Electronic Supplementary Material (ESI) for RSC Advances.

Supporting information

Polypeptide-Participating Complex Nanoparticles with Improved Salt-tolerance As Excellent Candidates for Intelligent Insulin Delivery

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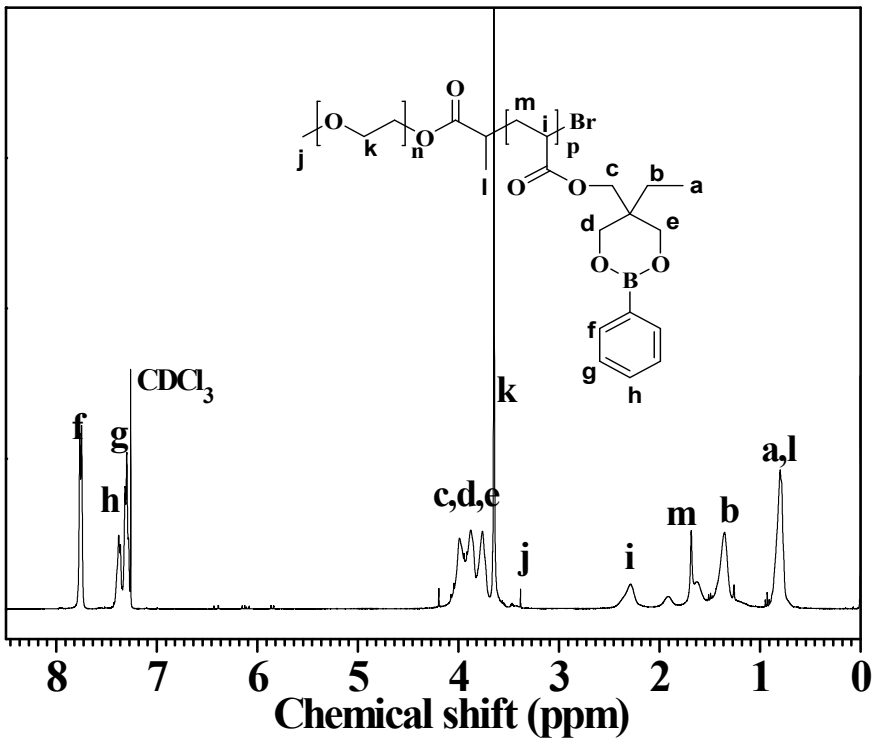


Fig. S1 ^{1}H NMR spectrum of $MPEG_{110}$-*b*-$PPBDEMA_{75}$.

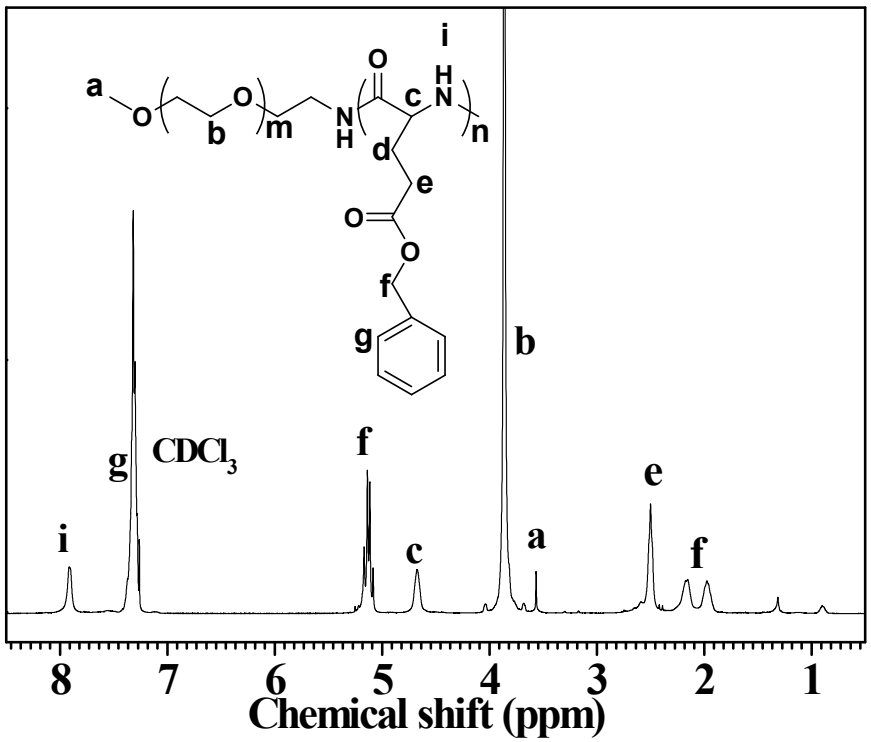


Fig. S2 ^{1}H NMR spectrum of $MPEG_{110}$-*b*-$PBLG_{20}$.

