Supplementary Information

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1. Experimental Section

Synthesis and characterization of acetalated dextran (AD). AD was synthesized as previously reported procedure.[1] Firstly, dextran (MW = 9000-11000 g/mol, 3.0 g, Sigma-Aldrich, USA) was dissolved in 30.0 mL anhydrous dimethyl sulfoxide (Sigma-Aldrich, USA) in a dry flask. Then pyridinium *p*-toluenesulfonate (46.8 mg, Sigma-Aldrich, USA) and 2- methoxypropene (10.6 mL, Sigma-Aldrich, USA) were added sequentially. The reaction lasted for 4 h under the protection of N_2 at room temperature. After that, triethylamine (2.0 mL, Sigma-Aldrich, USA) was added to the mixture to quench the reaction. With the addition of distilled water (pH 8.5), the acetalated dextran (AD) was precipitated. The obtained AD was washed thoroughly with distilled water (pH 8) and isolated by centrifugation (6118 ×*g*, 20 min). The supernatant was discarded and the resulting precipitation was dissolved with ethanol and subsequently precipitated in water (pH 8) for purification. The precipitation was placed in a vacuum oven at 50 ℃ for 24 h to remove the residual water. The yielded white powder was AD. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, acetal), 3.21 (br, acetal), 3.07, 3.55, 3.87(br, dextran).

Synthesis and characterization of spermine modified acetalated dextran (ADS). ADS was synthesized according to the protocol as previously described.[2] Dextran (MW = 9000-11000 g/mol, 5.0 g) was dissolved in 20.0 mL distilled water, which was oxidized by sodium periodate (1.1 g, Sigma–Aldrich, USA). The reaction was stirred at room temperature for 5 h. The resultant solution was purified by dialysis (MWCO 3500, Spectrum, USA) against distilled water. After replacing dialysis water 5 times, the remaining solution was lyophilized and the obtained white powder was partially

oxidized dextran. After that, the partially oxidized dextran (1.0 g) was dissolved in anhydrous dimethyl sulfoxide (10.0 mL, Sigma-Aldrich, USA), followed by the addition of spermine (1.0 g, Afa Aesar). The reaction was performed at 50 ℃ for 22 h. $NaBH_4$ (1.1 g, Aladdin) was added to the reaction system and the mixture was stirred at room temperature for 18 h. Finally, ADS was precipitated by distilled water (pH 8.5). After thoroughly washing with water， ADS was collected by centrifugation (6118 ×*g*, 20 min) and the residual water was removed by vacuum oven at 50 ℃ for 24. After that, ADS was obtained. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.28 (s, acetal), 1.42, 1.84, 2.64 (br, spermine), 3.28 (br, acetal), 3.49, 3.87, 4.06 (br, dextran).

Preparation of protein colloids. All protein colloids were prepared by the nanoprecipitation method.[3] In terms of insulin (INS, China Dongbao Enterprise Group Co., Ltd.), the poor solvent, acetone (4.5 mL), was added dropwise into insulin aqueous solution (0.5 mL, 20 mg/mL, in 0.012 M hydrochloric acid). With moderate stirring, insulin colloids were formulated. The obtained insulin colloids were flocculated with the addition of ethyl acetate and collected by centrifugation (1781 ×*g*, 5 min). Glucose oxidase (GOD, Sigma-Aldrich, USA) and catalase (CAT, Sigma-Aldrich, USA) colloidal particles were prepared in a modified method by applying acetonitrile as the poor solvent. The size distribution of obtained protein colloids was analyzed by dynamic light scattering (Zetasizer Ultra, Malvern Instruments Ltd., UK) at an angle of 173º at 25 ℃.

High-performance liquid chromatography for protein quantitative analysis. The amount of insulin was measured by high-performance liquid chromatography (1260 II,

Agilent Technologies Inc., USA) with a diode array detector and a C_{18} chromatographic column (4.6×100 mm, 2.7 μm, Agilent Technologies Inc., USA). For the measurements, the sample injection volume and the temperature of column were set as 50.0 μL and 40°C, respectively. Besides, the detection wavelength was set at 214 nm. Acetonitrile (phase A; Tedia Company, Inc., USA) and 0.1% (v/v) trifluoroacetic acid (pH 2.2, phase B; Sigma-Aldrich, USA) aqueous solution were used as mobile phases in a gradient system. The ratio of phase A increased from 20% to 50% (v/v) within 4 min and then decreased to 20% (v/v) within 0.5 min. Finally, the ratio of phase A was maintained at 20% (v/v) for 2.5 min.

