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Supporting Information

Transdermal drug delivery using a porous microneedle device driven by a hydrogel electroosmotic pump

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Experimental materials

A precursor of poly(dimethylsiloxane) (PDMS) (SILPOT 184) was purchased from Dow Corning Toray Co., Ltd., Tokyo, Japan. Polyethylene glycol (PEG, 10 kDa), trimethylolpropane trimethacrylate (TRIM), Trichloro(1H,1H,2H,2H-perfluorooctyl) silane, 2-Acrylamido-2-methyl-1-propanesulfonic acid sodium salt solution (NaAMPS) (655821-250, 50 wt%), 2-hydroxy-2-methylpropiophenone, fluorescein isothiocyanate-dextran (FITC-dextran, MW = 10000) were purchased from Sigma-Aldrich. Glycidyl methacrylate (GMA), triethylene glycol dimethacrylate (TEGDMA), tetrahydrofuran (THF) (204-08745), N,N'-methylenebisacrylamide (MBAAm), D-PBS(-), Sodium Chloride, Ethanol (057-00451) were purchased from FUIJFILM Wako Pure Chemical Corporation, Ltd., Osaka, Japan. Diethylene glycol monomethyl ether (DEG), (3-acrylamidopropyl) trimethylammonium chloride (APTAC), 2-Isopropylthioxanthone was purchased from Tokyo Chemical Industry Co., Ltd, Tokyo, Japan. Irgacure 184, Omnirad 819 (former Irgacure 819) and Irgacure 2959 were purchased from IGM Resins B.V.

Fabrication of porous microneedle

The geometry of porous microneedle (PMN) was designed to be composed of an array of 37 needles (300 μm-length) with cylindrical supporting posts (height: 300 μm, diameter: 450 μm) at 1 mm intervals on a porous substrate (diameter: 8 mm, thickness: 0.8 mm) (**Fig. S1**). First, a female PDMS mold was fabricated from a male PDMS mold, prepared via molding. In brief, a plate of poly (methyl methacrylate) (35 mm × 35 mm) was obtained using a laser cutting system (Universal Laser System) and drilled by a 5-axis CNC machine (PRODIA M45, Modia Systems) with a square-end mill (diameter 300 μm, Nissin tool) and a conical drill bit (tip diameter < 10 μm, tip taper angle 13.5°, custom-made by DoCraft). A male PDMS mold was obtained by pouring the PDMS into the obtained mold and cured at 80℃ for 2 hr. After that, the male PDMS mold was placed in a disposable cup, and treated with plasma for 1 min, followed by the salinization of Trichloro(1H,1H,2H,2H-perfluorooctyl) silane for 6 hr in a fume hood. Finally, the female PDMS mold was obtained by pouring the PDMS onto the silaned male PDMS, cured at 80℃ for 3 hr, detached and trimmed (**Fig. S2**). After that, the monomer stock solution was prepared as a mixture of glycidyl methacrylate (GMA, 10 mL, 73.3 mmol), trimethylolpropane trimethacrylate (TRIM, 5.23 mL, 16.4 mmol) and triethylene glycol dimethacrylate (TEGDMA, 15.7 mL, 57.6 mmol). The porogen solution was prepared by mixing polyethylene glycol (PEG, 10 kDa, 5.0 g, 2 mmol) with diethylene glycol monomethyl ether (DEG, 100 mL). Both monomer solution and porogen solution were thoroughly dissolved overnight at 65℃ using a hot plate. After that, the monomer and porogen solution (11:9 in volume) with the addition of 1 wt% Irgacure 184 were mixed, followed by vortexing, stirring and bathing at 37℃ for 15 min, which was then poured into the female PDMS mold and photopolymerized by UV irradiation at 365 nm for 3 hr. Finally, the polymerized microneedles were gently peeled off, and the porous microneedle was obtained by immersing the microneedle into the ethanol/water (1:1 in volume) and stirring at 60℃ for 24 hr and drying (**Fig. S3**). The porosity of the naked PMN was estimated based on the equation below:

$$Porosity = \frac{V_{pore}}{\frac{W_{dry}}{d} + V_{pore}} \quad \text{(Eq. S1)}$$

where W_{dry} (g), d (g cm^{-3}), and V_{pore} (cm^3) are the weight of the dry PMN, the density of solid PGMA without pore, and the pore volume of the PMN, respectively. The V_{pore} (cm^3) was calculated from the difference of weight of PMN dried and filled with DI water.

