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OPEN PEER REVIEW

Development and Ex-Vivo Skin Permeation of Sildenafil Citrate Microemulsion System for Transdermal Delivery

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

2 comments · 20 Sep 2023 – 23 Sep 2023

Referee 1 Reviewer

MAJOR REVISION 20 Sep 2023

Dear Editor,
The manuscript is an attempt to develop sildenafil microemulsions for transdermal application. This reviewer is aware of the effort made by the authors to collect all the information presented here. However, in my opinion, the manuscript should be revised further before being published.
Comments:
1. The novelty of the present manuscript is not clear. It is suggested that a paragraph regarding the novelty be provided at the end of the introduction. The following articles have studied the preparation of sildenafil microemulsions for transdermal, sublingual, and intranasal drug delivery. The present study should state what is novel compared with the previous studies:

- Ali Alazzo, Mohanad Alfahad, Mahmood H. M. Jasim, Radhwan Nidal Al-Zidan. MICROEMULSION: A POTENTIAL APPROACHFOR TRANSDERMAL DELIVERY OF SILDENAFIL CITRATE. Mil. Med. Sci. Lett. 2023; 92:1-9. doi: 10.31482/mmsl.2023.031
- Atipairin A, Chunhachaichana C, Nakpheng T, Changsan N, Srichana T, Sawatdee S. Development of a Sildenafil Citrate Microemulsion-Loaded Hydrogel as a Potential System for Drug Delivery to the Penis and Its Cellular Metabolic Mechanism. Pharmaceutics. 2020 Nov 4;12(11):1055. doi: 10.3390/pharmaceutics12111055.
- Sheu MT, Hsieh CM, Chen RN, Chou PY, Ho HO. Rapid-Onset Sildenafil Sublingual Drug Delivery Systems: In Vitro Evaluation and In Vivo Pharmacokinetic Studies in Rabbits. J Pharm Sci. 2016 Sep;105(9):2774-2781. doi: 10.1016/j.xphs.2016.01.015.
- Lu HT, Chen RN, Sheu MT, Chang CC, Chou PY, Ho HO. Rapid-onset sildenafil nasal spray carried by microemulsion systems: in vitro evaluation and in vivo pharmacokinetic studies in rabbits. Xenobiotica. 2011 Jul;41(7):567-77. doi: 10.3109/00498254.2011.563877.
- Elshafeey AH, Bendas ER, Mohamed OH. Intranasal microemulsion of sildenafil citrate: in vitro evaluation and in vivo pharmacokinetic study in rabbits. AAPS PharmSciTech. 2009;10(2):361-7. doi: 10.1208/s12249-009-9213-6.

2. The present version of the manuscript is too hard to read. Indeed, it needs some figures, for example, to be more accessible to readers. In my opinion, the authors should improve the quality of the present manuscript. The full factorial design was carried out to investigate the effect of formulation parameters on various physicochemical characteristics. Pareto charts, contour plots, or three-dimensional response surface plots could be added. Moreover, drug release experiments and permeation studies were performed, and the results were presented as release profiles over 2 and 24 h in Table4 and permeation parameters in Table 5, respectively. Adding in vitro drug release profiles of the formulations could help readers understand the release behavior of the drug from the formulation over time. Also, including the permeation profiles, in terms of the cumulative amount of drug that permeated through the skin, would provide valuable data for the characterization of the transdermal microemulsions.

3. A full factorial design was employed in this study; however, no information is provided regarding the ANOVA results, interactions between the parameters, or equations describing the relationship between the factors and the response variables. The addition of these results would provide a comprehensive understanding of the factors that have the most significant impact on the response variable.

4. The drug content and pH should be measured in the stability test.

5. Sildenafil content in the microemulsions should be determined.

6. To measure the sildenafil concentration in the solubility, release, and permeation studies, UV-visible spectroscopy was utilized. A fully validated method and calibration curve should be used for accurate and precise quantification of sildenafil.

7. To investigate the solubility of sildenafil in various media, UV-visible spectroscopy was mentioned in section 3.4. The absorbance of the oil, surfactant, and co-surfactant should be measured to ensure that there is no interference with the measurement of sildenafil absorbance.

8. It is stated that some experimental tests were performed, including differential scanning calorimetry (in the abstract), physical stability testing at various temperatures (4, 25, and 37 °C), and stability testing under centrifugation stress (in the methods). Physicochemical properties such as clarity, phase separation, and particle size were evaluated during the stability analysis. However, no data are provided in the results section, and only particle size 6 months after preparation was reported (without mentioning the temperature).

9. Drug release experiments were performed using phosphate buffer and methanol in a ratio of 1:4; however, the ex vivo permeability studies were performed using a ratio of 1:2. Moreover, the in vitro drug release and ex vivo permeability studies were conducted over 24 and 48 h, respectively. Convincing reasons should be added for altering the ratio of the release medium and extending the ex vivo study duration.

10. Convincing data should be provided for choosing ME-S-7 as an optimum formulation.

11. The effect of each formulation parameter on the various physicochemical properties of microemulsions should be discussed in relation to previous studies.

12. The term “factorial state” in Table 1 should be described, and the meaning of the signs (+-) used in this table should be defined.

13. Statistical analysis should be added to the materials and methods section.

14. In section 4.1, the results of the solubility study should be stated. Also, it should be mentioned which components were chosen for further analysis.