Fabrication of the co-flow microfluidic device. The co-flow microfluidic device was composed of two types of borosilicate glass cylindrical capillary (OD/ID: 1.1/0.58 mm, OD/ID: 1.5/1.12 mm World Precision Instruments, USA). One end of the thinner capillary was trapped into a cone type by micropipette puller (P-1000, Sutter instrument, USA). The tip of the cone should be enlarged to approximately 100 μm with sandpaper and served as the inner capillary. Simultaneously, the diameter of the end of the other capillary was polished into ~400 μm and served as the outer capillary. Afterward, the thinner capillary was coaxially inserted into the outer capillary and fixed on a slide. One injection needle was used to connect the inner and the outer capillary. The 5 min Epoxi was employed to seal the microchannels where necessary.

2. Supplementary Results

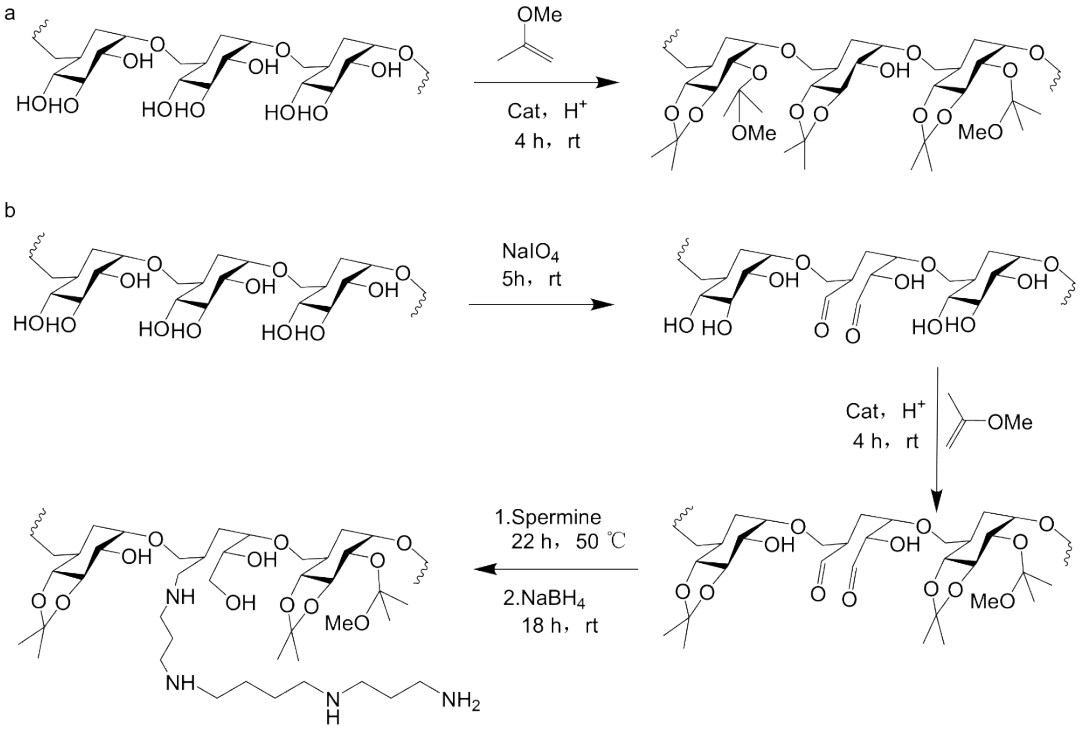

Figure S1. Synthesis route of polymers used in this study. (a) Acetalated dextran (AD), and (b) spermine modified acetalated dextran (ADS).

