

Bioresorbable Batteries for Transient Ingestible Bioelectronics

Corresponding Author: Professor Giovanni Traverso

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Comments for the Author)

A bioresorbable Mg–MoO₃ paper battery with an output of 1.84 V is proposed in this paper. The authors conducted in vivo studies in swine models and claim that the system demonstrates robust operation within the GI tract and compatibility with clinically relevant use cases. This manuscript reports the design, fabrication, and in vivo evaluation of biodegradable magnesium-based batteries for ingestible bioelectronic systems. The authors present circular and large-area battery architectures integrated into capsule platforms and demonstrate gastric retention, wireless detection, and electrical stimulation in a swine model. The work addresses an important challenge in ingestible bioelectronics by enabling transient, bioresorbable power sources with multi-day operation and is of potential interest to the bioelectronics and translational biomedical engineering communities.

However, despite these merits, the manuscript suffers from significant issues in clarity, organization, consistency, and technical accuracy. Several claims are overstated or insufficiently supported, terminology and references are inconsistent, and multiple figures and supplementary materials are poorly described or incorrectly cited. As currently written, these issues substantially hinder the reader's ability to evaluate the validity, safety, and system-level implications of the work.

Comments:

1. In the Introduction, the authors state that the biodegradable ionic liquid electrolyte is synthesized from choline chloride (ChCl). However, Supplementary Figure S4(d) labels the electrolyte as CHCl₂, and the caption states: "Preparation of the gel electrolyte by mixing CHCl₃, gelatin, glycerol, and PBS." CHCl₃ corresponds to chloroform, which raises concerns regarding chemical consistency and biocompatibility. Please clarify whether this is a labeling error or whether chloroform was used, and discuss any health considerations if applicable.
2. The radar plot in Supplementary Figure S8 provides a qualitative comparison but does not clearly support the claim that operating voltage, areal capacity, energy density, and power density are all significantly higher than prior systems. Several referenced batteries exhibit comparable or higher values in individual metrics. Please soften this claim or provide a quantitative comparison table with absolute values and consistent test conditions.
3. The manuscript refers to SGF immersion tests without defining SGF. Please explicitly define SGF (simulated gastric fluid) at first mention. Similarly, GCD should be defined when first introduced (and it appears to be undefined throughout).
4. Battery terminology is inconsistent (e.g., large-area battery, large battery, small battery, circular battery, 000-size battery). Please adopt a consistent nomenclature and define each battery type clearly.
5. The statement, "measurements taken post-retrieval indicated functional retention and a gradual capacity decrease consistent with the designed degradation kinetics (Figure 2d)," is not clearly supported by Figure 2d. Please clarify how Figure 2d demonstrates retention and degradation kinetics, or revise the claim.
6. Please correct typographical and referencing issues, including: an extra parenthesis in "(Figure 2e). ."; incorrect figure-order references (e.g., Figure 2f and 2g in the text appear to correspond to Figures 2g and 2h); Supplementary Figure S12 is referenced as showing OCV and discharge data, but no such data appear; and inset axis labels in Supplementary Figure S13(a) are not visible.
7. For Supplementary Figures S13 and S14, please clarify whether the same batteries were used across SGF immersion and in vivo retention experiments. If so, explain the observed increase in OCV at 72 h compared to 24 h for the large-area battery (Battery-1).
8. In Supplementary Figure S15, an increase in battery voltage from 36 h to 72 h is observed. Please comment on the

possible mechanism responsible for this behavior.

9. Supplementary Note 1 contains a missing citation. Please add the appropriate reference.

10. The description of RSSI behavior is incorrect. A shift from $-40/-50$ dBm to approximately -60 dBm indicates signal attenuation rather than an increase in signal strength. Please revise the wording accordingly.

11. Several figure references appear incorrect: flexible electrode fabrication is attributed to Supplementary Figure S15, which does not show this information; and the electrical stimulation PCB is referenced as Figure 5d, which does not exist (this appears to be Figure 4d).

12. In Section 2.4, the authors discuss degradation and bioresorption of the batteries during GI transit but do not address the fate of the non-bioresorbable circular PCB. Please clarify how this component behaves during prolonged gastric retention and subsequent passage.

13. The safety discussion is currently insufficient. The manuscript implies safety because the device contributes only a small fraction of the daily recommended mineral intake; however, this alone does not establish safety under realistic use. Please strengthen the safety argument, including the fate of dissolution products (Mg ions and molybdenum oxides), local exposure considerations, and any relevant toxicology/biocompatibility evidence.

14. Relatedly, the in vivo evaluation appears to reflect a “clean” (fasted) GI condition. Please discuss (and ideally test) how the system may behave under more representative human conditions (food, fiber, mucus, altered motility), including the possibility of localized retention that could create a dissolution “hot spot.”

15. Please clarify whether the observed OCP/OCV reduction over time is dominated by discharge or dissolution. It would be more informative to provide discharge potential vs. time (at different current densities) and dissolution/open-circuit behavior vs. time (at different current densities), to reflect resistance evolution and degradation effects.

16. It would be helpful to include a simplified DC battery model (e.g., a Thevenin equivalent model) to support system-level interpretation and comparison.

17. The term “edible” is used ambiguously and inconsistently. Please clearly define what is meant technically and use the chosen term consistently.

18. The sentence “We demonstrated the capability of the battery through three key in vivo applications using swine models” is repeated twice in immediate succession and should be revised to remove redundancy.

Reviewer #2

(Comments for the Author)

The manuscript reports a fully bioresorbable Mg–MoO₃ paper battery designed for powering ingestible bioelectronic systems. The authors demonstrate two applications: (1) a battery-assisted RFID capsule capable of meter-scale wireless tracking, and (2) a degradable gastric electrical stimulation system validated in swine. The topic is timely and the results are promising. However, several key scientific and engineering questions must be addressed before publication.

Comments:

1. The manuscript does not quantitatively compare its energy density, discharge performance, and degradation behavior with prior Mg-based or Zn-based transient batteries. A comparison table and clearer novelty discussion are needed.

2. The degradation pathways of Mo and MoO₃ in gastric fluid, expected ionic dissolution products, and potential toxicological concerns are not adequately discussed. These are essential for assessing clinical relevance. In addition, mass-loss curves, EIS evolution, mechanical integrity measurements, or dissolution-rate constants should be provided to support the claims of reproducible and safe biodegradation.

3. The manuscript claims enhanced RFID range due to “active backscatter,” but does not provide a link budget or explain the modulation mechanism from an RF engineering perspective. Quantitative analysis is needed to support the reported 4-m range.

4. It is mentioned “Once in the esophagus, the signal increased to approximately 60 dBm, reflecting the influence of the tissue environment”. The observation that RSSI increases after ingestion contradicts typical expectations of tissue attenuation. Additional explanation, modeling, or experimental validation is required.

5. Only limited subjects were tested, and no sham-control cohort is included. Statistical analysis and impedance tracking during stimulation are needed to substantiate the therapeutic effect.

Reviewer #3

(Comments for the Author)

The manuscript describes the design and development of biodegradable Mg–MoO₃ batteries. Two battery form factors are described: one fitting inside a size 000 ingestible capsule and one larger battery for bigger devices with higher power needs. The biodegradable batteries are tested in three pig experiments. Focusing on two major use cases: long-distance RFID tags for medication adherence and gastric stimulation to increase the feeling of satiation.

Biodegradable batteries could address important needs in the field of ingestible and implantable electronics, such as e-waste issues and risk of retention of ingestibles. Biodegradable batteries could also enable new applications in this space. This manuscript shows interesting proof-of-concept applications. However, the maturity of the devices is overstated and critical analysis of the data and presented use cases is lacking.

General remarks:

- Mg-MoO₃ batteries are not new, they have been widely studied. Interesting in this manuscript is the relatively small form factor and the specific applications. The validation studies are not as convincing as they could be though. Why only focus on the esophagus and the stomach? For ingestibles, it would be very valuable to have batteries that would survive the full passage through the tract.

- For the RFID use case, why are the devices placed in the esophagus? In the real use case, it will pass through the esophagus in seconds. Probably even too quick to pick up a change. Also, only the performance in air is shown (for 20 cm up to 4 m). But the body will have a huge impact on the signal strength. Why are these experiments not performed in a body-mimicking phantom? How much tissue could be penetrated? The claims that are now being made on improved range are not substantiated (8x improved?). So either this data needs to be added, or the claims need to be toned down, and showing this data only as proof-of-concept.

- Is RSSI a reliable method to measure drug adherence? There are several factors influencing RSSI, such as distance between receiver and RFID, body composition, stomach filling, location in GI tract, environmental factors, etc. How could this practically work in a real-life scenario?

- For the electroceutical use case, in pigs the device might stay in the stomach for prolonged periods, in human it will probably pass much quicker (minutes – hours). How would you retain the device in the stomach?

- The manuscript lacks scientific rigor. Cross references to (sub-)figures are incorrect; or the figures do not show what is mentioned in the text. References are missing. Duplicate sentences. Abbreviations not explained. Figures unclear or too small to read properly. Critical analysis of the work and its limitations is missing; discussion section is practically non-existing. Proper proofreading should have detected a lot of these. It can be hard for the reader to find the essential information, please re-check the flow and make a clearer distinction between main message and additional information. Also adding line numbers would have made the reviewing process easier.

- Bioresorbable and biodegradable are used interchangeably, but are not the same. This should be addressed and supported with references. How likely is it that (a large part of) the device is resorbed, giving the degradation rates? And how long would you like to have degrading electronics in the body? Is biodegradable good enough? It is mentioned that “complete structural degradation after several months in simulated fluid”, is it the idea that the devices stay in the body for such time windows?

- The maturity of the system is overstated. For example, “These in vivo results establish the clinical potential far beyond those of simple proof-of-concept devices”. This manuscript is really just proof-of-concept. There is a lot of variation in performance between the batteries. This is not properly addressed. Also, the needed steps towards clinical applications need to be addressed.

Abstract:

- ‘The battery proves a stable output voltage of 1.84V’. This seems a rather optimistic number and contradicting with the results presented on stable voltage. On page 6 (Fig 2c) it’s mentioned that up to 1.6V stable voltage was achieved for the big battery.

- “and fully bioresorbable capsule system for electroceutical therapy” This is not true, the PCB’s are not bioresorbable.

- Reducing ‘infection risk’ is mentioned as a potential benefit. How do these batteries reduce infections? It is not mentioned anywhere else in the text.

Page 2:

- Silver-oxide batteries are commonly used in ingestibles and should also be mentioned.

- The second paragraph. What do you mean with “implantable batteries”. If you would directly swallow or implant any type of battery, there would be some serious health risks indeed. But this is of course not how ingestibles/implantables are used. The batteries are carefully encased so they are never in direct contact with the body. The injuries that are listed here are not relevant, as long as the encasing is sufficient. Also, ISO 10993 is only applicable when the material has direct or indirect body contact. When it is encased, it also does not need to be an issue. There are of course good arguments to be made for biodegradable batteries, and it is good to highlight the risk of direct contact with batteries, but as such it is not a good introduction to the problem. What are the safety risks of biodegradable batteries? Unexpected discharges? Heating of tissue? Breaking down in sharp fragments? Any chemical reaction expected when the biodegradable battery gets in direct contact with the gut?

- In the third paragraph, ‘surgical retrieval’ and ‘long-term exposure’ is most likely only relevant for implantables, not ingestibles since they pass the whole GI tract in a matter of days. In rare cases there can of course be capsule retention. This nuance between the needs for implantable batteries and ingestibles batteries should be added.

Page 3:

- Also add the specification for reference 14 (in V), as done for the other 2 references.

- The sentence “We demonstrated the capability of the battery through three key in vivo applications ...” is repeated twice.

- “These in vivo results establish the clinical potential far beyond those of simple proof-of-concept devices”. This is too bold of a statement. It is nice to see the in vivo results, but it is only validated in an animal model and still far from clinical application. This is still a proof-of-concept device.

Page 4:

- 'We designed two battery formats.... larger-area batteries suited for more advanced capsule electronics'. What do you mean here with more advanced capsule electronics? That's not clear from the context. Why could that not be done in the capsule format? Would more 'more power consuming', be more accurate?
- Where Figure 1b is mentioned in the text, it should be Figure 1b and 1c.

Page 5:

- Where Fig 1d is mentioned should probably be 1e, showing the essential components of the battery.
- PLGA: add meaning of abbreviation. There should be an 'and' or 'or' be added to the sentence to improve readability.

Page 6:

- "The open circuit voltage 1.77V...., which is notably higher than that of previously reported Mg-MoO₃ cells". This directly contradicts with another statement on page 5. Where the same references are quoted and is written "Earlier demonstrations voltages of 1.6-1.8 V". 1.77V is not notably higher than this quoted range.

Page 7:

- Add explanation abbreviation SGF.
- "The beeswax-encapsulated batteries retained.... for several days". Several days is rather vague, please specify.
- In Supplementary Fig S9, I was expecting to see the data on the "mechanical integrity and stable electrochemical performance for days". Please add that data to the figure.
- "The batteries were assembled with natural wax encapsulation layers, ... in 3D printed capsules..". What was the material of the 3D printed capsules?? How are you testing here battery integrity if everything is protected and encapsulated anyways?
- "The flexible core ... minimizing local tissue irritation". How is it checked that is minimizes tissue irritation?

Page 8:

- "Figure 2f shows the ..." This should most likely be Figure 2g
- "The open-circuit voltage decreased from 1.77 V on Day 0.." Here you are talking about the mean of the three samples? That should be added in the text. Also, there is a huge spread between the samples, that should be addressed in the discussion.
- Explain the abbreviation OCV.
- "Supplementary Figure S12 shows the results of the open-circuit voltage and continuous discharge tests for batteries fully immersed in SGF." This is not shown in the Figure.

Page 9:

- Three different current densities are compared. What is the impact on the battery size? That should be discussed.
- Figure 2g and 2h are very difficult to read. A box plot for 2 or 3 measurements does not make a lot of sense. It gives the false impression of knowledge of the underlying data distribution, which is hardly defensible with so few data points. The individual data points should be shown more clearly.

Page 10:

- "Despite their potential, ...Despite their promise...". These sentences are repetitions, should be rephrased.

Page 11:

- Why is the wireless performance only measured in air? Why not test it in a representative phantom? The 20 cm to 4 m in air does not give any indication of the working range within a body. How much tissue can you penetrate? What type of BMI can you handle? The presented data is not sufficient to claim the long distance RFID support.
- How reliable is RSSI to use as an indication of medication ingestion? As you showed in Fig 3F, the distance between the RFID tag and receiver has a big influence on the RSSI. How could you distinguish the distance effect and the ingestion effect? Fig 3I is not directly very convincing.
- "The molybdenum antenna ... within a few months under accelerated dissolution conditions". Please specify what these accelerated conditions entail. How are these conditions validated? Are they representative of the human body?
- "This long-range communication system enables reliable recording of ingestion events, supports electronic medication adherence, and paves the way for future digital health applications" This too strong of a claim. Only under very controlled settings some tests were done.

Page 12:

- "demonstrated an 8x improvement in the communication range" compared to what? Can that be claimed if only in air measurements are shown and non-representative measurements in the esophagus of the pigs.

Page 14:

- Supplementary Fig S15 should be S16.

Discussion:

- There is no critical analysis of the data, addressing the limitations of this study, and next steps. Add:
- Limitations of these batteries? Shelf-life? Size? How robust are they giving the variation between samples? Stability?
- What is needed to get this in human applications and what are the biggest hurdles?
- The use cases are all focused on ingestibles while in the introduction also implantables are mentioned. Add some thoughts about opportunities in implantables.

- Is drug adherence using long-distance RFID tags a viable application? Drug adherence using RFID has not shown very promising.

Materials and Methods

- Dissolution test. What was used for which experiment? SGF, FaSSIF, RGF, fresh? Also add explanations of the abbreviations.
- Explain abbreviation GCD.
- REF missing in Supplementary Note 1.

Version 1:

Reviewer comments:

Reviewer #1

(Comments for the Author)

The authors addressed the concerns we raised, hence recommending publication of the manuscript.

Reviewer #2

(Comments for the Author)

The rebuttal improves the manuscript, but several important concerns are still not fully addressed.

1. The necessity of using a bioresorbable battery in ingestible electronics is still not sufficiently justified. The authors emphasize the advantage of bioresorbable battery for ingestible devices. However, in this work, the device is expected to pass through the GI tract and be excreted from the body before the battery starts significant degradation. In this case, it is still unclear why a bioresorbable battery is necessary at the system level, instead of being only an additional safety feature. The current rebuttal mainly mentions capsule rupture, retention, and reduction of e-waste, but these points are still rather general and not quantitatively supported. The authors should clarify more clearly whether bioresorbable is a true functional requirement for ingestible electronics, or only a desirable safety margin in some special situations.

2. The event detection by active RFID seems to rely only on backscatter amplitude, but this may not be specific enough. From the current data and explanation, the occurrence of an event seems to be judged mainly from the amplitude change of the backscattered RFID signal. However, in practice, the signal amplitude can also strongly depend on the distance between reader and RFID tag, as well as the alignment and orientation between them. Therefore, it is not clear whether the observed signal change is really caused by the event itself, or partly by geometric factors of the RF link. The authors should discuss this point more carefully and provide stronger evidence that the amplitude-based detection is robust against reader-tag distance variation, misalignment, and body motion.

3. The explanation for the relatively high OCV of the Mg–MoO₃ battery is still not convincing enough. The authors report that their battery shows a higher OCV than some similar systems. In the rebuttal, they mention that different electrolytes were tested and that the bio-IL electrolyte performed better than PBS- and urea-based systems. However, it is still not clear whether the higher OCV should really be attributed to the electrolyte. The authors should explain this point more mechanistically. For example, is the higher OCV caused by electrolyte chemistry itself, by reduced parasitic reactions, by improved interfacial contact, or by different measurement conditions? At present, the discussion is still too descriptive.

4. The manuscript should separate proof-of-concept from translational claim. The study is promising, but some parts of the discussion still sound overstated for the current stage. For example, the system includes some components that are not yet fully bioresorbable in the stimulation platform, and the in vivo studies are still limited in sample size and testing conditions. The authors should make clearer which parts are already demonstrated and which parts remain future engineering targets. This would improve the balance of the paper.

