Measurement and Correlation of the Solubility of Cinildipine in Supercritical CO_2

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Abstract. Solubilities of cinildipine in supercritical carbon dioxide was measured at T = (313, 323, and 333) K over the pressure range (12.0 to 36.0) MPa by a flow type apparatus. The solubility behavior of the solid shows an analogous trend with a crossover region of the isotherms in 15.0-18.0 MPa. The experimental solubility data are well correlated with semi-empirical density-based models including the Chrastil, Bartle, and MST models with the absolute average relative deviation (AARD) from (7.0 to 7.5)%, and the solubility data satisfy the self-consistency test according to the MST model.

Keywords: Cinildipine, Supercritical CO_2, Solubility, Modeling.

1. Introduction

Supercritical CO_2 extraction is an important method of samples pretreatment for determination in the field of environmental protection. Knowledge of the solubility of pure solid substances in supercritical CO_2 is essential for evaluating the viability of supercritical fluid separation processes and for their subsequent design.

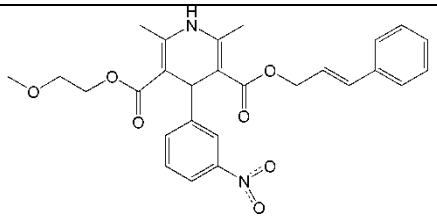
An extensive review on the solubility of over 380 different pure solid compounds, without or with cosolvents, and of 29 binary, two ternary, and one multicomponent solid systems in sub- and supercritical fluids were published in the literature between 2005 and 2010[1-2]. The general conclusion of all review papers examined is that new reliable experimental data and proper correlation models for specialty chemicals are needed.

Cinildipine is pale yellow solid at room temperature. It is well known to be calcium channel blockers, which is used for the treatment of cardiovascular diseases such as hypertension, angina pectoris, and other spastic smooth muscle disorders [3].In this work, the solubilities of cinildipine in Sc-CO_2 was determined by using a flow type apparatus at pressures (12.0 to 36.0) MPa and temperatures (313, 323 and 333) K, as these conditions are easily achieved and often used in pharmaceutical industry. The measured solubility data were modeled with semi-empirical correlations including the Chrastil [4], Bartle [5], and Méndez-Santiago-Teja (MST) [6] models.

2. Materials and methodology

The description of the cinildipine and other chemicals was listed in Table 1. These compounds were used without further purification.

Table 1. Chemical sample description

Compounds	Source	Purity	Structure
Cinildipine CAS: 132203-70-4	Energy Chem. Co., China	98 wt.%	
Carbon dioxide	Lianbo Gas Co. China	99.99%	CO_2
Methanol	Energy Chem. Co., China	99.8% wt.%	CH_3OH

2.1. Equipment and Procedure.

The dynamic method was used to determine the solubility of cinildipine. The apparatus and process are the same as that in the literature [7].

The solubility of cinildipine was calculated by UV-vis spectrophotometer (model 2100 Shimadzu). Three replicates were performed at each experimental condition, and the solubility was obtained as an average of these results. yerr is the average absolute difference of the triplicate measurements at each measurement condition, which was calculated by

$$y_{err} = \frac{1}{3}\sum_{i=1}^{3}|y_{2i} - \bar{y}_{2i}| \quad (1)$$

Where y_{2i} is the measured value, and $\bar{y}_{2i}$ is the average value at each measurement condition.

2.2. Correlation of solubility data.

The experimental results were correlated by the semi-empirical density-based models: Chrastil, Bartle and MST models.

The Chrastil model [4] is given as:

$$\ln S(\mathrm{kg \cdot m^{-3}}) = c\ln\rho(\mathrm{kg \cdot m^{-3}}) + a + b/T(\mathrm{K}) \quad (2)$$

Where S is the concentration of cinildipine in carbon dioxide, ρ is the density of carbon dioxide, T is the absolute temperature.

The Bartle model [5] is given as:

$$\ln\left(\frac{py_2}{p_{ref}}\right) = a + \frac{b}{T} + c(\rho - \rho_{ref}) \quad (3)$$

Where y2 is the mole fraction solubility, Pref is a reference pressure of 0.1Mpa, ρref is a reference density of 700 $kg \cdot m^{-3}$.

