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Cerasome Versus Liposome: A Comparative Pharmacokinetic Analysis Following Intravenous Administration into Rats

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About this report

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1 Original submission

3 comments · 17 Jul 2023 – 18 Jul 2023

Referee 1 Reviewer

ACCEPT 17 Jul 2023

Comments to the Author
The manuscript investigates the pharmacokinetic behavior of cerasome in comparison to liposome in a well-designed study, and it also presents the influence of PEGylation of the formulated delivery systems on increasing the blood circulation of these vesicles.
The design of the study is adequate. Nevertheless, the paper needs some minor modifications. For instance:
1. The title can be modified to indicate the need for PEGylation as well (it is not essential).
2. English proofreading is suggested (it is not necessary).
3. The information related to the design of "pharmacokinetic studies" (lines 180-182) could be reconsidered in light of the result section to better explain the formulations being compared. It is better to mention the difference between the two studied cerasome formulations.
4. How do the authors justify the different distribution phases (two different distribution phases) and elimination phases of the administered formulations? It would be great if they could clarify whether the justification is based solely on the log-transformed profiles or whether other approved studies are available.

Referee 2 Reviewer

MINOR REVISION 18 Jul 2023

The study described very interesting data regarding the comparative PK of cerasomes versus liposomes. It is almost ready for publication. There are a few comments as follows:
In Figures 1 and 2, major peaks should be marked on the spectra. It is better to show major ticks on all graphs.
Please make the figure legend in Figure 3 a bit larger.

Associate Editor

MINOR REVISION 18 Jul 2023

Please address the reviewers' 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.

Responses to the reviewers' comments

Manuscript: 138362

Title: Cerasome versus liposome: A comparative pharmacokinetic analysis following intravenous administration into rats

We would like to thank the respected referees for their time in reviewing the manuscript and their valuable comments and suggestions, all of which have been considered carefully during the revision. Point-by-point responses to reviewers are as follows:

Reviewer 1:

The study described very interesting data regarding the comparative PK of cerasomes versus liposomes. It is almost ready for publication. There are a few comments as follows:

In Figures 1 and 2, major peaks should be marked on spectra. It is better to show major ticks on all graphs. Please make figure legend in Figure 3 a bit larger.

Thanks for this helpful comment. Major peaks were marked on all spectra and major ticks were shown on all graphs. The legend in Figure 3 became a bit larger.