Reviewer #3

(Comments for the Author)

The authors have improved the quality of the manuscript substantially. The claims are more balanced. Valuable context has been added to the data and discussion. Numerous figures have been added to the supplementary data, aiding the interpretability of the work.

Some initial comments are still not addressed.

Reviewer 3 - Response 8

This comment was about the abstract. Changes have been made in other parts of the manuscript, but the abstract was not updated.

Battery voltage

The author agrees that there is a clear distinction between 1.84V of peak initial open-circuit voltage and 1.6V stable operating power. The abstract is not updated however, as initially requested. It still has the ubiquitous statement: 'The battery provides a stable output voltage of 1.84 V'. This should be either clearly 1.84V of peak initial open-circuit voltage, or 1.6V of stable operating voltage.

PCB

'fully biodegradable capsule systems for electroceutical therapy', this is still incorrect. The PCB's are not biodegradable. This needs to be reworded:

'fully biodegradable capsule systems (excluding PCB) for electroceutical therapy'.

Infection

'reduce infection risk' is still stated in the abstract, despite the author claimed to have removed every mention of infection risk.

Infection is also still mentioned on line 105 of page 4.

Reviewer 3 - Comment 22

Regarding explanation of used abbreviations. The author noted that GCD is no longer used as abbreviation, hence does not need explanation.

However, GCD is still used in Supplementary Figure 13, 15 and 16. Either explain the abbreviation, or rework the figures.

Version 2:

Reviewer comments:

Reviewer #2

(Comments for the Author)

The authors have responded to all of my comments. I believe that the revised manuscript is now suitable for publication.

Reviewer #3

(Comments for the Author)

The authors addressed all raised concerns. The manuscript is ready for publication.

made.

In cases where reviewers are anonymous, credit should be given to 'Anonymous Referee' and the source.

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Point-by-point response – Nature Chemical Engineering – Manuscript #:
NATCHEMENG-25112374

Referee #1 (Remarks to the Author)

Summary Comment: A bioresorbable Mg–MoO₃ paper battery with an output of 1.84 V is proposed in this paper. The authors conducted in vivo studies in swine models and claim that the system demonstrates robust operation within the GI tract and compatibility with clinically relevant use cases. This manuscript reports the design, fabrication, and in vivo evaluation of biodegradable magnesium-based batteries for ingestible bioelectronic systems. The authors present circular and large-area battery architectures integrated into capsule platforms and demonstrate gastric retention, wireless detection, and electrical stimulation in a swine model. The work addresses an important challenge in ingestible bioelectronics by enabling transient, bioresorbable power sources with multi-day operation and is of potential interest to the bioelectronics and translational biomedical engineering communities.

However, despite these merits, the manuscript suffers from significant issues in clarity, organization, consistency, and technical accuracy. Several claims are overstated or insufficiently supported, terminology and references are inconsistent, and multiple figures and supplementary materials are poorly described or incorrectly cited. As currently written, these issues substantially hinder the reader's ability to evaluate the validity, safety, and system-level implications of the work.

Response: We sincerely appreciate the reviewer's constructive feedback and have carefully revised our manuscript to address each point raised.

Comment 1: In the Introduction, the authors state that the biodegradable ionic liquid electrolyte is synthesized from choline chloride (ChCl). However, Supplementary Figure S4(d) labels the electrolyte as CHCl₂, and the caption states: "Preparation of the gel electrolyte by mixing CHCl₃, gelatin, glycerol, and PBS." CHCl₃ corresponds to chloroform, which raises concerns regarding chemical consistency and biocompatibility. Please clarify whether this is a labeling error or whether chloroform was used, and discuss any health considerations if applicable.

Response 1: We appreciate the feedback from the reviewer for pointing out this typo. We have made the appropriate changes. We have updated Supplementary Figure S4(d). All of our inks are water based and we confirm that there is no chloroform use in the electrolyte preparation.

Comment 2: The radar plot in Supplementary Figure S8 provides a qualitative comparison but does not clearly support the claim that operating voltage, areal capacity, energy density, and power density are all significantly higher than prior systems. Several referenced batteries exhibit comparable or higher values in individual metrics. Please soften this claim or provide a quantitative comparison table with absolute values and consistent test conditions.

Response 2: We thank the reviewer for this constructive comment. We have added a quantitative comparison table (Supplementary Table 2) summarizing absolute values of operating voltage,

areal capacity, energy density, and power density for the present work and selected prior biodegradable battery systems. This table provides a clearer and more transparent basis for comparison and complements the values reported in the manuscript.

Modification to the manuscript:

On page 22, Supplementary Table 2 is included in the SI:

Reference	Battery Type	Voltage	Power	Capacity	Energy Density
Huang. et.al., 2023 ^[1]	Zn	0.7 V	6 μ W	1.728 mWh	-
Jia et.al.,2016 ^[2]	Mg	1.75 V	64.6 μ W cm ⁻² (80 μ A/cm ²)	3.79 mAh cm ⁻² (10 μ A/cm ²)	4.70 mWh/cm ²
Karami-Mosammam et.al.,2022 ^[3]	Mg	1.7 V	196 μ W/cm ²	4.7 mAh (45 μ A/cm ²)	1.72 mWh/ cm ²
Huang et.al., 2018 ^[4]	Mg	1.6 V	0.27 mW/cm ²	6.5 mAh (12.5 μ A/cm ²)	6.5 mWh/cm ²
Bandodkar et.al.,2020 ^[5]	Mg	1.8 V	-	3 mAh (1 mA)	-
This work	Mg	1.84 V	239 μW/cm²	3.5 mAh 3.5 mAh/cm² (0.2mA/cm²) (V_{Cut-off}=0.8 V)	4.13 mWh/cm²
Huang et.al., 2022 ^[6]	Mg-I ₂	1.8 V	0.7 mW cm ⁻²	2.45 mAh 9.8 mAh cm ⁻² (0.4 mA cm ⁻²) (V _{Cut-off} = 1.2V)	17.7 mWh/cm ²

Comment 3: The manuscript refers to SGF immersion tests without defining SGF. Please explicitly define SGF (simulated gastric fluid) at first mention. Similarly, GCD should be defined when first introduced (and it appears to be undefined throughout).

Response 3: We thank the reviewer for this important point. We have updated the manuscript with the SGF, SIF definitions.

Comment 4: Battery terminology is inconsistent (e.g., large-area battery, large battery, small battery, circular battery, 000-size battery). Please adopt a consistent nomenclature and define each battery type clearly.

Response 4: We thank the reviewer for this valuable comment. Throughout the manuscript, for the small size we use 000-size battery and for the larger format, we use the term large-area battery.

Modification to the manuscript:

On page 7, we have added a text to describe nomenclature:

“We define two formats: (i) 000-size and (ii) large-area batteries.”

Comment 5: The statement, “measurements taken post-retrieval indicated functional retention and a gradual capacity decrease consistent with the designed degradation kinetics (Figure 2d),” is not clearly supported by Figure 2d. Please clarify how Figure 2d demonstrates retention and degradation kinetics, or revise the claim.

Response 5: We thank the reviewer for this helpful comment and agree that the original cross-reference to Figure 2d did not clearly support the stated claim. In the revised manuscript, Figure 2d has been retained but is now described explicitly as a schematic illustration, and it is no longer referenced as evidence of functional retention or degradation kinetics.

The statement regarding post-retrieval functional retention and gradual capacity decrease has been removed from Figure 2d cross-referencing and relocated to the concluding discussion of Figure 2, where it is supported by the quantitative electrochemical measurements and retention experiments described in the text (Page 9, line 262). This revision clarifies the distinct roles of schematic illustration and experimental data.

Comment 6: Please correct typographical and referencing issues, including: an extra parenthesis in “(Figure 2e). .”; incorrect figure-order references (e.g., Figure 2f and 2g in the text appear to correspond to Figures 2g and 2h); Supplementary Figure S12 is referenced as showing OCV and discharge data, but no such data appear; and inset axis labels in Supplementary Figure S13(a) are not visible.

Response 6: We thank the reviewer for raising this important point. We have corrected the cross-referencing to figures.

Comment 7: For Supplementary Figures S13 and S14, please clarify whether the same batteries were used across SGF immersion and in vivo retention experiments. If so, explain the observed increase in OCV at 72 h compared to 24 h for the large-area battery (Battery-1).

Response 7: We thank the reviewer for requesting clarification. The SGF immersion and in vivo gastric retention experiments were performed using different, independently fabricated batteries, not the same devices across conditions. We have revised the Supplementary Figures and captions to make this explicit.

The testing protocols were as follows:

- 24 h gastric retention experiments: For each battery, the open-circuit voltage (OCV) was first measured at Day 0 (prior to implantation). The battery was then subjected to a 24 h gastric retention test, retrieved, and the OCV was measured again to quantify voltage loss due to in vivo exposure. After this post-retention OCV measurement, the battery was subjected to a galvanostatic discharge test.
- 72 h gastric retention experiments: For the 72 h retention studies, batteries with comparable initial electrochemical states were selected. Prior to implantation, the OCV of each battery was measured and confirmed to be within the range of 1.6–1.8 V. The batteries were then retained in the stomach for 72 h, retrieved, and their OCV was measured immediately, followed by galvanostatic discharge testing.
- SGF immersion experiments: For simulated gastric fluid (SGF) experiments, batteries with identical initial OCVs (1.6–1.8 V) were used. The batteries were immediately immersed in SGF, and OCV was recorded prior to initiating the discharge test.

Because different batteries were used for each experimental condition and all devices were pre-screened to ensure similar initial OCVs, small differences in absolute OCV values between the 24 h, 72 h, and SGF datasets reflect normal device-to-device variation rather than voltage recovery or enhancement effects. Importantly, after correction of labeling and clarification of protocols, all conditions consistently show a decrease in OCV with increased exposure time.

We have updated Supplementary Figures 15 and 16, their captions, and the Methods section to clearly describe these procedures and eliminate misunderstanding.

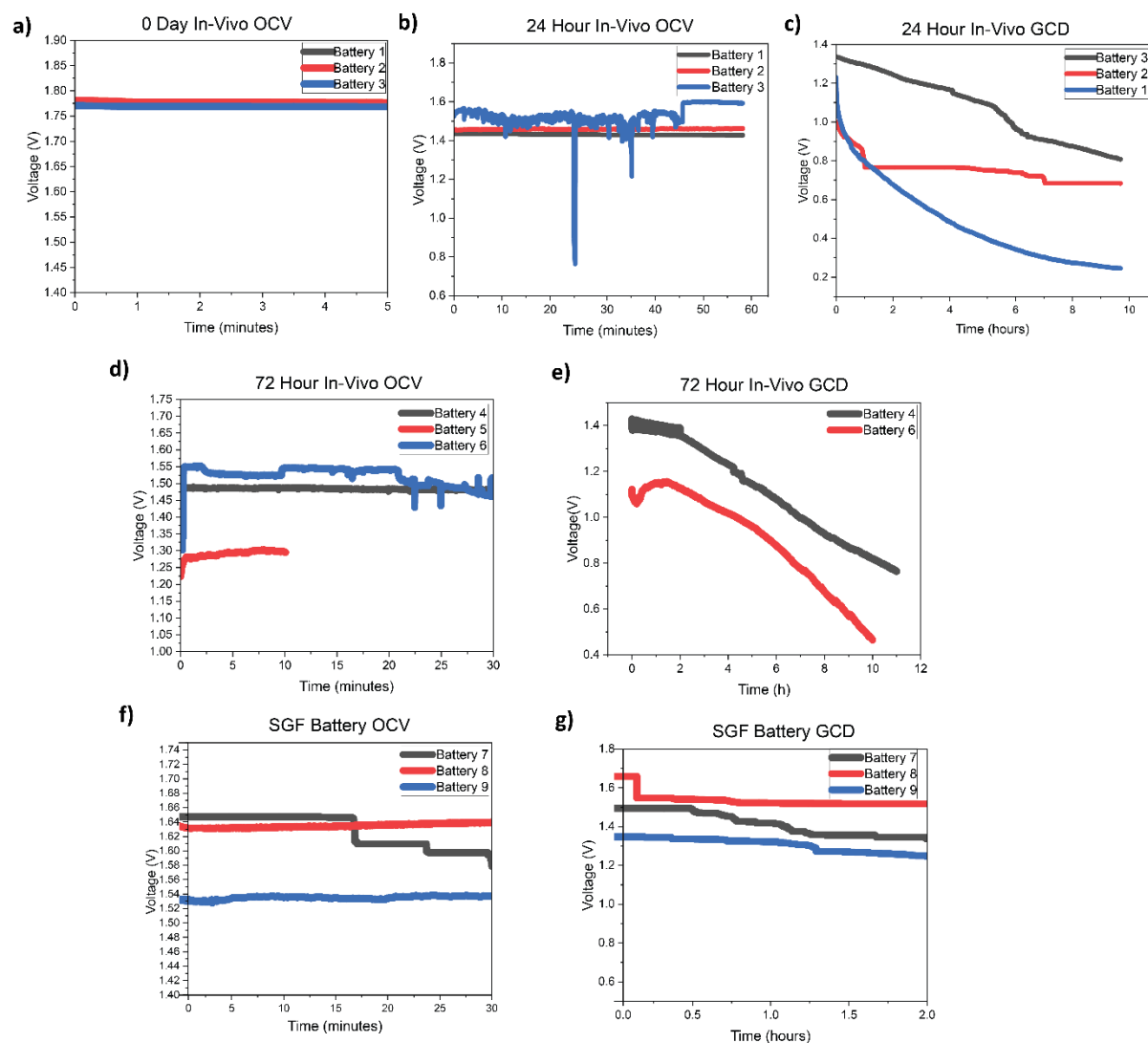
Modification to the manuscript:

On page 21, we have added a text to methods:

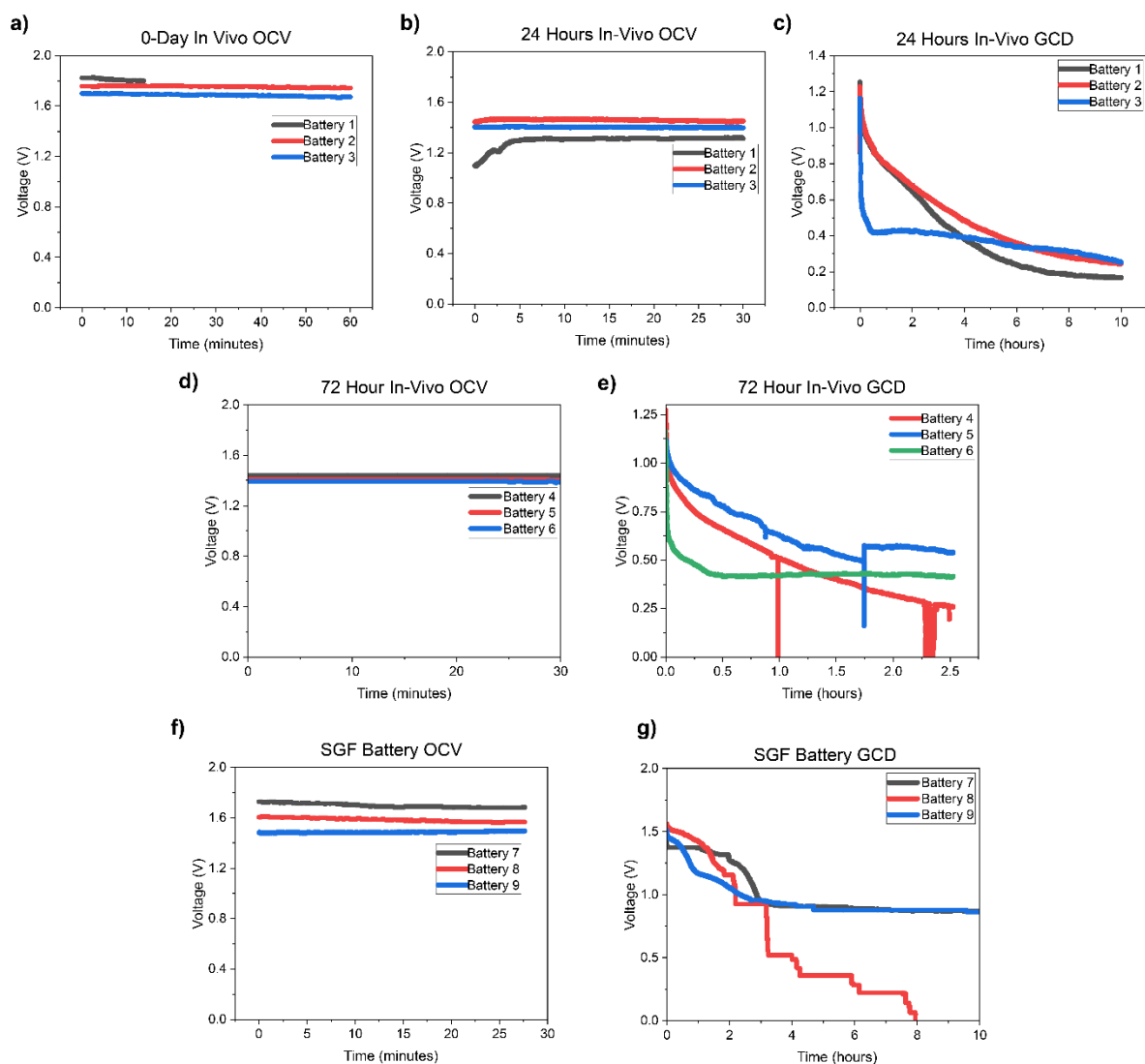
“For all retention and immersion experiments, different batteries were used for each test condition (24 h gastric retention, 72 h gastric retention, and SGF immersion). Prior to testing, each battery’s OCV was measured, and only batteries with initial OCVs between 1.6 and 1.8 V were selected to ensure comparable starting conditions. For analysing the effect of gastric retention on battery voltage and capacity, OCV was measured before capsule ingestion and again after retrieval (24 h or 72 h), followed by galvanostatic discharge testing. For SGF experiments, batteries with matched initial OCVs were immediately immersed in SGF, and OCV was recorded prior to discharge measurements. “

Modification to the Supplementary Information:

We have updated the Supplementary Figures 15 and 16.



