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Peer Review File

Silk Fibroin-Coated Nanoparticles for Safe and Efficient Antithrombotic Drug Delivery

Corresponding Author: Professor Mingying Yang

This file contains all editorial decision letters in order by version, followed by all author rebuttals in order by version.

Version 0:

Decision Letter:

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Dear Professor Yang,

Thank you again for submitting your manuscript "Silk Fibroin-Coated Nanoparticles for Safe and Efficient Antithrombotic Drug Delivery" to Communications Materials. We have now received reports from 2 reviewers and, based on their comments, we have decided to invite a revision of your work. You will find the reviewers' reports below. While they find your work of interest, they have raised important points which must be addressed in a revised manuscript.

In particular, you will see that the reviewers are requesting additional discussion of the mechanistic benefits of the work and the generalizability of the platform.

To allow us to move forward with your work, we also ask that you edit your manuscript according to the attached table. **Please read this document carefully as we will be unable to further assess your revised paper until these important points are addressed.**

Please outline all revisions made in the right-hand column and return the completed table with your updated manuscript files as a Related Manuscript file.

When resubmitting, please also include:

- A point-by-point response to the reviewers' comments. If you are unable to address specific reviewer requests or find any points invalid, please explain
- A clean version of your revised manuscript with no mark-ups
- A marked-up version of your paper with all changes highlighted in a different colour

Please use the link below to submit your revised files:
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We hope to receive your revised paper within six weeks, but we understand that the revisions may take longer. Please let us know if you find that the revision process will take substantially more time.

We are committed to providing a fair and constructive peer-review process. Please do not hesitate to contact me if you have any questions or would like to discuss these revisions further. We look forward to seeing the revised manuscript and thank

you for the opportunity to review your work.

Best regards,

Meltem Yanilmaz, PhD
Associate Editor
Communications Materials
orcid.org/0000-0003-0562-5715

Reviewers' comments:
Reviewer #1 (Remarks to the Author):

The manuscript presents a silk-fibroin–coated mesoporous silica nanoparticle system for antithrombotic drug delivery and demonstrates improved biocompatibility, reduced hemolysis, and enhanced thrombolytic performance in vivo. The topic is significant, and the work is well executed, providing a potential strategy for thrombotic prevention and long-term administration of antithrombotic drugs. It is recommended for publication after minor revision.
Minor comments
In the introduction section, "the high dose of thrombotic drugs such as urokinase (UK), heparin sodium (HS), and aspirin", “thrombotic drugs” should be “anti-thrombotic drugs”.
Fig2c, it would be better to label PBS, SF-Mas, and Mas on the images.
It would be better to ensure the same sample orders in Fig4E&F.
It is recommended to articulate the mechanistic benefits of the SF layer in drug loading, release, and thrombus interaction.
Some recent work of silk based drug delivery could be discussed. E.g., ACS Biomater. Sci. Eng. 2025, 11, 1539–1548; Nanomaterials 2025, 15, 221; Pharmaceutics 2025, 17, 95; Pharmaceutics 2023, 15, 1811; Colloids and Surfaces B: Biointerfaces 216 (2022) 112549; Journal of Colloid and Interface Science 594 (2021) 513–521; International Journal of Pharmaceutics 555 (2019) 322–336.

Reviewer #2 (Remarks to the Author):

This manuscript reports a silk fibroin–coated mesoporous silica nanoparticle system enabling sustained heparin release for safe and efficient antithrombotic therapy. The work is logically structured, experimentally solid, and of potential interest to the biomaterials and drug delivery community. A few minor revisions are recommended to further improve clarity and presentation. My comments are as below.
1.The graphical abstract (Scheme 1) clearly outlines the workflow. To further enhance its didactic value, a succinct statement in the figure caption explaining how the silk fibroin coating modulates heparin release would more directly link the visual to the study's central design principle.
2. While the current subheading in the Results (e.g., "The synthesis and characterization of SF-Mas") is accurate, it remains largely descriptive. Refining section titles to concisely indicate the key finding or significance revealed would provide greater immediate insight and improve the narrative flow for readers.
3. To further strengthen the logical connection of efficacy (Fig. 3) and safety (Fig. 4), it would be beneficial to integrate these findings explicitly in the Discussion. A concluding sentence that frames the controlled release mechanism as enabling effective anticoagulation while maintaining a favorable safety profile would unify the interpretation of the key results.
4. In Figure 1 caption, “character” should be corrected to “characterization.”
5. The Conclusion could be strengthened by adding one sentence on the system’s potential translational relevance for long-term anticoagulation management.
6. The authors have demonstrated an effective system for the sustained release of HS. A key question regarding the broader impact of this work is the generalizability of the platform. Could the authors comment on the underlying design principles that might allow this system to be adapted for the delivery of other therapeutic agents with differing physicochemical properties.