The Méndez-Santiago and Teja (MST) model [6] is given as:

$$T\ln\left(y_2\frac{P}{P_{ref}}\right) = a + b\rho(\mathrm{kg \cdot m^{-3}}) + cT(\mathrm{K}) \quad (4)$$

Where y2 is the mole fraction solubility, P is the pressure, Pref is the standard pressure, Pref = 1 bar.

In solubility correlation, the AARD, as defined bellow, was used as the objective function and the correlation results were compared.

$$\mathrm{AARD\%} = \frac{100}{N}\sum_1^N \frac{|y_2^{\exp} - y_2^{\mathrm{cal}}|}{y_2^{\exp}}\% \quad (5)$$

3. Results and discussions

3.1. Experimental solubility results.

In the dynamic method, the equilibrium time and the flow rate of CO_2 were studied at the severe condition (333 K and 36.0 MPa) for the two drugs in order to know their effect on the solubility determination. The equilibrium time of 15 min, 30 min and 60 min were investigated when the flow rate of CO_2 was 0.033 L/min.

Figure 1 showed that 45 min was enough for the two drugs to get the stable solubility values. Considering the amount of the loaded drugs, the flow rate of CO_2 was expressed by the contact time τ, which was defined as follows:

$$\tau = \frac{W}{F} \quad (6)$$

Where W (g) refers to the mass of drug loaded in the sample chamber and F (g·s-1) is the mass flow rate of CO_2. When the equilibrium time was 45 min, the flow rate of CO_2 was set at 0.022, 0.033 and 0.067 L/min respectively. As the mass of drug was 1 g in all the experiments, the values of τ were 500, 1000 and 1500 s respectively.

The results in Figure 2 showed that when τ was equal to or greater than 1000 s, the solubility of the drug reached the stable values. So in the following solubility determination, the equilibrium time and flow rate of CO_2 were set at 45 min and 0.033 L/min respectively.

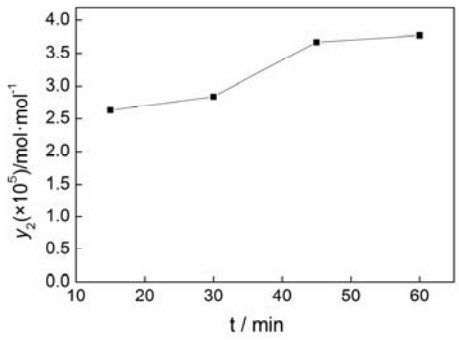


Figure 1. Effect of the equilibrium time

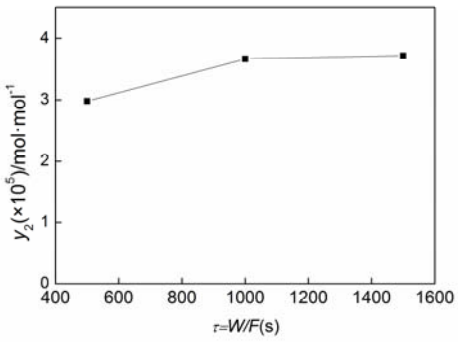


Figure 2. Effect of the flow rate of CO_2

The solubility data of cinildipine in SC-CO_2 was measured by the dynamic method at temperatures of 313-333 K and pressures of 12.0-36.0 MPa, as shown in Table 2.

Table 2. Solubility data for cinildipine (2) in sc-CO_2 (1) expressed as mole fractions, y2

P /MPa	T /K	$y_2 \pm y_{err} \cdot 10^5$ /mol·mol^{-1}	P /MPa	T /K	$y_2 \pm y_{err} \cdot 10^5$ /mol·mol^{-1}	P /MPa	T /K	$y_2 \pm y_{err} \cdot 10^5$ /mol·mol^{-1}
12.0	313	0.51±0.05	12.0	323	0.35±0.02	12.0	333	0.12±0.03
15.0	313	0.88±0.08	15.0	323	0.73±0.10	15.0	333	0.57±0.10
18.0	313	0.91±0.09	18.0	323	1.08±0.14	18.0	333	1.08±0.18
21.0	313	1.15±0.14	21.0	323	1.34±0.14	21.0	333	1.56±0.25
24.0	313	1.26±0.12	24.0	323	1.68±0.19	24.0	333	2.36±0.25
28.0	313	1.60±0.11	28.0	323	2.07±0.17	28.0	333	3.10±0.19
32.0	313	1.90±0.14	32.0	323	2.87±0.29	32.0	333	3. 69±0.22
36.0	313	2.15±0.18	36.0	323	3.20±0.33	36.0	333	3.99±0.29

