Supporting information

Smart erythrocyte-hitchhiking insulin delivery system for prolonged automatic blood glucose control

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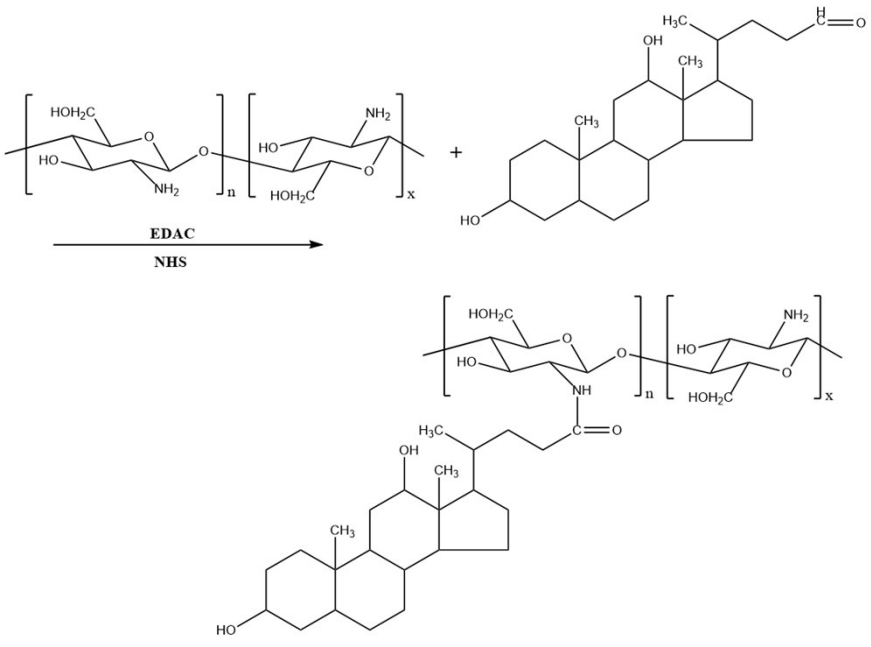
Step 1:



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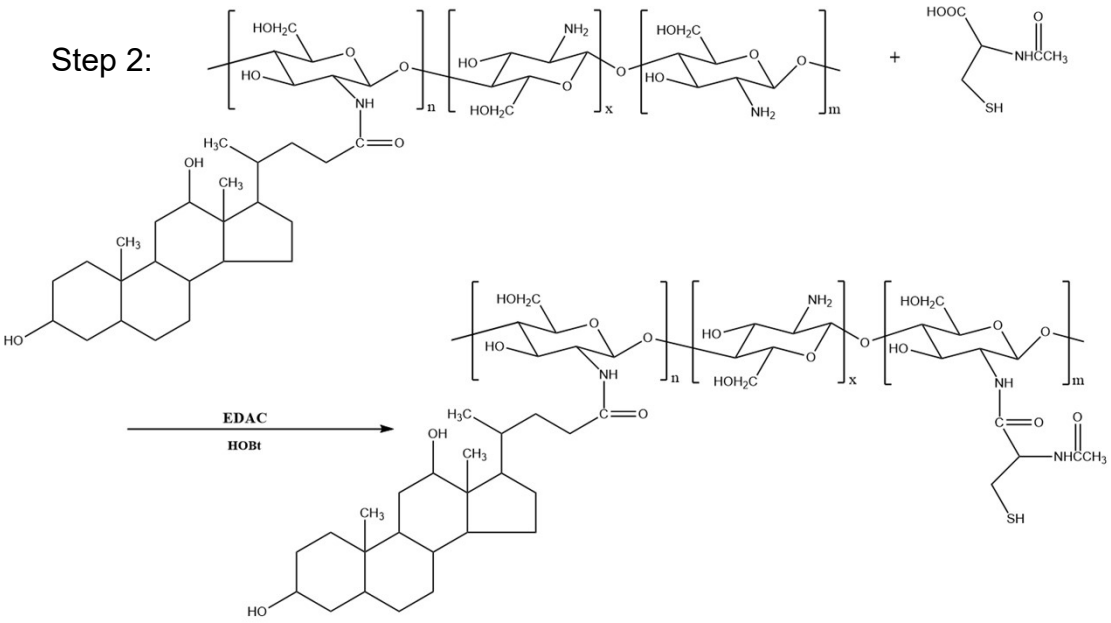