Supplementary Figure 15. Electrochemical characterization of 000-size batteries following gastric retention and simulated gastric fluid (SGF) immersion. a) Open-circuit voltage (OCV) measured at Day 0 prior to the 24 h in vivo gastric retention study. b) OCV and c) galvanostatic discharge (GD, 0.1 mA cm^{-2}) of batteries retrieved after 24 h of in vivo gastric retention. d) OCV measured after 72 h of in vivo gastric retention, followed immediately by (e) galvanostatic discharge (Battery 5 discharge curve excluded due to complete depletion). f) OCV of batteries immediately after SGF immersion, followed by g) galvanostatic discharge. Different batteries were used for each retention and immersion condition ($n = 9$ total; $n = 3$ per condition).



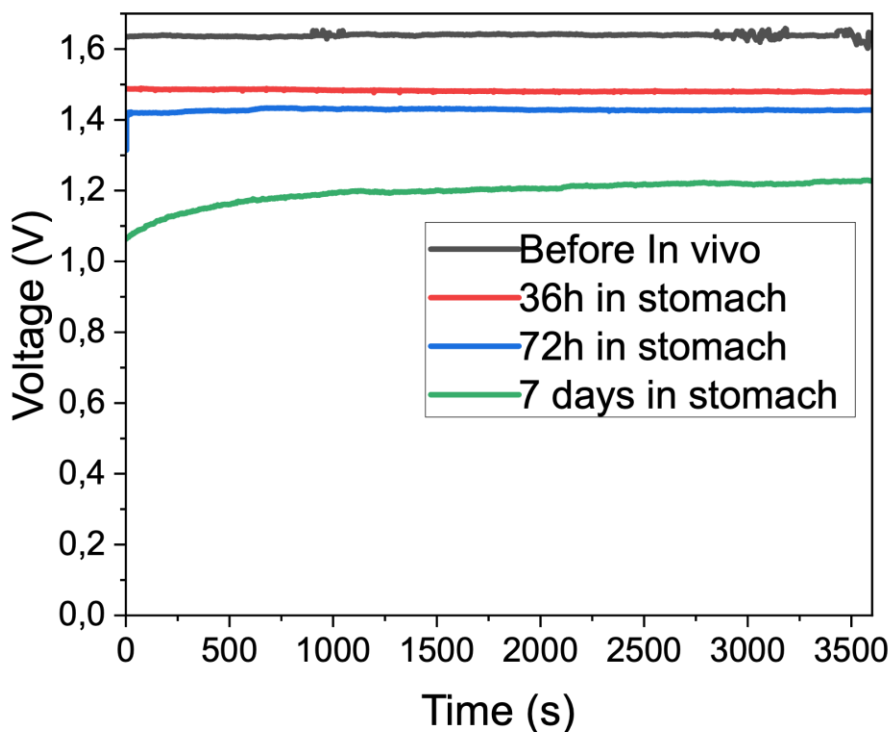
Supplementary Figure 16. Electrochemical characterization of large-area batteries following gastric retention and SGF immersion. a) OCV measured at Day 0 prior to the 24 h in vivo gastric retention study. b) OCV and c) galvanostatic discharge (GD, 0.1 mA cm^{-2}) of batteries retrieved after 24 h of in vivo gastric retention. d) OCV measured after 72 h of in vivo gastric retention, followed immediately by e) galvanostatic discharge. f) OCV of batteries immediately after SGF immersion, followed by g) galvanostatic discharge. Different batteries were used for each retention and immersion condition ($n = 9$ total; $n = 3$ per condition).

Comment 8: In Supplementary Figure S15, an increase in battery voltage from 36 h to 72 h is observed. Please comment on the possible mechanism responsible for this behavior.

Response 8: We thank the reviewer for raising this point. We note that the figure has been corrected, and the previously perceived voltage increase resulted from an earlier labeling error. In the corrected Supplementary Figure 17, the battery voltage decreases with increasing gastric retention time, consistent with self-discharge, partial gel electrolyte dehydration, and material degradation. This behavior is observed across all tested batteries and reflects the expected electrochemical and degradation processes during prolonged exposure to gastric conditions. The figure and caption have been updated accordingly to avoid ambiguity.

Modification to the Supplementary Information:

We have updated the Supplementary Figures 17.



Supplementary Figure 17. In vivo retention and open-circuit voltage (OCV) comparison at multiple time points. OCV measured before in vivo placement (Day 0) and after 36 h, 72 h, and 7 days of gastric retention.

Comment 9: Supplementary Note 1 contains a missing citation. Please add the appropriate reference.

Response 9: We appreciate the reviewer's note. The relevant reference was cited in the Supplementary Information.

Comment 10: The description of RSSI behavior is incorrect. A shift from $-40/-50$ dBm to approximately -60 dBm indicates signal attenuation rather than an increase in signal strength. Please revise the wording accordingly.

Response 10: We thank the reviewers for identifying this error and agree that the original wording incorrectly described RSSI behavior. We have revised the text to correctly reflect that the observed shift from approximately $-40/-50$ dBm (in air) to approximately -60 dBm (after ingestion) corresponds to signal attenuation rather than an increase in signal strength.

In the revised manuscript, we clarify that the key observation is not an increase in RSSI magnitude, but a distinct and reproducible change in RSSI associated with transition from an air environment to a tissue environment. This attenuation is consistent with RF propagation through biological tissue and serves as a reliable indicator of ingestion.

We have removed language suggesting signal enhancement and now describe the RSSI shift as an environmental signature that enables wireless, passive detection of capsule ingestion without requiring additional modeling. The revised text avoids claims beyond the demonstrated sensing capability and aligns with established expectations of tissue-induced RF attenuation.

Modification to the manuscript:

To reflect this point clearly, we have added the following sentences to page 12:

“This ~ 10 dB change in RSSI provides a clear and distinct signature of capsule ingestion, supporting the use of BA-RFID tags for noninvasive, real-time monitoring of medication adherence “.

Comment 11: Several figure references appear incorrect: flexible electrode fabrication is attributed to Supplementary Figure S15, which does not show this information; and the electrical stimulation PCB is referenced as Figure 5d, which does not exist (this appears to be Figure 4d).

Response 11: We thank the reviewer for noting these mistakes. We have corrected the cross-referencing to figures for both electrode fabrication and stimulation PCB.

Comment 12: In Section 2.4, the authors discuss degradation and bioresorption of the batteries during GI transit but do not address the fate of the non-bioresorbable circular PCB. Please clarify how this component behaves during prolonged gastric retention and subsequent passage.

Response 12: We thank the reviewer for highlighting this important point. We agree that clarification regarding the fate of the non-bioresorbable printed circuit board (PCB) is necessary.

In the revised manuscript, we now explicitly clarify that while the battery and electrode components are designed to undergo biodegradation and bioresorption, the circular PCB used in this proof-of-concept system is not bioresorbable, designed to be excreted naturally.

During the in vivo passage experiments reported here, the PCB remains structurally intact and excreted naturally. Its dimensions and encapsulation are comparable to those used in established ingestible electronic systems, which are known to safely transit the gastrointestinal tract following completion of their functional task.

We have added a text to Section 2.4 to clarify that the present work focuses on demonstrating biodegradable power delivery and stimulation functionality. The faith of the PCB is discussed in the page 17, line 493.

Modification to the manuscript:

To reflect this point clearly, we have added the following sentences:

“The stimulation PCB is compact, remained intact, and was naturally excreted in all passage tests. Its size is well within the range shown to be safe in prior studies, which have demonstrated the safe passage of significantly larger ingestible capsules^[7]. “

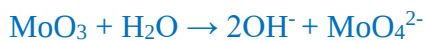
Comment 13: The safety discussion is currently insufficient. The manuscript implies safety because the device contributes only a small fraction of the daily recommended mineral intake; however, this alone does not establish safety under realistic use. Please strengthen the safety argument, including the fate of dissolution products (Mg ions and molybdenum oxides), local exposure considerations, and any relevant toxicology/biocompatibility evidence.

Response 13: We thank the reviewer for highlighting this important point.

First, we clarify the fate of dissolution products. Upon operation and degradation, the magnesium anode converts to Mg^{2+} ions, which are naturally present in gastrointestinal fluids and are efficiently regulated through established absorption and excretion pathways. Magnesium-based biodegradable implants and ingestible devices have been widely reported to degrade into Mg^{2+} without inducing adverse tissue responses, supporting the biological tolerance of these ions under transient exposure conditions.

For the cathode, molybdenum trioxide gradually dissolves to form molybdate species (MoO_4^{2-}), which are known trace elements in human physiology and are primarily cleared via renal excretion.

The revised manuscript now describes the expected oxidation and dissolution mechanisms of Mo and MoO_3 in aqueous environments, including acidic and near-neutral conditions, and places these processes in the context of prior literature on transient electronics and biodegradable battery systems. Specifically, metallic molybdenum undergoes gradual oxidation in aqueous media to form soluble molybdate species, while MoO_3 can hydrolyze to yield molybdate ions, which represent the dominant and biologically relevant dissolution products:



Second, we address local exposure considerations (Supplementary Table 1). Unlike accidental ingestion of commercial batteries—where alkaline electrolyte leakage, sharp edges, and rapid localized chemical injury dominate—the bioresorbable battery reported here:

- Contains no corrosive liquid electrolytes,
- Does not generate high local pH,
- Degrades into soluble or finely dispersed products rather than rigid or sharp fragments.

Third, we expand the discussion of toxicology and biocompatibility evidence. The revised manuscript now explicitly references prior studies on magnesium-based bioresorbable electronics and molybdenum-containing transient materials that demonstrate compliance with established biocompatibility frameworks.

- With respect to toxicological considerations, we have expanded the discussion to place the quantities of released species in the context of established nutritional and toxicological data. The total Mg and molybdenum content per device is minimal, and estimated exposure levels are well below reported safety thresholds. For example, the recommended dietary allowance for Mg in adults is approximately $400 \text{ mg} \cdot \text{day}^{-1}$, which is orders of magnitude higher than the Mg content of a single device. Prior studies have also reported no observable toxicity in rats at molybdenum exposure levels up to $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ^[8], and molybdenum is known to be efficiently excreted via renal clearance as molybdate^[9].

Consistent with this understanding, long-term implantation studies of thin molybdenum films ($\approx 25 \text{ } \mu\text{m}$) have reported no evidence of tissue injury or measurable organ accumulation over extended durations^[10]. These findings, together with the low material loading and efficient physiological clearance of molybdenum species, suggest minimal risk of accumulation under the proof-of-concept conditions studied here.

Modification to the manuscript:

On page 17, we added a discussion paragraph: From a safety and translational perspective, the material composition of the battery platform and its intended applications aligns with established dietary and biomedical exposure limits. Molybdenum and magnesium are present in milligram-scale quantities per battery or capsule, which are below levels associated with clinically relevant toxicity^[11]. Upon degradation, the primary dissolution products—molybdenum oxides and magnesium ions—correspond to essential micronutrients with well-regulated gastrointestinal absorption and renal clearance pathways^[8,11].

Assuming complete exposure of a large-area battery to PBS or bodily fluids for 24 h, only partial dissolution of Mg anode would be expected, based on the corrosion rates of approximately $1\text{-}10 \text{ } \mu\text{m}/\text{day}$ ^[6]. In this case, the maximum local concentration is estimated to be approximately 3.4 mg of Mg-derived products, primarily Mg^{2+} and $\text{Mg}(\text{OH})_2$. For the cathode, partial degradation of Mo ($0.025 \text{ } \mu\text{m}/\text{day}$ ^[12]) and dissolution of MoO_3 (solubility: 1 g/L ^[4]) would generate MoO_4^{2-} at an estimated level of $<1 \text{ mg}/\text{day}$. These estimated values are below daily intake levels for magnesium ($420 \text{ mg}/\text{day}$ ^[6]) and molybdenum ($2 \text{ mg}/\text{day}$ ^[13]).

Previous studies of molybdenum-based ingestible devices, using inductively coupled plasma mass spectrometry (ICP-MS), have demonstrated short-term degradation and clearance in vivo^[14]. In addition, molybdenum implant studies have reported minimal risk of long-term accumulation^[10], while prior in vivo investigations of magnesium-based batteries and galvanic cells have similarly demonstrated favorable biocompatibility and safety profiles^[6,15].

Comment 14: Relatedly, the in vivo evaluation appears to reflect a “clean” (fasted) GI condition. Please discuss (and ideally test) how the system may behave under more representative human conditions (food, fiber, mucus, altered motility), including the possibility of localized retention that could create a dissolution “hot spot.”

Response 14: We thank the reviewer for this important point. The in vivo studies were intentionally performed under controlled, fasted conditions to minimize variability and enable clear interpretation of battery performance, retention behavior, and electrostimulation application. We agree that human gastrointestinal conditions are more complex and include food bolus, mucus layers, gastric pH can fluctuate between approximately 1 and 6 depending on individual factors such as diet, fasting state, and medical conditions (e.g., obesity, motility disorders). variable motility, and heterogeneous fluid composition, all of which can influence device residence time and local dissolution dynamics.

Under fed conditions, the presence of food and mucus is expected to electrolyte exposure, potentially slowing degradation rather than accelerating it. In addition, the wax encapsulation and paper-based battery architecture are designed to promote gradual, diffusion-limited access of gastrointestinal fluids, reducing the likelihood of rapid localized dissolution or thermal/chemical “hot spots.” Importantly, magnesium-based bioresorbable systems degrade through self-limiting corrosion mechanisms, and no exothermic reactions are expected at the power densities reported here.

We have added a discussion of fed-state GI conditions, variable motility, and the potential for localized retention to the Discussion section, outlining how these factors may influence degradation kinetics and device behavior in future translational studies.

Modification to the manuscript:

On page 20, we added a discussion paragraph: While the in vivo evaluations in this study were conducted under controlled, fasted conditions, future investigations will examine device behaviour under more physiologically representative fed gastrointestinal states, including the presence of food, pH variability, mucus, and altered motility. These factors may influence local residence time and fluid access, thereby modulating degradation kinetics. However, the diffusion-limited corrosion of magnesium, together with the natural wax–encapsulated battery architecture, is expected to mitigate rapid or highly localized dissolution.

Comment 15: Please clarify whether the observed OCP/OCV reduction over time is dominated by discharge or dissolution. It would be more informative to provide discharge potential vs. time (at different current densities) and dissolution/open-circuit behavior vs. time (at different current densities), to reflect resistance evolution and degradation effects.

Response 15: We thank the reviewer for this helpful suggestion. In Figures 2f and 2g, as well as Supplementary Figure 16, the battery voltage and capacity decrease with increasing gastric retention time, consistent with progressive material degradation and partial gel electrolyte dehydration. During benchtop testing, the battery was able to continuously power the PCB for up to 3 days (Supplementary Figures 23 and 24), demonstrating stable operation under controlled conditions. However, once placed in the stomach, exposure to humidity, gastric fluids, and self-discharge processes leads to a gradual and near-linear decrease in open-circuit voltage (OCV), accompanied by a reduction in capacity. This behavior was consistently observed across all tested batteries and reflects the combined electrochemical and degradation processes occurring during prolonged exposure to gastric conditions.

Modification to the manuscript:

On page 9, we added a text: While both discharging at constant current and material degradation over time contribute, the near-linear OCV decay under open-circuit conditions (Supplementary Figures 15, 16 and 17) suggests that self-discharge and corrosion dominate, whereas capacity loss under load reflects the combined effects.

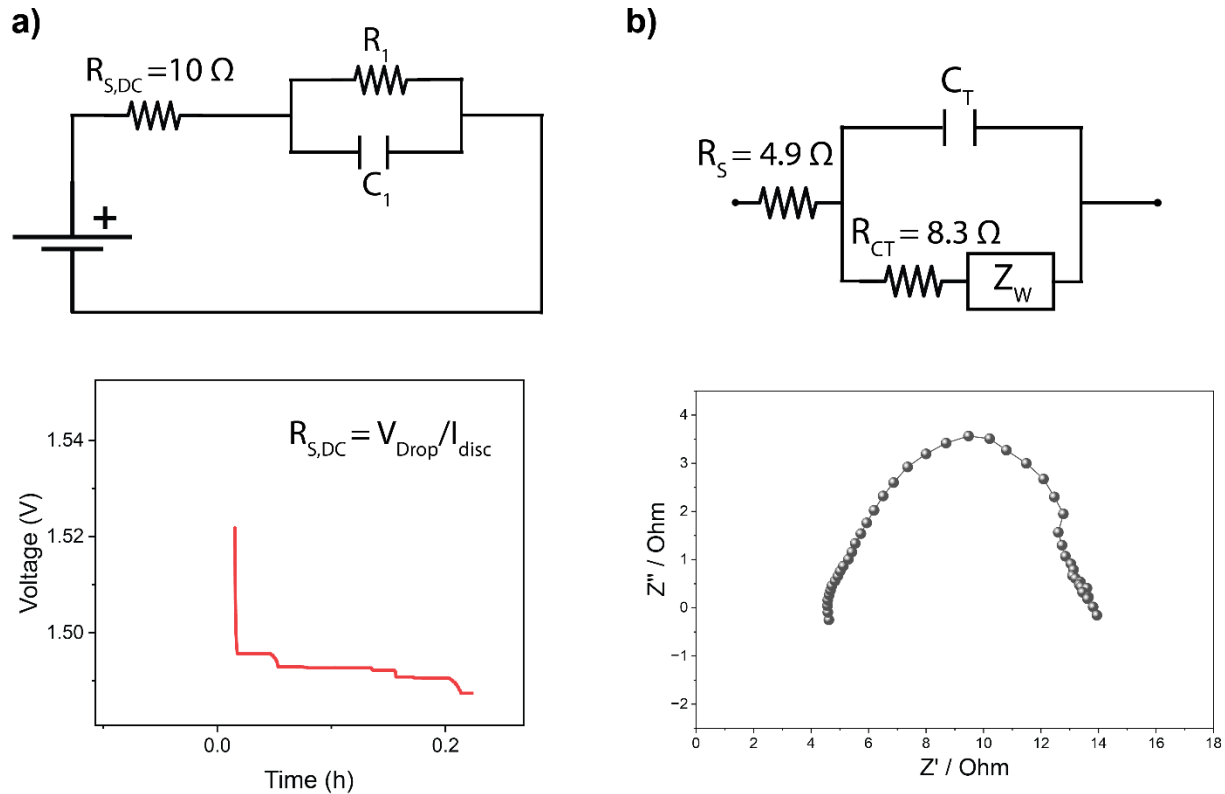
Comment 16: It would be helpful to include a simplified DC battery model (e.g., a Thevenin equivalent model) to support system-level interpretation and comparison.

