Supporting information

Heat-based transdermal delivery of a ramipril loaded cream for treating hypertension

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Experimental details

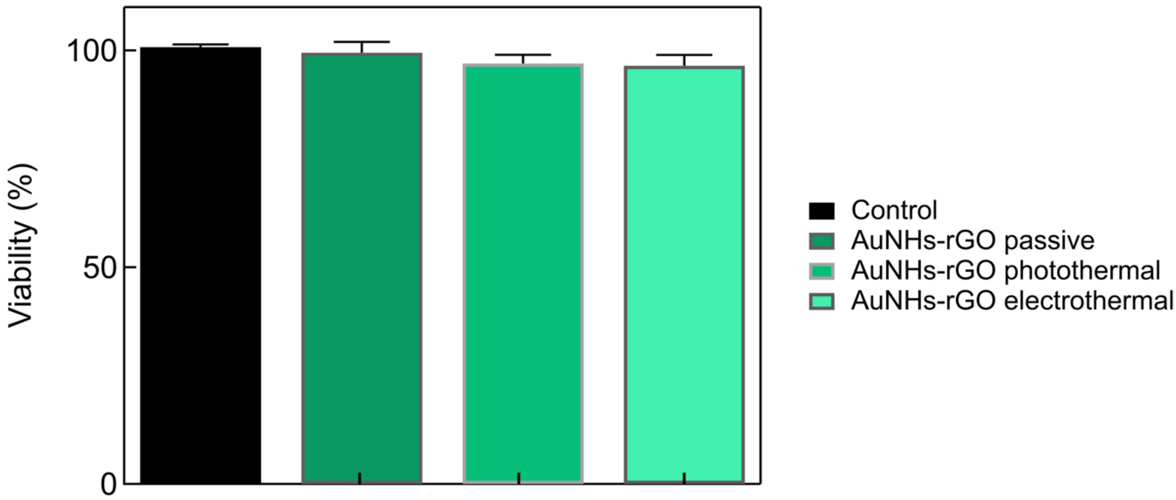

Figure S1. Cell viability of rGO-coated nano-heaters. HeLa cells viability in the presence of rGO-coated nano-heaters (loaded with 5 mg mL^{-1}) without and with heat activation for 10 min either photothermally (1 W cm^{-2}) or electrothermally (1.0 V). Error bars (n=3) represent standard error of the mean (SEM). The HeLa cells, derived from cervical carcinoma from a 31-year old female [ATCC® CCL-2™, ECACC, Sigma Aldrich, Saint-Quentin Fallavier, France], were cultured and maintained in Dulbecco's Modified Eagle's medium (DMEM, Gibco®) high glucose with 2 mM Glutamine, DMEM/F12 media with 2 mM Glutamine and DMEM supplemented with 10% fetal bovine serum (FBS, Gibco®) and 1% penicillin-streptomycin (Gibco®), respectively, in a humidified incubator at 37 °C and 5% CO_2. Cells were seeded at a density of 10^4 cells/well in a 96-well plate and grown for 24 h before assay. The cell viability was evaluated using resazurin cell viability method. Briefly, 1 mL of the resazurin solution (11 µg mL^{-1}) in complete medium was added to each well containing the gel and the plate was incubated for 4 h in the humidified incubator. The fluorescence emission of each well was measured at 593 nm (20-nm bandwidth) with an excitation at 554 nm (18-nm bandwidth) using a Cytation™ 5 Cell Imaging Multi-Mode Reader (BioTek Instruments SAS, France). Each condition was replicated three times.