Figure S1: Synthetic routine of DCN

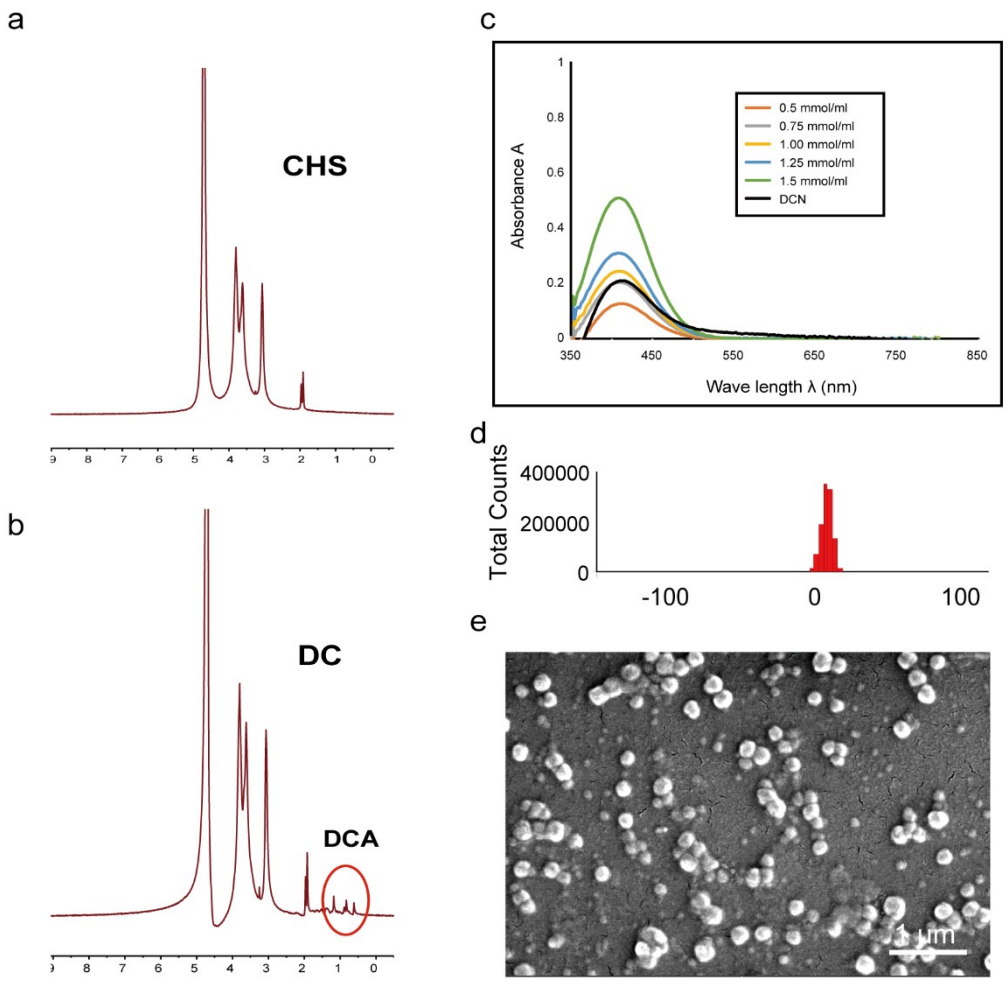

Figure S2: Characterization of DCN carriers and SIDS: a-b)^{1}H NMR spectrum of the carrier materials, a) spectrum of CHS and b) spectrum of DC. the spectrum of DC showed characteristic absorption peaks of

deoxycholic acid methylene and methine at approximately 1.0 ppm. c) The ultraviolet spectrum of the sulfhydryl content in DCN determined by Elliman method. d) The zeta potential distribution diagram of SIDS. e) SEM image of SIDS.

