Systematic analysis of the relevant literature, bibliographies, and interactions with investigators.

Results:

From the investigation of different literatures, it was found that various factors of solvent evaporation technique may be controlled in

order to design the micro and nanospheres of suitable morphology, entrapment and release characters.

**Responses for Reviewer B:**

-To my opinion, the authors need to be aware of the fact that the references that address these important questions are not up-to-date (references 40-46 in authors’ response), which also questions the originality of the paper.

**Response:**

The references are updated after the analysis of the relevant literature and bibliographies. (Many researchers 21,24,26, 31,32,34-37,41,42 have demonstrated the ability of EC to sustain the release of drugs). Also, these references were mentioned in the text of the Manuscript in red color (pages: p.3, p.6, p.7, p.9, p.15 and p.16).

-Furthermore, the medium for this prolonged release must not be the same pH 1.2, but different. On the other hand, the release will be governed by different processes, not only diffusion, thus I suggest to omit release data given after 100 min.

**Response:**

-We have presented the release data until 100 min as recommended by the reviewer (see the Fig. 4 in page 11).

-Moreover, pH of 8.0 is not gastrointestinal simulated medium, but rather intestinal simulated medium, and therefore, again, the complementary study would lead to wrong results.

**Response**:

-These remarks have been corrected and applied in the text of the Manuscript (p.14).

-The authors also stated that the prepared microspheres were washed several times by using only deionized water (and vacuum), but to the vast experience in making these types of emulsion systems, this is not enough to wash out all the solvents and surfactants out of the microspheres/beads.
 **Response**:

Using solvent evaporation method, the prepared microspheres are washed by using only deionized water (and vacuum) to avoid the risk of breaking the obtained microspheres.

So, that is because there is a risk of breaking microspheres if they are washed with another organic solvent. The use of deionized water for washing the microspheres is in order to overcome the problems of active agent degradation during the process and stability of microspheres after the process.

In addition, the microencapsulation using solvent evaporation method is based on principle steps and was reviewed in detail.43,44 Several researchers21,23,24,31,35-37 have prepared microspheres of various active materials using this technique.

**Oil-in-water solvent evaporation method (o/w):**

In this technique water acts as a non-solvent to the polymer. This method is also known as “in-water drying” developed for encapsulation of drugs and its use with various polymers were reviewed in detail 21,23,24,31,37,43,44. This technique is showing a promising future for drug targeting and throwing challenges to pharmaceutical scientist such as: lower residual solvent potential compared to other processes, scale-up problems, use of non-organic solvents, and the use of deionized water for washing the prepared microspheres to overcome the problems of active agent degradation during the process and after the process.

This technique is based on the evaporation of the internal phase of an emulsion by agitation. Generally, once the emulsion is stabilized, agitation is maintained and the solvent evaporates after diffusing through the continuous phase resulting in solid microspheres. The microspheres are recovered by filtration, washed by deionized water and dried.

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- The title of the manuscript was modified, please see the page 1.

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