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

**Dear Prof. Mirjana Kijevčanin**

The revised version of manuscript entitled “**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**” 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: The last part of the Introduction section starting from line 66 should not stand at the end of this section and can be moved above (before the part explaining what has been done in this work).

Answer to comment 1 (Page 2, lines 49-59): The last part of the Introduction section was moved before the part explaining what has been done in this work.

Comment 2: In Figures I to IV provide literature source for experimental data.

Answer to comment 2 (Pages 10, 11, 14 and 15, Figures I, II, III and IV): The literature source for experimental data were provided in the captions of Figures I to IV.

Comment 3: I do not understand the discussion given in lines 194-198, e.g. in which way the molecular weight can influence the non-ideal behavior at different temperatures? Also, the last sentence in that paragraph is unclear, be more precise which physical and thermodynamic properties could affect the accuracy of the calculation results?

Answer to comment 3(Pages 7 and 8, lines 194-218): It was discussed again on Pages 7 and 8, Lines 194-218.

Comment 4: Line 245: Table IV instead of VIII?

Answer to comment 4 (Page 12, line 275): Table VIII was replaced with Table IV.

Comment 5: I believe that the discussion given in lines 248-265 is not correct:

- In my opinion the statement "As it can be seen, the semi-empirical equations yield smaller average deviations than the present solution approach and the results are in good agreement with experimental data." (Lines 254-256) is not true. If someone compares the results obtained by CEOS models (Table III) and polynomial eq 32, for example for cetirizine, metaxalone and niflumic acid it is obvious that the average deviations at all temperatures and pressures are lower for the CEOS models than by the eq 32?

- Have you considered all experimental points since the number of experimental points in Figures I to IV is not the same as in the Tables III and IV?

- The obtained AARDs differs a lot for different compounds. Do you have any explanation for big differences in correlation results by polynomial eq 32. It should be discussed in the manuscript.

Answer to comment 5: (Page 13, lines 286-299): This part of discussion is corrected as below:

“Here, a single semi-empirical equation was used to show the minimum %AARD for all four solid compounds of this study. However, due to different properties of drug compounds, two of them showed higher errors than the others. If for each compound a separate equation is proposed, less %AARD is certainly obtained.

As it can be seen, the results of the semi-empirical equation are in good agreement with experimental data. However, for benzamide, the semi-empirical equation yields smaller average deviations than the present solution approach. In the case of niflumic acid, the amounts of errors for semi-empirical equation and solution approach are close to each other. For two other solid compounds, namely cetirizine and metaxalone, the deviations for solution approach are less than the proposed equation. Although a semi-empirical equation is less theoretical consideration and has the lack of generalization and limited application, in the absence of experimental data at different temperatures and pressures, and due to high expense and time-consuming experiments, the proposed equation can be used to correlate the solubility of solid compound in supercritical CO2 with fairly acceptable accuracy.”

* (Page 13, lines 286-289): The experimental data for benzamide are 5 points for each of three temperatures. So, the total number of points are 15. The experimental data for cetrizine are 7 points for each of four temperatures. So, the total number of points are 28. The experimental data for metaxalone and niflumic acid are 7 points for each of three temperatures. So, the total number of points for each compound are 21. The number of experimental points in Figures I-IV are exactly the same as Tables III and IV.

Here, a single semi-empirical equation was used to show the minimum %AARD for all four solid compounds of this study. However, due to different properties of drug compounds, two of them showed higher errors than the others. If for each compound a separate equation is proposed, less %AARD is certainly obtained.

Comment 6: My question related to the last sentence of conclusion section: Have you tried to predict solubilities of other drugs by using the obtained parameters. When you confirm this statement you can include it in this section, otherwise this sentence should be omitted from the manuscript.

Answer to comment 6 (Page 17): We have not used this equation to predict the solubilities of other drug compounds. It meant that a separate equation can be presented for other drugs in a similar way to our method to predict their solubility in supercritical CO2. The mentioned sentence is corrected in the manuscript.

Comment 7: SI units should be used.

Answer to comment 7 (Pages 7, 9, 11, 12, 14 and 15):All units were converted to SI throughout the revised manuscript.

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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