Supporting Information

Revealing Drug Release and Diffusion behavior in Skin Interstitial Fluid by Surface-Enhanced Raman Scattering Microneedles

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Experimental Section

Detection of DTTC in gels at different concentrations by D-MN. Weigh 0.2 g of agarose and dissolve it in 10 ml of deionized water. After cooling to 60 °C at room temperature, add different levels of DTTC solution to the agarose solution separately and shake well. The final concentrations of DTTC in agarose solution were 10^{-8}, $10^{-7,}$ 3×10^{-7}, 10^{-6}, and 3×10^{-6} M. Subsequently, they were placed in an incubator at 37 °C. Finally, the D-MNs were inserted into agarose hydrogels with different DTTC concentrations for 10 min, followed by SERS signal detection.

ICP-MS analysis. D-MNs before and after the insertion to mouse skin were immersed in 1 mL of freshly prepared aqua regia solution for 2 h, respectively. Then, the aqua regia solutions were diluted 50 times for detecting the Au element content of D-MNs by ICP-MS analysis. ^{115}In was selected as an internal standard element for quantification. The leached Au concentration in mouse skin was determined by the value of the subtraction. The data was obtained as a mean value with a standard deviation of the measurements from four D-MNs (n = 4). Au element content of one D-MN before insertion was 3.92 μg. After the mouse skin insertion, the value became 3.7 μg. Therefore, the lost AuNPs from one D-MN was 0.22 μg.

Preparation of therapeutic microneedle with SA as drug carrier. Weigh 0.6 g of sodium alginate and 0.1 g of PVP-k30 and mix to make a 5 % aqueous solution. Weigh 0.01 g of DTTC solid dispersion and add it to 1 ml of sodium alginate aqueous solution to form a mixture. Take 150 μL of the mixture and add it to the PDMS mold, vacuum under negative pressure for 5 min, and cycle 2-3 times. Subsequently, the air bubbles were sucked away and the PDMS molds were filled with the mixture and dried by the blast at 40 °C for 24 h. Finally, the microneedles were immersed in $CaCl_2$-saturated ethanol solution for 10 s, followed by blast drying at 50 °C for 4 h to form microneedles.

Preparation of therapeutic microneedle with CV as a drug model. Weigh 0.0041 g of CV solid powder and add it to 10 ml of water to form a 10^{-3} M CV solution. Subsequently, 0.04 g of HA was weighed and mixed with 1 ml of CV solution to form a mixture. Take 150 μL of the mixture and add it to the PDMS mold, vacuum under negative pressure for 10 min, suck out the air bubbles and then fill the PDMS mold with the mixture, followed by blast drying at 45 °C for 4 h. After natural de-molding, microneedles were formed.