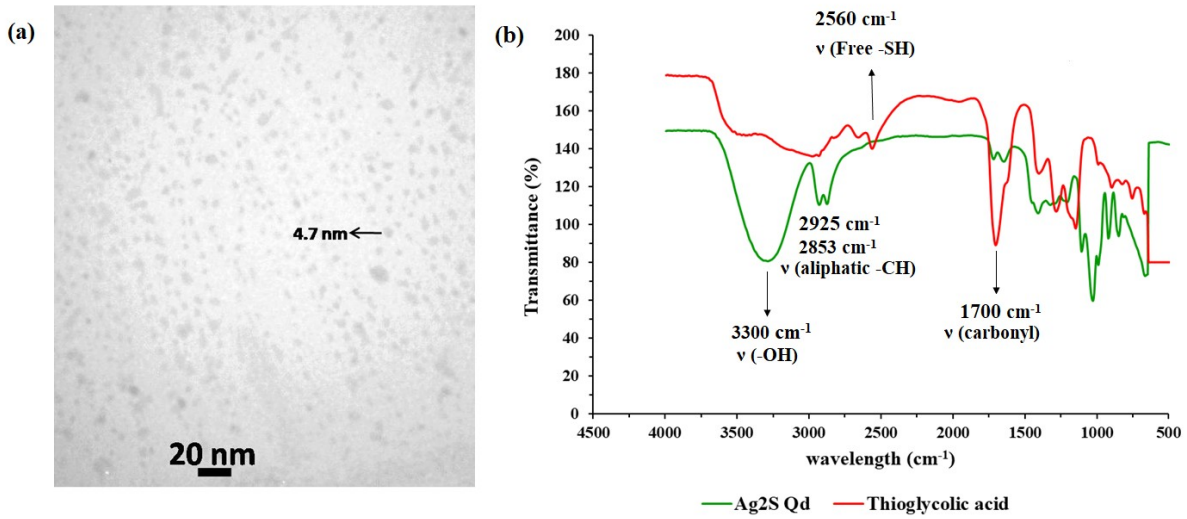


Figure 1. The TEM image (a) and FT-IR spectra (b) of the synthesized Ag_2S Qds

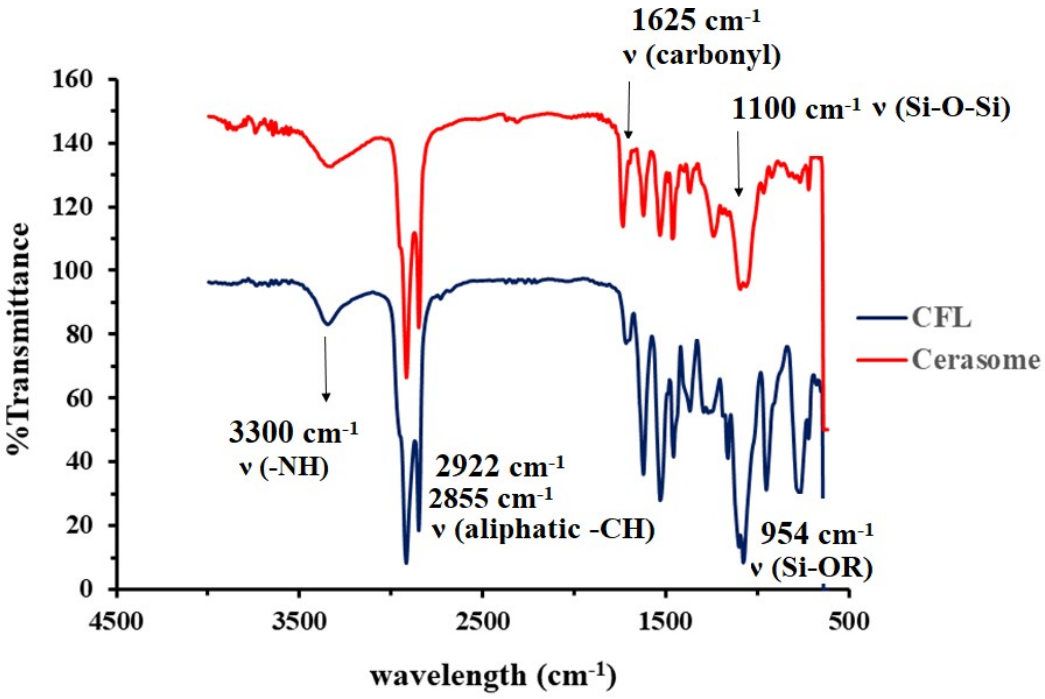


Figure 2. The FT-IR spectrum of cerasome forming lipid (CFL) and cerasome

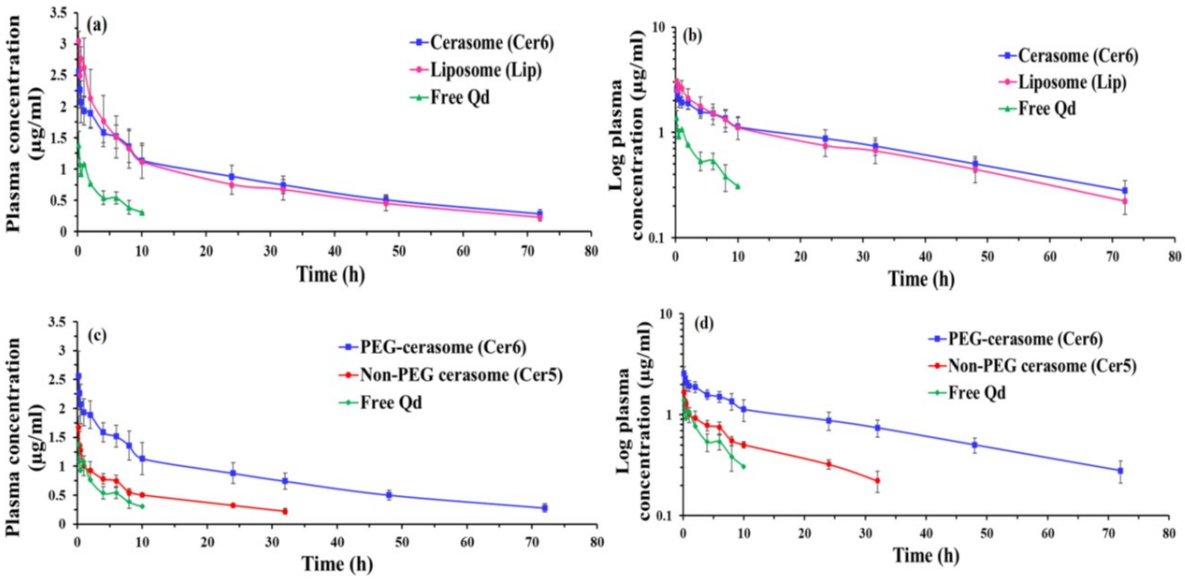


Figure 3. Plasma concentration-time profiles of Ag_2S Qds (dose= 125 μg/kg) following IV administration of the free Qds (marker) and Qds-loaded PEGylated cerasomes and liposomes (a and b) as well as PEGylated and non-PEGylated cerasomes (c and d) into rats. (n = 6, Mean ± SD)

Reviewer 2:

The manuscript investigates the pharmacokinetics behavior of cerasome in comparison to liposome in a well-designed study and it also presents the influence of PEGylation of the formulated delivery systems on increasing the blood circulation of these vesicles.

The design of the study is adequate. Nevertheless, the paper needs some minor modifications. For instance:

1. The title can be modified to indicate the need for PEGylation as well (It is not essential).

Thanks for this suggestion. We would like to indicate the need for PEGylation in the title, but it would be too long which is not in accordance with the journal policy. However, we can modify the title if the reviewer advises.

2. English proofreading is suggested (It is not necessary).

The manuscript was carefully re-checked in terms of English writing and corrected wherever it was necessary.

3. The information related to the design of "pharmacokinetic studies" (line 180-182) could be reconsidered according to the result section to better explanation of compared formulations. It is better to mention the difference between two studied formulations.

Thanks for this helpful comment. The design of "pharmacokinetic studies" was revised as follows:

"The rats were randomly divided into four groups (n=6 in each group) and were administered three selected formulations including non-PEGylated cerasome (Cer5), PEGylated cerasome (Cer6) and liposomal formulation (Lip), as well as free Qds (as the marker). All formulations were dispersed in dextrose 5%."