Response 16: We thank the reviewer for this suggestion. In response, we have now included a simplified DC battery model based on a first-order Thevenin equivalent circuit (Supplementary Figure 8). To extract physically meaningful parameters, electrochemical impedance spectroscopy data were fitted using a Randles equivalent circuit.

The fitted Randles parameters define the effective series resistance and charge transfer resistance. This approach enables a compact and physically interpretable system-level representation of the battery behavior under the operating conditions relevant to this work.

Modification to the Supplementary Information:

On page 7, we added a figure to Supplementary Information.



Supplementary Figure 9. Simplified DC battery model and impedance spectroscopy of biodegradable battery. a) First-order Thevenin equivalent circuit used for system-level representation of the biodegradable battery, consisting of an open-circuit voltage source (V_{OC}), series resistance (R_s), and a parallel RC element ($R_1 \parallel C_1$). b) Electrochemical impedance spectroscopy (EIS) Nyquist plot using a Randles equivalent circuit. The high-frequency intercept corresponds to the effective series resistance R_s , while the semicircle reflects the charge-transfer resistance and double-layer capacitance.

Modification to the manuscript:

On page 7, we added a text: The internal resistance and interfacial charge-transfer characteristics of the bioresorbable battery were further analyzed using electrochemical impedance spectroscopy (EIS) and equivalent circuit modeling is given (Supplementary Figure 9).

Comment 17: The term “edible” is used ambiguously and inconsistently. Please clearly define what is meant technically and use the chosen term consistently.

Response 17: We thank the reviewer for this note. We have only used edible for once while describing the previous batteries, where the studies described as ‘edible’. For our work, we use bioresorbable battery to explain the concept for ingestible electronics applications. For the battery

concept, we use ‘bioresorbable’ and this refers to materials that degrade into physiologically absorbable products and does not imply nutritional value or food-grade classification.

Modification to the manuscript:

On page 7, line 149, we added a text: In our work, ‘bioresorbable’ refers to materials that degrade into physiologically processable products and does not imply nutritional or food-grade classification.

Comment 18: The sentence “We demonstrated the capability of the battery through three key in vivo applications using swine models” is repeated twice in immediate succession and should be revised to remove redundancy.

Response 18: We thank the reviewer for this suggestion. We have removed the sentence repeating accordingly.

Referee #2 (Remarks to the Author)

Summary Comment: The manuscript reports a fully bioresorbable Mg–MoO₃ paper battery designed for powering ingestible bioelectronic systems. The authors demonstrate two applications: (1) a battery-assisted RFID capsule capable of meter-scale wireless tracking, and (2) a degradable gastric electrical stimulation system validated in swine. The topic is timely and the results are promising. However, several key scientific and engineering questions must be addressed before publication.

Response: We appreciate the reviewer's recognition of our work. We sincerely appreciate the reviewer's constructive feedback and have carefully revised our manuscript to address each point raised.

Comment 1: The manuscript does not quantitatively compare its energy density, discharge performance, and degradation behavior with prior Mg-based or Zn-based transient batteries. A comparison table and clearer novelty discussion are needed.

Response 1: We thank the reviewer for this constructive comment. In response, we have added a quantitative comparison table (Supplementary Table 2) summarizing key performance metrics—including energy density, discharge characteristics, and degradation behavior—for the present work and previously reported Zn-based and Mg-based transient batteries. Wherever possible, reported values under comparable operating conditions were used, and relevant differences in testing protocols are noted.

In addition, we have revised the Discussion section to more clearly articulate the novelty of this work relative to prior transient battery systems. Rather than claiming record performance in individual metrics, the revised text emphasizes the unique combination of (i) battery-powered operation within a fully biodegradable platform, (ii) stable discharge behavior under physiologically relevant conditions, (iii) controlled and gradual degradation behavior, and (iv) validation through in vivo demonstrations. These revisions clarify the contribution of the present work within the broader landscape of transient Mg- and Zn-based batteries.

Modification to the manuscript:

To reflect this point clearly, we have revised the section in the main manuscript and added Supplementary Table 2:

Reference	Battery Type	Voltage	Power	Capacity	Energy Density
Huang. et.al., 2023 ^[1]	Zn	0.7 V	6 μ W	1.728 mWh	-
Jia et.al.,2016 ^[2]	Mg	1.75 V	64.6 μ W cm ⁻² (80 μ A/cm ²)	3.79 mAh cm ⁻² (10 μ A/cm ²)	4.70 mWh/cm ²

Karami-Mosammam et.al.,2022 ^[3]	Mg	1.7 V	196 $\mu\text{W}/\text{cm}^2$	4.7 mAh (45 $\mu\text{A}/\text{cm}^2$)	1.72 mWh/ cm^2
Huang et.al., 2018 ^[4]	Mg	1.6 V	0.27 mW/ cm^2	6.5 mAh (12.5 $\mu\text{A}/\text{cm}^2$)	6.5 mWh/ cm^2
Bandodkar et.al.,2020 ^[5]	Mg	1.8 V	-	3 mAh (1 mA)	-
This work	Mg	1.84 V	239 $\mu\text{W}/\text{cm}^2$	3.5 mAh 3.5 mAh/cm^2 (0.2mA/cm^2) ($V_{\text{Cut-off}}=0.8$ V)	4.13 mWh/cm^2
Huang et.al., 2022 ^[6]	Mg-I ₂	1.8 V	0.7 mW cm^{-2}	2.45 mAh 9.8 mAh cm^{-2} (0.4 mA cm^{-2}) ($V_{\text{Cut-off}} = 1.2\text{V}$)	17.7 mWh/ cm^2

Comment 2: The degradation pathways of Mo and MoO₃ in gastric fluid, expected ionic dissolution products, and potential toxicological concerns are not adequately discussed. These are essential for assessing clinical relevance. In addition, mass-loss curves, EIS evolution, mechanical integrity measurements, or dissolution-rate constants should be provided to support the claims of reproducible and safe biodegradation.

Response 2: We thank the reviewer for raising this important point. In response, we have substantially expanded the discussion of degradation pathways, dissolution products, and safety considerations associated with Mo- and MoO₃-based components under gastric conditions.

The revised manuscript now describes the expected oxidation and dissolution mechanisms of Mo and MoO₃ in aqueous environments, including acidic and near-neutral conditions, and places these processes in the context of prior literature on transient electronics and biodegradable battery systems. Specifically, metallic molybdenum undergoes gradual oxidation in aqueous media to form soluble molybdate species, while MoO₃ can hydrolyze to yield molybdate ions, which represent the dominant and biologically relevant dissolution products:



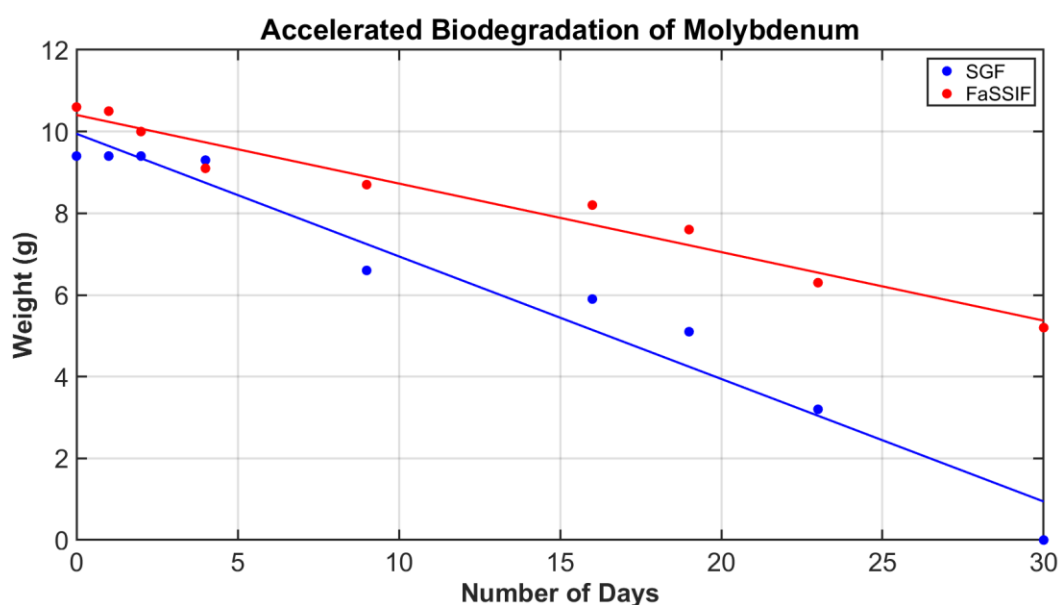
To further support the reproducibility and controlled nature of biodegradation, we have added quantitative degradation characterization to the revised manuscript. Prior studies have reported dissolution rates of Mg and Mo foils on the order of $\approx 1\text{--}10 \mu\text{m}\cdot\text{day}^{-1}$ and $\approx 0.02 \mu\text{m}\cdot\text{day}^{-1}$, respectively, in simulated biofluids (pH 7.4, 37 °C)^[12]. In addition, Karami-Mosammam *et al.* demonstrated the degradation behavior of Mg-based biodegradable battery components, including

Mg anodes and MoO₃-based cathodes, in phosphate-buffered saline, where rapid Mg dissolution and gradual structural changes of the MoO₃ cathode were observed^[3].

Motivated by these prior observations, and to better represent gastrointestinal conditions relevant to the present work, we have included new accelerated dissolution experiments using molybdenum foil (25 μm) in simulated gastric fluid (SGF) and fasted-state simulated intestinal fluid (FaSSIF). These results are presented in Supplementary Figure 6 and demonstrate gradual, repeatable dissolution behavior under both conditions.

Modification to the Supplementary Information:

We have added the Supplementary Figure 6.



Supplementary Figure 6. Accelerated dissolution of Mo foil (25 μm) in both SGF and FaSSIF. Specifically, metallic molybdenum undergoes gradual oxidation in aqueous media to form soluble molybdate species, while MoO₃ can hydrolyze to yield molybdate ions, which represent the dominant and biologically relevant dissolution products.

Equations related to the dissolution $2\text{Mo} + 2\text{H}_2\text{O} + 3\text{O}_2 \rightarrow 2\text{H}_2\text{MoO}_4$ and $\text{MoO}_3 + \text{H}_2\text{O} \rightarrow 2\text{OH}^- + \text{MoO}_4^{2-}$

Modification to the manuscript:

We have added a sentence clarifying the dissolution, page 6:

“The dissolution kinetics and mass-loss of Mo under accelerated degradation conditions in gastrointestinal fluids are shown in Supplementary Figure S6, illustrating linear biodegradation behavior. “

Based on our current design and available toxicological and nutritional data:

With respect to toxicological considerations, we have expanded the discussion to place the quantities of released species in the context of established nutritional and toxicological data. The total Mg and molybdenum content per device is minimal, and estimated exposure levels are well below reported safety thresholds. For example, the recommended dietary allowance for Mg in adults is approximately $400 \text{ mg} \cdot \text{day}^{-1}$, which is orders of magnitude higher than the Mg content of a single device. Prior studies have also reported no observable toxicity in rats at molybdenum exposure levels up to $40 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ ^[8], and molybdenum is known to be efficiently excreted via renal clearance as molybdate^[9].

Consistent with this understanding, long-term implantation studies of thin molybdenum films ($\approx 25 \text{ } \mu\text{m}$) have reported no evidence of tissue injury or measurable organ accumulation over extended durations^[10]. These findings, together with the low material loading and efficient physiological clearance of molybdenum species, suggest minimal risk of accumulation under the proof-of-concept conditions studied here.

Finally, while the available data and prior literature support the safety of the constituent materials at the demonstrated scale, comprehensive long-term toxicological and pharmacokinetic studies will be required as part of future translational development. Even under conservative assumptions of one battery per day, cumulative Mg and Mo exposure would remain well within normal dietary intake ranges and below toxicity thresholds. Given the capsule's dissolution and the efficient physiological excretion of these trace metals, subclinical accumulation or long-term perturbation of mineral balance is not anticipated.

Modification to the manuscript:

On page 17, we added a discussion paragraph: From a safety and translational perspective, the material composition of the battery platform and its intended applications aligns with established dietary and biomedical exposure limits. Molybdenum and magnesium are present in milligram-scale quantities per battery or capsule, which are below levels associated with clinically relevant toxicity^[11]. Upon degradation, the primary dissolution products—molybdenum oxides and magnesium ions—correspond to essential micronutrients with well-regulated gastrointestinal absorption and renal clearance pathways^[8,11]. Previous studies of molybdenum-based ingestible devices, using inductively coupled plasma mass spectrometry (ICP-MS), have demonstrated short-term degradation and clearance in vivo^[14]. In addition, molybdenum implant studies have reported minimal risk of long-term accumulation^[10], while prior in vivo investigations of magnesium-based batteries and galvanic cells have similarly demonstrated favorable biocompatibility and safety profiles^[6,15].

Comment 3: The manuscript claims enhanced RFID range due to “active backscatter,” but does not provide a link budget or explain the modulation mechanism from an RF engineering perspective. Quantitative analysis is needed to support the reported 4-m range.

Response 3: We thank the reviewer for this insightful question and feedback. To evaluate the wireless communication link budget of the proposed active backscatter system using the EM4325

BAP RFID chip at 915 MHz, a Friis-based link budget was conducted, accounting for free-space path loss, tissue propagation effects, antenna gains, and receiver sensitivity.

- The operating frequency of 915 MHz gives a free-space wavelength of $\lambda = \frac{c}{f} = 0.328$ m. However, within biological tissue, the electromagnetic wave experiences both compression and attenuation due to the medium's complex permittivity and conductivity.

Using a relative permittivity of $\epsilon' = 65$ and a conductivity $\sigma = 1.19$ S/cm, the complex relative permittivity is expressed as $\epsilon^* = \epsilon' - j(\sigma/\omega\epsilon_0)$, where the imaginary component evaluates to $\epsilon'' = 23.38$, giving a loss tangent of $\tan \delta = 0.360$.

The complex wavenumber in tissue is obtained from $k = k_0\sqrt{\epsilon^*}$, where $k_0 = 19.16$ rad/m is the free-space wavenumber at 915 MHz. Decomposing $\sqrt{\epsilon^*}$ into its real and imaginary parts yields a phase constant of $\beta = 156.9$ rad/m and an attenuation constant of $\alpha = 27.32$ Np/m. The wavelength inside tissue is therefore $\lambda_{tissue} = \frac{2\pi}{\beta} = 4.0$ cm, approximately eight times shorter than in free space — a critical consideration for implanted/ ingestible antenna design.

For example, the one-way power attenuation through tissue is given by $L_{tissue} = 8.686 \times \alpha \times d = 2.37$ dB (at the implant depth of $d = 10$ mm).

- **Link Budget Analysis:** The link budget is decomposed into two independent one-way links, as is appropriate for an active backscatter architecture in which the tag is battery-assisted and actively drives its return transmission, thereby eliminating the round-trip path-loss penalty of passive backscatter systems. The reader antenna gain is 9 dBi on both transmit and receive, the simulated tag antenna directivity is -2 dBi at minimum (from Figure 30F in Supplementary note 1), and the reader transmit power is 15 dBm. The 4 m separation between the skin surface and the external reader is treated as an air-only path, with tissue loss applied as a separate additive term. The free-space path loss over 4 m at 915 MHz is computed as:

$$FSPL = 20 \cdot \log(4\pi R) = 43.7 \text{ dB}$$

For the downlink, the power delivered to the tag chip is,

$$\begin{aligned} P_{rx_tag} &= P_t + G_{reader} + P_{tag} - FSPL - L_{tissue} \\ &= 15 + 9 + (-2) - 43.7 - 2.37 = -24.1 \text{ dBm} \end{aligned}$$

The EM4325 in BAP mode at its most sensitive setting has a minimum read/write sensitivity of -31 dBm, yielding an activation margin of $+6.9$ dB — sufficient for reliable tag wake-up at this range.

For the uplink, the power received at the reader is

$$\begin{aligned}
P_{rx_reader} &= EIRP_{tag} + G_{reader} - FSPL - L_{tissue} \\
&= (-2) + 9 - 43.7 - 2.37 = -39.1 \text{ dBm}
\end{aligned}$$

The effective noise floor at the reader receiver is

$$N = 174 \frac{\text{dBm}}{\text{Hz}} + NF + 10 \log B(\text{Hz})$$

Where dBm is thermal noise at room temperature, NF is the Noise Figure in dB, and B is the system bandwidth in Hz,

$$N = -127 + 5 = -122 \text{ dBm}$$

$N = -122 \text{ dBm}$ giving an uplink SNR margin of $-39.1 - (-122) = +82.9 \text{ dB}$, which is more than sufficient for error-free demodulation even in the presence of orientation-dependent amplitude variations and multipath effects.

These results demonstrate that the proposed active backscatter system operating at 915 MHz with the EM4325 in BAP mode is feasible at a reader-to-skin distance of 4 m. Both the downlink activation margin (+6.9 dB) and the uplink SNR margin (+82.9 dB) are positive and robust under the conservative assumptions applied, indicating reliable bidirectional communication without requiring an increase in reader transmit power beyond the assumed 15 dBm.

