International Journal of Thermodynamics (IJoT)
ISSN 1301-9724 / e-ISSN 2146-1511
https://dergipark.org.tr/en/pub/ijot

Vol. 27 (No. 1), pp. 064-071, 2024
doi: 10.5541/ijot.1338341
Published online: March 1, 2024

Research Article

Thermodynamic Modeling of Solubility of Some Antibiotics in Supercritical Carbon Dioxide Using Simplified Equation of State Approach

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Received 5 August 2023, Revised 18 November 2023, Accepted 7 January 2024

Abstract

Antibiotics are playing crucial role in the treatment of humans since the last few centuries. Their usage has several benefits along with side effects. The efficacy of antibiotics for the treatment of ailments may be retained by controlling the drug dosage. This may be achieved with supercritical fluid technology (SFT). The antibiotic drug solubility in supercritical carbon dioxide ($scCO_2$) is available only at specific temperature and pressure conditions, for effective utilization of SFT, solubility at various conditions are required. Equation of state (EoS) method is used for solubility data modeling and it requires critical properties of the solute, molar volume of the solute and sublimation pressure of the solute along with fugacity coefficient, pressure and temperature. These properties are estimated using group contribution methods. For antibiotics solute critical properties, molar volume and sublimation pressure are unavailable and existing group contribution methods are also not applicable due to the lack of functional group contributions in their techniques. Thus, there is a need to address EoS methodology without using solute properties. Hence, a new EoS methodology for solubility modeling is, proposed without using critical properties of the solute, molar volume of the solute and vapour pressure of the solute. Thus, this study focuses on the development of new solubility model that correlates antibiotics using equation of state (EoS). Importantly, the proposed solubility model does not use the critical properties of the antibiotics. Correlating ability of the proposed model is indicated in terms of regression coefficient and arithmetic average relative deviation percentage (AARD %).

Keywords: *Antibiotics; equation of state; solubility; supercritical carbon dioxide.*

1. Introduction

The use of carbon dioxide as a supercritical solvent has replaced various organic solvents in the pharmaceutical industry [1]. Particle formation steps depend on the ability to quickly change the solvent power of dissolved chemicals and, consequently, the rate of super saturation and nucleation [1-4]. This is possible due to the ease of tuning pressure, physical properties, and the solvent power. Additionally, $scCO_2$ is a perfect medium for pharmaceutical applications since it has a low critical temperature, is non-toxic and non-flammable, and it leaves the system residue-free after decompression [5,6]. Despite the high expenses involved in processing pharmaceutical compounds under high pressure, which significantly increases the value of the finished goods, this kind of technology is more environmentally friendly because it does not use organic solvents. The creation of new particle micronization techniques has increased over the last few decades, encouraging the implementation of supercritical technology to in the field of pharmaceutical industry [2]. Broadly, micronization techniques fall under two categories, namely, rapid expansion of supercritical saturated solution and its extended methods as well as supercritical anti solvent process and its extensions [7,8]. These methods involve the creation of a supersaturated solutions which are exploited for crystallisation and thereby particle formation [6,7]. To understand and implement these processes, a thorough knowledge of the solubility of drug solute in the supercritical solvent is essential. But limited data is available only at specified conditions, thus, it is impossible to get experimental data at every desired condition. This creates the need for a good model that represents the solubility. Due to the high non linearity prevailing in the available solubility data, it is difficult to represent data in a single model effectively [9.10]. However, to address this complexity, several frameworks have evolved. Notable frameworks are, phase equilibrium models and density models [10,11,12,13]. Among the phase equilibrium models, Equation of state (EoS) models and expanded liquid models are effective in data correlation. To implement the phase equilibrium models, critical properties of the solute and the solvent are required [10,14,15,16]. Density models are quite simple and require only the pressure, temperature, and density of solvent. If all the

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necessary data is available, both the methods perform satisfactorily for several solute-supercritical solvent combinations [10]. Unfortunately, the experimental and group contribution based critical properties of the drug solutes are unavailable [17]. Thus, usage of EoS methods for drug- supercritical solvent systems has become limited. Therefore, in this work, we have proposed a modification to EoS based solubility model that requires only the pressure, temperature, and density of the solvent like that of the density models [18-22]. More details can be seen in the following sections.

