A Fully-Integrated Wireless Ingestible Drug Delivery Chip with Electrochemical Energy Harvesting and pH-Based MPPT

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Advances in personalized medicine are spurring the development of ingestible electronics for controlled, on-demand drug delivery in the gastrointestinal (GI) tract, enhancing therapeutic efficacy further beyond traditional oral pills. These systems rely on electronically controlled drug release actuation mechanisms, like micro-pumps [1] and reservoir-based designs [2], for precision dosing [3], [4]. However, they often require substantial energy and space [5]. While conventional batteries have powered ingestible electronics, they pose challenges due to their bulkiness, limited energy density, and safety risks associated with toxic materials [6], [7]. Consequently, battery-free energy harvesting solutions and energy-efficient drug delivery actuation mechanisms are crucial for progress in this field. Among other energy-harvesting methods, such as thermal or vibrational energy harvesters, a galvanic cell (GC), which converts chemical energy from acidic GI fluid, is particularly well-suited for high-power applications like drug delivery [6]. However, the maximum power point (MPP) of GC is a nonlinear function of pH and open-circuit voltage [2], necessitating the sampling of real-time pH data of the GI fluid to perform maximum power point tracking (MPPT) for efficient energy harvesting. For drug delivery, a reservoir-based system sealed with an electrochemically dissolvable metal membrane offers a compact design and protection of sensitive payloads such as unstable drugs from the harsh environment of the GI tract [2], [8]. However, the activation voltage for dissolving the metal membrane of the reservoir-based systems also varies with pH, further highlighting the need to sample the GI pH in real-time [9].

To address these challenges, we present a fully integrated, battery-free ingestible chip that enables wirelessly controlled, on-demand drug delivery, adaptable to spatiotemporal pH variations within the GI tract, as shown in Fig. 1. Our system detects the pH of surrounding GI fluid, performs MPPT, and dynamically adjusts the drug delivery voltage bias to optimize both energy harvesting and drug release. The device features a 13.56 MHz RF communication interface for wireless drug delivery control. The system supports various clinical scenarios with three drug delivery modes: Burst, Balanced, and Low-Energy Dissolution. Burst mode applies maximum voltage to the metal membrane, enabling rapid drug release within 10 minutes for emergencies like seizures or opioid-related incidents. Low-Energy Dissolution mode reduces energy usage by 80% compared to Burst, extending device lifespan for long-term treatments such as antibiotics or birth control. Balanced mode provides moderate energy use and dissolution time, suitable for general applications. To our knowledge, this is the first battery-free ingestible electronic device that integrates energy harvesting with MPPT based on GI pH and RF-triggered drug release in a single, compact platform.

Fig.2 illustrates the system architecture. Energy harvested by the GC powers up the chip. The power-management unit (PMU) consists of a reconfigurable switched-capacitor power converter (SCPC), which charges an off-chip capacitor (C_{store}) and two low-dropout regulators (LDOs) to provide stable supplies to the pH monitoring, receiver chain, non-overlapping (NOL) clock generator, and hysteresis control circuits. An off-chip coil captures incoming RF signals, decoded by the receiver chain to trigger the drug chamber membrane dissolution, adjust its speed ,and stop it. The hysteresis controller generates the DISSOLVE_EN signal which controls the switch S_{mem} to toggle the system between the duty-cycled operation of dissolution and charging periods.

To design the key building blocks within the IC, the GC and the drug reservoir membrane were initially characterized in the electrolyte solution that mimics the GI environment. We measured the MPPs for the GC and the voltage ranges to dissolve metal membrane at different pH in simulated gastric fluid (SGF) (Fig. 3). Load-pull and cyclic voltammetry techniques were used for the GC and membrane characterization, respectively. Based on these measurement results, we used a reconfigurable SCPC (Fig. 3) with different branches running at various clock frequencies, enabling energy harvesting at MPP at each pH. Additionally, a hysteresis controller with three distinct hysteresis windows (Fig. 3) was designed to regulate the bias voltage at the metal membrane (hysteresis window for V_{out} during metal dissolution), enabling a higher voltage hysteresis window for balanced mode and smaller for low-energy dissolution mode, at each pH. Fig. 3 shows the table of the SCPC branch configuration, hysteresis window (labeled as HYS) for V_{out} during metal dissolution, and clock frequency for each pH and dissolution speed case. The digital controller in Fig. 2 performs the reconfiguration of the SCPC and selects the hysteresis window, mapping them to the values on the table, based on the real-time GI pH reading and the received RF commands.