Mechanical strength test

The PMN was placed on the stage of the force gauge stand with the tip of the needle facing upward and the tip of the needle was deemed as the origin of the force gauge. A metal jig was pushed from above onto the tip of a microneedle at a rate of 5 mm/min. A force gauge recorded the force on the metal jig and displacement, and fracture force was defined as the force where the inflection point was observed reflecting the deformation of the needle tip.

Fabrication of hydrogel filled tube for electroosmosis flow generation

Briefly, 2-Acrylamido-2-methyl-1-propanesulfonic acid sodium salt (NaAMPS) and (3-Acrylamidopropyl)trimethylammonium chloride (APTAC) were employed as an anionic hydrogel monomer and a cationic hydrogel monomer, respectively. The pre-gelation PBS solutions (1.0 M monomer (NaAMPS or APTAC), 4 mol% MBAAm and 1 wt% Irgacure 2959) were filled into the silicon tubes (3 mm diameter and 100 mm length) to make the center of the tube with 60 mm monomer solution of each monomer solution, followed by photopolymerization with UV irradiation for 4 hr. The gel-filled tube was immersed in PBS solution for more than 6 hours to swell the hydrogel.

Integration of porous microneedle and hydrogel electroosmotic pump

A drug reservoir was designed to integrate porous microneedle and hydrogel pump. First, a 3D model of drug reservoir was created using 3D-CAD software (SOLIDWORKS; Dassault Systèmes SolidWorks Corporation). The triethylene glycol dimethacrylate (TEGDMA) resin was prepared with the addition of Omnirad 819 (1% w/w), a photoinitiator, and 2-Isopropylthioxanthone (1% w/w), a photosensitizer. After that, the mixture was wrapped in aluminum foil to protect it from light and stirred for 4 hours using a magnetic stirrer with a hot plate (60°C, 60 rpm) to dissolve it completely. Based on the 3D model created, the drug reservoir was printed from the TEGDMA resin using a DLP 3D printer (QIDI TECH Shadow 5.5 S 3D Printer, QIDI Technology Co.Ltd) and the excess resin was washed away with 95% ethanol and cured by irradiation with a UV lamp for 5 minutes. The PMN was then mounted to the A/C-hydrogel combination tube pump (outer diameter: 5 mm) using the drug reservoir and the peripheral side of the PMN substrate was shielded with a resin glue to prevent liquid leakage.

Evaluation of water flow and FITC-dextran transportation using Franz cell

For the evaluation of water flow, the integrated device was mounted to the Franz cell. The resulting device was bound to a receiver cell equipped with a horizontal capillary to evaluate the water ejection via the PMN quantitatively. The transport of dextran was evaluated by using a receiver chamber handmade from acrylic plates and silicone sheets. The receiver chamber was previously filled with 1.5 mL PBS solution. During the current application to the pump, a 100 μL portion was sampled from the receiver chamber at 5 min intervals. The sample analysis by a microplate reader (FluoroscanAscent, Thermo Fisher Scientific, MA, USA) used the excitation and emission wavelengths of 485 nm and 525 nm, respectively.

Parylene C coating of porous microneedle

The fabrication process of PMN was optimized with coating of parylene C before the elution of porogen (PEG). The coating of parylene C was based on chemical vapor deposition technique performed by a deposition system (SCS Labcoter 2 Parylene, Specialty Coating Systems Inc.) until the deposition thickness became ca. 2 μm. To mask the needle tip and prevent it from the parylene C coating, the needle tip of PMN was pressed using a 20 g weight onto a PDMS sheet. After that, the porogen (PEG) was eluted with 60 °C ethanol/water (1:1 volume) for 12 hr to obtain the parylene C coated PMN.

