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OPEN PEER REVIEW

The Impact of Process and Formulation Parameters on the Fabrication of Efavirenz Nanosuspension to Improve Drug Solubility and Dissolution

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1 Original submission

1 comment · 9 Jul 2022

Referee 1 Reviewer

MAJOR REVISION 9 Jul 2022

The manuscript described the preparation and characterization of efavirenz nanosuspensions by the wet milling approach. The study is important esp. in designing products for pharmaceutical industries, and the manuscript is properly written. However, the following issues should be addressed in the revised version:
-Some important factors were screened with the “one factor at the time” approach and some factors were investigated by the Box-Behnken design. As the Box-Behnken design can be used for screening, why did the authors choose two approaches that make the study seem unsystematic? Moreover, the first section is more than a preliminary study. Most of the factors in the first part can be simply investigated by a screening design. In addition to justification, please provide articles that utilize this strategy.
-Please discuss the observed trends in PDI as the factors presented in Fig. 1b change.
-Why was drug content measured by HPLC, while drug concentrations in dissolution and solubility studies, which involve lower concentrations, were quantified with UV spectrophotometry?
-Are there any data available regarding the dissolution profiles in acidic medium (SGF) and SIF?
-It is recommended to analyze the SEM images and report the average size of particles.
-Why did the author not choose CMC concentrations of 0.25% and 0.5%?
Minor comments
-Merge the objective of the study with the introduction.
-Avoid writing results and discussion in the M&M section, e.g., in 3.5.
-Avoid too many subheadings in the results section.
-Many parts of the discussion are descriptions of observed data. Transfer them to the results section, e.g., DSC, FTIR, and XRD.
-The data presented in Figure 2 make the comparison of different surfactants hard. Please revise it to make the comparison much easier.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

RESPONSES TO THE REVIEWERS' COMMENTS:

Reviewer #1

The manuscript described the preparation and characterization of efavirenz nanosuspensions by the wet milling approach. The study is important esp. in designing products for pharmaceutical industries and the manuscript is properly written. However, the following issues should be addressed in the revised version:

Comment:

-Some important factors were screened with the "one factor at the time" approach and some factors were investigated by the Box-Behnken design. As the Box-Behnken design can be used for screening, why did the authors choose two approaches which make the study seems not systematic? Moreover, the first section is more than a preliminary study. Most of the factors in the first part can be simply investigated by a screening design. In addition to justification, please provide articles that utilize this strategy.

Response:

Thanking the reviewer's comment, investigating the effect of different factors on the preparation of nanosuspensions could be carried out by OVAT (one variable at a time) approach as well as experimental methods. In the present study, suitable stabilizers along with primary conditions which could lead to the formation of nanosuspensions were determined using OVAT approach as preliminary studies, and then the three important factors were studied and optimized via experimental design. This is a common process which has also been applied in other researches to select the appropriate preparation conditions as well as the suitable working range for each

variable. In the below references, both OVAT and experimental design have been used by the researchers.

References:

1. Alshora D, Ibrahim M, Elzayat E, Almeanazel OT, Alanazi F. Defining the process parameters affecting the fabrication of rosuvastatin calcium nanoparticles by planetary ball mill. International Journal of Nanomedicine. 2019;14:4625.

2. Patel PJ, Gajera BY, Dave RH. A quality-by-design study to develop nifedipine nanosuspension: examining the relative impact of formulation variables, wet media milling process parameters and excipient variability on drug product quality attributes. Drug Development and Industrial Pharmacy. 2018 Dec 2;44(12):1942-52.

3. Abdelbary AA, AbouGhaly MH. Design and optimization of topical methotrexate loaded niosomes for enhanced management of psoriasis: application of Box–Behnken design, in-vitro evaluation and in-vivo skin deposition study. International Journal of Pharmaceutics. 2015 May 15;485(1-2):235-43.

Comment:

-Please discuss the observed trends in PDI by changing factors that are presented in Fig. 1b.

Response:

This comment was addressed in the manuscript (Line 468-473).

Increment in the bead weight from 6 to 8 g reduced PDI values, reflecting the more uniform size distribution. This could be due to the enhanced collision between the milling beads and EZ particles (50). This phenomena was not observed comparing the bead weights of 4 and 6 g. It is probable that using 6 g beads was not adequate enough to uniformly decrease the size, leading to enhanced PDI values. An almost similar result was observed in an earlier study (51).

Comment:

-Why drug content was measured by HPLC and dissolution and solubility studies that deal with lower drug concentration quantified with UV spectrophotometry?