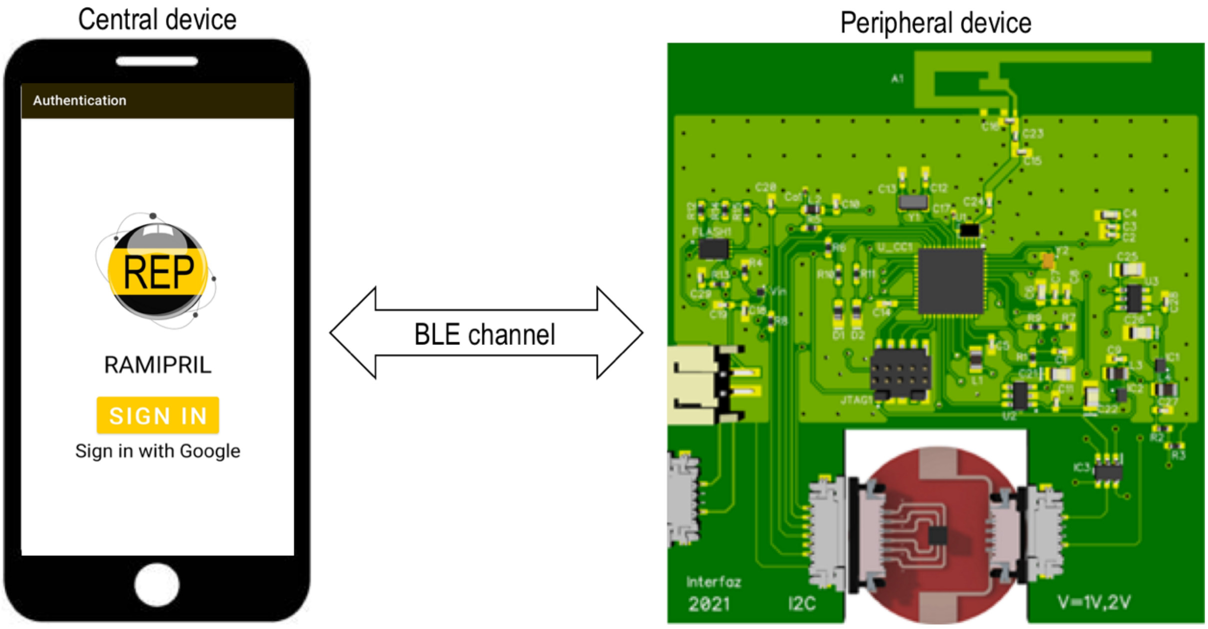

Figure S2. Central and peripheral devices. The electronic system considered for wireless control (BLE – Bluetooth low energy) in this application consists of a peripheral device (the electrothermal patch and the associated electronic board, right) and a central device (the smart phone, left). It allows straightforward qualification of electrothermal patches before and after use.

