

Journal of the American Oil Chemists' Society - Manuscript ID JAOCS-19-0107

Pam Landman <onbehalf@manuscriptcentral.com>
to me, sraharjo, chusunu, ronnymartien
23-Mar-2019

Sat, Mar 23, 2019, 2:50 PM

Dear Mrs. Rohmah

Your manuscript entitled "Application of Response Surface Methodology for the Optimization of β -Carotene-loaded Nanostructured Lipid Carrier from Mixtures of Palm Stearin and Palm Olein" has been successfully submitted online and is presently being given full consideration for publication in the Journal of the American Oil Chemists' Society.

Your manuscript ID is JAOCS-19-0107.

Please mention the above manuscript ID in all future correspondence or when calling the office with questions. If there are any changes in your affiliation, please log in to ScholarOne Manuscripts at <https://mc.manuscriptcentral.com/jaocs> and edit your user information as appropriate.

You can also view the status of your manuscript at any time by checking your Author Center after logging in to <https://mc.manuscriptcentral.com/jaocs>.

Thank you for submitting your manuscript to the Journal of the American Oil Chemists' Society.

Sincerely,
JAOCS Editorial Office

miftakur rohmah
Thank you so much

Sat, Mar 23, 2019, 2:52 PM

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Journal of the American Oil Chemists' Society - Decision on Manuscript ID JAOCS-19-0107

Suzana Ferreira-Dias <onbehalf@manuscriptcentral.com>
to me
05-Jul-2019

Sat, Jul 6, 2019, 3:25 AM

Dear Mrs. Rohmah

Manuscript ID JAOCS-19-0107 entitled "Application of Response Surface Methodology for the Optimization of β -Carotene-loaded Nanostructured Lipid Carrier from Mixtures of Palm Stearin and Palm Olein" that you submitted to the Journal of the American Oil Chemists' Society, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s) comments and submit a revision.

To revise your manuscript, click here *** PLEASE NOTE: This is a two-step process. After clicking on the link, you will be directed to a webpage to confirm. ***

https://mc.manuscriptcentral.com/jaocs?URI_MASK=b7aaf5d2e47478fa7635968a10b78033 or log into <https://mc.manuscriptcentral.com/jaocs> and enter your Author Center, where you will find your manuscript title listed under "Manuscripts with Decisions." Under "Actions," click on "Create a Revision." Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center. Please note that effective January 2018, the in-text citations and reference list style have been updated to (Author name, year) in text and alphabetical order in the reference list. If you have not already done so, please format these items as noted at https://peicrjcs.peicrjcs.com/page/journal/15589331/homepage/forauthors.html#_4_PREPARING_YOUR.

When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the comments by including a point-by-point response to the reviewer's comments. You may also provide these responses in a word processing document which you can upload with your manuscript files. Failure to provide a pointwise response will result in the delay of the review of your revision.

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the comments by including a point-by-point response to the reviewer's comments. You may also provide these responses in a word processing document which you can upload with your manuscript files. Failure to provide a pointwise response will result in the delay of the review of your revision.

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of the American Oil Chemists' Society, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision within 90 days, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of the American Oil Chemists' Society. I look forward to receiving your revision.

Sincerely,
Dr. Suzana Ferreira-Dias
Associate Editor, Journal of the American Oil Chemists' Society
suzanafdias@mail.telepac.pt

If you feel that your paper could benefit from English language polishing, you may wish to consider having your paper professionally edited for English language by a service such as Wiley's at <http://wileyeditingservices.com>. Please note that while this service will greatly improve the readability of your paper, it does not guarantee acceptance of your paper by the journal.

Reviewer(s) Comments to Author

Reviewer: 1

Comments to the Author

The manuscript entitled "Application of Response Surface Methodology for the Optimization of β -Carotene-loaded Nanostructured Lipid Carrier from Mixtures of Palm Stearin and Palm Olein" reports the use of response surface methodology, Box-Behnken design to optimize the formulation of β -Carotene-NLC by varying palm stearin fraction ratio, lipid surfactant ratio and lipid + surfactant water ratio. Several analysis were performed for β -Carotene-NLC characterization, namely particle size, polydispersity index, FTIR, X-ray diffraction and transmission electron microscopy

The work led to interesting results. Nevertheless, the authors should revise some issues before the manuscript could be accepted.

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Reviewer: 1

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The work led to interesting results. Nevertheless, the authors should revise some issues before the manuscript could be accepted.

I do recommend a meticulous revision of the manuscript. There are a few misprints all over the document as well as some sentences that should be rewritten for clarity. Some examples are listed below:

- P.1, L.55 and L.57 – write "[β -NLC]" instead of "[NLC]"
- P.2, L.9 – add a space between "the combination"
- P.2, L.11 – write "responses concerning ..."
- P.2, L.14 – add a space between "polydispersity index"
- P.2, L.25 – write "and" before "an encapsulation"
- P.4, L.27 – remove "of" before "published"
- P.4, L.39 – add a comma after "So far" and remove "published". After "palm oil" write "has been published"
- P.5, L.57 – remove the parenthesis before "was" and add it after "Merck"
- P.6, L.15 – write "in the blend of PS and PO" instead of "in PS and PO the mixture"
- P.6, L.17 – remove "mollen"
- P.7, L.17 – "wavelength" is a single word
- P.9, L.50 – add "limited" before "number"
- P.10, L.7 – Replace "Figure 2" by "Figure 1"
- P.10, L.10 – There is no Table 4 in the manuscript
- P.13 – "wavenumber" is a single word. Correct it along the manuscript.
- P.13, L.33 – write "wavenumber range" instead of "wavenumber area"

"Abstract"

In the manuscript there is no reference to the composition of the optimized formulation. Please, add this information to the text, namely, to the abstract.

