Supplementary information for

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S1. Calculations for membrane puncture

The actuation of the inflatable membrane herein relied solely on the pressure difference between the drug reservoir and the air chamber within the device. To calculate the number of moles of air in the air chamber, the ideal gas law was applied as follows:

$$n = \frac{PV}{RT},$$

where P is the pressure (1 atm), V is the volume of the air chamber (26.02 mm^3), R is the ideal gas constant (0.0821 L·atm/(mol·K)), and T is the temperature (37 ℃, 310.15 K). Using these values, the air chamber initially contained approximately 1.02 μmol of air. Assuming complete and equimolar reaction between ascorbic acid and sodium bicarbonate in the effervescent tablet of 4.32 mg, 10.22 μmol of CO_2 was generated via the effervescent reaction. After CO_2 generation, the total number of moles increased to 11.24 μmol. The ideal gas law was then applied again to calculate the pressure of the air chamber after the reaction and the final pressure of the air chamber P_{final} was found to be 11.02 atm. Therefore, the pressure difference between the drug reservoir and the air chamber (ΔP) right before the actuation was found to be:

$$\Delta P = P_{final} - P_{drug\ reservoir} = 11.02\ atm - 1\ atm = 10.02\ atm \approx 1.02\ MPa.$$

Given the needle holder's base area of $A_{needle\ holder\ base}$ = 5.82 mm^2, the total pushing force on the needle could be calculated as:

$$F_{push} = \Delta P \times A_{needle\ holder\ base} = 1.02\ MPa \times 5.82\ mm^2 \approx 5.93\ N.$$

Next, the stress applied by the needle on the sealing membrane was evaluated. Considering the tolerance of the laser-cutting technique, the cut length of the needle tip could be l_c = 0.05 mm. Given that the thickness of the metal plate used to prepare the needle was t = 0.2 mm, the needle tip area was:

$$A_{tip} = l_c \times t = 0.05\ mm \times 0.2\ mm = 1 \times 10^{-8}\ m^2.$$

Thus, the resulting local stress on the sealing membrane was calculated as:

$$\sigma = F_{push}/A_{tip} = 5.93\ N/(1 \times 10^{-8}\ m^2) = 593\ MPa.$$

Given that the typical ultimate tensile strength of titanium ranges from 264 to 385 MPa [1, 2], the applied stress of 593 MPa should be sufficient to fracture the membrane. Therefore, under these conditions, puncture of the membrane is expected to occur.

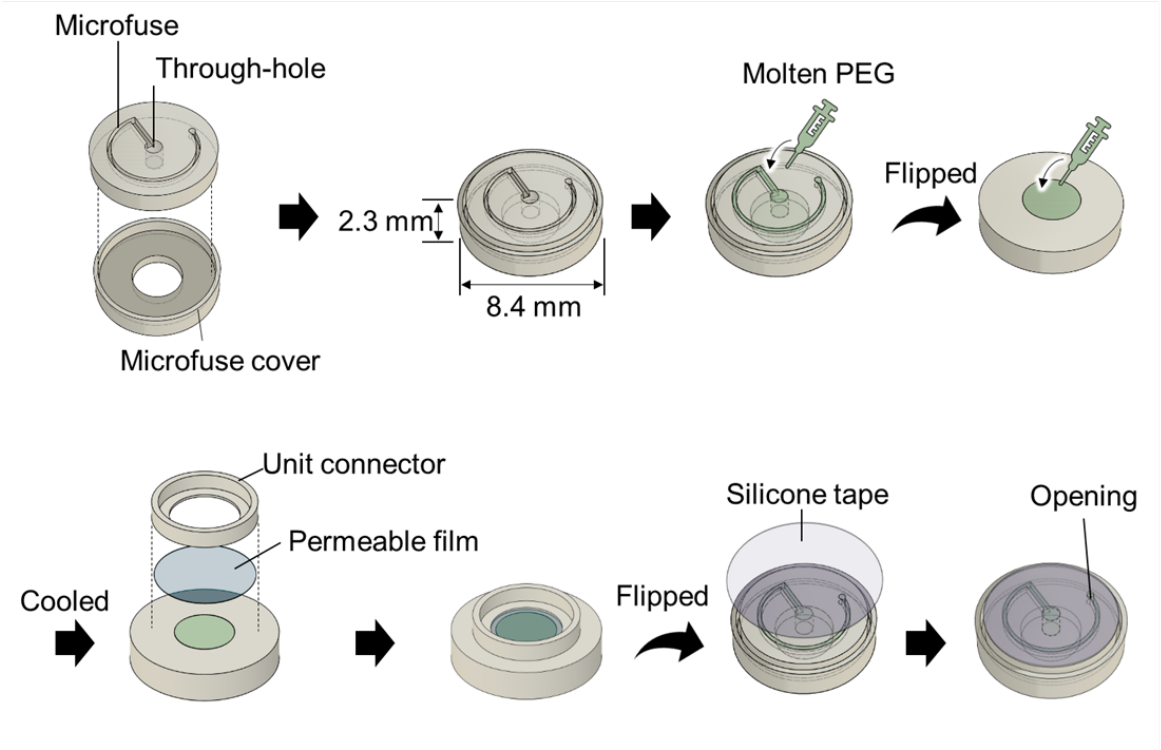

Figure S1. Detailed schematic description of delay unit fabrication.

