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Prediction of Solubility of Solid Biomolecules in Supercritical Solvents Using Group Contribution Methods and Equations of State

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Abstract: The purpose of this study is to present a method to estimate the solubility of solid solutes in supercritical fluids when only the molecule structure is known. The solubility of solid solutes in a supercritical fluid is an important thermo-physical property that needs to be determined if one is to develop a generic supercritical fluid extraction model. Due to the general lack of solubility data and/or pure component property data needed to estimate solubility, a need exists to develop methods to estimate the solubility of solid solutes in a supercritical solvents using limited information. Group contribution methods were used to estimate pure component properties, equations of state (Lee-Kesler-Plocker (LKP) and Mohsen-Nia-Moddaress-Mansoori (MMM) were then used to estimate the PVT behaviour of the solvent and the fugacity coefficient of solute in the solute-solvent mixture. The solubilities of β-carotene, cholesterol, nimodipine and nimbin in supercritical solvents were determined. Our results show that the LKP model provides the best fit for β-carotene and nimodipine in $SCCO_2$ and the MMM model is best for cholesterol in $SCCO_2$ and SCC_2H_6 and for nimbin in $SCCO_2$. The Aromaticity Index (AI) seems to be an important parameter for determining which model will perform best; based on the systems analysed here, one should use the LKP EOS when AI > 0.3, otherwise use the MMM EOS.

Key words: Solubility, supercritical fluid extraction, group contribution methods, equations of state, modelling, phase equilibrium

INTRODUCTION

Supercritical fluids exhibit liquid-like density, gas-like viscosity and diffusion coefficients. These properties are ideally suited for extraction of solutes from dense botanical materials as well as producing new products that cannot be obtained by traditional manufacturing processes. As a result supercritical fluids are widely used as solvents in either liquid-liquid or solid-liquid extraction systems. However, there is still a general lack of fundamental solubility data that limits the rapid development of new Supercritical Fluid Extraction (SFE) processes. As a result of this lack of data, modelling of SFE systems from first principles is currently not possible. Data requirements include that to determine PVT behaviour of supercritical solvents and solutes, boiling points, critical points, sublimation pressures, solid molar volumes, acentric factors and diffusion coefficients of solutes in solvents all over a range of operating temperatures and pressures.

The PVT behaviour of solvents, especially CO_2, has been studied by others and can be easily estimated using a variety of Equations of State (EOS), (Bowers, 1995; Ajchariyapagorn, 2003;

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Cismondi and Mollerup, 2005). Ajchariyapagorn (2003) compared the estimates of density predicted by several EOS with the experimental data for supercritical CO_2 over a range of temperatures (300-345 K) and pressures (8-18 MPa). The Sum of Squared Errors, Eq. 1, calculated from experimental data and the Peng-Robinson, Redlich-Kwong-Soave, Lee-Kesler-Plocker, Peng-Robinson with Boston-Mathias alpha function and Non-Random Two Liquid (NRTL) equations of state are approximately 12, 14, 15, 15 and 34, respectively.

$$SSE = \sum_{i=1}^{N} \left(\log y_{2,i}^{exp} - \log y_{2,i}^{calc} \right)^2 \quad (1)$$

From this analysis, all, but the NRTL equation, are deemed suitable for predicting the PVT behaviour of supercritical CO_2.

However, the behaviour of solutes has not received the same attention. Existing research on solute solubility in supercritical fluids can be broadly classified into two categories, experimental studies (Bartle *et al*., 1991; Yun *et al*., 1991; Singh *et al*., 1993; Subra *et al*., 1997; Medina and Bueno, 2001; Sovova *et al*., 2001; Tonthubthimthong *et al*., 2001; Sue *et al*., 2004; Vedaraman *et al*., 2004; Sauceau *et al*., 2004; Pauchon *et al*., 2004; Vatanara *et al*., 2005; Sciaini *et al*., 2005; Gordillo *et al*., 2005a; Ozcan and Ozcan, 2006; Valderrama *et al*., 2006) providing valuable data against which to compare models and modelling studies (Engelhardt and Jurs, 1997; Hartono *et al*., 2001; Cheng *et al*., 2002; Murga *et al*., 2003; Valderrama and Alvarez, 2004; Khayamian and Esteki, 2004; Chafer *et al*., 2005; Vieira de Melo *et al*., 2005; Serrano-Cocoletzi *et al*., 2005). Most of the modelling studies were based on empirical models or first principles models incorporating fitted parameters obtained from experiments. Only one paper was found that was based entirely on a first principles model and available pure component properties (Gracin *et al*., 2002).

A summary of the experimental studies focussing on measuring solubility of solutes in supercritical solvents over the past 15 years, arranged chronologically, follows. The solubility of slightly volatile compounds in supercritical CO_2 is presented by Bartle *et al*. (1991). Yun *et al*. (1991) determined the solubility of cholesterol in supercritical carbon dioxide at 313 K and from 9.23 to 22.14 MPa. Singh *et al*. (1993) also determined the solubility of cholesterol, however they use supercritical ethane as the solvent at 313 K and 11.07 to 22.14 MPa. Subra *et al*. (1997) measured the solubility of β-carotene in supercritical carbon dioxide at 340 K and from 22.92 to 25.84 MPa. In 2001 Tonthubthimthong *et al*. (2001) performed experiments to extract nimbin from neem seeds using supercritical CO_2 over a range of conditions, (308 to 333 K and 10 to 26 MPa). Using their experimental data it was possible to determine one value of the solubility of nimbin in supercritical CO_2. Medina and Bueno (2001) determined the solubility of nimodipine in supercritical carbon dioxide at a temperature of 313 K and 9.23 to 25.83 MPa. Sovova *et al*. (2001) determined the solubility of β-carotene in supercritical CO_2 at a temperature of 313 K and 11.07 to 22.68 MPa. Sue *et al*. (2004) proposed a simple technique to measure solubilities in supercritical fluids. Measurements of the solubility of silicone dioxide in supercritical water agreed with literature values and new measurements were reported for titanyl phthalocyanine in supercritical acetone. Vedaraman *et al*. (2004) determined the solubility of modified amino acids in supercritical carbon dioxide. They found that the chemical modification of amino acids resulted in increased solubility and concluded that supercritical fluid extraction techniques can be used for their separation. Sauceau *et al*. (2004) measured the solubility of eflucimibe in supercritical carbon dioxide at 308.15 and 318.15 K and from 8 to 30 MPa. Two co-solvents, ethanol and dimethylsulphoxide, were found to significantly enhance the solubility. Pauchon *et al*. (2004) developed an apparatus for the determination of solubility in supercritical carbon dioxide. Measurements were made with naphthalene, to validate the apparatus and with triphenylmethane at 308.15, 318.15 and 328.15 K the measured solubilities were correlated using the model of Adachi and Lu (1983). Vatanara *et al*. (2005) determined the solubility of glucocorticoids at