- P.2, L.11 – write "X3" after (lipid + surfactant) water ratio
- P.2, L.9 and L.11 – X1, X2 and X3 are expressed as (% w/w). Provide this information.

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P2, L 9 and L 11 – X1, X2 and X3 are expressed as (% w/w). Provide this information.

"Materials and Methods"

- Since β -carotene is a labile compound, easily degraded by heat, light and oxygen, it would be interesting to carry out stability assays for β -carotene along time (e.g., for 15 days).

- There is no reference to the number of replicate measurements performed for each analysis. Add this information.

P6, L 12 – The concentration of β carotene was 0.025%. Was it expressed as %(w/w), %(w/v) or %(v/v)?

P6, L 22- rewrite the sentence as "24000 rpm for 30 min using a high speed homogenizer (IKA..."

P6, L 59 – instead of "aquabidest" write "double distilled water"

P7, L 8-17 – The encapsulation efficiency was evaluated by analysing the unloaded β -carotene in a UVVIS spectrophotometer at 454 nm. I suppose a calibration curve was used for β -carotene quantification. Add this information to the manuscript.

P7 – Provide the equation for encapsulation efficiency calculation.

P7, L 10 – replace "ml" by "mL". Correct it along the text.

P8 and P9 – number the equations.

P8, L 53 – write "per diffusion area" instead of "per area diffusion"

P9, L 22 – write 1 (for time) in lower case

P9, L 24 – rename the subtopic "Data analysis" as "Statistical Analysis"

"Results and discussion"

- Provide the values of R2 adjusted for the models described by equations 1 to 3.

- According to the Box-Behnken design (Table 2), three replicates of the center points were carried out (runs 13 to 15), which led to experimental responses with high variability, namely for Y1 (values ranging from 99 to 503 nm) and Y4 (values between 61 and 87%). Therefore, more replicates of the center points would be recommended. Please, comment this issue.

"Tables and Figures"

Table 2 – Remove "experimental" after "Box-Behnken". Replace comma by point in the values of standard deviation. In Table legend, identify the dependent and the independent variables and add the information that results are presented as mean \pm standard deviation. Provide the number of replicate measurements performed (n value).

Table 3 – What was the composition of the optimized formulation regarding PS fraction ratio, LS ratio and LS/water ratio? Add this information to table legend.

Figure 1 – Identify the plots as A, B, C, and D for Particle size, Polydispersity index, Zeta potential and EE (%), respectively.

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"References"

Revise the list of references. There are several published works cited in the text that are missing in the references list, namely:

P2, L 45 – Bach & Rohmer, 2016 ; P5, L 16 – Yolmen & Jafari, 2017, P5, L 25 – Pimentel-Moral et al., 2019, P8, L 21 – Thatipamula et al., 2011; P8, L 21 – Griesser et al., 2018, P9, L 51 – Zhang et al., 2010

P10, L 51 - Singh et al., 2017, P10, L 56 - Zhang et al., 2011; P15, L 36 – Han et al., 2008

Reviewer: 2

Comments to the Author

The paper presents the stabilization study of β -carotene using lipid nanostructures as carriers. It is an interesting approach to protect unstable bioactives. In my opinion, the text should be improved in order to be ready for publication.

1. Firstly, a general review to correct spelling and English errors is needed
2. It would be more efficient for the reader to use the decoded variables in the text and Table 2 (instead of Y2 use EE, e.g.). This is obvious in the abstract, were the name of independent and response variables is enough.
3. page 6, line 6. Which was the ratio mass of β -carotene/mass of lipids used?
4. page 7. How was EE calculated? Is this the mass of β -carotene per mass of particles? Or it is the percentage of the mass of β -carotene added that was effectively entrapped in the particles?
5. page 13, lines 9-11. The explanation for the absence of the endothermic peak in β C-NLC is not clear.
6. page 15. Study of in vitro diffusion

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5. page 13, lines 9-11. The explanation for the absence of the endothermic peak in bC-NLC is not clear.
6. page 15. Study of in vitro diffusion
- 6.1. This study was performed with various types of samples containing b-carotene. Here, it is not clear how were prepared the b-carotene in emulsion samples (bC-E).
- 6.2. Results are presented in terms of "diffused of b-carotene" over time (figure 6A) and flux of b-carotene (figure 6B). Here the units are not correct in figure 6B or in figure 6A. It must be clarified in which figure is presented the flux and in which figure is the mass of b-carotene released over time.
- 6.3. The methodology for diffusion experiments described in page 8, indicates that "the donor compartment was filled with 2ml sample+ 10ml buffer...". The question is, what was the overall mass of b-carotene on those 2 ml of sample? Was it the same for bC-NLC, bC-E, bC-T and bC-PBS samples? It should be the same, otherwise the driving force for diffusion is different, and the flux results cannot be compared. The authors should take that into account.