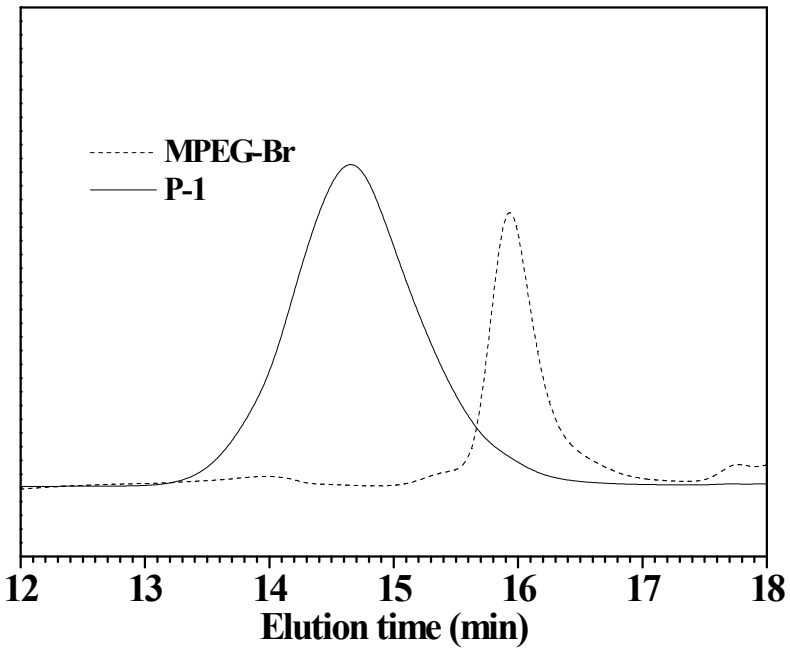


Fig. S3 GPC curves of $MPEG_{110}$-*b*-$PPBDEMA_{75}$ and macroinitiator MPEG-Br.

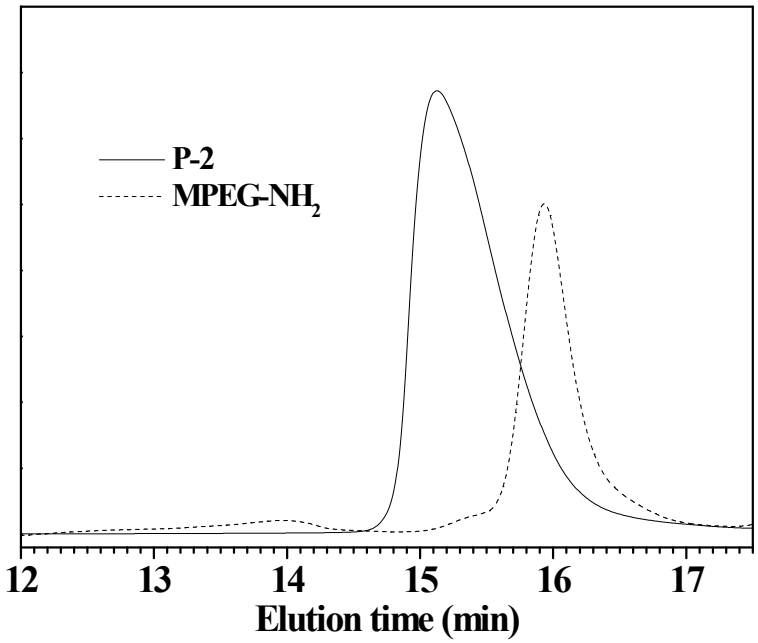


Fig. S4 GPC curves of $MPEG_{110}$-*b*-$PBLG_{20}$ and macroinitiator MPEG-NH_2.

