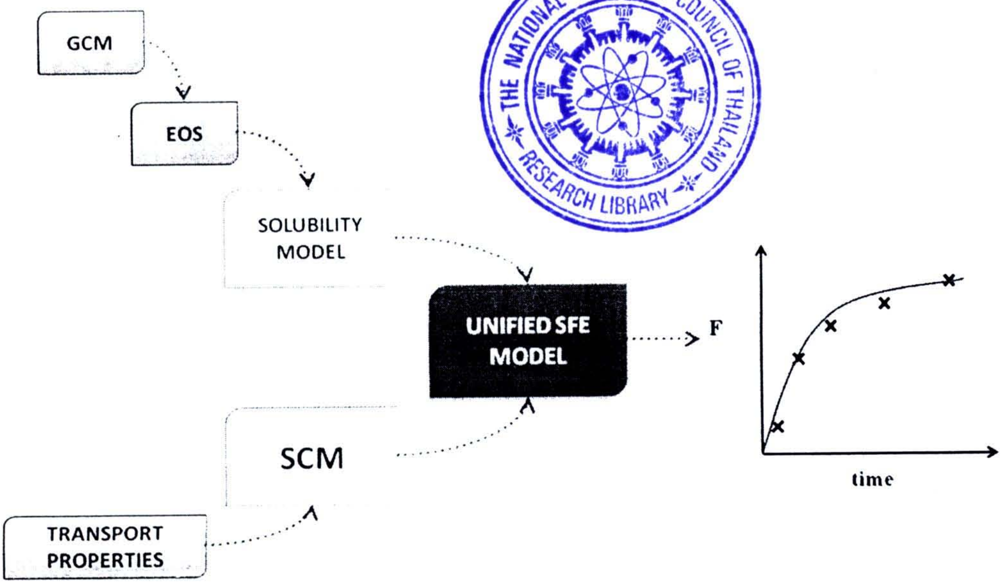
CHAPTER 3 MODEL DEVELOPEMENT

This chapter covers the conceptual models that explain all assumptions, concepts, and applicability of the model. The proposed supercritical fluid extraction model contains two main parts: the solubility model and the shrinking core model as shown in Figure 3.1. The solubility of biomolecules in supercritical fluids was predicted using equations of state (EOSs) as described in section 3.1. Critical properties required in EOSs can be estimated by group contribution methods (GCMs) and available correlations. After that, development and validation of the supercritical extraction yield model were presented in section 3.2. Transport properties in critical region obtained from literature correlations were required for extraction yield prediction. Finally, the extraction yield was described as a function of operating conditions, extractor geometry, model parameters, and time. Moreover, the effects of model parameters on the prediction yield are determined using sensitivity analysis.



$$EXTRACTION\ YIELD\ (F) = f\,(P, T, Q, d_p, \varepsilon_p, CS, k_f, y^*_2, D_e, D_L, \rho_m, \mu_m \text{ and } t)$$

Figure 3.1 Supercritical fluid extraction model of this research.

3.1 Calculation of Solid Solubility in Supercritical Fluids

Solid solubility in SCFs refers to its composition in the supercritical fluid phase. The interesting solids are from natural products or pharmaceuticals, which have complex where v is a SCF molar volume (m^3/gmol). ϕ_i^{scf} in Equation 3.4 can be obtained by using an EOS. n_i and n_j are mole numbers of component i and j respectively. Z is a compressibility factor (Equation 3.5).

$$Z = \frac{Pv}{RT} \tag{3.5}$$

When both fugacity coefficients (ϕ_i^s and ϕ_i^{scf}) from Equation 3.2 and 3.3 are substituted into Equation 3.1, equilibrium expressions yield Equation 3.6:

$$P_i^{sub}\phi_i^s \exp\left(\int_{P_i^{sub}}^{P} \frac{v_i^s}{RT} dP\right) = y_i\phi_i^{scf} P \tag{3.6}$$

It is generally assumed that a solid is pure, neither a solvent nor a cosolvent dissolves in solid (Walas, 1985). v_i^s does not change with pressure and P_i^{sub} is very low. ϕ_i^s is normally at its saturation. Therefore ϕ_i^s can be assumed to be unity, Equation 3.6 becomes:

$$y_i^* = \frac{P_i^{sub}}{P\phi_i^{scf}} \exp\left[\frac{(P - P_i^{sub})v_i^s}{RT}\right] \tag{3.7}$$

According to Equation 3.7, P_i^{sub} and v_i^s of a solute are required for calculating its solubility in SCCO$_2$ (y_i*).

The usual approach is to compute a solid solubility by locating a mole fraction that satisfies an isofugacity criterion Equation 3.7, which might lead to numerical pitfalls, as multiple solutions to an equifugacity condition could exist. Nonuniqueness is a particular problem, and special care should be taken to determine a correct solubility root. Thus, a stability analysis routine based on a modified tangent-plane function and a phase identification procedure was employed to determine all roots to the equifugacity condition.

Many efforts successfully modelled a solid-gas equilibrium based on cubic EOSs with one or two interaction parameters by correlating experimental data (Cross and Akgerman, 1998). Any uncertainties of solid component properties can affect on an accuracy of predicted solubilities (Gordillo et al., 2005). In this work, six EOSs are selected to calculate a fugacity coefficient of a solid solute in fluid phase without any adjustable parameter. This research also focuses on how to estimate pure physical properties of all components used precisely. More details of the EOSs and model development will be described in the following section (Figure 3.2).

