

Electronic Supplementary Information (ESI)

Point-of-care Detection and Real-time Monitoring of Intravenously Delivered Drugs via Tubing with an Integrated SERS Sensor

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Fabrication of PNA substrates

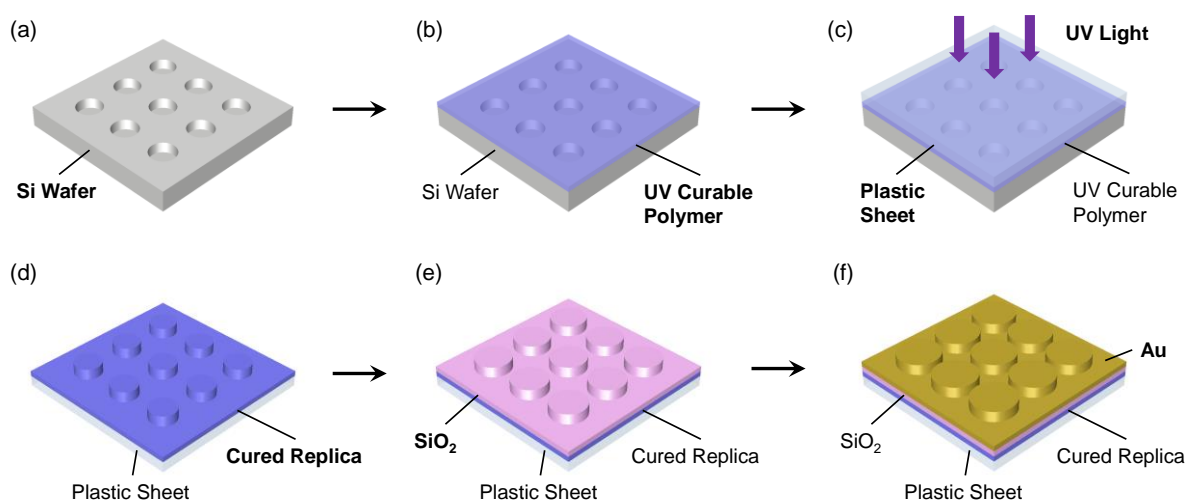


Fig. S1 Schematic illustration of the nanoreplica molding process. (a) Fabrication of silicon master wafer template with two-dimensional array of circular holes using nanoimprint lithography, followed by reactive ion etching. (b) Uniform distribution of liquid-state UV curable polymer on the silicon master wafer. (c) Placement of PET sheet and exposure to UV light for rapid polymer solidification. (d) Release of the PET sheet, resulting in a polymer replica of the silicon wafer structure adhering to the PET substrate. (e) Deposition of SiO₂ on the replicated surface by electron-beam evaporation. (f) Deposition of Ti/Au using electron-beam evaporation.

An 8-inch silicon wafer was patterned with a two-dimensional array of circular holes (period = 400 nm, diameter = 250 nm, and depth = 130 nm) using nanoimprint lithography (Molecular Imprints), in which an 8×12 array of $8 \times 8 \text{ mm}^2$ die, containing the hole arrays, were stepped and repeated every 1 cm in the x and y direction. The patterned silicon wafer was treated with dimethyl dichlorosilane (GE Healthcare) solution for the purpose of facilitating release of cured polymer replica as a reusable molding template. In order to form the negative shape of the features of the silicon mold template, a total volume of $\sim 500 \text{ }\mu\text{L}$ liquid curable polymer (Gelest) droplets was dispensed onto the template surface and then evenly distributed between the silicon wafer and a 200- μm -thick flexible polyethylene terephthalate (PET) sheet by using a Teflon roller. The liquid polymer was then cured to a solid state by exposure to UV light at room temperature and the molded structure was subsequently released from the silicon wafer by peeling off the flexible PET sheet, resulting in a polymer replica of the silicon wafer structure adhering to the PET substrate. To minimize the separation distance between adjacent polymer cylinders, 70 nm of SiO_2 was conformally deposited over the surface of polymer cylinders, followed by a 10 nm Ti adhesion layer and a 180-nm-thick Au film using electron beam evaporation system (Temescal), to complete the device. The SEM image of the resulting PNA structure is shown in Figure 1(b) in the text.

