Electronic Supplementary Information (ESI)

H_2O_2-Responsive Mesoporous Silica Nanoparticles Integrated with Microneedle Patches for Glucose-Monitored Transdermal Delivery of Insulin

Bin Xu,[a] Guohua Jiang,[a,b,c,*] Weijiang Yu,[a] Depeng Liu,[a] Yang Zhang,[a] Junyi Zhou,[a] Shiqing Sun [a] and Yongkun Liu[a]

a Department of Materials Engineering, Zhejiang Sci Tech University, Hangzhou 310018, China

b National Engineering Laboratory for Textile Fiber Materials and Processing Technology (Zhejiang), Hangzhou 310018, China

c Key Laboratory of Advanced Textile Materials and Manufacturing Technology (ATMT), Ministry of Education, Hangzhou 310018, China

* Corresponding author. Tel: +86 571 86843527; E-mail address: ghjiang_cn@zstu.edu.cn (G. Jiang)

Preparation of Functional Mesoporous Silica Nanoparticles

Mesoporous silica nanoparticles (MSN) were prepared by following previous reports [1,2]. Briefly, cetyltrimethylammonium bromide (CTAB, 0.5 g) was dissolved in 250 mL deionized water. Then, NaOH (2M, 1.75 mL) was added to the above solution and the reaction mixture was heated to 80 ℃ in a water bath with stirring. After the temperature was stabilized, tetraethyl orthosilica (TEOS, 2.5 mL) was dropped into the mixture solution and the reaction mixture was stirred for another 2 h. Afterwards, the white precipitate was separated by centrifugation (8000 rpm, 10 min) and washed 2 times with deionized water and methanol. Finally, the white precipitate was dried in vacuum. The as-synthesized white precipitate (0.5 g) was dispersed in a mixture solution, which containing methanol (50 mL) and hydrochloric acid (3 mL). The reaction mixture was refluxed at 60 ℃ in an oil bath overnight in order to remove surfactant (CTAB). The precipitate was collected by centrifugation (8000 rpm, 10 min) and washed 3 times with methanol before it was dried in vacuum to obtain mesoporous silica nanoparticles (MSN).

Amino-functionalized mesoporous silica nanoparticles (MSN-NH_2) were synthesized by previous reports [3], with slight modification. Briefly, the as-synthesized MSN (1.0 g) was dissolved in toluene (40 mL) and 3-aminopropyltriethoxysilane (APTES, 1.5 mL) was added to solution. The reaction mixture was refluxed at 110 ℃ in an oil bath for 20 h under N_2 conditions protection. Finally, the precipitate was collected by centrifugation (8000 rpm, 10 min) and washed 3 times with methanol before it was dried in vacuum to obtain MSN-NH_2.