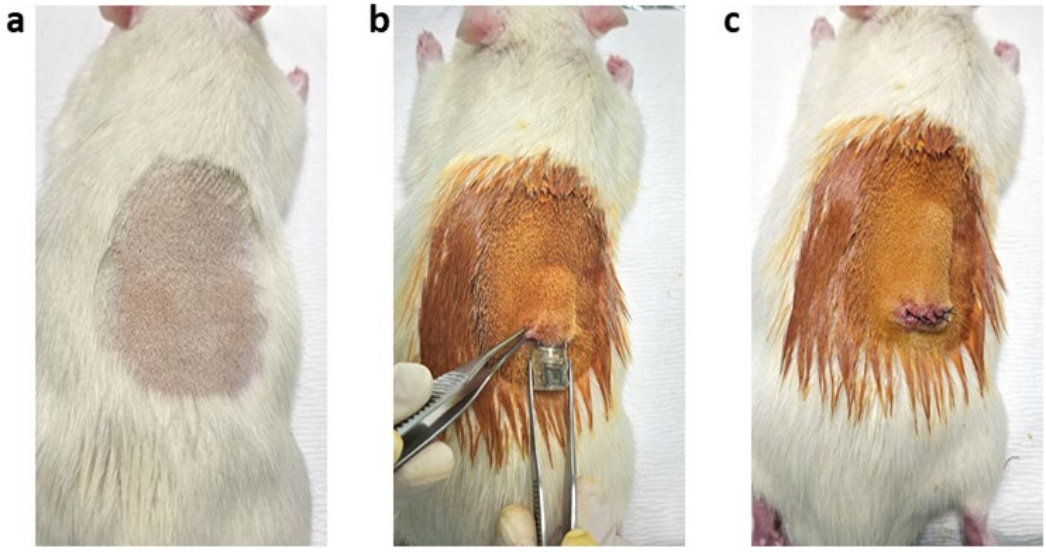

Figure S2. Surgical procedure of FUSED implantation. (a) The animal was anesthetized by isoflurane inhalation, and the hair on the dorsal area was shaved and cleaned with betadine. (b) Through a 1-cm incision made on the bare skin, the FUSED was implanted into the subcutaneous pocket. (c) The incision was sutured and disinfected with betadine. Finally, gentamicin (10 mg/kg) was given to the animals by intramuscular injection.

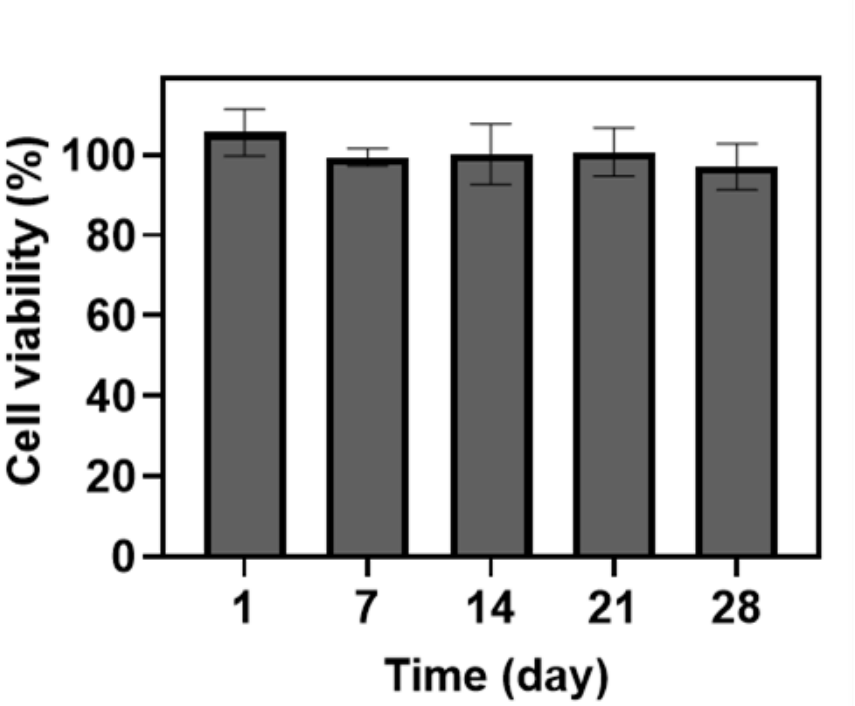

Figure S3. Cytotoxicity evaluation results of the device using L929 fibroblasts, which exhibited no cytotoxic effect. Error bars represent the standard deviation (*n*=4). For this evaluation, a blank set with MF270 was immersed in RPMI 1640 medium supplemented with 10% fetal bovine serum, 100 units/ml penicillin, and 100 μg/ml streptomycin at 37 °C in a humidified atmosphere containing 5% CO_2. On days 1, 7, 14, 21, and 28, the medium was completely collected and replaced with an equal volume of fresh medium. The same type of medium was used to culture L929 cells, which were seeded in a 96-well plate at a density of 10,000 cells per well. After 24 h of incubation under the same conditions, 100 μl of the collected medium was added to each well, followed by an additional 24-h incubation. The medium in each well was then replaced with fresh medium, and 10 μl of Ez-Cytox reagent was added and incubated for 2 hours. Absorbance was measured at 450 nm and 600 nm using a microplate reader. Cell viability was calculated using the following equation: cell viability (%) = (absorbance at 450 nm of the treated well – absorbance at 600 nm of the treated well) / (absorbance at 450 nm of the untreated control well – absorbance at 600 nm of the untreated control well) × 100.

References

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