***Responses to Reviewers***

***THERMAL ANALYSIS STUDIES ON THE COMPATIBILITY OF FUROSEMIDE WITH SOLID STATE AND LIQUID CRYSTALLINE EXCIPIENTS***

***Reviewer B:***

Referee’s comments and suggestions are listed below:

1. The English language should be improved through the manuscript.

***The revised manuscript was proof-read by a native English speaking colleague.***

1. Page 2, line 34 and Page 3, lines 59-60: statement “(part of the innovative excipient, called “liposome”)” is unnecessary. In 2019 liposomes are very good known.

***The term “innovative excipients” was deleted throughout the manuscript. According to the reviewer’s comment, we changed this term with “liposomes”.***

1. Page 2, line 38: instead “fluidlike” term fluid-like can be used, without quotation-marks.

***We used the term “fluid-like” instead of “fluidlike”***

1. Introduction part should be rearranged. Second paragraph, lines 55-60, should be at the end of the introduction part, before the sentence “To the best of our knowledge, this is the first report in the literature on pre-formulation studies using solid and liquid crystalline state excipients, for comparison purposes, with and without furosemide.”

***According to the reviewer’s comment, we rearranged the introduction part. We moved the second paragraph, lines 55-60 before the proposed sentence.***

1. The sentence “The results produced by these investigations demonstrated the co-operability of these materials and their suitability for preparing solid and colloidal pharmaceutical formulations of furosemide.” is more appropriate for the Results and Discussion and/or Conclusion than for the Introduction part.

***The sentence was deleted and was moved to the Conclusion part.***

1. Page 5, Part 2.3 Differential Scanning Calorimetry: the authors omitted to denote measurements atmosphere.

***We added: “The measurements took place under a N2 atmosphere”.***

1. Results and discussion: all DSC graphs should be corrected to have numeric y-axis. Heat flow should be presented in Watt per the sample weight in the appropriate units, it is usually W per g.

***We did use numeric y-axis because usual in DSC measurements to avoid value range in the y-axis. Additionally, all the values of ΔΗ are normalized to sample size. For the above reasons, we did not have numeric y-axis. We corrected the units (mW/mg).***

1. Almost 30% of the references which the authors cited in the manuscript are older than 10 years. If it is possible the authors should cover the most current research in the field.

***We used these references because they are appropriate in explaining from the results of our experiments. Furthermore, some of the excipients are well-established in the literature regarding their thermal behavior and their DSC profiles have appeared in the literature long ago. We also added two more recent research papares***

1. References list: reference 17 should be completed with year; volume: pages.

***The additional details requested are: Journal of Dispersion Science and Technology, 35:6, 848-858***

1. References list: reference 18 should be completed.

***The additional details requested are: DOI: 10.13140/2.1.3578.4640 Conference: IX Brazilian Congress in Thermal Analysis and Calorimetry, At Serra Negra - São Paulo, Volume: 1***

***Reviewer C:***

ADDITIONAL COMMENTS

 The present manuscript needs some improvements and corrections to be ready for publication:

Introduction:

Please explain better the choice of testing the interaction of furosemide with chimeric liposomes. To state that chimeric liposomes are innovative excipient is not exhaustive.

***According to the reviewer’s comment, we explained the choice of testing the interaction of furosemide with chimeric liposomes: “Chimeric or polymer-grafted liposomes are used in order to overcome stability limitations of liposomes. In parallel, liposomes are attractive drug delivery carriers with numerus biomedical applications. Furthermore, to the best of our knowledge this is the first report in the literature, where DSC is used for the quantification of interactions of furosemide with chimeric liposomes. The results could serve as a roadmap for the design and the development of liposomal formulations of furosemide.” The term “innovative excipients” was deleted through the manuscript. According to the reviewer’s comment, we changed this term with “liposomes”.***

Rewrite the last part of the introduction (line 69-73). This part sounds as a conclusion. Please, instead, explain the real aim of the work.

***We re-wrote the last part of introduction as follows: “****The aim of this investigation was to study the co-operability of these materials and their suitability for preparing solid and colloidal pharmaceutical formulations of furosemide. These pre-formulation studies could serve as the first step to develop diverse formulation of furosemide, i.e. tablets and liquid liposomal suspensions.****“***

Materials and method:

Line 77 Please indicate viscosity for sodium alginate.

