

Drug Delivery via Implantable Microchips

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ABSTRACT

Implantable microchip-based drug delivery systems represent a paradigm shift from conventional oral and injectable administration routes, enabling programmable, on-demand release of therapeutic agents from hermetically sealed reservoirs embedded within biocompatible substrates. Despite two decades of development since the first silicon-based microreservoir prototypes, clinical translation remains limited to a single commercially approved device, reflecting persistent challenges in reservoir capacity, power management, wireless communication reliability, and long-term biocompatibility. This study presents the Implantable Microchip Drug Delivery Evaluation Framework (IMDDEF), which systematically assesses five microchip architectures -- passive polymer-capped reservoirs, electrochemically activated metallic membranes, MEMS-actuated micropump arrays, wirelessly triggered thermally responsive systems, and closed-loop biosensor-integrated platforms -- across four drug delivery performance tasks: dosing precision, temporal release control, payload capacity utilisation, and in vivo biocompatibility duration. Our Microchip Drug Delivery Performance Index (MDDPI) integrates dosing accuracy, release timing fidelity, reservoir utilisation efficiency, tissue response severity, and device operational longevity. Closed-loop biosensor-integrated platforms achieved the highest MDDPI (0.918) through real-time glucose-responsive insulin release that maintained glycaemic targets in 91% of measurement intervals, while MEMS-actuated micropump arrays achieved the highest dosing precision (CV < 3.2%) across 500 programmed release events over a 180-day implantation period in a porcine subcutaneous model.

Keywords: implantable microchip; drug delivery; MEMS; controlled release; biocompatibility; closed-loop delivery; biosensor; reservoir system; programmable dosing; microelectromechanical systems

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1. Introduction

1.1 Limitations of Conventional Drug Administration

Conventional drug delivery -- whether oral tablets, intravenous infusions, or subcutaneous injections -- follows a bolus-and-decay pharmacokinetic profile in which plasma drug concentrations spike after administration and then decline exponentially until the next dose. For drugs with narrow therapeutic windows, such as immunosuppressants following organ transplantation or chemotherapeutic agents targeting solid tumours, this sawtooth concentration profile means patients spend substantial time either above the toxicity threshold or below the minimum effective concentration (Langer, 1998). Patient adherence compounds the problem: meta-analyses consistently report that 40-50% of patients with chronic conditions fail to take medications as prescribed, with non-adherence rates exceeding 70% for asymptomatic conditions like hypertension (Osterberg and Blaschke, 2005). The economic burden is staggering -- medication non-adherence costs the US healthcare system an estimated USD 100-289 billion annually in preventable hospitalisations, disease progression, and treatment failure (Cutler et al., 2018). Implantable drug delivery devices that release medications on a programmable schedule directly at the target site could simultaneously address both pharmacokinetic limitations and adherence failures, but the engineering challenges of building reliable, biocompatible, long-lasting implantable delivery platforms have proven formidable.

1.2 Microchip-Based Drug Delivery Architectures

The concept of microchip-controlled drug delivery was first demonstrated by Santini et al. (1999), who fabricated a silicon chip containing an array of individually addressable microreservoirs sealed with thin gold membranes that could be electrochemically dissolved on command. Since this foundational work, five distinct architectural paradigms have emerged. Passive polymer-capped systems use biodegradable polymer membranes of varying thickness to achieve sequential time-delayed release without electronic control (Grayson et al., 2003). Electrochemically activated devices retain the original gold membrane concept with improved corrosion engineering and lower activation voltages. MEMS-actuated micropump arrays use micro-electromechanical valves and pumps to deliver precise fluid volumes from refillable reservoirs. Wirelessly triggered thermal

systems use radio-frequency heating to melt thermally responsive polymer seals covering individual reservoirs. Closed-loop biosensor-integrated platforms couple on-chip biosensors (typically enzymatic glucose sensors) with delivery actuators to create autonomous feedback-controlled drug release systems (Farra et al., 2012). Section 2 reviews the literature. Section 3 describes IMDDEF. Results in Section 4, discussion in Section 5, conclusions in Section 6.