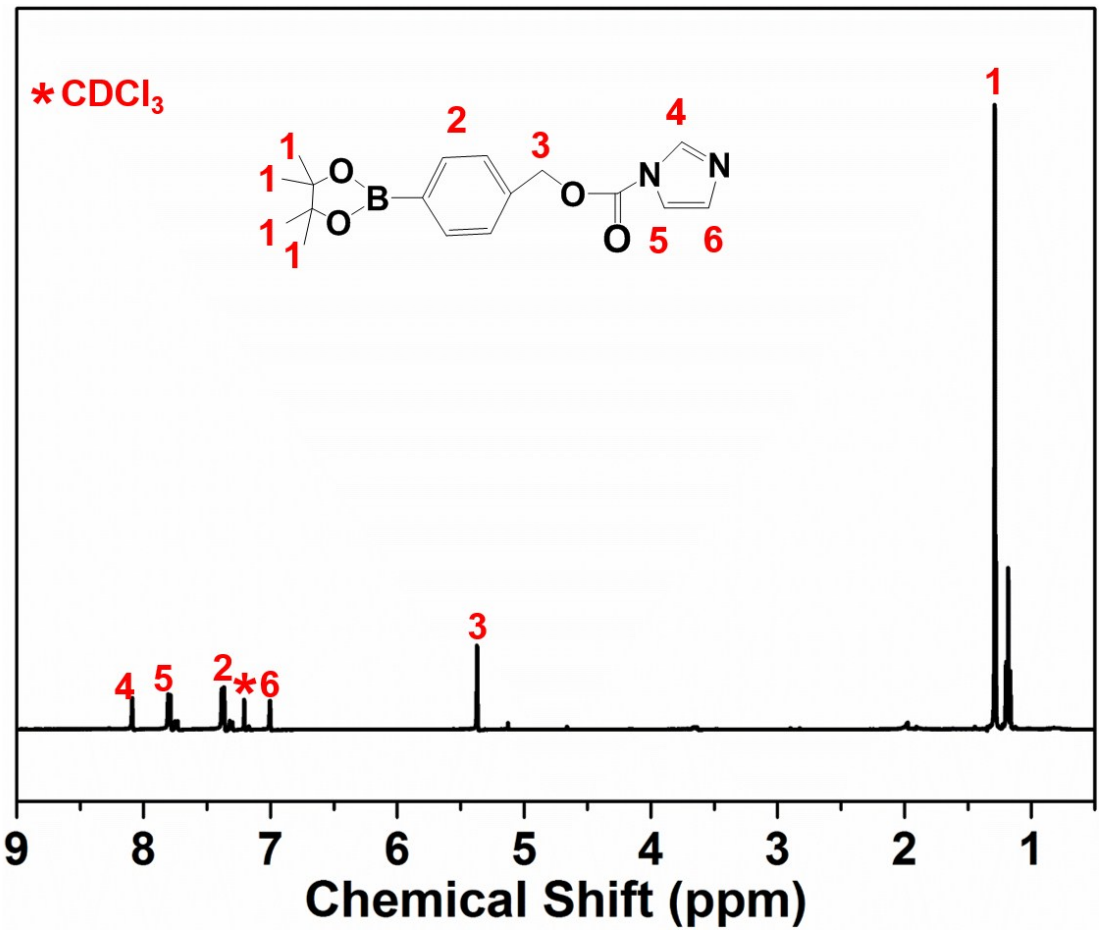

Fig. S1 ^{1}HNMR spectrum of 4-(Imidazoyl carbamate)phenylboronic acid pinacol ester (ICBE). ^{1}HNMR (400 MHz, $CDCl_3$) δ 1.34 (s, 12H), 5.43 (s, 2H), 7.05 (s, 1H), 7.45 (m, 3H), 7.85 (d, 2H), 8.15 (s, 1H).

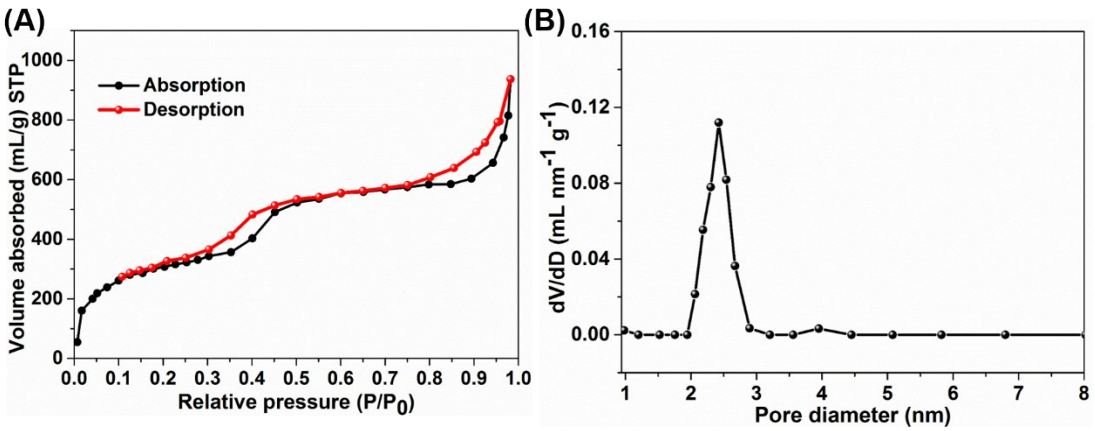

Fig. S2 Nitrogen sorption isotherm (A) and pore size distribution (B) of MSN.

