**Reviewer A**

**Question: 1.**

It is strongly recommended to check the language throughout the whole manuscript, so please find someone fluent in English to revise the text. There is a lot of missing spaces between the words through the whole manuscript (lines 50, 51, 65, 86, 88, etc.).

**Answer 1: Apply (see paper, page number: 2)**

**Question 2:**

PMMA has been known as non-biodegradable polymer. Therefore, the authors should revise keywords (biodegradable polymers).

**Answer: Apply (see paper, page number: 1)**

Also, it is not clarify why the authors used polymer blends of biodegradable and non-degradable PMMA as polymer matrix for drug loading.

**Answer: We chose PMMA as the matrix because the latter is widely used as a matrix in microncapsulation and we also want to see the effect of the molecular weight of the different PMMA fractions on the release of HCTZ. This is a study already done for other active ingredients studied in our laboratory**

**Question 3:**

It is necessary to make a difference between the terms "efficiency of encapsulation" and "drug loading". It is common in the literature to use those two terms, not loading efficiency.

**Answer: Apply (see paper, page number: 6, 7, 8)**

In the revising document, please try to use integer to present the efficiency of encapsulation, yield, drug loading, diameter size and drug release (for example 94, 60, 71 % or 31 μm, etc.) both in the text and in the tables.

**Answer: Apply in drug release see paper, page number 15, 16, 17)**

**Question 4:**

It is strongly recommended to avoid abbreviations in the Abstract before previous introduction into a full name. Abstract should be contracted and the explanation related to formulation 5 and formulation 7 should be omitted from the abstract since the reader is not informed from this section which samples are 5 and 7.

**Answer: apply (see paper page number 1)**

**Question 5:**

In the Introduction section, sentences "Examples of such as..." from line 50 to line 56 is not clear to me and need to be carefully revised. Abbreviation "BCS" (line 67) need to be clarified.

**Answer: Apply (see paper page number 2)**

**Question 6:**

The Experimental part must be revised and reorganized carefully. Chemicals and materials are the same, so please try to distinguish Materials part from Characterizations.

**Answer :Apply (see paper page number 5, 6 ,7)**

In the supplementary, authors need to add IR and 13C NMR spectra of the synthesized PMMA (three fractions).

**Answer : Apply (see Fig. 6 supplementary materials and Fig. 7 supplementary materials)**

**Note: a slight change of the wavenumber values (spectra FTIR) corrected in the page 5 (change apparatus of FTIR)**

**Question 7:**

It is suggested to the authors not to use numbers for denoting samples and different polymer microspheres since it is demanding to follow the explanations through the manuscript. Further, from the Table I, the difference between samples 4, 5 and 6 (lot 4, lot 5 and lot 6) is not defined, so please organize in the Table I polymers and their characteristics (molecular weight, composition, etc.).

**Answer: Apply (see all papers and page number 5)**

**Question 8:**

In the revised form, the authors need to add structures of drug and all of the used polymers.

**Answer: Apply (see paper page number 4)**

**Question 9:**

In the part Microspheres characteristics, present the equations with abbreviations and its specifications, not with words (line 156 and line 158). It is common to use yield, not a practical yield, so please revise that part. In the equations (3), (4), (5) and (6) all the parameters should be specify below.

**Answer : Apply (see paper page number 6)**

Text written from line 169 to 173 is more appropriate to transfer in the characterization part (equipment).

**Answer: Apply (see paper page number 5, 7)**

**Question 10:**

There is significant influence of polymer matrix type, composition and molecular weight on particles size. It is necessary to better explain this phenomenon, as well as which parameter had the greatest impact on particle size.

**Answer: Apply (see paper page number 9)**

In Table II, superscript "a" was not specifying. Standard deviation of particles diameter must be given in Table II.

**Answer: concerning index "a" it is an error and for the standard deviation of particles diameter (see the paper page 8)**

**Question 11:**

In the part of SEM analysis results, the authors explained the irregular shape of the obtained microspheres with PMMA as followed: "There are forms of sticks in the three batches which may correspond to the PMMA matrix not incorporated in the microspheres." How can be explained this (incompatibility between differences polymers in blends)

**Answer : Apply (see paper page number 9)**

and why the authors did not prepare PMMA-HCTZ microspheres since the all other (EC, PCL, EC/PCL) were prepared.

**Answer : EC was taken as a base polymer and we wanted to compare our results with previous studies**

In addition, the sentence: "However, the microparticles containing EC and β-CD (Fig.1-7) appear spherical, of porous surface and containing powders at the surface which can correspond to the drug." need to be further discussed. What can be the reason of the drug remainance on the particle surface?

**Answer: We redid the size distribution of all batches and found that in L7 are microspheres of small size and the results were checked and corrected in Table II page 8**

**Question 12:**

According to XRD analysis, it is quite difficult to distinguish which characteristic peak in EC/β-CD-HCTZ is coming from polymers and which one from drug since the all three showed very strong peak at about 20o. Thus, for those systems, XRD might not be reliable for the estimation wheather the encapsulated drug is in an amorphous form or not.

**Answer : Apply (see paper page number 9,10, 11)**

**Question 13:**

From the FTIR spectra of drug encapsulated microspheres, it is quite difficult to characterize and analyse peaks. According to presented spectra, the most dominant were the peaks coming from EC polymer due to a higher content in blends.