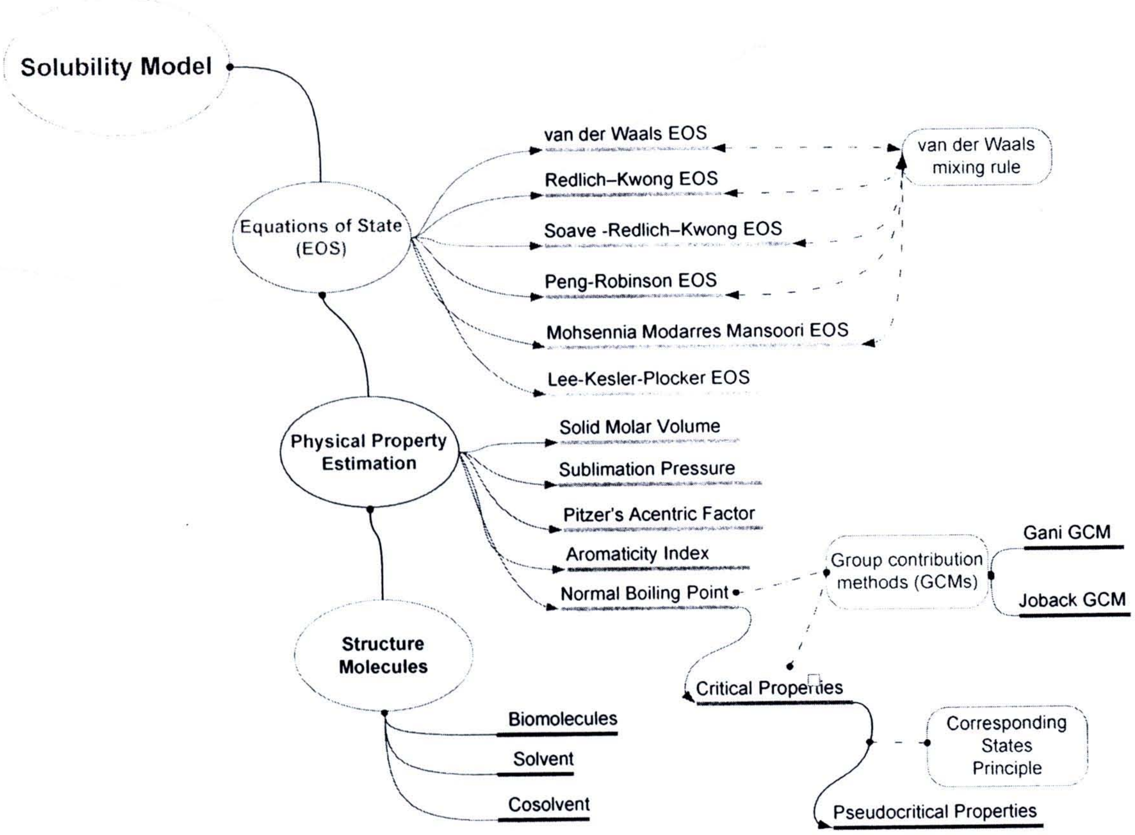


Figure 3.2 The summary of all methods used on the solubility estimation.

3.1.1 Equations of State

Equations of state (EOSs) are equation relating any three intensive, thermodynamic variables. Basically, all of cubic EOSs are originally developed to characterise hydrocarbons, and they embody a very wrong component of corresponding state theory (CST). Various procedures have been proposed in the literature to predict solubilities of non-volatile liquids or solids in supercritical fluids (Hartono, Mansoori and Suwono, 2001). The most computationally straightforward and thermodynamically consistent method for modelling high-pressure phase equilibria is to apply EOSs. In a problem, if pressure and temperature are known and volume of is required. Z values can be used to identify phase of fluid (Table 3.1). A cubic EOS gives three roots for Z as can be seen in Figure 3.3. A single positive real root (or three equal positive real roots) in a given phase means that a pure component exists. When applied to mixtures, the largest positive real root is taken as a value of Z when a mixture is in a vapour phase, while the smallest positive real root is taken for Z when the mixture is in the liquid phase. Once Z from cubic EOSs is solved, a derivative of pressure (P) with respect to mole fraction of component i (n_i) is obtained as shown in Equation 3.8.

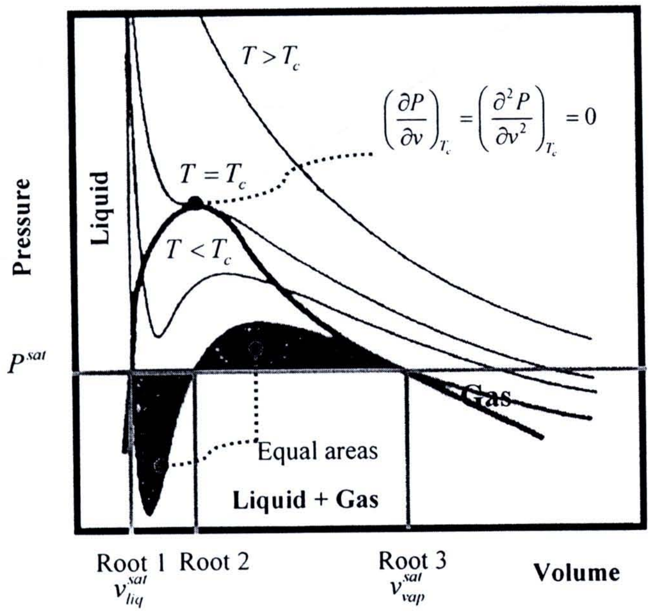


Figure 3.3 Diagram of states of a substance in volume (v) – pressure (P) coordinates: temperatures (T) are isotherms calculated according to EOS (Prausnitz, Lichtenthaler and de Azevedo, 1998).

Table 3.1 Compressibility factors range at different fluid phases.

Fluid Phase	**Compressibility Factor (Z)**
Ideal gas	$Pv = RT \rightarrow Z = 1$
Dense gases or liquids	$Z \neq 1$ Usually $Z < 1$ Supercritical states $Z > 1$

In this study, six EOSs were evaluated regarding their ability to describe solid-fluid equilibria. There are five cubic EOSs, i.e. van der Waals (van der Waals, 1873), Redlich-Kwong (Redlich and Kwong, 1949), Soave-Redlich-Kwong (Soave, 1972), Peng-Robinson (Peng and Robinson, 1976), Mohsennia-Modarres-Mansoori (Mohsen-Nia, Modaress and Mansoori, 1993)) EOSs combined with a mixing rule are presented in Table 3.2. The last one is the Lee-Kesler-Plöcker EOS which is a non-cubic EOS (Plöcker, Knapp and Prausnitz, 1978).

3.1.1.1 van der Waals Equation of State

The van der Waals (vdW) EOS is the first capable equation for representing vapour-liquid coexistence based on the assumption that there are characteristic interaction energy (a) and finite volume (b). This, in turn, captures two basic types of physical forces which are attractive (a/v^2) and repulsive (v-b) terms (van der Waals, 1873).