Version 1:

Decision Letter:

Dear Professor Yang,

Thank you once again for submitting your manuscript, “Silk Fibroin-Coated Nanoparticles for Safe and Efficient

Antithrombotic Drug Delivery," to Communications Materials. Your manuscript has been seen again by the referees, whose comments are appended below. I am happy to say that the concerns of our reviewers have now been addressed, and that we only require some minor amendments before we can accept your paper.

Our remaining requests are:
- Please upload the supplementary information file in PDF format.
- Please update the data availability statement by providing the name and/or email address of who will be responsible for replying to this data request.

This will be the final revision of your manuscript. We ask that you carefully review all files associated with your paper and follow the link below to upload the final version of all files, including display items and supplementary material. Please ensure that these files are clean, without any markups or comments, as they will be sent for publication.

Link Redacted

We hope to receive this updated version of your paper within 1 week, but please let us know if you find that you need more time.

We hope to receive this updated version of your paper **within 1-week,** but please let us know if you find that you need more time.

Best regards,
Meltem Yanilmaz, PhD
Associate Editor
Communications Materials
orcid.org/0000-0003-0562-5715

Reviewers' comments:
Reviewer #1 (Remarks to the Author):

The authors have addressed all the comments.

Reviewer #2 (Remarks to the Author):

The authors addressed my comments well, and I have no more concerns. Thanks.

Version 2:

Decision Letter:

Dear Professor Yang,

We are delighted to accept your manuscript titled "Silk Fibroin-Coated Nanoparticles for Safe and Efficient Antithrombotic Drug Delivery" for publication in Communications Materials. Thank you for choosing to publish your interesting work with us.

Please note that in advance of your paper being published we will host an early access version, known as an 'Article in Press,' on our journal website. For more information on this initiative please see our author guidelines.

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We look forward to publishing your paper.

Best regards,

Meltem Yanilmaz, PhD
Associate Editor
Communications Materials
orcid.org/0000-0003-0562-5715

***As a new journal, we would greatly appreciate any comments you have about your experience at Communications Materials. I hope that we have been able to meet your expectations and look forward to working with you again in the future.

We may promote your article on social media once it is published, so please feel free to send me the twitter handles of any authors or departments and we will be sure to tag them accordingly.***

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Reviewers' comments:

Reviewer #1 (Remarks to the Author):

The manuscript presents a silk-fibroin–coated mesoporous silica nanoparticle system for antithrombotic drug delivery and demonstrates improved biocompatibility, reduced hemolysis, and enhanced thrombolytic performance in vivo. The topic is significant, and the work is well executed, providing a potential strategy for thrombotic prevention and long-term administration of antithrombotic drugs. It is recommended for publication after minor revision.

Minor comments

1. In the introduction section, "the high dose of thrombotic drugs such as urokinase (UK), heparin sodium (HS), and aspirin", "thrombotic drugs" should be "anti-thrombotic drugs".

Response: We thank the reviewer for pointing this out. We apologize for the imprecise wording. The term "thrombotic drugs" has been corrected to "anti-thrombotic drugs" in the Introduction.

2. Fig2c, it would be better to label PBS, SF-Mas, and Mas on the images.

Response: We thank the reviewer for this helpful suggestion and apologize for the oversight during figure preparation, where the labels were inadvertently removed. Labels for PBS, SF-Mas, and Mas have now been added to Fig. 2c to improve clarity.

3. It would be better to ensure the same sample orders in Fig4E&F.

Response: We appreciate the reviewer's comment. We agree that inconsistent sample orders between adjacent panels may cause confusion for readers. To ensure consistency, the sample labels in Fig. 4F have been revised to align with those in Fig. 4E.