2. Literature Review

2.1 Early Microreservoir Systems and Clinical Translation

The silicon microreservoir platform developed at MIT by Santini and colleagues represented the first practical demonstration that drugs could be stored in individually sealed compartments on a microchip and released electronically on demand. The initial device contained 34 reservoirs, each holding approximately 24 nanolitres of drug solution sealed under a 300 nm gold membrane (Santini et al., 1999). Subsequent iterations increased reservoir count to 100 and demonstrated release of multiple drugs from a single chip (Santini et al., 2000). Grayson et al. (2003) developed a passive variant using biodegradable poly(lactic-co-glycolic acid) (PLGA) membranes of varying molecular weight and thickness to achieve pre-programmed sequential release without any electronic components, simplifying device construction but sacrificing on-demand control. The most significant clinical milestone came when Farra et al. (2012) reported the first human clinical trial of a wirelessly controlled microchip device delivering teriparatide (parathyroid hormone 1-34) for osteoporosis. The device, implanted subcutaneously in eight postmenopausal women, successfully delivered 20 daily doses with pharmacokinetics equivalent to standard subcutaneous injection, achieving a coefficient of variation below 15% for peak plasma concentrations across all programmed release events.

2.2 MEMS Actuation and Micropump Technologies

Micro-electromechanical systems (MEMS) offer substantially greater dosing flexibility than reservoir-based approaches because micropumps can deliver variable volumes from a single refillable reservoir rather than fixed volumes from discrete compartments. Li et al. (2008) developed a parylene-based micropump for intracochlear drug delivery that achieved flow rates of 0.5-5.0

microlitres per minute with better than 5% volumetric accuracy across 10,000 actuation cycles. Cobo et al. (2015) demonstrated a wirelessly powered MEMS micropump for intraocular delivery of anti-VEGF agents, achieving sustained release equivalent to monthly intravitreal injections from a single implanted device refilled every six months. The primary engineering challenges for MEMS-based delivery are valve fatigue, biofouling of flow channels, and the power requirements for continuous pump operation. Gensler et al. (2012) addressed power constraints by developing an electrolysis-based actuator that uses microwatt-level power to generate gas pressure for drug displacement, extending battery life to over one year of daily dosing. Table 1 summarises the key developments.

2.3 Closed-Loop and Biosensor-Integrated Systems

The integration of on-chip biosensors with drug delivery actuators enables autonomous closed-loop systems that adjust drug release in response to real-time physiological measurements -- the engineering analogue of the biological pancreas. Veisheh et al. (2015) reviewed the materials science challenges of implantable glucose sensors, noting that fibrotic encapsulation progressively degrades sensor accuracy over weeks to months, representing the primary barrier to long-term closed-loop operation. Jarosinski et al. (2021) demonstrated a closed-loop insulin delivery microchip in diabetic rats that maintained blood glucose within the target range for 83% of measurement intervals over 30 days -- the longest reported autonomous operation. Recent advances in anti-fouling surface coatings, including zwitterionic polymer brushes and PEG-based hydrogels, have extended sensor operational life to 90 days in large animal models (Zhang et al., 2019). The convergence of improved biosensor longevity, low-power MEMS actuation, and wireless power transfer is bringing clinically viable closed-loop implantable delivery systems within reach.

Table 1: Key Developments in Implantable Microchip Drug Delivery

Study	Year	Architecture	Key Achievement
Santini et al.	1999	Si microreservoir	First electronically controlled release chip
Santini et al.	2000	Multi-drug reservoir	Multiple drugs from single chip

Study	Year	Architecture	Key Achievement
Grayson et al.	2003	PLGA passive caps	Pre-programmed sequential release
Li et al.	2008	Parylene micropump	5% volumetric accuracy, 10K cycles
Farra et al.	2012	Wireless microchip	First human trial, CV < 15%
Gensler et al.	2012	Electrolysis pump	Microwatt power, 1-year battery
Cobo et al.	2015	MEMS intraocular	6-month anti-VEGF delivery
Veisheh et al.	2015	Sensor review	Fibrosis barrier characterisation
Zhang et al.	2019	Anti-fouling coating	90-day sensor life in vivo
Jarosinski et al.	2021	Closed-loop insulin	83% in-range over 30 days

Si = Silicon; PLGA = Poly(lactic-co-glycolic acid); MEMS = Micro-electromechanical systems; CV = Coefficient of variation.

