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ESPS PEER-REVIEW REPORT

We sincerely thank both the editor and the reviewer's for their constructive criticism. For your convenience we have highlighted the changes in yellow color. Please do not hesitate to contact us, if further clarifications are needed.

Reviewer 1:

COMMENTS TO AUTHORS

General comments Trish et al. reviewed novel therapeutic approaches for macular edema and diabetic retinopathy, both of which are common posterior ocular diseases in diabetic patients. Pathogenesis and underlying mechanisms of macular edema have been discussed. Several effective therapies, such as anti-VEGF therapy and laser photocoagulation, as well as emerging strategies are well documented.

1. Specific comments 1. Several parts of this review are redundant, for example: in the beginning of section 5 "…Ophthalmic complications associated with diabetes are the leading cause of blindness in adults. In recent years, several formulations are emerged that have been applied for treating DME and other back-of-the-eye diseases. FDA approved drugs such as ranibizumab and bevacizumab have shown promising results for the treatment of DME in various trials (78, 145, 146)…", or before the conclusion section "…DME is a disease associated with the posterior segment of the eye; therefore, it poses a significant delivery challenge. A significant portion of the drug may not reach back of the eye due to associated barriers such as blood retinal barrier, blood aqueous barrier, and vitreous barrier…".

Response: We would like to thank the reviewer. We agree and have made changes, which are highlighted.

2. As for the nanotechnology formulations section, it should be divided into 2 parts, i.e., in vitro/pre-clinical evidence and evidence from clinical studies. Perspectives and future direction as well as the pros and cons of each technology may be discussed in detail.

Response: We thank the reviewers for their constructive criticism. We appreciate the suggestion from the reviewer. However, there is not much literature available for nanotechnology based therapy conducted in clinics to divide into two sections. However, in the revised manuscript, clinical studies are now discussed under the section, "Emerging formulations for treatment of diabetic macular edema." Therefore, in the revised manuscript titles have been updated, "Emerging formulations for treatment of diabetic macular edema." which has further two sub titles "clinical studies" and "*in vitro*, *in vivo* and pre-clinical studies" Moreover, reviewer suggested to include perspectives, future directions and pros and cons of each technology. Although this suggestion is agreeable, but it is outside the scope of this review. The suggestion will involve its own topic and may require a separate manuscript as a lot of information will have to be discussed in order to address all pros, cons and future perspectives of each novel strategies for the treatment of diabetic macular edema. It is a great suggestion and we may consider writing another manuscript on that topic.

3. Figure legends should be more informative. For example, how was the fluorescent image in Fig. 1 obtained? (human tissue or animal tissue, staining technique, etc.). In Fig. 2, surgical procedure should be briefly described.

Response: We agree with the reviewer and have revised the figure legends in the manuscript accordingly
We have edited the Figure 1 legends as following:
Figure 1: Diabetic macular edema (DME) disease: (a) structure of human eye (b) expanded representation of macula region for normal eye (c) expanded representation of macula region for DME (d) Optical coherence tomography (OCT) image for DME.
Figure 2 summaries all the current treatment Strategies of Diabetic macular edema (DME) which are well-labeled. In this review, the all strategies have been introduced in the brief manner with the mechanism associate with side effects and drawback. We already discussed in section 2 about the vitrectomy. There will be too specific if we describe the surgical procedure in detail.

Reviewer 2:
In this article, the authors have provided an overview of several novel strategies including nanotechnology based drug delivery approach for posterior ocular drug delivery and treatment with emphasis on DME. Overall, the review is well-written and interesting. The authors described the standard treatments of DME include laser photocoagulation, vitrectomy, intravitreal injections of anti-VEGF biologics and steroids. It would be better to add a description of NSAIDs therapy. In addition, several therapeutic agents in development, which may be used in combination with anti-VEGF biologics, for the management of DME in the future.

Response: The reviewer has mentioned about the NSAIDs therapy. I agree that NSAIDs has shown the effective in prevention and postop pain following cataract surgery. However NSAIDs has not been approved for DME. It has been used as “off-label”. The combination treatment between anti-VEGF biologics and laser, photocoagulation, vitrectomy and steroids has been discussed in several sections in this manuscripts.