Table 1 N, C, H content in CHS and DCA-CHS

	N [%]	C [%]	H [%]
CHS	7.62	40.64	6.81
DCA-CHS	7.24	40.32	7.01

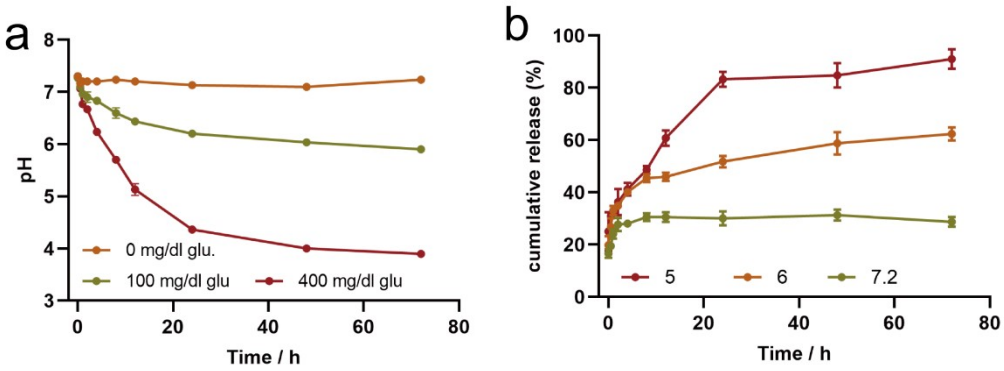

Figure S3. a）The pH change caused by SIDS at different glucose concentrations. Data points represent mean ± SD (n = 3). b) In vitro accumulated insulin release of SIDS in different pH. Data points represent mean ± SD (n = 3)

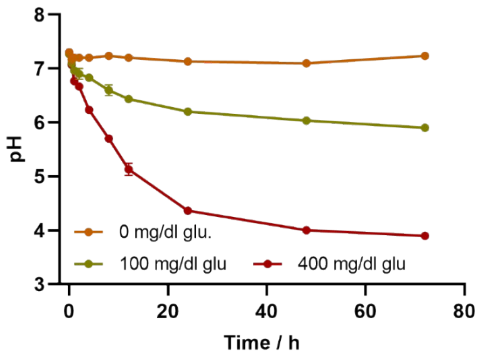

Figure S4. The change of size in different glucose concentration (0 mg/ml、100 mg/ml，400 mg/ml) , Data points represent mean ± SD (n = 3)

