**Response to Reviewers comments**

**Manuscript title:** Surface Modification and Functionalization of Sorafenib-Loaded PLGA  
Nanoparticles for Targeting Hepatocellular and Renal Cell Carcinoma  
**Manuscript ID: pharmaceuticals-2580103**

We are grateful to the reviewer for his valuable suggestions. The manuscript has been extensively revised. The point by point response has been made to the reviewers’ comments. The changes have been incorporated in the manuscript and were highlighted.

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| **S/N** | **Comments** | **Response to Comments** |
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| 7 | comment 7 - The question was not about why the authors performed FTIR, but what kind of apparatus was used as two different ones appear in the text. It is still not corrected. | Thank you for highlighting this issue. The PerkinElmer spectrum BX FTIR (Waltham, MA, USA) has been used. The correction has been made. |
| 10 | comment 10 - There is no elaboration on the possible reasons for the observed results. | The data showed that increasing the concentration of the drug in formulation resulted in the larger size nanoparticles. The increase in nanoparticle size was due to the increased amount of drug in the emulsion nano-droplets. (*Sharma, N., P. Madan, and S. Lin, Effect of process and formulation variables on the preparation of parenteral paclitaxel-loaded biodegradable polymeric nanoparticles: A co-surfactant study. Asian Journal of Pharmaceutical Sciences, 2016.* ***11****(3): p. 404-416*.) |
| 11 | comment 11 - The SEM images still do not correspond to the presented particle sizes. In the revised version of the manuscript the scale bars are missing, but the images are the same. Previous scale bars equaled 1 micrometer. And the observed particles for SPF are much bigger than the scale bar. Yet, in the Table 1 and current Figure 1 the presented size is approximately 140nm. The data is inconsistent | We are thankful to the reviewer. The new images have been added to the manuscript with scale bars. Now the values in table, figure, and SEM image are in line with each others. |
| 13 | comment 13 - The authors have rephrased the sentence, but no possible explanation has been provided. There is no comparison with previous findings. | The possible explanation has been provided as per literature (Sharma, N., P. Madan, and S. Lin, Effect of process and formulation variables on the preparation of parenteral paclitaxel-loaded biodegradable polymeric nanoparticles: A co-surfactant study. Asian Journal of Pharmaceutical Sciences, 2016. **11**(3): p. 404-416) as given in the discussion section of the manuscript. |
| 15-17 | comments 15-17 - Proper information about the control "solution" should be presented in the text. It is still missing. It is incorrect to use the term solution when it is a suspension. In the pharmacokinetic data it is unclear which data belongs to the control "solution". Figure 7 and Table 4 lack the data of the control suspension for comparison. | Thank you for the correction. The data has been added in section **4.2** regarding the preparation of control SFB nanosuspension and was added to both figure and table. |
|  | There are also other issues observed: | |
|  | 1. Figures and tables require more careful and better presentation of the results | The corrections have been made. The resolution of the Figures has been improved and the presentation of the results in tables has been improved. |
|  | - Figure 1 does not show the formulations with their coding, plain NPs are again missing, axes are not labeled properly, units are missing; | All the missing informations have been added as suggested. |
|  | Table 1 - why the authors present amount encapsulated and EE% for the plain nanoparticles | Thank you for the correction. It was a typographic mistake that has been corrected. |
|  | The FTIR and the DSC spectra could be better presented. The images are directly extracted from the apparatus software and are not suitable for publication in their current form. | Thank you for the suggestion. The resolution of the images has been improved by Photoshop as suggested. The figures are provided in tiff format with the manuscript. |
|  | The marked peaks on Figure 4 are impossible to read. | The resolution of Figure 4 has been improved as suggested. |
|  | Figure 6 provides as units for time (Hr) which is not an accepted SI unit. | The *in-vitro* and *in-vivo* data is given in hours (Hr) as per previous literature please check. “*In vivo biodistribution, biocompatibility, and efficacy of sorafenib-loaded lipid-based nanosuspensions evaluated experimentally in cancer”* ***and “****Formulation and Optimization of Polymeric Nanoparticles for Intranasal Delivery of Lorazepam Using Box-Behnken Design:*In Vitro*and*In Vivo*Evaluation*” |
|  | Figure 5 scale bar is missing. | The scale bar of Figure 5 has been corrected as suggested. |
|  | Table 3 - what does reference stand for? | The reference in table 3 stands for control SFB Nanosuspension. The correction has been made as suggested. |
|  | Table 4 - what do R.Total and R.Excreted stand for | R. Total means Radioactivity Total  R. Excreted means radioactivity excreted. |
| 2 | The authors should explain why the in vitro dissolution is investigated up to 350th hour and from the distribution data it is evident that the nanoformulations would be eliminated from the organism within 24h. Would a released amount not more than 30% would be sufficient. | The *in-vitro* and *in-vivo* release is shown the manuscript. They both correlate with each other showing that the drug is sustained for almost fourteen (14) days, while the imaging studies was performed for the physical targeting of the nanoformulations and the radioactivity faded away in 24 hours. The data was provided as per reported literature. |
| 3 | Why such difference is observed between the SEM images of SPF1, SPF2 and SPF4. In the case of SPF4 different clusters appear which are not seen in the other batches | The new images of the SEM results have been added in the manuscript. |
| 4 | In order to use SEM to prove stability, the authors should present the SEM images before and after storage. Currently, they show only 3 images and it is unclear when they are taken. | The Scanning Electron Microscopy is an expensive technique that’s why random samples were observed after freeze drying and SEM images were taken. The particle size of the formulations was confirmed by the Zeta sizer before and after freeze drying. |
| 5 | The nanosuspension which the authors used for comparison should be well explained in the manuscript. Its characterization should also be shown especially when the authors discuss differences. Currently, there is no data about the size of the drug particles, the concentration, the in vitro release and the distribution in main organs. Please change the term in the text correspondingly to Nanosuspension. | The Nanosuspension was explained in the nanoparticles preparation section as well as in the tables showing characterization and in-vivo studies as well as in Figures of in-vitro release and organ distribution studies. The term was also changed from solution to control SFB nanosuspension. |
| 6 | Overall the discussion section should provide better elaboration of the findings and comparison with other studies. | The discussion section has been elaborated further with reference to the reported studies as suggested by the reviewer. |
| 7 | There is inconsistent information. In section 4.3.7. Formulation optimization authors define zeta potential ≥± 30 mV. In the Conclusion section ≤ -10 appears. Which one is correct and how the threshold was defined? | The zeta potential ≥± 30 mV is an ideal range which corresponds to better physical targeting and stability as per previous literature. While ≤ -10 is the results of our data. Please check;  “*In vivo biodistribution, biocompatibility, and efficacy of sorafenib-loaded lipid-based nanosuspensions evaluated experimentally in cancer”* |