

**BUKTI KORESPO NDING PAPER DI IJB (Q2) JUDUL**  
**" *Synthesis and Characterization of Nanohydroxyapatite-Gelatin Composite with Streptomycin as Antituberculosis Injectable Bone Substitute* by**  
**Dyah Hikmawati<sup>1</sup>, Hendita N Maulida<sup>2</sup>, Alfian P Putra<sup>2</sup>, Aniek S**  
**Budiatin<sup>3</sup>, Ardiyansyah Syahrom<sup>4 5</sup>**

**1. BUKTI SUBMIT**

On Thu, Dec 20, 2018 at 2:03 PM, International Journal of Biomaterials  
<reta.atalla@hindawi.com> wrote:

Dear Dr. Hikmawati,

This is regarding your manuscript titled "Nano Hydroxyapatite-Gelatin-Based Injectable Bone Substitute with Addition of Streptomycin for Spinal Tuberculosis Case" in International Journal of Biomaterials. Please register an ID with Open Researcher and Contributor ID (ORCID) and link it to your Manuscript Tracking System (MTS) account, as we need to include authors' ORCID IDs in the article metadata that we submit to various indexing services.

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In order to create an ORCID ID and link it to the MTS, please go to <http://mts.hindawi.com/orcid/>, where you will be asked to log in using the email address "[dyah.hikmawati@yahoo.co.id](mailto:dyah.hikmawati@yahoo.co.id)" and the password that you previously registered on the system. If you do not remember your password, you can use the following link to reset it: <http://mts.hindawi.com/reset.password/70d9e718-494a-4846-83f3-cc77cb3a989f/>. You will then be directed to ORCID.org where you can create your ID.

Please make sure to use the name format that is on the MTS when creating your ORCID ID, since it is highly preferred that you use the same format in all of the systems dealing with your professional activities. However, if your name on the MTS is not currently correct, let me know the format you prefer, and I will update it accordingly.

I look forward to your cooperation.

Best regards,

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\*\*\*\*\*  
Reta Atalla  
Editorial Office  
Hindawi  
<http://www.hindawi.com>  
\*\*\*\*\*

Fw: Your Manuscript 7179243

Dari: Dyah Hikmawati, S.Si., M.Si (dyah.hikmawati@yahoo.co.id)

Kepada: pramuditaalfian@gmail.com

Tanggal: Selasa, 25 Desember 2018 pukul 08.35 WIB

[Sent from Yahoo Mail on Android](#)

On Sun, Dec 23, 2018 at 3:51 PM, International Journal of Biomaterials <reta.atalla@hindawi.com> wrote:

Dear Dr. Hikmawati,

This is regarding your manuscript titled "Nano Hydroxyapatite-Gelatin-Based Injectable Bone Substitute with Addition of Streptomycin for Spinal Tuberculosis Case" in International Journal of Biomaterials. Please access the below URL to register an ORCID ID and link it to your Manuscript Tracking System (MTS) account:

<http://mts.hindawi.com/orcid/>

Your prompt action is appreciated.

Best regards,

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7179243.v1 (Research Article)

|                   |   |
|-------------------|---|
| Title             | Nano Hydroxyapatite-Gelatin-Based Injectable Bone Substitute with Addition of Streptomycin for Spinal Tuberculosis Case |
| Journal           | International Journal of Biomaterials   |
| Issue             | Regular   |
| Manuscript Number | 7179243 (Research Article)  |
| Submitted On      | 2018-12-17  |
| Author(s)         | Dyah Hikmawati,  Hendita Nur Maulida, <b>Alfian Putra</b> ,  Aniek Setiya Budiadin                                      |
| Editor            |   |
| Status            | Under Review  |

## 2. PERMINTAAN UNTUK REVISI

Fw: 7179243: Major Revision Required

Dari: Dyah Hikmawati, S.Si., M.Si (dyah.hikmawati@yahoo.co.id)

Kepada: anieksb@yahoo.co.id

Tanggal: Senin, 30 Agustus 2021 pukul 14.54 WIB

----- Pesan yang Diteruskan -----

**Dari:** Feng-Huei Lin <ijbm@hindawi.com>

**Kepada:** "alfian.pramudita@fst.unair.ac.id" <alfian.pramudita@fst.unair.ac.id>

**Cc:** "dyah.hikmawati@yahoo.co.id" <dyah.hikmawati@yahoo.co.id>; "henditamaulida@gmail.com" <henditamaulida@gmail.com>; "anieksb@yahoo.co.id" <anieksb@yahoo.co.id>