4. How do the authors justify the different distribution (two different distribution phases) and elimination phases of administered formulations? It would be great if they could clarify that the justification is just done according to the log transformed profiles or whether other approval studies are available.

A description was added to the text to discuss the observed three-phase profiles as suggested by the referee. It is worth noting that the diagnosis of a three-phase profile was based on log-transformed profiles and this point was mentioned in the text.

Page 18, the first paragraph: "As illustrated in Figure 3b (the log-transformed profile), the concentration-time profiles of Cer6 and Lip displayed similar patterns with three distinct phases including a rapid initial distribution phase, a second slower distribution phase, and a terminal elimination phase. The observed three-phase profiles could be explained as follows. Following systemic administration, classic vesicles are rapidly taken up by RES mainly the macrophages of the liver and spleen. It has been well known that incorporation of PEG in the composition of nanoparticles reduces the macrophage clearance of nanoparticles, but cannot eliminate this phenomenon completely. The available evidence indicates that a fraction of intravenously administered PEGylated nanocarriers is rapidly taken up by RES cells (6). It seems that the heterogeneous surface properties of the injected vesicles are one of the reasons for the lack of sufficient and complete protection of the particles. Some groups of vesicles appear to have inadequate surface coverage by PEG molecules which allow opsonic binding to uncovered areas (6). This explanation can justify the first rapid disposition phase. The second relatively fast disposition phase is more likely due to the fact that, in addition to macrophages, nanoparticles generally rapidly distribute to organs that have fenestrated capillaries namely the liver, spleen and

bone marrow which have capillaries with fenestrated endothelial lining (31). The third phase is the elimination and terminal clearance phase which is the slowest process.”

2 Revision 1

0 comments

No public comments in this round.