Solubility of Azoxystrobin and Benflumetol in compressed CO$_2$ - measured by the static precise mass measuring method

Li, Qingguo; Pan, Piaopiao; Lu, Tiejun; Blackburn, Stuart; Leeke, Gary A.

Link to publication on Research at Birmingham portal

Solubility of Azoxystrobin and Benflumetol in Compressed CO_2;

Measured by Static Precise Mass Measuring Method

Qingguo Li[a,b,△], Piaopiao Pan[a,△], Tiejun Lu[b], Stuart Blackburn[c], Gary A. Leeke[d]*

[a] School of Pharmaceutical Sciences, Guangzhou University of Chinese Medicine, Guangzhou 510006, PR China

[b] Centre for Formulation Engineering, School of Chemical Engineering, University of Birmingham, B15 2TT, UK

[c] Interdisciplinary Research Centre, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK

[d] School of Water, Energy and Environment, Cranfield University, Cranfield, Bedfordshire MK43 0AL, UK

[△] QL and PP contributed equally to this paper.

[*] Corresponding author: Gary A. Leeke, School of Water, Energy and Environment, Cranfield University, Cranfield, Bedfordshire, MK43 0AL, UK, E-mail: Gary.A.Leeke@cranfield.ac.uk

ABSTRACT The solubilities of hardly soluble solutes in compressed CO_2 were measured using a new Static Precise Mass Measuring (SPMM) method. The solubility of two solutes, azoxystrobin a substituted pyrimidine, and benflumetol an anti-malarial drug were determined at pressures and temperatures from 80 to 250 bar and 301K to 323K. Solubility of these two compounds were 64-661 mg/kg CO_2 and 1.3-19.7 mg/kg CO_2, respectively. The measured solubilities were correlated using the density-based model proposed by Chrastil and theory of dilute solutions based model proposed by Mendez-Santiago and Teja. A linear relationship between the solubility and the solvent density was obtained.

1. INTRODUCTION

Extraction, reaction and particle production processes using compressed CO_2 have received considerable interest as alternatives to methods that use conventional solvents[1-7]. The main advantages of such processes manifest themselves in terms of high quality products, environmentally friendly operation, time and energy savings and, in some cases, lower operational costs of the plant.

The solubility of a solute in compressed CO_2 or in a mixture of CO_2 with some

other organic solvent is a key parameter in a supercritical fluid process especially for the development and optimisation of the process. This work reports a method to measure the solubility of virtually insoluble solutes in compressed CO_2. The method eliminates the erroneous collection of samples that would have, by their nature, extremely low masses. In addition, the method avoids the use of spectrophotometric equipment to measure solubility.

In general, the methods for measuring solute solubility in compressed CO_2 can be divided into two main categories: dynamic and static methods[8]. In the dynamic method, a CO_2-rich phase is passed or recycled through a fixed solid or liquid sample bed until the CO_2 is saturated. A sample is then taken from the fluid phase and the amount of CO_2 and solute is measured gravimetrically or by a high pressure online spectroscopic technique such as UV absorption or chromatography. In the static method, compressed CO_2 contacts the sample with a sufficient contact area and time to ensure saturation of the solvent phase and then a sample is taken from the saturated CO_2 phase and the masses are determined. Another common static method used to measure solubility is cloud point observation, where a sample of known mass is totally dissolved in high pressure CO_2 through agitation. The system is then depressurised by altering the volume to decrease the solvent power of CO_2, which causes the dissolved solute to reach its saturation point. The solute begins to form a cloud which appears opaque to the viewer – as the solute begins to emerge from the CO_2 solution. The pressure and temperature are then noted and the volume of CO_2 measured at this point. The solubility can then be calculated from the mass of original solute.

All of these methods need sufficient solute solubility; the static method also needs a reasonable dissolution rate, whereas the spectroscopic techniques need additional high pressure online equipment which can be expensive, and the creation of a calibration curve at extremely low dilution. When the solubility is lower than 1 g solute per kg CO_2, the measurement is difficult either because a representative amount of sample has to be collected from a large volume of CO_2 leading to disturbances in the equilibrium, relatively weak responses from the low concentrations on spectroscopic detectors or there is too little solute dissolved to produce a visible cloud point.

The solubilities of two compounds have been measured in this work. The first, a hydrophilic agrochemical named azoxystrobin and the second benflumetol, a type of clinical medicine used for malaria treatment. The need to generate solubility data in compressed CO_2 of these two compounds is necessary for the design and optimisation of subsequent particle production processes[5, 9], as well as adding new solubility data to the literature. Because of their chemical nature, their solubility measurements using traditional approaches were found to be impossible and consequently a new approach was developed to measure their solubility. The method is described herein and named the Static Precise Mass Measuring (SPMM) method. One of the characteristics of this method is that if the impurities in the sample are insoluble in CO_2, they will not interfere with the result. If impurities are soluble in CO_2, a pre-extraction purification removes them and purifies the sample. This method was used to determine the solubility of azoxystrobin and benflumetol from 301K to 323K and 80 to 250 bar in CO_2. The method was validated by measuring solubility data for caffeine in CO_2 and comparing to those in the literature. The data for azoxystrobin and benflumetol were correlated using models proposed by Chrastil[10] and Mendez-Santiago and Teja[11].

