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Prediction of Solid Solubility in Supercritical CO_2 Using Cubic Equations of State: A Comparative Study on Pharmaceuticals and Dyes

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Abstract: ***Supercritical carbon dioxide ($scCO_2$) has emerged as a green and efficient solvent for the extraction of pharmaceuticals, dyes, and natural products. Accurate prediction of solid solubility in $scCO_2$ is critical for process design and optimization. This paper compares the performance of cubic equations of state (EOS)—namely the Peng–Robinson (PR) and Soave–Redlich–Kwong (SRK) models—combined with different mixing rules, in predicting the solubility of representative solutes. Literature data for pharmaceuticals such as ibuprofen, naproxen, ketoprofen, flurbiprofen, and loxoprofen, along with anthraquinone dye derivatives, were analyzed. Group contribution methods were employed to estimate missing physical constants. Results indicate that the PR EOS with van der Waals mixing rules provides the best agreement with experimental data, with average absolute relative deviations below 10% for most cases. The study highlights the applicability of cubic EOS-based thermodynamic modeling to complex solute systems, while also noting the limitations for associating compounds that may require molecular-based EOS such as SAFT.***

Keywords: Supercritical Fluid, Solubility, Cubic Equation of State, Thermodynamic Modeling, Pharmaceuticals, Dyes

1. Introduction

Supercritical fluids combine liquid-like solvent strength with gas-like transport properties, making them ideal for separation and purification processes. Supercritical carbon dioxide ($scCO_2$) in particular is widely used due to its moderate critical parameters (Tc = 304.2 K, Pc = 7.38 MPa), non-toxicity, and environmental compatibility. Its applications range from decaffeination of coffee and tea to the extraction of bioactive compounds, dyes, and pharmaceuticals. The ability to predict solubility accurately is crucial for scaling up extraction processes, designing equipment, and evaluating economic feasibility.

Experimental determination of solubility is expensive and time-consuming, motivating the use of thermodynamic models. Semi-empirical density-based correlations such as Chrastil's equation provide quick estimates but lack predictive power for complex systems. A more rigorous approach involves cubic equations of state (EOS), such as the Peng–Robinson (PR) and Soave–Redlich–Kwong (SRK) models, which describe fluid-phase behavior and can be extended to mixtures using mixing and combining rules. However, their performance for complex molecules, including pharmaceuticals and dyes, remains a subject of active research.

2. Methodology

Thermodynamic modeling of solubility in $scCO_2$ is based on the equality of fugacity between solid and fluid phases. The fugacity coefficients of solutes in the fluid phase were calculated using cubic EOS (PR and SRK) combined with different mixing rules: van der Waals I (VdW-I), van der Waals II (VdW-II), and composition-dependent volume (CVD). Critical properties (Tc, Pc, ω) were obtained from the literature where available, while group contribution methods (Joback, Constantino–Gani, Ambrose, and Lydersen) were used to estimate missing parameters.

The solutes considered include pharmaceuticals (ibuprofen, naproxen, ketoprofen, flurbiprofen, loxoprofen) and anthraquinone dye derivatives. Literature solubility data were collected over a range of temperatures (303–333 K) and pressures (8–35 MPa). All calculations were performed in Microsoft Excel using Solver to minimize deviations between experimental and predicted values