Figures and Tables

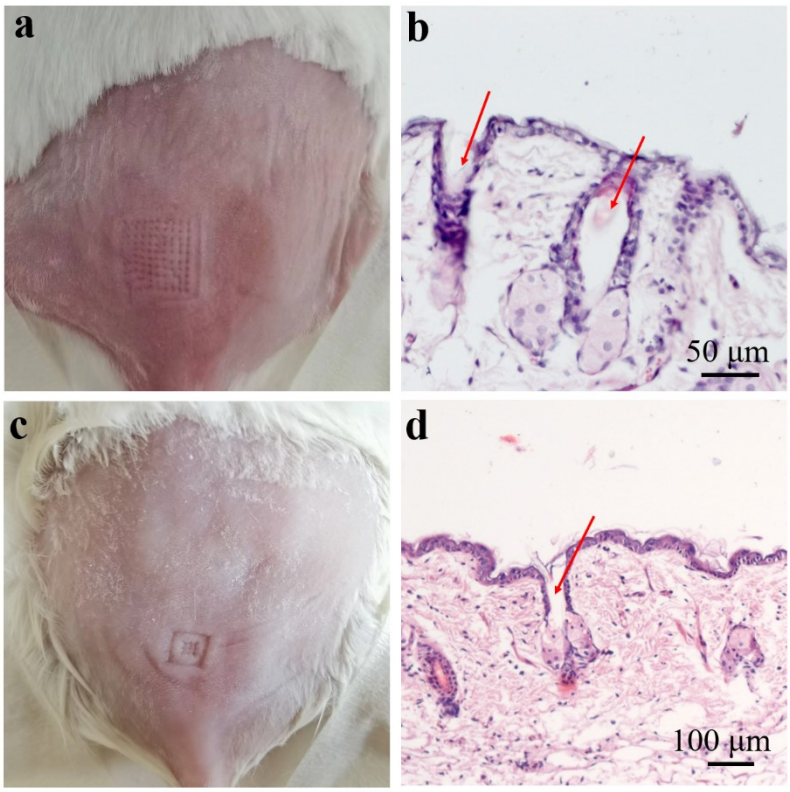

Figure S1 Investigation on the mechanical strength of T-MN and D-MN. a) A picture of T-MN puncturing the skin of a mouse. b) An H&E stained histological image of mouse skin after insertion of T-MN, the red arrow shows the inserted micropores with an effective penetration depth of approximately 200 μm. c) A picture of D-MN puncturing the skin of a mouse. d) An H&E stained histological image of mouse skin after insertion of D-MN, the red arrow shows the inserted micropores with an effective penetration depth of approximately 200 μm.

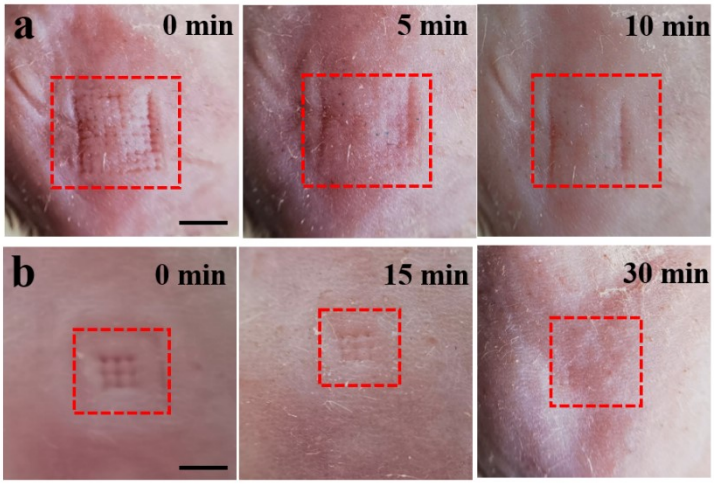

Figure S2 Examination of the biosafety of T-MN and D-MN. a) Images of mouse skin recovery after removal of a T-MN. The scale bar is 0.5 cm. b) Images of mouse skin recovery after removal of a D-MN. The scale bar is 0.25 cm.

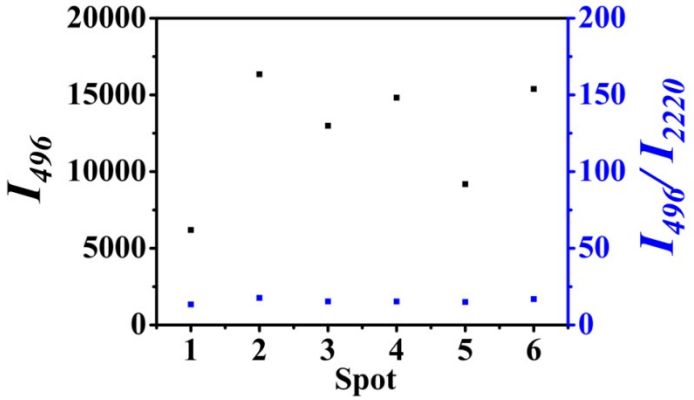

Figure S3 Scatter plot of I_{496} values (black square, without calibration) versus ratio I_{496}/I_{2220} (blue square, with calibration) for the detection of DTTC from six tips of one microneedle.

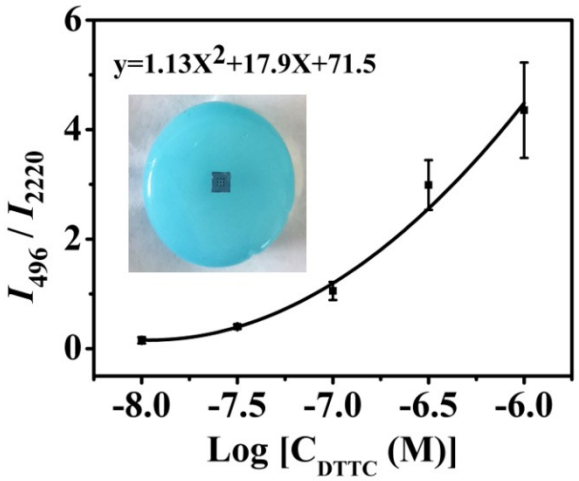

Figure S4 The curve of DTTC concentration and SERS intensity ratio (I_{496}/I_{2220}). The data is obtained as a mean value with a standard deviation of 6 measurements from 6 tips of a D-MN. R^2=0.96. The insert picture shows a D-MN inserted into an in vitro gel to simulate skin ISF.