2. EXPERIMENTAL
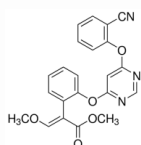
2.1 Materials and Reagents

Figure 1. Chemical Structure of Azoxystrobin

Azoxystrobin

(Methyl-(E)-2-{2-[6-(2-cyanophenoxy)pyrimidin-4-yloxy]phenyl}-3-methoxyacrylate, $C_{22}H_{17}N_3O_5$, see figure 1, CAS: 131860-33-8), was provided by Syngenta, an agrochemical manufacture in UK with a purity of 99.001% (by DSC), and purified by CO_2 extraction at 313K, 250 bar prior to use.
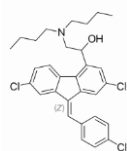
Figure 2. Chemical Structure of Benflumetol

Benflumetol

(lumefantrine,(9Z)-2,7-Dichloro-9-[(4-chlorophenyl)methylene]-α-[(dibutylamino)methyl]-9*H*-fluorene-4-methanol, $C_{30}H_{32}Cl_3NO$, see figure 2, CAS: 82186-77-4) (> 98%, lot number: 201508037) was kindly donated by Haiboyuan Chemical Company in China and purified by CO_2 extraction at the measurement conditions prior to be measured.

Caffeine was obtained from Sigma-Aldrich at a purity of 99% and purified by CO_2 extraction at 313K, 140 bar prior to use.

Carbon dioxide (≥99.8%) was purchased from BOC UK and was dried with molecular sieve 5A prior to use.

The physicochemical properties of azoxystrobin, benflumetol and caffeine are shown in Tables 1 and 2.

Table 1. Physicochemical Properties of Compounds[12]

	Azoxystrobin	Benflumetol	Caffeine
Formula	$C_{22}H_{17}N_3O_5$	$C_{30}H_{32}Cl_3NO$	$C_8H_{10}N_4O_2$
Density (g/cm³)	1.33	1.252	1.23
Melting point (°C)	116 °C	129-131°C	238
PubChem CID	3034285	6437380	2519
Molar mass (g/mol)	403.394	528.942	194.194

Table 2. Detailed Information on the Experimental Materials Used in This Work

Chemicals	Source	initial mass fraction purity	purification Method	final mass fraction purity	analytical method
Azoxystrobin	Syngenta, Huddersfield Works, UK	0.99	CO_2 extraction	-	DSC
Benflumetol	Haiboyuan Chemical Company, China	0.98	CO_2 extraction	-	-
Caffeine	Sigma-Aldrich, UK	0.99	CO_2 extraction	-	-

- Indicates no measurement

2.2. Equipment and Methods

2.2.1 Pre-solubility measurements

The measurements were carried out in a SS316L Parr reactor (W6886-01, Parr Instrument Co, USA) as shown in Figure 3. It was equipped with two in-line sapphire windows, heating/cooling jacket and a magnetic stirrer with a working range up to 345 bar from 283K to 373K. The pressure was recorded using a transducer (Druck PTX 1400) with a dedicated display to within 0.1 bar, and the temperature was recorded and maintained to within 0.1K using a Tecam circulator (C-40) and J-type thermocouple. The vessel formed part of the experimental rig which is shown in Figure 4.
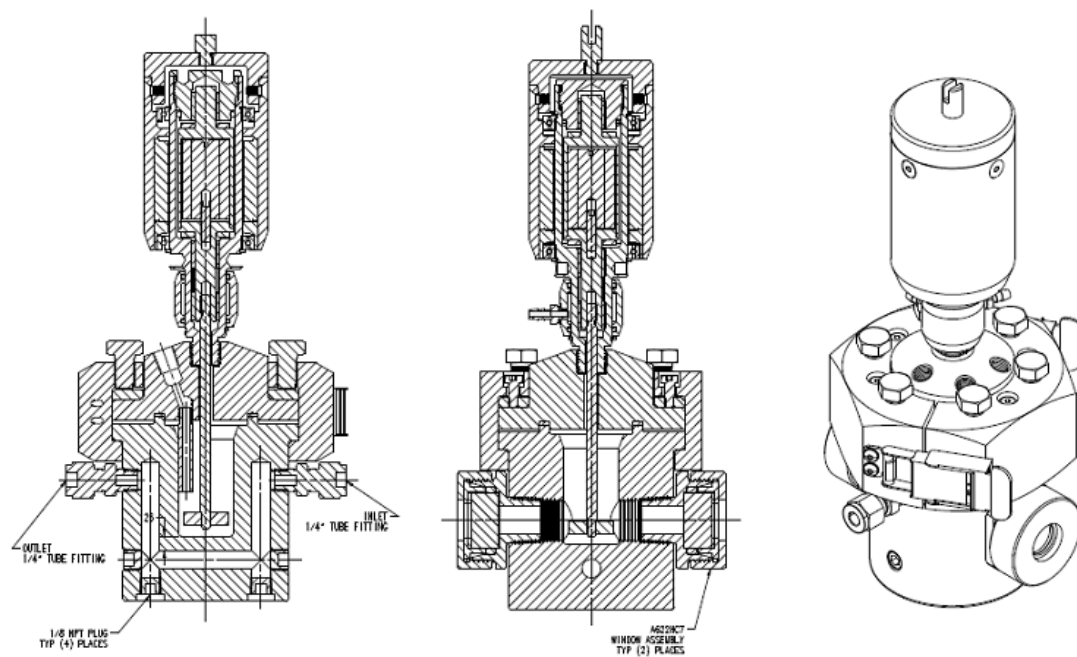
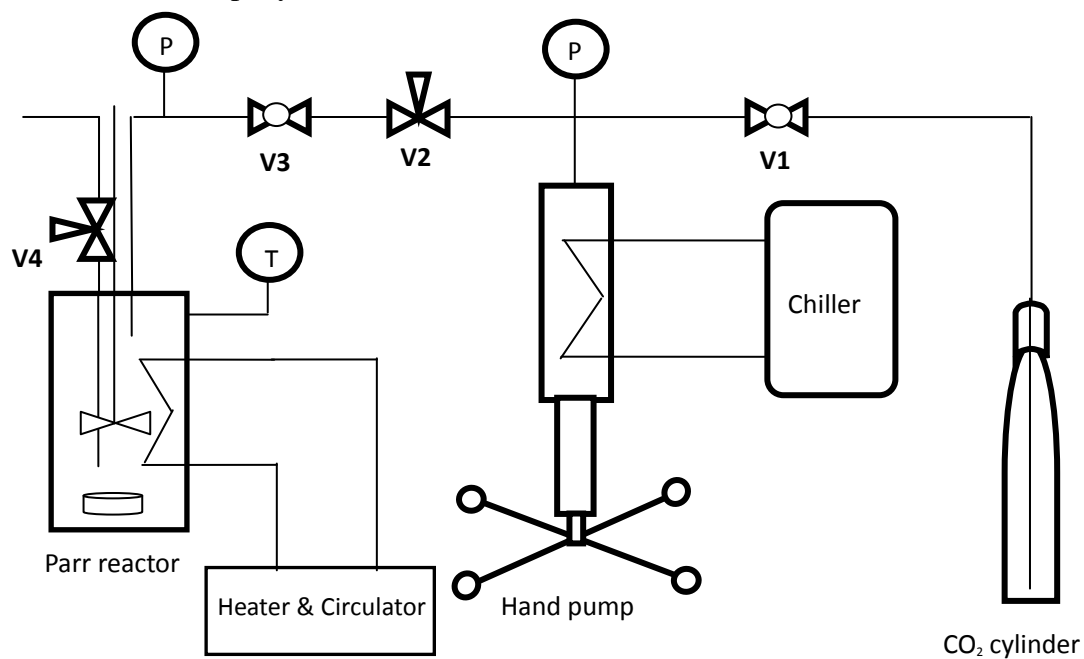**Figure 3.** View and Internal Structure of Pressure Reactor (drawings from Parr Instrument Company, USA)