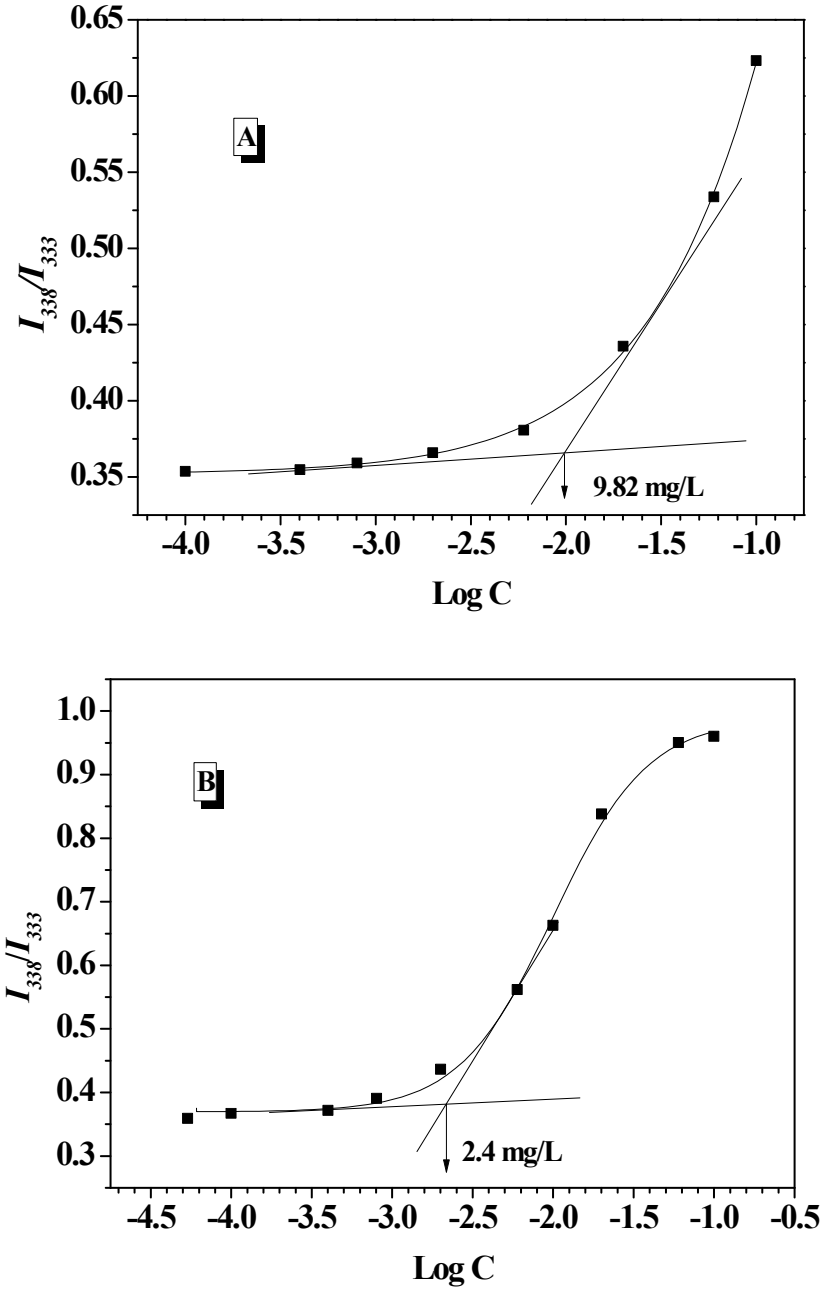


Fig. S5 CMCs of MPEG-*b*-PPBDEMA (A) and MPEG-*b*-PBLG (B).