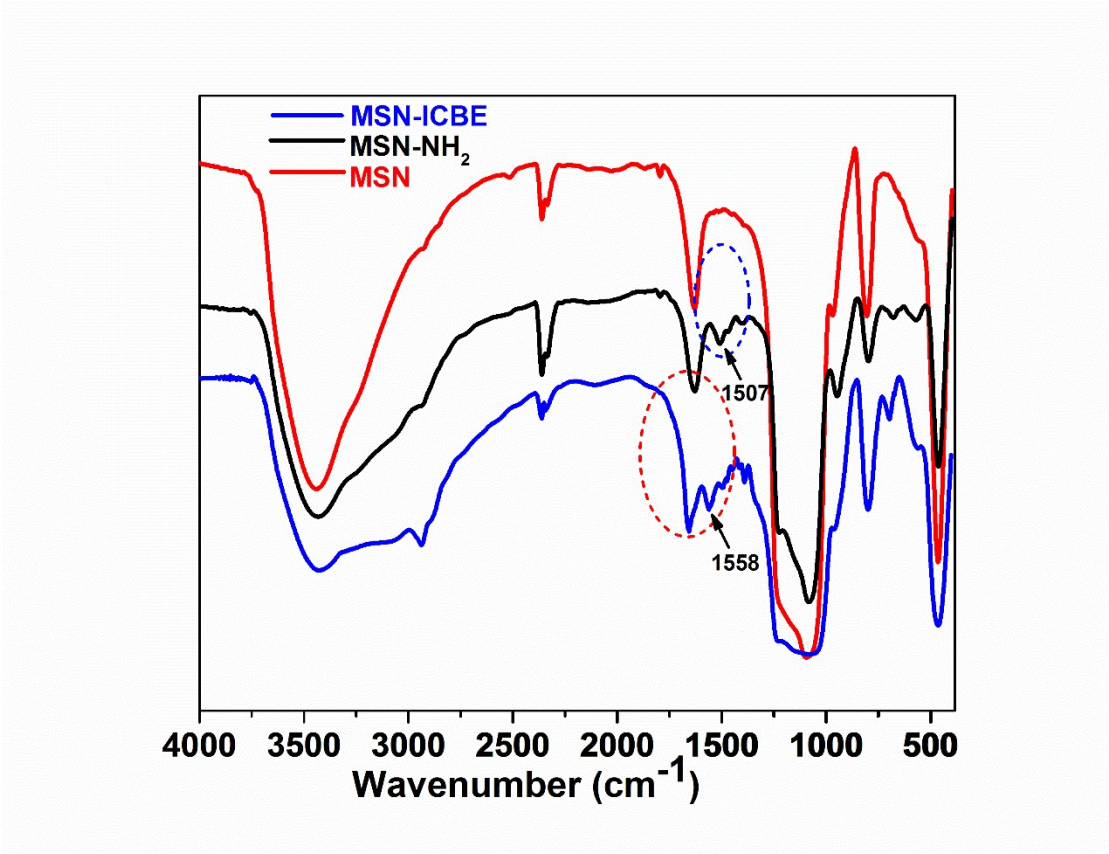

Fig. S3 FTIR spectra of MSN, MSN-NH_2 and MSN-ICBE showing the changes of functional groups.