Figure 4. Apparatus for measuring solubility in compressed CO_2

Figure 5. (a) The sample pans and the cover   (b) Assembled pan and cover

Before the SPMM method be applied, it was necessary to know the actual vessel volume rather than rely on the one quoted by the manufacture. This enables the actual amount of CO_2 used in a measurement to be obtained over the CO_2 density range. This volume included the items inside the vessel, the vessel overheads and the window and gauge recesses. The internal volume was obtained by placing the sample pan and cover (see Figure 5) into the vessel, pumping in CO_2 with V1, V4 closed and V2, V3 opened, increasing the pressure and temperature to a constant desired value. The CO_2 was then depressurized across a micro-metering valve V4 (Hoke, 1315G4Y) and the gas volume measured at ambient conditions by passing the expanded stream through a wet-gas meter (Model DM3A 0.25 dm^3 per rev., Alexander Wright). The total mass of CO_2 was calculated from the ideal gas equation of state and the vessel volume calculated from the density of CO_2 taken from NIST Chemistry Web Book[13] at the pressure and temperature condition. The vessel volume results are shown in Figure 6. These measurements were carried out in the range from 78 to 245 bar and 295K to 323K at different combinations of temperature and pressure. The average vessel volume was found to be 61 ml with a STDEV of 3.22%.
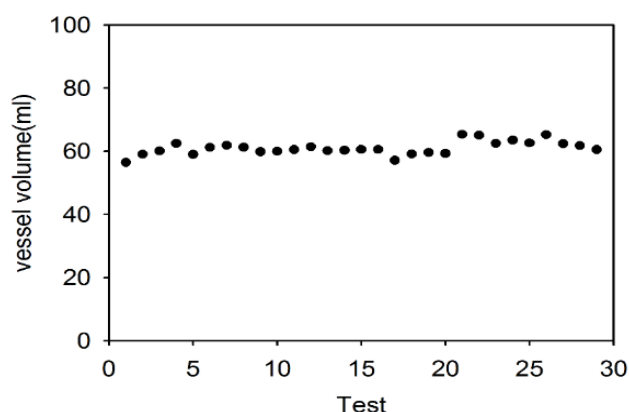
Figure 6. The results of the reactor volume measurement

The minimum time for the system to reach equilibrium for a given pressure and temperature was also determined. This is a key operation datum for the static method. Only when the processing time is in excess of the minimum equilibrium time, can correct solubility data be obtained. This time was found by measuring the loading of azoxystrobin in CO_2 at a typical working condition (100 bar, 313K and 130 rpm stirring speed) until consistent data were obtained.

Figure 7 shows that the sample loading in the CO_2 increases rapidly with time in the first 3 hours and reaches a value of almost 0.03 g/kg at 3 hours. The average loading showed little fluctuation from 3 to 17 hours and showed a very limited increase, which was within the experimental error given in the results section. Consequently, 3 hours was considered satisfactory to attain equilibrium; however for assurance, a minimum of 4 hours was used for the solubility measurements.