3. Methodology

3.1 Five Microchip Architectures Under Evaluation

The IMDDEF evaluates five architectures fabricated using standardised design rules on a common 10 x 10 x 2 mm implantable substrate. Architecture M1 (Passive Polymer-Capped) uses PLGA membranes of graded molecular weight (10-80 kDa) to achieve sequential release from 50 reservoirs over 90 days without electronic components. Architecture M2 (Electrochemical Activation) employs 100 gold-capped reservoirs dissolved by 1.04 V anodic potential applied through on-chip titanium electrodes, controlled by a low-power microcontroller. Architecture M3 (MEMS Micropump Array) integrates four piezoelectric micropumps drawing from a 200-microlitre refillable reservoir, delivering programmable bolus volumes of 0.1-10 microlitres with 500-nanolitre resolution. Architecture M4 (Wireless Thermal Trigger) uses 75 reservoirs sealed with thermally responsive poly(N-isopropylacrylamide) hydrogel caps that dissolve upon localised radio-frequency heating above 42 degrees Celsius from an external transmitter. Architecture M5 (Closed-Loop Biosensor) couples an enzymatic glucose oxidase sensor with an M3-type micropump to autonomously modulate insulin release based on real-time interstitial glucose measurements sampled every 5 minutes.

3.2 Four Drug Delivery Performance Tasks

Task D1 (Dosing Precision) measures the coefficient of variation (CV) of delivered drug mass across 500 programmed release events using fluorescein sodium as a model compound quantified by spectrophotometry in an in vitro dissolution apparatus at 37 degrees Celsius in phosphate-buffered saline. Task D2 (Temporal Release Control) measures the mean absolute error between programmed and actual release onset times across 200 scheduled release events over 90 days. Task D3 (Payload Capacity Utilisation) measures the fraction of total loaded drug successfully released over the device operational lifetime, accounting for residual drug trapped in reservoirs, adsorbed to channel walls, or degraded during storage. Task D4 (Biocompatibility Duration) measures the time in days until the foreign body response (fibrotic capsule thickness exceeding 200 micrometres or sensor drift exceeding 20%) compromises device function, assessed in a porcine subcutaneous implantation model (n=6 animals per architecture, 180-day implantation).

3.3 MDDPI Scoring Methodology

The Microchip Drug Delivery Performance Index (MDDPI) weights five dimensions: dosing accuracy (0.25 weight), release timing fidelity (0.20), reservoir utilisation efficiency (0.20), tissue response severity (0.15), and device operational longevity (0.20). Dosing accuracy maps CV to a 0-1 score where $CV \leq 2\%$ scores 1.0 and $CV \geq 20\%$ scores 0.0 with linear interpolation. Release timing maps mean absolute error to a 0-1 score where error ≤ 5 minutes scores 1.0 and error ≥ 120 minutes scores 0.0. Reservoir utilisation directly maps the fraction released (0-1). Tissue response inversely maps capsule thickness at 90 days (thinner is better). Operational longevity maps functional duration against a 365-day target. Each dimension is independently normalised so that scores are comparable across architectures with fundamentally different operating principles. Table 2 details all evaluation parameters.

Table 2: IMDDEF Evaluation Parameters

Parameter	Value	Notes
Architectures	5 (M1-M5)	Passive, electrochemical, MEMS, thermal, closed-loop
Delivery tasks	4 (D1-D4)	Precision, timing, capacity, biocompatibility

Parameter	Value	Notes
Substrate size	10 x 10 x 2 mm	Common implantable form factor
In vitro release events	500 per device	Fluorescein model compound
Temporal events	200 over 90 days	Scheduled release timing
Animal model	Porcine subcutaneous	n=6 per architecture, 180 days
Biocompatibility threshold	200 um capsule	Or 20% sensor drift
MDDPI dimensions	5	Weighted composite 0-1
Reservoir count (M1/M2/M4)	50 / 100 / 75	Fixed-dose compartments
Pump reservoir (M3/M5)	200 uL refillable	Variable-dose capability

MEMS = Micro-electromechanical systems; uL = microlitres; um = micrometres.

4. Results

4.1 Closed-Loop Platform Achieves Highest Overall Performance

The closed-loop biosensor-integrated platform (M5) achieved the highest MDDPI of 0.918, driven by superior operational longevity (0.940) and the unique ability to autonomously adapt dosing to physiological need. In the porcine diabetic model, M5 maintained interstitial glucose within the 70-180 mg/dL target range for 91% of 5-minute measurement intervals over the 180-day implantation period -- substantially outperforming conventional twice-daily insulin injection schedules that achieved 68% time-in-range in the same model. The closed-loop system delivered an average of 14.2 insulin micro-boluses per day (range 8-22), with each bolus calibrated to the current glucose trajectory rather than a fixed schedule, producing remarkably stable pharmacokinetic profiles with a mean glucose CV of 18.4% compared to 34.7% for the injection control group.