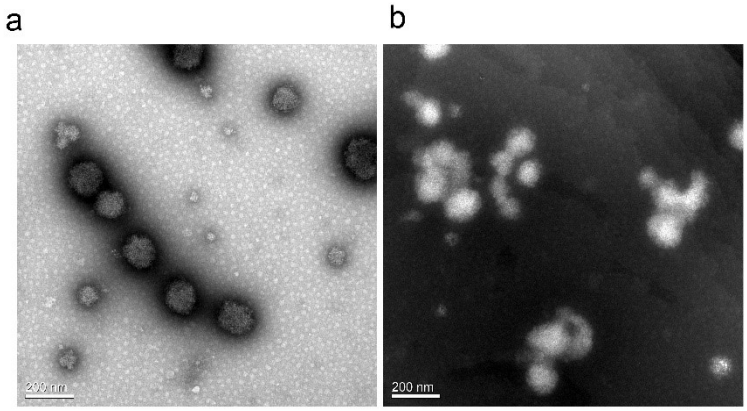

Figure S5. SEM of swollen SIDS. a) In 0 mg/ml glucose; b) 400 mg/ml glucose

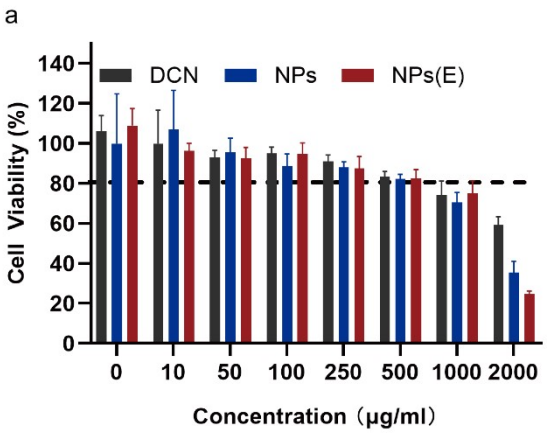

Figure S6: a) Cytotoxicity assay of IDS, SIDS or SHIDS to RAW264.7 cells after 24 h incubation. The error bars are based on the standard deviation (SD) of triplicated samples. b) AUC of plasma insulin concentrations in diabetic mice after treatment with inulin solution, IDS, SIDS, or SHIDS, respectively. Data points represent mean ± SD (n=5).

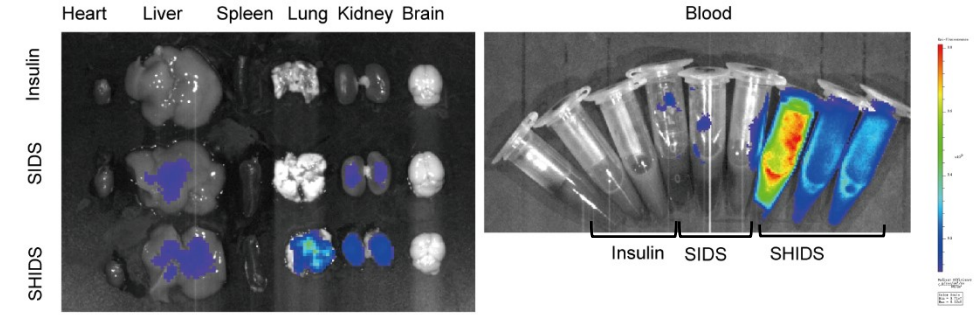

Figure S7: Biodistribution of Cy5.5 labeled insulin, SIDS or SHIDS in main organs and blood post 24 h.