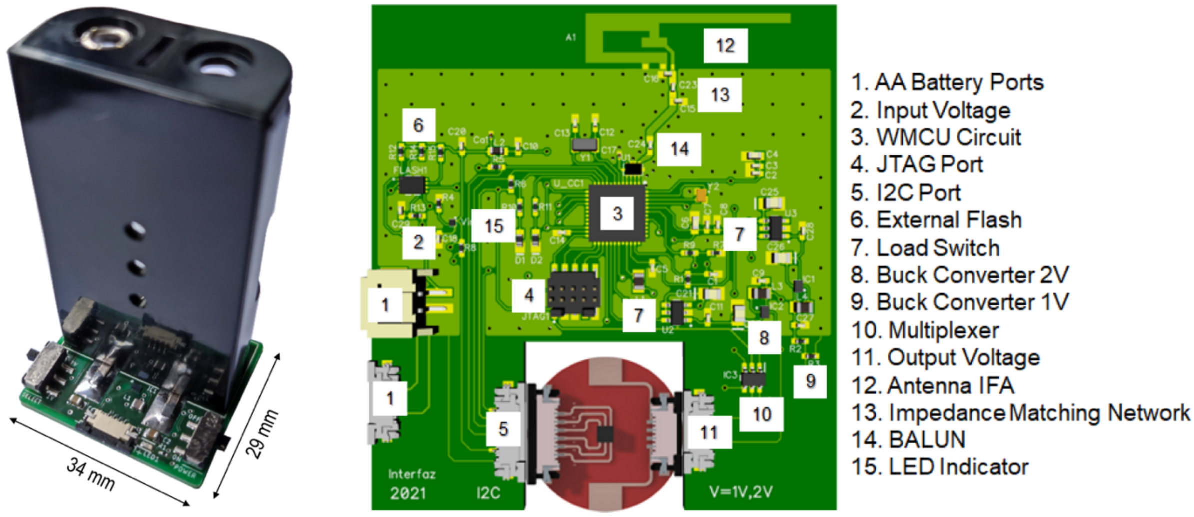

Figure S3. Details of the power module and the peripheral device. (right) The SimpleLink® CC1352R wireless microcontroller unit (WMCU) is the main component of the peripheral device, which can be programmed on-board through the Texas Instruments XDS110 JTAG debug probe. The WMCU has a 32-bits 48 MHz Arm Cortex-M4F central processor unit (CPU). The CC1352R includes a radio-frequency (RF) module that contains an Arm Cortex-M0 processor; it manages data from and to the CPU core. It is multi-protocol and multi-band, offering sub-1 and 2.4 GHz capabilities. It is commonly used in medical devices due to low-power and connectivity requirements. It supports a wide voltage range from 1.8 to 3.8 V. Here it is powered with 3 V using by two batteries AA of 1.5 V each one. A central function of the printed circuit board (PCB) is to enable readout from the 16-bit temperature sensor TMP116, which is placed on the electrothermal patch. It operates in the temperature range, according to the data sheet, from -55 to 125°C. The communication between the WMCU and TMP116 is through Inter-Integrated Circuit (I2C) protocol. The TMP116 reads continuously the temperature from the patch and the WMCU receives the data from the temperature sensor. The received data are shown in real-time in the smart phone, which acts as a display. The inverted-F antenna (IFA) and the balanced/unbalanced (BALUN) filter are used for Bluetooth communication. At the same time, the WMCU monitors that the patch temperature is always below 52°C. Light emitting diode (LED) indicators are used to indicate the status of the bias voltage – ON/OFF. If the temperature is greater than 52°C, the WMCU deactivates the output voltage. (left) After the quality testing and temperature profile calibration, the electrothermal patches can be used directly (via flat flexible cables) in conjuction with a simpler and compact PCB that provides regulated bias voltage by employing two AA batteries.