2. Modeling

The use of EoS modeling in correlation of solubility of drugs in supercritical carbon dioxide is sought-after in literature. Amongst the several EoSs available, Redlich-Kwong (RK) EoS, Soave-Redlich-Kwong (SRK) EoS and Peng-Robinson (PR) EoS are the vividly used equations of state [23,24]. Amid the three, PR EoS correlates better for the solubility modeling, thus, it is persuaded here[25,26].

2.1 Thermodynamic Modeling

Solubility is expressed as [23,24],

$$y_2 = \frac{p_2^S \hat{\varphi}_2^S}{P\hat{\varphi}_2^{ScF}} exp\left[\frac{(P-p_2^S)v_2}{RT}\right] \quad (1)$$

where the parameters have their usual definitions, the subscript 2 stands for the solute. For modeling, fugacity coefficient at saturation for the solid is assumed unity. $\hat{\phi}_2^{scf}$ is evaluated with PR EoS with the following thermodynamic relation as [20,21].

$$\ln(\hat{\phi}_2^{scf}) = \frac{1}{RT}\int_v^\infty \left[\left(\frac{\partial P}{\partial n_2}\right)_{T,v,n_1} - \frac{RT}{v}\right] dv - \ln(Z) \quad (2)$$

The obtained fugacity coefficient is

$$\ln(\hat{\phi}_2^{scf}) = \frac{\hat{b}}{b}(Z-1) - \ln\left(Z\left(1-\frac{b}{v}\right)\right) + \frac{a}{2\sqrt{2}RT}\left[\frac{\hat{a}}{a} - \frac{\hat{b}}{b}\right]\ln\left(\frac{Z-0.414b}{Z+2.414b}\right) \quad (3)$$

vdW mixing rules are

$$a_{12} = (1-k_{12})\sqrt{a_{aa}a_{22}} \quad (4)$$

$$b_{12} = (1-l_{12})\left(\frac{b_{11}+b_{22}}{2}\right) \quad (5)$$

The equations (1) and (5) are combined for the solubility evaluation as

$$y_2 = f(a_1, b_1, a_2, b_2, P, T, p_2^s, \hat{\varphi}_2^{SCF}, k_{12}, l_{12}) \quad (6)$$

More details about PREoS and vdW mixing rules is reported in literature [23,24]. The major limitations in evaluating equation (6) lie in the determination of critical properties, molar volume, and the sublimation pressure of the antibiotics (solute). These properties are estimated using group contribution methods. For antibiotics (solute) critical properties, molar volume and sublimation pressure are unavailable and existing group contribution methods are also not applicable due to the lack of functional group contributions in their techniques [23]. Thus, there is a need to address EoS methodology without using solute properties. Hence, a new methodology in EoS frame work is inevitable.The following subsection deals with the new methodology and it can be used for any EoS along with suitable mixing rules.

2.2 New Methodology

The limitations mentioned in section 2.1 may be subjugated by treating the solute's parameters a_2 and b_2 as adjustable constants(keeping k_{12}, l_{12} as zero), replacing sublimation pressure with suitable temperature function, *f*(T)(as it is a function of temperature),replacing molar volume of the drug with the suitable $scCO_2$density function, $g(\rho_1)$ (since it can be expressed as a function of solvent density) and replacing$\hat{\varphi}_2^{scf}$ estimated at infinite dilution with $\hat{\varphi}_2^{\infty}$[25-27]. Thus, the solubility expression is

$$y_2 = \frac{f(T)}{P\hat{\varphi}_2^{\infty}} \exp\left(\frac{(P - f(T))g(\rho_1)}{RT}\right) \quad (7)$$