3.1.1.2 Redlich-Kwong Equation of State

Redlich and Kwong (1949) proposed the first modified vdW-EOS used extensively for engineering calculations for vapour phase properties of a mixture containing nonpolar components. The Redlich Kwong (RK) EOS gives more accurate solution by introducing temperature-dependence for the attractive term. RK-EOS is an empirical equation by fitting experimental data for nonpolar (or slightly polar) fluids and their mixtures. Therefore, RK-EOS is not recommended to apply for polar substances. Substances not forming hydrogen bonding and with nonpolar character will be comparatively better represented by RK-EOS (Redlich and Kwong, 1949).

3.1.1.3 Soave-Redlich-Kwong Equation of State

The RK-EOS improved by Soave (Soave, 1993), SRK-EOS, is one of the most popular EOS and is widely used in process simulation. Wilson (1966) expressed $\alpha(T)$, an adimensional factor which becomes unity at $T = T_c$, as a function of a reduced temperature ($T_r = T/T_c$) and an acentric factor (ω) for the RK-EOS. A new $\alpha(T)$ function for heavy hydrocarbons was used with SRK-EOS (Soave, 1972). The binary interaction parameters were obtained by forcing SRK-EOS to the vapour pressure for nonpolar hydrocarbon compounds at $T_r = 0.7$.

3.1.1.4 Peng-Robinson Equation of State

The RK-EOS, improved by Peng and Robinson is also one of the most popular EOS. It is an empirical equation by fitting experimental data as same as The SRK-EOS. This equation is often used to predict the effect of pressure on fluid density because of its accurate density predictions at high pressure and its relatively simple form. Even thought, the PR-EOS exhibits performance similar to the SRK-EOS for the most part but it performs the liquid density calculation of nonpolar and slightly polar components for mid-range hydrocarbons more accurately than the SRK-EOS (Peng and Robinson, 1976).

3.1.1.5 Mohsennia-Modarres-Mansoori Equation of State

The MMM-EOS is based on a statistical mechanics model of repulsive and attractive forces (Mohsen-Nia, Modarress and Mansoori, 2003). This EOS is suitable for both polar and nonpolar substances. In general, the binary interaction parameters, obtained from correlating solid-gas equilibrium data, may have either positive or negative values and are function of temperature. They often include the possible errors in the thermophysical properties of the solid (vapour pressures and critical properties). Moreover, a single interaction parameter is often not sufficient (Mohsen-Nia, Modaress and Mansoori, 1993; Huang et al., 2007).

3.1.1.6 Lee-Kesler-Plöcker Equation of State

The Lee-Kesler-Plöcker EOS is based on the deviations of PVT properties of interesting substance from simple fluid and particular reference substance. It is an accurate general method for non-polar substances and mixtures (Plöcker, Knapp and Prausnitz, 1978). The compressibility (Z) from this EOS was developed by starting from a polynomial form in acentric factor (ω) but it is reduced form of two terms of the compressibility factors of the simple fluid, $z^{(o)}$ and the reference fluid, $z^{(r)}$. They are calculated separately by a modified Benedict–Webb–Rubin (BWR) equation as functions of reduced variables $T_r = T/T_c$, $P_r = P/P_c$, $V_r = VP_c/(RT_c)$ and $\square_i^{scf}$ is determined by LKP-EOS, Equation 3.13 (Hartono, Mansoori and Suwono, 2001; Coutsikos, Magoulas and Kontogeorgis, 2003).

$$\ln\phi_i^{scf} = \ln\phi_M - \frac{1}{T}\frac{\Delta h_M}{RT_{cM}}\sum_{j\neq i} Z_j(\frac{dT_{cM}}{dz_j})_{z_k} + \frac{Z_M - 1}{P_{cM}}\sum_{j\neq i} Z_j(\frac{dP_{cM}}{dZ_j})_{z_k}$$
$$-\left(\frac{\partial \ln\phi_M}{\partial\omega_M}\right)_{T_r,P_r}\sum_{j\neq i} Z_j\left(\frac{d\omega_M}{dZ_j}\right)_{z_k} \quad ;(k\neq i,j) \tag{3.13}$$

$$\left(\frac{\partial \ln\phi_M}{\partial\omega_M}\right)_{T_r,P_r} = \frac{1}{\omega^{(r)}}\left[(\ln\phi_M)^{(r)} - (\ln\phi_M)^{(o)}\right] \tag{3.14}$$

$$\left(\frac{dT_{cM}}{dZ_j}\right)_{z_k} = \frac{\left[2\sum_l Z_l(V_{clj}{}^{\eta}T_{clj} - V_{cli}{}^{\eta}T_{cli}) - \eta V_{cM}{}^{\eta-1}\left(\frac{dV_{cM}}{dZ_j}\right)_{z_k} T_{cM}\right]}{V_{cM}{}^{\eta}}, \ \eta = 0.25 \tag{3.15}$$

$$\left(\frac{dV_{cM}}{dZ_j}\right)_{z_k} = 2\sum_l Z_l(V_{clj} - V_{cli}) \tag{3.16}$$

$$\left(\frac{dP_{cM}}{dZ_j}\right)_{z_k} = P_{cM}\left[\left(\frac{dZ_{cM}}{dZ_j}\right)/Z_{cM} + \left(\frac{dT_{cM}}{dZ_j}\right)_{z_k}/T_{cM} - \left(\frac{dV_{cM}}{dZ_j}\right)_{z_k}/V_{cM}\right] \tag{3.17}$$

$$\left(\frac{dZ_{cM}}{dZ_j}\right)_{z_k} = -0.085\left(\frac{d\omega_M}{dZ_j}\right)_{z_k} \tag{3.18}$$

$$\left(\frac{d\omega_M}{dZ_j}\right)_{z_k} = \omega_j - \omega_i \qquad ,k\neq i,j \tag{3.19}$$

where indices *i* and *j*, respectively, refer to solute and supercritical fluid. Mixing rules for pseudo critical properties using in LKP-EOS are as follows:

$$T_{cM} = \left(\frac{1}{V_{cM}^{\eta}}\right)\sum_i\sum_j y_i y_j V_{c_{ij}}^{\eta} T_{c_{ij}} \tag{3.20}$$