Figure 7. Time to reach equilibrium solubility

2.2.2 The static precise mass measuring procedure.

A precise Mettler balance (Mettler MT5, Mettler Ltd., Switzerland) with had an accuracy of 0.001 mg was used to determine the masses of the sample.   A known mass of sample was weighed into the sample panwhich was plac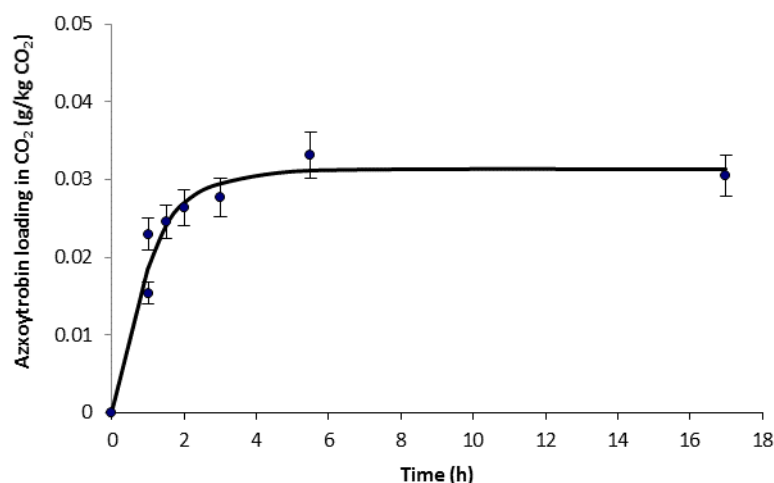ed inside the pressure vessel. The sample pan was then covered by the pan cover. The pan and pan cover (Fig. 5a) were made in-house and have diameters of 15 and 22 mm, respectively.

The pan cover is 12 mm in height and has arches on its sides to allow CO_2 to diffuse in and out as shown in Fig. 5b. For solubility measurements, pure CO_2 was pumped into the reactor and after 4 hours stirring CO_2 became saturated with the solute. The stirrer was turned off and the CO_2 vented and measured using the wet gas meter. The pan containing sample that had not been solubilised was removed from the vessel and weighed. The mass loss from the sample was calculated by difference, and hence the solubility. The beauty of the SPMM method is that during depressurisation most of the dissolved sample will precipitate in the vessel, however, the special pan cover allows the dissolved sample to precipitate on top of it, but prevents the precipitated particles returning into the sample pan. The SPMM method was validated by comparing the solubility of caffeine in CO_2 with data commonly available in the literature.

2.2.3 Solubility-Density correlation.

The Chrastil and MST models were used to fit the experimental data. Chrastil's model relates the solubility of solutes directly to the density of a compressed gas solvent and avoids the complexity of equations of state[10]. On the basis of the theory that the solute and gas solvent molecules associate to form a solvato complex, and combined with the entropy of the components, the following equation can be derived:

$$\ln(S) = k \ln(\rho) + \frac{a}{T} + b \qquad (1)$$

where S is the solute concentration in the solvent gas (kg/m^3), ρ is the density of the gas (kg/m^3), k is an association constant which is characteristic for a given gas and solute and is independent of both temperature and pressure, a is dependent on the heat of solvation and vaporization of the solute, and b is dependent on the molecular masses of the solute and solvent and on the melting points of the solute. Chrastil observed that a log-log plot of S against ρ for a given isotherm resulted in a linear relationship with a slope of k. At different temperatures, the isothermal plots should be parallel to one another.

The MST model developed by Mendez-Santiago and Teja[11], is a simplified correlation to solid solubility data based on the theory of dilute solutions. It is one of the most used semi-empirical models. Like the Chrastil model, it based on simple error minimization and uses only available independent variables like pressure, temperature and density of the pure solvent. It represents the solubility in terms of temperature, pressure and density as:

$$T\ln(Py) = k\rho + aT + b \qquad (2)$$

Where y is the solubility in mol/mol, P is the pressure in MPa, ρ is the density of the compressed gas, T is the temperature in K and a, b and k are the temperature independent constants. Thus a plot of $T\ln(Py) - aT$ vs. ρ would be linear with all the isotherms collapsing on to a single straight line.