**Terkirim:** Selasa, 2 April 2019 16.01.05 GMT+7

**Judul:** 7179243: Major Revision Required

Dear Dr. Putra,

Following the review of Research Article titled "Nano Hydroxyapatite-Gelatin-Based Injectable Bone Substitute with Addition of Streptomycin for Spinal Tuberculosis Case" by Dyah Hikmawati, Hendita Nur Maulida, Alfian Putra and Anek Setiya Budiati, I recommend that it should be revised taking into account the changes requested by the reviewer(s). Since the requested changes are major, the revised manuscript will undergo a second round of review by the same reviewer(s). Please login to the Manuscript Tracking System to read the submitted review report(s) and submit the revised version of your manuscript no later than Tuesday, April 30, 2019.

To submit the revised version of your manuscript, please access "Author Activities" in your account and upload the PDF file of your revised manuscript. Also, please submit your replies to the comments of the reviewer(s) as an additional PDF file.

Best regards,

Feng-Huei Lin

**3. KARENA MAJOR REVISION MEMINTA IJIN MENAMBAH Dr Ardiyansyah Syahrom SEBAGAI AUTHOR dan perubahan judul.**

Dear Reta Atalla,

Thank you for your consideration.

You could find the added author's data below.

Name: Ardiyansyah Syahrom

Affiliation: Applied Mechanics and Design, School of Mechanical Engineering, Faculty of Engineering, Universiti Teknologi Malaysia (UTM), Johor Bahru, 81310, Malaysia

Medical Devices and Technology Centre (MEDITEC), Institute of Human Centred and Engineering (iHumEn), Universiti Teknologi Malaysia (UTM), Johor Bahru, 81310, Malaysia

Email address: ardi@utm.my

The added author was not added from the beginning of the submission because we think that **Dr. Ardiyansyah Syahrom made a significant contribution in this manuscript in supervising us in revising this manuscript.** At first, we were not sure to do the revision since the comment from reviewers seemed hard to do, especially in the in vitro test part. But, He encouraged us and also helped us in reviewing and revising our manuscript based on the comment from the reviewers. Based on his advices, we revised the manuscript and submitted it to the editor. Based on this reason, we add him to the author's list.

Here is the list of author's contribution of this manuscript.

Dyah Hikmawati : Conceptualization, funding acquisition, resources, writing original draft, writing – review and editing, supervision

Hendita Nur Maulida : Synthesis and Characterization Statistical analysis, writing original manuscript

Alfian Pramudita Putra: Characterization, project administration, writing original manuscript, writing – review and editing

Aniek Setiya Budiadin : Methodology, resources, supervision

Ardiyansyah Syahrom: Validation, writing – review and editing, supervision

Thank you in advance.

Best regards,

#### 4. REVIEWER'S COMMENTS DAN JAWABAN

4/2/2019

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##### 7179243.v1 Review Report

|   |
|---|
| <b>Subject appropriateness of the manuscript</b>  |
| The topic of this manuscript does not fall within the scope of International Journal of Biomaterials  |
| <b>Recommendation</b>   |
| Consider after major changes  |
| <b>Comments for the author</b>  |
| 1. please cite the original and latest references<br>2. the language needs to be polished<br>3. The article is lack of part of the discussion<br>4. It is a promising material, however, the distribution of the drug in the material needs to be tested. If the material can be a refuge for the bacterial? and the effect of the material on the bone cells should be detected. |

### Reply to the reviewers' comments

Dear Editor of International Journal of Biomaterials,

We would like to say thank you for the opportunity to submit the revised version of our manuscript entitled "Nano Hydroxyapatite-Gelatin-Based Injectable Bone Substitute with Addition of Streptomycin for Spinal Tuberculosis Case" in International Journal of Biomaterials. Here, we send the response to the reviewers' comments with point-by-point explanation in table below. We hope that these explanations could answer and satisfy the comments from the reviewers.