Transdermal delivery of FITC-dextran using pig skin

The pig skins (thickness: ~4 mm) with epidermis, dermis, and hypodermis (Landrace swine, 6-month-old, castrated males, not pigmented, DARD Corp., Tokyo, Japan) were transported with ice cooling at ~0 °C without freezing and stored in a refrigerator at 4 °C. The PMN device was pressed against a pig

skin, and the PBS solution containing 5 mg/mL FITC-dextran was injected for 30 min at 5 mA. The specimens were immediately frozen with liquid nitrogen and sliced into 40 μm sections using a cryostat (CM1950; Leica Biosystems, Tokyo, Japan) for cross-sectional observation by a fluorescence microscope.

Statistical analysis

All experiments were carried out multiple times (more than three times), and the data was presented as mean ± standard deviation (SD). Statistical analysis was carried out using Microsoft 365 Excel.

Figures

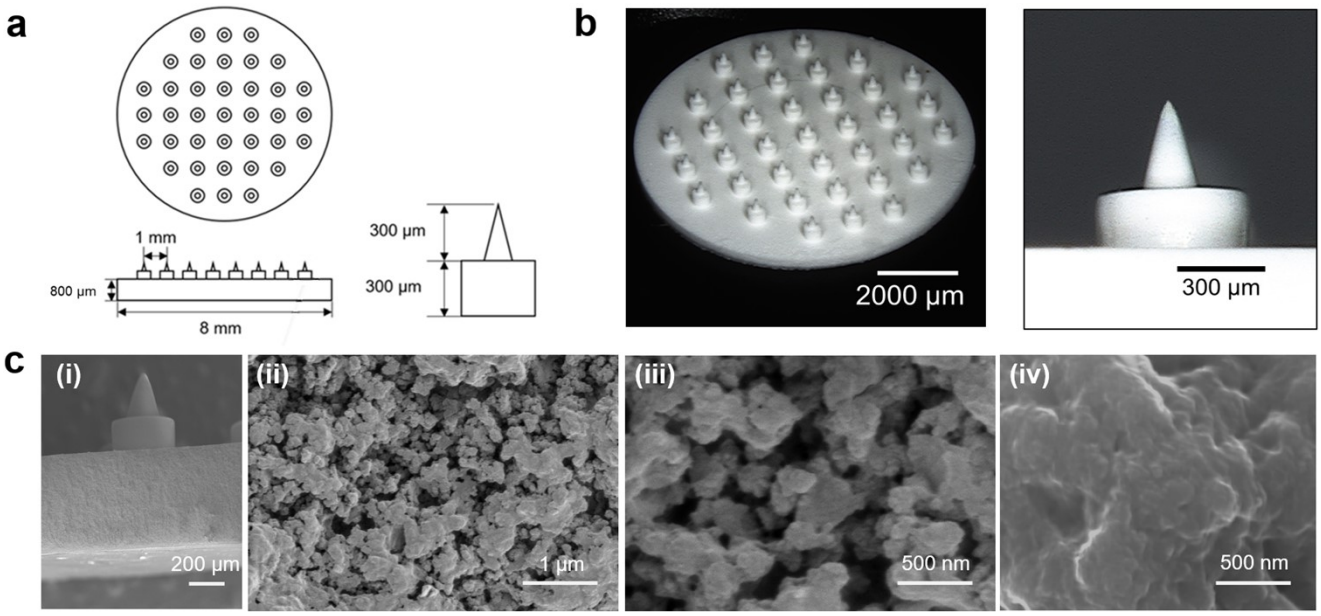

Fig. S1 Characterization of porous microneedles. (a) Sketch diagram indicating the dimension of porous microneedle (PMN) (b) Optical images of PMN. (c) SEM images of the entire microneedle (i); interconnecting voids (ii and iii); and PMN without porogen elution (iv).

