**“Response to the Reviewers’ Comments”**

**Dear Prof. Mirjana Kijevčanin**

The revised version of manuscript entitled “**A simple thermodynamic model for predicting the solubility of drug compounds in supercritical CO2**” with manuscript ID “7561” is resubmitted and all the reviewer comments are responded as below. The comments were applied to the manuscript which are highlighted and it helped to improve the quality of our manuscript. We hope it could address all the reviewers’ comments.

Comment 1: Title is too general, it should be more specific: "a simple thermodynamic model"-well known cubic equations of state are used, someone could conclude from the title that the new model was introduced in this work.

Answer to comment 1 (Page 1, lines 1-3): The title has been changed to more specific one as “**A thermodynamic approach for correlating the solubility of drug compounds in supercritical CO2 based on Peng-Robinson and Soave-Redlich-Kwong equations**

**of states coupled with van der Waals mixing rules**”.

Comment 2: Introduction section is too long and too general describing well known theoretical background about supercritical fluid extraction. It contains unnecessary literature review regarding previous modelling (this part should be shortened). On the other hand the purpose of this research is insufficiently justified. Basic data regarding pressure and temperature conditions as well as literature source for experimental data is not provided in this section.

Answer to comment 2 (Page 2, lines 31-40, 49-53, 59-63, and page 3, lines 64-66): The unnecessary contents of introduction and literature review are deleted and this part has been shortened to appropriate content. The purpose of the manuscript has been highlighted in this part and operational conditions of temperature and pressure for modelling of four drug compounds and the basis of experimental data are mentioned.

Comment 3: Every variable of each equation should be defined right after equation if it is mentioned for the first time there.

Answer to comment 3: In Pages 3-6 of revised manuscript, every variable of each equation was defined right after the equation it is mentioned for the first time there.

Comment 4: Lines 120, 126 and 155: What do φ2sat,s and φ2scf stand for? They are not mentioned in any of equations in the manuscript. Also, define same properties consistently, e.g. φ or , , etc.

Answer to comment 4 (Pages 3-5, lines 89, 94 and 134): in line 89 is defined after Eq. (2), and then it is assumed to be equal to 1, due to low vapor pressure of solid compounds. So, it is not mentioned in the following equations. in line 94 is also defined after Eq. (3), which is identical to  in equation (21) on line 134. In fact, we can calculate  from equation (21). Other properties like φ or were also corrected in the revised manuscript.

Comment 5: Line 153: It is not clear what experimental data, at what conditions?

Answer to comment 5 (Page 5, lines 130-131): The experimental conditions of solubility data for four drug compounds were given in Figures I-IV at different temperatures and pressures.

Comment 6: Lines 183-185: it should be specified precisely which methods were used to calculate critical parameters, acentric factor, vapour pressure (all the parameters from Table II).

Answer to comment 6 (Page 6, lines 163-168):Critical temperature and pressure were estimated using the group contribution method presented by Joback. Other properties like molecular weight, density and molar volume of solid compounds were taken from Merck Millipore site based on their CAS numbers. Acentric factor and vapor pressure values were also estimated using Ambrose-Walton corresponding-state method.

Comment 7: Table I: Which conditions (temperature and pressure) are presented density data related to? Specify the literature source?

Answer to comment 7 (Page 6, lines 165-167):Density data are related to conditions of 20 °C and atmospheric pressure and are found from Molbase Chemical E-commerce Platform site based on their CAS numbers.

Comment 8: In all tables the number of significant digits is too large.

Answer to comment 8 (Page 8):The number of significant digits in Table III were rewritten based on four decimal digits. Other Tables were changed to figures in the revised manuscript.

Comment 9: For some systems the correlation results obtained with vdW1 are better that for vdW2 which is not logic, at least the same correlation quality should be obtained? Please, explain it or check it again.

Answer to comment 9 (Page 8):After rechecking the results, only two sets of the data, one for Cetrizine at 338.15 K and another for Metaxalone at 308.2 K were inserted wrongly in the previous manuscript. It means that %AARD for PR vdW1 for Cetrizine is 15.4744 and for PR vdW2 is 6.9122. For Metaxalone, %AARD for PR vdW1 is 5.2235 and for PR vdW2 is 5.1620. For all other sets of data the %AARD for vdW2 mixing rule is less than that related to vdW1 mixing rule as they should be.