$$T_{c_{ij}} = \sqrt{T_{c_i}T_{c_j}} \tag{3.21}$$

$$T_{c_{ii}} = T_{c_i}\ ;\ T_{c_{jj}} = T_{c_j} \tag{3.22}$$

$$V_{cM} = \sum_i\sum_j y_i y_j V_{c_{ij}} \tag{3.23}$$

$$V_{c_{ij}} = \frac{1}{8}\left(V_{c_i}^{\frac{1}{3}} + V_{c_j}^{\frac{1}{3}}\right)^3 \tag{3.24}$$

$$V_{c_i} = \frac{Z_{c_i} R T_{c_i}}{P_{c_i}} \tag{3.25}$$

$$Z_{c_i} = 0.2905 - 0.085\omega_i \tag{3.26}$$

$$P_{c_M} = \frac{Z_{c_M} R T_{c_M}}{V_{c_M}} \tag{3.27}$$

$$Z_{c_M} = 0.2905 - 0.085\omega_M \tag{3.28}$$

$$\omega_M = \sum_i y_i \omega_i \tag{3.29}$$

The fugacity coefficient of a pure component (ϕ) is estimated as follows:

$$\ln \phi = Z - 1 - \ln Z + \frac{B}{V_r} + \frac{C}{2V_r^2} + \frac{D}{5V_r^5} + E \tag{3.30}$$

$$Z = Z^{(o)} + \frac{\omega}{\omega^{(r)}}(Z^{(r)} - Z^{(o)}) \tag{3.31}$$

$$Z = \frac{P_r V_r}{T_r} = 1 + \frac{B}{V_r} + \frac{C}{V_r^2} + \frac{D}{V_r^5} + \frac{c_4}{T_r^3 V_r^2}(\beta + \frac{\gamma}{V_r^2})\exp(-\frac{\gamma}{V_r^2}) \tag{3.32}$$

where B, C, D, and E are expressed as functions of temperature which are calculated from Equation 3.33 - 3.36, respectively. There are two sets of constants of b_1, b_2, b_3, b_4, c_1, c_2, c_3, c_4, d_1, d_2, β, and γ. One set is used for the simple fluid (superscript "o") and the other set is used for the reference fluid (superscript "r") as following in Table 3.3.

$$B = b_1 - \frac{b_2}{T_r} - \frac{b_3}{T_r^2} - \frac{b_4}{T_r^3} \tag{3.33}$$

$$C = c_1 - \frac{c_2}{T_r} + \frac{c_3}{T_r^3} \tag{3.34}$$

$$D = d_1 + \frac{d_2}{T_r} \tag{3.35}$$

$$E = \frac{c_4}{2T_r^3 \gamma}\left[\beta + 1 - (\beta + 1 + \frac{\gamma}{V_r^2})\exp(-\frac{\gamma}{V_r^2})\right] \tag{3.36}$$

Table 3.2 Summary of five equations of state used in P-v-T and Z forms, and their fugacity coefficient

EOS	Formula and parameters	EOSs in the compressibility factor (Z) form and Fugacity coefficient
vDW	$P=\frac{RT}{v-b_m}-\frac{a_m}{v^2}$ $a_i=\frac{27(RT_{c_i})^2}{64P_{c_i}},\ b_i=\frac{RT_{c_i}}{8P_{c_i}}$	$Z^3-(1+B)Z^2+A\cdot Z-A\cdot B=0$ where $A=\frac{a_mP}{(RT)^2},\ B=\frac{b_mP}{RT}$ $\phi_i=\exp\left\{\frac{b_i}{v-b_m}-\ln[Z(1-b_m/v)]-\frac{2\sum_j y_ja_{ij}}{vRT}\right\}$
RK	$P=\frac{RT}{v-b_m}-\frac{a_m}{T^{0.5}v(v+b_m)}$ $a_i=0.42748\frac{R^2T_{c_i}^{2.5}}{P_{c_i}},b_i=\frac{0.08664RT_{c_i}}{P_{c_i}}$	$Z^3-Z^2+(A-B-B^2)Z-A\cdot B=0$ where $A=\frac{a_mP}{(RT)^2},\ B=\frac{b_mP}{RT}$ $\phi_i=\exp\left\{\frac{b_i}{b_m}(Z-1)-\ln[Z(1-b_m/v)]+\frac{1}{b_mRT^{1.5}}\left[\frac{ab_i}{b_m}-2\sum_j y_ja_{ij}\right]\ln(1+b_m/v)\right\}$
SRK	$P=\frac{RT}{v-b_m}-\frac{a_m(T)}{v(v+b_m)}$ $a_i(T)=0.42748\frac{R^2T_{c_i}^{2.5}}{P_{c_i}}\alpha(T_{r_i},\omega_i),\ b_i=\frac{0.08664RT_{c_i}}{P_{c_i}}$ $\alpha(T_{r_i},\omega_i)=\left[1+\kappa_i(1-T_{r_i}^{0.5})\right]^2$ $\kappa_i=0.48+1.574\omega_i-0.176\omega_i^2$	$Z^3-Z^2+(A-B-B^2)Z-A\cdot B=0$ where $A=\frac{a_mP}{R^2T^2},\ B=\frac{b_mP}{RT}$ $\phi_i=\exp\left\{\frac{b_i}{b_m}(Z-1)-\ln(Z-B)-\frac{A}{B}\left[\frac{2\sum_j y_ja_{ij}}{b_m}-\frac{b_i}{b_m}\right]\ln\left(\frac{Z+B}{Z}\right)\right\}$

Table 3.2 Summary of five equations of state used in *P-v-T* and Z forms, parameters, mixing rules, and their fugacity coefficient (con't.)