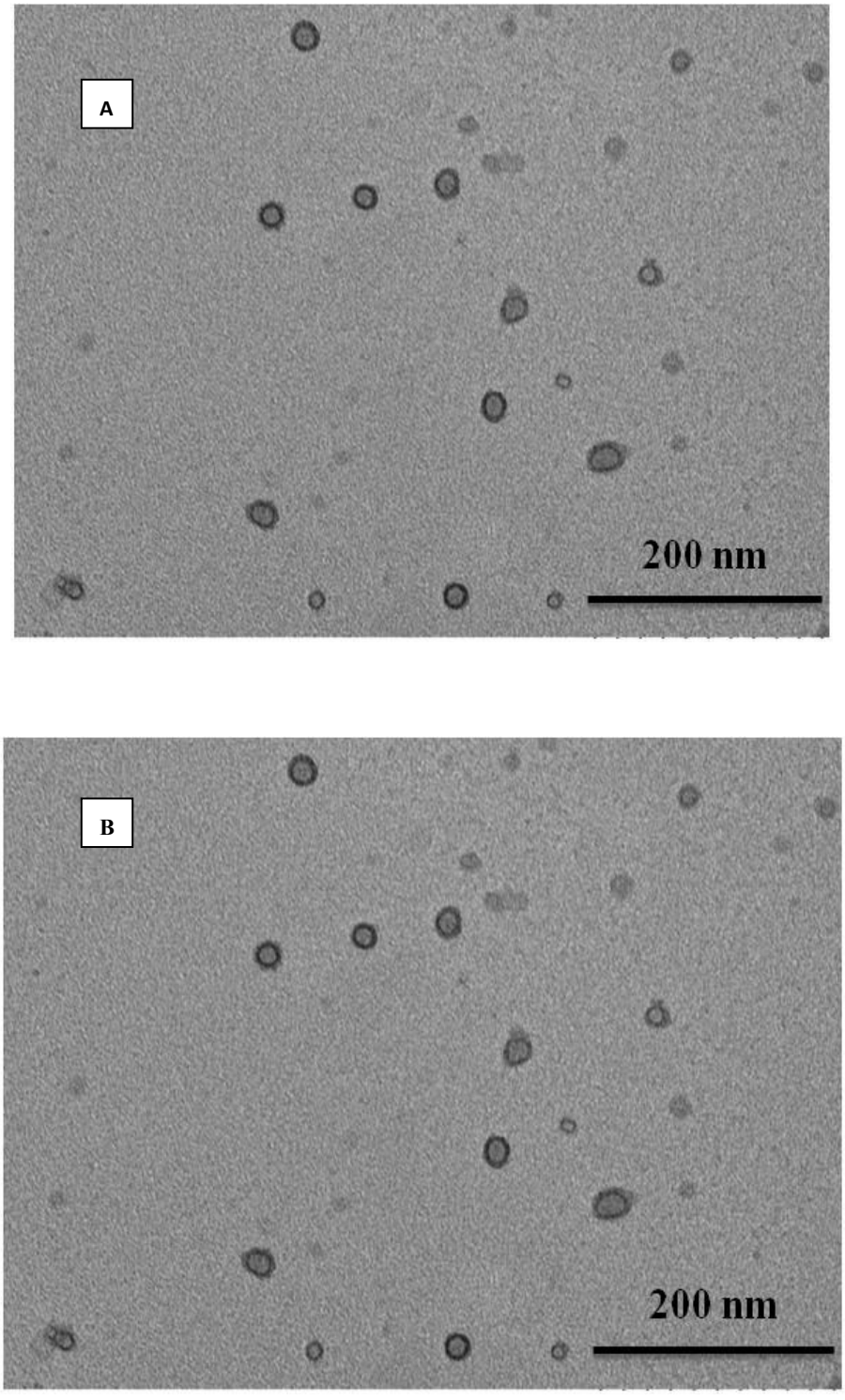


Fig. S6 TEM images of CNPs with 30% content of P-2 (A); 50% content of P-2 (B);

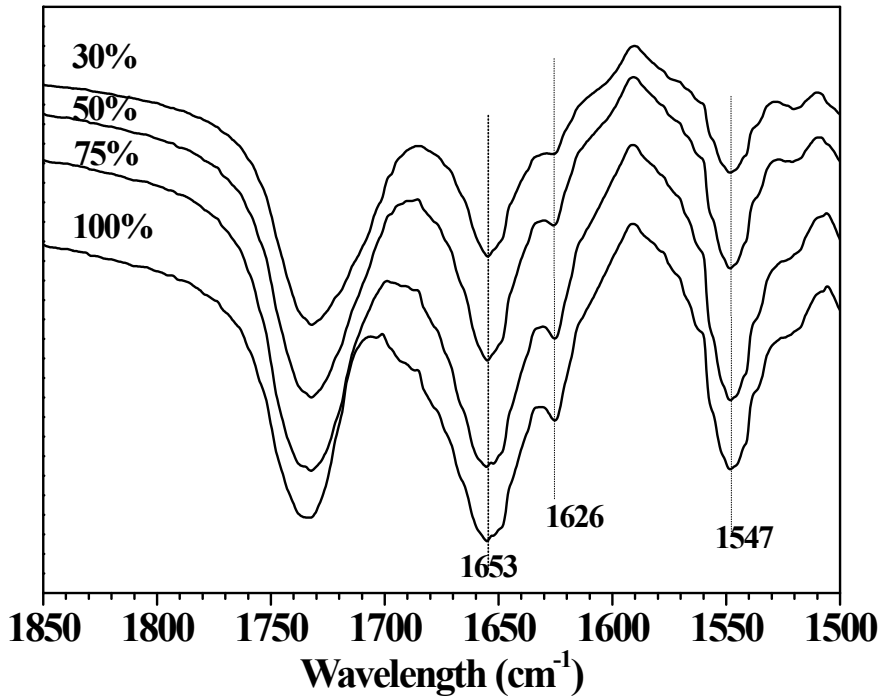


Fig. S7 FTIR spectra of complex nanoparticles with different weight fraction of P-2 in the solid state.