- The superiority of active backscatter over passive backscatter in this application can be understood both conceptually and quantitatively. In passive backscatter, the tag carries no independent power source and must reflect a portion of the incident reader signal back toward the receiver. This imposes a round-trip path loss on the system, where the received power scales with the fourth power of the distance $(\lambda/4\pi R)^4$ and is further attenuated by the squared reflection-coefficient modulation term $|\Delta\Gamma|^2$. The net effect is that every doubling of range incurs 12 dB of additional loss rather than the 6 dB penalty of a one-way link. In active backscatter, the battery-assisted tag drives its own return transmission independently, reducing the uplink to a one-way Friis equation and breaking the round-trip dependency entirely. This architectural difference translates directly and substantially into link budget performance.
- Quantitatively, comparing the two architectures under matched conditions — same frequency (915 MHz), same reader transmit power (15 dBm), same antenna gains (9 dBi reader, -2 dBi tag), same 4 m air path, and same 2.37 dB tissue loss — the passive backscatter received power at the reader would be

$$\begin{aligned}
P_{rx_passive} &= P_t + G_{reader} + G_{tag} + (\lambda/4\pi R)^4 \cdot |\Delta\Gamma|^2 \\
P_{rx_passive} &= 15 + 9 + (-2) + (-2 \cdot 43.7) + 20 \log(|\Delta\Gamma|^2)
\end{aligned}$$

At a typical impedance modulation depth of $\Delta\Gamma = 0.5$ (-6 dB), yields

$$P_{rx_passive} = 15 + 9 - 2 - 87.4 - 4.74 - 6 = -76.1 \text{ dBm}$$

By contrast, the active backscatter uplink delivers -39.1 dBm to the reader receiver. The active architecture, therefore, recovers 37.0 dB relative to passive backscatter under identical operating conditions. In terms of SNR margin, passive backscatter would yield $-76.1 - (-122) = +45.9$ dB, compared to +82.9 dB for active backscatter — a difference of 37.0 dB, consistent with the power comparison. This gain arises from the elimination of the second FSPL term (43.7 dB), the second tissue-loss term (2.37 dB), and the reflection-coefficient penalty (6 dB), partially offset by modest improvements in these quantities, totaling 37.0 dB of recovered link margin.

Comment 4: It is mentioned “Once in the esophagus, the signal increased to approximately 60 dBm, reflecting the influence of the tissue environment”. The observation that RSSI increases after ingestion contradicts typical expectations of tissue attenuation. Additional explanation, modeling, or experimental validation is required.

Response: We thank the reviewer for pointing out this inconsistency. We agree that the original wording was incorrect. In the revised manuscript, we have corrected the description to reflect that the RSSI shifts from approximately -40/-50 dBm in air to approximately -60 dBm after ingestion, corresponding to signal attenuation due to the tissue environment. We now emphasize that the key observation is the reproducible change in RSSI associated with ingestion, rather than an increase in signal strength. Claims implying signal enhancement have been removed, and no additional modeling is required to support this corrected interpretation.

Modification to the manuscript:

To reflect this point clearly, we have added the following sentences to page 12:

“This ~10 dB change in RSSI provides a clear and distinct signature of capsule ingestion, supporting the use of BA-RFID tags for noninvasive, real-time monitoring of medication adherence”.

Comment 5: Only limited subjects were tested, and no sham-control cohort is included. Statistical analysis and impedance tracking during stimulation are needed to substantiate the therapeutic effect.

Response 5: We thank the reviewer for this important comment. We agree that larger cohorts, sham controls, and comprehensive statistical analyses are essential for establishing therapeutic efficacy. The present study is intended as a proof-of-concept demonstration of battery-powered gastrointestinal stimulation using a biodegradable system rather than a definitive efficacy study. In the revised manuscript, we now clarify the experimental scope and explicitly report that gastrointestinal stimulation experiments were conducted in three stimulated subjects and one sham-control subject. The sham experiment followed identical surgical placement and handling procedures but without active electrical stimulation.

- To address concerns regarding electrode–tissue interface stability, we have added impedance characterization of the stimulation electrodes measured in simulated gastric fluid (SGF) before and after stimulation. These data, included in the Supplementary Information (Supplementary Figure 20), show that electrode impedance remains within the same order of magnitude before and after stimulation, supporting stable electrochemical behaviour during the stimulation period.

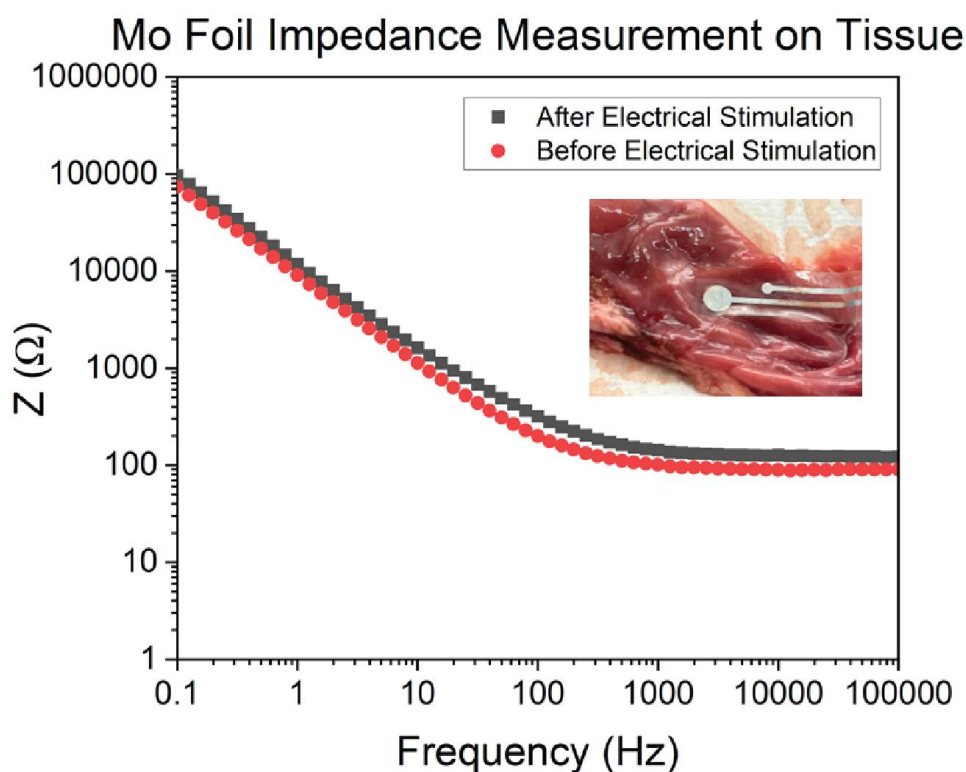


Figure S21. Ex vivo tissue impedance spectroscopy of Mo electrode before and after stimulation on gastric tissue (20 minutes, 0.5 mA, 14 Hz), ($Z_{\text{before, 14 Hz}} = 856.3 \Omega$; $Z_{\text{after, 14 Hz}} = 1252.1 \Omega$)

- Given the limited cohort size, we have refrained from making statistical claims regarding therapeutic efficacy and have revised the text to describe the in vivo stimulation results qualitatively. The revised manuscript now emphasizes feasibility, functional operation, and acute physiological response rather than statistically powered outcome measures.

We have also added a statement in the Discussion explicitly noting that future studies will incorporate larger animal cohorts, fully powered sham-controlled designs, longitudinal impedance tracking during stimulation, and quantitative physiological endpoints to rigorously assess therapeutic efficacy.

Referee #3 (Remarks to the Author)

Summary Comment: The manuscript describes the design and development of biodegradable Mg-MoO₃ batteries. Two battery form factors are described: one fitting inside a size 000 ingestible capsule and one larger battery for bigger devices with higher power needs. The biodegradable batteries are tested in three pig experiments. Focusing on two major use cases: long-distance RFID tags for medication adherence and gastric stimulation to increase the feeling of satiation.

Biodegradable batteries could address important needs in the field of ingestible and implantable electronics, such as e-waste issues and risk of retention of ingestibles. Biodegradable batteries could also enable new applications in this space. This manuscript shows interesting proof-of-concept applications. However, the maturity of the devices is overstated and critical analysis of the data and presented use cases is lacking.

Response: We sincerely thank the reviewer for their thoughtful comments. We would like to highlight importance of

Comment 1: Mg-MoO₃ batteries are not new, they have been widely studied. Interesting in this manuscript is the relatively small form factor and the specific applications. The validation studies are not as convincing as they could be though. Why only focus on the esophagus and the stomach? For ingestibles, it would be very valuable to have batteries that would survive the full passage through the tract.

Response 1: We thank the reviewer for these comments and agree that Mg-MoO₃ batteries have been widely studied. The novelty of our work lies in the miniaturization into capsule-compatible formats and the integration of fully degradable capsule electronics, which, to our knowledge, have not been demonstrated previously.

- Specifically, we designed two battery formats: a compact 000-size battery for space-constrained capsules and a larger-area battery optimized for more power-consuming capsule electronics, such as electrostimulation and sustained wireless operation. This highlights the ability to tailor battery design to different power demands while maintaining a bioresorbable architecture.
- Regarding in vivo validation, we focused on the esophagus and stomach to functionality for two distinct applications powered using the proposed battery: an ingestible sensor operating in the esophagus, and hormone regulation via electrical stimulation of the stomach—both representing first demonstrations of their kind using fully degradable electronics. We acknowledge that survival and performance throughout the entire gastrointestinal tract is an important target for broader ingestible applications.
- In addition, we have performed safe passage tests, in which the degradable encapsulation materials were successfully administered, transited the GI tract, and were safely collected after passage. These results provide evidence that the materials and device design support predictable degradation, safe operation in vivo, and tolerance of normal physiological conditions.

Taken together, these studies highlight both the novelty of small-form-factor, degradable Mg–MoO₃ batteries and their practical integration into transient ingestible electronics, demonstrating functional capabilities in controlled GI environments while providing a clear path toward safe, full GI tract applications.

Comment 2: For the RFID use case, why are the devices placed in the esophagus? In the real use case, it will pass through the esophagus in seconds. Probably even too quick to pick up a change. Also, only the performance in air is shown (for 20 cm up to 4 m). But the body will have a huge impact on the signal strength. Why are these experiments not performed in a body-mimicking phantom? How much tissue could be penetrated? The claims that are now being made on improved range are not substantiated (8x improved?). So, either this data needs to be added, or the claims need to be toned down, and showing this data only as proof-of-concept.

Response 2: We thank the reviewer for raising these important points regarding the RFID use case, anatomical placement, and experimental validation. We have added ex vivo experimental data and supplied a link budget analysis for the RFID application.

- The esophagus was selected as an initial test environment to demonstrate controlled and repeatable detection of ingestion-related RSSI changes under well-defined experimental conditions. In our prior SAFARI^[14] study (Say et.al., Nat. Commun. 2026), longer antenna structures were employed to maximize coupling efficiency and detection yield in gastric environments. In contrast, for the present battery-assisted RFID platform, strict size constraints associated with ingestible form factors necessitated a substantial reduction in antenna dimensions (battery + tag). To meet these constraints, we employed a compact paper-clip antenna integrated with an RFID chip operating in a battery-assisted mode. While this miniaturized antenna enables battery-assisted operation within a swallowable capsule (000), the reduced electrical length results in decreased RF coupling efficiency in the stomach environment, leading to a lower detection yield for gastric-based measurements. Consequently, in this study we focused on esophageal-based event detection, where the shorter propagation distance and reduced tissue volume provide a more reliable and repeatable environment for demonstrating the core BA-RFID sensing principle under controlled conditions. Even though the capsule passes through the esophagus within seconds, the system is capable of capturing transient RSSI changes during this interval; these changes, when compared to baseline measurements in air, provide a detectable marker of an ingestion event under controlled conditions. This controlled placement allows isolation of the RF attenuation effects associated with tissue exposure and enables validation of the sensing principle.

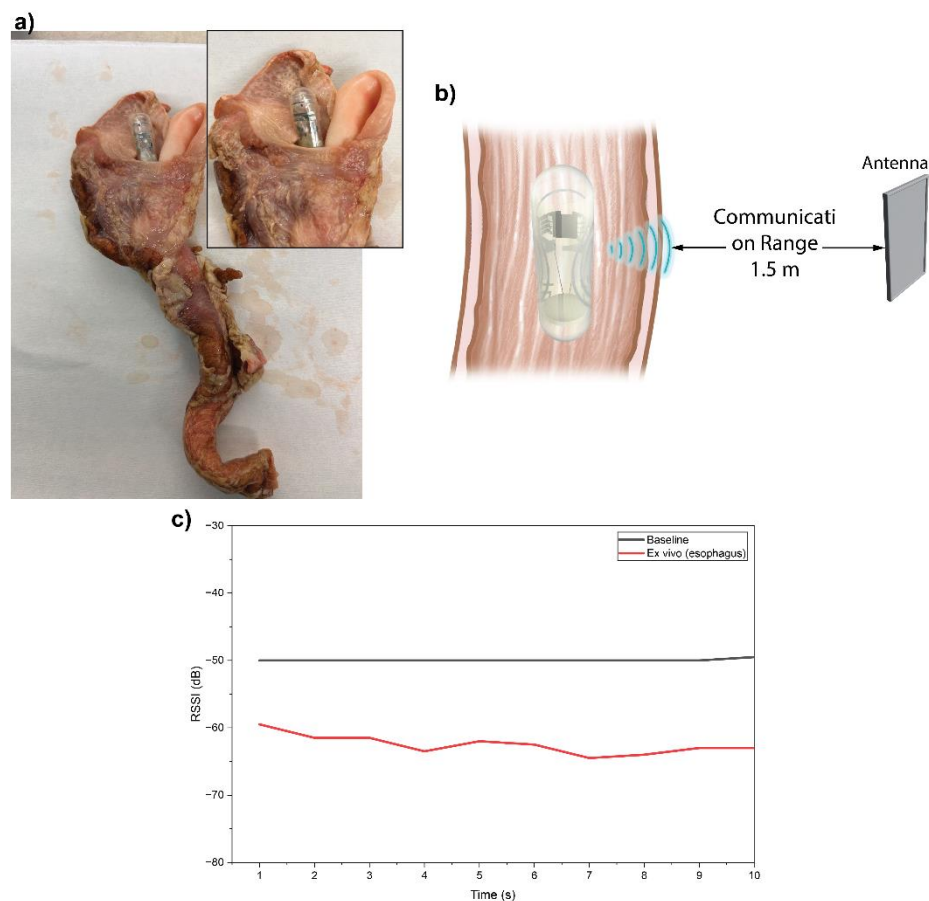
We acknowledge that the body has a significant impact on RF signal propagation. To address this, we performed ex vivo experiments using swine esophageal tissue (Supplementary Figure 19), which provides a more physiologically relevant environment than air alone. These measurements demonstrate detectable RSSI changes through biological tissue and support the feasibility of ingestion event detection beyond in-air testing. We agree that body-mimicking phantoms or dynamic transit models would be valuable for future studies and have clarified this as a next step rather than a completed validation.

Regarding penetration depth and communication range, we have revised the manuscript to remove quantitative claims such as “8× improvement” and instead describe an improved and extended communication range relative to passive RFID operation under controlled conditions. The current results are therefore positioned explicitly as a proof-of-concept demonstration of battery-assisted RFID operation and RSSI-based ingestion detection, rather than a fully validated clinical performance assessment.

We have revised the text throughout the manuscript to moderate the claims accordingly and to clearly distinguish between in-air, ex vivo, and in vivo experiments, emphasizing the limitations and intended scope of the present study.

Modification to the manuscript:

We have added Supplementary Figure 19, to clarify the ex vivo experiments.



Supplementary Figure 19. Ex vivo evaluation of the biodegradable, battery-assisted RFID tag. a) Optical image of the device encapsulated in a 000 gelatin capsule within the ex vivo swine esophagus. b) Schematic of the RSSI measurement setup through the ex vivo esophagus. c) RSSI recorded from the device through ex vivo tissue.

Modification to the manuscript:

On page 12, we have added a sentence, “Ex vivo experiments using a swine esophagus further validated the system’s performance through tissue (Supplementary Figure S19).”

Modification to the supplementary information:

We have added link budget analysis to Supplementary Note 1.

Comment 3: Is RSSI a reliable method to measure drug adherence? There are several factors influencing RSSI, such as distance between receiver and RFID, body composition, stomach filling, location in GI tract, environmental factors, etc. How could this practically work in a real-life scenario?

Response 3: We thank the reviewer for this insightful question. We agree that Received Signal Strength Indicator (RSSI) is influenced by multiple factors, including tag–reader distance, tissue composition, gastric contents, and body. For this reason, in both our work and related ingestible RFID adherence systems, changes in RSSI are not interpreted as absolute measures of adherence but rather as binary or robust event signatures indicative of an ingestion event.

In the revised manuscript, we now align our description with recent work in the field. For example, in our previous work, we demonstrate that biodegradable passive RFID capsules can reliably detect ingestion events in vivo using changes in RFID response, even in complex biological environments, by employing shielding and structural methods to discriminate between “unexposed” and “exposed” states of the tag. Importantly, this prior work confirms that ingestible passive RFID signals can be robustly detected through tissue in large animal models, despite expected variability in propagation conditions.

We clarify in the manuscript that in our system, RSSI shifts are used as contextual event markers rather than quantitative metrics of adherence strength. For practical real-world deployment, an ingestible RSSI-based adherence indicator would be integrated into a protocol or classifier, for example:

- Monitoring for a consistent, reproducible change in RSSI above a device- and reader-specific threshold, rather than relying on a single absolute value.
- Calibrating against baseline tissue conditions and reader geometry in a user’s typical environment, similar to existing ingestible adherence systems.
- Incorporating reader placement strategies (e.g., wearable, bedside, or belt-worn readers) to minimize variability in distance and orientation, as adopted in recent clinical ingestible device studies.

These approaches, combined with the design principles demonstrated in SAFARI and related work, support the use of RSSI as a practical, real-time ingestion indicator that is resilient to typical physiological and environmental variability. We have revised the text to emphasize this interpretation and to avoid suggesting that absolute RSSI values alone are a direct measure of dose ingestion without contextual signal interpretation.

Modification to the manuscript:

On page 19 (Discussion), we added a sentence: “Ingestible RFID systems do not use RSSI as an absolute metric but instead detect reproducible changes associated with exposure to the GI environment. Similar to other ingestible adherence platforms, robust ingestion detection is achieved by defining event-specific thresholds and reader configurations that account for typical physiological and environmental variability.”