The proposed self-powered drug delivery IC was fabricated in 65 nm CMOS process, occupying a core area of 6 mm^2 (Fig. 7). The ex-vivo measurement setup and galvanic cell with zinc and gold electrodes (3 mm x 30 mm each) are shown in Fig. 4. For ex-vivo testing, the prototype was deployed in a stomach harvested from a Yorkshire pig 30 minutes after euthanasia. All work involving tissue procurement and handling was conducted under protocols approved by the Massachusetts Institute of Technology Committee on Animal Care (MIT CAC) prior to initiation. Gastrointestinal tissue was obtained from local slaughterhouses (Lemay & Sons, and Blood Farm) and/or from animals previously euthanized. To contain SGF (120 mL, pH 1) in the stomach during testing, retort stands and hemostats were employed, and SGF and the prototype were introduced via the stomach's openings. Fig. 4 shows the measured transient waveform of chip operation at pH 1. After a cold start, the pH is sampled, followed by the assertion of the HYS sequence and change of the clock frequency for MPPT, setting V_s to its MPP. A 13.56 MHz ASK-modulated signal is transmitted by a commercial RFID antenna to the prototype for controlled drug delivery. These RF signals trigger the duty-cycled dissolution of the metal membrane in the low-energy dissolve mode. During this period, C_{store} is connected to the membrane when V_{out} reaches 1.1V, and as C_{store} gets discharged, the hysteresis controller disconnects it from the membrane and toggles the chip back into the charging period. The detection of three additional RF pulses increases the dissolution speed by raising the trip voltages to 1.3V and 1.5V. A final pulse stops the dissolving, allowing C_{store} to recharge to 2V, in preparation for the next pH sampling or the next dissolution period.

Fig. 5 shows the in-vitro transient measurement of pH sampling at different levels and the corresponding MPPT. For this measurement, the GC was immersed in a pH 2 solution and 1% hydrochloric acid and 1% sodium hydroxide solutions were mixed to mimic the change in GI pH over time. To monitor the GI pH, the GC is briefly disconnected from the SCPC, connected to the AFE and then quantized by the on-chip Flash ADC. To save power, the pH sensing block is power-gated and turns on once every 10 minutes (controlled by the 1 Hz relaxation oscillator in Fig. 2). The ADC digital code corresponding to different GI pH is also shown in Fig. 5.

We demonstrated the self-powered drug delivery capability of our system using a chamber loaded with fluorescein as a model drug (Fig. 6). The chamber was sealed with a 5 μm-thick molybdenum (Mo) foil, electrically connected via copper tape to the back of the chamber. To quantify drug release characteristics, we measured the concentration of fluorescein in SGF over time at pH 1 and 3 using a fluorescence microplate reader (Infinite 200 Pro, Tecan). We tested three drug release modes for each pH condition, with a C_{store} of 3F for burst mode, and 970μF for both balanced and low-energy dissolve modes. The time and energy consumed for each drug release condition are shown in Fig. 6. Low-energy dissolve mode requires 15 to 20% less energy than balanced mode, while burst mode consumes four times more energy to achieve immediate release. This result confirms the adaptive capability of our chip to modulate drug delivery based on clinical needs, balancing release timing with energy efficiency.

The performance summary of the chip is provided in Fig. 6. The chip uses the energy harvested from a galvanic cell, boosts the voltage, and creates regulated voltages of 1.2V and 0.7V with a cold start active power consumption of 10μW. To track the variations of pH within the GI tract for maximum power point tracking and set the etching conditions, pH is sampled every 10 minutes by an on-chip Flash ADC. By incorporating an RF envelope detector, it is also able to adjust the therapy conditions based on external RF commands during operation. In conclusion, it is the first fully integrated, battery-free IC that achieves pH sensing and MPPT in the GI tract, and wirelessly adjustable drug delivery. By addressing the challenges of energy efficiency and precise, externally adjustable drug delivery, this technology paves the way for more adaptable, responsive, and patient-specific therapies in gastrointestinal drug delivery.

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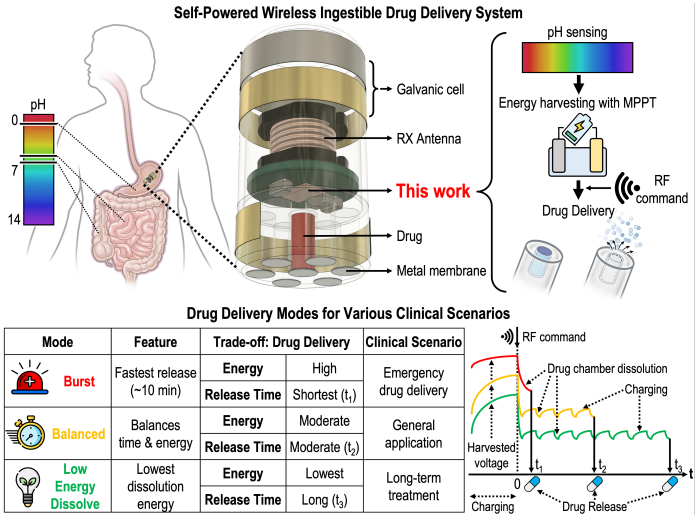


Fig. 1. The concept of self-powered wireless drug delivery chip, its main features, and modes of drug delivery.

