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A New Empirical Model to Correlate the Solubility of Penicillin G and Penicillin V in Supercritical Carbon Dioxide

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Abstract: *A new empirical model based on the degree of freedom analysis has been proposed to model Penicillin G and Penicillin V. The model has three temperature independent constants. Penicillin G and Penicillin V – Supercritical Carbon dioxide binary system was successfully correlated with the new model.*

Keywords – *Empirical Model, Penicillin G, Penicillin V, Solubility, Supercritical Carbon Dioxide*

I. INTRODUCTION

Supercritical carbon dioxide ($ScCO_2$) is widely used in pharmaceutical compound processing, due to its attractive properties like critical temperature near to ambient and moderate critical pressure. Equation of state (EOS) based models, semi empirical models or empirical models are quite frequently employed to correlate the solubility of the substances under various conditions. The EOS based models require parameters such as a critical pressure, a critical temperature, an acentric factor, a molar volume and a vapor pressure of the solute. They are usually not available for the pharmaceutical compounds; in this regard, group contribution methods are often utilized in the estimation of these quantities. On the other hand, estimating all these physico-chemical properties by group contribution methods would result in enormous error, whereas semi-empirical models or empirical models do not require this information. Therefore the semi-empirical models or the empirical models are quite often utilized in correlating the solubility of the solids [1,2]. The model, frequently used in the literature is that of Chrastil [3], which is based on the concept of formation of a solvate complex between the organic solute and the solvent molecules. The Chrastil's model relates the solubility of the solute and the density of the pure solvent and it is:

$$c = \rho^{\kappa} \exp\left(\frac{a}{T} + b\right) \tag{1}$$

where c is the solubility of the solute in kg/m^3, ρ is the supercritical fluid density in kg/m^3, κ is an association number, a is a function of the enthalpy of solvation and enthalpy of vaporization, b is a function of the association number and molecular weights of the solute and the supercritical fluid. The Chrastil's model, as pointed out by D.L. Sparks *et al*. [4], is dimensionally inconsistent when the association number κ is not unity. However, later the model was corrected for dimensional consistency by C. Garlapati and G. Madras [5]. This model is known as three parameter model. The experimental fit to the model depends on the adjustable variables. So, a higher number of adjusted variables lead to a higher accuracy. Therefore, more adjustable parameters models are correlated better. The experimental investigation of the solubility of Penicillin G was made by M.D. Gordillo *et al*. [6] in 1999 and the solubility of Penicillin V was investigated by M. Ko *et al*. [7] in 1991. The modelling of these compounds with a three parameter model was not very successful. The primary objective of this study was to propose a new model to correlate the solubility of Penicillin G and Penicillin V in $ScCO_2$ with minimum number of adjustable parameters and high accuracy.

II. THEORY

According to the Gibbs' phase rule the degree of freedom (F) for the single pure compound dissolving in supercritical fluid are 3 (2 compounds (C) and 1 phase (P) take part in the dissolution process, so F=C+2-P=3). Therefore, the three independent parameters which influence on the process are pressure, temperature and the component composition. However, literature show that the effects of the density and the temperature are more significant compared to the effects

of the pressure and the temperature [8]. The composition effect is insignificant since the solute concentrations are very low. Therefore, we can say that the solubility of the compound is a function of the density of $ScCO_2$ and the temperature of the system i.e.,

$$\text{Solubility} = f(\rho, T) \tag{2}$$

If the solubility of the solute is expressed in terms of a dimensionless parameter such as a mole fraction (y_2), we can represent the density of the $ScCO_2$ in terms of a reduced density and the temperature in terms of a reduced temperature.

$$\text{Therefore } y_2 = f(\rho_r, T_r) \tag{3}$$

A simple three parameter model we can propose as follows:

$$y_2 = a(\rho_r)^b (T_r)^c \tag{4}$$

III. METHODOLOGY AND RESULTS

The density of the $ScCO_2$ required for the modelling was determined with 27 parameters equation [9]. The optimization procedure reduces the percentage average absolute deviation, AARD %. It is defined as:

$$AARD\ (\%) = \frac{100}{N_i} \sum_{i=1}^{N_i} \frac{\left| y_2^{calc} - y_2^{\exp} \right|}{y_2^{\exp}} \tag{5}$$

where N_i is the number of data points, y_2 represents the molar solubility of the solute and superscripts *calc* and *exp* denotes the calculated and experimental values, respectively. The correlation of the experimental solubility data requires an optimization process where the constants for the empirical models are determined by using the nonlinear regression. Table 1 and Table 2 show the experimental solubilities of Penicillin G and Penicillin V, respectively, under various conditions. Data for the modelling were taken from the literature [6, 7]. Fig. 1 shows the model predictions for Penicillin G, based on equation (4). The model equations for both drugs are shown in Table 3.

Table 1. Solubility of Penicillin G ($y_2 \times 10^5$) in $ScCO_2$

p/MPa	**T/K**		
	313.15†	**323.15**†	**333.15**†
10.0	0.535	0.462	0.420
15.0	0.485	0.613	0.849
20.0	1.430	1.820	2.390
25.0	1.850	2.700	3.890
30.0	2.000	3.870	5.290
35.0	1.980	4.620	6.330

† Data taken from ref. 6

Table 2. Solubility of Penicillin V ($y_2 \times 10^5$) in $ScCO_2$

p/MPa	**T/K**		
	314.85*	**324.85***	**334.85***
8.076	6.23	5.87	5.45
9.014	9.70	9.94	9.23
11.468	17.70	20.30	21.50
14.397	21.30	24.50	31.20
17.299	26.80	30.80	39.10
20.773	32.80	40.10	43.30
24.254	37.30	43.70	52.00
28.045	43.20	50.10	57.60

* Data taken from ref. 7

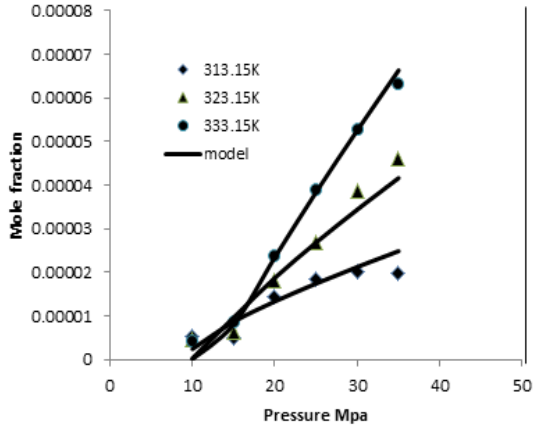

Figure 1. Solubility of Penicillin G, (y_2) at: ○, 313.15 K; Δ, 323.15 K; □, 333.15 K. The lines are model predictions based on the equation 4.

Table 3. Model equations for Penicillin G and Penicillin V

Compound Name	Equation	R^2
Penicillin G	$y = 2.156\times10^{-7}(T_r)^{23.62}(\rho_r)^{5.869}$	0.9729
Penicillin V	$y = 8.274\times10^{-5}(T_r)^{10.118}(\rho_r)^{1.745}$	0.955

IV. CONCLUSION

A new empirical model was developed for correlating the solubility's of pharmaceutical compounds (Penicillin G and Penicillin V) in $ScCO_2$ based on the degree of freedom analysis. The new model is dimensionally consistent. The same idea can be extended to more parameter models.

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