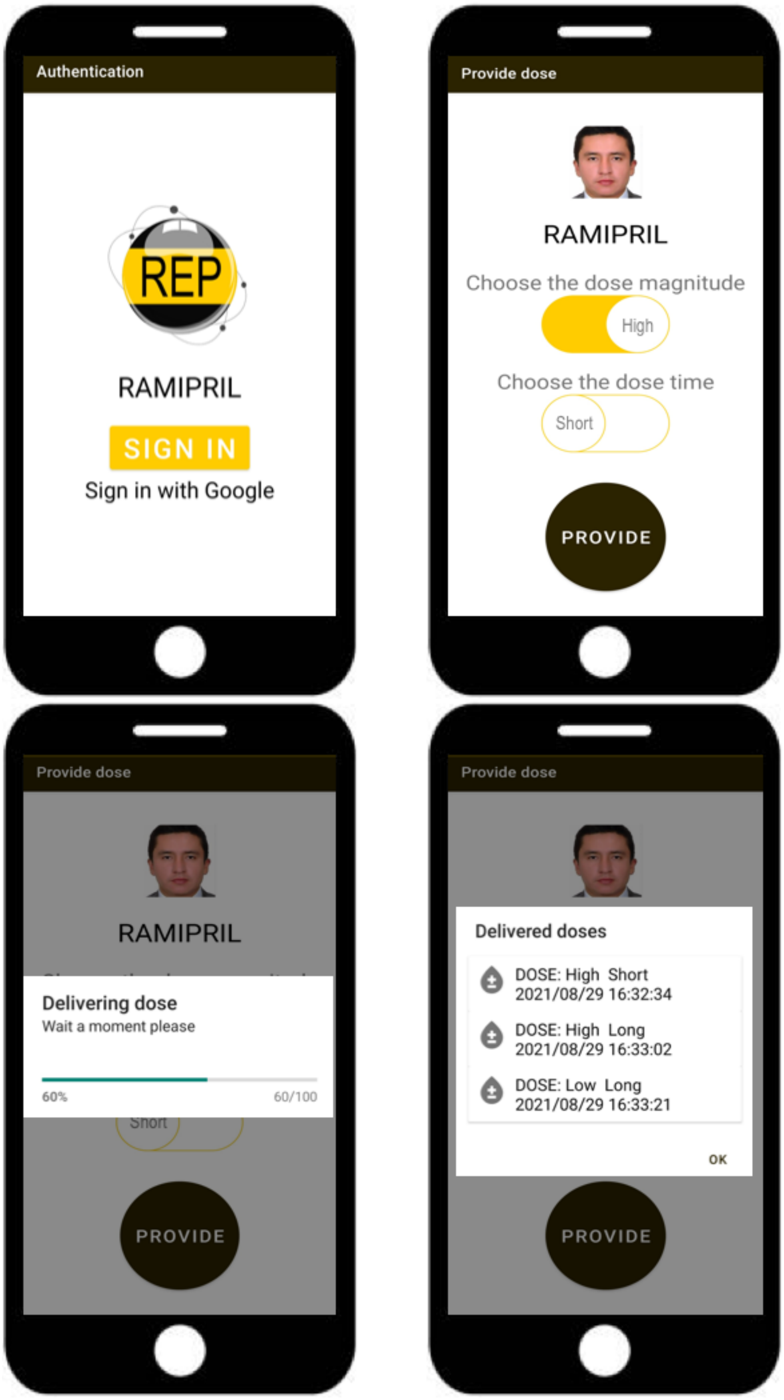

Figure S4. The REP App communicates with the electronic board. The REP App can manage the electrothermal patch through an electronic board. The left top photograph shows the home screen, where the user must login. The right top photograph shows the main screen, where the parameters for the dose should be chosen (essentially pulse height and length). The left bottom photograph shows the delivery screen, where drug delivery is ongoing. The right bottom screen shows the history screen, with the recordings of the delivered doses.