There is a strong temperature and density dependence on the solubility of cinildipine in condensed carbon dioxide. As the density increased at a fixed temperature (by increasing the carbon dioxide pressure), the solubility increased. It might because that the solvating power of carbon dioxide tends to increase with increasing density as there are more molecules of carbon dioxide available for forming a solvating shell around the solid molecule and dissolving it [8, 9] The effect of temperature is more complex, and crossover point of cinildipine is in the interval of 15.0 to 18.0 MPa. At the crossover pressure, the effects of solute vapor pressure and solvent density on solid solubility balance each other [10]. When the pressures are above the crossover pressure, the solubility of cinildipine increase with temperature.

To the best of our knowledge, the solubility of cinildipine in SC-CO_2 had been investigated previously, and no such data are available in the open literature. The solubilities of similar compounds (felodipine and nitrendipine) in compressed carbon dioxide were examined by Weinstein et al. [3] at (298, 308, and 318) K at pressures between (8 and 25) MPa. Their data showed similar trends and order of magnitude to our data in this work.

3.2. Modeling results.

The correlation results of the solubility of cinildipine using the semi-empirical models are listed in Figures. 3-5 and Table 3.

Table 3. Obtained fitting constants for three density-based model correlations

Model	Constant			AARD%
	a	*b*	*c*	
Chrastil	-5730.9958	-27.2697	6.4325	7.0
Bartle	18.4172	-8153.7157	0.0108	7.5
MST	-10958.1288	3.5668	30.8684	7.3

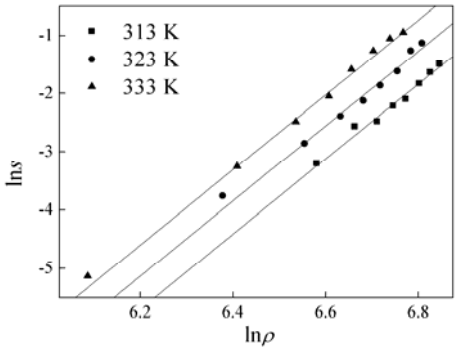


Figure 3. Solubility data of cinildipine and predicted by the Chrastil model

For the most commonly used density-based Chrastil's model, the correlation obtained by using the model for cinildipine plotted as lnS versus lnρ, based on eq.1. As shown in Figure 3, the specific straight lines are obtained. It performs very well for cinildipine with the AARD of 9.4%. The total reaction heat ΔH_{tot} (heat of solvation plus heat of vaporization of the solute) may be approximated by $\Delta H_{\mathrm{tot}} = -bR$. The estimated ΔH_{tot} value of cinildipine is 47.65 kJ·mol^{-1}.

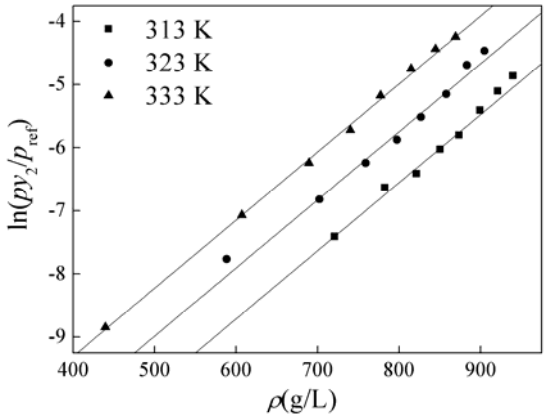


Figure 4. Solubility data of cinildipine and predicted by the Bartle model

The Bartle model was also used to predict the trend of measured solubility data. The ln(y2p/pref) values were plotted against density (Figure 4), and the values were fit with a straight line by least-squares regression to estimate the a, b and c parameters, as seen in Table 3. It is indicated that that the Bartle method provided a good fit, with the absolute average relative deviations (AARD) of 8.8% for cinildipine (Table 3). The estimated $\Delta_{\mathrm{sub}}H$ value of cinildipine is 67.82 kJ·mol^{-1}.