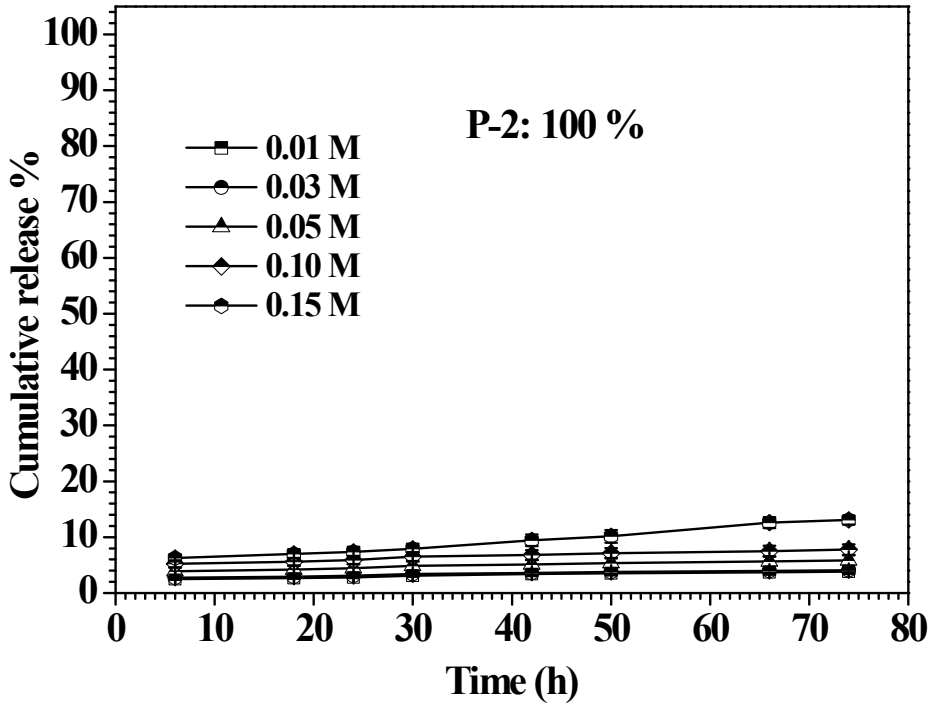
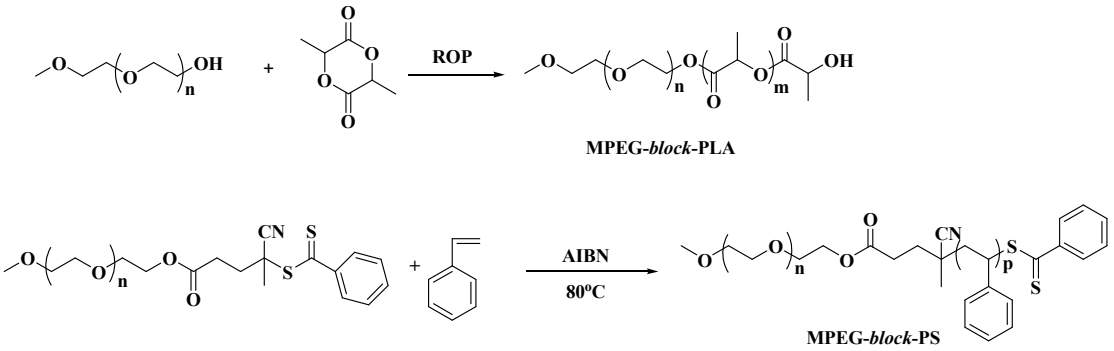


Fig. S8 The salt stability of the nanoparticles formed from P-2 alone at varying salt concentration.



Scheme S1. Synthesis routes of MPEG-*b*-PLA and MPEG-*b*-PS.

Synthesis of MPEG-*block*-PLA. Into 25 mL Schlenk was added *L*-lactide (1.5 g, 10.5 mmol), MPEG-OH (220 mg, 0.052 mmol), $Sn(Oct)_2$ (42.3 mg, 1.05 mmol) and 3.0 mL toluene. The reaction was maintained at 70 °C oil bath for 4 h. Subsequently, the reaction was diluted in $CHCl_3$ and precipitated in methanol three times. The product was dried in vacuum and afforded in yield of 78.0%. ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 4.95-5.53 (m, nH, OC<u>H</u>CH_3COO), 4.26-4.36 (m, 4H, -<u>H</u>(CH_3)C-OH), 3.48-3.82 (m, nH, -OC<u>H_2</u>-), 1.36-1.72 (m, nH, -C<u>H_3</u>, OCHC<u>H_3</u>COO).

Preparation of RAFT macroCTA (CTA-PEG). Into one 100 mL three-neck bottle containing MPEG-OH (4.5 g, 1.1 mmol), DCC (0.9 g, 4.4 mmol), DMAP (0.06 mg, 0.5 mmol) and 80 mL CH_2Cl_2 was droplet added the solution of 4-cyanopentanoic acid dithiobenzoate (CPADTBA, 0.9 mg, 3.3 mmol) in 20 mL CH_2Cl_2. The reaction was maintained at room temperature for 24 h. Then, the concentrated reaction solution was precipitated in ethyl ether, and the pink solid was obtained after vacuum in a yield of 71% (3.4 g). ^{1}H NMR (400 MHz，$CDCl_3$)，δ (ppm)：7.93 (*s*，2H，*o*-C_6H_5), 7.68 (*m*，1H，*p*-C_6H_5)，7.51 (*s*，2H，*m*-C_6H_5)，3.39-3.67 (*m*，4mH，mOCH_2CH_2O). m represented repeating unit number.

Preparation of poly(ethylene glycol)-*block*-polystyrene (PEG-*b*-PS). Similar RAFT polymerization operation was conducted to fabricate PEG-*block*-PS except using styrene (1.3 g, 13.0 mmol) as monomer, AIBN (4.3 mg, 0.026 mmol) as initiator, PEG-*block*-PS (0.6 g, 0.13 mmol) and 3.0 mL toluene at 65 ºC for 15 h. The reaction solution was precipitated into ethyl ether to afford pink polymer. Subsequently, the pink polymer dissolved in toluene was reacted with AIBN (0.4 g, 2.6 mmol) under N_2 atmosphere at 65 ºC for 10 h. The solution was precipitated in the ethyl ether for three times, and the slight yellow solid was afforded in yield of 49% (0.9 g). ^{1}H NMR (400 MHz，$CDCl_3$)，δ (ppm)：6.85-7.30 (*m*，3nH，nC_6H_5)，

6.20-6.80 (*m*，2nH，nC_6H_5)，3.39-3.67 (*m*，4mH，mOCH_2CH_2O)，1.80-2.01 (*m*，nH，C*H* on the backbone)，1.30-1.50 (*m*，2nH，CH_2 on the backbone).

