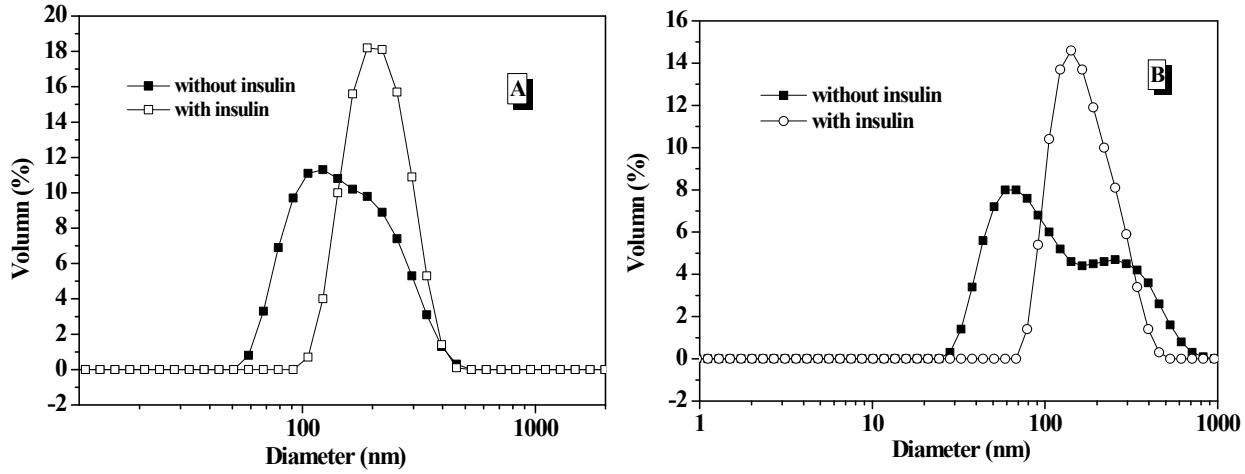


Figure S9. Diameter of polymeric micelles from BP-2 (A) and BP-3 (B) without and with insulin.

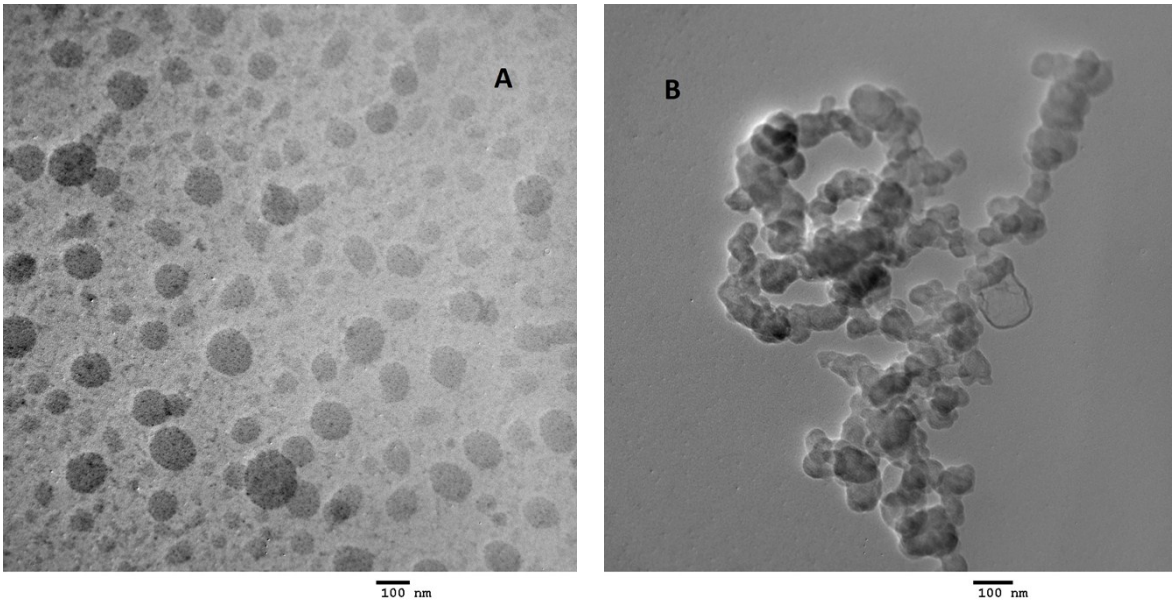


Figure S10. TEM images of BP-2 (A) and BP-3 (B).

Standard curve of FITC-insulin. FITC-insulin varying concentration from 0.2 to 8.0 μg/mL was prepared in 0.15 M PBS (pH = 7.4), and the emission intensity was measured by fluorescence spectroscopy at an emission wavelength of 525 nm upon excitation at 494 nm.