Fabrication of the flow cell integrated with a PNA SERS substrate

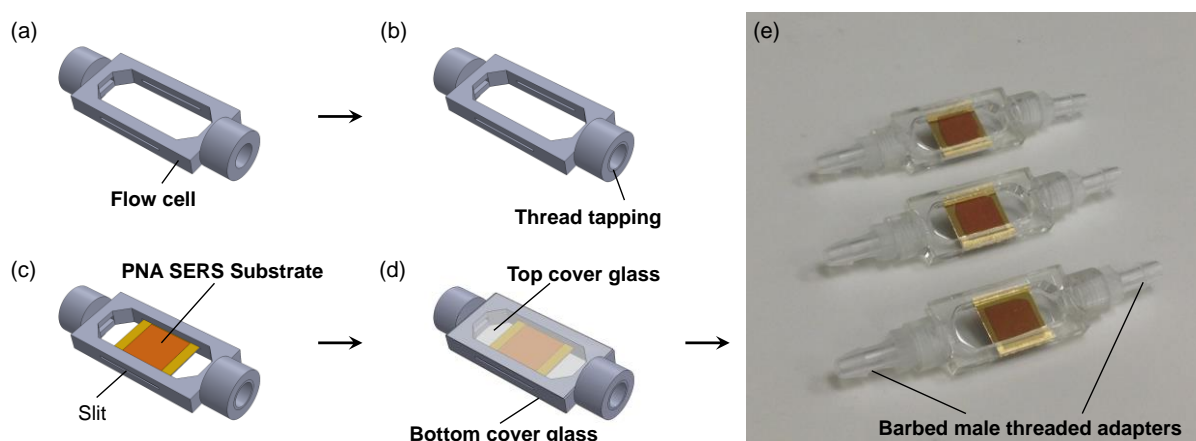


Fig. S2 Schematic representation of the flow cell with an integrated PNA SERS substrate. (a) Design and fabrication of the flow cell using 3D CAD software, SolidWorks (Dassault Systems, France) and a stereolithography system. (b) Tread tapping of two cylindrical openings by a tap wrench. (c) Insertion of PNA SERS substrate into the middle slit of the flow cell with UV-cured adhesive and exposure to UV light. (d) Successive attachment of top and bottom cover glass to flow cell surfaces with the same UV-cured adhesive by exposure to UV light. (e) Screw-in barbed male threaded adapters for connection to biomedical tubing as an in-line SERS sensor.

FDTD simulation

3D finite-difference time-domain (FDTD) simulation was performed to simulate the optical responses of the PNA structure using a commercial software package (FDTD solution, Lumerical Inc. Vancouver, Canada). The PNA structure with a water superstrate was illuminated with a normally incident, unit magnitude plane wave propagating in the $-z$ direction with an electric field polarization along the x -axis. The simulation region was set to one unit volume of the periodic PNA structure along with periodic boundary conditions imposed on the sidewalls of the simulation boundary. Perfectly matched layer (PML) boundary conditions were imposed at boundaries along the z direction to properly absorb incident radiation. A uniform fine mesh size of 1 nm (x , y and z directions) was used within the nanogap region. Monitors were placed in close proximity to PMLs to calculate the amount of reflected and transmitted power as a function of wavelength. The optical properties of Au and SiO₂ were respectively taken from Johnson and Christy¹ and Palik's handbook,² and then fit by the multi-coefficient model in the wavelength range from 600 nm to 1000 nm. A homogenous refractive index of water superstrate ($n = 1.327$) and UVCP substrate ($n = 1.46$) were used although they are slightly wavelength-dependent.