3. RESULTS AND DISCUSSION

3.1 Caffeine solubility in supercritical CO_2

The SPMM approach was validated by comparing solubility data of caffeine in CO_2 at $40^{\circ}C$ from 85 to 140 bar with those commonly found in the literature[14-21]. Figure 8 shows that the data obtained is comparable to the literature data and the error is acceptable. The literature cited used a range of techniques to measure the solubility which included both dynamic and static approaches coupled with UV-Vis spectrophotometry and supercritical fluid chromatography analyses. Our approach shows that solubility data can be obtained without the need for chromatographic and spectrometric equipment.
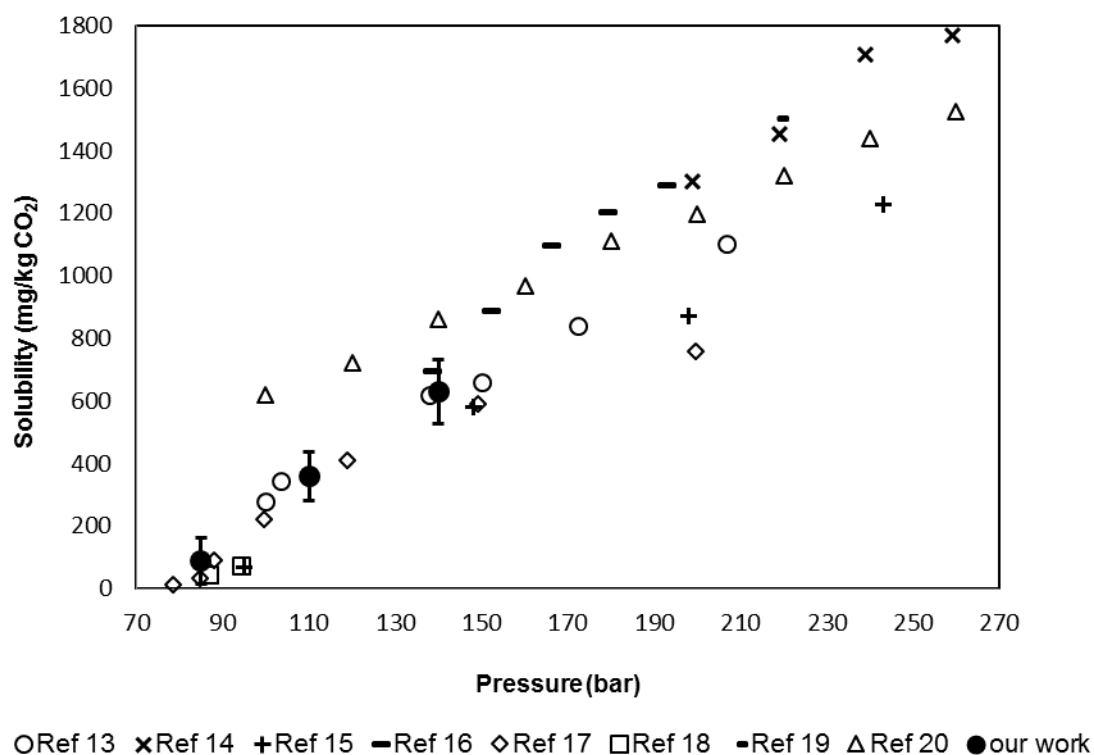

Figure 8. Solubility of caffeine in CO_2 measured by the SPMM method and plotted with literature data.

Table 3. Solubility (S) of Caffeine in CO_2 at 40°C Measured by SPMM Method (mg Caffeine/kg CO_2)

P (bar)	Solubility (mg/kg)	$u_r(S)$	CO_2 Density[13] (mol/m^3)
85	89	0.84	8040
110	359	0.21	15527
140	628	0.16	17339

Standard uncertainties u are = $u(T)$ = 0.1 K , $u = u(P)$ = 0.01 MPa, $u_r(S)$ values are displayed in each pressure row.

3.2 Azoxystrobin Solubility in Sub- and Supercritical Carbon Dioxide

The solubility of azoxystrobin in compressed CO_2 was measured using the SPMM method between 100 to 250 bar and 301K to 323K and the results are shown in Table 2 and Figure 9. The measurements were repeated up to 5 times and the variance was no greater than 8.8 %. It can be seen that although the solubility is very low, it shows the same tendency to that of other CO_2/solute systems. For a given temperature, the solubility increases with an increase of pressure and there exists a cross-over point at around 125 bar. Below the cross-over pressure, the solubility decreases with an increase in temperature, whereas above this pressure the opposite effect occurs; solubility increases with temperature. This agrees with the general rule of solute solubility at elevated pressure where CO_2 density and solute vapour pressure compete against each other. At lower pressures where the effect of CO_2 density dominates, the higher the CO_2 density the higher the solubility of the azoxystrobin in CO_2. At higher pressures, the vapour pressure of the solute has a greater effect and hence a higher temperature leads to higher the solubility.

Table 3. Solubility (S) Data of Azoxystrobin in Carbon Dioxide (mg Azoxystrobin/kg CO_2)

P (bar)	301 (K)			313 (K)			323 (K)		
	S (mg/kg)	u_r (S)	CO_2 density[13] (mol/m^3)	S (mg/kg)	u_r (S)	CO_2 density[13] (mol/m^3)	S (mg/kg)	u_r (S)	CO_2 density[13] (mol/m^3)
100	61	0.18	18007	32	0.16	14354	13	0.85	8788
150	133	0.14	19540	147	0.10	17753	209	0.17	15930
200	231	0.15	20469	281	0.15	19100	446	0.14	17841
250	385	0.23	21161	527	0.10	19999	664	0.27	18971