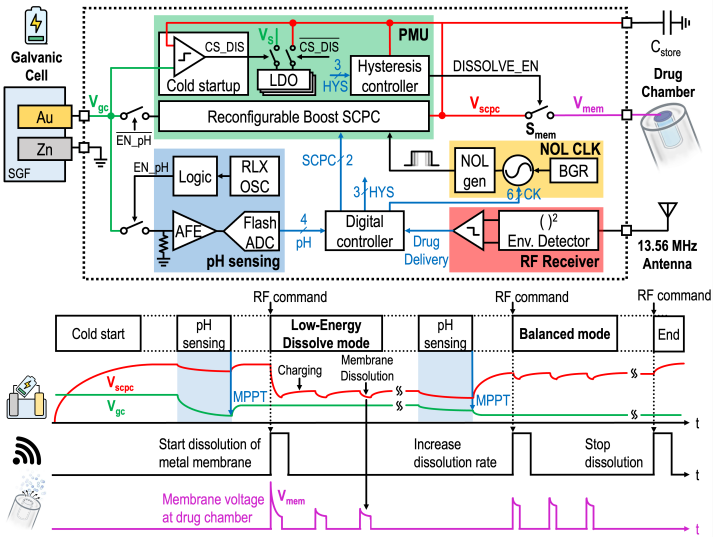


Fig. 2. System diagram and operation of the self-powered wireless drug delivery chip.

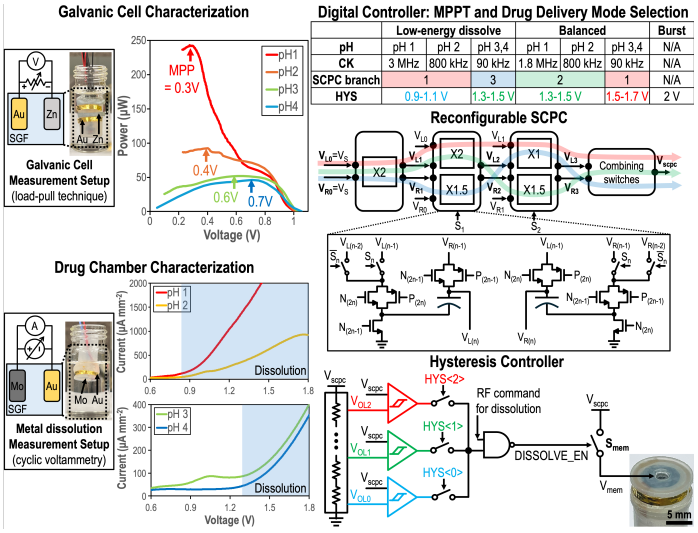


Fig. 3. Characterization of MPP of Galvanic cell and dissolution voltage of drug chamber membrane across different pH, schematics of reconfigurable SCPC and Hysteresis controller, table of SCPC branch, clock frequency and hysteresis window at different pH and mode of drug delivery.

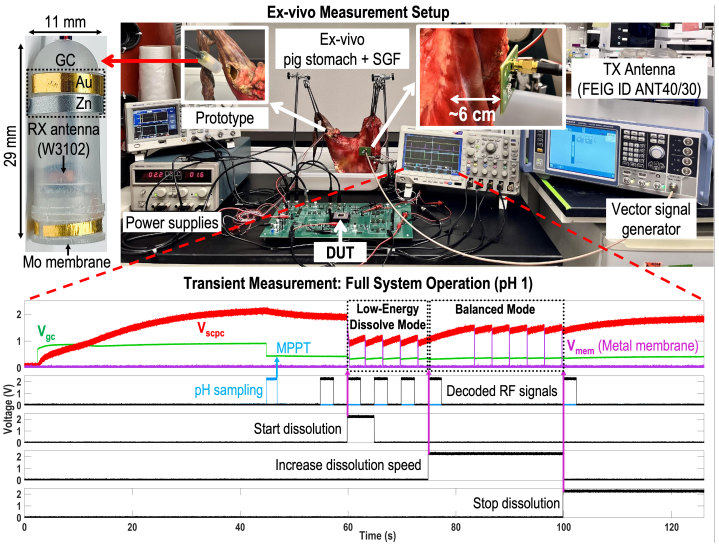


Fig. 4. Ex-vivo measurement setup and transient measurement of the full system in the simulated gastric fluid of pH 1.