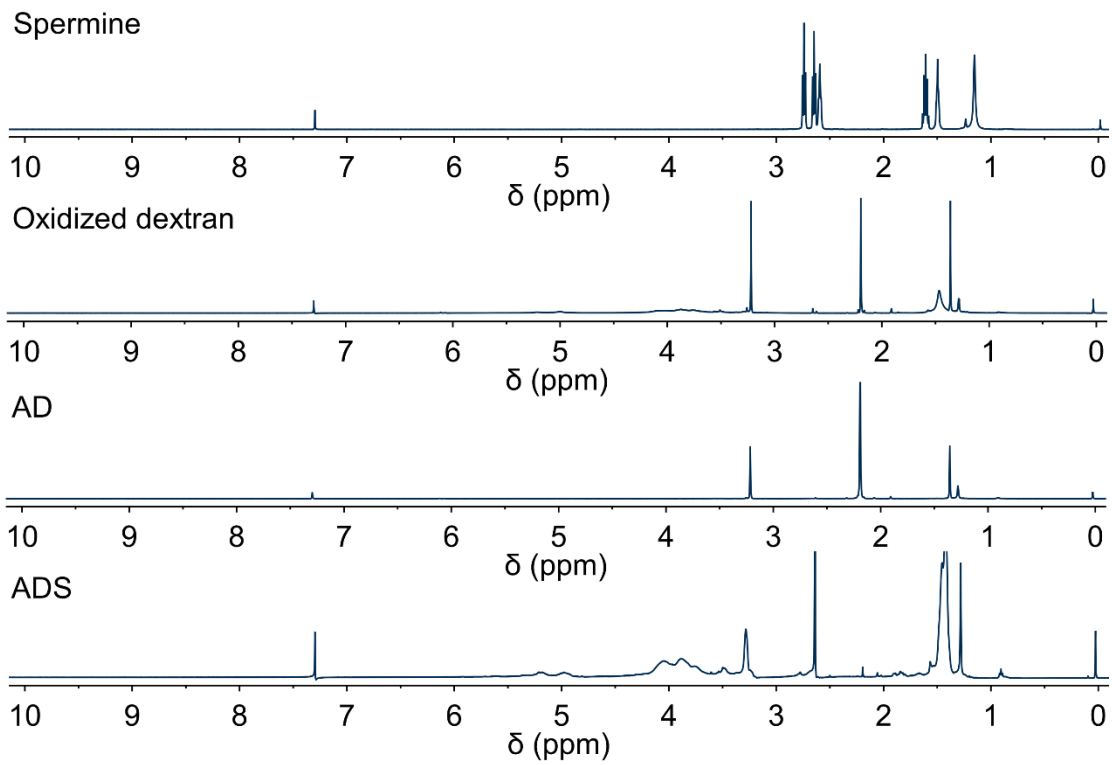

Figure S2. ^{1}H NMR spectra of synthesized polymers. Spermine, oxidized dextran, AD and ADS were dissolved in $CDCl_3$.

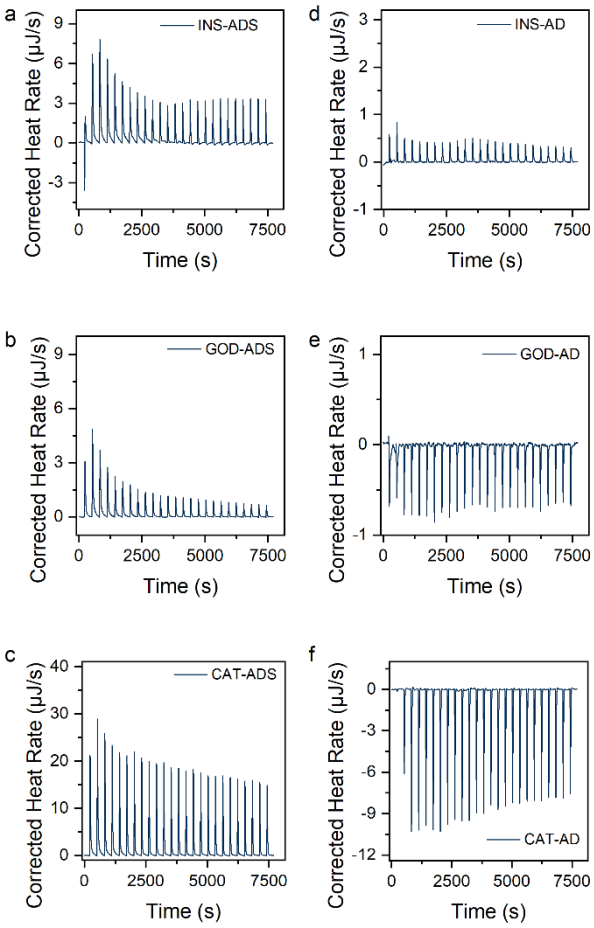

Figure S3. Corrected heat rates of the titration for the adsorption of ADS with insulin (a), glucose oxidase (b) and catalase (c) colloids; Corrected heat rates for the adsorption of AD with insulin (d), glucose oxidase (e) and catalase (f) colloids.

Table S1. Thermodynamic parameters calculated from ITC measurement for multiple types of protein colloids.