where, $f(T) = \exp(A - B/T)$; $g(\rho_1) = \exp(C\ln(\rho_1) + D)$

Optimization is done with the following objective function eq.(8) [25]

$$OF = \sum_{i=1}^{N} \frac{\left|y_{2i}^{\exp} - y_{2i}^{cal}\right|}{y_{2i}^{\exp}} \quad (8)$$

where N is the number of solubility data points. Evaluation was carried in MATLAB® platform with the help of built in function (*fminsearch*)that uses Neldar-Mead algorithm. The adjustable parameters in the solubility model are a_2, b_2, A, B, C and D.This study can be used conveniently when solute's properties such as molar volume, critical properties, and sublimation pressure are unavailable.

3. Results and Discussion

In this work, fourteen antibiotics' belonging to different classes with their solubilities in $scCO_2$ were considered [29-37]. These drugs are proved to be highly beneficial in the treatment of several ailments. On the other hand, these drugs have adverse effects too. The details of the drugs, their classes, chemical formulae, molecular structure along with their adverse effects are mentioned in the literature. The solubility, temperature, and pressure ranges for all the drugs considered in the study are shown in table 1.The proposed new methodology resulted in a simplified EoS solubility model (eq.7) and it is evaluated using an objective function (eq.8) with PREoS and vdW mixing rules without binary interaction parameters. The correlation constants are given in the table 2. The correlation results are quantified with statistical parameters namely square of coefficient of regression (R^2) and absolute average relative deviation (AARD). The correlation results also provide information about the molar volume of the solute and sublimation pressure and they are presented in the table 3 and 4 respectively. Molar volume of the solute is calculated with $v_2 = \exp(C\ln(\rho_1) + D)$ and the sublimation pressure is calculated with $\ln(p_2^s) = A - B/T$. Figures 1-14 show the

correlating ability of the proposed EoS model for all the drug compounds considered in the work. It is evident that the correlating ability of the proposed method is good for seven systems namely Amoxicilin-scCO$_2$,ciprofloxacin-scCO$_2$, clarithromycin-scCO$_2$, clemastine fumarate-scCO$_2$, enrofloxacin-scCO$_2$, gatifloxacin-scCO$_2$ and penicillin V-scCO$_2$.For all these systems the corresponding R^2values are more than 0.95 thus, they are considered as correlated well. For remaining 7 systems theR^2values are less than 0.95 thus they are considered as poorly correlated. However, in terms of AARD % the error are in the range between 4.78- 25.1 for compounds considered in the study.

Table 1. Details of Antibiotic-scCO$_2$systems.

Solute-Solvent[Ref]	T range K	P range bar	y_2 range 10^6
Amoxicilin-scCO$_2$[32]	308.15-338.15	160-400	10.8-7230
Azithromycin-scCO$_2$[33]	308-348	122-355	69-273
Cefuroxime Axetil-scCO$_2$[29]	308-328	80-250	0.22-11.2
Ciprofloxacin-scCO$_2$[37]	313-333	120-360	0.0265-0.189
Clarithromycin-scCO$_2$[33]	308-348	122-355	131-328
Clemastine Fumarate-scCO$_2$[36]	308-338	120-270	1.61-9.41
Clindamycin-scCO$_2$[33]	308-348	122-355	177-1146
Enrofloxacin-scCO$_2$[37]	313-333	120-360	0.061-5.61
Erythromycin-scCO$_2$[33]	308-348	122-355	54-312
Gatifloxacin-scCO$_2$[37]	313-333	120-360	0.106-1.61
Metronidazole Benzoate-scCO$_2$[35]	308-348	122-355	70-4550
Naproxen-scCO$_2$[35]	308-348	122-355	10-120
Penicillin G-scCO$_2$[30]	313.15-333.15	100-350	4.2-63.3
Penicillin V-scCO$_2$ [31]	314.15-334.15	80.76-280.45	54.5-576

Table 2. Correlation parameters.