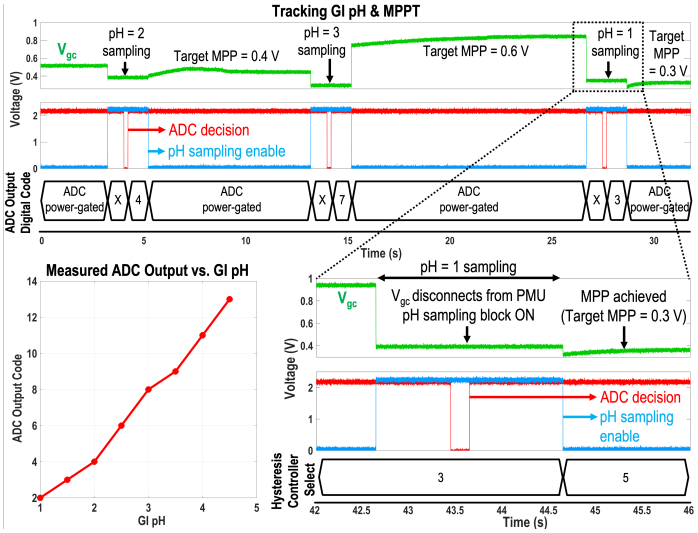
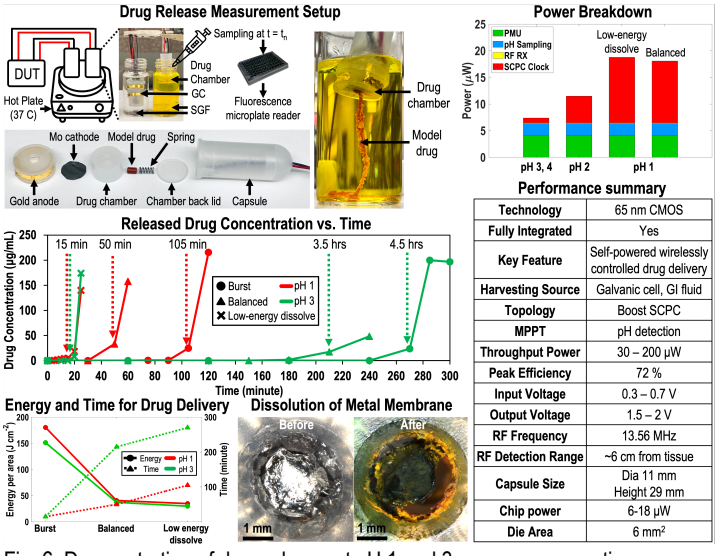


Fig. 5. Transient measurements: Sampling of GI pH and maximum power point tracking for different pH, ADC output code across various GI pH.



Technology	65 nm CMOS
Fully Integrated	Yes
Key Feature	Self-powered wirelessly controlled drug delivery
Harvesting Source	Galvanic cell, GI fluid
Topology	Boost SCPC
MPPT	pH detection
Throughput Power	30 – 200 μW
Peak Efficiency	72 %
Input Voltage	0.3 – 0.7 V
Output Voltage	1.5 – 2 V
RF Frequency	13.56 MHz
RF Detection Range	~6 cm from tissue
Capsule Size	Dia 11 mm Height 29 mm
Chip power	6-18 μW
Die Area	6 mm²

Fig. 6. Demonstration of drug release at pH 1 and 3, power consumption breakdown and performance summary of the system.

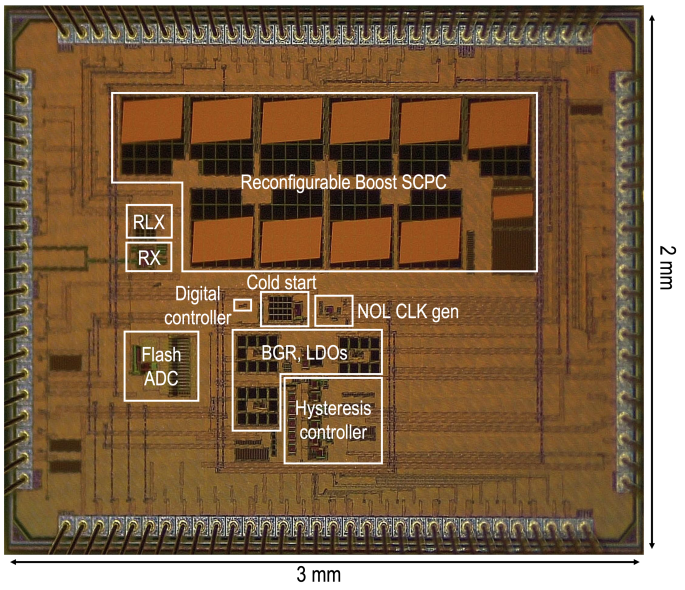


Fig. 7 Diephoto

Acknowledgements

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