Revised manuscript entitled: "**Freeze-thawing method to prepare chitosan-poly (vinyl alcohol) hydrogels without crosslinking agents and diflunisal release studies"**.

Answers to Reviewer #1

First of all, we would like to thank the amendments suggested. We have taken into account all the corrections received because we have found them very useful.

Considering the requested corrections, we have made the following changes in the manuscript; all of them are highlighted in red in the document:

Major Concerns:

1. **The Figure 1 should include the chitosan and PVA FTIR curves as controls.**
   In Figure 1 (renumbered like Figure 2) the FT-IR of pure chitosan and PVA were included as controls.

2. **In the Figure 2, the scale bar should be included in the SEM pictures. Also, the CP4-80 picture is duplicated. One of the CP4-80 SEM image should be removed. Moreover, the manuscript states that the CP4-4 hydrogel has bigger pores than the CP4-80 hydrogels. However, the CP4-4, CP4-20 and CP4-80 hydrogels seems very similar in SEM.**
   In Figure 2 (renumbered like Figure 3) the scale bars are automatically included at the bottom (outside) of each SEM micrograph. Indeed, this figure was restructured in order to eliminate CP4-80 SEM duplication and to conserve the comparison lines (effect of the temperature, left to right; effect of the number of freezing cycles, top to bottom). Finally, porosimetry curves (from the original Figure 3) were inserted in the same Figure (Figures 3-a, 3-b).

   Concerning the results, it is true that it is not easy to appreciate the differences between hydrogels CP4-4, CP4-20 and CP4-80 from SEM Images, however these differences can be batter appreciated by the porosimetry results.

3. **In the Table 1, how many replicates of measurements were conducted? The standard deviation should be included in the data.**
   Porosity measurements were done once, as shown in several works including similar studies, for example:

   1. Morgado, P.I. *et al.* Poly(vinyl alcohol)/chitosan asymmetrical membranes: Highly controlled morphology toward the ideal wound dressing. *Journal of Membrane Science*. **469**, 262–271, doi: 10.1016/j.memsci.2014.06.035 (2014).

2. Temtem, M., Barroso, T., Casimiro, T., Mano, J.F., Aguiar-Ricardo, A. Dual stimuli responsive poly(N-isopropylacrylamide) coated chitosan scaffolds for controlled release prepared from a non residue technology. *Journal of Supercritical Fluids*. **66**, 398–404, doi: 10.1016/j.supflu.2011.10.015 (2012).

3. Balaji, S. *et al.* Preparation and comparative characterization of keratin-chitosan and keratin-gelatin composite scaffolds for tissue engineering applications. *Materials Science and Engineering C*. **32** (4), 975–982, doi: 10.1016/j.msec.2012.02.023 (2012).

4. **The release profiles were fitted into different models. However, the model equations were missing in the manuscript. In the Table 3, the n and k values were not defined. Moreover, it is not clear how the conclusion of diffusion-controlled release mechanism was made based on the result of fitting.**

   In section 6.5 the model equations were described (Eq. 4-7). Indeed, in this section, the *n* and *k* values were defined (Table 3). Moreover, we describe how to interpret the *n* values obtained and the procedure to follow to conclude the predominant release mechanisms (lines 202-206).

5. **The manuscript mentioned in multiply places about the crystalline zones formed due to the PVA chain interaction during freeze-thawing process. However, this was not strongly supported by the SEM images of the hydrogels.**

   To our knowledge, the crystalline zones formed by polymeric chains couldn't be observed by SEM, even nor by TEM, due either by the resolution needed and also because the polymeric material hasn't the contrast enough. Other techniques can be used for that purpose. However, this characterization was not the objective of our study. In fact, according to the literature, these crystalline zones in the PVA hydrogels are well characterized by Hassan, C.M. and Peppas, N.A. in Structure and Applications of Poly (vinyl alcohol) Hydrogels Produced by Conventional Crosslinking or by Freezing / Thawing Methods. *Advances in Polymer Science*. **153**, 37–65, doi: 10.1007/3-540-46414-X_2 (2000).

Minor Concerns:

1. In Line 181, section 6.3: "Measure the absorbance at 252 nm of the supernatant solutions at 252 nm" has two "at 252 nm".

Thank you, the second "at 252 nm" has been deleted (line 185).

Moreover, this section did not mention about the instrument has been used.

As required in the "Standard Manuscript Template", all the instruments specifications are enlisted in the "Table of Materials" (attached Excel document).

The encapsulation efficiency is not defined in the manuscript.

The Encapsulation Efficiency (EE) was defined by Eq. 3, lines 193.

2. It is better to include the structures of chitosan, PVA and diflunisal in the manuscript

The structures of chitosan, PVA and diflunisal were included in Figure 1 and cited in lines 78, 92, and 116, respectively. Therefore, all the Figures have been renumbered.