Solute-Solvent	Correlation parameters $a_2, b_2, A, B, C, D, R^2$,AARD%
Amoxicilin-scCO$_2$	1.9816×10^{-3}; 2.5422×10^{-3}; 58.604; 39417; 0.36186; -8.3132; 0.987;18.6.
Azithromycin-scCO$_2$	1.9708×10^{-4}; 3.1006×10^{-4}; 14.422; 4621.2; 0.29283; -9.7727;0.953;5.94.
Cefuroxime Axetil-scCO$_2$	7.6968×10^{-4}; 1.3046×10^{-3}; -15.049;6672.7; -0.30725; -4.1811;0.992;2.51.
Ciprofloxacin-scCO$_2$	2.1401×10^{-3}; 5.3582×10^{-4}; 17.654; 8733.4e+03; 0.32084; -10.688;0.971,8.72.
Clarithromycin-scCO$_2$	9.4354×10^{-5}; 2.3627×10^{-4}; 14.159; 3778.9; 0.48557; -11.257e+01;0.944;4.78.
Clemastine Fumarate-scCO$_2$	1.0560×10^{-4}; 1.5823×10^{-4}; 14.579; 4718.6; 0.48706; -11.139e+01;0.945;7.32.
Clindamycin-scCO$_2$	2.5866×10^{-4}; 3.3511×10^{-4}; 20.7; 6480.8; 0.53272; -11.346e+01; 0.93;10.8.
Enrofloxacin-scCO$_2$	1.6022×10^{-3}; 2.3258×10^{-3}; -11.509; 17995; 0.43952; -2.8189;0.971;9.04
Erythromycin-scCO$_2$	4.7026×10^{-5}; 3.7179×10^{-4}; 16.484; 6243.7; 0.32607; -9.6460;0.924;12.2.
Gatifloxacin-scCO$_2$	3.7132×10^{-4}; 9.1555×10^{-4}; 1.7970; 9276.6; -0.527; -2.9693;0.964;9.42
Metronidazole Benzoate-scCO$_2$	2.2778×10^{-4}; 9.1954×10^{-4}; 2.4213; 7480.8; 0.53416; -2.8445;0.85;19.5
Naproxen-scCO$_2$	6.1199×10^{-5}; 7.0094×10^{-4}; 1.1112; 6124.1; 0.66991; -2.0872;0.918;12.7
Penicillin G-scCO$_2$	6.7693×10^{-4}; 3.2338×10^{-4}; 21.066; 7325.8; 0.52116; -11.379;0.935;21.9
Penicillin V-scCO$_2$	4.8247×10^{-4}; 2.9869×10^{-4}; 17.927; 4971.4; 1.0657; -15.302;0.989;5.65

Table 3. Computed solid drug average molar volume.

Drug	Molar volumem^3/mol
Amoxicilin	2.84×10^{-3}
Azithromycin	4.05×10^{-4}
Cefuroxime Axetil	1.95×10^{-3}
Ciprofloxacin	2.00×10^{-4}
Clarithromycin	3.34×10^{-4}
Clemastine Fumarate	3.73×10^{-4}
Clindamycin	4.19×10^{-4}
Enrofloxacin	3.05×10^{-3}
Erythromycin	5.75×10^{-4}
Gatifloxacin	1.45×10^{-3}
MetronidazoleBenzoate	1.62×10^{-3}
Naproxen	1.40×10^{-3}
Penicillin G	3.88×10^{-4}
Penicillin V	2.83×10^{-4}

Table 4. Computed drug vapourpresure.