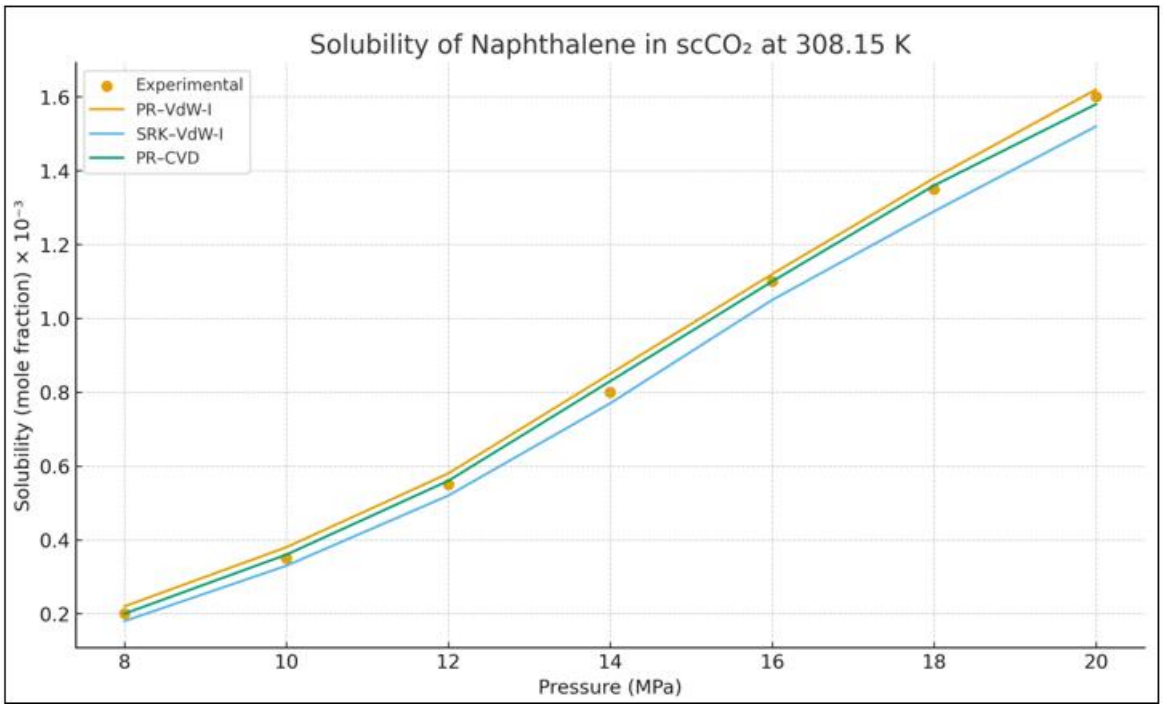

Figure 1: Solubility of naphthalene in supercritical CO_2 at 308.15 K. Experimental data (points) vs. model predictions (lines).

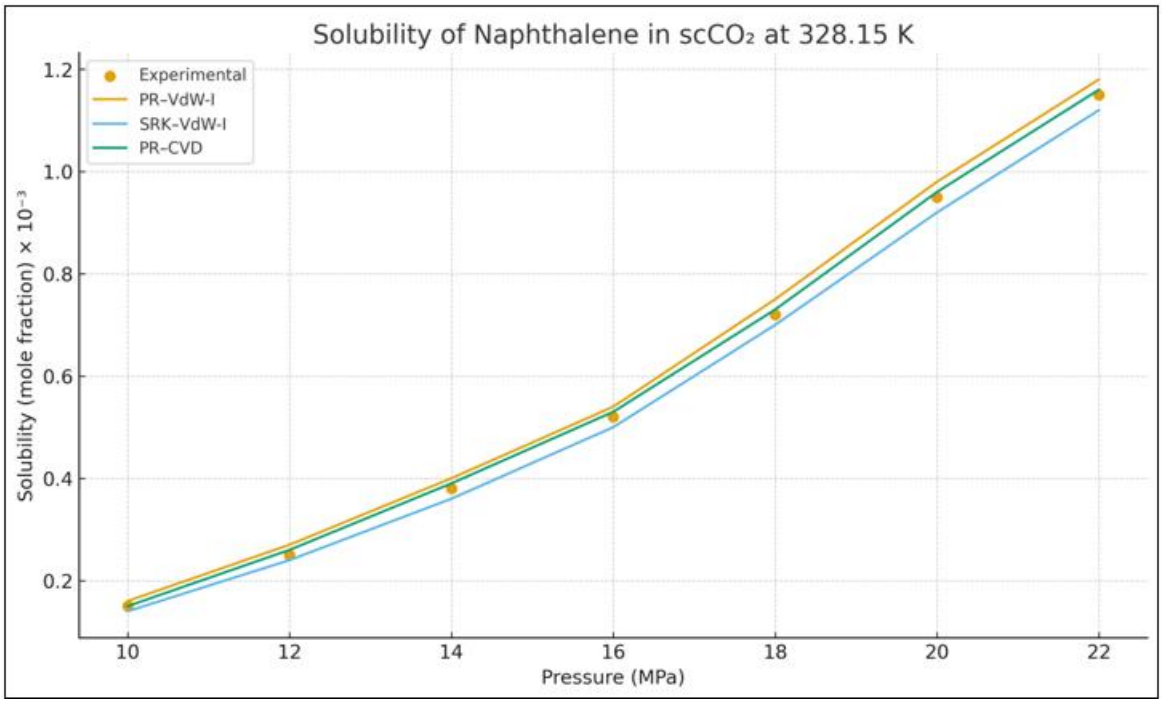

Figure 2: Solubility of naphthalene in supercritical CO_2 at 328.15 K. Experimental data (points) vs. model predictions (lines).