Comment 4: For the electroceutical use case, in pigs the device might stay in the stomach for prolonged periods, in human it will probably pass much quicker (minutes – hours). How would you retain the device in the stomach?

Response 4: We thank the reviewer for raising this important translational consideration. We agree that gastric residence time differs substantially between large animal models and humans, and that prolonged retention cannot be assumed in human use without dedicated design features.

The present study is intended as a proof-of-concept demonstration of battery-powered gastrointestinal stimulation enabled by a biodegradable power source, rather than a fully optimized human retention system. In the pig model, gastric residence time was sufficient to demonstrate device operation and stimulation feasibility. In humans, shorter residence times (minutes to hours) are expected for non-retained capsules.

Importantly, established strategies already exist to extend gastric retention in ingestible devices and could be readily integrated into future iterations of the system. These include expandable or unfolding geometries, endoscopic anchoring approaches such as endoclip systems, and mucoadhesive designs that enable transient attachment to gastrointestinal tissue after ingestion. In this work, we explored retention-relevant delivery and anchoring strategies in the context of hormone regulation studies, where capsules were delivered endoscopically and endoclip-based fixation was successfully tested. Similar gastric-retentive and endoscopic deployment approaches have been widely investigated in ingestible drug delivery technologies and electronic platforms, and are compatible with the power requirements and form factor of the battery-assisted system reported here.

We have clarified this point in the revised manuscript and now explicitly state that future translational development will incorporate gastric-retentive designs to match the intended therapeutic time window in humans.

Modification to the manuscript:

On page 17 (Discussion), we added a sentence: “While the present study demonstrates feasibility without active retention in humans, future electroceutical implementations will incorporate established gastric-retentive or endoscopic anchoring strategies to align device residence time with the intended therapeutic window.”

Comment 5: The manuscript lacks scientific rigor. Cross references to (sub-)figures are incorrect; or the figures do not show what is mentioned in the text. References are missing. Duplicate sentences. Abbreviations not explained. Figures unclear or too small to read properly. Critical analysis of the work and its limitations is missing; discussion section is practically non-existing. Proper proofreading should have detected a lot of these. It can be hard for the reader to find the essential information, please re-check the flow and make a clearer distinction between main message and additional information. Also adding line numbers would have made the reviewing process easier.

Response 5: We thank the reviewer for raising this important point. We addressed all the issues and confirmed the text is referring the figures and supplementary information. Additionally, we have improved the flow by adding more explanation on experimental settings and discussion. We have uploaded pdf versions of the main figures to maintain better quality.

Comment 6: Bioresorbable and biodegradable are used interchangeably, but are not the same. This should be addressed and supported with references. How likely is it that (a large part of) the device is resorbed, giving the degradation rates? And how long would you like to have degrading electronics in the body? Is biodegradable good enough? It is mentioned that “complete structural degradation after several months in simulated fluid”, is it the idea that the devices stay in the body for such time windows?

Response 6: We thank the reviewer for this important clarification. We agree that bioresorbable and biodegradable are not interchangeable terms and have revised the manuscript to clearly distinguish their usage.

- In this work, the battery components are designed using bioresorbable materials that can dissolve and be resorbed under physiological conditions over time. In contrast, certain structural elements of the capsule electronics are biodegradable but not fully bioresorbable within short physiological timeframes. We now explicitly differentiate these material classes in the revised manuscript and provide appropriate references.
- Regarding degradation time scales, the intended operational window of the present system is short-term (days to weeks), consistent with gastric retention applications. The mention of “complete structural degradation after several months in simulated fluid” refers to accelerated in vitro studies intended to demonstrate long-term material breakdown, not to suggest that the device is designed to remain in the body for months. For transient applications, the goal is to maintain functionality during the required monitoring period while ensuring that materials either safely resorb or degrade into biocompatible byproducts.
- For longer gastric-retention configurations, structural integrity is required during the functional period; however, material selection prioritizes safe degradation behavior in case of delayed passage.

Modification to the manuscript:

On page 19 (Discussion), we added a sentence:

“For retention-specific applications, we prioritize maintaining complete structural integrity during the functional period, ensuring reliable operation for hours to days in the gastrointestinal tract. For transient ingestion scenarios, the system remains fully operational while all bioresorbable components partially degrade safely after use. This design balances functional performance with safe material clearance, providing a framework for future short-term, ingestible electroceutical and sensing devices.”

Comment 7: - The maturity of the system is overstated. For example, “These in vivo results establish the clinical potential far beyond those of simple proof-of-concept devices”. This manuscript is really just proof-of-concept. There is a lot of variation in performance between the batteries. This is not properly addressed. Also, the needed steps towards clinical applications need to be addressed.

Response 7: We thank the reviewer for this comment and have revised the manuscript to better reflect the proof-of-concept nature of our work. We agree that the in vivo studies demonstrate feasibility rather than clinical readiness, and we have removed overly strong language.

We have added a section on future steps toward clinical translation, including: optimization of battery uniformity and encapsulation, long-term safety and pharmacokinetics studies, scaling of functional lifetime, and expanded testing across the full gastrointestinal tract. This clarifies that while our current results establish a promising proof-of-concept, further work is required before clinical application.

Modification to the manuscript:

On page 19 (Discussion), we added a sentence: “Variability between battery units was observed, likely due to fabrication tolerances (contact between layers, electrolyte performance) and differences in encapsulation.

...

Future work will focus on improving device performance, conducting long-term safety and pharmacokinetic studies, and validating performance throughout the full gastrointestinal tract. These steps are essential for translation toward clinically viable ingestible electroceutical systems.”

Comment 8 - Abstract: The battery proves a stable output voltage of 1.84V’. This seems a rather optimistic number and contradicting with the results presented on stable voltage. On page 6 (Fig 2c) it’s mentioned that up to 1.6V stable voltage was achieved for the big battery.

- “and fully bioresorbable capsule system for electroceutical therapy” This is not true, the PCB’s are not bioresorbable.

- Reducing ‘infection risk’ is mentioned as a potential benefit. How do these batteries reduce infections? It is not mentioned anywhere else in the text.

Response 8: We thank the reviewer for noting these points.

- Battery voltage: We thank the reviewer for noting this discrepancy. The reported 1.84 V value corresponds to the peak initial open-circuit voltage of a test battery, whereas the 1.6 V value in Fig. 2c represents the stable operating voltage under load for the larger battery used in functional demonstrations. We have revised the text to clarify this distinction and avoid overstating the voltage performance.

Modification to the manuscript:

On page 7, we revised the sentence: “Under continuous discharge, the battery maintained a stable operating voltage of approximately 1.6 V for a day long operation.”

- PCB: We agree that the wording should be clarified. While the battery and electrode components are bioresorbable, the circular PCB is not. In Section 2.4 (page 13), we now explicitly state:

“Our system represents the first demonstration of a capsule-based electrostimulation device constructed primarily from bioresorbable materials (excluding the PCB).”

We also included the fate of PCB for the passage test.

Modification to the manuscript:

On page 17, we have added the sentence: “The stimulation PCB excreted naturally for all 3 passage tests and safe due to its size.”

- Infection risk: We thank the reviewer for this comment. As the manuscript does not include data supporting reduced infection, we have removed any mention of infection risk from the abstract.

Comment 9 – Page 2: Silver-oxide batteries are commonly used in ingestibles and should also be mentioned.

- The second paragraph. What do you mean with “implantable batteries”. If you would directly swallow or implant any type of battery, there would be some serious health risks indeed. But this is of course not how ingestibles/implantables are used. The batteries are carefully encased so they are never in direct contact with the body. The injuries that are listed here are not relevant, as long as the encasing is sufficient. Also, ISO 10993 is only applicable when the material has direct or indirect body contact. When it is encased, it also does not need to be an issue. There are of course good arguments to be made for biodegradable batteries, and it is good to highlight the risk of direct contact with batteries, but as such it is not a good introduction to the problem. What are the safety risks of biodegradable batteries? Unexpected discharges? Heating of tissue? Breaking down in sharp fragments? Any chemical reaction expected when the biodegradable battery gets in direct contact with the gut?

- In the third paragraph, ‘surgical retrieval’ and ‘long-term exposure’ is most likely only relevant for implantables, not ingestibles since they pass the whole GI tract in a matter of days. In rare cases there can of course be capsule retention. This nuance between the needs for implantable batteries and ingestible batteries should be added.

Response 9:

We thank the reviewer for pointing out these issues.

- The manuscript to explicitly mentions silver-oxide batteries as a commonly used chemistry in ingestible electronic capsules. Now in page 3 mentions silver oxide batteries: “ Solid-state batteries have powered sensing and communication modules in electronic pills ^[16–18], but typically rely on silver oxide or lithium-ion chemistries that are not biodegradable.”

We thank the reviewer for this detailed feedback. We agree that the original paragraph generalizes the risks of ingestible batteries and did not clearly distinguish implantable versus ingestible devices.

In the revised manuscript, we clarified that:

- Ingestible batteries are carefully encased, so the severe tissue injuries listed in the original text are prevented under normal operation. ISO 10993 testing is only required if the battery contacts tissue directly.
- Biodegradable batteries provide an additional safety margin in the rare case of capsule rupture or retention, with predictable dissolution that avoids sharp fragments, unexpected discharges, or local heating.
- Implantable and ingestible batteries have distinct risk profiles: implantables may require long-term biocompatibility testing, whereas ingestibles transit the GI tract in hours to days.

Modification to the manuscript:

On page 2, we have modified the paragraph, “ ...These standards ensure safe long-term operation when battery components remain in direct contact with tissue. Ingestible electronic devices, by contrast, are designed for transient passage through the gastrointestinal tract and are carefully encased to prevent direct tissue contact, eliminating the severe risks associated with accidental battery ingestion. For example, accidental ingestion of conventional batteries such as button cells, can lead to severe clinical complications, including esophageal perforations, tracheoesophageal and aortoesophageal fistulas, and even fatalities^[19,20]. Injuries are not only limited to the upper GI tract and are often caused by alkaline electrolyte leakage, direct tissue compression, or necrosis from local chemical burns, especially in children^[19,21]. Biodegradable batteries provide an additional safety margin in scenarios such as capsule rupture or retention, as they degrade predictably in vivo without generating sharp fragments, excessive heat, or toxic byproducts^[22]. Together, these considerations motivate the development of bioresorbable power sources for

transient ingestible biomedical devices, which combine functional performance with enhanced gastrointestinal safety.”

- We have revised the manuscript to clarify that surgical retrieval and long-term exposure are generally relevant only for implantable batteries. Ingestible devices naturally transit the gastrointestinal tract within hours to a few days, and under normal operation, surgical retrieval is not required. Cases of capsule retention are acknowledged, and we note that biodegradable batteries provide predictable in vivo degradation in such scenarios, minimizing the potential for adverse effects. The revised text now accurately distinguishes implantable versus ingestible use cases while highlighting the safety benefits of biodegradable battery designs.

Modification to the manuscript:

On page 3, we have modified the paragraph, “...Ingestible devices naturally transit the gastrointestinal tract within hours to a few days, eliminating the need for surgical retrieval and minimizing prolonged tissue exposure. ... Biodegradable designs provide an additional safety margin in cases of capsule rupture or retention, as they degrade predictably and partially absorbed by the body.”

Comment 10 – Page 3: Also add the specification for reference 14 (in V), as done for the other 2 references.

- The sentence “We demonstrated the capability of the battery through three key in vivo applications ...” is repeated twice.
- “These in vivo results establish the clinical potential far beyond those of simple proof-of-concept devices”. This is too bold of a statement. It is nice to see the in vivo results, but it is only validated in an animal model and still far from clinical application. This is still a proof-of-concept device.

Response 11: We appreciate the feedback from the reviewer. The voltage specification for reference 14 has now been added for consistency with the other cited references. The repeated sentence has been removed, and the paragraph has been edited for clarity and conciseness.

We appreciate the reviewer’s thoughtful feedback and agree that the original wording overstated the clinical readiness of the device. We have revised this sentence to adopt a more measured and accurate tone, emphasizing the proof-of-concept nature of the work and the relevance of the in vivo validation without implying immediate clinical translation. The revised text now reads:

Modification to the manuscript:

On page 3, we have modified the paragraph

“These in vivo results demonstrate the feasibility of bioresorbable batteries for transient biomedical applications and provide an important step beyond benchtop validation toward future translational device development.”

Comment 11- Page 4: ‘We designed two battery formats.... larger-area batteries suited for more advanced capsule electronics’. What do you mean here with more advanced capsule electronics? That’s not clear from the context. Why could that not be done in the capsule format? Would more ‘more power consuming’, be more accurate?

- Where Figure 1b is mentioned in the text, it should be Figure 1b and 1c.

Response 11: We have revised the text to replace “more advanced capsule electronics” with “more power-consuming ingestible electronics” to more accurately describe the motivation for the larger-area battery format, particularly for powering stimulation PCBs. This revision clarifies that the distinction between battery formats is driven by power demand rather than functional complexity.

In addition, we corrected the figure citation to refer to Figure 1b and 1c where both formats are shown.

Comment 12- Page 5: Where Fig 1d is mentioned should probably be 1e, showing the essential components of the battery.

- PLGA: add meaning of abbreviation. There should be an 'and' or 'or' be added to the sentence to improve readability.

Response 12: We thank the reviewer for raising this point. We have added Poly(lactic-co-glycolic acid) (PLGA) to the text and improve the flow accordingly.

Comment 13- Page 6: The open circuit voltage 1.77V..., which is notably higher than that of previously reported Mg-MoO₃ cells". This directly contradicts with another statement on page 5. Where the same references are quoted and is written "Earlier demonstrations voltages of 1.6-1.8 V". 1.77V is not notably higher than this quoted range.

Response 13: We thank the reviewer for pointing out the apparent discrepancy. The 1.77 V OCV corresponds to the small 000-size battery (radius 7.5 mm), whereas the previously cited range of 1.6–1.8 V refers to larger batteries with different cathode compositions and binders. To clarify, the manuscript now states that the small 000-size battery achieves a voltage comparable to prior Mg–MoO₃ cells, while the large-area battery reaches 1.84 V, slightly higher than previous reports, reflecting the scalable performance of our design. This revision resolves the seeming contradiction and accurately represents the measurements.

Modification to the manuscript:

Modification to the manuscript:

On page 7, we have modified the paragraph (line 182), "The open-circuit voltage (OCV) was measured to be approximately 1.77 V, comparable to earlier demonstrations of Mg–MoO₃ cells"

On page 7, we have modified the paragraph (line 195), "The large-area battery, optimized for power-demanding applications, exhibited an open-circuit voltage of approximately 1.84 V, slightly higher than previous reports."

Comment 14- Page 7: Add explanation abbreviation SGF.

- "The beeswax-encapsulated batteries retained.... for several days". Several days is rather vague, please specify.

- In Supplementary Fig S9, I was expecting to see the data on the "mechanical integrity and stable electrochemical performance for days". Please add that data to the figure.

- "The batteries were assembled with natural wax encapsulation layers, ... in 3D printed capsules..". What was the material of the 3D printed capsules?? How are you testing here battery integrity if everything is protected and encapsulated anyways?

- "The flexible core ... minimizing local tissue irritation". How is it checked that is minimizes tissue irritation?

Response 14: We thank the reviewer for these important points and have revised the manuscript and Supplementary Information to improve clarity, specificity, and experimental transparency.

- We now explicitly define SGF (simulated gastric fluid) at its first occurrence in the Methods section and in all relevant figure captions. The composition and pH conditions used in this study are also clarified.
- We have replaced the phrasing “several days” with a quantitative description. Specifically, beeswax-encapsulated batteries retained structural integrity and stable electrochemical performance for simulated gastric conditions and in vivo. This clarification has been implemented in the main text.
- We thank the reviewer for this comment. We agree that the original statement overstated the data presented in Supplementary Figure S9. That data is discussed in the battery performance. The figure currently shows representative images demonstrating preservation of the capsule’s structural integrity over retention period. We have revised the manuscript text to clarify that Supplementary Figure S9 supports mechanical integrity over the test period, and we have removed the explicit claim of stable electrochemical performance from this sentence.
- We now specify that the 3D-printed capsules were fabricated from PLA and details regarding the capsule printing has been added to the Methods section. Importantly, the integrity tests were designed to evaluate the battery– natural wax encapsulation system, reflecting the intended operational configuration for ingestible use. While the external capsule (degradable materials) provides initial mechanical protection from the vigorous environment of GI tract, degradation and electrolyte ingress occur through controlled pathways, allowing us to assess encapsulation robustness, functional lifetime, and failure modes under physiologically relevant conditions.
- We thank the reviewer for this point. The flexible core enables folding of the arms, which is essential for gastric retention and allows the device to conform to the stomach environment. In our endoscopic investigations, no tissue damage was observed from the arm structure. This design builds on prior work demonstrating that such geometries extend residence time while maintaining device functionality^[23]. We have updated the manuscript accordingly and removed the previous mention of tissue irritation.

Modification to the manuscript:

To reflect this point clearly, we have edited the sentence, page 8, line 230:

“The flexible core enables folding of the arms, which is essential for gastric retention and allows the inserted batteries to conform to the stomach environment.”

Comment 15- Page 8: “Figure 2f shows the ...” This should most likely be Figure 2g

- “The open-circuit voltage decreased from 1.77 V on Day 0..” Here you are talking about the mean of the three samples? That should be added in the text. Also, there is a huge spread between the samples, that should be addressed in the discussion.
- Explain the abbreviation OCV.

- “Supplementary Figure S12 shows the results of the open-circuit voltage and continuous discharge tests for batteries fully immersed in SGF.” This is not shown in the Figure.

Response 15: We thank the reviewer for these points. The figure citation has been corrected from Figure 2f to Figure 2g. The reported open-circuit voltage (OCV) values now explicitly represent the mean of three tested batteries, and the observed variation between samples is discussed in the revised manuscript. The abbreviation “OCV” is now defined in the text. Regarding Supplementary Figure 15, we have updated the figure and caption to accurately reflect the OCV and continuous discharge tests for batteries fully immersed in SGF.

Comment 16- Page 9: Three different current densities are compared. What is the impact on the battery size? That should be discussed.