**Answer :We repeated the FTIR spectra of microspères, HCTZ and polymers (see paper page number 13), is a noted that a slight change of the wavenumber values (spectra FTIR of HCTZ) corrected in the page (11, 12) (change apparatus of FTIR)**

In the FTIR analysis part, the authors claimed that there were no physical or chemical interactions between polymers and drug. From the other hand side, in the XRD analysis part, authors concluded that there was an interaction between HCTZ and EC. Those two completely opposite assumptions must be revised.

**Answer: Apply (see paper page number 12)**

**Question 14:**

The influence of polymer matrix, composition and particle size have to be explained in detail in the part of drug release profiles.

**Answer: Apply (see paper page number 14, 16)**

**Question 15:**

Known that PCL is relatively hydrophobic polymer and that drug could be released preferentially by diffusion from PCL matrix, the sentence from line 292 to 294 (The presence of polymeric carriers such as EC, PCL and β-CD improves the solubility of the microspheres...") should be revised since the PCL would hardly improve solubility of microspheres.

**Answer :Apply (see paper page number 14**

**Reviewer D**

**Question 1:** line 18: an abbreviation of PCL should be introduced

**Answer 1: Apply (see paper page number 1)**

**Question 2.**    line 25: please report the results by controlling the number of digits, i.e. significant figures should only be reported. This note also applies to the other results presented in the manuscript.

**Answer 2: Apply (see paper page number 1, 8)**

**Question 3:** lines 27-28: the sentence ″FTIR and XRD results indicate that the presence of drug and polymers in the microparticle″ is not clear and it needs to be rephrased

**Answer 3: Apply (see paper page number 1)**

**Question 4:** lines 30 – 32: a short description of formulation 5 should be given, additionally, a better release should be replaced with the highest drug release? In this section the authors state that ″The latter is the favorable medium for the dissolution of HCTZ compared with the gastric medium″, which is questionable, and the authors are recommended to check in the literature dissolution testing for dosage forms containing hydrochlorthiazide (e.g. Hydrochlorthiazide Tablets, USP).

**Answer 4: Apply (see paper page number 19); remove from abstract and corrected in the conclusion**

**Question 5:** lines 33-34: the authors state that: ″The results also showed that the pharmacological effect of HCTZ in formulation 7 (lot 7) was increased by solubility improvement promoted by cyclodextrin″, however, in the manuscript there is no description of the method used for estimation of pharmacological effect?

**Answer 5: We mean that the improvement of the solubility of HCTZ, in particular in formulation 7 (EC / β-CD (50/50) -HCTZ) in the medium of pH 7.4 will certainly improve the pharmacological effect due to the HCTZ.**

**Introduction section:**

**Question 1:** Lines 37: KINETIC STUDY OF THE CONTROLLED RELEASE OF HYDROCHLOROTHIAZIDE should be omitted.

**Answer 1: Apply see paper page number 1**

**Question 2:** Lines 52-54: the sentence ″Thus, the use of synthetic biocompatible and biodegradable polymers matrix materials which have been extensively studied and available on the market for the long-term treatment in various applications″ is not clear and it needs to be rephrased.

**Answer 2: Apply see paper page number 2**

**Question 3:** Lines 79-81: in the last sentence of Introduction section the authors state that HCTZ controlled release microspheres were prepared. Taking into account that the main mechanism for controlled drug release from the pharmaceutical point of view was not completely revealed this state should be omitted.

**Answer 3: apply (see paper page number 3)**

**Experimental section:**

**Question 1:** Lines 84-93: data regarding manufactures and suppliers of the chemicals used in experimental work should be checked (e.g. abbreviations, country of origin of purity of chemicals are missing).

**Answer 1: apply (see paper page number 3)**

**Question 2:** Lines 175-179: the authors should give a detailed description of the dissolution testing method (media compositions, description of dissolution apparatus, etc.). Furthermore, the authors should explain, why the dissolution testing was performed in both simulated gastric liquid and simulated intestinal fluid. According to USP, the dissolution should be performed in 0.1 N HCl?

**Answer 2: media compositions (see page 3) , Description of dissolution apparatus: see paper page 7. On the other hand for the choice of the second medium (pH 7.4) it must be said that it is optional for HCTZ; is at least this is done to demonstrate that the rest of undissolved HCTZ in the gastric medium, will certainly be dissolved in the intestinal medium.**

**Question 3** Line 187: the authors are recommended to perform experiments at least in triplicate.

**Answer 3: Sincerely the limited amount of microspheres we have obtained does not allow us to do the kinetics three times and in addition to the characterizations of these microspheres.**

**Results and discussion section:**

**Question 1**: Results of XRD and FTIR analysis should be related to the samples that were the most significant for the aim of this work, which is enhancement of the dissolution profile of hydrochlorthiazide? For instance, the sample 5, which had the highest release is neither presented nor discussed.Additionally, the amorphous state of the drug which is important for drug release kinetics is not adequately discussed.

**Answer 1: FTIR spectrum of L5 is added and the interpretation of HCTZ's amorphocity is discussed in the page 9, 10**

**Question 2:** lines 286-287: the authors should explain why the release time was 500 min?

**Answer 2: we took the time of 500 mm because it is the average stay time in the digestive tract**

**Question 3:** The quality of the figures (legends labelling) should be improved.

**Answer 3: apply**

Section Conclusion:

**Question 1 :** lignes 426-433: cette partie de la Conclusion devrait être modifiée conformément aux remarques précédentes. Les auteurs déclarent que «le taux de libération pourrait être contrôlé en ajustant les polymères sélectionnés et les différents rapports de porteurs», mais puisque dans cet article, les polymères sélectionnés sont utilisés dans un nombre limité de polymère: médicament, être effectué.

**Answer 1: Apply see paper page number 19**

**References section** **1**.  Revised