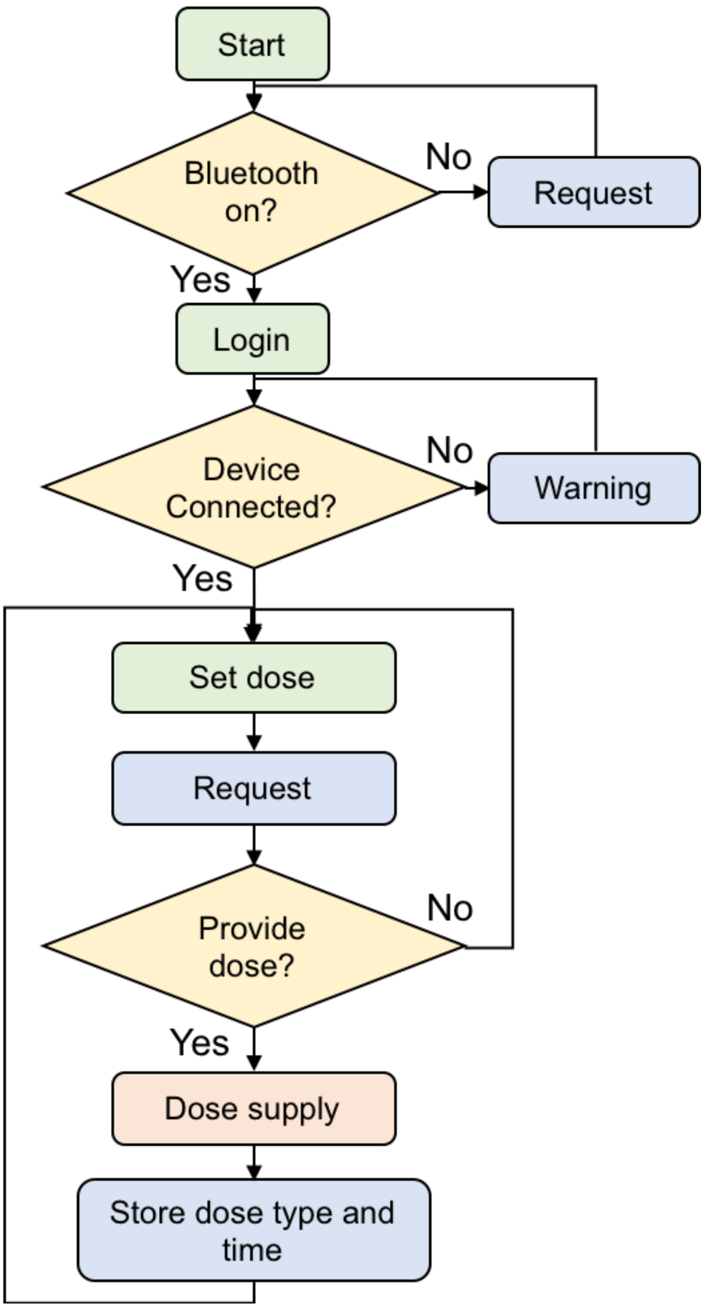

Figure S5. Flowchart of the REP App. The flowchart used in the design of the user interface for the mobile application is shown. At the beginning, the user needs to log into the App with a user name and a password. If the login is correct, the App is linked directly with the electronic board. Afterwards, the user can select the dose parameters, before pressing the activation button. Once the user presses the activation button the output voltage will be enabled according to requested parameters, allowing the drug delivery. When the activation button is pressed the App will also start to record the shape of the electrical pulse and the temperature profile (limited to maximum 52°C). The REP App provides a user-friendly interface to interact with the electrothermal patch from the smart phone through Bluetooth protocol.

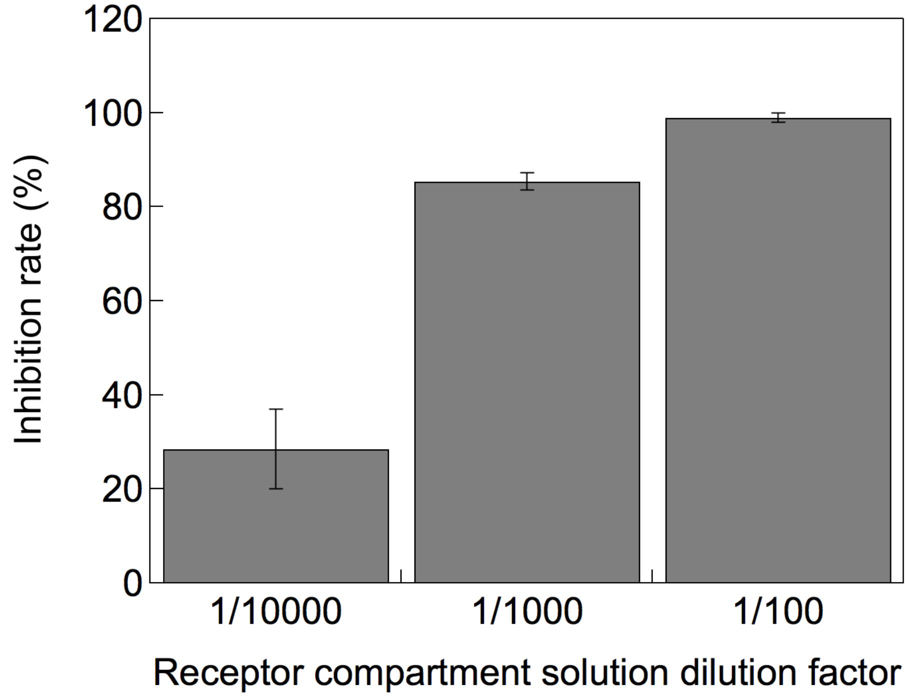

Figure S6. *In vitro* activity of ramipril after skin crossing. ACE inhibition rate as a function of the dilution factor of the Franz cell's receptor compartment solution.