| Reviewer Number | Original comments of the reviewer                 | Reply by the author(s)  | Changes done on page number and line number |
|-----------------|---|---|---|
| 1               | 1. please cite the original and latest references | <p>Thank you for the comment. We already update and add some original references, such as:</p> <p>[5] J. Dong et al., "Expert Opinion on Drug Delivery Novel alternative therapy for spinal tuberculosis during surgery: reconstructing with anti-tuberculosis bioactivity implants Novel alternative therapy for spinal tuberculosis during surgery: reconstructing with anti-tube," <i>Expert Opin. Drug Deliv.</i>, 11(3), pp. 299–305, 2014.</p> <p>[6] J. Liu et al., "Is nonstructural bone graft useful in surgical treatment of lumbar spinal tuberculosis?," <i>Medicine (Baltimore)</i>, pp. 1–7, 2016.</p> <p>[12] C. Chang, C. Hu, Y. Chang, and P. Hsieh, "Two-stage revision arthroplasty for Mycobacterium Tuberculosis periprosthetic joint infection: An outcome analysis," <i>PLoS One</i>, 13(9), pp. 1–13, 2018.</p> <p>[18] K. Saribrahimoglu, J. G. C. Wolke, S. C. G. Leeuwenburgh, L. Yubao, and J. A. Jansen, "Injectable biphasic calcium phosphate cements as a potential bone substitute," <i>J. Biomed. Mater. Res. - Part B Appl. Biomater.</i>, 102B, pp. 415–422, 2014.</p> | References section                          |

|   |  |  |  |
|---|--|--|--|
|   |  | [23] J. Dong, S. Zhang, J. Ma, H. Liu, Y. Du, and Y. Liu, "Preparation, Characterization, and In Vitro Cytotoxicity Evaluation of a Novel Anti-Tuberculosis Reconstruction Implant," PLoS One, 9(4), pp. 1–10, 2014.   |  |
| 1 | 2.the language needs to be polished  | Thank you for the comments. We also improved the English of some parts of the manuscript, such as the grammatical errors, word choice, and complex sentences   |  |
| 1 | 3. The article is lack of part of the discussion   | <p>We also added more discussion regarding the result of this study. Some of the improvements are shown below.</p> <p>Functional group test:</p> <p>"...There was no specific change in the functional groups happening in the sample which showed that there was no interaction between the materials used in this study. There was only physical interaction among the materials which were HA, GEL, HPMC, and streptomycin."</p> <p>Injectability test:</p> <p>"...Injectability was one of the most important properties in terms of IBS application since it should have high injectability to insert the IBS to the bone. Injectability is affected by the solvent and solute of the sample, the viscosity of the sample and the syringe diameter. Both of the IBS and the syringe play important role in the IBS application [18]."</p> <p>Acidity test:</p> <p>"...The acidity could also determine the setting process of the IBS since the IBS should be set at human body pH. Normally, the IBS should be set at pH of around 7.4. The sample with HA:GEL ratio of 65:35 was the most suitable one which had pH of 7.4 with little oscillation overtime."</p>   | Several parts throughout the manuscript  |
|   |  | <p>Cytotoxicity test:</p> <p>"The other cytotoxicity test was also performed to emphasize the effect of the sample towards the human cells. Human hepatocyte cells were used in this test. The best concentration of the sample based on the result of the other characterization was used in this was which was the sample with HA:GEL ratio of 65:35. The result of this test showed that the cell viability of that sample was 93.69% with the amount of streptomycin of 100 mg/ml which equals to 10%. This result showed that the sample was non-toxic, even after it was tested by using human hepatocyte cells [16]. Human hepatocyte cells in this test was successful to emphasize the cytotoxicity test that was using BHK-21 fibroblast cells. The further study of this sample by using human osteoblast cells is needed to observe the behaviour of the osteoblast cells when the IBS is applied."</p> <p>Antibacterial test:</p> <p>"...The spinal tuberculosis is caused by Mycobacterium tuberculosis. This bacteria is neither gram-positive nor gram-negative bacteria since it has the characteristics of both types. The streptomycin could kill this bacteria by inhibition of protein synthesis of mycobacteria in the ribosome [22]. This process also happens in S. aureus."</p> <p>Streptomycin release test:</p> <p>"The standard curve was then used to determine the streptomycin concentration released by the IBS-injected bone scaffold. The result was shown in Figure 10. The release profile of streptomycin was quite linear and in 4 hour, the amount of streptomycin released was almost 2.5% [23]. The initial concentration was 10%. The result of cytotoxicity test showed that with the concentration of 10% could still give high cell viability [14]. In the spinal tuberculosis case, the Mycobacterium tuberculosis could be killed by streptomycin. By the result of this test, the amount of streptomycin could</p> |  |
|   |  | release at desired concentration to its surrounding."  |  |
| 1 | 4. It is a promising material, however, the distribution of the drug in the material needs to be tested. If the material can be a refuge for the bacterial? and the effect of the material on the bone cells should be detected. | <p>Thank you for the compliment and the comment. We really appreciate it. We added the streptomycin release test to justify the amount of the streptomycin that could be release from the IBS. In here, we used bone scaffold to simulate the bone structure and injected the IBS into it. Then, the bone scaffold was immersed in the PBS solution and the amount of streptomycin released to PBS solution was measured by using UV-Vis spectrophotometer.</p> <p>The result was shown in Page 10-11 which consisted of the streptomycin absorbance, the standard curve of the streptomycin and the release profile of the streptomycin. The result showed that the after 4 hours, the amount of streptomycin that has been released was 2.5%</p> <p>For the cytotoxicity test, we also added the same test (MTT assay) with another cell, which was human hepatocyte cells. The cell viability was 93.69% with 10% of streptomycin. This result showed that the sample was non-toxic.</p> <p>For further studies, the IBS sample needs to be tested in human bone cells to evaluate its behavior.</p>  | <p>Streptomycin release test: page 4, 10-11</p> <p>Human hepatocyte cells cytotoxicity test (MTT assay): Page 3-4, 9</p> |