Protein-Polymer	N	ΔH (KJ/mol)	ΔS (J/mol·K)	ΔG (KJ/mol)
Insulin-AD	0.018	-511.5	-1598	-35.04
Insulin-ADS	0.05	-3905	-13033	-19.41
CAT-AD	0.2	13.33	-140.7	-28.73
CAT-ADS	0.636	-5000	-16702	-20.13
GOD-AD	0.17	36.11	182.6	-18.33
GOD-ADS	0.915	-4999	-16699	-20.66

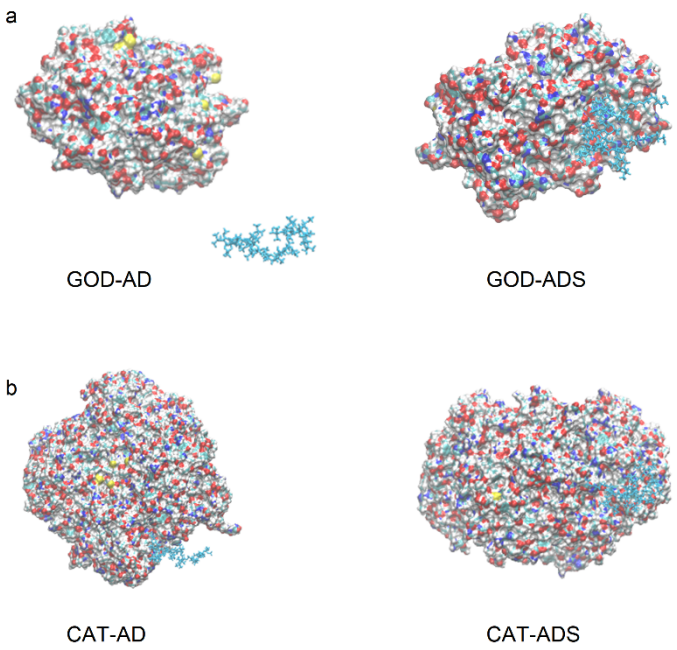

Figure S4. Snapshots of the interaction between polymers and protein molecules. The interaction between (a) glucose oxidase and polymer molecules (AD and ADS), and (b) between catalase molecule and polymer molecules (AD and ADS) after 100 ns. Solvent molecules were hidden for clarity.

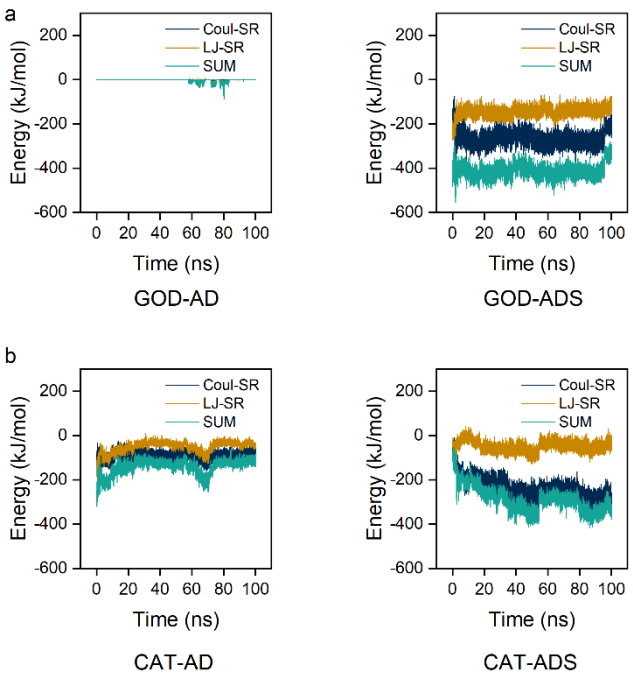

Figure S5. The potential energy as a function of time for AD (left) or ADS (right) interacted with glucose oxidase (a) and catalase (b).