Response:

According to the efavirenz monograph in USP, the drug dissolution test is based on UV spectrophotometry. Also, UV and HPLC methods were used by Gurumukhi & Bari for dissolution and drug content analysis, respectively.

Reference: Gurumukhi VC, Bari SB. Fabrication of efavirenz loaded nano-formulation using quality by design (QbD) based approach: exploring characterizations and in vivo safety. Journal of Drug Delivery Science and Technology. 2020 Apr 1;56:101545

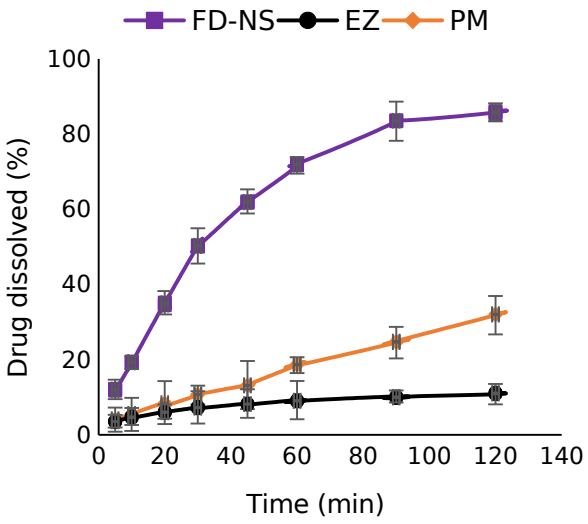
On the other hand, in stability studies, the UV absorption peak of substances resulting from drug decomposition is likely to appear at wavelengths close to the drug in UV spectrum. Therefore, it was more appropriate to use HPLC method in order to determine the exact amount of the drug in the optimized sample before and after stability test.

Comment:

-Is there any data available regarding the dissolution profiles in acidic medium (SGF) and SIF?

Response:

In addition to the SLS aqueous solution (0.1 % w/v), the dissolution of the optimum formulation was studied in the phosphate buffer solution (pH=6.8) containing 0.1 % SLS (Line 236-238). The obtained profiles and the dissolution parameters were represented in Appendices Figure 1 and Appendices Table 5. This was also mentioned in the manuscript (Line 432-434).



Appendices Figure 1. Dissolution profiles of EZ, FD-NS and related PM in phosphate buffer (pH=6.8) containing 0.1 % SLS (n= 3)

Appendices Table 5 Dissolution parameters of the intact drug and prepared formulations in phosphate buffer (pH=6.8) containing 0.1 % SLS (mean ± SD, n=3)

Sample	(%) Q_{30}[a]	(%) DE_{60}[b]	(%) DE_{120}	MDR[c] (%min^{-1})
EZ	1.53 8.77±	8.29 0.09±	0.047 9.62±	0.39 ± 0.064
PM	0.25 17.92±	17.75 ± 0.06	21.98±0.023	0.53 ± 0.03
FD-NS	±0.28 48.25	43.68 0.04±	57.77±0.116	0.99 0.017±

[a]Q_{30}: amount of drug dissolved in 30 min; [b]DE: dissolution efficiency; [c]MDR: mean dissolution rate

Comment:

-It is recommended to analyze the SEM images and report the average size of particles.

Response:

Considering the reviewer's comment, FE-SEM analysis with higher magnification was performed on the dried optimum nanosuspension (Line 216-219), which confirmed the size reduction to a range of less than 500 nm. This was addressed in the manuscript as follows (Line 415-418).

The modification in the morphology and shape of drug particles in FD-NS was obvious in FE-SEM micrographs. The effectiveness of wet milling process in changing the EZ original powder to the submicron particles (less than 500 nm) was also confirmed, which was found compatible with the results of the DLS method.

Comment:

-Why the author did not choose CMC concentrations 0.25% and 0.5%?

Response:

Two different concentrations of CMC (0.25 and 0.5 %) were used in this study. The concentration of 1 % was not used due to the very high viscosity of the solution.

Minor comments

Comment:

-Merge the objective of the study with the introduction.

Response:

The "Objective" was merged with the "Introduction" (Line 104-112).

Comment:

-Avoid writing results and discussion in the M&M section e.g. in 3.5.

Response:

The mentioned section was revised.

Comment:

-Avoid too many subheadings in the result section.

Response:

The manuscript was revised based on the reviewer's comment.