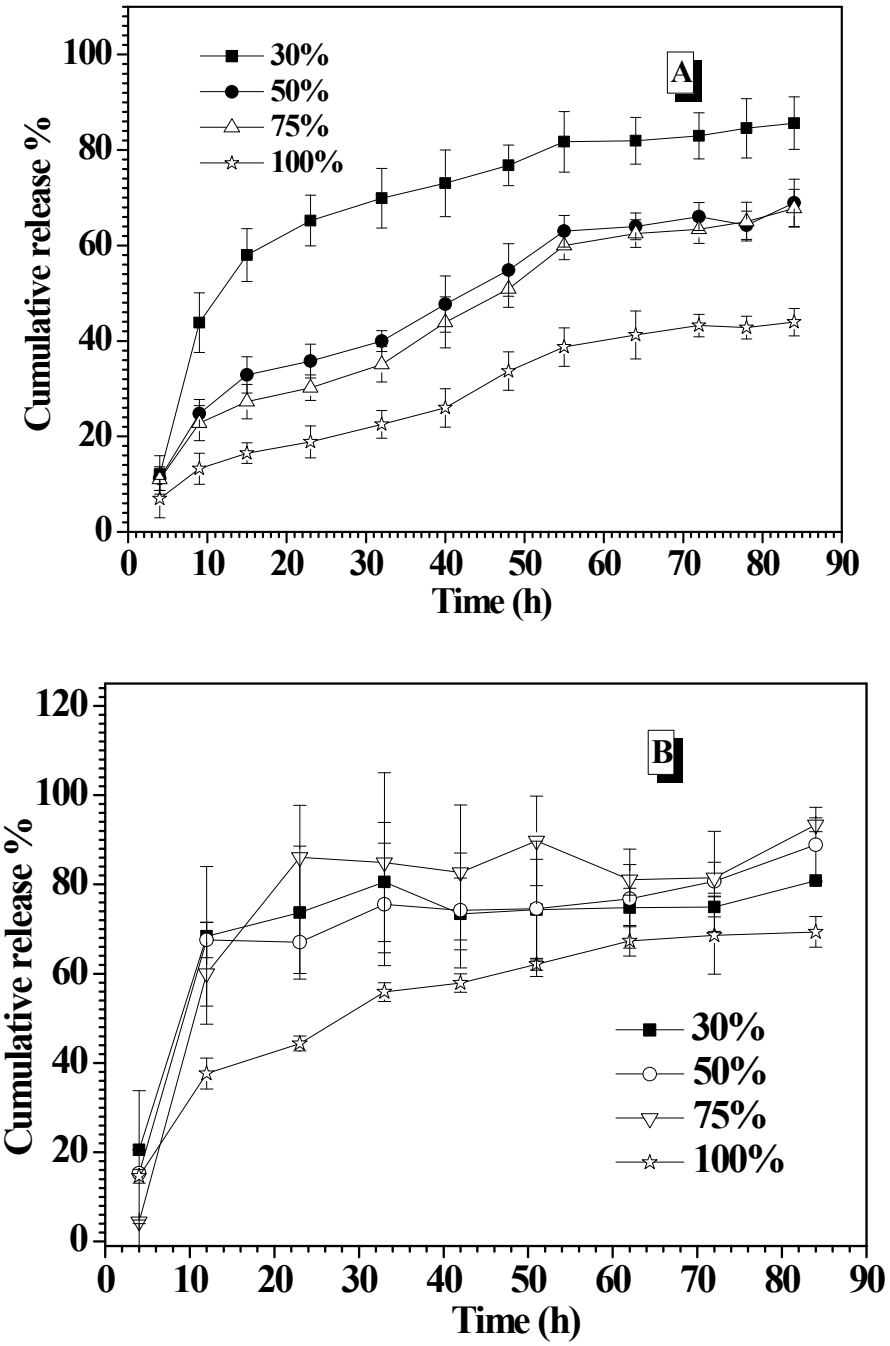


Fig. S9 (A) Effect of PEG-*b*-PLA weight ratio on the stability of the complex nanoparticles formed from P-1 and PEG-*b*-PLA. (B) Effect of PEG-*b*-PS weight ratio on the stability of the complex nanoparticles formed from P-1 and MPEG-*b*-PS at 0.15 M PBS, pH 7.4 and 37 ºC.