Standard uncertainties u are $= u(T) = 0.1$ K, $u = u(P) = 0.01$ MPa, $u_r(S)$ values are displayed in each pressure row.
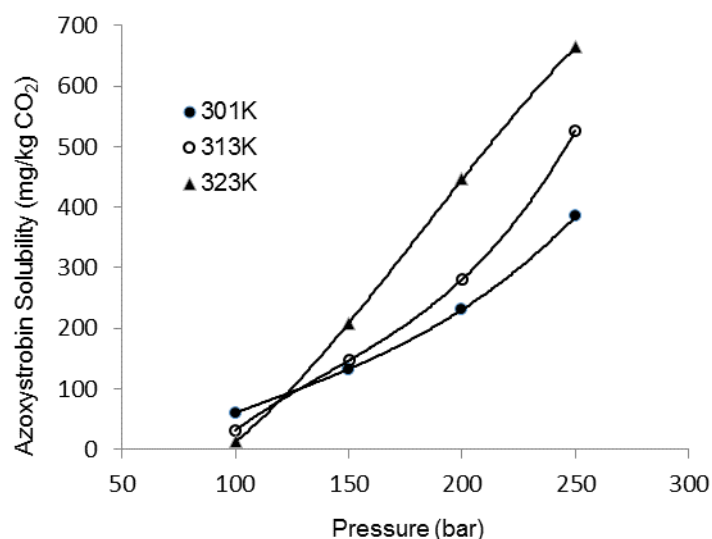

Figure 9. Azoxystrobin solubility in compressed CO_2 measured with SPMM technique. The lines show best fit to the experimental data.

3.3 Benflumetol Solubility in Supercritical Carbon Dioxide

The solubility of benflumetol in compressed CO_2 was measured using the SPMM method between 80 to 180 bar and 308K to 323K and the results are shown in Table 4 and Figure 10. The solubility of benflumetol has the similar tendency to that of azoxystrobin, and there exists a cross-over point at around 100 bar. That is to say that below this pressure, CO_2 density dominated the solubility of benflumetol; the higher the CO_2 density the higher the solubility of benflumetol in CO_2. Above this pressure,

temperature becomes the critical factor that influences the solubility of benflumetol leading the higher the solubilities at higher temperature.

Table 4. Solubility (S) of Benflumetol in Carbon Dioxide (mg Benflumetol/ kg CO_2）

P (bar)	308 (K)			313 (K)			323 (K)		
	S (mg/kg)	u_r (S)	CO_2 density[13] (mol/m^3)	S (mg/kg)	u_r (S)	CO_2 density[13] (mol/m^3)	S (mg/kg)	u_r (S)	CO_2 density[13] (mol/m^3)
80	1.3	0.23	9912	1.0	0.10	6351	0.8	0.13	4993
100	3.0	0.17	16243	1.9	0.21	14287	2.6	0.15	8788
120	4.7	0.15	17460	3.0	0.17	16346	5.6	0.13	13340
140	4.5	0.13	18234	6.9	0.10	17371	8.1	0.15	15308
160	5.0	0.14	18816	7.4	0.12	18085	10.3	0.15	16434
180	5.7	0.12	19288	8.4	0.11	18641	19.7	0.12	17226

Standard uncertainties u are $= u(T) = 0.1$ K , $u = u(P) = 0.01$ MPa, u_r(S) values are displayed in each pressure row.
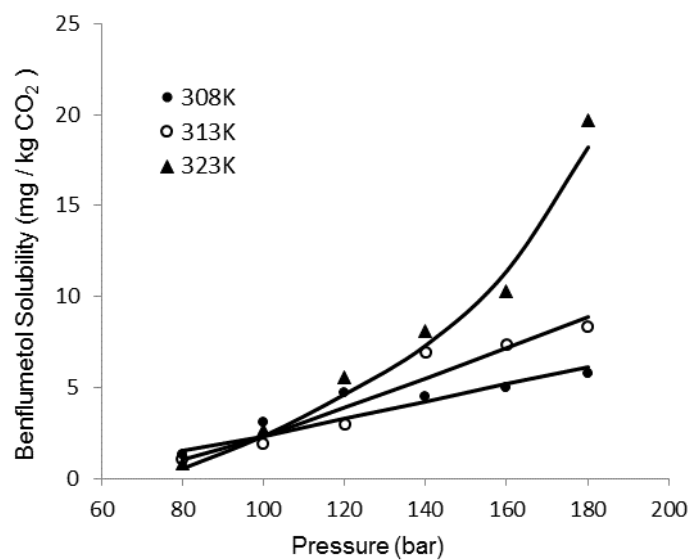

Figure 10. Benflumetol solubility in compressed CO_2 measured using SPMM technique. The lines show best fit to the experimental data.

3.4 Solubility-Density correlation.

Using CO_2 densities from NIST[13], equations 1 and 2 were fitted to the solubility data of azoxystrobin and benflumetol by minimizing the average deviation between the experimental and calculated values for the isotherms simultaneously by adjusting the fitting constants a, b, and k. k is adjustable parameters that can be obtained by fitting the least-squares method to experimental data. The outputted values for azoxystrobin and benflumetol are shown in Table 5. Figures 11 and 12 show the fitted data plots. The association constant k is not an integer, as most solvato complexes are not stoichiometric. It gives an average equilibrium association number, which is a characteristic constant for a given gas and solute. It is clear in Figure 11 that at CO_2 densities greater than 629 kg/m^3 ($\ln(\rho) = 6.44$) the experimental data of azoxystrobin agree well with the Chrastil model. The point at 384 kg/m^3 ($\ln(\rho) = 5.95$) is out of range as the model can only give a reasonable prediction of solubilities at temperature conditions where solvent density has a predominant effect[22]. The average deviation between the experimental and calculated solubility data was calculated to be 11.02 %. The experimental data agree even better with the MST model than those modelled by the Chrastil model over the entire test range and the average deviation between the experimental and calculated solubility data using the MST model was 5.01 %.