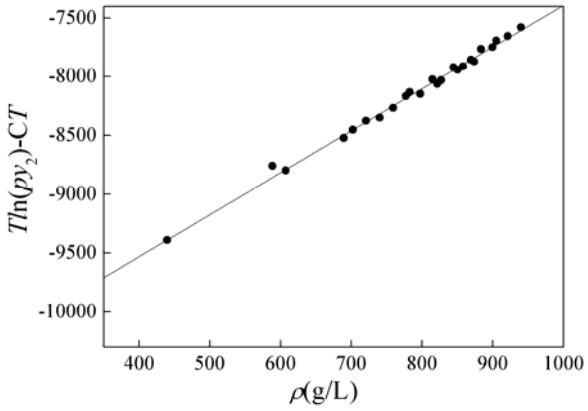


Figure 5. Solubility data of cinildipine and predicted by the MST model (—)

For the self-consistency test from the MST model, the experimental results of $\ln\left(\mathrm{y}_2 \frac{p}{p_{\mathrm{ref}}}\right) - \mathrm{cT}$ were plotted against the density of supercritical CO_2, and a linear curve was observed (Figure 5). The results confirm that the measured solid solubility data are consistent at all experimental conditions.

Therefore, these density-based experience models (Chrastil, Bartle and MST) give good agreement with the experimental solubility data at a high density zone. However, at the low CO_2 density zone, the predicted errors are relatively bigger.

4. Conclusion

This study presents novel solubility data for cinildipine at T=(313, 323 and 333) K and over the pressure range (12.0 to 36.0) MPa. The solubility values, in mole fractions, obtained are in the range of 0.12 to $3.99 \cdot 10{-}5$ mol·mol^{-1}. Three semi-empirical density-based models (Chrastil, Bartle, and MST) were used to correlate the solubility data of cinildipine in sc-CO_2. These models demonstrate good correlative abilities. All the models obtain better agreement with the experimental solubility data at a high CO_2 density zone than the low density zone.

References

[1] J.P. Coelho, G. P. Naydenov, D. S. Yankov, R. P.Stateva, Experimental Measurements and Correlation of the Solubility of Three Primary Amides in Supercritical CO_2: Acetanilide, Propanamide, and Butanamide, J. Chem. Eng. Data. 58 (2013) 2110−2115.

[2] M. Skerget ,Z. Knez, M. K. Hrncic, Solubility of Solids in SubandSupercritical Fluids: a Review, J. Chem. Eng. Data. 56 (2011) 694−719.

[3] R. D.Weinstein, W. H.Hanlon, J. P. Donohue, M. Simeone, A. Rozich, and K. R .Muske, Solubility of Felodipine and Nitrendipine in Liquid and Supercritical Carbon Dioxide by Cloud Point and UV Spectroscopy, J. Chem. Eng. Data. 52 (2007) 256−260.

[4] J. Chrastil, Solubility of Solids and Liquids in Supercritical Gases. J. Phys. Chem. 86 (1982), 3016–3021.

[5] K. D. Bartle, A. A.Clifford, S. A. Jafar, G. F. Shilstone, Solubilities of solids and liquids of low volatility in supercritical carbon dioxide. J. Phys. Chem. Ref. Data. 20 (1991) 713−756.

[6] J. Méndez-Santiago, A. S. Teja, The solubility of solids in supercritical fluids. Fluid Phase Equilib. 158 (1999) 501−510.

[7] H.R Li, D.D Jia, Q.Q Zhu, B.Q Shen,Determination correlation and prediction of the solubilities of niflumic acid, clofenamic acid and tolfenamic acid in supercritical CO2, Fluid phase equlibria. 392 (2015) 95-103

[8] R.D. Weinstein, L.L.Grotzinger, P. Salemo, D.M. Omiatek, C.A. Bessel, Solubility of several short-chain lithium dialkyldithiocarbamates in liquid and supercritical carbon dioxide. J. Chem. Eng. Data, 50 (2005) 2088−2093.

[9] I. Medina, J. L. Bueno, Solubilities of 2-nitroanisole and 3-phenyl-1-propanol in supercritical carbon dioxide, J. Chem. Eng. Data, 45 (2000), 298−300.

[10] N. R Foster, G.S. Gurdial, J. S. L. Yu, K. Keat Liong, K. D.Tilly, S. S. T. Ting, J. H. Lee, Significance of the Crossover Pressure in Solid-Supercritical Fluid Phase Equilibria. Ind. Eng.Chem. Res. 30 (1991)1955−1964.