EOS	**Formula and parameters**	**EOS in the compressibility factor (*Z*) form and fugacity coefficient ($\square_i$)**
PR	$P=\frac{RT}{v-b_m}-\frac{a_m(T)}{v(v+b_m)+b_m(v-b_m)}$ $a_i=\frac{0.45724R^2T_{c_i}^2}{P_{c_i}}\alpha(T_{r_i},\omega_i),\ b_i=\frac{0.07780RT_{c_{ii}}}{P_{c_{ii}}}$ $\alpha(T_{r_i},\omega_i)=\left[1+\kappa_i(1-T_{r_i}^{0.5})\right]^2$ $\kappa_i=0.37464+1.5422\omega_i-0.26922\omega_i^2$	$Z^3+(B-1)Z^2+(A-2B-3B^2)Z+(B^3+B^2-A\cdot B)=0$ where $A=\frac{a_mP}{(RT)^2},B=\frac{b_mP}{RT}$ $\phi_i=\exp\left\{\frac{b_i}{b_m}(Z-1)-\ln(Z-B)-\frac{A}{2\sqrt{2}B}\left[\frac{2\sum_j y_ja_{ij}}{a_m}-\frac{b_i}{b_m}\right]\ln\left(\frac{Z+(1+\sqrt{2})B}{Z+(1-\sqrt{2})B}\right)\right\}$
MMM	$P=\frac{RT(v+1.3191b_m)}{v-b_m}-\frac{a_m}{T^{0.5}v(v+\sum_i y_ib_{ii})}$ $a_i=0.48748\frac{R^2T_{c_i}^{2.5}}{P_{c_i}},b_i=\frac{0.064662RT_{c_i}}{P_{c_i}}$	$\phi_i=\exp\left[\begin{array}{l}2.3191\left[\frac{3\left(2\sum\limits_j y_jb_{ij}-\sum\limits_i\sum\limits_j y_iy_jb_{ij}\right)+b_{ii}}{4(v-b_m)}-\ln(1-\frac{b_m}{v})\right]-\ln Z\\+\frac{a_m}{RT^{1.5}\sum\limits_i y_ib_i}\left[\begin{array}{l}\left(\frac{b_i}{\sum\limits_i y_ib_i}-\frac{2\sum\limits_j y_ja_{ij}}{a_m}\right)\ln\left(1+\frac{\sum\limits_i y_ib_i}{v}\right)\\-\frac{b_i}{v+\sum\limits_i y_ib_i}\end{array}\right]\end{array}\right]$

Table 3.3 Two sets of constants of simple fluid (o) and reference fluid (r)

Constants	**Simple fluids (*o*)**	**Reference Fluids (*r*)**
b_1	0.118	0.203
b_2	0.266	0.332
b_3	0.155	0.028
b_4	0.030	0.203
c_1	0.024	0.031
c_2	0.019	0.050
c_3	0	0.017
c_4	0.043	0.042
d_1	1.55×10^{-5}	4.87×10^{-5}
d_2	6.24×10^{-5}	0.74×10^{-5}
β	0.054	1.226
γ	0.06	0.038

3.1.2 Conventional van der Waals Mixing Rule

The classical vdW one fluid quadratic mixing rules (Kwak and Mansoori, 1986) have been adapted to extend the vDW, RK, SRK, and PR-EOSs for mixtures. The parameter a_m and b_m calculated according to:

$$a_m = \sum_{i=1}^{nc}\sum_{j=1}^{nc} y_i y_j a_{ij} \tag{3.37}$$

$$b_m = \sum_{i=1}^{nc}\sum_{j=1}^{nc} y_i y_j b_{ij} \tag{3.38}$$

Note: If the MMM-EOS is used, the parameter b_m is defined as following

$$b_m = \frac{1}{4}\left(3\sum_{i}^{nc}\sum_{j}^{nc} y_i y_j b_{ij} + \sum_{i}^{nc} y_i b_{ii}\right) \tag{3.39}$$

where nc is the number of components in the mixture and a_{ij} and b_{ij} are the cross parameters which can be obtained from a set of combining rules, such as:

$$a_{ij} = (1 - k_{ij})\sqrt{a_{ii}a_{jj}} \tag{3.40}$$

$$b_{ij} = \frac{(b_i + b_j)}{2}(1 - l_{ij}) \tag{3.41}$$

where k_{ij} and l_{ij} are the binary interaction parameters and are usually determined by fitting phase equilibrium experimental data. Their numerical values are typically in the range of -1 to +1 and have large effect on the accuracy of phase equilibria calculations. For instance, values of k_{ij} larger than 1 will yield negative values for the a_{ij} parameter which means that the attractive term gives a positive contribution.

3.1.3 Solubility Model Algorithm

The fugacity coefficient calculation was shown in Figure 3.4. This procedure was done using MATLAB. As it was shown, this algorithm required operating condition inputs and component of solute, solvent, and cosolvent. The necessary properties of the compound critical temperature and pressure, molar volume and acentric factor were estimated using GCMs in Aspen Plus. Once all properties were determined, EOS could be chosen. After carrying out the calculations, the calculated solubility data were shown in the screen as a plot between the solubility of the input compound in supercritical fluids and pressure. Each calculation began with the initial guess value of the compositions. It would be recommended if there are the experimental value exists. The initial value of composition taken from the experiment can accelerate the program to calculate faster and more precisely. To validate our proposed method, the calculated biomolecule solubilities for each EOS were compared to experimental solubilities.

We now utilize the above expressions for fugacities in order to predict the solubility of solids in supercritical gas at different temperature and pressures, and compare the results with the experimental data. First of all, to calculate the solubility and phase stability of a solute in a supercritical fluid using an EOS it is necessary to find critical properties and acentric factors of all components, and molar volumes and sublimation pressures of the solid components. When some of these values are not available, as is the case here, estimation techniques must be employed. When neither critical properties nor acentric factors are available in the literature, it is desirable to determine the normal boiling point (T_b) of the compound since some estimation techniques require only T_b and molecular structure. Molar volumes may be available from crystallography studies. Some of the estimation techniques used below, where only the molecular structure and/or molecular weight required is available in ASPEN Properties™ and we have used this tool to estimate the T_b, T_c, P_c and V_c of studied biomolecules.

