Date: May 9, 2017

Dr. Vladimir Torchilin
EDITORS IN CHIEF of Drug Delivery
RE: UDRD-2018-0236.R1

Dear Dr. Vladimir Torchilin

We are submitting the revised version. We appreciated the reviewers for valuable comments. All changes are highlighted in the revised manuscript. We respond to the reviewer's comment as follows:

Reviewer's comments:

1. Fig. 2, only one nanoparticle is observed, and is not very clear. This is rather surprising as one should observe plenty of nanoparticles. TEM images should be better than SEM.

⇨ Thank you for the valuable comment. In this study, we tried to understand the morphology of DTBM using available electron microscope. Following the comments, morphology of the numerous micelle was observed again and substituted to one with more particles. Fig. 2b was updated as it follows:

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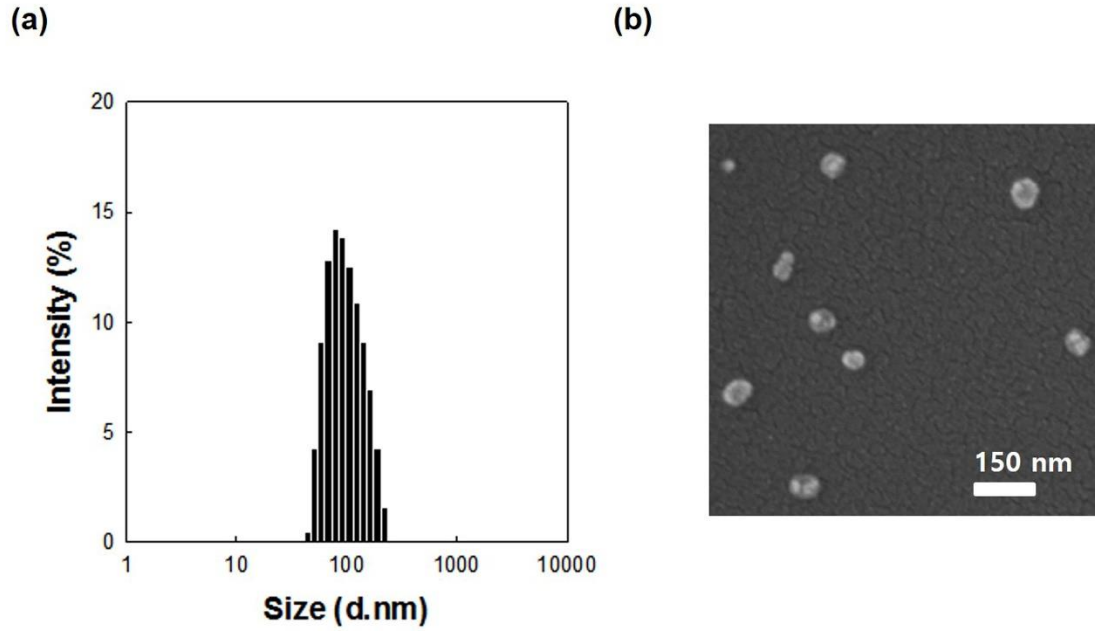

Figure 2. Characterization of DTBM (targeting 10%): (a) Particle size distribution by DLS and (b) morphologies by FE-SEM.

2. Does Fig. 3c show cumulative drug release? Why Nanoxel M showed a decrease after a maximum?

⇨ Thank you for the kind comments. We evaluated the drug release by measuring the drug concentration in the continuous outer phase maintaining sink condition instead of cumulative release methods. The slight decrease after the maximum at 12 h would be caused by recrystallization or precipitation of the solubilized drug released from micelles. (Ref: 1. *Mol Pharm. 15(5):2017-2026*, 2. *Int J Pharm. 2017 531(1):313-323*). The description was revised on the manuscript as following:

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The released DTX in the continuous outer phase was evaluated by HPLC analysis.

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To investigate DTX release from the formulation, Nanoxel M and DTBM-R were exposed to PBS at pH 7.4 (**Figure 3c**). Nanoxel M showed a drastic increase in DTX release. It gave a maximum release rate of drug at 12 h followed by slight decrease. At 12 h, the drug released from the commercial product might be entirely dissolved as a supersaturated form in the release medium. Moreover, with the elapsed time, the slight decrease after the maximum at 12 h would be caused by recrystallization or precipitation of the solubilized drug released from micelles (Xie *et al.*, 2017, Schver and Lee, 2018). In contrast, DTBM-R showed sustained drug release with less than 50% maximum cumulative drug release over 72 h.

3. The authors should be very cautious with data precision. In Table 1, data like 84.1±2.03 or 0.26 ± 0.015 are meaningless as DLS has a large error range. Are the data obtained from averaging several measurements?

⇨ Thank you for the valuable comment. Data on Table 1 was changed with more reasonable values. Each of the sample was measured in triplicate. The description was revised as follows:

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The average $D_{eff.}$ was calculated from three measurements of each sample (n = 3).

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Table 1. Characterization of DTBM (n=3)

Target content (%) [a]	Loading Content (%) [b]	Loading efficiency (%) [c]	Size (nm)	PDI [d]
10	7.4	81.9	125 ± 2.7	0.24 ± 0.01
20	10.9	65.3	84 ± 2.0	0.26 ± 0.02
30	12.4	53.5	83 ± 4.2	0.29 ± 0.02

4. In the SI, carboxylated PEG (PEG-COOH) was prepared by the reaction of PEG with succinic anhydride. But in the Scheme, mPEG-PLA-COOH was prepared. Which one is the good reaction route?

⇨ We really appreciate the reviewer for a great valuable comment on the confused explanation. We found the error to explain the method. mPEG-PLA-COOH was prepared by the reaction using succinic anhydride. After the carboxylation, PEG was conjugated to mPEG-PLA-COOH by Steglich esterification DCC and DMAP as Scheme S1. They were substituted on the supporting information as below:

(**Supporting information**)
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Carboxylated PEG-PLA (PEG-PLA-COOH) was prepared by the reaction of PEG-PLA with succinic anhydride in the presence of DMAP, TEA, and pyridine. First, PEG-PLA, succinic anhydride, and DMAP were reacted in 20 mL of DCM for 3 h, followed by the addition of TEA and pyridine. The reaction was carried out overnight and PEG-PLA-COOH was obtained by precipitation in an excess amount of diethyl ether. The final product was filtrated and dried in vacuum for 2 days. To prepare PEG-PLA-PEG triblock copolymer, the synthesized PEG-PLA-COOH and PEG were conjugated by Steglich esterification in DCM using DCC and DMAP as coupling reagent and catalyst, respectively. The reaction was carried out overnight and the final products were obtained by precipitation in an excess amount of diethyl ether, subsequent filtration, and drying in vacuum for 2 days (**Scheme S1a**).

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PEG-PLA-PEG triblock copolymers targeting molecular weight of 2K-6K-2K were synthesized by Steglich esterification between PEG-PLA-COOH diblock copolymers and PEG (**Scheme S1**) [22].

We would like to submit the revised manuscripts and hope that it would be accepted. Thank you for your consideration.

With best regards,

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