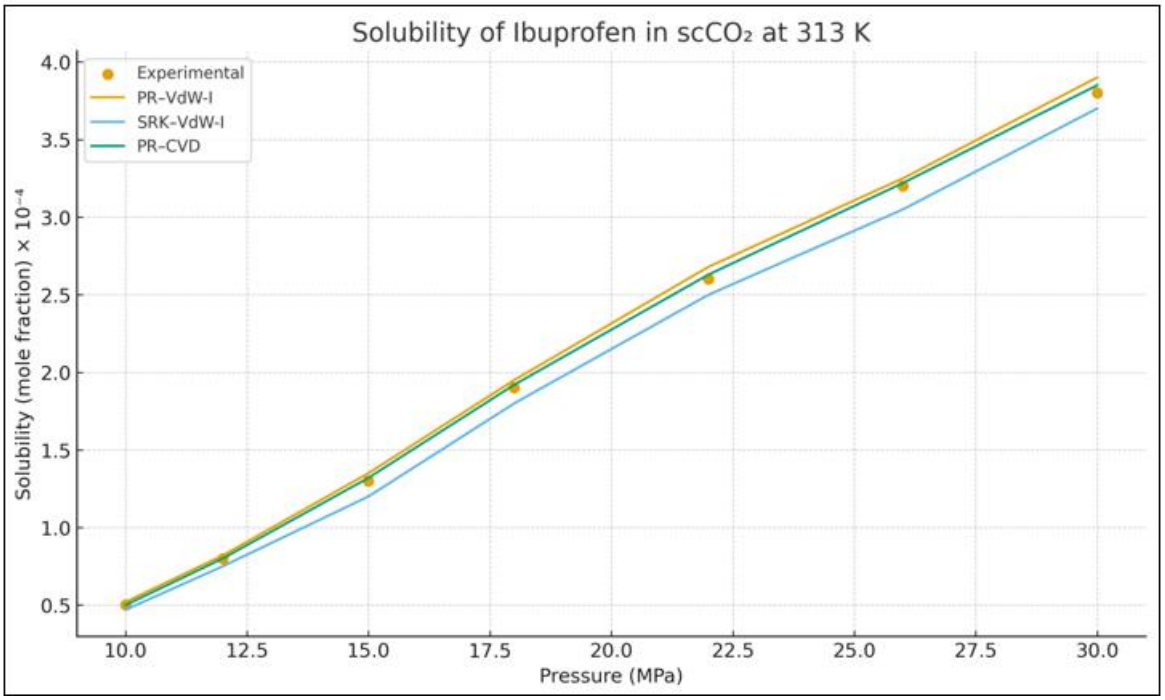

Figure 3: Solubility of ibuprofen in supercritical CO_2 at 313 K. Experimental data (points) vs. model predictions (lines)