temperatures from 338 to 358 K and pressures from 213 to 385 bar in supercritical CO_2. The solubilities were correlated using the semi-empirical Bartle model (Bartle *et al*., 1991; Ozcan *et al*., 1997). Results show that the Bartle method holds in the pressure range of 24.3-35.5 MPa. Sciaini *et al*. (2005) measured the solubilities of crystalline NaI, KI and CsI in supercritical ammonia at 420 K. Gordillo *et al*. (2005b) measured the solubility of a dispersed dye in supercritical carbon dioxide at 313 to 353 K and 10 to 35 MPa. The measured solubilities correlated well with models based on equations of state. Physical properties and critical parameters of the solid were estimated using group contribution methods. The thermodynamic model was developed by fitting solid sublimation pressures with binary interaction parameters. The results indicated that the choice of group contribution method is more important than the choice of equation of state. Ozcan and Ozcan (2006) measured the solubility of acid red 57 (AR57) in supercritical carbon dioxide. A semi-empirical equation was developed to correlate the experimental solubilities by means of the density of carbon dioxide in methanol-modifier supercritical carbon dioxide. Valderrama *et al*. (2006) determined the solubility and sublimation pressure of capsaicin in supercritical carbon dioxide at 298, 308 and 313 K. The experimental data was modelled and tested using the Peng-Robinson equation of state.

Several studies focussed on predicting the solubility in supercritical solvents. In all cases the models were either empirical models fitted to experimental data or first principles models with adjustable parameters determined from experimental data. Engelhardt and Jurs (1997) used the existing data of 58 organic compounds taken from the literature to create neural network models for the prediction of the solubility in supercritical carbon dioxide. Although the models were able to predict the solubility of the test data in principle they were not able to predict the solubility of new components. Hartono *et al*. (2001) estimated the solubility of β-carotene and cholesterol in supercritical fluids using the van der Waals (vdW), Redlich-Kwong (RK) and Mohsen-Nia-Moddaress-Mansoori (MMM) equations of state using available experimental data and pure component properties. They found that the MMM cubic equation of state was suitable to estimate the solubility of β-carotene and cholesterol. Cheng *et al*. (2002) estimated the solubility of several steroids, antioxidants, xanthines, drugs and heavy aromatic compounds using the regular solution theory model coupled with the Flory-Huggins equation. The molar volume of the solute in the supercritical phase was fitted using the experimental solubility data. Satisfactory results of solid solubility were obtained which are comparable to those calculated from the equation-of-state method or semi-empirical equations with more adjustable parameters. Murga *et al*. (2003) used the Peng-Robinson (PR) cubic equation of state and fitted the binary parameters with experimental data to estimate the solubility of three hydroxycinnamic acids in supercritical CO_2. Valderrama and Alvarez (2004) developed temperature independent mixing rules to correlate the solubility of 2,3-dimethylnaphthalene, 2,6-dimethylnaphthalene, naphthalene, phenanthrene, anthracene, pyrene, benzoic acid and caffeine in supercritical carbon dioxide. Their model correlates the solute concentration in the gas phase better than models that use temperature dependent constants and temperature dependent mixing rules. Khayamian and Esteki (2004) proposed a neural network model to predict the solubility of naphthalene, biphenyl, fluorine, phenanthrene and triphenylene in supercritical carbon dioxide at 308-333K and 8-13.5 MPa. Their model agreed well with literature data; however, in general, it could not be extended to other molecules. Chafer *et al*. (2005) reported on the solubility of carnosic acid in supercritical CO_2, with ethanol as a modifier over a range of temperatures, pressures and ethanol content. The Group Contribution Associating Equation of State, (GCA-EOS) (Gros *et al*., 1997) was used to correlate the experimental data. Due to the lack of data, the solid volume, critical properties and sublimation pressures of carnosic acid were estimated. Future work will focus on extending the model to represent solid-gas phase equilibria. Vieira de Melo *et al*. (2005) presented a method to predict solubility using the Peng-Robinson equation of state with the UNIFAC activity coefficient model and experimental solubility data of caffeic acid in supercritical CO_2 as a reference. Serrano-Cocoletzi *et al*. (2005) measured the solubility of thiophene in CO_2 and in CO_2 + ethanol mixtures at

temperatures from 313 to 363 K. The experimental results were compared with those calculated values from Peng-Robinson equation of state using classical mixing rules. Gordillo *et al.* (2005b) modelled the thermodynamics of supercritical fluid-solid phase equilibrium of Penicillin G over the range 100 to 350 bar and from 313 to 333 K. They presented an algorithm to fit the two binary interaction parameters with experimental solubility data for the Van der Waals and Lorentz-Berthelot mixing rules applied to the Peng Robinson Equation of state and the sublimation pressure to the Clauius-Clapeyron equation. Nicolas *et al.* (2005) applied the Sanchez-Lacombe Equation of state with various mixing rules to the system of solid-supercritical fluids (carbon dioxide, ethane, ethylene and xenon) and compared the solubility results with the Peng Robinson EOS. Su and Chen (2007) presented a model for estimating the solubility of solid-pharmaceutical compounds containing steroids, antioxidants, antibiotics, analgesics and specific functional drugs in supercritical carbon dioxide compared to the semi-empirical model from the literature. They conclude their model is better than the semi-empirical equations with the same number of adjustable parameters. Only one study was found in which solubilities were estimated entirely from first principles. Gracin *et al.* (2002) estimated the solubility of solid organic compounds at 293 and 298 K in various solvents using a UNIFAC estimate of the activity coefficient of the solute in the solvent. Predicted solubility of nine compounds in a variety of solvents is compared with experimental data. The solubility mole fraction was calculated iteratively by:

$$a^s = x^{sat}\,\gamma^{sat} = \exp\left[\frac{\Delta h_m^{fus}}{R}\left(\frac{1}{T_m}-\frac{1}{T}\right)\right]$$

The accuracy in the prediction by this method was found to depend on the accuracy of the UNIFAC prediction of the activity coefficient of the solute in the saturated solution, as well as on the accuracy of the estimation of the activity of the pure solid.

From a review of the literature from 1991 to 2006, although several experimental studies have been carried out, little work has been done on the development of models to predict solubility of solutes in supercritical fluids from first principles without the use of experimental data. This then provides the main motivation to investigate the development of general methods and models to estimate the solubility of solutes in supercritical fluids using only molecular structure of the molecule. In this work, the physical properties of the pure solute were estimated using group contribution methods and the PVT behaviour was estimated using equations of state.

THEORY

The equations needed to estimate the solubility of a solute in a supercritical solvent are presented below. First, the fundamental equation for solubility is presented in Eq. 2, followed by equations to estimate physical properties and PVT behaviour needed to solve Eq. 2. In general, subscript 1 represents the solvent or Supercritical Fluid (SCF) and subscript 2 represents the solute to be dissolved in the solvent; this study focuses on the estimation of the solubility of the solute in the solvent, y_2^*.