Drug	Sublimation pressure expression, $\ln(p_2^s)$ is
Amoxicilin	$58.604 - 39417/T$
Azithromycin	$14.422 - 4621.2/T$
Cefuroxime Axetil	$-15.049 - 6672.7/T$
Ciprofloxacin	$17.654 - 8733.4/T$
Clarithromycin	$14.159 - 4718.6/T$
Clemastine Fumarate	$14.579 - 4718.6/T$
Clindamycin	$20.7 - 6480.8/T$
Enrofloxacin	$-11.509 - 17995/T$
Erythromycin	$16.484 - 6243.7/T$
Gatifloxacin	$1.797 - 9276.6/T$
MetronidazoleBenzoate	$2.4213 - 7480.8/T$
Naproxen	$1.1112 - 6124.1/T$
Penicillin G	$21.066 - 7325.8/T$
Penicillin V	$17.927 - 4971.4/T$

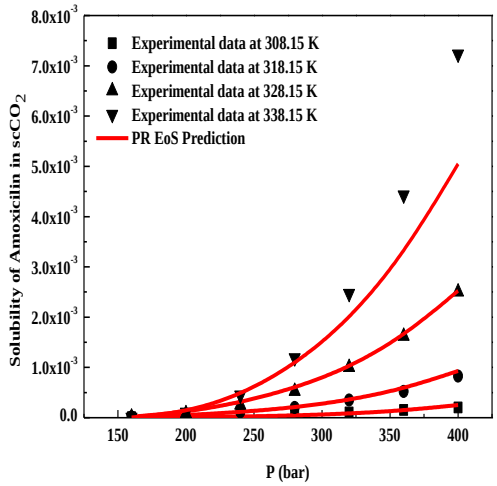

Figure 1.Solubility of Amoxicilin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [32].Lines are PR EoS model prediction.

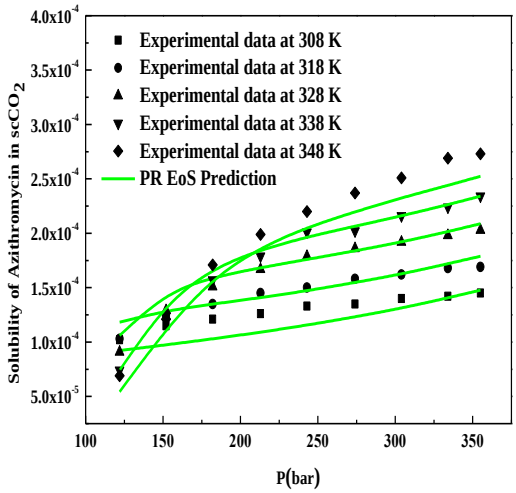

Figure 2. Solubility of Azithromycin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [33].Lines are PR EoS model prediction.

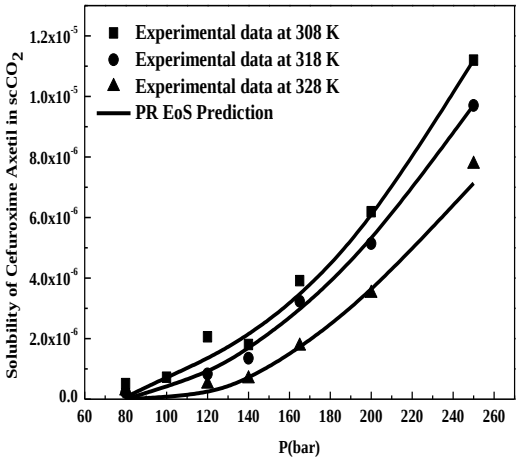

Figure 3. Solubility of Cefuroxime Axetil in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [29].Lines are PR EoS model prediction.

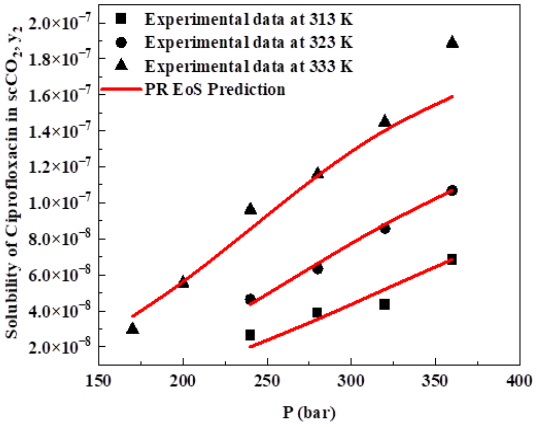

Figure 4. Solubility of Ciprofloxacin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [37].Lines are PR EoS model prediction.