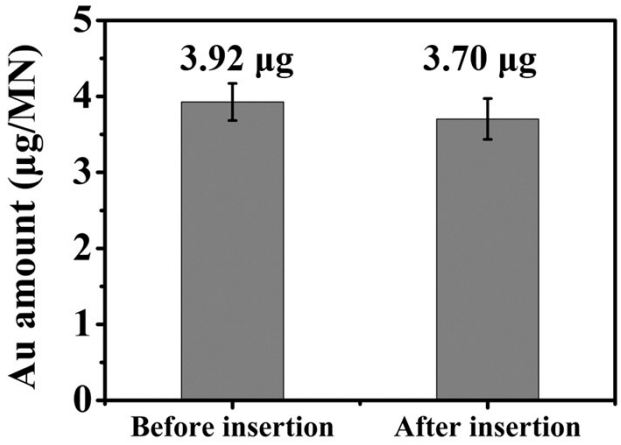

Figure S5 Au concentration determination of D-MN before and after the insertion of a mouse skin by ICP-MS analysis. The data is obtained as a mean value with a standard deviation of the measurements from four D-MNs (n=4).

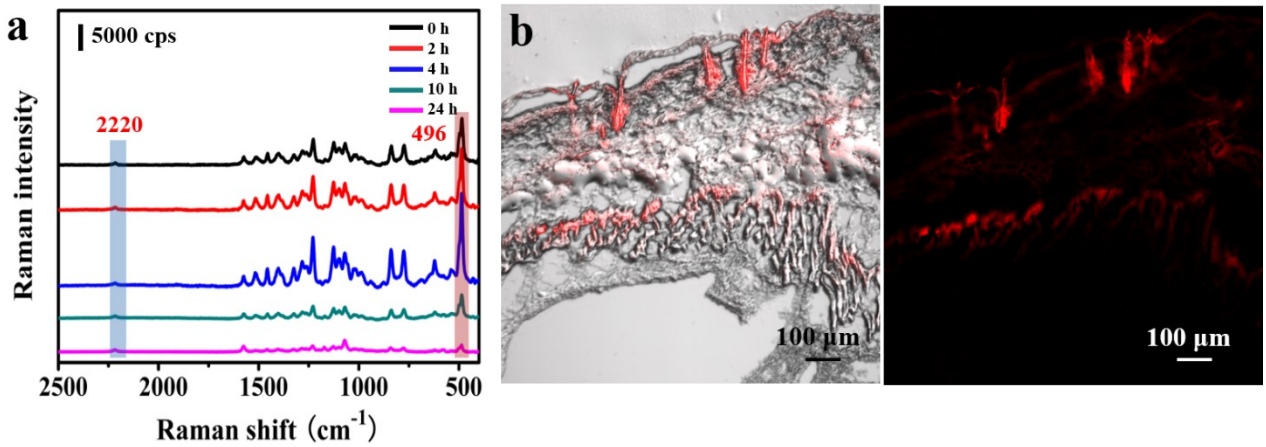

Figure S6 Verify DTTC diffusion in the skin ISF. a) SERS spectra of DTTC in the drug release site at different times. b) CLSM images of a skin tissue section after 4 h DTTC release to ISF from T-MN. The red fluorescence indicates the spread of DTTC.

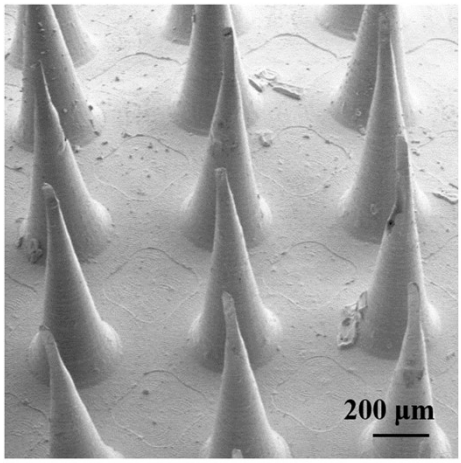

Figure S7 SEM image of a T-MN prepared with sodium alginate as a drug delivery material.

