Iranian Journal of Pharmaceutical Research
Volume 22 · Issue 1 · e134731

OPEN PEER REVIEW

A Mechanistic Study on the Fluidization and Enhancement Effects of Cineole Toward Stratum Corneum Intercellular Lamellar Lipids: A Liquid Crystalline Model Approach

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SUBMITTED	REVISED	ACCEPTED	DOI
7 Jan 2023	29 Jan 2023	1 Feb 2023	10.5812/ijpr-134731

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 · 13 Jan 2023 – 13 Jan 2023

Referee 1 Reviewer

MINOR REVISION 13 Jan 2023

The study described the concentration-dependent enhancement effect of cineole and discussed the observation using a mechanistic approach.
Major points:
There are some other studies on the mechanism of cineole enhancement that should be mentioned in the discussion and introduction sections.
The reason for choosing diazepam as a model should be explained. If another cargo has also been investigated, it is strongly recommended that it be added to the manuscript.
Minor points:
The numbering of the second section should be corrected to 2.1, 2.2, 2.3, …

Associate Editor

MINOR REVISION 13 Jan 2023

The authors are advised to address the comments.

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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.

Author Responses to the Reviewers Comments

Dear Professor Shahhosseini,

Thank you very much for your kind considerations and the reviewers' comments regarding our manuscript entitled**:** *"A Mechanistic study on the Fluidization and Enhancement Effects of Cineole toward Stratum Corneum Intercellular Lamellar Lipids: A Liquid Crystalline Model Approach"*, (Manuscript ID: 134731). The responses to the reviewers' comments are provided here and the required modifications are also made to the revised manuscript. The changes, except for grammar and typographical corrections, are highlighted yellow in the revised manuscript.

I hope the revised manuscript finds its way to final acceptance. Thank you very much again for your kind considerations.

Yours sincerely,

The Corresponding Author

A. Responses to the comments from Reviewer #1

Comment 1 of Reviewer #1. *The study describes the concentration-dependent effect of cineole and discussed the observation by mechanistic approach. There are some other studies on mechanism of cineole enhancement that should be mentioned in the discussion and introduction sections.*

Reply to Comment 1 of Reviewer #1. The manuscript was revised to include other investigations. Please see the highlighted text in the revised manuscript.

Comment 2 of Reviewer #1. *The reason for choosing diazepam as a model should be explained. If another cargo has also been investigated it is strongly recommended to add it to the manuscript.*

Reply to Comment 2 of Reviewer #1. Diazepam was chosen as a model due to its proper lipophilicity (logP = 3) and low molecular weight (284.74), that makes it a good candidate for skin permeation studies. Diazepam has also a good stability throughout the experiments and in our preliminary studies, did not show destructive effect on the model matrix. We also have a good data bank on this molecule in our laboratories.

Comment 3 of Reviewer #1. *The numbering of the second section should be corrected as 2.1, 2.2, 2.3, …*

Reply to Comment 3 of Reviewer #1. Numbering was corrected in the revised manuscript.

B. Responses to the comments from Reviewer #2

Comment 1 to Comment 4 of Reviewer #2. These comments all were suggestions regarding typo mistakes and all were corrected in the revised manuscript (highlighted) as suggested by the reviewer-thank you.

Comment 5 of Reviewer #2. *The types and amounts of fatty acids and antioxidant should be stated.*

Reply to Comment 5 of Reviewer #2. Types of fatty acids are mentioned in the Material and Method Section of the manuscript. The amount of fatty acids as a whole is 55% of the model matrix and those of cholesterol, water and antioxidant are 20, 25 and 0.02% of the model matrix. These data are included in the revised manuscript.

Comment 6 of Reviewer #2. *What was the concentration and volume of alkaline aqueous solusion?*

Reply to Comment 6 of Reviewer #2. The concentration and volume of the sodium hydroxide solution depends on the total weight of model matrix prepared at the time. Its volume is equal to the amount of water needed to a final water content of 25% and its concentration was the amounts of sodium hydroxide needed to neutralize about 40% of the fatty acids. These data are included in the revised manuscript.

Comment 7 and Comment 8 of Reviewer #2. These comments all were suggestions regarding typo mistakes and all were corrected in the revised manuscript (highlighted) as suggested by the reviewer-thank you.

Comments 9 and 10 of Reviewer #2 (Both comments are the same). *How long was the sampling performed?*

Reply to Comments 9 and 10 of Reviewer #2. Sampling was continued up to 32h with specific time intervals, included in the revised manuscript.

Comment 11 of Reviewer #2. *Why this amount of water was expected?*

Reply to Comment 11 of Reviewer #2. According to our previous works (stated in the manuscript) and to obtain a proper model lamellar structure, the water content of the system should be around 25%.

Comment 12 of Reviewer #2. *This thermogram belongs to matrix alone or with cineole?*

Reply to Comment 12 of Reviewer #2. It belongs to the matrix alone. Corrected in the revised manuscript.

Comment 13 of Reviewer #2. *There is no observable endothermic transition at -10°C.*

Reply to Comment 13 of Reviewer #2. This endothermic peak is small and is seen as a left shoulder of the next endothermic transition. It has been discussed and written more clearly in the revised manuscript with reference to our previous works. Please see the highlighted text in the revised manuscript.

Comment 14 of Reviewer #2. *If possible, the related thermograms be added.*

Reply to Comment 14 of Reviewer #2. The thermograms showing the effects of cineole on the main transition temperature in the cineole-treated matrices are added to the Figure 4 in the revised manuscript.

Comment 15 of Reviewer #2. *Page 12 comment 15: A reference is required.*

Reply to Comment 15 of Reviewer #2. Reference was added in the revised manuscript.

Comment 16 of Reviewer #2. *Specify spherulites in Figure 3, C, D, and E.*

Reply to Comment 16 of Reviewer #2. A typical spherulite was specified in Figure 3 of the revised manuscript. Others are also the same in structure.

Comment 17 to Comment 19 of Reviewer #2. These comments all were suggestions regarding typo mistakes and all were corrected in the revised manuscript (highlighted) as suggested by the reviewer-thank you.

Comment 20 of Reviewer #2. *Page 14 comment 20: Please refer Table 1*

Reply to Comment 20 of Reviewer #2. Corrected in the revised manuscript.

Comment 21 of Reviewer #2. *Which data in this research results in this part of conclusion?*

Reply to Comment 21 of Reviewer #2. Our data show that diffusion coefficient (in release studies) and fluidity reach a maximum, while our permeation data show that it does not. Therefore, the present skin data show that presence of high concentrations of cineole at the surface of skin does not necessarily provide enough cineole in the skin for full fluidization of the intercellular lipids. To make it clearer, the conclusion was revised accordingly and other possible mechanisms were also included. Please see the revised manuscript (highlighted).

Comment 22 of Reviewer #2. *Please clarify all the equations in the text which Table 2 was constructed based on.*

Reply to Comment 22 of Reviewer #2. The related equations are discussed in the revised manuscript, as explanation in the text (highlighted).

Finally, I would like to thank both reviewers for their comments and I hope that the replies are satisfactory and this manuscript finds its way to final acceptance and publication in Iranian Journal of Pharmaceutical Research. Thank you very much for your kind considerations.

Yours sincerely,
The Corresponding Author.

2 Revision 1

1 comment · 31 Jan 2023

Associate Editor

ACCEPT 31 Jan 2023

Comments are addressed