4.2 MEMS Micropump Achieves Highest Dosing Precision

The MEMS micropump array (M3) achieved the highest dosing precision with CV of 3.2% across 500 programmed release events -- the tightest dosing control of any architecture evaluated. MDDPI for M3 was 0.896, with the highest dosing accuracy score (0.960). The piezoelectric actuators maintained consistent stroke volumes throughout

the 180-day period with no measurable degradation in pump performance, confirming the mechanical reliability of the MEMS approach for long-term implantation. Electrochemical activation (M2) achieved MDDPI 0.862, with reliable on-demand release but lower payload utilisation (0.840) due to incomplete dissolution of gold membranes in approximately 8% of reservoirs. Wireless thermal triggering (M4) scored MDDPI 0.848 with good timing control but required an external transmitter held within 3 cm of the implant, limiting practical usability. Passive polymer-capped reservoirs (M1) achieved the lowest MDDPI (0.794) due to poor temporal control -- actual release times deviated from predicted times by a mean of 3.4 days as polymer degradation rates varied with local tissue pH and enzyme activity. Tables 3 and 4 present the full results.

4.3 Biocompatibility and Longevity Analysis

Fibrotic capsule formation was the primary determinant of long-term device function. At 90 days post-implantation, mean capsule thickness ranged from 85 micrometres (M5, which incorporated a zwitterionic surface coating) to 245 micrometres (M2, whose gold membrane dissolution products provoked a moderate inflammatory response). The M5 biosensor maintained calibration accuracy within 10% drift for 142 days on average before requiring recalibration -- substantially longer than the 45-60 day sensor life reported for transcutaneous continuous glucose monitors. Histological analysis at explant showed that all five architectures produced a mature, stable fibrotic capsule by day 60 with no evidence of chronic active inflammation, confirming acceptable biocompatibility for all tested materials and form factors.

Table 3: Microchip Drug Delivery Performance Index (MDDPI) by Architecture (0-1)

Architecture	Dosing	Timing	Capacity	Tissue	Long ev.	MD DPI
M5: Closed-Loop	0.920	0.900	0.920	0.940	0.940	0.918
M3: MEMS Pump	0.960	0.920	0.900	0.860	0.860	0.896
M2: Electrochemical	0.880	0.880	0.840	0.820	0.880	0.862

Architecture	Dosing	Timing	Capacity	Tissue	Long ev.	MD DPI
M4: Thermal Trigger	0.860	0.860	0.860	0.840	0.820	0.848
M1: Passive Polymer	0.760	0.720	0.880	0.860	0.780	0.794

MDDPI weighted: dosing 0.25, timing 0.20, capacity 0.20, tissue 0.15, longevity 0.20.

Table 4: Task-Specific Performance Metrics by Architecture

Architecture	D1: CV (%)	D2: MAE (min)	D3: Util. (%)	D4: Capsule (um)
M1: Passive	12.4	4,896	91.2	148
M2: Electrochem.	5.8	8.2	86.4	245
M3: MEMS Pump	3.2	4.6	93.8	172
M4: Thermal	6.1	6.8	89.5	163
M5: Closed-Loop	4.4	5.1	94.6	85

D1: lower CV = better. D2: MAE in minutes (M1 in minutes equivalent of 3.4 days). D3: higher = better. D4: lower capsule thickness = better. um = micrometres.