Solubility of Solid Solutes in Supercritical Fluids

The solubility of a solid solute, y_2^*, in a solvent is calculated directly from the iso-fugacity criterion as follows, (Prausnitz *et al.*, 1998):

$$y_2^* = \frac{P_2^s}{P\phi_2}\exp\left[\frac{(P-P_2^s)V_2^s}{RT}\right] \quad (2)$$

In order to solve Eq. 2 for y_2^{sat} at T and P one needs to estimate P_2^s, the sublimation pressure of the pure solid, V_2^s the solid molar volume and ϕ_2, the fugacity coefficient of the solute in the supercritical phase. P_2^s and V_2^s are calculated directly from Eq. 3-6, below and ϕ_2 is estimated from a suitable equation of state. Group contribution methods are used to estimate the pure component properties required in Eq. 3-6.

The pure component properties of many pharmaceutical substances are not available in the literature. However, so-called, group contribution methods for prediction of pure component properties such as critical properties, vapour pressure, heat capacity and acentric factor that rely only on molecular structure of the substance are available in the literature (Reid *et al*., 1987).

Solid Molar Volume, V_2^s

The molar volume of a solid solute, V_2^s is the volume per mole of a substance and it was estimated using Eq. 3 and 4 as follows (Immari and Perini, 1977):

$$\overline{V}_s = \sum_i m_i v_i \tag{3}$$

$$V_2^s = \frac{\overline{V}_s}{1.66} \tag{4}$$

where, $\overline{V}_s$ is calculated crystal volume for a single molecule, m_i is the relative stoichiometric multiplicity determined from the molecular structure and v_i is the unit volume of an atomic element and presented in Table 1 and 2.

Table 1: First-order groups and their contributions for the physical properties (Constantinou and Gani, 1994)

Group	t_{c1i}	p_{c1i} (bar$^{-0.5}$)	v_{c1i} (m^3/kmol)	t_{b1i}
CH_3	1.6781	0.001990	0.07504	0.8894
CH_2	3.4920	0.010558	0.05576	0.9225
CH	4.0330	0.001315	0.03153	0.6033
C	4.8823	-0.010400	-0.00034	0.2878
$CH_2 = CH$	5.0146	0.025014	0.11648	1.7827
CH = CH	7.3691	0.017865	0.09541	1.8433
$CH_2 = C$	6.5081	0.022319	0.09183	1.7117
CH = C	8.9582	0.012590	0.07327	1.7957
C = C	11.3764	0.002044	0.07618	1.8881
$CH_2 = C = CH$	9.9318	0.031270	0.14831	3.1243
ACH	3.7337	0.007542	0.04215	0.9297
AC	14.6409	0.002136	0.03985	1.6254
$ACCH_3$	8.2130	0.019360	0.10364	1.9669
$ACCH_2$	10.3239	0.012200	0.10099	1.9478
ACCH	10.4664	0.002769	0.07120	1.7444
OH	9.7292	0.005148	0.03897	3.2152
ACOH	25.9145	-0.007440	0.03162	4.4014
CH_3CO	13.2896	0.025073	0.13396	3.5668
CH_2CO	14.6273	0.017841	0.11195	3.8967
CHO	10.1986	0.014091	0.08635	2.8526
CH_3COO	12.5965	0.029020	0.15890	3.6360
CH_2COO	3.8116	0.021836	0.13649	3.3953
HCOO	11.6057	0.013797	0.10565	3.1459
CH_3O	6.4737	0.020440	0.08746	2.2536
CH_2O	6.0723	0.015135	0.07286	1.6249
CH-O	5.0663	0.009857	0.05865	1.1557
FCH_2O	9.5059	0.009011	0.06858	2.5892
CH_2NH_2	12.1726	0.012558	0.13128	3.1656
$CHNH_2$	10.2075	0.010694	0.07527	2.5983
CH_3NH	9.8544	0.012589	0.12152	3.1376

Table 1: Continued

Group	t_{c1i}	p_{c1i} ($bar^{-0.5}$)	v_{c1i} (m^3/kmol)	t_{b1i}
CH_2NH	10.4677	0.010390	0.09956	2.6127
CHNH	7.2121	-0.000460	0.09165	1.5780
CH_3N	7.6924	0.015874	0.12598	2.1647
CH_2N	5.5172	0.004917	0.06705	1.2171
$ACNH_2$	28.7570	0.001120	0.06358	5.4736
C_5H_4N	29.1528	0.029565	0.24831	6.2800
C_5H_3N	27.9464	0.025653	0.17027	5.9234
CH_2CN	20.3781	0.036133	0.15831	5.0525
COOH	23.7593	0.011507	0.10188	5.8337
CH_2Cl	11.0752	0.019789	0.11564	2.9637
CHCl	10.8632	0.011360	0.10350	2.6948
CCl	11.3959	0.003086	0.07922	2.2073
$CHCl_2$	16.3945	0.026808	0.16951	3.9300
CCl_2	****	****	****	3.5600
CCl_3	18.5875	0.034935	0.21031	4.5797
ACCl	14.1565	0.013135	0.10158	2.6293
CH_2NO_2	24.7369	0.020974	0.16531	5.7619
$CHNO_2$	23.2050	0.012241	0.14227	5.0767
$ACNO_2$	34.5870	0.015050	0.14258	6.0837
CH_2SH	13.8058	0.013572	0.10252	3.2914
I	17.3947	0.002753	0.10814	3.6650
BR	10.5371	-0.001770	0.08281	2.6495
CH ≡ C	7.5433	0.014827	0.09331	2.3678
C ≡ C	11.4501	0.004115	0.07627	2.5645
Cl-(C ≡ C)	5.4334	0.016004	0.05687	1.7824
ACF	2.8977	0.013027	0.05672	0.9442
HCON $(CH_2)_2$	****	****	****	7.2644
CF_3	2.4778	0.044232	0.11480	1.2880
CF_2	1.7399	0.012884	0.09519	0.6115
CF	3.5192	0.004673	****	1.1739
COO	12.1084	0.011294	0.08588	2.6446
CCl_2F	9.8408	0.035446	0.18212	2.8881
HCClF	****	****	****	2.3086
$CClF_2$	4.8923	0.039004	0.14753	1.9163
F (except as above)*	1.5974	0.014434	0.03783	1.0081
$CONH_2$	65.1053	0.004266	1.44310	10.3428
$CONCHCH_3$	****	****	****	****
$CONCHCH_2$	****	****	****	****
$CON(CH_3)_2$	36.1403	0.040149	2.50310	7.6904
$CONCH_3CH_2$	****	****	****	****
$CON(CH_2)_2$	****	****	****	6.7822
$C_2H_5O_2$	17.9668	0.025435	0.16754	5.5566
$C_2H_4O_2$	****	****	****	5.4248
CH_3S	14.3969	0.016048	0.13021	3.6796
CH_2S	17.7916	0.011105	0.11650	3.6763
CHS	****	****	****	2.6812
C_4H_3S	****	****	****	5.7093
C_4H_2S	****	****	****	5.8260