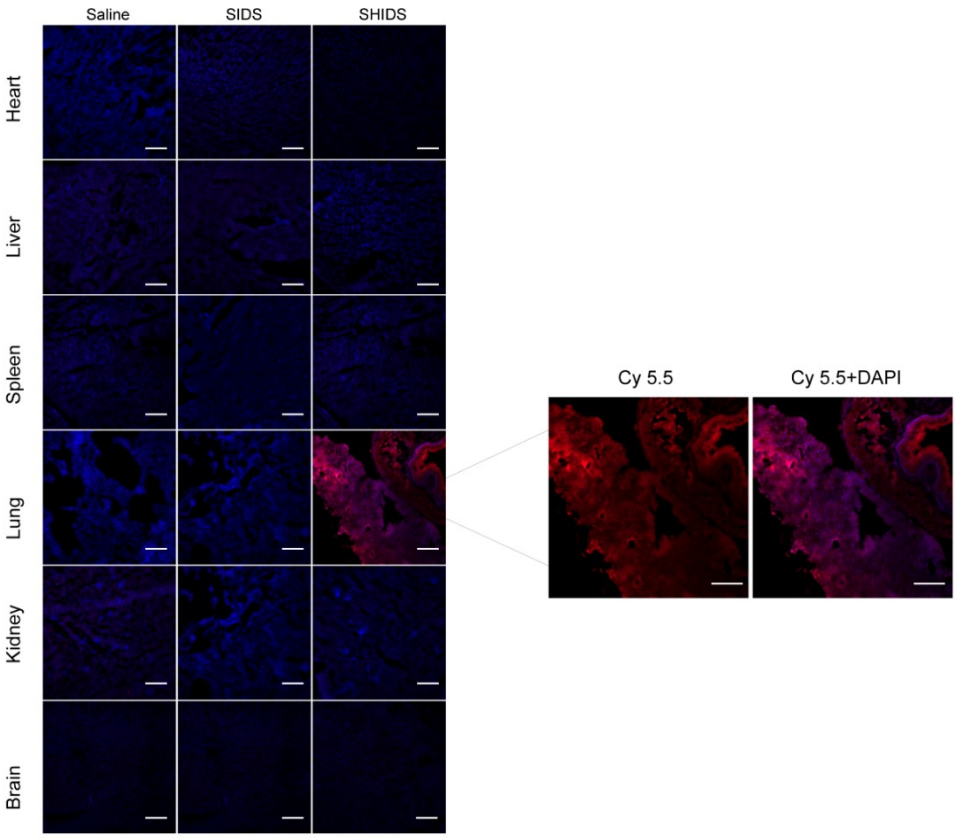

Figure S8. Fluorescence in main organs (heart, liver, spleen, lung, kidney, brain) images of Cy5.5 labeled insulin, SIDS, or SHIDS treated group when administrated after 12 h

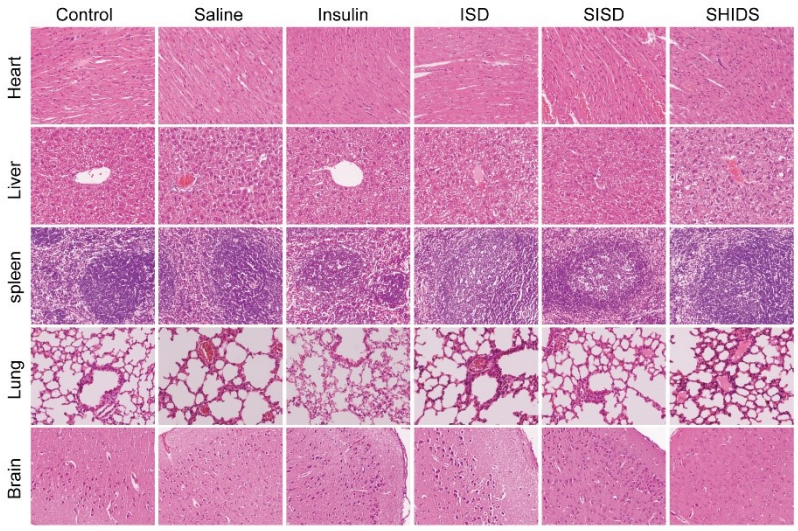

Figure S9: Hematoxylin & eosin (H&E) staining assay of heart, liver, spleen, lung, and brain in diabetic mice after two-week treatment of saline or insulin solution. Photomicrographs were taken with a microscope camera at 200× magnification.

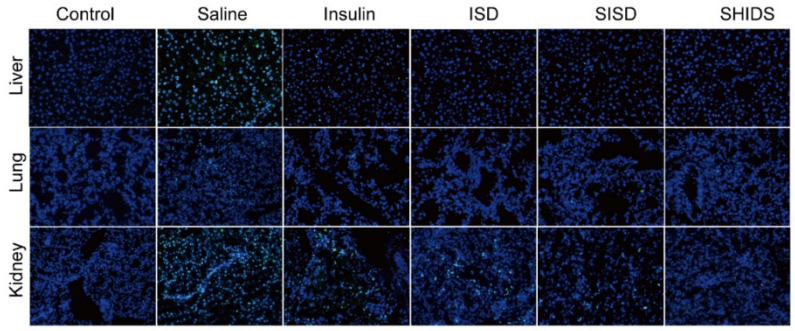

Figure S10. TUNEL staining assay of liver, lung and kidney in diabetic mice after two-week treatment. Photomicrographs were taken with a microscope camera at 200× magnification.

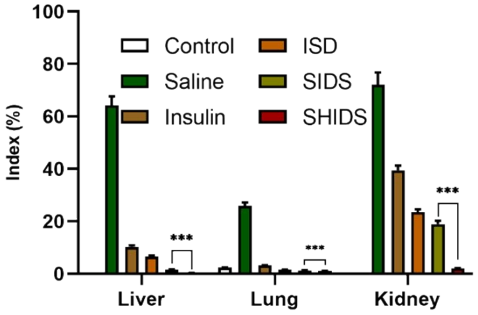

Figure S11. Relative apoptotic index in all treated groups were semi-quantitatively scored based on Tunel. The results are expressed as mean ± SD (n = 10). ***, denote $p < 0.001$, for SHIDS compared with SIDS group.

