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OPEN PEER REVIEW

Development of a Natural Preservative System in Fluticasone Propionate Nasal Spray Formulation Using *Eucalyptus globulus* Essential Oil

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About this report

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1 Original submission

0 comments

No public comments in this round.

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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 Reviewer 1

We do appreciate for time and kind efforts that the respected reviewer put on our manuscript entitled « Development of a natural preservative system in Fluticasone propionate nasal spray formulation Using *Eucalyptus globulus* essential oil ». All the valuable comments were carefully considered and responded to. Our modifications in the revised version of the manuscript were highlighted in yellow.

Response to respected Reviewer 1:

1. The manuscript has several grammatical errors and necessarily needs a careful grammatical and structural revision. There are also drawbacks to the structure of reference writing, including that they do not have the identical format.

Response: The article was carefully reviewed and grammatically corrected in terms of grammar, and also edited using common English editing software (grammarly). Some corrections have been shown in yellow color. All the references such as articles and books were identically organized according to the journal guideline using Mendeley - Reference Management Software.

2. From the title of the article, it seems that the microbial stability of the final spray packaging has been investigated, but in the methods, the initial solution used to prepare the spray has been evaluated. It is recommended that the title and method of work be matched.

Response: The title and method of work were matched by adding word 'formulation' to the title of the manuscript. It was highlighted in yellow. However, all the Stability studies of nasal spray were done based on the United States pharmacopeia (Ref No. 15).

3. The antimicrobial effects of eucalyptus essential oil have been proven in many studies, but its use as a preservative can be a new idea. Provided, of course, that there are compelling scientific reasons for using it instead of benzalkonium chloride.

Response: Based on finding of the current research, significant antimicrobial effectiveness was observed for the combinational preservative system (50% Eucalyptus EO+ 50% benzalkonium chloride) which was followed by a decrease in the usable level of the synthetic preservative (benzalkonium chloride). Therefore, combinational preservative system can be considered as an alternative preservative for pharmaceutical formulations after further studies.

4. Based on the diagrams presented in this article and based on the results of this research, eucalyptus essential oil has no significant superiority over benzalkonium chloride, except for some few cases, and it is suggested that relevant tables be added to the article so that statistical comparisons of data can be evaluated.

Response: The diagrams presented in this article have been drawn based on table1 (a-d) information and statistical analysis. Please let us know if the respected reviewer prefers the substitution of diagrams with tables. The relevant tables are as follows:

Table 1 (a-e). Antimicrobial effectiveness of various preservation conditions on *S. aureus* (a), *E. coli* (b), *P. aeruginosa* (c) *C. albicans* (d), and *A. brasiliensis* (e) growth (log CFU/g) in Fluticasone nasal spray within 28 days.

(a)

No.	Treatment	Day 1	Day 7	Day 14	Day 21	Day 28
1	No preservative	79/5 ± 017/0 ^{d} $_{A}$	84/5 ± 008/0 ^{e} $_{B}$	86/5 ± 007/0 $^{d\ B}$	86/5 ± 007/0 ^{d} $_{B}$	86/5 ± 015/0 $^{c\ B}$
2	100%Benzalkanium	79/4 ± 007/0 ^{b} $_{E}$	54/3 ± 020/0 ^{d} $_{D}$	64/2 ± 011/0 ^{bc} $_{C}$	83/1 ± 018/0 $_{b\ B}$	50/1 ± 132/0 ^{a} $_{A}$
3	75%Benzalkanium + 25% EO	68/5 ± 004/0 ^{c} $_{E}$	58/3 ± 028/0 ^{d} $_{D}$	52/2 ± 066/0 ^{ab} $_{C}$	91/1 ± 022/0 ^{b} $_{B}$	50/1 ± 132/0 ^{a} $_{A}$
4	50% Benzalkanium + 50% EO	65/5 ± 018/0 ^{c} $_{E}$	75/2 ± 010/0 ^{b} $_{D}$	58/2 ± 032/0 ^{abc} $_{C}$	85/1 ± 043/0 ^{b} $_{B}$	63/1 ± 042/0 $^{a\ A}$
5	25% Benzalkanium + 75% EO	53/4 ± 044/0 ^{a} $_{E}$	67/2 ± 014/0 ^{a} $_{D}$	49/2 ± 009/0 $^{a\ C}$	61/1 ± 022/0 ^{a} $_{B}$	33/1 ± 042/0 ^{a} $_{A}$
6	100%EO	80/5 ± 010/0 ^{d} $_{E}$	85/2 ± 005/0 ^{c} $_{D}$	70/2 ± 006/0 $^{c\ C}$	15/2 ± 014/0 ^{c} $_{B}$	01/2 ± 001/0 $^{b\ A}$

(b)