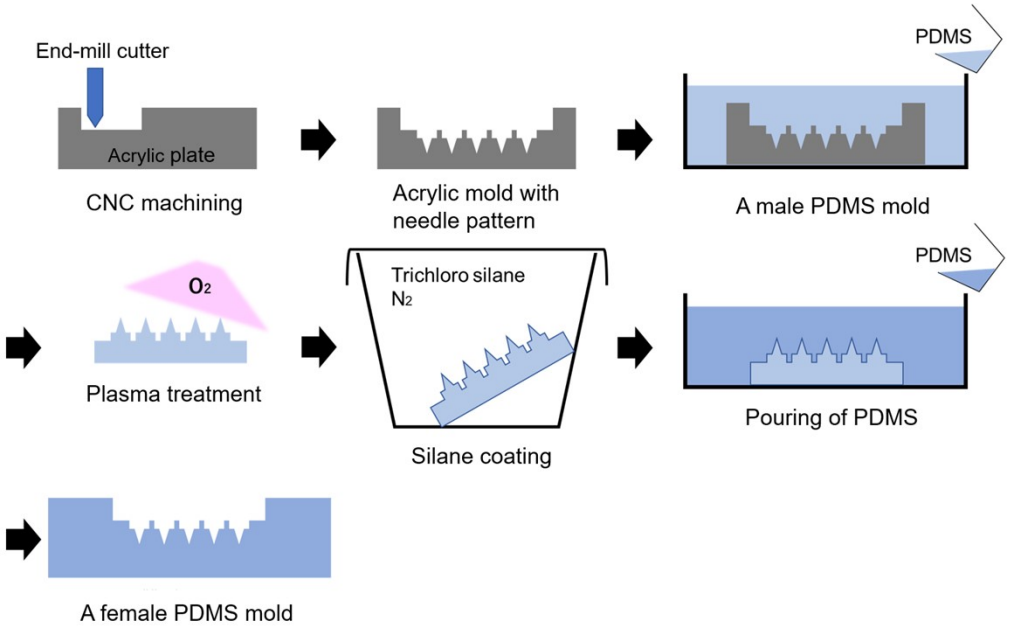

Fig. S2 Fabrication of female PDMS mold for porous microneedle.

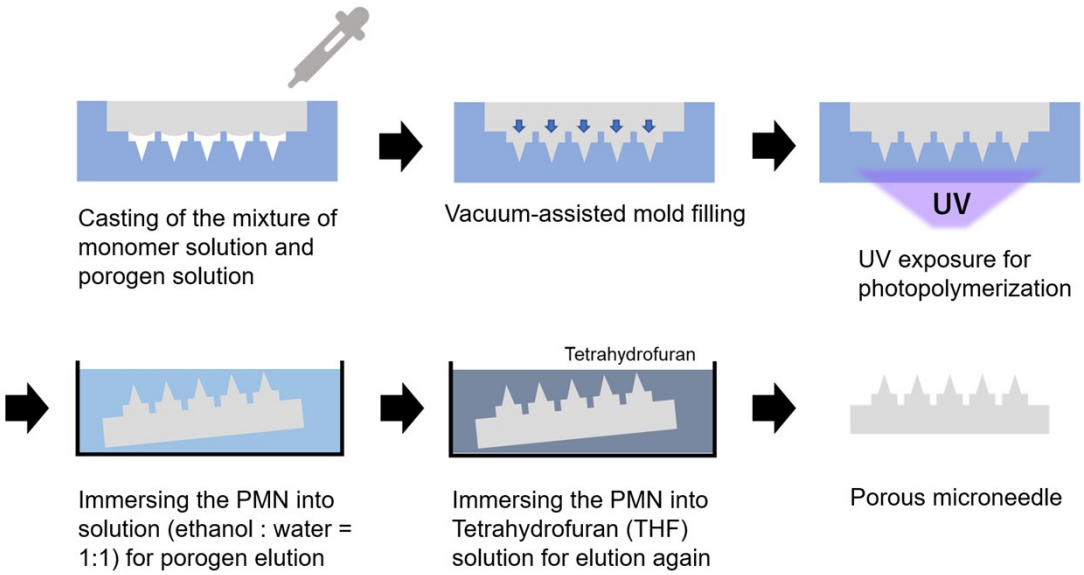

Fig. S3 Fabrication of porous microneedle.