Associate Editor Comments to Author

Associate Editor
Comments to the Author:
Dear Prof. Sri Raharjo,

First, I wanted to apologize for the great delay in the revision of this manuscript. The manuscript is under the scope of the Journal of the American Oil Chemists' Society but, according to reviewers' opinion

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Associate Editor Comments to Author

Associate Editor
Comments to the Author:
Dear Prof. Sri Raharjo,

First, I wanted to apologize for the great delay in the revision of this manuscript. The manuscript is under the scope of the Journal of the American Oil Chemists' Society but, according to reviewers' opinion and mine, it is not suitable for publication in this form and a major revision is suggested.

In addition to the comments of the reviewers, I also have the following comments:

General comments

- 1) The rationale of your work and the potential technological/pharmaceutical applications of the beta-carotene-loaded nanostructured lipid carrier should be better explained.
- 2) The objectives of the in vitro diffusion study should be also presented.
- 3) Neither in the abstract nor in the text, the conditions to obtain the "optimum formulation" are presented. You say (Page 12, l. 24) "The confirmation results for the optimum conditions are presented in Table 3". However, in Table 3, you just have "Table 3. Comparison of the observed and predicted values in the NLC prepared under predicted optimum conditions". I could not find the optimum conditions. Please add this information to the manuscript.
- 4) How did you find the best conditions to get the optimal formulation?
- 5) The model equations fitted to the experimental data-points should only consider the significant terms (linear, quadratic and/or linear interactions) of the factors and NOT all the factors. You must present in the manuscript the significance level of the effects, select only those that are significant and after fit a new polynomial model considering only those that are significant. Instead of presenting the model equations along the manuscript, I suggest you could put all in a Table (together with p value, R², adjusted R²). It will be easier for the reader to find the equations in the table than in the text. In addition, the meaning of the factors A, B, and C should be presented in the heading of the table.
- 6) The factors in the response surfaces in Fig 1 are in coded values? You must indicate it in the legend.

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6) The factors in the response surfaces in Fig 1 are in coded values? You must indicate it in the legend.

7) Along the manuscript, you never refer to the shape of the response surfaces and only make comments about the increase in a factor and the corresponding effect on the response. You should comment about the shape of each response surface: some of them seem to be convex with a maximum in the experimental domain, others seem to be saddle-like surfaces.

8) The results should be presented in SI units

Specific comments:

Page 3, L. 6-7, you say "Absorption of β -carotene has been found to be inefficient and highly varied due to its low solubility (C Log P = 17.62)..."

Low solubility in what solvent? I suppose it is in water because of the definition of the calculated Log P (C Log P), where P is the partition coefficient in the system octanol/water. If you want to refer the Log P of beta-carotene, you must define it.

Page 5, L. 21. Since candesartan cilexetil and ifosfamide are drugs to reduce blood pressure and an anti-cancer chemotherapy drug, respectively, and JAACS is not a Pharmaceutical Journal, you should rewrite the sentence because most of the readers do not know what these compounds are for.

Along the manuscript, please replace "triglyceride(s)" by "triacylglycerol(s)".

Page 5, Section "Experimental design". Table 1 should be presented here and not in the Results section.

Page 6, L. 58. Please replace "aquabidest" by "double distilled water".

Page 8: Study in vitro diffusion: in the method followed, you used buffers with different pH values (6.8 and 7.4) while in the corresponding section in Results, you mention pH 7. Please clarify/correct this. Also, the composition, molarity or ionic strength of the buffers used should be indicated.

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Equation 1: something is wrong because the expression you use as the "amount of substance concentration in the first sampling" is in microg/mL, while the expression C_nV is in microgram. Also, how can you use an expression represented by an addition of multiple values (from i = 1 to n-1) as the "amount of substance concentration in the first sampling"?

Page 9, line 11. You did not use a multiple linear regression but a non-linear regression because (i) you have a three-level design, which allows fitting curved models, and (ii) all the equations presented to describe the response surfaces are second-order polynomials. Please correct it.

Page 11, lines 26-27: the following sentence is not correct "There was no statistically significant difference between each variable and PDI value." Do you mean that there is no significant effect of each factor on the PDI value? Please correct it!

Table 2: the meaning of each factor X₁, X₂ and X₃, and of the responses Y₁, Y₂, Y₃ and Y₄, must be added to the heading of this table.

Table 4 is missing but is referred in page 10, line 9.

Fig. 6-A: Why did you use a log scale? Please correct the yy' axis title to "Cumulative amount of diffused beta-carotene (microg/cm²)".

I hope these comments will help you to improve your manuscript.

Best regards,
Suzana Ferreira-Dias

Signature: miftakhur rohmah -miftakhurrohmah8@gmail.com-
to: suzanafdias

Date: Jul 6, 2019, 5:44 AM

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