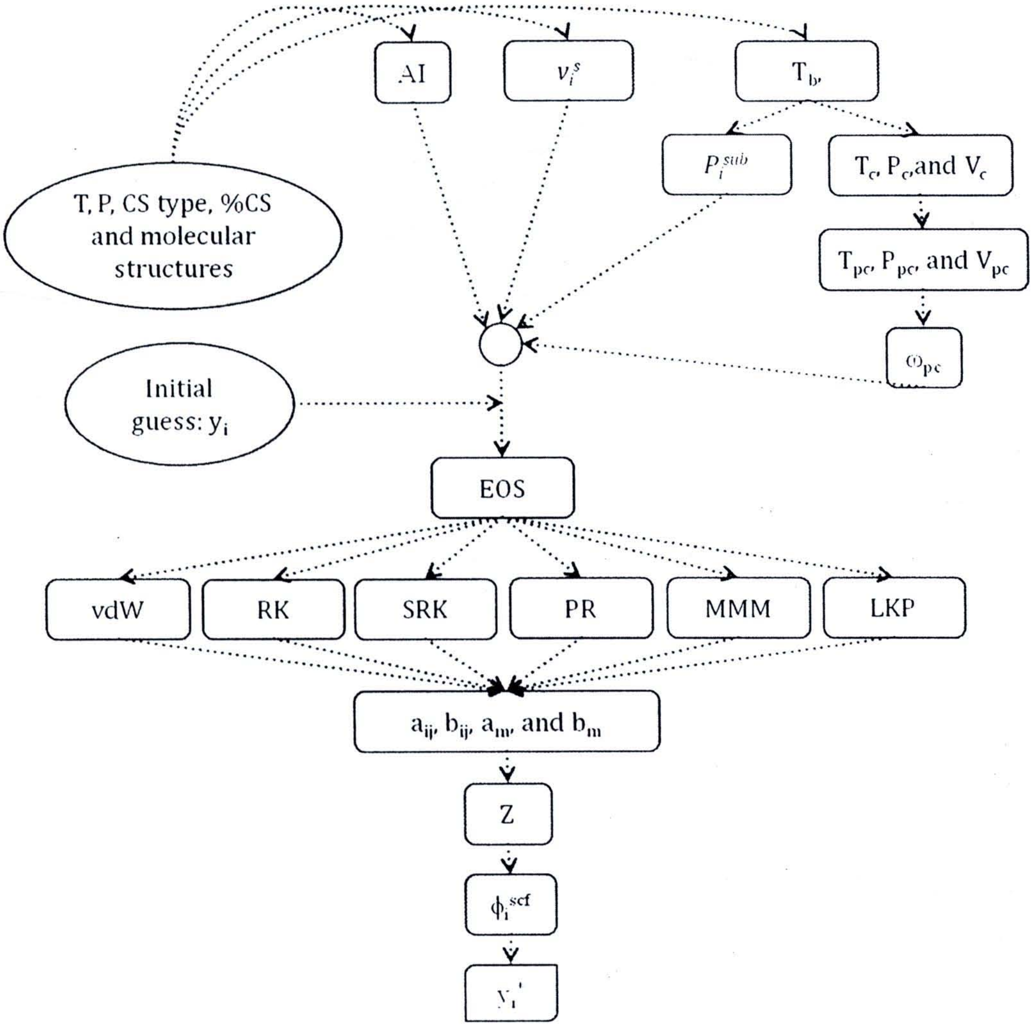


Figure 3.4 Calculation of Fugacity coefficient.

3.1.4 Estimation of Properties

To calculate the solubility and phase stability in supercritical region using an EOS, it is necessary to have critical properties and acentric factors of all components, and molar volumes and sublimation pressure of the solid components as following:

3.1.4.1 Solid Molar Volume

The Immirzi and Perini method was developed based on data for over 500 organic crystalline compounds with molecular weights ranging from 50 to 1,000. To account for the empty space in an organic crystal, the method uses atomic volumes based upon the number of other atoms bonded to the specific atom. The additivity of the Immirzi and Perini method can be expressed using the following equation (Immirzi and Perini, 1977).

$$\overline{v}_s = \sum_i m_i v_i \tag{3.42}$$

where $\overline{v}_s$ is the calculated crystal volume for a single molecule (angstrom^3/molecule), m_i is the relative stoichiometric multiplicities and v_i is the volume increments of elements or ions (angstrom^3). Table A.1 lists the values for common elements and ions. Once $\overline{v}_s$ is determined, the following equations which were revised by Cao et al. (2008) using the corrective factors can be used to calculate solid molar volume (v_s) (cm^3/mol) or the solid density(ρ_s) (g/cm^3) at room temperature.

$$v_s = \frac{\overline{v}_s}{1.66} \times \frac{1}{(100\% - 0.9\%)} = \frac{\overline{v}_s}{1.645} \tag{3.43}$$

$$\rho_s = \frac{1.66M}{\overline{v}_s} \times (100\% - 0.9\%) = \frac{1.645}{\overline{v}_s} \tag{3.44}$$

where M is the molecular weight of the compound. The restrictions of this method is: (1) compounds not solid at room temperature, or having structural disorder are excluded; (2) compounds containing molecules of solvent (solvates) are excluded, except for water; (3) only the elements H, C, O, N, S, F, Cl, Br, I, Na, K and Rb are considered; (4) cyclic compounds are limited to benzene and naphthalene derivatives (Immirzi and Perini, 1977; Lyman, Reehl and Rosenblatt, 1982).

3.1.4.2 Normal Boiling Point and Critical Properties

The normal boiling point (T_b) is the temperature at which the vapour pressure equals 101,325 Pa. As mentioned above, T_b is a key property to estimate critical properties.

The critical point is the set of physical conditions at which the physical properties such as (critical temperature (T_c), critical pressure (P_c), and the critical volume (V_c)) of the liquid and gas become identical. They are crucial for an accurate representation of experimental behaviour. Two methods were used to estimate these properties: and Joback (Joback and Reid, 1987) and Constantinou and Gani GCMs (Constantinou and Gani, 1994) as shown in Table 3.4.

Table 3.4 Joback and Gani equations for estimating boiling point and critical properties (Joback and Reid, 1987; Constantinou and Gani, 1994).