Characterization of the scattering volume

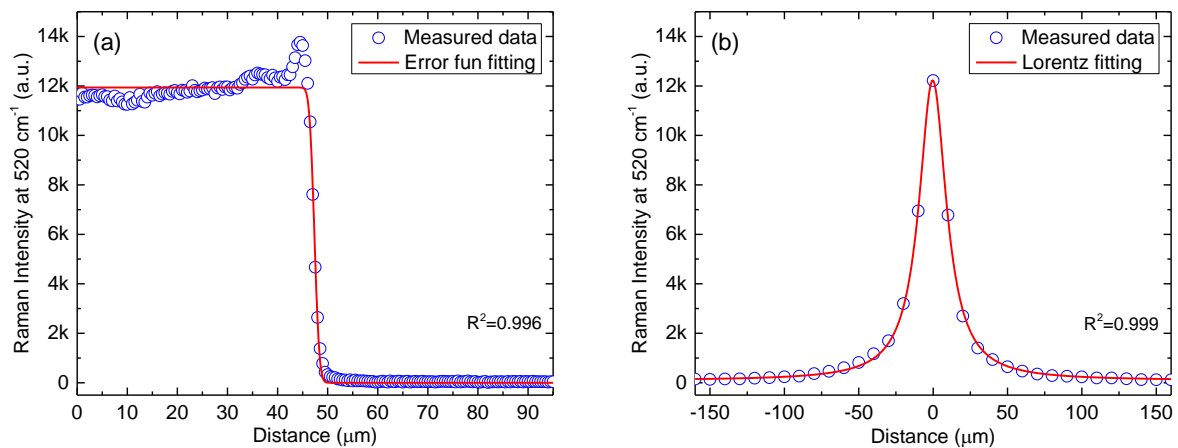


Fig. S3 (a) Silicon Raman intensity at 520 cm⁻¹ as a function of the displacement as the knife edge of silicon wafer was translated across the laser beam.³ A slight overshoot of the intensity stemmed from the additional contribution from the diffracted beam as laser beam is half-way through the knife edge. (b) Silicon Raman intensity at 520 cm⁻¹ as a function of the distance z from the focal plan ($z = 0$). 785-nm laser and a 50× (NA = 0.5) objective was used in both measurements. Measured data were respectively fit to the error function and the Lorentzian function for the calculation of laser spot size and the effective probe length.

For the Raman setup utilized in the present study, the laser spot size (diameter) and the effective probe length were respectively characterized to be 3.13 μm and 44.86 μm . When the laser beam is focused on the surface, the laser probe volume (the detection region) is modeled as a cylinder with a diameter and a height equivalent to the laser spot size and half the effective probe length (22.43 μm).

Detection of diltiazem diluted in DI water and PBS

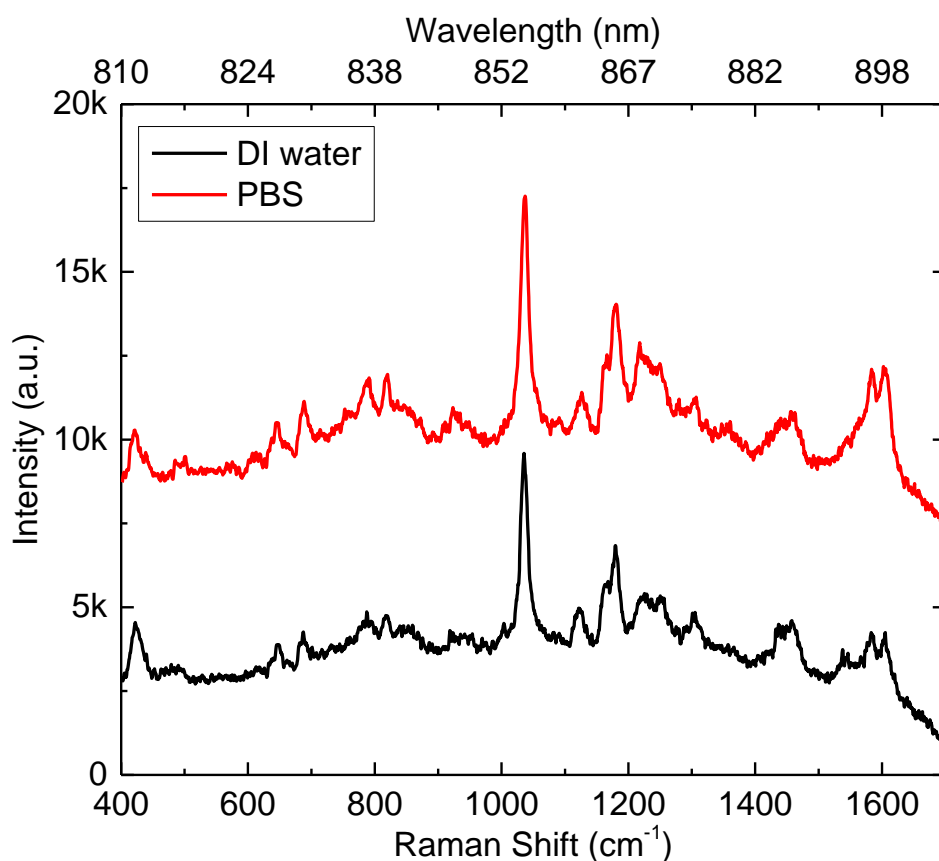


Fig. S4 SERS spectra of 1 mg/ml diltiazem diluted in DI water and PBS. Both spectra show the same profile with a dominant SERS intensity peak located at 1033 cm^{-1} .

References

1. P. B. Johnson and R. W. Christy, *Physical Review B*, 1972, **6**, 4370-4379.
2. E. D. Palik, *Handbook of optical constants of solids*, Academic Press: Orlando, FL, 1985.
3. E. C. Le Ru, E. Blackie, M. Meyer and P. G. Etchegoin, *Journal of Physical Chemistry C*, 2007, **111**, 13794-13803.