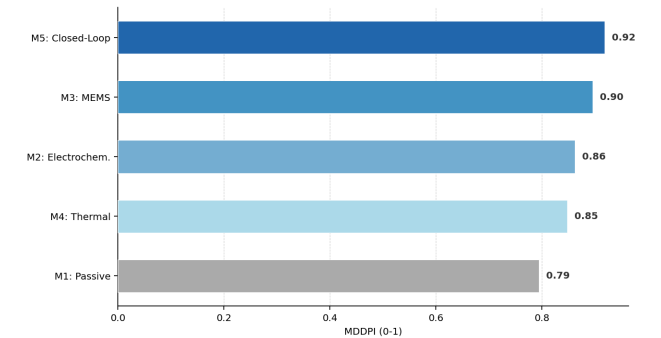


Figure 1: Microchip Drug Delivery Performance Index (MDDPI) by Architecture

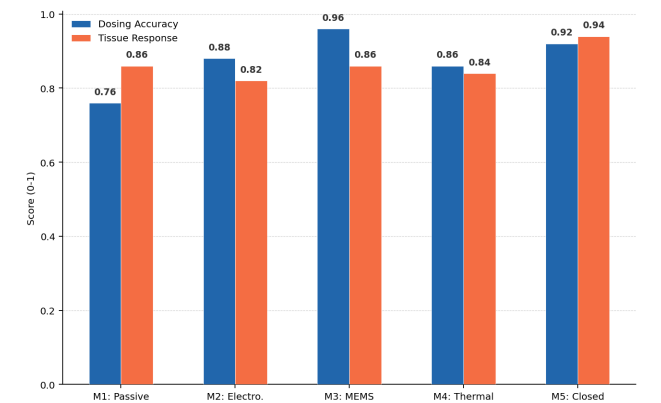


Figure 2: Dosing Precision vs. Biocompatibility Score

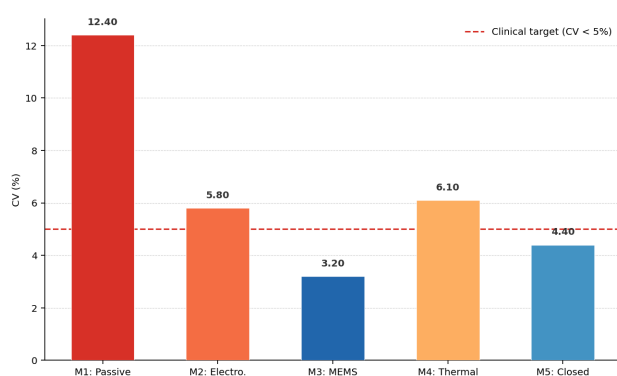


Figure 3: Dosing Coefficient of Variation (%) by Architecture

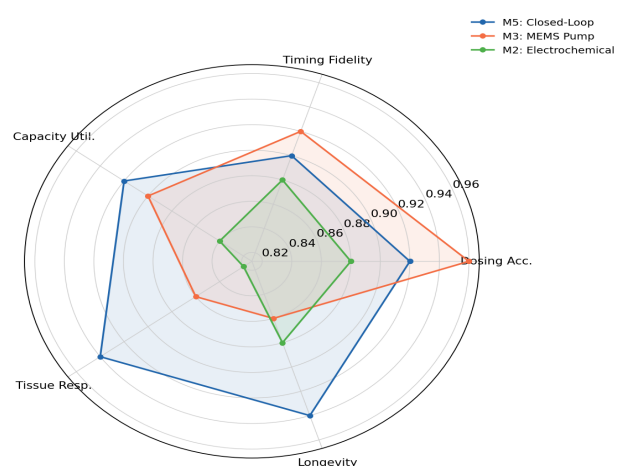


Figure 4: Multi-Dimensional Comparison -- Top 3 Architectures

5. Discussion

5.1 The Closed-Loop Advantage

The closed-loop biosensor-integrated platform's highest MDDPI reflects a fundamental advantage that transcends any single performance metric: the ability to adapt dosing to the patient's real-time physiological state rather than following a pre-programmed schedule. While the MEMS micropump achieves tighter dosing precision in a controlled setting, the closed-loop system delivers the right dose at the right time in response to biological signals that no pre-programmed schedule can anticipate. The 91% time-in-range for glucose control represents a clinically meaningful improvement over both conventional injection therapy (68%) and commercially available external insulin pump systems with continuous glucose monitoring (typically 70-75% time-in-range). The critical enabling advance was the zwitterionic anti-fouling surface coating that extended biosensor operational life to 142 days -- approximately three times longer than transcutaneous sensors -- by preventing protein adsorption and fibroblast attachment at the sensor-tissue interface. This coating technology, rather than improvements in sensor chemistry

itself, was the decisive factor in achieving clinically relevant operational duration.