 For benflumetol, the outputted values from the Chrastil and MST models and the subsequent plots are shown in Table 5 and Figure 12. The value of the association constant k in the Chrastil equation is greater for azoxystrobin than that of benflumetol due to the presence of CO_2-philic sites on the azoxystrobin molecule. The presence of ether and carbonyl groups enhances CO_2-philicity by providing sites for specific interactions with CO_2 and therefore leads to a higher CO_2 solubility[23,24] The Average Absolute Relative Deviation values of the Chrastil and MST models are 3.63% and 3.52%, respectively within the range of the experimental method. In general, it can be seen that there are correlations between the solubility of azoxystrobin and benflumetol in supercritical CO_2 and its pressure and temperature. It is therefore meaningful to predict the solubilities of azoxystrobin and benflumetol at different temperatures and pressures using these models.

Table 5. Values of Chrastil and MST Model Parameters and Average Absolute Deviation (AAD) for Azoxystrobin and Benflumetol Data

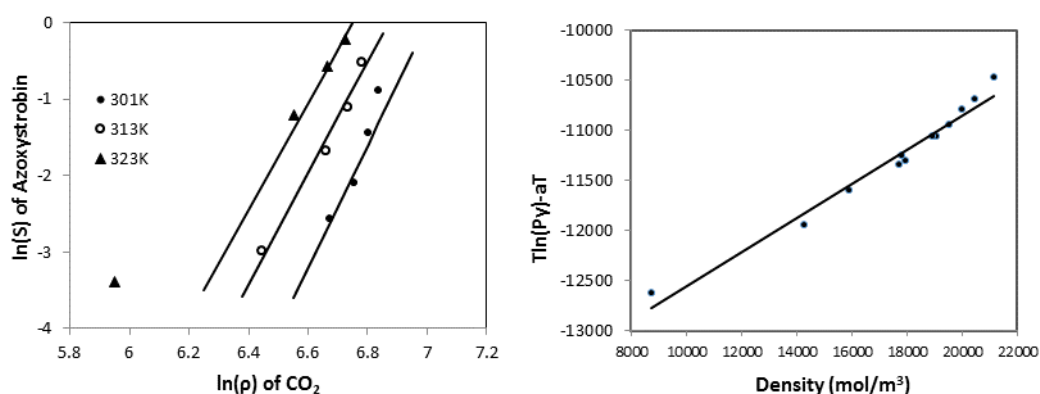| Sample	Model Name	equation	k	a	b	AAD (%)
Azoxystrobin	Chrastil	$\ln(S) = k\ln(\rho) + \dfrac{a}{T} + b$	9.975	-7478.8	44.522	11.02
	MST	$T\ln(Py) = k\rho + aT + b$	0.223	27.9	-15250	5.01
Benflumetol	Chrastil	$\ln(S) = k\ln(\rho) + \dfrac{a}{T} + b$	1.045	-5488.5	-1.136	3.63
	MST	$T\ln(Py) = k\rho + aT + b$	753.569	31.220	9709.342	3.52

Figure 11. Experimental data (Azoxystrobin) fitted with the Chrastil (left) and MST (right) models
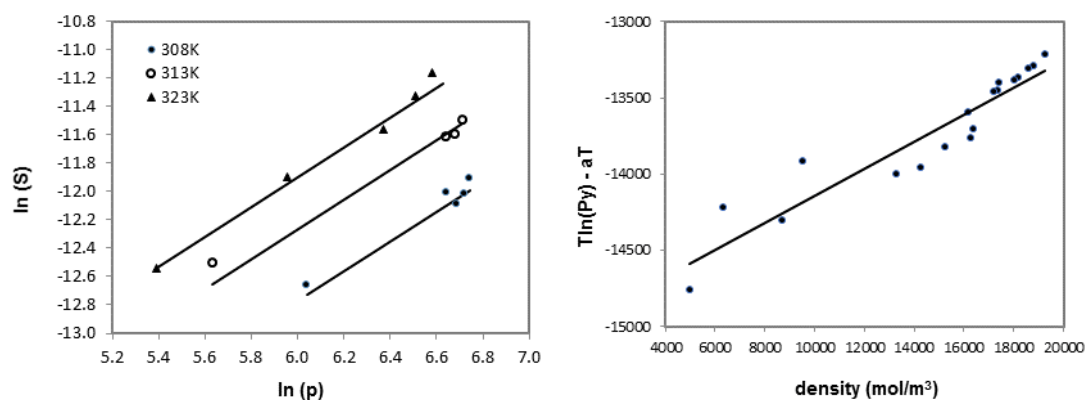

Figure 12. Experimental data (Benflumetol) fitted with the Chrastil model（left）and MST model (right)

4. CONCLUSIONS

The SPMM method offers a simple and reliable approach to measure very low solubilities of solutes in compressed CO_2 as validated by comparing solubility data of caffeine with those found in the literature. The special pan cover prevents the dissolved sample from returning to the sample pan upon depressurisation. This approach eliminates sampling errors encountered when recovering samples that have extremely low masses and avoids the use of spectrophotometric equipment to measure solubility. The solubilities of azoxystrobin and benflutemol were successfully determined using the technique and provide data for the solubility of components in supercritical CO_2.