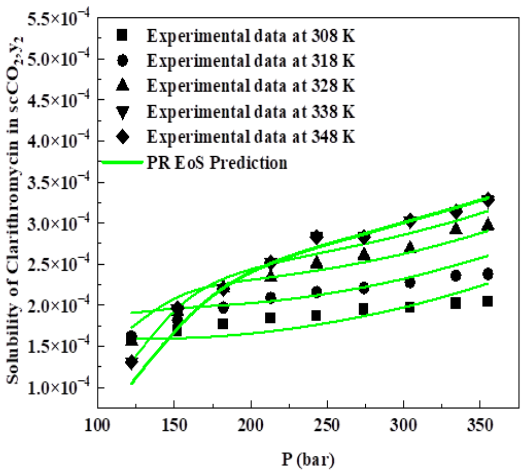

Figure 5. Solubility of Clarithromycin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [33].Lines are PR EoS model prediction.

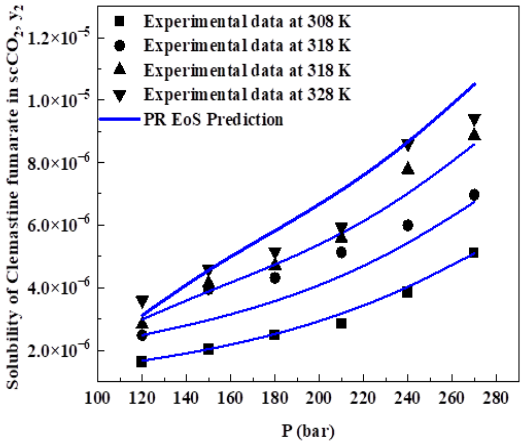

Figure 6. Solubility of Clemastine fumarate in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [33].Lines are PR EoS model prediction.

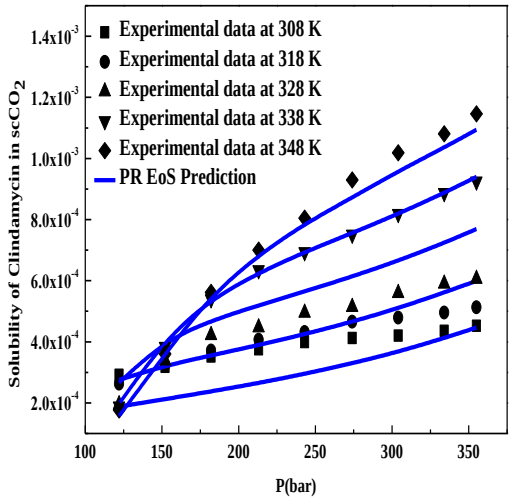

Figure 7. Solubility of Clindamycin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [33].Lines are PR EoS model prediction.

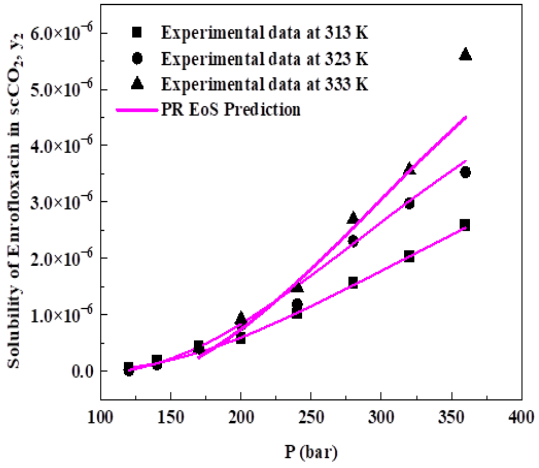

Figure 8. Solubility of Enrofloxacin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [34].Lines are PR EoS model prediction.