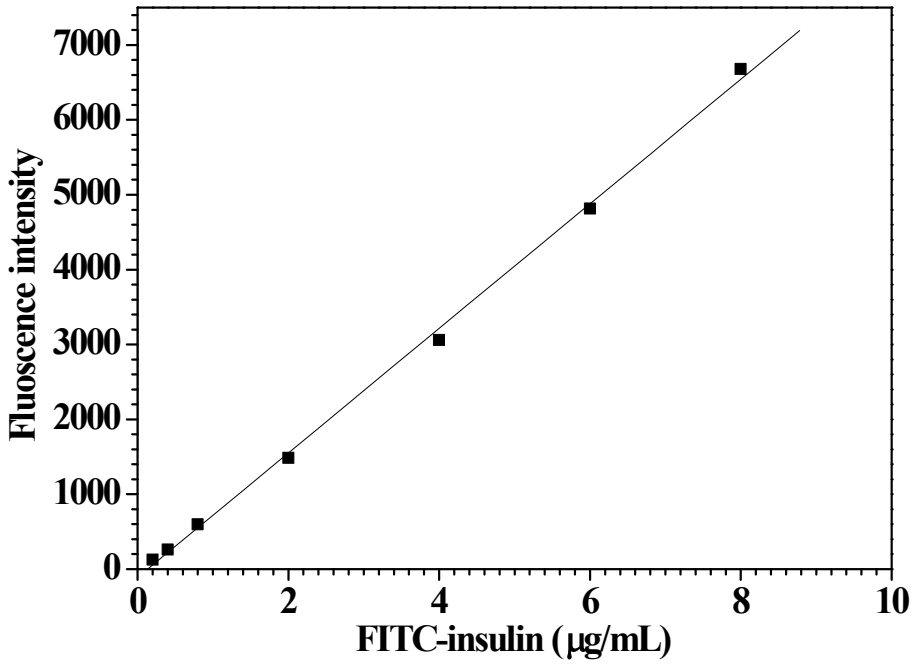


Figure S11. Standard curve of fluorescence intensity at various concentration of FITC-insulin.

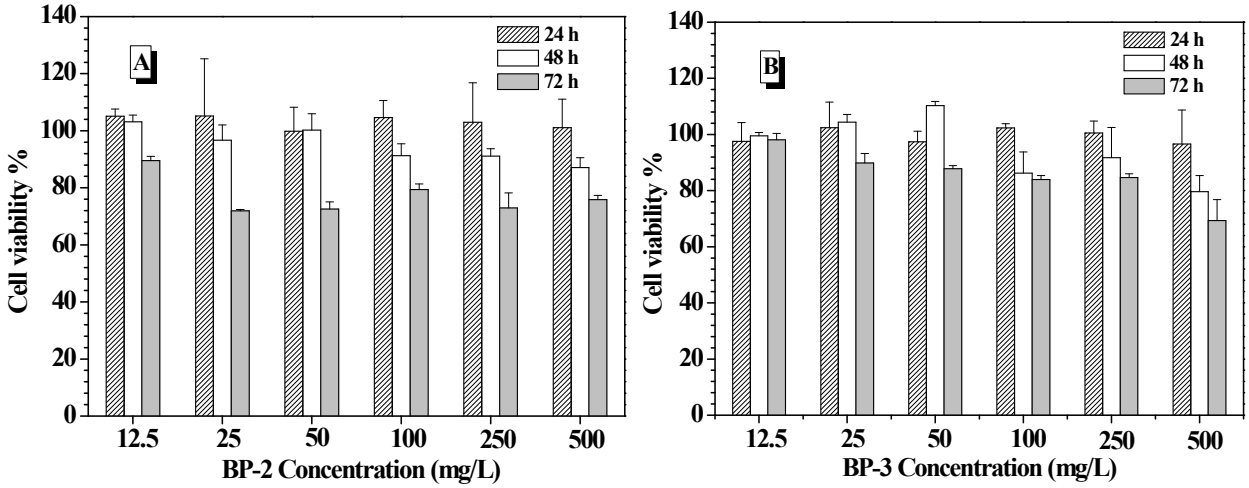


Figure S12. Cell viability assay in NIH3T3 mouse fibroblast cell lines. The cells were treated with polymeric micelles formed from BP-2 (A) and BP-3 (B) at various concentrations at 37 ºC for 24, 48 and 72 h, respectively.

References

[1] Breton, G, W. *J. Org. Chem.***1997**, *62*, 8952-8954

[2]Alam, M. Mujahid; Varala, Ravi; Adapa, Srinivas R. *Synthetic commun*. **2003**, *33*, 3035-3040.

[3] Yao, Y.; Wang, X. M.; Tan, T. W.; Yang, J. *Soft Matter.* **2011**, *7*, 7948-7951.