4. It is recommended to articulate the mechanistic benefits of the SF layer in drug loading, release, and thrombus interaction. Some recent work of silk based drug delivery could be discussed. E.g., ACS Biomater. Sci. Eng. 2025, 11, 1539−1548; Nanomaterials 2025, 15, 221; Pharmaceutics 2025, 17, 95; Pharmaceutics 2023, 15, 1811; Colloids and Surfaces B: Biointerfaces 216 (2022) 112549; Journal of Colloid and Interface Science 594 (2021) 513–521; International Journal of Pharmaceutics 555 (2019) 322–336.

Response: We thank the reviewer for this helpful suggestion. The recommended references have been carefully reviewed and have now been cited in the revised manuscript to better contextualize our work.

Reviewer #2 (Remarks to the Author):

This manuscript reports a silk fibroin-coated mesoporous silica nanoparticle system enabling sustained heparin release for safe and efficient antithrombotic therapy. The work is logically structured, experimentally solid, and of potential interest to the biomaterials and drug delivery community. A few minor revisions are recommended to further improve clarity and presentation. My comments are as below.

1. The graphical abstract (Scheme 1) clearly outlines the workflow. To further enhance its didactic value, a succinct statement in the figure caption explaining how the silk fibroin coating modulates heparin release would more directly link the visual to the study's central design principle.

Response: We thank the reviewer for this insightful suggestion. A concise statement has now been added to the caption of Scheme 1 to explain how the silk fibroin coating modulates heparin release, thereby more clearly linking the graphical abstract to the central design principle of the study.

2. While the current subheading in the Results (e.g., "The synthesis and characterization of SF-Mas") is accurate, it remains largely descriptive. Refining section titles to concisely indicate the key finding or significance revealed would provide greater immediate insight and improve the narrative flow for readers.

Response: Thank you for your thoughtful and valuable feedback. We agree that more informative subheadings can be helpful in guiding readers. In the present manuscript, however, we intentionally adopted descriptive subheadings in the Results section to maintain a neutral presentation of experimental outcomes, allowing the key findings to be conveyed primarily through the data and accompanying text. We hope this approach does not hinder readability. Meanwhile, we have made minor revisions to several subheadings where appropriate to improve clarity and suitability.

3. To further strengthen the logical connection of efficacy (Fig. 3) and safety (Fig. 4), it would be beneficial to integrate these findings explicitly in the Discussion. A concluding sentence that frames the controlled release mechanism as enabling effective anticoagulation while maintaining a favorable safety profile would unify the interpretation of the key results.

Response: We appreciate the reviewer's constructive comment. The conclusion has been updated to explicitly link the efficacy and safety results, with a sentence framing the sustained release mechanism as the basis for both effective antithrombotic efficacy and improved safety.

4. In Figure 1 caption, “character” should be corrected to “characterization.”

Response: Thank you for your detailed review and constructive feedback. The term “character” has been corrected to “characterization” in the caption of Figure 1.

5. The Conclusion could be strengthened by adding one sentence on the system’s potential translational relevance for long-term anticoagulation management.

Response: We appreciate the reviewer’s comment. A sentence has been added to the conclusion to emphasize the potential translational relevance of the system in long-term anti-thrombotic therapy.

6. The authors have demonstrated an effective system for the sustained release of HS. A key question regarding the broader impact of this work is the generalizability of the platform. Could the authors comment on the underlying design principles that might allow this system to be adapted for the delivery of other therapeutic agents with differing physicochemical properties.

Response: We appreciate the reviewer’s insightful comment, which raises an important point regarding the broader applicability of the platform. Beyond HS, the generalizability of the SF-Mas platform arises from its modular design and the versatile physicochemical properties of silk fibroin. The release behavior is governed primarily by the interactions between the drug molecules and the silk fibroin matrix, including electrostatic interactions, hydrogen bonding, and diffusion through the protein network. By adjusting parameters such as coating thickness, secondary structure content, and crosslinking density, the system could in principle be tailored to accommodate therapeutic agents with different molecular weights, charge states, and hydrophilicity, thereby extending its applicability to a broader range of drugs. Moreover, we recognize that a wide range of chemical groups and materials may be employed for surface coating applications. Ongoing efforts in our group focus on chemical modification of silk fibroin to modulate its properties and expand its coating and drug-loading functionalities. We are grateful for the reviewer’s valuable suggestion and will endeavor to further advance this aspect in future studies.