Table 2: Second-order groups and their contributions for the physical properties (Constantinou and Gani, 1994)

Group	t_{c2i}	p_{c2i} ($bar^{-0.5}$)	v_{c2i} (m^3/kmol)	t_{b2i}
$(CH_3)_2CH$	-0.5334	0.000488	0.00400	-0.1157
$(CH_3)_3C$	-0.5143	0.001410	0.00572	-0.0489
$CH(CH_3)CH(CH_3)$	1.0699	-0.001849	-0.00398	0.1798
$CH(CH_3)C(CH_3)_2$	1.9886	-0.005198	-0.01081	0.3189
$CH(CH_3)_2C(CH_3)_2$	5.8254	-0.013230	-0.02300	0.7273
3 membered ring*	-2.3305	0.003714	-0.00014	0.4745
4 membered ring*	-1.2978	0.001171	-0.00851	0.3563
5 membered ring*	-0.6785	0.000424	-0.00866	0.1919
6 membered ring'	0.8479	0.002257	0.01636	0.1957
7 membered ring'	3.6714	-0.009799	-0.02700	0.3489

Table 2: Continued

Group	t_{c2i}	p_{c2i} (bar$^{-0.5}$)	v_{c2i} (m^3/kmol)	t_{b2i}
$CH_n = CH_m$-$CH_p = CH_k$				
k,n,m,p ∈ (0,2)	0.4402	0.004186	-0.00781	0.1589
$CH_3 = CH_m = CH_n$				
m,n ∈ (0,2)	0.0167	-0.000183	-0.00098	0.0668
CH_2=CH_m=CH_n				
m,n ∈ (0,2)	-0.5231	0.003538	0.00281	-0.1406
CH-$CH_m = CH_n$ or				
C-$CH_m = CH_n$				
m,n ∈ (0,2)	-0.3850	0.005675	0.00826	-0.0900
Alicyclic side chain				
$C_{cyclic}C_m$				
m>1	2.1160	-0.002546	-0.01755	0.0511
$CH_3 = CH_3$	2.0427	0.005175	0.00227	0.6884
CHCHO or				
CCHO	-1.5826	0.003659	-0.00664	-0.1074
CH_3COCH_2	0.2996	0.001474	-0.00510	0.0224
CH_3COCH or CH_3COC	0.5018	-0.002303	-0.00122	0.0920
C_{cyclic} (=O)	2.9571	0.003818	-0.01966	0.5580
ACCHO	1.1696	-0.002481	0.00664	0.0735
CHCHOOH or CCOOH	-1.7493	0.004920	0.00559	-0.1552
ACCOOH	6.1279	0.000344	-0.00415	0.7801
CH_3COOCH or CH_3COOC	-1.3406	0.000659	-0.00293	-0.2383
$COCH_2COO$ or COCHCOO or COCCOO	2.5413	0.001067	-0.00591	0.4456
CO-O-CO	-2.7617	-0.004877	-0.00144	-0.1977
ACCOO	-3.4235	-0.000541	0.02605	0.0835
CHOH	-2.8035	-0.004393	-0.00777	-0.5385
COH	-3.5442	0.000178	0.01511	-0.6331
$CH_m(OH)CH_n(OH)$				
m,n ∈ (0,2)	5.4941	0.005052	0.00397	1.4108
$CH_{m\,cyclic}$-OH				
m ∈ (0,1)	0.3233	0.006917	-0.00297	-0.0690
$CH_m(OH)CH_n(NH_p)$				
m,n,p ∈ (0,3)	5.4864	0.001408	0.00433	1.0682
$CH_m(NH_2)CH_n(NH_2)$				
m,n ∈ (0,2)	2.0699	0.002148	0.0058	0.4247
$CH_{m\,cyclic}$-NHp-$CH_{n\,cyclic}$				
m,n,p ∈ (0,2)	2.1345	-0.005947	-0.0138	0.2499
CH_m-O-CH_n=CH_p				
m,n,p ∈ (0,2)	1.0159	-0.000878	0.00297	0.1134
AC-O-CH_m				
m ∈ (0,3)	-5.3307	-0.002249	-0.00045	-0.2596
$CH_{m\,cyclic}$-S-$CH_{n\,cyclic}$				
m,n ∈ (0,2)	4.4847	****	****	0.4408
CH_m=CH_n-F				
m,n ∈ (0,2)	-0.4996	0.000319	-0.00596	-0.1168
$Ch_m = CH_n$-Br				
m,n ∈ (0,2)	-1.9334	-0.004305	0.00507	-0.3201
$Ch_m = CH_n$-I				
m,n ∈ (0,2)	****	****	****	-0.4453
ACBr	-2.2974	-0.009027	-0.00832	-0.6776
ACI	2.8907	0.008247	-0.00341	-0.3678
$CHm(NH_2)$-COOH				
m ∈ (0,2)	****	****	****	****

Sublimation Pressure, P_2^s

The sublimation pressure of the solid solute, P_2^s, was estimated from the Watson correlation for solids, given by Eq. 5 and 6 (Lyman *et al*., 1982):

$$\ln P_2^s \approx \frac{\Delta H_{vb}}{\Delta Z_b R' T_b}\left[1 - \frac{(3 - 2T_{pb})^m}{T_{pb}} - 2m(3 - 2T_{pb})^{m-1} \ln T_{pb}\right] \quad (5)$$

Table 3: Values of the additional adjustable parameters (Constantinou and Gani, 1994)

Adjustable parameter value (universal constants)	Value
t_o	181.28 K
P_{c1}	1.3705 bar
P_{c2}	0.100220 $bar^{-0.5}$
v_{co}	-0.004350 m^3/kmol
t_{bo}	204.359 K

$$\frac{\Delta H_{vb}}{T_b} = K_F(8.75 + R \ln T_b)$$
$$\text{if} \quad T_{\rho b} > 0.6; \; m = 0.36 \qquad (6)$$
$$\text{if} \quad 0.6 > T_{\rho b} > 0.5; \; m = 0.8$$
$$\text{if} \quad T_{\rho b} < 0.5; \; m = 1.19$$

K_F is the so-called Fishtine constant (Fishtine, 1963), presented in Table 4 and 5 and it depends on the dipole moments of polar and non-polar molecules. ΔH_{vb} is the enthalpy at the boiling temperature and m is a parameter dependent on

$$T_{\rho b} = \frac{T}{T_b}, \; T_b,$$

the normal boiling point of solute is estimated using group contribution methods below. The parameter Δz_b is assumed to have the value of 0.97 (Miller, 1964).