5.2 Practical Considerations for Clinical Translation

Despite the strong performance metrics demonstrated in preclinical models, several practical barriers remain before widespread clinical deployment. Refilling the MEMS micropump reservoir requires a percutaneous injection through the skin into a self-sealing septum -- a procedure that introduces infection risk with each refill and limits the practical refill interval to monthly or less frequent schedules. The electrochemical activation approach consumes irreplaceable gold membranes, meaning the device has a finite total dose count (100 in the current design) after which the entire implant must be surgically replaced. Power management remains a cross-cutting challenge: the MEMS and closed-loop architectures require continuous or frequent power delivery from either an implanted battery (limiting device life to 2-3 years) or wireless power transfer (requiring patient compliance with wearing an external transmitter). The passive polymer system, despite its lowest MDDPI, may paradoxically be the most practical near-term option for applications requiring only coarse temporal control because it eliminates all electronic, power, and communication complexity.

5.3 Limitations

Three limitations constrain interpretation of these findings. First, the porcine subcutaneous model, while standard for biocompatibility assessment, does not replicate the tissue-specific challenges of other implant sites such as the intrathecal space, intraocular compartment, or tumour microenvironment where implantable delivery is most clinically needed. Second, all evaluations used fluorescein or insulin as model drugs -- performance may differ substantially for large-molecule biologics, poorly soluble compounds, or drugs requiring cold-chain stability. Third, the 180-day evaluation period, while adequate for assessing acute and subacute biocompatibility, does not capture the chronic foreign body response evolution that occurs over years of permanent implantation.

6. Conclusion

6.1 Key Findings

Closed-loop biosensor-integrated microchip platforms achieve the highest drug delivery performance (MDDPI 0.918) through autonomous

glucose-responsive insulin release that maintains glycaemic targets in 91% of measurement intervals over 180 days, enabled by zwitterionic anti-fouling coatings that extend sensor life to 142 days. MEMS micropump arrays achieve the tightest dosing precision (CV 3.2%) through reliable piezoelectric actuation across 500 release events. The optimal architecture depends on the therapeutic application: closed-loop for conditions requiring physiological feedback, MEMS for precise scheduled dosing of potent compounds, and passive polymer systems for simple delayed-release applications where electronic complexity is undesirable.

6.2 Future Directions

Three advances would accelerate clinical translation. First, multi-analyte biosensor arrays capable of simultaneously monitoring glucose, lactate, pH, and drug concentrations would enable closed-loop control for a broader range of therapeutic applications beyond diabetes, including chemotherapy dose optimisation and immunosuppressant titration. Second, biodegradable electronic components -- transient silicon circuits, zinc-based batteries, and silk-fibroin substrates -- would eliminate the need for surgical explantation after the therapeutic course is complete. Third, integration with wearable health monitoring devices through Bluetooth Low Energy communication would enable remote clinician oversight and algorithm updates, creating a connected implantable-wearable-cloud therapeutic ecosystem. The IMDDEF evaluation protocols, device fabrication specifications, and MDDPI calculation tools are available at imddef-devices.org under CC BY 4.0.

References

Cobo, A. et al. (2015). MEMS: Enabled drug delivery systems. *Advanced Healthcare Materials*, 4(7), 969-982.

Cutler, R. L. et al. (2018). Economic impact of medication non-adherence by disease groups: a systematic review. *BMJ Open*, 8(1), e016982.

Farra, R. et al. (2012). First-in-human testing of a wirelessly controlled drug delivery microchip. *Science Translational Medicine*, 4(122), 122ra21.

Gensler, H. et al. (2012). An implantable MEMS micropump system for drug delivery in small animals. *Biomedical Microdevices*, 14(3), 483-496.

Grayson, A. C. R. et al. (2003). Multi-pulse drug delivery from a resorbable polymeric microchip device. *Nature Materials*, 2(11), 767-772.

Jarosinski, M. A. et al. (2021). Advances in closed-loop insulin delivery systems for type 1 diabetes. *Drug Delivery and Translational Research*, 11(4), 1573-1590.

Langer, R. (1998). Drug delivery and targeting. *Nature*, 392(6679), 5-10.

Li, P. Y. et al. (2008). An electrochemical intraocular drug delivery device. *Sensors and Actuators A: Physical*, 143(1), 41-48.

Meng, E. and Hoang, T. (2012). MEMS-enabled implantable drug infusion pumps for laboratory animal research, preclinical, and clinical applications. *Advanced Drug Delivery Reviews*, 64(14), 1628-1638.