Joback GCM	**Constantinou and Gani GCM**
$T_b = 198 + \sum_k N_k \Delta_{BJ}$	$T_b = 204.359 \ln\left[\sum_k N_k t_{b1k} + W \sum_j M_j t_{b2j}\right]$
$T_c = \dfrac{T_b}{0.584 + 0.965 \sum_k N_k (tck) - \left(\sum_k N_k (tck)\right)^2}$	$T_c = 181.128 \ln\left[\sum_k N_k t_{c1k} + W \sum_j M_j t_{c2j}\right]$
$P_c = \dfrac{1}{1.01325\left[0.113 + 0.0032 n_A - \sum_k N_k (pck)\right]^2}$	$P_c = \left(1.3705 + \left[p_{c2}t + \sum_k N_k t_{m1k} + W \sum_j M_j t_{m2j}\right]^{1/2}\right) \cdot 10^{-5}$
$V_c = 17.5 + \sum_k N_k (vck)$	$V_c = (-0.00435 + \sum_k N_k v_{c1k} + W \sum_j M_j v_{c2j}) \cdot 10^{-3}$
where Δ_{BJ} represents group increments obtained in Table A-4. *tck*, *pck* and *vck* are contributions obtained in Table A-5.	where N_k is number of groups of type k in a molecule for first-order groups. M_j is number of groups of type j for second-order groups. t_{b1k} , t_{c1k} , t_{m1k}, and v_{c1k} are first-order group contributions given in Table A-2. t_{b2j}, t_{c2j}, t_{m2j}, and v_{c2j} are second-order group contributions given in Table A-3. W is weight for second-order groups. ($W = 0$ for first-order estimation only and $W = 1$ for full estimation or second-order estimation).

Joback GCM

Joback (1987) re-evaluated Lydersen's group contribution method. Several new functional groups were added and new contribution values were determined. However, this method produces an obvious overestimation of T_b since the Joback method was not originally designed for large molecules.

Constantinou and Gani GCM

Constantinou and Gani (1994) developed an advanced group contribution method based on the UNIFAC groups but they allow more sophisticated functions of the desired functions of the desired properties and by providing contributions at a second-order level. In case of small substance, the significant errors of the critical properties estimated using Gani method can be found. This occurs because group addictively is not so accurate for small molecules even though it may be possible to form them from available group. In general, the largest errors of the Gani method are for the very smallest and for the very largest molecules, especially fluorinated and larger ring compounds. Estimates may be either too high or too low; there is no obvious pattern to the errors (Constantinou and Gani, 1994).

3.1.4.3 Corresponding States Principle: The Pseudocritical Method

The direct application of mixing rules to the CSP correlations to describe mixtures, it is assumed that the mixture behaviour at reduced state is as same as a pure component (Reid and Leland, 1965). When the reducing parameters are critical properties and these are made functions of composition, they are called pseudocritical properties because the values are not generally expected to be the same as that of a pure component whose T_c and P_c are equal to the pseudocritical temperature (T_{cm}) and pressure (P_{cm}), respectively. Other CSP parameters such as acentric factor can also be made composition dependent adequately for reliable estimation purposes. The assumptions about intermolecular forces that allow CSP use for mixtures are the same as for pure components. However, here it is necessary to deal with the effects of interactions between unlike species as well as between like species. When the extract is assumed as a single pseudo-component, the T_{cm}, P_{cm}, and ω_{cm} of the extract is considered to be sum of the property of the main components multiplied by mole fraction of main components. The simplest mixing rule is a mole fraction (y_i) average method. This rule, often called one of Kay's rules can be satisfactory (Kay, 1936). Kay's rule assumes that the pseudocritical properties of gaseous mixtures are linear combinations of those of the components.

$$\theta_{cm} = \sum_{i}^{nc} y_i \theta_{ci} \tag{3.45}$$

where θ can be T_c, P_c or ω_c. The differences in T_{cm} are usually less than 2% for all components if the pure component critical properties are not extremely different. Thus, Kay's rules for T_{cm} is probably adequate for $0.5 < T_{ci}/T_{ij} < 2$ and $0.5 < P_{ci}/P_{ij} < 2$ (Kay, 1936). For all systems studied by Prausnitz and Gunn (1958), it was found that the pseudocritical volume could be predicted by a quadratic function of mole fractions (Prausnitz and Gunn, 1958).

$$V_{cm} = \sum_{i=1}^{nc} \sum_{j=1}^{nc} y_i y_j V_{c_{ij}} \tag{3.46}$$

$$V_{c_{ij}} = \frac{1}{2}\left(V_{c_i} + V_{c_j}\right) \tag{3.47}$$

It was also found that, when the ratio of the critical volumes of the pure components is less that about 3, the pseudocritical volume is a linear function of the composition. In that case Equation 3.46 becomes

$$V_{cm} = \sum_{i}^{nc} y_i V_{c_i} \tag{3.48}$$

Therefore, the mixture of cosolvent and CO_2 was treated as a quasi-pure solvent, so that the system is a quasi-binary system.

3.1.4.4 Sublimation Pressure

The sublimation pressure of the solid component (P_i^{sub}) is usually small for common industrially important solids and it is not often available. Therefore, in this work P_i^{sub} is estimated using Watson correlation (Equations 3.49 - 3.51) (Lyman, Reehl and Rosenblatt, 1982).

$$\ln P_i^{sub} \approx \frac{\Delta H_{vb}}{\Delta Z_b R' T_b}\left[1 - \frac{(3-2T_{\rho b})^m}{T_{\rho b}} - 2m(3-2T_{\rho b})^{m-1} \ln T_{\rho b}\right]; \; T_{\rho b} = \frac{T}{T_b} \tag{3.49}$$

$$\frac{\Delta \mathrm{H}_{vb}}{T_b} = K_F(8.75 + R\ln T_b) \tag{3.50}$$

If $T_{\rho b} < 0.5$; m = 1.19

$0.6 > T_{\rho b} > 0.5$; m = 0.8

$T_{\rho b} > 0.6$; m = 0.36

ΔH_{vb} is the enthalpy at the boiling temperature and m is a parameter dependent on $T_{\rho b}$. K_F is the so-called Fishtine constant (Fishtine, 1963) as mentioned in Table A.6 and A.7. It depends on the dipole moments of polar and nonpolar molecules. The parameter ΔZ_b is assumed to have the value of 0.97.