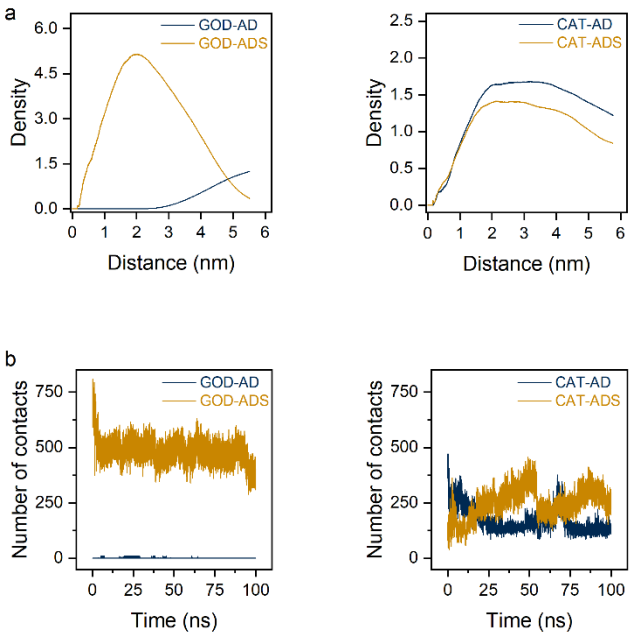

Figure S6. (a) The density variation of AD and ADS near the glucose oxidase (left) and catalase molecule (right). (b) Number of contact points between polymers and glucose oxidase (left) and catalase molecule (right) within 4 Å.

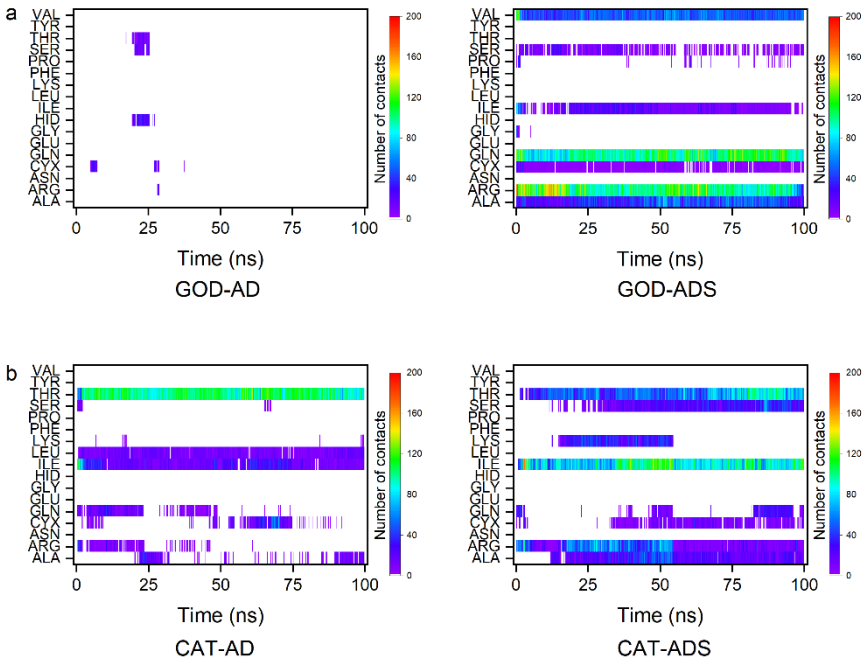

Figure S7. Heat map of contact points between polymers (AD and ADS) and amino acid residues of glucose oxidase (a) and catalase (b) over 100 ns of simulation. The color bar on the right side represents the number of contact points (1-200).