***We added: “The viscosity of sodium alginate is 4-12cP, 1% in water (25°C).***

Line 77-78 add Dalton unit for the reported MWs.

***We added the Dalton units throughout the manuscript.***

Line 77 Please indicate the form (α- or β- form) for lactose.

**The form of lactose is α.**

Line 79-80 and 84 Please indicate the city and country for Merck, Riedel-De Haen and Sigma-Aldrich providers.

***Merck (Athens, Greece), Riedel-De Haen (Bucharest, Romania) and Sigma-Aldrich (Darmstadt, Germany)***

Line 84-85 Please add more information about synthesis and characterization of the used block copolymer or add references, if reported elsewhere. What is PPA? Specify.

***At the materials section we stated that Poly(n-butylacrylate)-b-poly(acrylic acid) (******PnBA-b-PAA) block copolymers with 70% content of PAA were also used. So, PAA is poly(acrylic acid). The synthesis of the PnBA-b-PAA is reported in Reference [24].***

Results

In the case of sodium alginate DSC traces, please explain better the dehydration process and the decomposition. Is the peak at 160 °C referred to loss of physical bounded water or to a chemical dehydration process? The loss of moisture at 160°C is quite uncommon and generally, it occurs at a temperature below or around 100 °C.

***According to the reviewer’s comment, we added: “The first degradation occurs in the temperature range of 30oC - 100oC, possibly due the initially dehydration process. The loss of physically bounded water took place in this temperature range. Two more degradation processes occur in the regions of 100oC - 130oC and 130oC - 180oC, probably due to alginate backbone destruction and hydroxyl groups loss (chemical degradation process).”***

Line 132-137 Please describe more clearly the endothermic peaks in DSC traces of magnesium stearate. Particularly, it is not univocally written to which transition each peak refers to. See also J Therm Anal Calorim (2009) 97:355–357 for comparison.

***We added: According to the literature, the DSC curve of magnesium stearate shows endothermic events: the first at 84.3–97.4 °C corresponds to dehydration; second at 112.6–121.9 °C and a third at 150.6–158.7° C, indicating the melting of palmitic and stearic acid compounds.***

***We also added a new reference:***

***Freire, F.D., Aragão, C.F.S., de Lima e Moura, T.F.A. et al. J Therm Anal Calorim (2009) 97: 355. https://doi.org/10.1007/s10973-009-0258-2***

Line 140 Are you sure that “decarboxylation of the disaccharides occurs” at 147°C? Why after dehydration the β-lactose portion melts and not the anhydrous form of lactose?

***The sentence “More specifically, with a center at 147.0 °C decarboxylation of the disaccharide occurs, during which the crystallization water molecules are eliminated” was deleted.***

***We revised as follows: “The DSC diagram shows an endothermic peak at 147°C, which represents the loss of crystalline water.”***

***We also added a new reference:***

***GombÁs, Á., Szabó-Révész, P., Kata, M. et al. Journal of Thermal Analysis and Calorimetry (2002) 68: 503. https://doi.org/10.1023/A:1016039819247***

Line 149-153. No glass transitions are visible for PVP in DSC traces presented in figure 2. The showed peaks seems to be some melting events. Please explain.

***The term “glass transition” was deleted. We used the term “melting events”.***

Line 255 the sentence is referring Figure 7 and not Figure 6.

**We changed the number of the figure.**

Line 256 Where is table 2 (and also table 1) in the manuscript?

***The tables were included in a previous form of the manuscript. We deleted them.***

Line 275 On which base according to DSC traces, it can be stated that “liposomal systems were found to offer facile release of furosemide”?

***As it is stated in the manuscript, according to the DSC studies, we observed a “fluid-like” model for the interactions of the drug with the polymer-grafted lipid bilayers. For this reason, we predict a facile release of furosemide due to the absence of strong interactions. We rephrased: “Moreover, the chimeric liposomal systems, characterized as “fluid-like” by their DSC curves, were found to offer facile release of furosemide due to the limited interactions of the drug with the polymer grafted lipid bilayers”.***

TGA analysis would be very useful for the improvement of the manuscript.

***The aim of this investigation is to highlight the role of DSC for the preformulation studies. For this reason, we did not use TGA to study the degradation process of the excipients and drug/excipients mixtures. Additionally, for the pre-formulation studies, the interactions between the different materials are the key point for future formulations studies. This kind of information is obtained by DSC, too.***