Comment 10: Line 205: "These results confirm that the given solution model yielded satisfactory accuracy for solubility **prediction** of solid drugs". In my opinion the solubilities were correlated not predicted. Namely, you correlated experimental data to obtain solubilities. If you used the obtained interaction parameters to calculate solubilities at other conditions, e.g. temperatures then it would be prediction.

Answer to comment 10 (Page 7, line 191):It is absolutely true. So, the term of “prediction” was replaced by “correlation”.

Comment 11: Table III Caption: “***Optimum*** values of binary interaction parameters...” should be corrected, e.g. “*Optimized* values of binary interaction parameters...”

Answer to comment 11 (Page 8, line 199):The word “Optimum” is replaced by “Optimized” in the caption of table III.

Comment 12: Lines 210-215: The paragraph is a bit unclear, it should be revised.

Answer to comment 12 (Page 7, lines 193-195 and page 8, lines 196-198):This paragraph is revised in the new submitted manuscript as below:

In the case of benzamide, %AARD is higher at 328 K than other temperatures. This is due to the fact that more important factors like molecular weight and molecular interaction of solid compound affect the non-ideality of system. Therefore, a less accuracy for solution model could be expected at these specific temperatures. Since the base of present approach is theoretical and factors such as physical and thermodynamic properties of compounds would affect the calculation results, the accuracy is lower at some desired conditions.

Comment 13: The significance of the proposed semi-empirical model, Eq. (32), should be explained better:

* lines 228 to 235 should be given as a new paragraph,
* line 229 "... different solid compounds" - someone could conclude that the modeling was done for completely different compounds, be specific regarding the compounds and conditions as well
* define r2; the values of r2 are not given in the Table VIII?
* line 243 - for which compounds the AARD are given? It is not clear.
* the discussion is very confusing and rather vague (see comment 16)

Answer to comment 13 (Page 11, lines 245-247):The below paragraph is added to show the significance of semi-empirical equation.

“This semi-empirical equation is useful for prediction of the solubility of these four solid compounds in supercritical CO2 at desired temperatures and pressures without need of performing additional experiments.”

* (Page 11, lines 239-240):Lines 228-235 in previous manuscript has been given a new paragraph.
* (Page 11, lines 239-240):It is specified that semi-empirical correlation is valid only for four solid compounds investigated in this study.
* (Page 11, lines 244-245):r2 is defined as R-squared value for regression of an equation. Its values for all of semi-empirical equations for four compounds are given in Table IV.
* (Page 12, lines 253-254):The AARD values for four compounds are specified precisely. “The AARDs for benzamide, cetirizine, metaxalone and niflumic acid are 2.71%, 18.56%, 18.09% and 6.52%, respectively.”
* (Pages 7-12):The discussion section has been revised.

Comment 14: Table VIII caption: Equation number (32) should be added to the Table caption to make it clearer.

Answer to comment 14 (Page 15):Equation number (32) is added to the table caption.

Comment 15: Conclusion section should be changed. The first sentence is confusing, in this work the well known PR and SRK cubic eqs were used, which thermodynamic model was proposed? Be more precise about the T and P conditions (line 265). The sentence "*The AARD% reported are acceptable and hence we can conclude that the proposed thermodynamic model for these solids can be trusted and used for* ***prediction of the solubility of solids****, especially drug compounds in supercritical CO2 at different pressures and temperatures*." is, in my opinion, misunderstanding. Have you tried to predict solubilities or just to correlate? The last sentence is also not clear, it is just an assumption and general statement not supported by the obtained results.

Answer to comment 15 (Page 16):All of the notes you mentioned in this comment have been taken into consideration and all the corrections are made in the conclusion section of the manuscript which are highlighted in the revised paper.

Comment 16: Discussion of the obtained results is pretty poor with a lot of repetition and general - not confirmed statements, so that section should be revised and enriched. Also, some figures are given in the Supplementary material but these figures are not mentioned at all in the text.

Answer to comment 16 (Pages 7-12):The “Results and Discussion” section of the manuscript has been rewritten and all the new content has been highlighted in yellow.

Comment 17: The manuscript lacks graphical representation of the results (for example the data given in tables IV-VII should be presented graphically and Tables IV-VII should be omitted from the manuscript or moved to the Supplementary material).

Answer to comment 17 (Pages 9, 10, 13 and 14):Tables IV-VII are omitted and replaced with Figures I-IV for better representation of the results graphically.

Thank you for your helpful suggestions. All changes according to above comments are highlighted in the manuscript.

We are thankful for giving us an opportunity to revise our manuscript.

Sincerely,

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