Normal Boiling Point, T_b

The normal boiling point, T_b is the temperature at which the vapour pressure equals 101,325 Pa. To obtain an estimate of T_b, the group contribution method developed by Constantinou and Gani (1994) was used; the constants for T_b are available Table 1-3:

$$T_b = t_{bo} \ln\left[\sum_i N_i t_{b1i} + W\sum_j M_j t_{b2j}\right] \qquad (7)$$

The constant W is assigned to unity in the second-level estimation (second-order approximation), where both first and second-order group contributions are involved and to zero in the basic level (first-order approximation), where only the contributions of first-order groups are employed.

Critical Properties, T_c, P_c and V_c

The critical point is the set of physical conditions at which the physical properties of the liquid and gas become identical. The critical temperature, T_c, critical pressure, P_c and the critical volume, V_c, define the critical point. One may estimate the critical properties by using Eq. (8-10), Constantinou and Gani (1994) and parameters in Table 1-3 as follows:

$$T_c = t_{co} \ln\left[\sum_i N_i t_{c1i} + W\sum_j M_j t_{c2j}\right] \qquad (8)$$

$$P_c = (p_{c1} + \left[p_{c2} + \sum_i N_i p_{c1i} + W\sum_j M_j p_{c2j}\right]^{1/2})\cdot 10^{-5} \qquad (9)$$

$$V_c = (v_{co} + \sum_i N_i v_{c1i} + W\sum_j M_j v_{c2j})\cdot 10^{-3} \qquad (10)$$

Table 4: K_F factors for Aliphatic and Alicyclic[a] organic compounds (Fishtine, 1963)

	No. of carbon atoms (N) in compound, including carbon atoms of functional group											
Compound type	1	2	3	4	5	6	7	8	9	10	11	12-20
Hydrocarbon												
n-Alkanes	0.97	1	1	1	1	1	1	1	1	1	1	1
Alkane isomers				0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99
Mono and dipolefins and isomers		1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1
Cyclic saturated hydrocarbons			1	1	1	1	1	1	1	1	1	1
Alkyl derivatives of cyclic saturated hydrocarbons				0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99	0.99
Halides (saturated or unsaturated)												
Monochlorides	1.05	1.04	1.03	1.03	1.03	1.03	1.03	1.03	1.02	1.02	1.02	1.01
Monobromides	1.04	1.03	1.03	1.03	1.03	1.03	1.02	1.02	1.02	1.01	1.01	1.01
Monoiodides	1.03	1.02	1.02	1.02	1.02	1.02	1.01	1.01	1.01	1.01	1.01	1.01
Polyhalides (not entirely halogenated)	1.05	1.05	1.05	1.04	1.04	1.04	1.03	1.03	1.03	1.02	1.02	1.02
Mixed halides (completely halogenated)	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01
Perfluorocarbons	1	1	1	1	1	1	1	1	1	1	1	1
Compounds containing the keto group												
Esters		1.14	1.09	1.08	1.07	1.06	1.05	1.04	1.04	1.03	1.02	1.01
Ketones			1.08	1.07	1.06	1.06	1.05	1.04	1.04	1.03	1.02	1.01
Aldehydes	-	1.09	1.08	1.08	1.07	1.06	1.05	1.04	1.04	1.03	1.02	1.01
Nitrogen compounds												
Primary amines	1.16	1.13	1.12	1.11	1.1	1.1	1.09	1.09	1.08	1.07	1.06	1.05b
Secondary amines		1.09	1.08	1.08	1.07	1.07	1.06	1.05	1.05	1.04	1.04	1.03b
Tertiary amines			1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01
Nitriles	-	1.05	1.07	1.06	1.06	1.05	1.05	1.04	1.04	1.03	1.02	1.01
Nitro compounds	1.07	1.07	1.07	1.06	1.06	1.05	1.05	1.04	1.04	1.03	1.02	1.01
Sulfur compounds												
Mercaptans	1.05	1.03	1.02	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01
Sulfides		1.03	1.02	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01	1.01
Alcohols												
Alcohols (single-OH group)	1.22	1.31	1.31	1.31	1.31	1.3	1.29	1.28	1.27	1.26	1.24	1.24b
Diols (glycols or condensed glycols)		1.33	1.33	1.33	1.33	1.33	1.33	1.33				
Triols (glycerol, etc.)			1.38	1.38	1.38							
Cyclohexanol, cyclohexyl						1.2	1.2	1.21	1.24	1.26		
Miscellaneous compounds												
Ethers (aliphatic only)		1.03	1.03	1.02	1.02	1.02	1.01	1.01	1.01	1.01	1.01	1.01
Oxides (cyclic ethers)		1.08	1.07	1.06	1.05	1.05	1.04	1.03	1.02	1.01	1.01	1.01

a: Carbocyclic or heterocyclic compounds having aliphatic properties. b: For N = 12 only; no prediction is made for K_F where N > 12, (1): Consider any phenyl group as a single carbon atom. (2): K_F factors are the same for all aliphatic isomers of a given compound. For example, K_F = 1.31 for n-butyl alcohol, i-butyl alcohol, t-butyl alcohol and s-butyl alcohol. (3): In organometallic compounds, consider any metallic atom as a carbon atom. (4): For compounds not included in this table, assume K_F = 1.06

Table 5: Values of K_F for aromatic hydrogen bonded systems[a] (Fishtine, 1963)

Compound type	K_F
Phenols (single-OH)	1.15
Phenols (more than one-OH)	1.23
Anilines (single-NH_2)	1.09
Anilines (more than one-NH_2)	1.14
N-substituted anilines (C_6H_5NHR)	1.06
Naphthols (single-OH)	1.09
Naphthylamines (single-NH_2)	1.06
N-substituted naphthylamines	1.03

a: For mixed systems, K_F for OH group takes precedence. Thus, K_F for p-aminophenol is 1.15

Pitzer's Acentric Factor, ω

Pitzer's acentric factor, ω, was estimated using the Lee-Kesler correlation (Reid *et al*., 1987) as shown in Eq. 11, where

$$\theta = \frac{T_b}{T_c}$$

$$\omega = \frac{3}{7}\frac{\theta}{1-\theta}\log_{10} P_c - 1.0 \tag{11}$$

Fugacity Coefficient, Φ_2

The fugacity coefficient of the solute in the supercritical phase ϕ_2 was estimated using equations of state. The two equations of state presented in this study are the non-cubic, corresponding states Lee-Kesler-Pollock (LKP) model and the cubic Mohsen-Nia-Moddaress-Mansoori (MMM) equation of state.