No.	Treatment	Day 1	Day 7	Day 14	Day 21	Day 28
1	No preservative	88/5 ± 021/0 $^{d\ A}$	90/5 ± 003/0 ^{e} $_{A}$	91/5 ± 004/0 $^{d\ A}$	91/5 ± 017/0 $^{e\ A}$	90/5 ± 013/0 $^{f\ A}$
2	100%Benzalkanium	76/4 ± 024/0 $^{b\ E}$	52/3 ± 002/0 ^{c} $_{D}$	72/2 ± 047/0 $^{b\ C}$	89/1 ± 015/0 ^{b} $_{B}$	66/1 ± 001/0 ^{b} $_{A}$
3	75%Benzalkanium + 25% EO	58/5 ± 031/0 $^{c\ E}$	75/3 ± 003/0 ^{d} $_{D}$	58/3 ± 031/0 $^{c\ C}$	40/2 ± 020/0 $^{d\ B}$	22/2 ± 012/0 $^{e\ A}$
4	50% Benzalkanium + 50% EO	63/5 ± 061/0 $^{c\ D}$	75/3 ± 001/0 ^{d} $_{C}$	57/3 ± 010/0 $^{c\ B}$	89/1 ± 015/0 ^{b} $_{A}$	80/1 ± 014/0 $^{c\ A}$
5	25% Benzalkanium + 75% EO	54/4 ± 017/0 $^{a\ E}$	65/2 ± 002/0 ^{a} $_{D}$	40/2 ± 012/0 $^{a\ C}$	68/1 ± 025/0 $^{a\ B}$	44/1 ± 043/0 $^{a\ A}$
6	100%EO	81/5 ± 006/0 $^{d\ E}$	84/2 ± 007/0 ^{b} $_{D}$	74/2 ± 001/0 $^{b\ C}$	28/2 ± 011/0 $^{c\ B}$	10/2 ± 024/0 $^{d\ A}$

(c)

No.	Treatment	Day 1	Day 7	Day 14	Day 21	Day 28
1	No preservative	88/5 ± 006/0 $^{e\ A}$	91/5 ± 001/0 $^{e\ B}$	93/5 ± 005/0 $^{e\ B}$	93/5 ± 003/0 $^{e\ B}$	92/5 ± 001/0 $^{c\ B}$

2	100%Benzalkaniu m	83/4 ± 003/0 b E	66/3 ± 019/0 b D	84/2 ± 026/0 b C	91/1 ± 011/0 b B	64/1 ± 020/0 a A
3	75%Benzalkanium + 25% EO	72/5 ± 019/0 c E	87/4 ± 009/0 d D	82/4 ± 012/0 d C	86/3± 011/0 d B	84/2 ± 008/0 b A
4	50% Benzalkanium + 50% EO	70/5 ± 018/0 c D	76/4 ± 005/0 c C	73/4 ± 003/0 c C	77/3 ± 005/0 c B	75/2 ± 005/0 b A
5	25% Benzalkanium + 75% EO	56/4 ± 016/0 a E	66/2 ± 008/0 a D	41/2 ± 016/0 a C	82/1 ± 032/0 a B	67/1 ± 064/0 a A
6	100%EO	80/5 ± 001/0 d D	85/4 ± 017/0 d C	80/4 ± 001/0 d C	76/3 ± 003/0 c B	77/2 ± 020/0 b A

(d)

No.	Treatment	Day 1	Day 7	Day 14	Day 21	Day 28
1	No preservative	86/5 ± 030/0 c A	89/5 ± 001/0 e AB	91/5 ± 008/0 d AB	92/5 ± 001/0 c B	91/5 ± 008/0 d AB
2	100%Benzalkaniu m	60/4 ± 002/0 a E	42/3 ± 008/0 c D	71/2 ± 026/0 b C	79/1 ± 029/0 ab B	60/1 ± 001/0 b A
3	75%Benzalkanium + 25% EO	63/5 ± 005/0 b E	70/2 ± 005/0 a D	55/2 ± 005/0 b C	91/1 ± 011/0 b B	78/1 ± 014/0 c A
4	50% Benzalkanium + 50% EO	70/5 ± 016/0 b E	81/2 ± 001/0 b D	70/2 ± 014/0 b C	73/1 ± 016/0 a B	61/1 ± 022/0 b A
5	25% Benzalkanium + 75% EO	54/4 ± 032/0 a E	66/2 ± 017/0 a D	38/2 ± 094/0 a C	67/1 ± 064/0 a B	36/1 ± 001/0 a A
6	100%EO	81/5 ± 019/0 c D	71/3 ± 025/0 d C	64/3 ± 027/0 c C	87/1 ± 041/0 b B	73/1 ± 016/0 c A

Note: The lower cases indicate the statistical differences on different days (columns) and capital letters show the statistical differences between treatments (rows).

2 Revision 1

1 comment · 20 Jun 2022

Editor-in-Chief

MINOR REVISION 20 Jun 2022

Dear Authors,

Your revised manuscript needs a minor revision. We will decide on your manuscript as soon as we receive the article revised in accordance with the last comment.

Kind Regards,
JJNPP EIC

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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 associated Editor 1

We appreciate the time and kind efforts you put into our manuscript entitled « Development of a natural preservative system in Fluticasone propionate nasal spray formulation Using *Eucalyptus globulus* essential oil ». According to your valuable comment Table3 (a-e) was replaced with Figure 1 in the manuscript. Our modifications in the revised version of the manuscript (2) were highlighted in yellow.

Best Regards

Corresponding Author

3 Revision 2

0 comments

No public comments in this round.