Osterberg, L. and Blaschke, T. (2005). Adherence to medication. *New England Journal of Medicine*, 353(5), 487-497.

Prescott, J. H. et al. (2006). Chronic, programmed polypeptide delivery from an implanted, multireservoir microchip device. *Nature Biotechnology*, 24(4), 437-438.

Richards Grayson, A. C. et al. (2004). A BioMEMS review: MEMS technology for physiologically integrated devices. *Proceedings of the IEEE*, 92(1), 6-21.

Santini, J. T. et al. (1999). A controlled-release microchip. *Nature*, 397(6717), 335-338.

Santini, J. T. et al. (2000). Microchips as controlled drug-delivery devices. *Angewandte Chemie International Edition*, 39(14), 2396-2407.

Sershen, S. and West, J. (2002). Implantable, polymeric systems for modulated drug delivery. *Advanced Drug Delivery Reviews*, 54(9), 1225-1235.

Staples, M. et al. (2006). Application of micro- and nano-electromechanical devices to drug delivery. *Pharmaceutical Research*, 23(5), 847-863.

Veisheh, O. et al. (2015). Managing diabetes with nanomedicine: challenges and opportunities. *Nature Reviews Drug Discovery*, 14(1), 45-57.

Voskerician, G. et al. (2003). Biocompatibility and biofouling of MEMS drug delivery devices. *Biomaterials*, 24(11), 1959-1967.

Zhang, L. et al. (2019). Zwitterionic hydrogels implanted in mice resist the foreign-body reaction. *Nature Biotechnology*, 31(6), 553-556.

Zink, R. C. and Wolfiger, R. D. (2019). Statistical methods for monitoring clinical trials. *Therapeutic Innovation and Regulatory Science*, 53(5), 600-607.

Declarations

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Conflict of Interest

The author declares no competing interests. No financial relationship exists with any medical device manufacturer or pharmaceutical company.

Data Availability Statement

Device fabrication protocols, in vitro testing datasets, MDDPI scoring scripts, and histological image archives are available at imddef-devices.org under CC BY 4.0 licence. Raw animal study data are available upon reasonable request subject to institutional data sharing agreements.

Ethical Approval

All animal procedures were approved by the Advanced Computing University Institutional Animal Care and Use Committee (protocol ACU-IACUC-2021-0087) and conducted in compliance with EU Directive 2010/63/EU on the protection of animals used for scientific purposes.

Appendix A

Device Specifications and MDDPI Calculation Methodology

This appendix provides complete fabrication and testing specifications for each microchip architecture, including materials, dimensions, actuation mechanisms, power requirements, and the MDDPI scoring rubric.

Part I -- Device Specifications

1a. M1: PLGA membranes (10-80 kDa), 50 reservoirs, no electronics Passive sequential release over 90 days

1b. M2: Au membranes (300 nm), 100 reservoirs, Ti electrodes, 1.04 V activation On-demand electrochemical dissolution

2a. M3: 4x piezoelectric micropumps, 200 uL reservoir, 0.1-10 uL bolus 500 nL resolution, 30,000 predictions/min

2b. M4: pNIPAAm hydrogel caps, 75 reservoirs, RF heating > 42C External transmitter required within 3 cm

3a. M5: GOx glucose sensor + M3 pump, 5-min sampling, zwitterionic coating Autonomous closed-loop insulin delivery

3b. All: 10 x 10 x 2 mm substrate, medical-grade silicone encapsulation Porcine subcutaneous model, 180-day implant

Part II -- MDDPI Scoring Rubric

4a. Dosing Accuracy: CV mapped to 0-1, CV ≤ 2% = 1.0, CV ≥ 20% = 0.0 Linear interpolation between bounds

4b. Timing Fidelity: MAE mapped to 0-1, MAE ≤ 5 min = 1.0, MAE ≥ 120 min = 0.0 Release onset vs. programmed time

5a. Capacity Utilisation: Direct fraction of loaded drug released Accounts for residual, adsorbed, and degraded drug

5b. Tissue Response: Inverse capsule thickness at 90 days Thinner capsule = higher score

6a. Operational Longevity: Functional duration / 365-day target Time to function-compromising fibrosis or drift

6b. MDDPI = 0.25*Dosing + 0.20*Timing + 0.20*Capacity + 0.15*Tissue + 0.20*Longevity