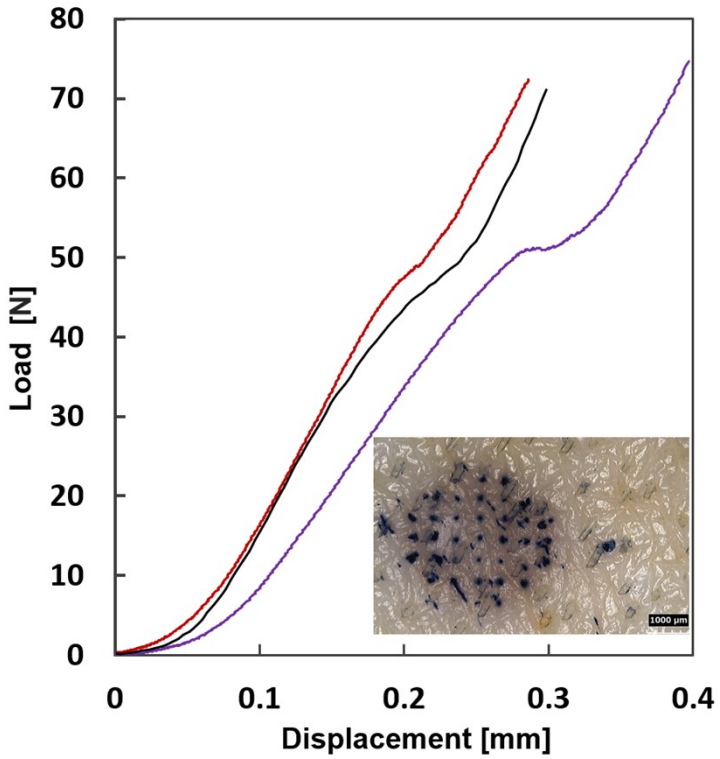

Fig. S4 Force-displacement curves of three samples of the PMN, indicating that the PMN can withstand around 40 - 50 N which is sufficient for the insertion into skin without fractures. The insect figure shows the surface observation of a pig skin after application of a PMN with a pressure of 30 N.

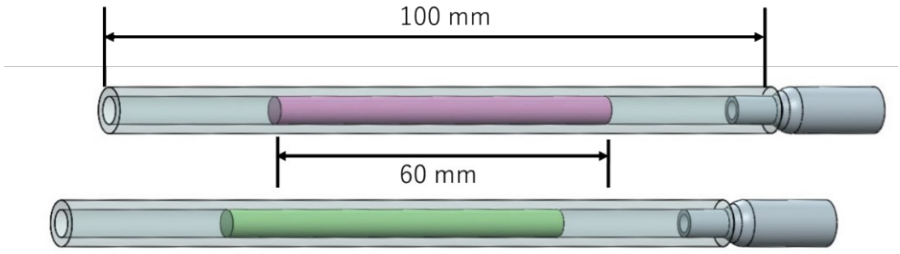

Fig. S5 Fabrication of anionic (Purple) and cationic (Green) hydrogel filled silicon tube. The filled length of the monomer solution is around 60 mm in center to prevent the leakage of hydrogel after swelling.