- Figure 2g and 2h are very difficult to read. A box plot for 2 or 3 measurements does not make a lot of sense. It gives the false impression of knowledge of the underlying data distribution, which is hardly defensible with so few data points. The individual data points should be shown more clearly.

Response 16: We appreciate the feedback from the reviewer.

- We thank the reviewer for this important question. The different current densities were selected to evaluate electrochemical performance under varying load conditions rather than to imply different battery geometries. In the present study, the battery size and geometry were kept constant across all experiments. However, in practical implementations, the required current density directly influences electrode area and therefore overall battery size. Lower current densities can be achieved with smaller electrode areas for low-power applications, whereas higher current demands require increased Mg amount and cathode material loading or larger electrode surface area, leading to a larger device footprint.
- We have updated the graphs and the figure with more visible points. Now, Figure 2g and h show the individual data points clearly.

Modification to the manuscript:

We have added a sentence, page 7: “The selected current density range reflects the intended size constraints of the device, as higher sustained current demands would require increased electrode area or active material loading”

Modification to the manuscript:

To reflect this point clearly, we have revised Figure 2g and 2h.

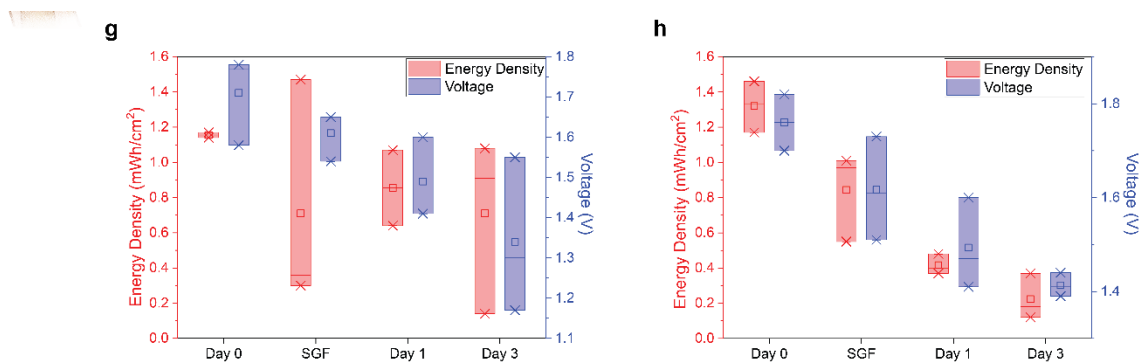


Figure R2. g, Change in the energy density and open circuit potential for the 000-size batteries in SGF and in vivo retention days spent in the stomach. **h,** Effect of retention on the energy density and open circuit potential for large-area batteries in SGF and in vivo retention days spent in the stomach. (Data are presented as means $\pm$ SD; $\times$ represents individual replicates, $\square$ represents mean, $n = 2$ or 3).

Comment 17- Page 10: “Despite their potential, ...Despite their promise...”. These sentences are repetitions, should be rephrased.

Response 17: Thank you for noting repetitions. We have corrected the section of the paragraph to avoid repetition.

Comment 18- Page 11: - Why is the wireless performance only measured in air? Why not test it in a representative phantom? The 20 cm to 4 m in air does not give any indication of the working range within a body. How much tissue can you penetrate? What type of BMI can you handle? The presented data is not sufficient to claim the long distance RFID support.

- How reliable is RSSI to use as an indication of medication ingestion? As you showed in Fig 3F, the distance between the RFID tag and receiver has a big influence on the RSSI. How could you distinguish the distance effect and the ingestion effect? Fig 3I is not directly very convincing.

- “The molybdenum antenna ... within a few months under accelerated dissolution conditions”. Please specify what these accelerated conditions entail. How are these conditions validated? Are they representative of the human body?

- “This long-range communication system enables reliable recording of ingestion events, supports electronic medication adherence, and paves the way for future digital health applications” This too strong of a claim. Only under very controlled settings some tests were done.

Response 18: We thank the reviewer for this important point and appreciate the constructive suggestions.

- The wireless range measurements reported in air were intended to establish an upper-bound communication distance under controlled conditions and to benchmark the performance of the battery-assisted active backscatter architecture. To address the reviewer’s concern regarding physiological relevance, we have now added ex vivo RSSI measurements through excised esophageal tissue, which provide a more representative propagation environment.

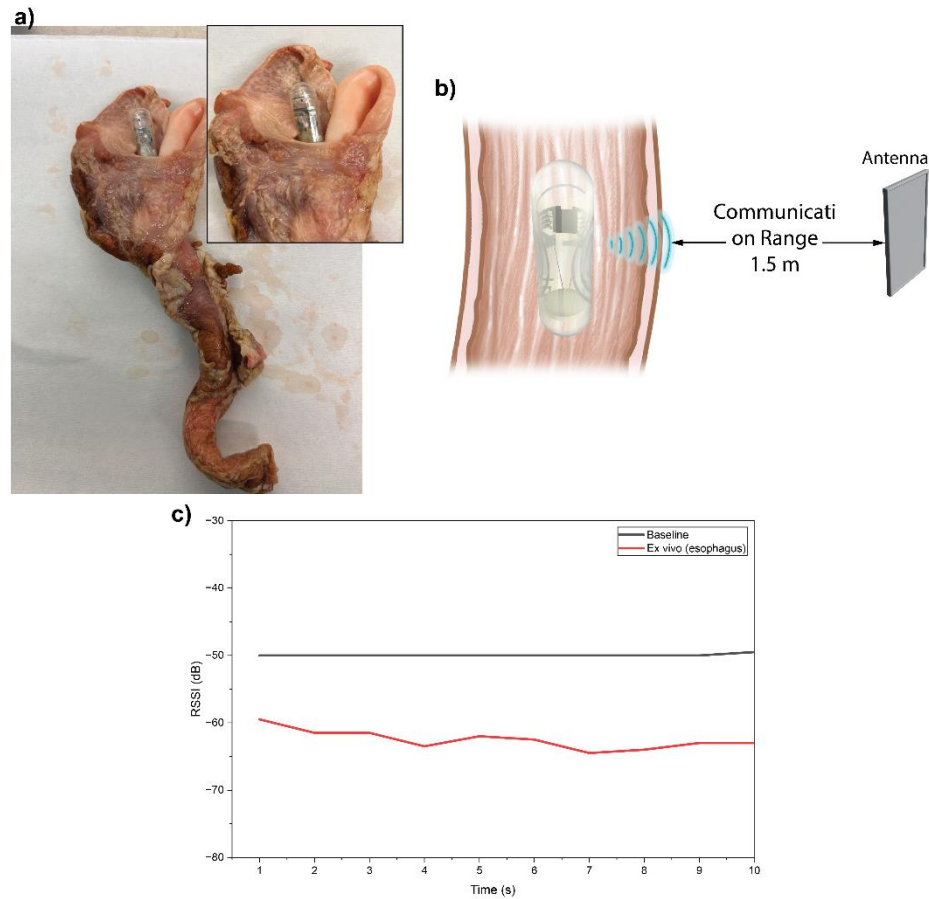
As shown in Figure 3f, RSSI is influenced by the distance between the battery-assisted RFID tag and the reader. Importantly, the measurements demonstrate that RSSI remains relatively stable up to approximately 2 m under these conditions. Based on this observation, a fixed reader distance of 1.5 m was selected for both ex vivo and in vivo experiments to minimize distance-related variability. A new supplementary figure (Supplementary Figure S19) has been added to support this analysis.

With respect to medication ingestion detection, RSSI was not used as a quantitative distance metric but rather as a relative and event-based indicator under controlled reader placement. In this context, ingestion is identified by a reproducible RSSI shift occurring immediately after capsule administration, rather than by absolute signal strength. This approach builds on our earlier work^[14], which demonstrated RSSI-based ingestion detection using a Faraday-cage-like switching mechanism and close receiver proximity. In the present study, we aimed to extend this concept by leveraging battery-assisted RFID to increase detection range and robustness, while introducing RSSI-based sensing as an additional ingestion-detection modality under challenging gastric and tissue conditions.

We have revised the manuscript to clarify that these experiments represent demonstrations under controlled settings, and that further studies involving with complicated in vivo settings will be required to fully quantify in-body communication range and long-term adherence reliability.

Modification to the manuscript:

We have added Supplementary Information 19, to clarify the ex vivo experiments.



Supplementary Figure 19. Ex vivo evaluation of the biodegradable, battery-assisted RFID tag. a) Optical image of the device encapsulated in a 000 gelatin capsule within the ex vivo swine esophagus. b) Schematic of the RSSI measurement setup through the ex vivo esophagus. c) RSSI recorded from the device through ex vivo tissue.

Modification to the manuscript:

On page 12, we have added a sentence, “Ex vivo experiments using a swine esophagus further validated the system’s performance through tissue (Supplementary Figure 19).”

- We appreciate the reviewer’s request for clarification. The accelerated dissolution experiments were conducted in simulated gastric and intestinal fluids at elevated temperature (75 °C) to approximate a worst-case chemical degradation scenario, rather than replicate physiological residence times. In the bioresorbable electronics community, higher temperatures (85–95 °C in PBS) are commonly used to demonstrate accelerated degradation [6,15]. In our work, we selected 75 °C in simulated gastric fluid to provide a physiologically relevant environment for observing dissolution trends while maintaining an accelerated timeframe. These experiments are intended to illustrate relative degradation behavior and reproducibility, rather than predict exact in vivo timelines. The manuscript now explicitly describes these accelerated conditions.

- We thank the reviewer for this comment and agree that the original wording could be interpreted as overstating system maturity. We have revised the text to clarify that the reported long-range communication and ingestion detection represent a proof-of-concept demonstration under controlled experimental conditions, while still emphasizing the technical advance enabled by battery-assisted RFID. The revised text avoids claims of clinical readiness, and instead frames the results as enabling capabilities that motivate future validation in more realistic environments.

Modification to the manuscript:

On page 13, we have edited the conclusion sentence, “The successful demonstration of a battery-assisted RFID system capable of detecting ingestion events and enabling wireless event detection over meter-scale distances under controlled experimental conditions provides a foundation for the development of future RSSI-based ingestible sensing devices. By supplementing harvested RF power with a bioresorbable battery, the system reduces reliance on energy harvested solely by the RFID circuitry and enables an improved communication range compared to passive operation using the same antenna and chip. Incorporating bioresorbable batteries into RFID tags extends device operational lifetime, improves signal robustness, and enables always-on communication over meter-scale distances under controlled settings, while also reducing electronic waste.”

Modification to the manuscript:

On page 16, we have updated the sentence with a reference that discusses accelerated aging: . To understand the dissolution, we tested the degradability of the capsule and its component layers in vitro at physiological temperature (37 °C) in SGF and later in the accelerated dissolution test^[24] (75°C, corresponding to approximately 15x acceleration relative to 37°C).

Comment 19- Page 12: demonstrated an 8x improvement in the communication range” compared to what? Can that be claimed if only in air measurements are shown and non-representative measurements in the esophagus of the pigs.

Response 19: We thank the reviewer for highlighting the need to clarify the reference point and experimental context for the reported “8× improvement in communication range.” The stated improvement refers specifically to a comparison between battery-assisted RFID (BA-RFID) operation and passive RFID operation using the same antenna geometry and RFID chip, measured under identical free-space condition. These air measurements were intentionally used to establish a controlled baseline and to isolate the effect of supplementing harvested RF power with a bioresorbable battery.

We agree that air measurements alone are not representative of in-body performance and therefore do not directly translate to achievable communication ranges in tissue. For this reason, we do not intend the 8× improvement to be interpreted as an absolute in vivo range enhancement. Rather, it demonstrates the relative performance gain enabled by battery assistance, independent of propagation losses introduced by biological tissue.

To address physiological relevance, we additionally have removed the reported “8× improvement in communication range.”. The manuscript has been revised to explicitly state the comparison

basis, the limitations of air measurements, and the role of tissue experiments as qualitative validation rather than range benchmarking.

Comment 20- Page 14: Supplementary Fig S15 should be S16.

Response 20: We have updated and cross-checked the supplementary figures.

Comment 21- Discussion: There is no critical analysis of the data, addressing the limitations of this study, and next steps. Add:

- Limitations of these batteries? Shelf-life? Size? How robust are they giving the variation between samples? Stability?
- What is needed to get this in human applications and what are the biggest hurdles?
- The use cases are all focused on ingestibles while in the introduction also implantables are mentioned. Add some thoughts about opportunities in implantables.
- Is drug adherence using long-distance RFID tags a viable application? Drug adherence using RFID has not shown very promising.

Response 21: We thank the reviewer for these comments and have revised the manuscript to include a more critical discussion of limitations, future steps, and broader opportunities.

Limitations: We now explicitly discuss limitations of the current battery formats, including variation between samples due to fabrication tolerances, constraints imposed by capsule size on capacity and energy density, and shelf-life considerations under storage. Stability and performance metrics are reported in both the main figures and supplementary materials to provide a transparent view of reproducibility.

Translation to human applications: For clinical use, several hurdles remain. These include ensuring consistent manufacturing of small-scale bioresorbable components, optimization of functional lifetime and degradation rates for human GI transit times, and extensive safety and pharmacokinetics studies to evaluate clearance of degradation products. Future work will address these challenges to enable safe translation.

Opportunities in implantables: While the current study focuses on ingestible devices, similar bioresorbable batteries could be adapted for short-term implantable applications where functional lifetime is on the order of hours to days, provided that power requirements, device geometry, and biocompatibility are carefully engineered. This is noted in the revised introduction and discussion.

Drug-adherence application: We have clarified that long-distance RFID monitoring for drug adherence is demonstrated here as a proof-of-concept, rather than a fully optimized clinical tool. We highlight that RSSI-based detection is influenced by many factors, and further optimization and validation would be needed before clinical deployment, as discussed in the revised text and citing our recent work (Say et.al., Nat. Commun. 2026).

Modification to the manuscript:

On pages 19 and 20, we have modified the Discussion section, “Variability between battery units was observed, likely due to fabrication tolerances (contact between layers, electrolyte performance) and variations in encapsulation thickness. Shelf-life and storage stability as well as long-term performance in simulated GI environments require further investigation, particularly in relation to thickness dependent natural wax encapsulation systems. ”

“Ingestible RFID systems do not use RSSI as an absolute metric but instead detect reproducible changes associated with exposure to the GI environment. Similar to other ingestible adherence platforms, robust ingestion detection is achieved by defining event-specific thresholds and reader configurations that account for typical physiological and environmental variability.”

“While the present study demonstrates feasibility without active retention in humans, future electroceutical implementations will incorporate established gastric-retentive or endoscopic anchoring strategies to align device residence time with the intended therapeutic window.”

“While this work focuses on ingestible devices, the battery design principles could also support short-term implantable applications, where transient electronics are required for hours to days. Key considerations would include device geometry, power demands, and biocompatibility of degradation products.

Translation to human applications will require consistent manufacturing, optimization of functional lifetime and degradation rates for full GI transit, and thorough safety and pharmacokinetic studies. Future work will focus on improving device performance, conducting long-term safety and pharmacokinetic studies, and validating performance throughout the full gastrointestinal tract. These steps are essential for translation toward clinically viable ingestible electroceutical systems.”

Comment 22- Materials and Methods: Dissolution test. What was used for which experiment? SGF, FaSSIF, RGF, fresh? Also add explanations of the abbreviations.

- Explain abbreviation GCD.
- REF missing in Supplementary Note 1.

Response 22: We thank the reviewer for these suggestions. The manuscript and Supplementary Notes have been updated accordingly. All abbreviations (SGF, FaSSIF, RGF) are now defined in the Methods and figure captions. In addition, we have removed the abbreviation “GCD” and now refer to the experiments simply as discharging tests for clarity.

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Point-by-point response – Nature Chemical Engineering – Manuscript #:
NATCHEMENG-25112374A

Referee #1 (Remarks to the Author)

The authors addressed the concerns we raised, hence recommending publication of the manuscript.

Referee #2 (Remarks to the Author)

Summary Comment: The rebuttal improves the manuscript, but several important concerns are still not fully addressed.

Response: We thank Reviewer #2 for identifying substantive points that require more rigorous treatment. We address each in full below, providing mechanistic arguments, discussions, and precise manuscript revisions.

Comment 1: The necessity of using a bioresorbable battery in ingestible electronics is still not sufficiently justified. The authors emphasize the advantage of bioresorbable battery for ingestible devices. However, in this work, the device is expected to pass through the GI tract and be excreted from the body before the battery starts significant degradation. In this case, it is still unclear why a bioresorbable battery is necessary at the system level, instead of being only an additional safety feature. The current rebuttal mainly mentions capsule rupture, retention, and reduction of e-waste, but these points are still rather general and not quantitatively supported. The authors should clarify more clearly whether bioresorbable is a true functional requirement for ingestible electronics, or only a desirable safety margin in some special situations.

Response 1: We thank the reviewer for pressing on this point. We now provide a more rigorous and structured answer distinguishing functional requirements from safety margins, and specifying the clinical context in which each applies.

First, we acknowledge that for a rapidly transiting, non-retained ingestible capsule (GI transit time ~1–3 days), the primary battery may largely pass intact, and bioresorbability is not a functional electrical requirement in that scenario. However, our work demonstrates three distinct use cases, and the functional necessity of bioresorbability differs across them:

- **Use Case 1:** Three-day gastric retention (Section 2.2). Here the battery is intentionally anchored to the stomach wall for up to 72 hours via arm-shaped capsule or endoclip. Over this period, partial Mg corrosion and encapsulation degradation are expected and documented (Figures 2g/2h, Supplementary Figures 15–17). For a retained device, the use of a non-resorbable conventional battery (e.g., silver oxide or lithium coin cell) would require either surgical retrieval of the battery or acceptance that a non-degradable power source remains in the GI tract for an extended, intended period. The bioresorbable battery eliminates this concern functionally. The retrieval is not required because the battery safely degrades in situ. This constitutes a functional, not merely safety, justification.
- **Use Case 2:** Medication adherence BA-RFID (Section 2.3). For a non-retained capsule, bioresorbability is primarily a safety margin and e-waste advantage, as the reviewer notes. We now explicitly state this in the manuscript. The quantitative case: ingestible RFID adherence monitoring is envisioned for chronic daily use in diseases such as tuberculosis

(6-month regimens), HIV (lifelong), and transplant immunosuppression. At one capsule per day over a 6-month TB treatment course, a patient would ingest approximately 180 capsule electronics. If each contains a non-degradable silver oxide battery (SR44, ~1.6 g), the cumulative retained mass in the GI tract assuming even 1% retention probability, consistent with data showing ~1–5% capsule retention rates in high-risk populations [Liao et al., *Gastrointest. Endosc.*, 2010] would be ~3 batteries^[1]. For a bioresorbable battery, this risk is minimal. This is a quantitative, patient-safety justification.