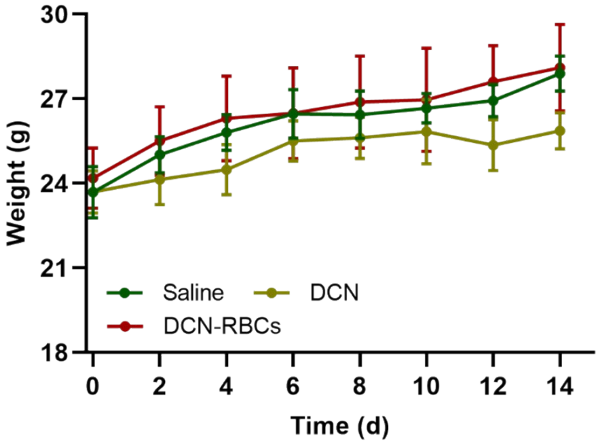

Figure S12. Mice body weight change curves after treatment with saline, DCN or DCN-RBCs; data points represent mean ±SD (n = 5).

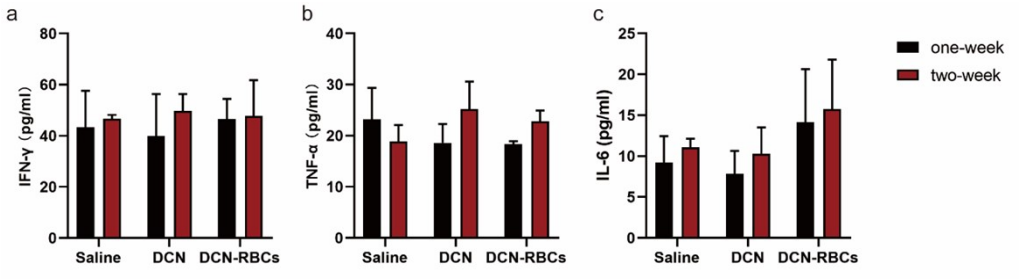

Figure S13: Immune factor levels after administration with saline, DCN, or DCN-RBCs, a) IFN-γ，b) TNF-α, and c) IL-6. data points represent mean ±SD (n = 5)

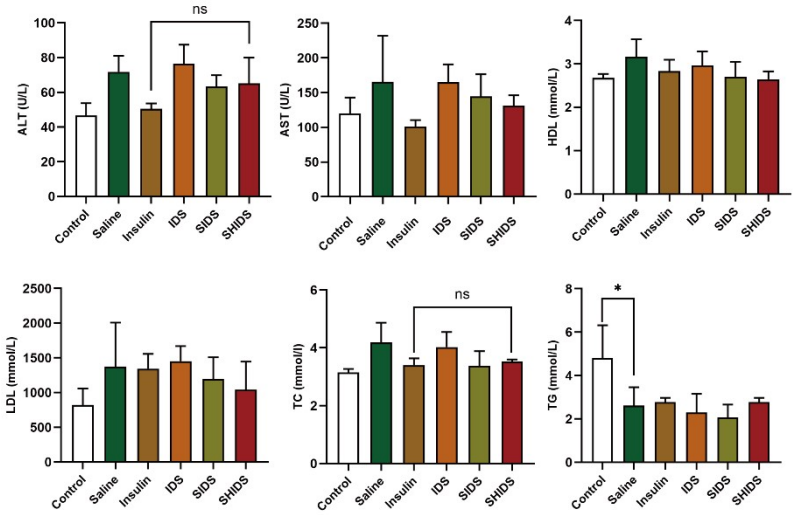

Figure S14: ALT, AST, HDL, LDL, TC and TG of mice in different group after treatment with saline, insulin solution, ISD, SIDS, and SHIDS for 2 weeks. Data points represent mean ±s.d., and * denotes $p < 0.01$; *** denotes $p < 0.001$.