Lee Kesler Plocker EOS

The functional form of Lee-Kesler-Pollock (LKP) equation of state (Plocker *et al*., 1978) is given by Eq. 12:

$$z = z^{(0)} + \frac{\omega}{\omega^{(r)}}(z^{(r)} - z^{(0)}) \tag{12}$$

where, $\omega^{(r)} = 0.3978$; $z^{(0)}$ is the compressibility factor of simple fluid and $z^{(r)}$ is the compressibility factor of a reference fluid. The compressibility factors, $z^{(0)}$ and $z^{(r)}$, are calculated using the Benedict-Webb-Rubin (BWR) equation of state:

$$z = \frac{P_r V_r}{T_r} = 1 + \frac{B}{V_r} + \frac{C}{V_r^2} + \frac{D}{V_r^5} + \frac{c_4}{T_r^3 V_r^2}\left(\beta + \frac{\gamma}{V_r^2}\right)\exp\left(-\frac{\gamma}{V_r^2}\right) \tag{13}$$

with

$$B = b_1 - \frac{b_2}{T_r} - \frac{b_3}{T_r^2} - \frac{b_4}{T_r^3}$$

$$C = c_1 - \frac{c_2}{T_r} + \frac{c_3}{T_r^3}$$

$$D = d_1 + \frac{d_2}{T_r}$$

There are two sets of constants for b_1, b_2, b_3, b_4, c_1, c_2, c_3, d_1, d_2, β and γ, one for the simple fluid and one for the reference fluid; these are presented in Table 6. The fugacity coefficient of a pure component, ϕ, is estimated as follows:

$$\ln\phi = z - 1 - \ln z + \frac{B}{V_r} + \frac{C}{2V_r^2} + \frac{D}{5V_r^5} + E$$

With

$$E = \frac{c_4}{2T_r^3\gamma}\left[\beta + 1 - \left(\beta + 1 + \frac{\gamma}{V_r^2}\right)\exp\left(-\frac{\gamma}{V_r^2}\right)\right]$$

Table 6: Constants for LKP equation of state (Plocker *et al*., 1978)

Constant	b1	b2	b3	b4	C1	c2	c3	c4	d1 (10^5)	d2(10^5)	B	g
Simple fluid (0)	0.118	0.266	0.155	0.030	0.024	0.019	0	0.043	1.55	6.24	0.654	0.060
Reference fluid (r)	0.203	0.332	0.028	0.203	0.031	0.050	0.017	0.042	4.87	0.74	1.226	0.038

The fugacity coefficient of component i in a mixture, ϕ_i is given by:

$$\ln\phi_i = \ln\phi_M - \frac{1}{T}\frac{\Delta h_M}{RT_{cM}}\sum_{j\neq i} z_j\left(\frac{dT_{cM}}{dz_j}\right)_{z_k} + \frac{z_M - 1}{p_{cM}}\sum_{j\neq i} z_j\left(\frac{dp_{cM}}{dz_j}\right)_{z_k} - \left(\frac{\partial \ln\phi_M}{\partial\omega_M}\right)_{T_r,P_r}\sum_{j\neq i} z_j\left(\frac{d\omega_M}{dz_j}\right)_{z_k} \quad \text{with}$$

$(k \neq i, j)$

$$\left(\frac{\partial \ln\phi_M}{\partial\omega_M}\right)_{T_r,p_r} = \frac{1}{\omega^{(r)}}\left[\left(\ln\phi_M\right)^{(r)} - \left(\ln\phi_M\right)^{(o)}\right]$$

$$\left(\frac{dT_{cM}}{dz_j}\right)_{z_k} = \frac{\left[2\sum_1 z_l\left(v_{clj}{}^{\eta}T_{clj} - v_{cli}{}^{\eta}T_{cli}\right) - \eta v_{cM}{}^{\eta-1}\left(\frac{dv_{cM}}{dz_j}\right)_{z_k} T_{cM}\right]}{v_{cM}{}^{\eta}}$$

$$\left(\frac{dv_{cM}}{dz_j}\right)_{z_k} = 2\sum_1 z_l\left(v_{clj} - v_{cli}\right)$$

$$\left(\frac{dp_{cM}}{dZ_j}\right)_{z_k} = p_{cM}\left[\left(\frac{dz_{cM}}{dz_j}\right)/z_{cM} + \left(\frac{dT_{cM}}{dz_j}\right)_{z_k}/T_{cM} - \left(\frac{dv_{cM}}{dz_j}\right)_{z_k}/v_{cM}\right]$$

$$\left(\frac{dz_{cM}}{dz_j}\right)_{z_k} = -0.085\left(\frac{d\omega_M}{dz_j}\right)_{z_k}$$

$$\left(\frac{d\omega_M}{dz_j}\right)_{z_k} = \omega_j - \omega_i \qquad , \quad k \neq i, j$$

$$\eta = 0.251$$

Mohsen-Nia-Moddaress-Mansoori EOS

The Mohsen-Nia-Moddaress-Mansoori (MMM) cubic equation of state is based on the statistical mechanical information available for repulsive thermodynamic functions and the phenomenological knowledge of the attractive intermolecular potential tail contributions to the thermodynamic properties (Mohsen-Nia *et al*., 1993). The MMM equation of state has the following form:

$$P = \frac{RT(v + 1.3191b)}{v - b} - \frac{a}{T^{0.5}v(v + \sum y_i b_{ii})} \tag{14}$$

$$a_{ii} = \frac{0.48748R^2T_{cii}{}^{2.5}}{P_{cii}} \qquad b_{ii} = \frac{0.064662RT_{cii}}{P_{cii}}$$

$$a = \sum_i\sum_j y_i y_j a_{ij}, \qquad b = \frac{3\left(\sum_i\sum_j y_i y_j b_{ij} + \sum_i y_i b_{ii}\right)}{4}$$

$$\phi_i = \exp\left[2.3191\left[\frac{3\left(2\sum_j y_j b_{ij} - \sum_i\sum_j y_i y_j b_{ij}\right)}{4(v-b)} + b_{ii} - \ln(1-\frac{b}{v})\right] - \ln z + \frac{a}{RT^{1.5}\sum_i y_i b_{ii}}\left[\left(\frac{b_{ii}}{\sum_i y_i b_{ii}} - \frac{2\sum_j y_j a_{ij}}{a}\right)\ln\left(1+\frac{\sum_i y_i b_{ii}}{v}\right) - \frac{b_{ii}}{v+\sum_i y_i b_{ii}}\right]\right]$$

RESULTS AND DISCUSSION

The solubility of four components, β-carotene, cholesterol, nimodipine and nimbin in supercritical CO_2 and C_2H_6, were predicted using the equations outlined above and the results were compared with available literature data. Equation (2-14) were solved numerically using MATLAB 7.1 (Mathworks Inc, 2005) to estimate the solubility,

Figure 1-4 show molecular structure of β-carotene, cholesterol (Hartono *et al*., 2001) nimodipine (Medina and Bueno, 2001) and nimbin (Agrawal *et al*., 2005) respectively. Table 7 contains the physical properties predicted for each biomolecule; the Aromaticity Index will be discussed also.