- **Use Case 3:** Gastric electrical stimulation (Section 2.4). Here the device is retained for the duration of stimulation (hours to days) and subsequently passes. During the retained phase, the battery is the active power source. A non-resorbable battery in a retained capsule raises the same regulatory and safety concerns as a retained implant. It requires retrieval or acceptance of a foreign body in the GI tract. The bioresorbable battery removes this barrier entirely, enabling a device that is functionally equivalent to an implant but without surgical risk or retrieval burden. Bioresorbability is therefore a functional design enabler for this application.

In summary, bioresorbability is a functional requirement for retained-device applications (Use Cases 1 and 3), and a clinically meaningful safety advantage for chronic non-retained use (Use Case 2). We have restructured the Introduction and Discussion to make this three-part distinction explicit, with the retention-based use cases quantitatively grounded. We also now state clearly that for a single-transit, non-retained ingestible capsule, conventional batteries with appropriate encapsulation would be functionally acceptable, and that the bioresorbable battery provides added safety margin in those scenarios, not a functional difference.

Modification to the manuscript: Introduction (page 3) and Discussion (page 19): New paragraph added distinguishing functional requirement (retained applications) from safety margin (non-retained daily use) to chronic daily adherence monitoring. Explicit statements were added:

Sentence added to Page 3: “The necessity of bioresorbability in ingestible energy storage, however, depends on the intended use case. For rapidly transiting capsules, bioresorbability functions primarily as a safety margin; for retention-based devices, it constitutes a functional design requirement that enables device operation without retrieval.”

Sentence added to Discussion:

“The role of bioresorbability in ingestible electronics differs across applications. For rapidly transiting capsules excreted within one to three days, using bioresorbable components functions primarily as a safety margin. For chronic daily use scenarios, even a small probability of capsule retention translates to a cumulative retained battery burden that bioresorbable designs eliminate entirely^[1]. For retention-based applications such as multi-day gastric retention or therapeutic applications, bioresorbability is a functional requirement, as a device anchored to the stomach wall would otherwise require endoscopic retrieval, reintroducing the procedural burden the ingestible form factor is designed to avoid.”

Comment 2: The event detection by active RFID seems to rely only on backscatter amplitude, but this may not be specific enough. From the current data and explanation, the occurrence of an event seems to be judged mainly from the amplitude change of the backscattered RFID signal. However,

in practice, the signal amplitude can also strongly depend on the distance between reader and RFID tag, as well as the alignment and orientation between them. Therefore, it is not clear whether the observed signal change is really caused by the event itself, or partly by geometric factors of the RF link. The authors should discuss this point more carefully and provide stronger evidence that the amplitude-based detection is robust against reader-tag distance variation, misalignment, and body motion.

Response 2: We thank the reviewer for this comment. This is a well-posed and important challenge. We address it at three levels: (1) the detection mechanism, (2) the experimental controls we have applied, and (3) what remains as future work.

- **Detection mechanism.** In our system, the signal change used for ingestion detection is not a single absolute RSSI value but a step-change from a stable baseline: the tag transitions from an air environment (measured at the same 1.5 m reader distance prior to administration) to a tissue environment upon ingestion. The key discriminating feature is therefore the reproducibility and direction of the RSSI shift, not its absolute magnitude. In our in vivo experiments (Figure 3i), all three swine showed a consistent ~10 dB attenuation shift upon esophageal entry, with the pre-ingestion RSSI stable at -40 to -50 dBm at the fixed 1.5 m distance and post-ingestion RSSI shifting to approximately -60 dBm. This is mechanistically grounded: RF propagation through soft tissue at 915 MHz introduces predictable additional path loss (~2–4 dB per cm of tissue, per the link budget in Supplementary Note 1), which is distinct from the slow, continuous variation caused by distance drift or body motion.
- **Confound controls.** To address the reviewer's concern about geometric confounds, we note the following controls present in our study: (i) Reader-tag distance was fixed at 1.5 m for all in vivo and ex vivo measurements. The distance effect visible in Figure 3f (RSSI vs. distance in air) is therefore not a confounder at fixed geometry. (ii) The ex vivo esophageal tissue experiment (Supplementary Figure 19) isolates the tissue propagation effect from motion and distance variation, confirming that a reproducible ~8–12 dB attenuation is attributable specifically to tissue exposure at constant geometry. (iii) The pre-administration baseline (tag in air at 1.5 m) provides a within-session, same-distance reference, making the ingestion event detectable as a relative change rather than an absolute threshold. This is the same approach used in clinical ingestible sensor systems^[2,3] [Chai et al., JAIDS, 2022; Hafezi et al., IEEE Trans. Biomed. Eng., 2015].
- **Limitations and future work.** We acknowledge that in free-living conditions, where reader distance, body position, and orientation may vary, pure RSSI-based detection will require additional robustness measures. These include: event-detection algorithms that operate on the rate of change or step profile rather than absolute RSSI; multi-reader triangulation to decouple distance from tissue effects; or temporal gating (detecting the brief transit event during swallowing, where the RSSI step occurs within seconds). Robust clinical deployment would also benefit from body-worn reader placement at a controlled distance, as implemented in the eTectRx ID-Cap system. We have now added this discussion to the manuscript, distinguishing what is demonstrated here (proof-of-concept, fixed geometry) from what is required for deployment robustness.

Modification to the manuscript: Section 2.3 and Discussion: Added explicit description of the step-change detection mechanism (relative shift, not absolute threshold). Noted that ex vivo data in Supplementary Figure 19 isolates tissue attenuation from geometric confounds. Added Discussion paragraph on limitations and future approaches for robust free-living RSSI-based detection, including event-profile algorithms, multi-reader approaches, and temporal gating during swallowing.

Sentences added to Page 12 : “Upon ingestion, the tag remained detectable by the external reader and exhibited a noticeable change in RSSI. **Ingestion detection in this system relies on a step-change in RSSI from a within-session baseline, rather than on an absolute signal threshold.** As shown in Figure 3i, prior to administration, the tags exhibited RSSI values of approximately -40 to -50 dBm when measured from a 1.5 m distance. After ingestion, the RSSI shifted to approximately -60 dBm, consistent with RF attenuation in the tissue environment. **Because both baseline and post-ingestion measurements were acquired under fixed reader-position conditions, the observed step-change is consistent with tissue exposure, although orientation and body-position effects remain important considerations for future free-living deployment.** Ex vivo experiments using a swine esophagus further validated the system’s performance through tissue (Supplementary Figure 19). This ~10 dB **attenuation shift** in RSSI provides a clear and distinct signature of capsule ingestion, supporting the use of BA-RFID tags for noninvasive, real-time monitoring of medication adherence. “

Discussion was modified, page 19: “In the ingestible RFID system, the bioresorbable battery enables always-on communication and improved readout range compared with passive tags. **Ingestion detection is based on a reproducible step-change in RSSI between a fixed-geometry air baseline and the tissue-attenuated post-ingestion signal, rather than on an absolute amplitude threshold.** This approach is consistent with other ingestible adherence platforms, where robust detection is achieved by defining event-specific thresholds that account for typical physiological and environmental variability. In vivo swine experiments confirmed that ingestion events could be wirelessly tracked in real time through RSSI signal changes, validating the sensing and communication capabilities of the device. **In free-living use, however, distance variability, body composition differences, and tag orientation would require additional algorithmic robustness, such as step-change profile detection or multi-reader triangulation. Developing and validating such algorithms for real-world adherence monitoring remains an important target for future translational work.**“

Comment 3: The explanation for the relatively high OCV of the Mg–MoO₃ battery is still not convincing enough. The authors report that their battery shows a higher OCV than some similar systems. In the rebuttal, they mention that different electrolytes were tested and that the bio-IL electrolyte performed better than PBS- and urea-based systems. However, it is still not clear whether the higher OCV should really be attributed to the electrolyte. The authors should explain this point more mechanistically. For example, is the higher OCV caused by electrolyte chemistry itself, by reduced parasitic reactions, by improved interfacial contact, or by different measurement conditions? At present, the discussion is still too descriptive.

Response 3: We thank the reviewer for pressing for a mechanistic rather than descriptive explanation. We now provide one.

The equilibrium cell voltage of a Mg–MoO₃ battery is determined by the difference in electrochemical potential between the anode (Mg/Mg²⁺) and cathode (MoO₃/Mo reduction) half-reactions. In an ideal, lossless system, this thermodynamic OCV is fixed by the Gibbs free energy of the cell reaction and is independent of electrolyte choice. The relevant half-reactions are:



The theoretical OCV of the Mg–MoO₃ cell in aqueous acid is therefore > 2.0 V. That practical OCV values of 1.6–1.84 V are observed reflects mixed-potential losses at both electrodes rather than fundamental thermodynamic differences between systems.

The difference in OCV between our bio-IL electrolyte and PBS- or urea-based alternatives is therefore not attributable to thermodynamic factors but rather to three kinetic and interfacial mechanisms:

- **Suppression of parasitic Mg corrosion.** In aqueous electrolytes, Mg undergoes spontaneous corrosion ($\text{Mg} + 2\text{H}_2\text{O} \rightarrow \text{Mg}(\text{OH})_2 + \text{H}_2$), which establishes a mixed potential at the anode that is significantly more positive than the equilibrium Mg/Mg²⁺ potential. This self-corrosion depresses the apparent anode potential. The ChCl/DL-lactic acid bio-IL, being a deep eutectic solvent, has significantly reduced water activity compared to PBS. Lower water activity suppresses the kinetics of the parasitic hydrogen evolution reaction (HER) at the Mg surface, allowing the anode to operate closer to its thermodynamic potential and thereby raising the measured OCV. This mechanism — reduced HER parasitic current is studied for Mg batteries in ionic liquid environments^[4] [Geng et al., ACS Energy Lett., 2022].
- **Cathode activity preservation.** MoO₃ is slightly soluble in aqueous media (solubility ~1 g/L in water, higher in acidic PBS)^[5]. Dissolution of MoO₃ into the electrolyte reduces the active cathode mass available for reduction, depressing cathode potential and thus OCV. The bio-IL gel electrolyte, with its reduced water activity and higher viscosity, limits MoO₃ dissolution during the early operation phase, preserving cathode potential closer to the thermodynamic value.
- **Improved electrolyte–electrode interfacial contact.** The gel electrolyte formed by incorporating the bio-IL into a gelatin matrix provides conformal mechanical contact with both the MoO₃ cathode and the Mg anode. This reduces interfacial resistance (confirmed by EIS: lower R_s and R_{ct} in the bio-IL system vs. PBS, Supplementary Figure 9), which means less ohmic drop even under quasi-open-circuit conditions during OCV measurement. In practical measurements over finite equilibration times, lower interfacial resistance allows the electrodes to relax closer to their open-circuit equilibrium values.

Modification to the manuscript: Mechanistic paragraph added explaining the three contributions to elevated OCV: (i) HER suppression in low-water-activity deep eutectic electrolyte; (ii) reduced interfacial resistance from conformal gel contact; (iii) suppressed MoO₃ dissolution. References added: Geng et al., ACS Energy Lett., 2022.

Sentence added to Page 7: “ The higher OCV of the bio-IL system relative to PBS and aqueous electrolytes may be attributed to three contributing factors: HER suppression through reduced water activity^[4], improved interfacial contact from the conformal gel electrolyte, and suppressed MoO₃ dissolution during early operation.”

Comment 4: The manuscript should separate proof-of-concept from translational claim. The study is promising, but some parts of the discussion still sound overstated for the current stage. For example, the system includes some components that are not yet fully bioresorbable in the stimulation platform, and the in vivo studies are still limited in sample size and testing conditions. The authors should make clearer which parts are already demonstrated and which parts remain future engineering targets. This would improve the balance of the paper.

Response 4: We thank the reviewer and agree that clearer separation between demonstrated capabilities and future translational targets improves the balance of the manuscript. We have revised the Discussion to explicitly frame the present work as a proof-of-concept demonstration of bioresorbable battery integration in ingestible systems.

The key revisions are: (i) the opening Discussion paragraph is rewritten to frame the work accurately as a proof-of-concept; (ii) a structured paragraph distinguishing demonstrated findings from future targets is added; and (iii) all language implying clinical readiness is removed or qualified.

Modification to the manuscript: Discussion is modified.

Sentence added to Page 19, the discussion starts with: “ This study presents a bioresorbable Mg–MoO₃ paper-based battery platform validated under physiologically relevant conditions and across multiple in vivo use cases. The results establish the electrochemical feasibility of the battery as a safe and reliable power source for ingestible devices. These batteries ...”

Sentences added to Page 20, paragraph modified: “Several components and capabilities require further work before clinical translation. The stimulation PCB is not yet biodegradable, and developing a fully bioresorbable circuit integration strategy remains a future engineering target. Shelf-life stability beyond the currently characterized two-week window also requires further investigation. The in vivo evaluations were conducted in fasted swine with small cohort sizes (n = 3 per condition); future studies will examine device behaviour under more physiologically representative conditions, including fed state, pH variability, mucus, and altered motility. These factors may... ”

Referee #3 (Remarks to the Author)

Summary Comment: The authors have improved the quality of the manuscript substantially. The claims are more balanced. Valuable context has been added to the data and discussion. Numerous figures have been added to the supplementary data, aiding the interpretability of the work.

Response: We thank Reviewer #3 for recognizing the substantial improvements made to the manuscript and supplementary information. We also appreciate the reviewer's careful identification of remaining inconsistencies in the Abstract, main text, and supplementary figure labels. We have now corrected these points explicitly and have checked the revised manuscript and Supplementary Information to ensure consistency.

Comment 1: Some initial comments are still not addressed. This comment was about the abstract. Changes have been made in other parts of the manuscript, but the abstract was not updated.

Reviewer 3 - Response 8

- Battery voltage
The author agrees that there is a clear distinction between 1.84V of peak initial open-circuit voltage and 1.6V stable operating power. The abstract is not updated however, as initially requested. It still has the ubiquitous statement: 'The battery provides a stable output voltage of 1.84 V'. This should be either clearly 1.84V of peak initial open-circuit voltage, or 1.6V of stable operating voltage.
- PCB
'fully biodegradable capsule systems for electroceutical therapy', this is still incorrect. The PCB's are not biodegradable. This needs to be reworded:
'fully biodegradable capsule systems (excluding PCB) for electroceutical therapy'.
- Infection
'reduce infection risk' is still stated in the abstract, despite the author claimed to have removed every mention of infection risk.
Infection is also still mentioned on line 105 of page 4.

Response 1: We thank the reviewer for carefully identifying these remaining inconsistencies. We have revised the Abstract in the manuscript, abstract in the submission system and main text accordingly:

First, we have corrected the voltage statement in the Abstract to distinguish peak open-circuit voltage from stable operating voltage. The Abstract no longer states that the battery provides a "stable output voltage of 1.84 V." Instead, it now states that the battery provides a "peak open-circuit voltage of 1.84 V." Where stable operation is discussed in the Results and Discussion, we refer separately to the approximately 1.6 V operating voltage under discharge.

Second, we have removed language implying that the entire electroceutical capsule system is fully biodegradable. We agree that this was inaccurate because the current stimulation prototype

includes a non-biodegradable PCB. We now reserve “bioresorbable” or “biodegradable” claims for the battery and biodegradable structural components, and we describe the electroceutical system as a capsule-scale ingestible electronic system incorporating a bioresorbable power source. We also explicitly state in the Discussion that developing a fully bioresorbable circuit integration strategy remains a future engineering target.

Third, we have removed the remaining references to “infection risk” from both the Abstract and the main text, including the mention on page 4. These statements have been replaced with more precise wording regarding reduction of retrieval burden, foreign-body exposure, and procedural burden.

Modification to the manuscript: The Abstract has been revised to read:

On page 2, the abstract is modified: “The battery provides a peak open-circuit voltage of 1.84 V and supports capsule-scale ingestible electronic systems incorporating bioresorbable power sources for two key gastrointestinal applications: battery-assisted RFID tags for wireless medication tracking and capsule systems for electroceutical therapy. “

In addition, the phrase “fully biodegradable capsule systems for electroceutical therapy” has been removed. References to “infection risk” have also been removed from the Abstract and main text and replaced with language referring to retrieval burden and transient operation.

Comment 2: Regarding explanation of used abbreviations. The author noted that GCD is no longer used as abbreviation, hence does not need explanation. However, GCD is still used in Supplementary Figure 13, 15 and 16. Either explain the abbreviation, or rework the figures.

Reviewer 3 - Comment 22

Response 2: We thank the reviewer for pointing this out. We have corrected the remaining abbreviation inconsistency in the Supplementary Information. The abbreviation “GCD” has been removed from Supplementary Figures 13, 15, and 16 and replaced with the explicitly defined term “galvanostatic discharge (GD)” in the corresponding figure captions and labels. We have also checked the Supplementary Information for consistency so that the abbreviation is defined before use.

Modification to the Supplementary Information: Supplementary Figures 13, 15, and 16 have been revised to replace “GCD” with “galvanostatic discharge (GD)” or “GD” after definition.

References

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Point-by-point response – Nature Chemical Engineering – Manuscript #:
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Referee #2 (Remarks to the Author)

Summary Comment: The authors have responded to all of my comments. I believe that the revised manuscript is now suitable for publication.

Response: We thank Reviewer #2 for their thorough and constructive engagement throughout the revision.

Referee #3 (Remarks to the Author)

Summary Comment: The authors addressed all raised concerns. The manuscript is ready for publication.

Response: We are sincerely grateful to Reviewer #3 for their comments during the revision process.