## 5. PROSES REVIEW DIANGGAP CUKUP DAN PAPER ACCEPTED dengan revisi judul menjadi

### Synthesis and Characterization of Nano Hydroxyapatite-Gelatin Composite with Streptomycin as Anti-Tuberculosis Injectable Bone Substitute

Fw: 7179243: Your manuscript has been accepted

Dari: Dyah Hikmawati, S.Si., M.Si (dyah.hikmawati@yahoo.co.id)

Kepada: aminatun1968@gmail.com

Tanggal: Kamis, 16 Mei 2019 pukul 22.08 WIB

[Sent from Yahoo Mail on Android](#)

On Thu, May 16, 2019 at 8:41 PM, Feng-Huei Lin <ijbm@hindawi.com> wrote:

Dear Dr. Putra,

The review process of Research Article 7179243 titled "Nano Hydroxyapatite-Gelatin-Based Injectable Bone Substitute with Addition of Streptomycin for Spinal Tuberculosis Case" by Dyah Hikmawati, Hendita Nur Maulida, Alfian Putra and Aniek Setiya Budiati submitted to International Journal of Biomaterials has been completed. I am pleased to inform you that your manuscript has now been accepted for publication in the journal.

The publication process of your manuscript will be initiated upon the receipt of electronic files. Please log in to the Manuscript Tracking System at the link below using your username and password, and upload the electronic files of your final accepted version within the next 2-3 days.

<http://mts.hindawi.com/author/7179243/upload.files/>

The electronic files should include the following:

- 1- Source file of the final accepted manuscript (Word or TeX/LaTeX).
- 2- PDF file of the final accepted manuscript.
- 3- Editable figure files (each figure in a separate EPS/PostScript/Word file) if any, taking into consideration that TIFF, JPG, JPEG, BMP formats are not editable.

If you have deposited your manuscript on a preprint server (e.g. arXiv, bioRxiv, chemRxiv), now would be a good time to update it with the accepted version. If you have not deposited your manuscript on a preprint server, you are free to do so.

Thank you again for submitting your manuscript to International Journal of Biomaterials.

Best regards,

Feng-Huei Lin

## 6. PERMINTAAN UNTUK KOREKSI DENGAN GALLEY PROOFS

On Sun, Jun 9, 2019 at 2:51 PM, International Journal of Biomaterials  
<reta.atalla@hindawi.com> wrote:

Dear Dr. Putra,

I am pleased to let you know that the first set of galley proofs of your Research Article 7179243 titled "Synthesis and Characterization of Nano Hydroxyapatite-Gelatin Composite with Streptomycin as Anti-Tuberculosis Injectable Bone Substitute," is ready. You can apply your corrections directly to the manuscript with the Online Proofing System (OPS).

Using the OPS, you can quickly and easily make corrections directly to your galley proofs and submit these corrections with a single click.

<https://ops.hindawi.com/author/7179243/>

If a new corresponding author is added, they must log into their manuscript tracking system account and add their ORCID ID. Any additional ORCID IDs added on during proofing will also need to be updated on that author's account. Delays can occur if this isn't done.

To expedite the publication of your manuscript, please send us your corrected galley proofs within three days.

Best regards,

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