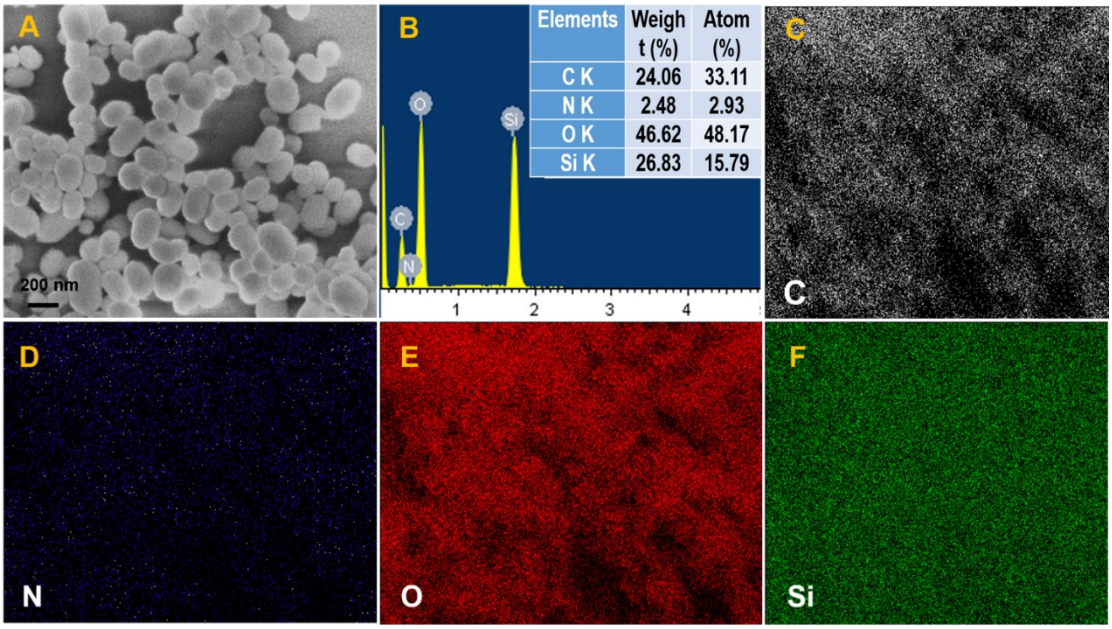

Fig. S4 The EDC and Mapping of MSN-NH_2. SEM images of MSN-NH_2 (A), EDC of MSN-NH_2 (B) and element on the surface of MSN-NH_2 (D, E and F).

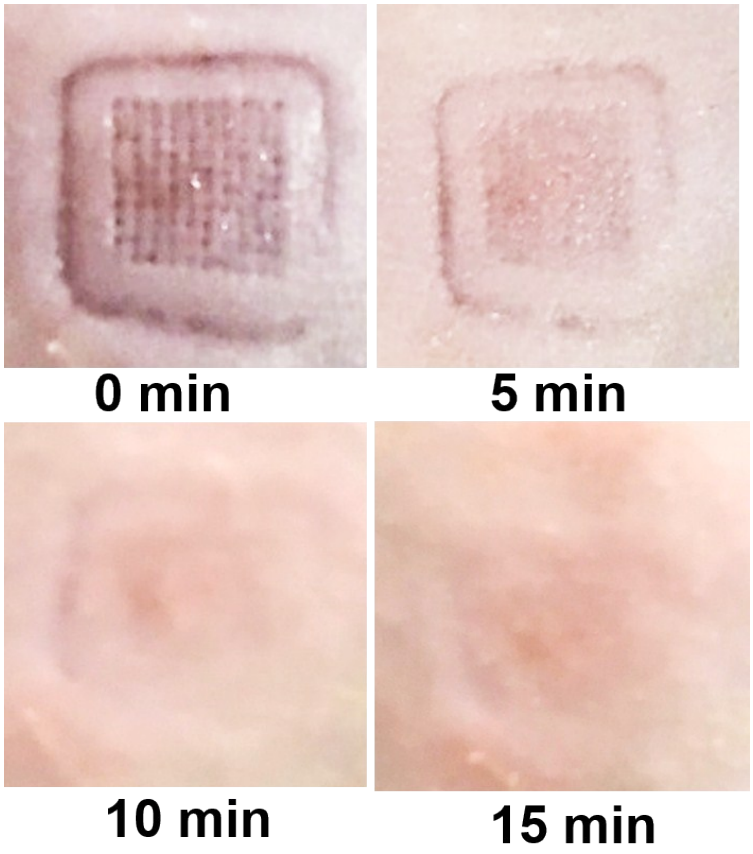

Fig. S5 The recovery of skin after applied microneedles on the living SD rats' skin.

Table S1. Mean size, polydispersity index (PDI), encapsulation efficiency (EE) and drug loading capacity (DLC) of nanoparticles (n=3).

	Size (nm)	PDI	EE (%)	DLC (%)
MSN	175 ± 1.7	0.136 ± 0.016	-	-
Ins-MSN-ICBE/α-CD	192 ± 3.5	0.218 ± 0.025	66.1	13.2

Table S2. Pharmacokinetic parameters of insulin-loaded nanoparticles after administration of microneedles patches on diabetic rats (n=3). AUC: area under the insulin plasma concentration-time curve, AAC: area above the curve of the blood glucose level.

	Insulin solution (S.C)	Ins-MSN-ICBE/α-CD
Dose (IU/Kg)	24	40
AAC	2371.4 ± 142.3	3560.8 ± 156.4
AUC	1286.2 ± 138.6	1984.8 ± 147.5
F_R (%)	-	92.6 ± 6.3
PA (%)	-	90.1 ± 5.4

References:

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3. Jin Zhang, Shanfu Lu, Haijin Zhu, Kongfa Chen, Yan Xiang, Jian Liu, Maria Forsyth and San Ping Jiang. Amino-functionalized mesoporous silica based polyethersulfone–polyvinylpyrrolidone composite membranes for elevated temperature proton exchange membrane fuel cells, RSC Advances 2016, 75, 581-588.