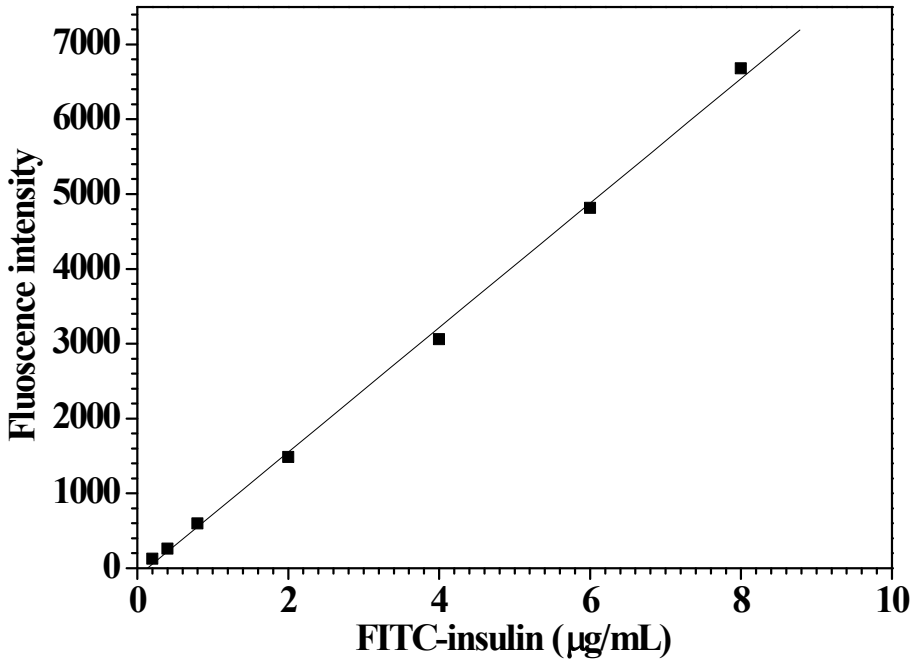
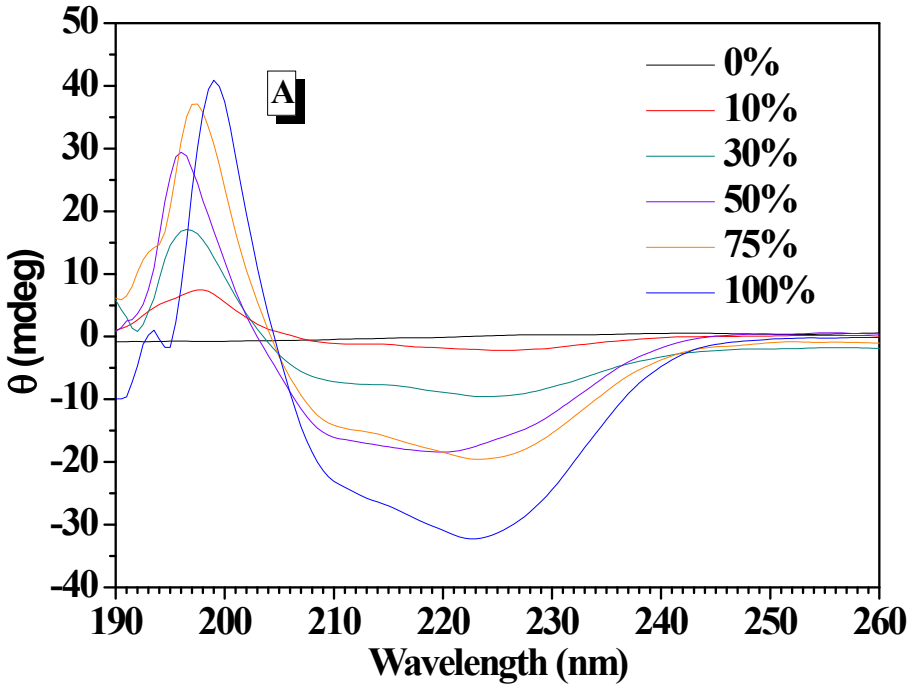


Fig. S10. Standard curve of fluorescence intensity at various concentration of FITC-insulin.



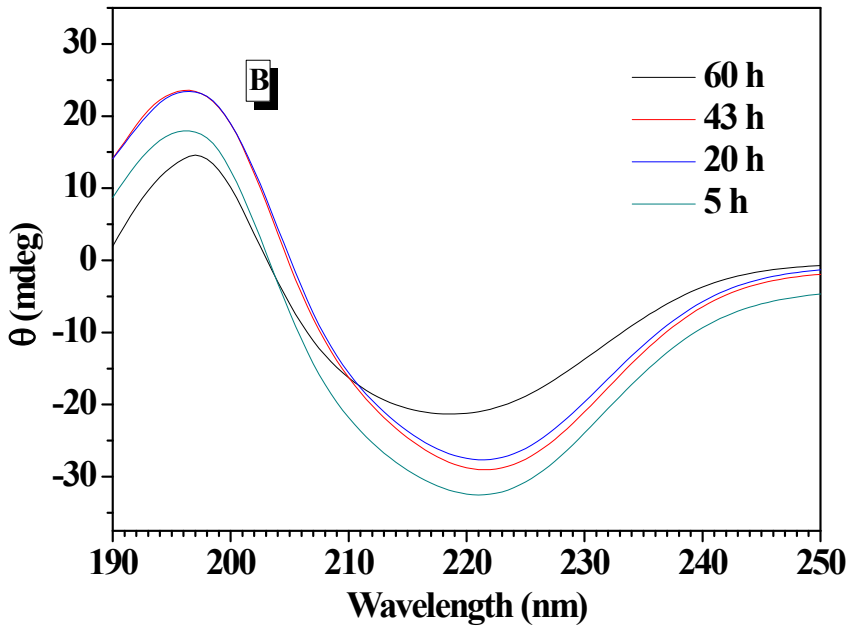


Fig. S11 (A) CD spectra of CNPs with different P-2 content in 0.15 M PBS; (B) CD curves of CNPs with 75% content of P-2 at 0.15 M PBS, pH 7.4 and 37 ºC for 60 h measurement.