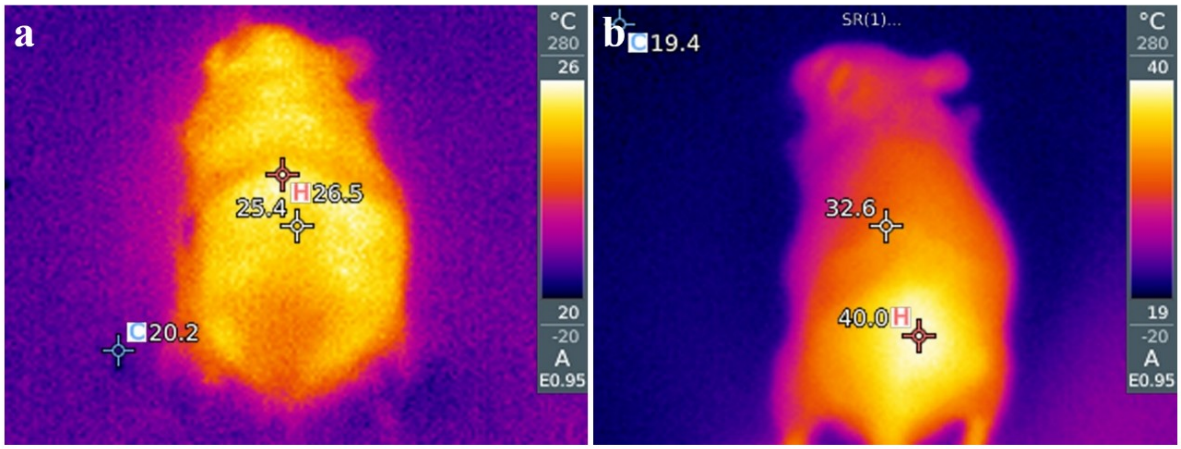

Figure S8 The skin temperature of a mouse is about 26.5 ℃ at room temperature a) and 40 ℃ under the irradiation of a heating lamp as detected by an infrared thermal imager.

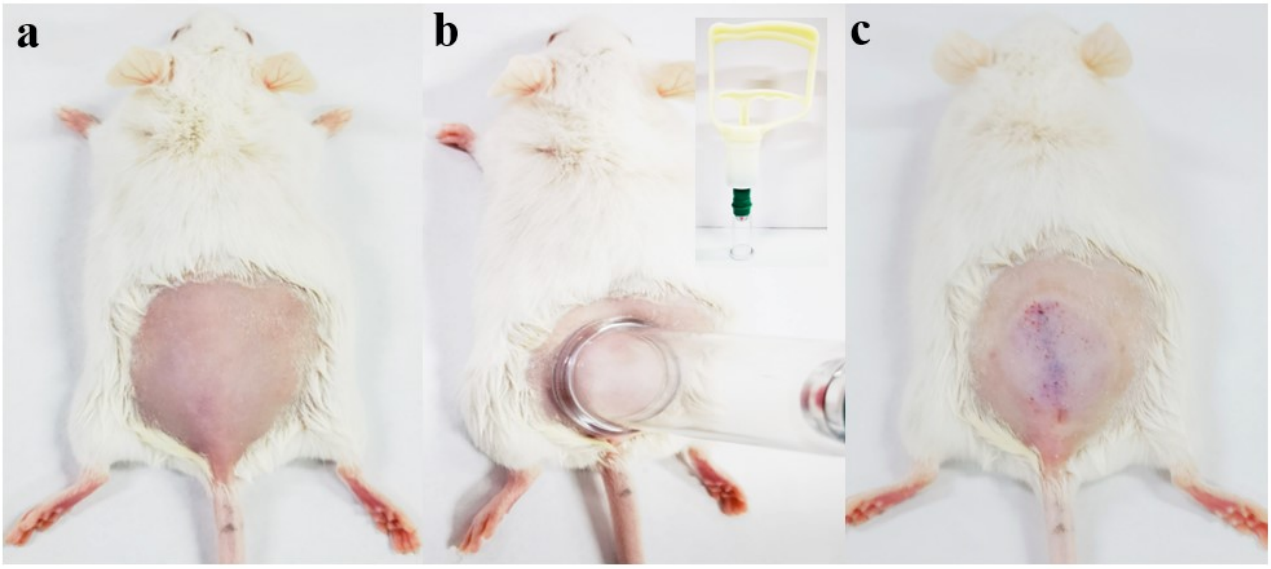

Figure S9 Schematic diagram of the skin suction process on a mouse skin. a) Normal mouse skin, b) underwent a suction process, negative pressure vacuum lasts 3-5 seconds and is repeated three times. the inset shows a suction device. c) the mouse after suction.