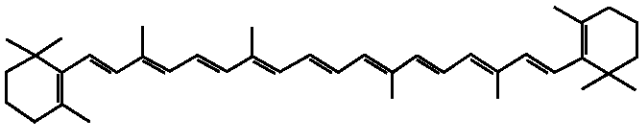

Fig. 1: Structure of β-carotene (Hartono *et al*., 2001)

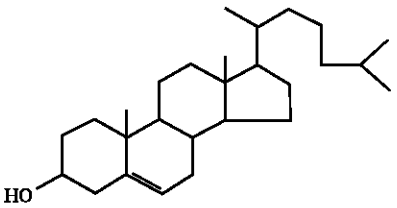

Fig. 2: Structure of cholesterol (Hartono *et al*., 2001)

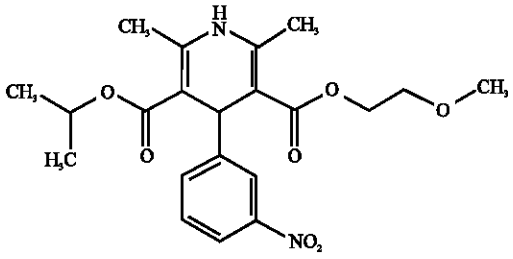

Fig. 3: Structure of nimodipine (Medina and Bueno, 2001)

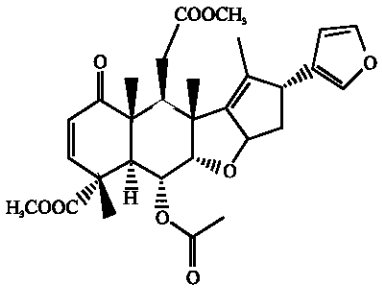

Fig. 4: Structure of nimbin (Agrawal *et al*., 2005)

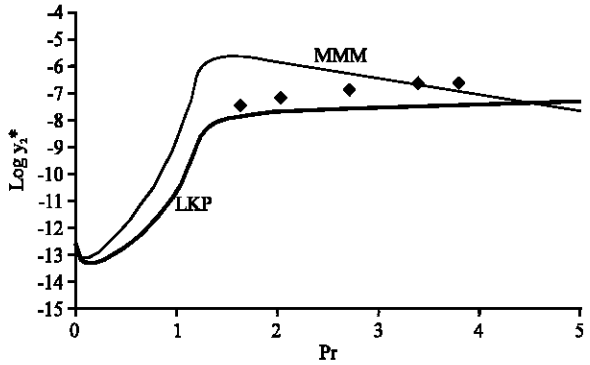

Fig. 5: Solubility of β-carotene in $SCCO_2$ at 313 K: ♦ 2 experimental data, Sovova *et al*. (2001)

Table 7: Physical properties of biomolecule

Biomolecule	T_b(K)	T_c(K)	P_c(MPa)
β-carotene	729.2	898.9	0.562
Cholesterol	656.6	845.6	1.0445
Nimodipine	1,088.1	1,334.6	1.410
Nimbin	1,2351.1	1,512.2	0.999

The solubility of β-carotene in $SCCO_2$ at 313 and 340 K is shown in Fig. 5 and 6, respectively. Although we are primarily interested in the supercritical region, P_r>1, we have plotted the predicted solubility from a reduced pressure, of 0 to 5. At $P_r \approx 0$ and $P_r \geq 1.5$ the slope of solubility curve is negative indicating that, with increasing pressure, the solubility decreases. This counter intuitive result has been observed by others but has yet to be explained (Hartono *et al*., 2001); it is thought to be an artefact of the equations of state. From Fig. 5 at 313 K, one can see that both the LKP and MMM EOS can reasonably fit the data obtained by Sovova *et al*. (2001) for reduced pressures greater than ~2.5. However, the LKP model, in general, appears to provide a better fit of the experimental data and the shape of the LKP model more closely represents the data because the MMM model exhibits a maximum which is not observed in the data. The agreement between the LKP model and the data of Subra *et al*. (1997) is more clearly illustrated in Fig. 6 at 340 K. In general, the LKP EOS is in good agreement with the experimental data and follows the same trend for both temperatures. The SSE, calculated from Eq. (1) was 2.29 and 1.12 for the LKP model at 313 and 340 K, respectively. Whereas the value for the MMM model was 5.35 and 7.65 for the same temperatures indicating a better fit for the LKP model. It is important to note that the only data used to estimate the solubility, y_2^*, was the molecular structure of the solute; keeping this in mind the goodness of fit is then quite good.

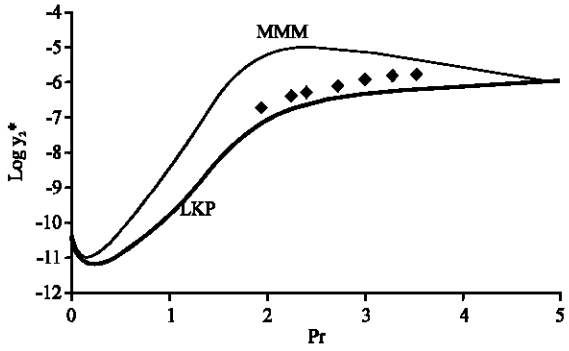

Fig. 6: Solubility of β-carotene in $SCCO_2$ at 340 K: ♦ experimental data, Subra *et al*. (1997)

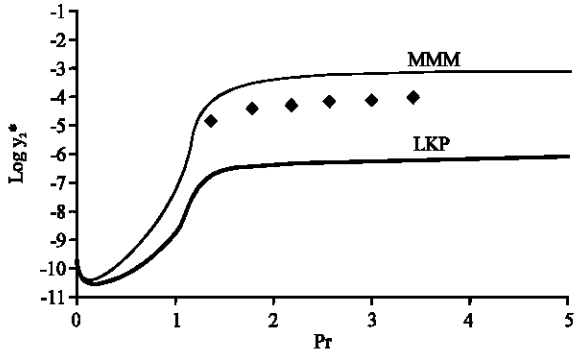

Fig. 7: Solubility of cholesterol in $SCCO_2$ at 313 K: ♦ experimental data, Yun *et al*. (1991)

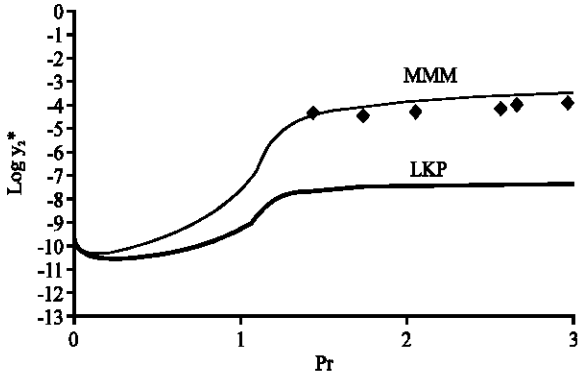

Fig. 8: Solubility of cholesterol in SCC_2H_6 at 313 K:♦ experimental data, Singh *et al*. (1993)

Figure 7 and 8 show the solubility of cholesterol at 313 K in $SCCO_2$ and SCC_2H_6, respectively. In both cases the figures show that the MMM equation of state provides a much better fit of the experimental data of Yun *et al*. (1991) and Singh *et al*. (1993) than does the LKP model. The goodness of fit is quantified by the SSE calculation; the value of which for the MMM model is 4.41 and 0.73 compared to the LKP model which has an SSE of 25.55 and 93.96, respectively.