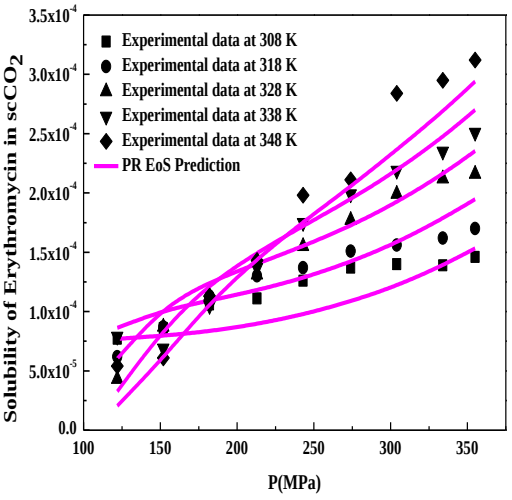

Figure 9. Solubility of Erythromycin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [34]. Lines are PR EoS model prediction.

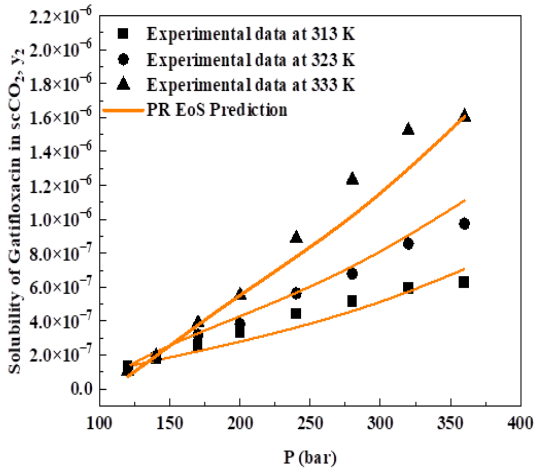

Figure 10. Solubility of Gatifloxacin in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [34].Lines are PR EoS model prediction.

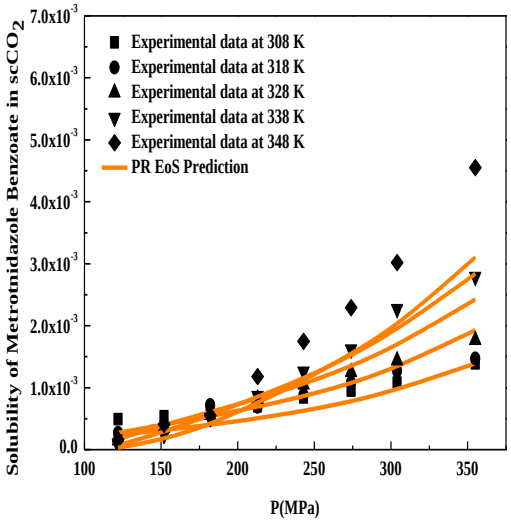

Figure 11. Solubility of Metrotnidazole Benzoate in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [30].Lines are PR EoS model prediction.

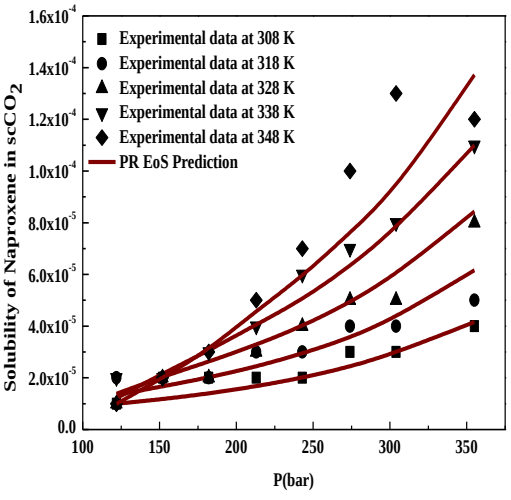

Figure 12. Solubility of Naproxene V in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [28] . Lines are PR EoS model prediction.