5. FUNDING SOURCES:

ORCID iD	
Qingguo Li	0000-0002-3676-2563
Tiejun Lu	0000-0003-0920-8134
Piaopiao Pan	0000-0002-2814-7712
Stuart Blackburn	
Gary Leeke	0000-0002-1097-1797

REFERENCES

1. Brunner, G. *Gas extraction: an introduction to fundamentals of supercritical fluids and the application to separation processes*; Steinkopff-Verlag Heidelberg: New York, **1994**, 387.
2. Bott, T. R.; King, M. B. *Extraction of natural products using near-critical solvents*; Chapman & Hall: Glasgow, **1993**, 325.
3. Krukonis, V. J.; Mchugh, M. A. *Supercritical fluid extraction: principles and*

practice; Butterworth-Heinemann: Stoneham, MA, USA, **1986**, 507.

4. Kiran, E.; **Levelt Sengers**, Johanna M.H. (Eds.); *Supercritical fluids: fundamentals for application*; Kluwer Academic Publishers: Dordrechl, **1994**, 796.

5. Bertucco, A.; Vetter, G. *High pressure process technology: fundamentals and applications*; Elsevier: Amsterdam, **2001**, 659.

6. Brunner, G. *Supercritical fluids as solvents and reaction media*; Elsevier: Amsterdam, **2004**, 641.

7. Sanghi, R.; Srivastava, M. *Green Chemistry: Environmental Friendly Alternatives*; Alpha Science International: Oxford, **2003**.

8. Shim, J. J.; Gupta, R. B. *Solubility in Supercritical Carbon Dioxide*; CRC Press: London, **2007**, 909.

9. Mastson, D. W.; Fulton, J. L.; Petersen, R. C.; Smith, R. D. Rapid expansion of supercritical solutions: solute formation of powders, thin films, and fibers. *Ind. Eng. Chem. Res.* **1987**, 26, 2298-2306.

10. Chrastil, J. Solubility of solids and liquids in supercritical gases. *J. Phys. Chem*. **1982**, 86, 3016-3021.

11. Mendez, S. J.; Teja A. S. The solubility of solids in supercritical fluids. *Fluid Phase Equilibr*. **1999**, 158, 501-510.

12. PubChem; URL: *https://pubchem.ncbi.nlm.nih.gov* and ChemicalBook, CAS DataBase; URL: *https://www.chemicalbook.com/ChemicalProductProperty_EN_CB7854882.htm*

13. Lemmon, E. W.; McLinden, M. O.; Friend, D. G. *Thermophysical Properties of Fluid Systems*. In NIST Chemistry WebBook; *NIST Standard Reference Database Number 69; National Institute of Standards and Technology*; Gaithersburg, MD, USA, 2001, https://webbook.nist.gov/chemistry/fluid/, 22nd June 2018.

14. Burgos-Solórzano, G.I.; Brennecke, J.F.; Stadtherr, M.A. Solubility measurements and modeling of molecules of biological and pharmaceutical interest with supercritical CO_2. *Fluid Phase Equil*. **2004**, 220, 57-69 .

15. Johannsen, M.; Brunner, G. Solubilities of the xanthines caffeine, theophylline and theobromine in supercritical carbon dioxide. *Fluid Phase Equil*. **1994**, 95, 215-226.

16. Li, S.; Varadarajan, G.S.; Hartland, S. Solubilities of theobromine and caffeine in supercritical carbon dioxide: correlation with density-based models. *Fluid Phase Equil*. **1991**, 68, 263-280.

17. Saldaña, M.D.A.; Mohamed, R.S.; Baer, M.G.; Mazzafera, P. Extraction of Purine Alkaloids from Maté (Ilex paraguariensis) Using Supercritical CO_2. *J. Agric. Food Chem.,* **1999**, 47, 3804–3808.

18. Stahl, E.; Schilz, W. Mikroanalytische untersuchungen zur Löslichkeit von Naturstoffen in überkritischem Kohlendioxid. *Talanta,* **1979**, 26, 675-679.

19. Tzvetkova, E. 2001, PhD thesis, Siegen University, Germany.

20. Johannsen, M.; Brunner, G. Measurements of Solubilities of Xanthines in

Supercritical Carbon Dioxide + Methanol, static method coupling an equilibrium cell to a supercritical fluid chromatographic system. *J. Chem. Eng. Data*, **1995**, 40, 431-434.

21. Li, B.; Guo, W.; Song, W.; Ramsey, E.D. Interfacing supercritical fluid solubility apparatus with supercritical fluid chromatography operated with and without on-line post-column derivatization: Determining the solubility of caffeine and monensin in supercritical carbon dioxide. *J. Supercrit. Fluids* **2016**, 115, 17-25.

22. Leeke, G. A.; Santos, R. C.; Seville, J.; Alduri, B.; Lee, C. K. Y.; Holmes, A. B. Solubilities of p-tolylboronic acid, bromobenzene, and 4-phenyltoluene in carbon dioxide at elevated pressures. *J. Chem. Eng. Data* **2004**, 49, 48-52.

23. Kilic, S.; Michalik, S.; Wang, Y.; Johnson, K.J.; Enick, R.M.; Beckman, E.J. Phase Behavior of Oxygen-Containing Polymers in CO_2. *Macromolecules* **2007**, 40, 1332-1341.

24. Wang, J.; Wang, M.; Hao, J., Fujita, S.; Arai, M.; Wu, Z.; Zhao, F. Theoretical study on interaction between CO_2 and carbonyl compounds: Influence of CO_2 on infrared spectroscopy and activity of C=O. *J. Supercrit. Fluids* **2010**, 54, 9-15.