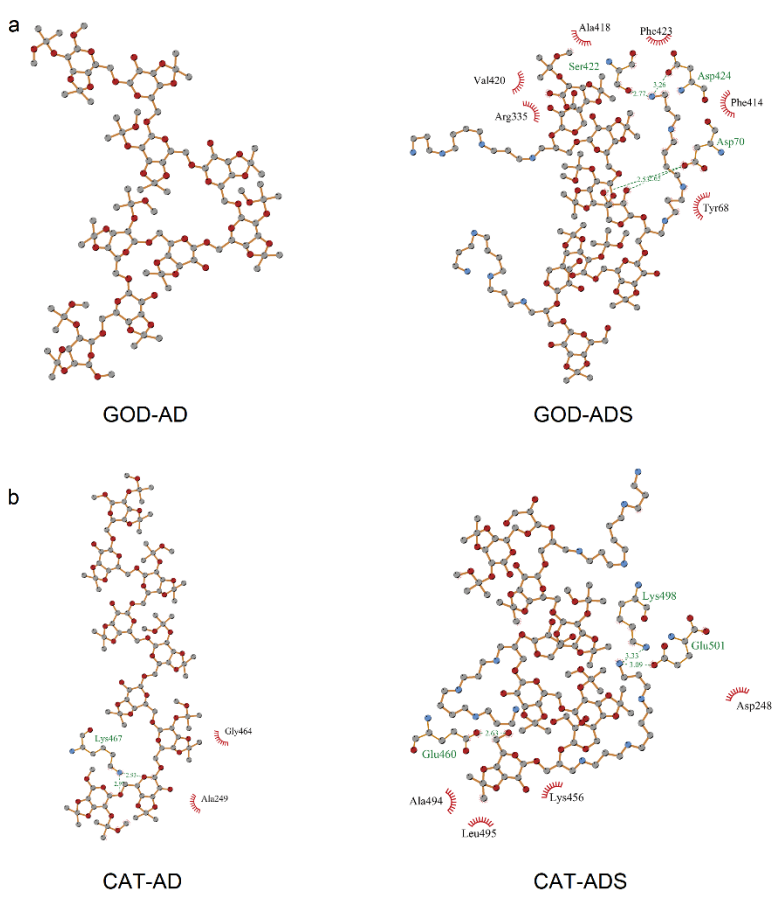

Figure S8. Snapshot of binding sites between polymers (AD and ADS) and glucose oxidase amino acid residues (a) and catalase amino acid residues (b) by Ligplus software. Dashed lines represent hydrogen bonds and eyelash icons represent hydrophobic interactions.

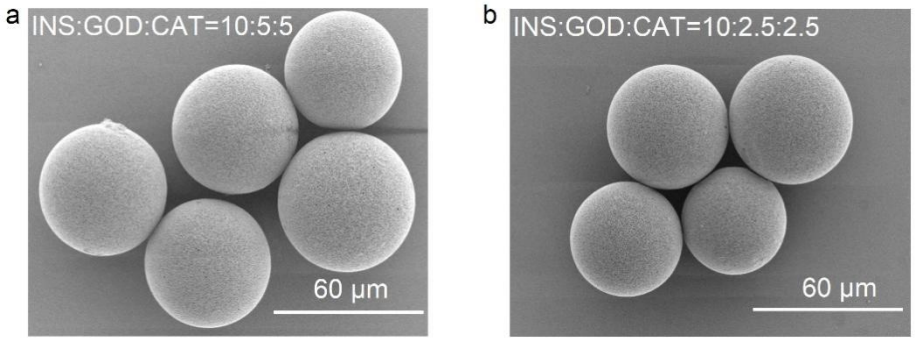

Figure S9. Scanning electron microscope images of the obtained microcomposites with different drugs ratio. (a) INS: GOD: CAT=10: 5: 5; (b) INS: GOD: CAT=10: 2.5: 2.5.

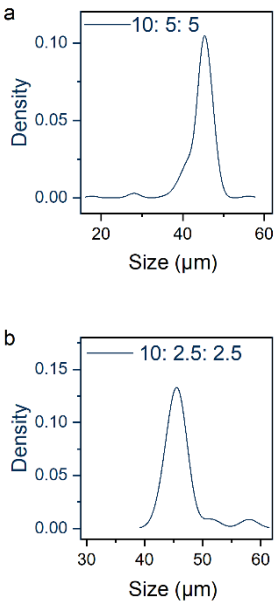

Figure S10. The size distribution of INS-enzymes@ADS microcomposites with different drugs ratio. (a) INS: GOD: CAT=10: 5: 5; (b) INS: GOD: CAT=10: 2.5: 2.5.

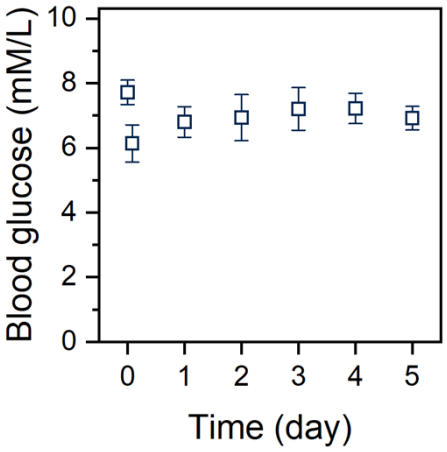

Figure S11. Effect of IGC@ADS microparticle on the blood glucose level in healthy rats.

Reference:

1. S. A. Meenach, Y. J. Kim, K. J. Kauffman, N. Kanthamneni, E. M. Bachelder and K. M. Ainslie, *Mol. Pharmaceutics*, 2012, **9**, 290-298.
2. J. L. Cohen, S. Schubert, P. R. Wich, L. Cui, J. A. Cohen, J. L. Mynar and J. M. Frechet, *Bioconjugate Chem.*, 2011, **22**, 1056-1065.
3. M. Tarhini, H. Greige-Gerges and A. Elaissari, *Int. J. Pharm.*, 2017, **522**, 172-197.