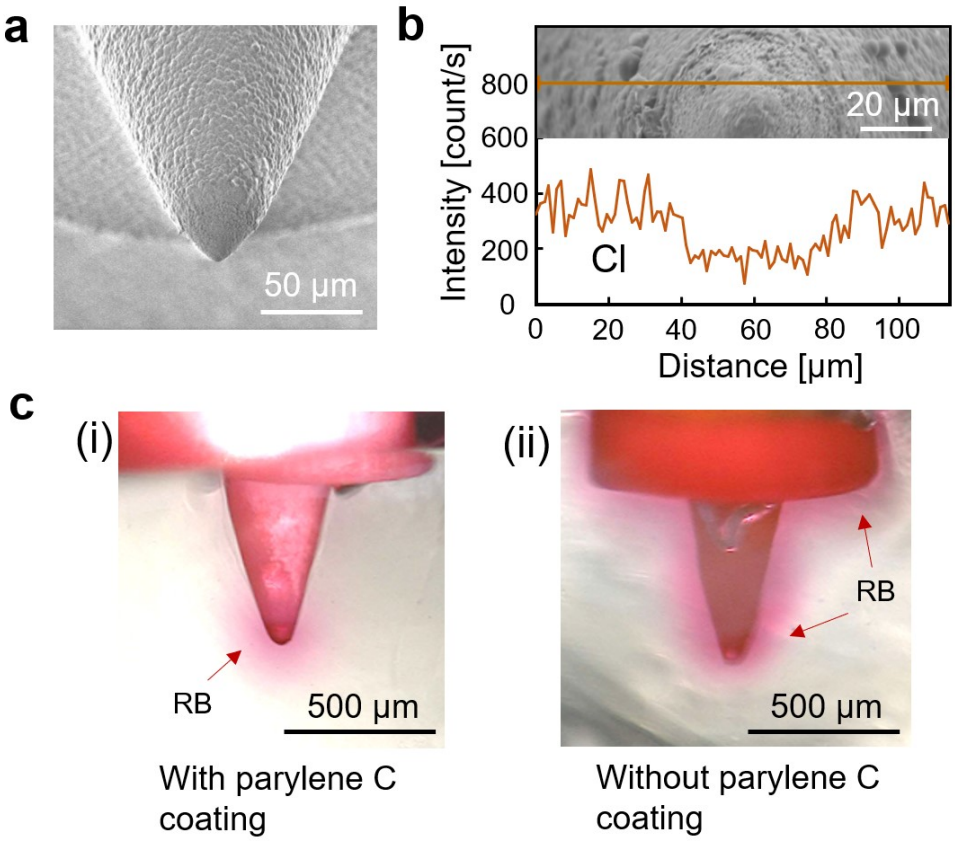

Fig. S6 Characterization of parylene C-coated porous microneedle. (a) SEM image of the covered area of a microneedle. (b) Energy Dispersive X-ray (EDX) spectrometry analysis along the brown line and the graph showing the intensity of Cl signal. (c) Release of Rhodamine B dye (RB) into a gellan gum hydrogel for 30s from (i) PMN with parylene C coating and (ii) PMN without parylene C coating, indicating that the protective function of parylene C layer.

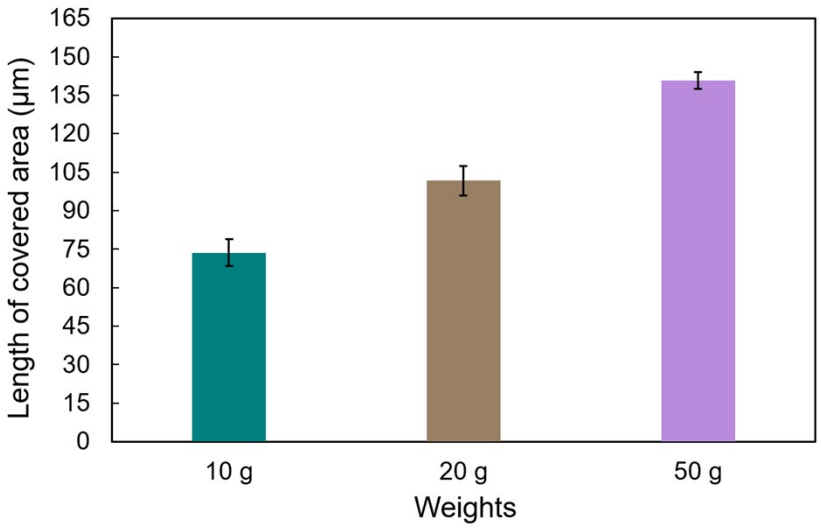

Fig. S7 The lengths of cover areas with varying weights (10 g, 20 g and 50 g; n = 3).