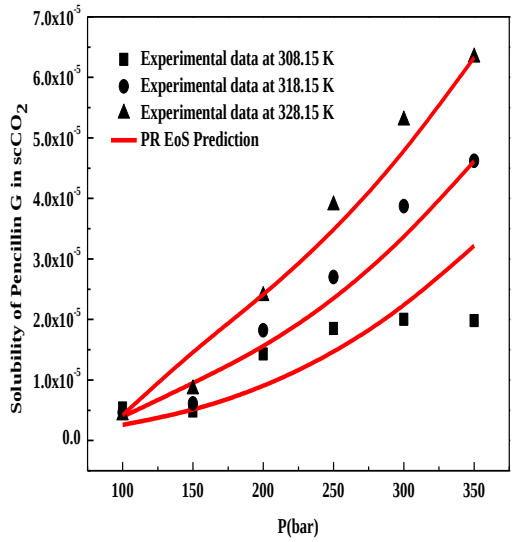

Figure 13. Solubility of Penicillin G in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [28].Lines are PR EoS model prediction.

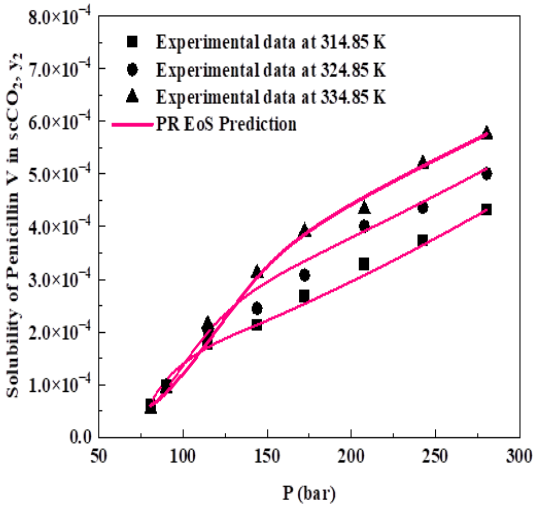

Figure 14. Solubility of Penicillin V in $scCO_2$, y_2 vs P. Symbols are experimental data points from literature [28].Lines are PR EoS model prediction.

4. Conclusion

In this work, a simplified solubility model is proposed based on EoS as a function of pressure, temperature and density of $scCO_2$, which resembles density models. The proposed model is validated with the solubility data of fourteen antibiotics in supercritical carbon dioxide and it is observed to fit data with AARD % ranging between 4.78-25.1 %. Clarithromycin and cefuroximeaxetil are observed to have the least and the highest AARD % respectively. Sublimation pressures and solute molar volume were also computed for all the drugs.

Acknowledgements:

Corresponding Author (Prof.Dr. Chandrasekhar Garlapati) would like to thank Prof. Dr. Giridhar Madras, Department of Chemical Engineering, IIT Hyderabad, Telangana, India for the inspiration and support.

Nomenclatures

a – PREoS parameter (J m^3 mol^{-1})
A – Vapour pressure parameter (bar)
b – PREoS parameter (m^3/mol)
B – Vapour pressure parameter
C – Molar volume parameter
D – Molar volume parameter
f – Vapor pressure function
g - Solute molar volume function
n - Moles
N – Total data points
P – Total pressure (bar)
p – Sublimation pressure
R – Gas constant (J mol^{-1} K^{-1})
T – Temperature (K)
v - Molar volume (m^3/mol)
y – Mole fraction
Z – Compressibility factor

Greek letters

$\hat{\varphi}$ – Fugacity coefficient
ρ – density (kg m^{-3})

Subscript and superscript

1 – Solvent
2 – Solute
$scCO_2$ – Supercritical carbon dioxide
exp - Experimental
calc - Calculated
∞ - Infinite

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