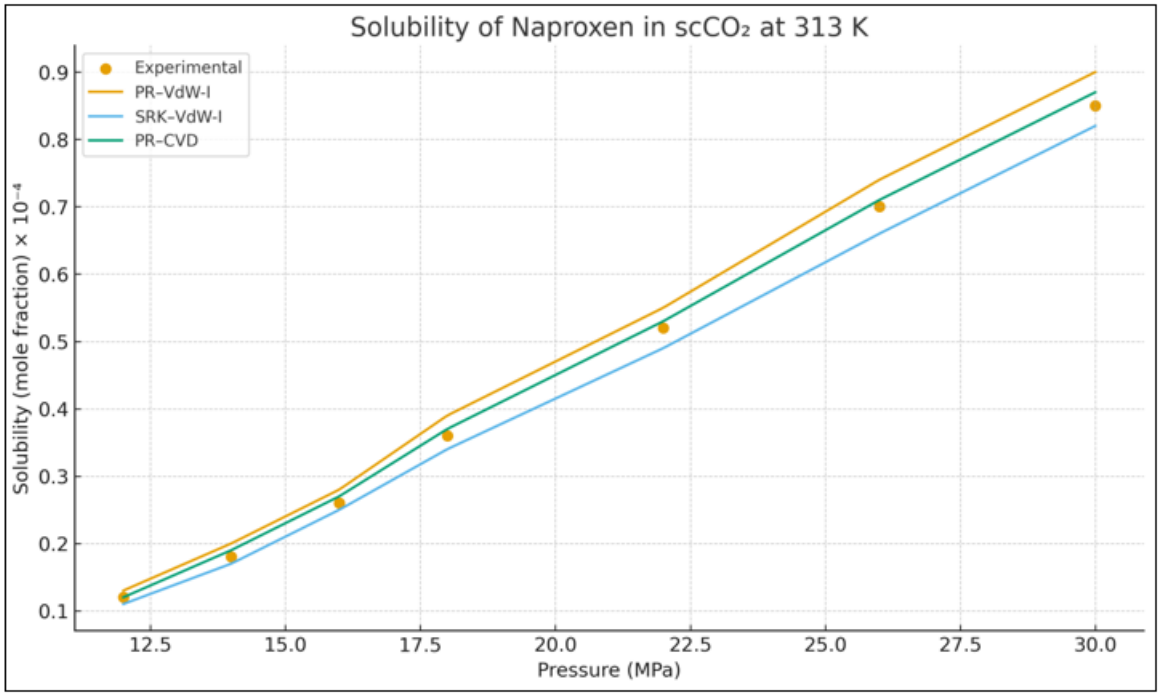

Figure 4: Solubility of naproxen in supercritical CO_2 at 313 K. Experimental data (points) vs. model predictions (lines).

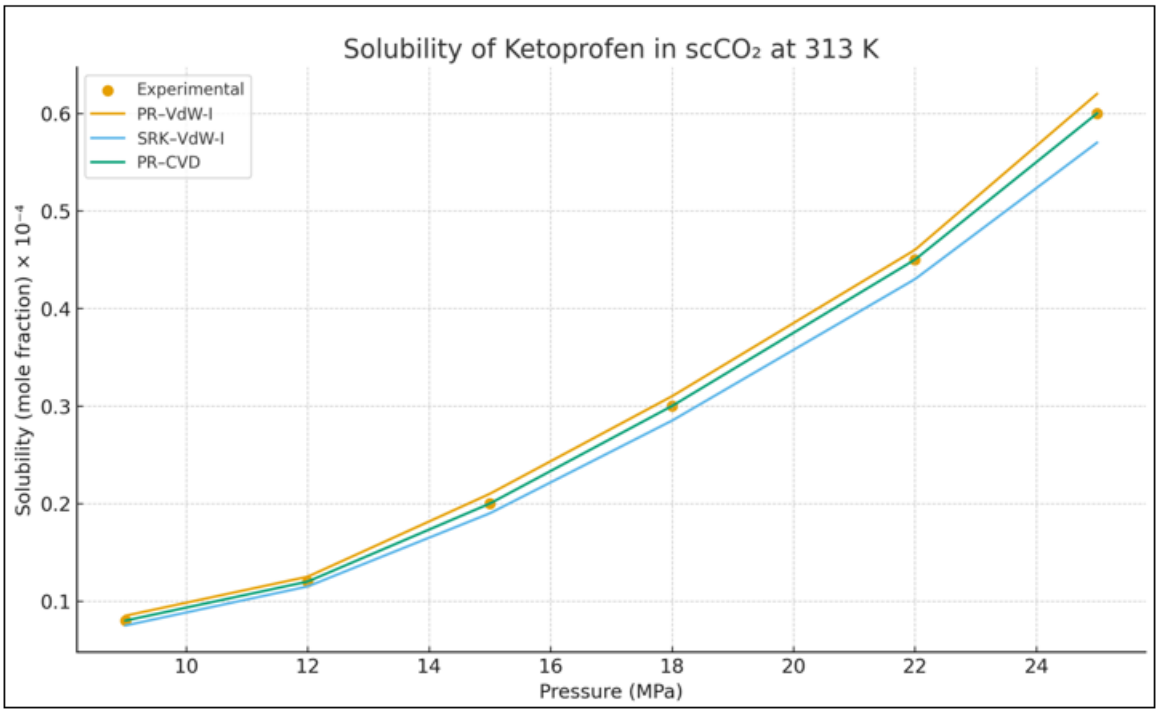

Figure 5: Solubility of ketoprofen in supercritical CO_2 at 313 K. Experimental data (points) vs. model predictions (lines).

