

Dear Editor,

Thank you very much for your letter and advice. We have revised the paper and would like to resubmit it for your consideration. We have addressed the comments raised by the reviewers, and the changes are highlighted in red in the revised manuscript. We hope that the revision is acceptable, and we look forward to hearing from you soon.

Yours sincerely, QinanWu

Endocrinology Department, Dazu Hospital of Chongqing Medical University, The People's Hospital of Dazu, Chongqing, 400900, China., 402360

Tel: +86-13452867542

E-mail: wqn11@126.com

Reviewer #1:

**Scientific Quality:** Grade B (Very good)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Minor revision

**Specific Comments to Authors:** In this review, authors summarized the application of diverse MSCs-based drug delivery systems in treating DFU and suggested potential avenues for the future research. The complication of diabetes, which is known as diabetic foot ulcer (DFU), is a significant concern due to its association with high rates of disability and mortality. It not only severely affects patients' quality of life, but also imposes a substantial burden on the healthcare system. The review is comprehensive and can be considered for publication after a minor revision.

1. There are a lot of typos and should be revised, like “withan”, “Wound debridement, which isthe standard treatment for DFUandinvolves surgical removal of thickened, necrotic, damaged or infected tissues, has been widely used in clinical practice;the wound isthen covered with dressing and/or treated with antibiotics to prevent infection”.

Reply: Thanks for your comment. The manuscript was grammatically re-edited, and some sentences were re-written.

2. A diagram scheme should be included to summarize the main content of the review.

Reply: Thanks for your comment. A diagram was drawn, representing the summary of the main content of the review (Please refer to Figure 1).

3. All of the figures should have the permissions from the pulisher.

Reply: Thanks for your comment. Figures 2 and 3 have been cited in the main text, and the list of references was updated (please refer to Ref. Nos. 75 and 112). Other figures were not published elsewhere.

4. Citations in table 1 was lost and should be added.

Reply: Thanks for your comment. Citations in Table 1 were added.

5. More discussions about the background are need, by citing the following papers: <https://doi.org/10.1016/j.ijbiomac.2022.12.032>; <https://doi.org/10.1016/j.msec.2022.112677>; <https://doi.org/10.1016/j.ijbiomac.2023.124960>.

Reply: Thanks for your comment. The above-mentioned documents were discussed and cited (refer to Ref. Nos. 16-18 please) as follows: The synthesis of iodine (I)-polyvinyl alcohol (PVA)@polydopamine (PDA) microspheres was documented in Yang et al.'s study<sup>16</sup>. The aim was to attain computed tomography images, drug loading and controlled release capabilities, as well as improved embolization of the liver portal vein. The *in vivo* embolization findings demonstrated the presence of focal necrosis in hepatocytes, along with necrotic cell fragments and infiltration of inflammatory cells in liver tissue. These observations provided evidence that the I-PVA@PDA microspheres exhibit a more potent embolization effect compared to PVA particles. Additionally,

the I-PVA@PDA microspheres were utilized for the delivery and controlled release of 5-fluorouracil, a chemotherapeutic drug. The results showed an initial rapid release (29.74% released) within the first 24 h, followed by sustained release (34.48%) over a period of 72 h. In Ouyang et al.'s research<sup>17</sup>, a multifunctional bio-hemostatic hydrogel (CODM) was prepared based on hydrogen bonding and Schiff base bonding by using modified alginate, polyvinylpyrrolidone (PVP), and carboxymethyl chitosan. The amino group-modified montmorillonite was uniformly dispersed in the hydrogel through amido bond formation with the carboxyl groups of carboxymethyl chitosan and oxidized alginate. The catechol group (-CHO) and PVP were able to form hydrogen bonds with the tissue surface, resulting in firm tissue adhesion and wound hemostasis. The addition of montmorillonite-NH<sub>2</sub> further improved the hemostatic ability, surpassing that of commercial hemostatic materials. Furthermore, the photothermal conversion capability (derived from polydopamine) was synergized with the phenolic hydroxyl group, quinone group, and protonated amino group, effectively eliminating bacteria both *in vitro* and *in vivo*. In a recent review<sup>18</sup>, it was reported that a multifunctional CH hyaluronic acid three-dimensional hydrogel possesses a notable capacity for water absorption. This property holds potential for its application in managing inflammatory bowel diseases (IBD), with a concentration on various aspects, such as adhesion, synergistic therapy, pH sensitivity, particle size, and temperature sensitivity. A desirable polymer hydrogel for hemostasis is expected to possess the following characteristics<sup>18</sup>: (1) it should exhibit a rapid gelation rate to promptly stop bleeding and promote active wound healing; (2) in dynamic and humid environments, the hemostatic hydrogel should demonstrate adequate adhesion and exceptional mechanical properties to effectively seal the wound and prevent the displacement of the hemostatic hydrogel from the bleeding site; and (3) it should exhibit favorable biocompatibility. Furthermore, it is important for the hydrogel to exhibit controllable swelling behavior as overly swollen hydrogels may exert pressure on the surrounding tissue.

Reviewer #2:

**Scientific Quality:** Grade A (Excellent)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** This is a laborious work. However, it should be better organized, and numerous data in a way more suitable for the readers. Many typos have to be corrected. Thus, it has to be accordingly rewritten.

Reply: Thanks for your comment. Several revisions were performed, the manuscript was grammatically re-edited, some sentences were re-written, a new figure was added (refer to Figure 1 in the revised version please), Figures 2-3 were cited, 3 citations were added (refer to Ref. 16-18 and newly added sentences in the revised version please), and the list of references was updated.

At last, during our revision process, Xi Jiazhuang also participated in the revision, therefore, we added him as the author.

Thank you again!

Sincerely yours,

QinanWu

Dear Editor,

Thank you very much for your letter and advice. We have revised the paper and would like to resubmit it for your consideration. We have addressed the comments raised by the reviewers. We hope that the revision is acceptable, and we look forward to hearing from you soon.

Yours sincerely, QinanWu

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E-mail: wqn11@126.com

1. 1. You need to provide a declaration file that requires the signatures of all authors, including 'Xi Jiazhuang'

Reply: Thanks for your comment. We provide a declaration file that requires the signatures of all authors, including 'Xi Jiazhuang' We also revised in the manuscript and highlighted in red..

Thank you again!

Sincerely yours,

QinanWu