Comment:

-Many parts of the discussion are the description of observed data. Transfer them to the result section, e.g. DSC, FTIR, and XRD.

Response:

The section was revised (Line 392-410).

Comment:

-The data presented in Figure 2 makes the comparison of different surfactants hard. Please revise it in a way to make the comparison much easier.

Response:

Figure 2 was revised based on the reviewer's comment as follows:

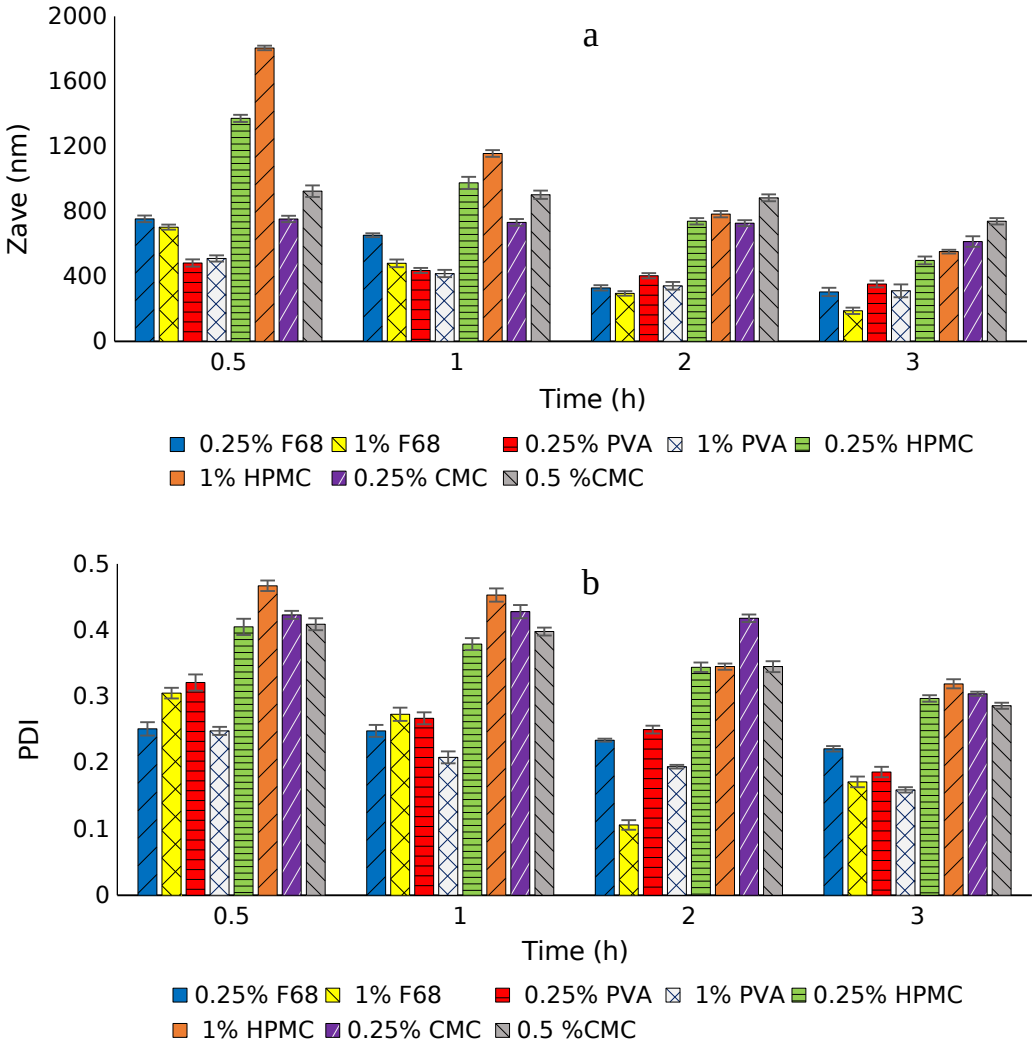


Figure 2. The effect of different stabilizers and their concentrations on the a) particle size and b) PDI of the EZ-NS in different milling times

Reviewer #2

Comment:

It is suggested that the percentage of increase in solubility compared to the normal sample is written in the text of the article (abstract, result and conclusion)

Response:

The increment in the solubility was mentioned in the “Abstract (Line 43), Results (Line 425) and Conclusion (Line 630)” sections.

2 Revision 1

1 comment · 27 Aug 2022

Associate Editor

ACCEPT 27 Aug 2022

I recommend accepting the manuscript as most comments were addressed properly.