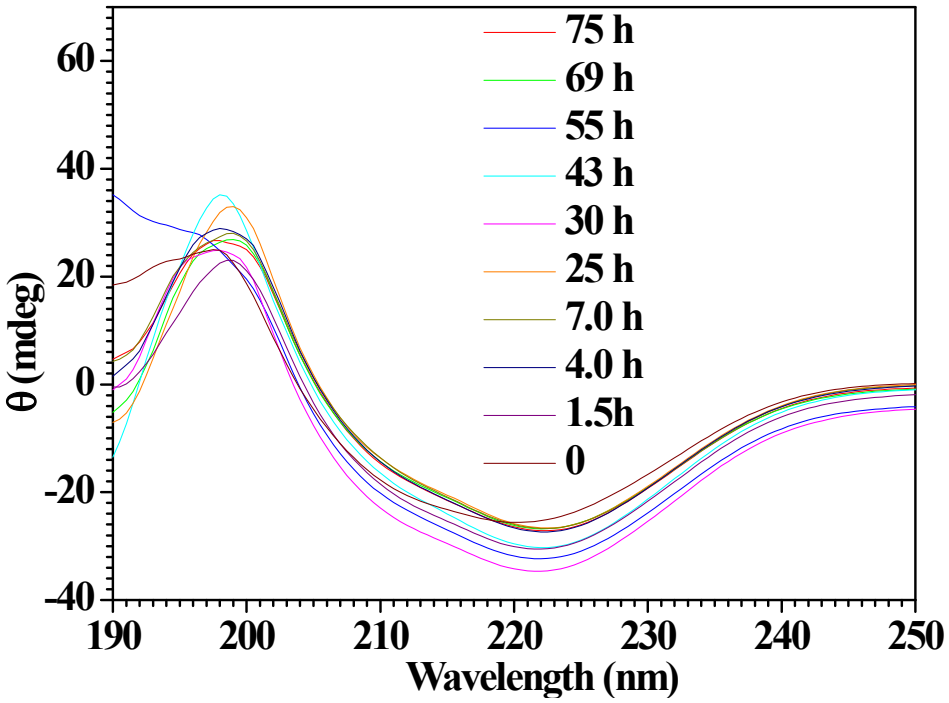


Fig. S12 CD curves of CNPs with 75% content of P-2 in the process of glucose response at 3.0 mg/mL glucose, 0.15 M PBS, pH 7.4 and 37 ºC.

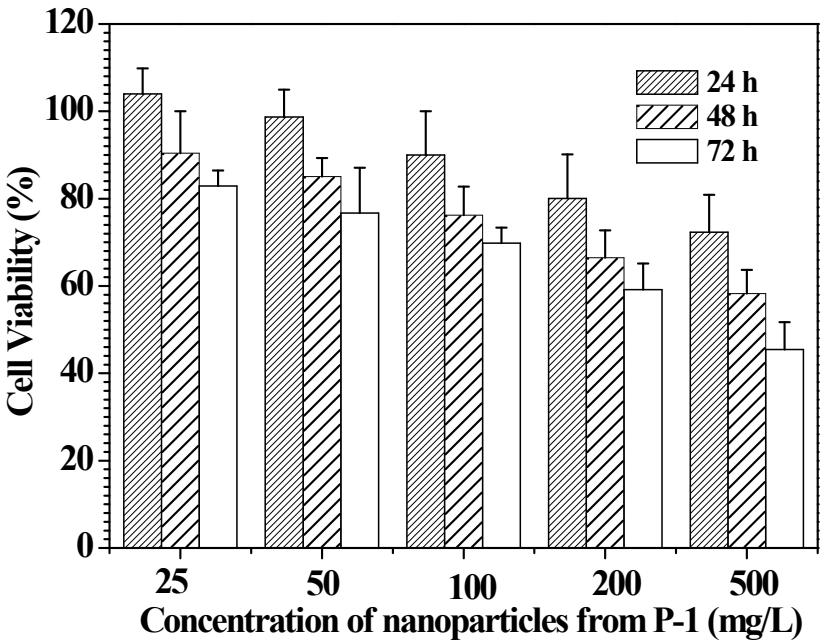


Fig. S13 Cell viability assay in NIH3T3 mouse broblast cell. The cells were treated with the nanoparticles formed from P-1 at various concentrations at 37 ºC for 24, 48 and 72 h, respectively.