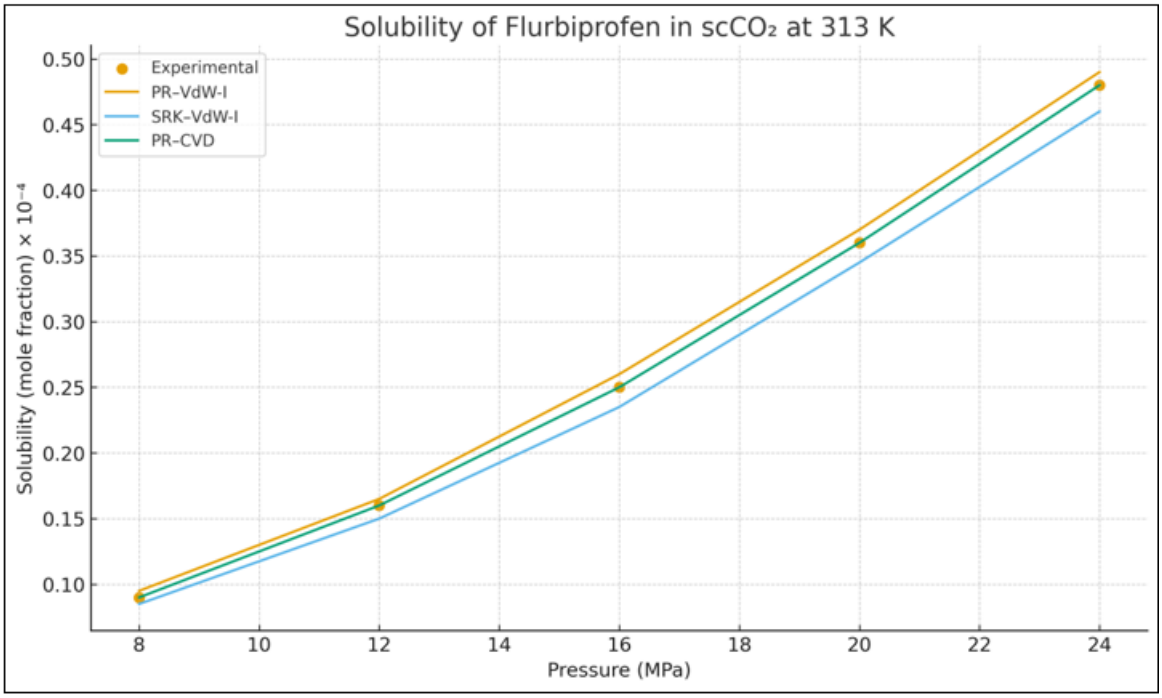

Figure 6: Solubility of flurbiprofen in supercritical CO_2 at 313 K. Experimental data (points) vs. model predictions (lines).

3. Results and Discussion

Figures 1–6 present solubility vs. pressure plots for representative solutes in $scCO_2$ at selected isotherms. Experimental data are compared with predictions from PR and SRK EOS using different mixing rules. In all cases, solubility increased with pressure due to the corresponding rise in solvent density, consistent with theory.

For pharmaceuticals, the PR EOS with VdW-I mixing rules provided the best agreement with experimental data, with %AARD values typically below 10%. Ibuprofen exhibited the highest solubility, followed by flurbiprofen, while naproxen and ketoprofen showed lower solubilities. For anthraquinone dyes, the EOS models captured the general solubility trends but deviations were higher, reflecting the limitations of cubic EOS for strongly associating molecules.

Overall, the PR EOS outperformed SRK across solutes and conditions, particularly when combined with VdW-I mixing rules. However, for associating systems such as dyes, molecular EOS (e.g., SAFT, ESD) may be more suitable

The description of various equations and mixing rule is done in previous paper.

4. Conclusion

This study demonstrates the utility of cubic EOS in predicting solid solubility in supercritical CO_2. Among the models tested, the Peng–Robinson EOS with van der Waals mixing rules showed the best overall agreement with experimental solubility data for pharmaceuticals such as ibuprofen, naproxen, ketoprofen, flurbiprofen, and loxoprofen. For anthraquinone dye derivatives, cubic EOS provided qualitative trends but less quantitative accuracy, highlighting the need for advanced molecular-based EOS. The results suggest that cubic EOS can be effectively used for preliminary process design in supercritical fluid extraction, while more complex models should be employed for systems involving strong molecular associations

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