The switch in goodness of fit from LKP, for β-carotene, to MMM, for cholesterol, was considered. Referring back to Fig. 1 and 2, one can see that β-carotene is a relatively straight chain molecule with double carbon bonds compared to cholesterol which is somewhat more aromatic with several benzene rings. Bird (1985) stated that the concept of aromaticity is virtually a tenet of faith to organic compounds yet its quantification has proved remarkably elusive. Koch and Dittmar (2006) defined the so-called aromaticity index (AI) as the ratio of the 'double-bond equivalent', DBE_{AI} to the carbon atom equivalent C_{AI}, as shown in Eq. 15:

$$AI = \frac{DBE_{AI}}{C_{AI}} = \frac{1 + C - O - S - 0.5H}{C - O - S - N - p} \quad (15)$$

where, C, O, S, H, N and P represents the number of atoms of carbon, oxygen, sulphur, hydrogen, nitrogen and phosphorous in the molecule that affect the degree of unsaturation or double atoms not the number of total atom in molecule. The AI of the solutes considered here is shown in Table 7 above.

It should be noted that a molecule that has a ring structure and generally referred to as aromatic actually has a lower Aromaticity Index than a straight chain molecule. This, then, suggests that the MMM model is more suitable for a solute with a low aromaticity index and the LKP model for a solute molecule with a high aromaticity index.

Nimodipine, the third solute considered, has an aromaticity index of 0.5 which is greater than that of β-carotene; as a result, one might expect that the LKP model would provide a more suitable fit of the experimental data. The predicted solubility of nimodipine in $SCCO_2$ at 313 K is shown in Fig. 9. As one can see there is a significant difference between the predictions of the MMM EOS and the LKP EOS. In addition, the MMM model does not exhibit any trend, it is essentially invariant with pressure whereas the LKP EOS and the data of Medina and Bueno (2001) exhibit a similar trend. The SSE for the MMM model is 114.53 and 8.54 for the LKP model. Although the fit is not as good as one might hope for, the LKP model is certainly better than the MMM model, as was predicted using the AI.

The final solute that was considered here is nimbin which has an aromaticity index of 0.150 which is lower than that of cholesterol and so one would expect that the MMM EOS would be more suitable than the LKP EOS. Figure 10 is a plot of the solubility of nimbin predicted by the two equations of state MMM and LKP; only one data point is available from the work of Tonthubthimthong *et al*., 2001. As theorised, the MMM EOS is significantly better at predicating the solubility than is the LKP EOS. Based on a single data point, the SSE for the two models was calculated to be 6.7 for MMM and 75.2 for the LKP model. Although a single data point is not adequate for model development or validation it does indicate that the MMM EOS does show promise to predict the solubility of nimbin. Future work will focus on the prediction of extraction of nimbin and comparison with the experimental extraction experiments of Tonthubthimthong *et al*. (2001).

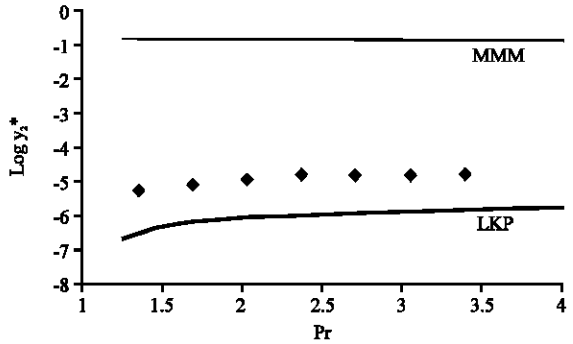

Fig. 9: Solubility of nimodipine in $SCCO_2$ at 313 K: ♦ experimental data, Medina and Bueno (2001)

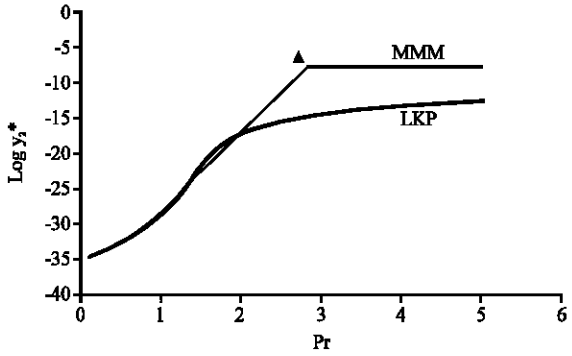

Fig. 10: Solubility of Nimbin in $SCCO_2$ at 328 K: ▲ experimental data, Tonthubthimthong *et al*. (2001)

Table 8: Sum of squared error (SSE) and aromaticity index (AI)

		SSE		
System	T(K)	MMM	LKP	AI
CO_2-β-carotene	313	5.345707	**2.292453**	**0.325**
CO_2-β-carotene	340	7.653367	**1.119651**	**0.325**
CO_2-Cholesterol	313	**4.411107**	25.54711	**0.154**
C_2H_6-Cholesterol	313	**0.726696**	93.96295	**0.154**
CO_2-Nimodipine	313	114.5257	**8.541477**	**0.500**
CO_2-Nimbin	328	**6.7554***	75.2192*	**0.150**

A summary of the Sum of Squared Errors (SSE) and the Aromaticity Index (AI) for each of the five systems is presented in Table 8. It is clear from this summary that systems with a low AI are best fitted using the MMM EOS whereas those with a high AI are best fitted using the LKP EOS. Based on the limited number of systems analysed, one can say that if AI > 0.3 then LKP should be used and if AI < 0.3 then MMM is more appropriate. However, the region 0.1 > AI > 0.5 has yet to be explored.

CONCLUSIONS

A methodology to estimate the solubility of a solid solute in a supercritical fluid was proposed requiring only that the molecular structure of the solute be known. Group contribution methods were used to estimate pure component properties and equations of state to estimate PVT behaviour; no experimental data was required.

Experimental solubility data of four solid solutes, β-carotene, cholesterol, nimbodipine and nimbin was compared with the model predictions. It was found that both the LKP and MMM EOS were suitable for estimating the solubility of test solutes in supercritical fluids. The LKP EOS was found to be suitable for estimating the solubility of β-carotene and nimodipine while the solubility of cholesterol and nimbin was best estimated using the MMM EOS.

The Aromaticity Index (AI) seems to be an important parameter for determining which model will perform best; the LKP EOS is most suitable for molecules with a high AI whereas the MMM EOS is most suitable for molecules with low AI values. Based on the four solutes analysed here the LKP EOS should be used when the AI > 0.3, otherwise use the MMM EOS. Given the fact that only four solutes were studied, one must also conclude that this study is preliminary and further research and testing should be undertaken.

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