15. The solubility of sildenafil in the mixture of Span 20 and Tween 80 was not studied, and no convincing data are provided for choosing this mixture as a surfactant in the preparation of microemulsions.

16. Equations in section 3.12. data analysis should be written in the same format. Calculation of Dapp and determination of Tlag should be added to this section.

17. It has been stated that ME-S-7 is the most effective formulation; however, in the abstract, the release of ME-S-1 is mentioned.

18. It has been written in the abstract that ME-S-1 exhibited 62.6% drug release over 24 h; this should be corrected to 26.6% based on the results provided in Table 4.

19. All abbreviations should be defined at first mention and used consistently throughout the text.

20. The whole manuscript needs a grammar check. The spacing between words should be checked. Some letters should be capitalized and some should be lowercase.

Regards

Associate Editor MAJOR REVISION 23 Sep 2023

I strongly recommend that the authors address all comments fully; otherwise, I regret to inform them that I will decide not to accept the manuscript.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thank you for comments of Reviewer . we response to these comments and highlight by yellow red in manuscript.

1. The novelty of this research and its major difference with the previous investigations is the part related to the calculations of permeability parameters and their relationship with the ratio of formulation components, which the article has examined in detail. The relevant paragraph was added to the end of the introduction.
2. Due to the limitation of the number of figures based on the format of this journal, many requested graphic data are not included in the text of the article. If the referee deems it appropriate, it will be sent directly to the respected reviewer.
3. The requested item was added to the text of the article.
4. The requested item was added to the text of the article.
5. The formulation content and pH after stability experiment were added to table 3.
6. The primary drug content and the calculated data were added to table 1 and table 3, respectively.
7. The validation tests of the spectrophotometric method in this research have been done completely and on consecutive days, and the results related to the accuracy and precision of the method are also available, but due to the limitation of the number of words related to the journal format, they are not included in the text of the article. It can be added to the text at the discretion of the respected referee and the editor's approval.
8. The requested item was added to the results.
9. This was a typographical error and was corrected.
10. The formulation 7 was chosen based on the higher values of J_{ss} and the relative high amount of ER_{flux}. The reason for the selection was added to the text.
11. The requested item was added.
12. The relevant section was modified.
13. The relevant section was modified.
14. The relevant section was modified.
15. The relevant section was studied and is added to the text.
16. T_{lag} and D_{app} formula were added.
17. The requested item was corrected.
18. The requested item was corrected.
19. The requested item was corrected.
20. The grammar of manuscript checked .

2 Revision 1

2 comments · 14 Jan 2024 – 16 Jan 2024

Referee 1 Reviewer

MINOR REVISION 14 Jan 2024

Dear Editor,

This reviewer appreciates the additional data that the authors have included in the manuscript and tables. I would like to request that the authors address the following issues in the next revision to ensure that the article meets the journal's standards for formatting, grammar, and clarity.

Comments:

1. I noticed that the formatting of the tables is not consistent throughout the article. The authors should make sure that all tables follow the same style and layout to maintain consistency and clarity for the readers.
2. Regarding grammar, while some improvements have been made, there are still several errors that need to be addressed. I would suggest that the authors carefully review the manuscript for grammatical errors and consult a native English speaker or a professional editing service to ensure that the language is clear and concise.
3. Additionally, there are several instances where there is insufficient space between words and punctuation marks, making it difficult to read and understand. The authors should ensure that there is sufficient space around punctuation marks and between words to improve readability.
4. There are some typographical errors that need to be corrected, such as Higushi.
5. All abbreviations should be defined at first mention and used consistently through the text. The authors should check that all abbreviations used in the abstract are also defined in the text where they first appear. This will help to maintain consistency and clarity throughout the article.

Regards

Associate Editor

MINOR REVISION 16 Jan 2024

The authors should address all comments thoroughly.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

Thank you for comments of Reviewer . we response to these comments and highlight by yellow red in manuscript.

1. I noticed that the formatting of the tables is not consistent throughout the article. Authors should make sure that all tables follow the same style and layout to maintain consistency and clarity for the readers.
   Tables formatting are corrected in MP .
2. Regarding grammar, while some improvements have been made, there are still several errors that need to be addressed. I would suggest that authors carefully review the manuscript for grammatical errors and consult a native English speaker or a professional editing service to ensure that the language is clear and concise.
   Grammar errors corrected in MP and manuscript language review again and highlight with yellow color in MP.
3. Additionally, there are several instances where there is insufficient space between words and punctuations, making it difficult to read and understand. Authors should ensure that there is sufficient space around punctuation marks and between words to improve readability.
   These errors are corrected in MP and highlight with yellow color in MP.

4. There are some typo errors that need to be corrected, such as Higushi.
   This errors is corrected in throughout MP.
5. All abbreviations should be defined at first mention and used consistently through the text. Authors should check that all abbreviations used in the abstract are also defined in the text where they first appear. This will help to maintain consistency and clarity throughout the article.
   All abbreviations check and used in abstract.

   Best regards

3 Revision 2

1 comment · 29 Feb 2024

Referee 2 Reviewer

ACCEPT 29 Feb 2024

Dear Editor,
I appreciate the effort the authors put into revising the article. The manuscript is accepted.