3.1.4.5 Pitzer's Acentric Factor

Pitzer's acentric factor (ω) is obtained from the deviation of the experimental vapour pressure-temperature function from that which might be expected for a similar substance. ω for all molecules were estimated using a correlation based on Lee-Kesler equation as shown in Equation 3.51 (Reid, Prausnitz and Sherwood, 1987).

$$\omega = \frac{3}{7}\frac{\theta}{1-\theta}\log_{10} P_c - 1.0 \ ; \theta = \frac{T_b}{T_c} \tag{3.51}$$

3.1.4.6 Aromaticity Index

In this work, the Koch and Dittmar (2006) classification was used in developing the aromaticity criteria, aromaticity index (AI). They address the potential formation of contribution of heteroatom to the 'double-bond equivalent' or DBE by calculating AI from an alternative DBE_{AI}/C_{AI} ratio as shown in Equation 3.52.

$$AI = \frac{DBE_{AI}}{C_{AI}} = \frac{1 + C - O - S - 0.5H}{C - O - S - N - P} \tag{3.52}$$

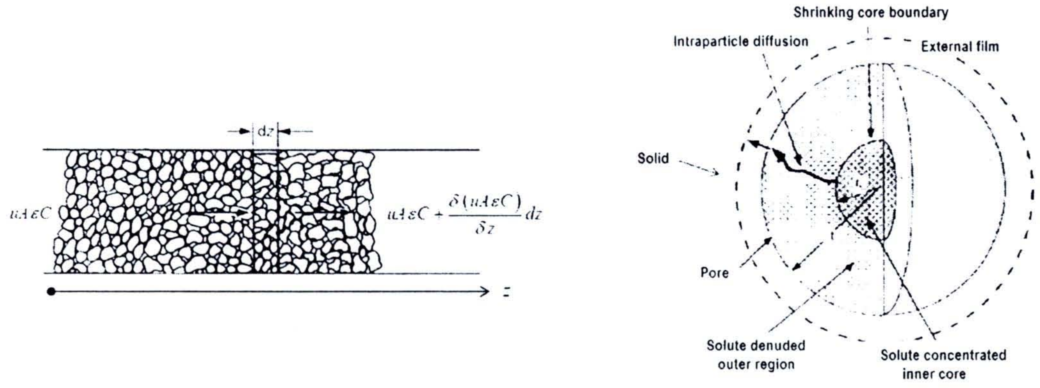
Where C, O, S, H, N and P are the number of atoms of carbon, oxygen, sulphur, hydrogen, nitrogen and phosphorous in the molecule that affect the degree of unsaturation or double atoms and not the number of total atom in molecule (Koch and Dittmar, 2006).

3.2 Mathematical Modelling of Supercritical Fluid Extraction

Most often, solid particles are arranged in a fixed bed configuration and the supercritical fluid flows through the bed extracting the desired solute. In this study, a mathematical model is set to simulate this process. Differential mass balances are used to elaborate a model that is described as following:

3.2.1 Model Equation

The SFE of solid compounds from plant materials in a fixed bed in which the SCF flows axially into an extractor packed with solid particles is modelled (Figure 3.5 (a)). The shrinking core model is applied to characterise the phenomena in the solid and fluid phases (Figure 3.5 (b)). Solid solutes diffuse through the solid matrix to the particle surface, then across a stagnant film around the particle to the bulk fluids. The following assumptions are made in the development of the model: isothermal and isobaric conditions, constant bed void fraction and particle porosity, considerable axial dispersion, and negligible pressure drop and radial dispersion. Even though the solute is a multicomponent mixture, the model parameters are determined by taking into account just a single solute component, called a "pseudo-component" representing the global behaviour.



(a) (b)

Figure 3.5 Schematic drawing of the fixed bed (a) and the large view of a particle (b) (Goto, Roy and Hirose, 1996).

The mass balance equations for the fluid and solid phases are:

Bulk phase:

$$\frac{\partial x_b}{\partial \theta} + a\frac{\partial x_b}{\partial Z} = \frac{a}{Pe}\frac{\partial^2 x_b}{\partial Z^2} - 3\,Bi\frac{(1-\varepsilon)}{\varepsilon}\left[x_b - x_p(1)\right] \tag{3.53}$$

Solid phase:

$$\varepsilon_p \frac{\partial x_p}{\partial \theta} + (1-\varepsilon_p) b \frac{\partial y}{\partial \theta} = \frac{1}{\xi^2} \frac{\partial}{\partial \xi}\left[\xi^2 \frac{\partial x_p}{\partial \xi}\right] \tag{3.54}$$

From Equation 3.53, one must modify the $[x_b - x_p(1)]$ term to remove the unknown parameter by writing the mass balance of solute within the solid particle as:

$$\frac{\partial}{\partial \xi}\left[\xi^2 \frac{\partial x_p}{\partial \xi}\right] = 0 \tag{3.55}$$

Initial and Boundary conditions (ICs and BCs) within the solid particle are:

$$t = 0,\ \theta = 0 \quad \rightarrow \quad \xi_c = 1 \text{ and } y = y_0 \tag{3.56}$$

$$r = R,\ \xi = 1 \quad \rightarrow \quad \frac{\partial x_p}{\partial \xi} = Bi\left[x_b - x_p(1)\right] \tag{3.57}$$

$$r = r_c,\ \xi = \xi_c \quad \rightarrow \quad C_p = C_{sat},\ x_p = 1 \tag{3.58}$$

When BCs in Equation 3.57 and 3.58 are substituted into Equation 3.55, one gets:

$$x_b - x_p(1) = \frac{x_b - 1}{1 - Bi(1 - 1/\xi_c)} \tag{3.59}$$

The change in the average solid phase concentration with respect to time is equal to the rate of mass transfer of the solute to the bulk fluid:

$$\frac{\partial \overline{y}}{\partial \theta} = 3bBi\left[x_b - x_p(1)\right] \tag{3.60}$$

The average solid phase concentration for the solute component can be expressed as a function of the core radius of that component and the particle radius:

$$\bar{y} = \xi_c^{\,3} \tag{3.61}$$

The initial condition on the fluid phase can be formulated as following

$$t = 0,\ \theta = 0 \quad \rightarrow \ x_b = x_{b0} \tag{3.62}$$

The Danckwerts' boundary conditions at the inlet (Z = 0) and at the outlet (Z = 1) of the fixed bed are given by

$$z = 0, Z = 0 \quad \rightarrow \quad x_b - \frac{1}{Pe}\frac{\partial x_b}{\partial Z} = 0 \tag{3.63}$$

$$z = L, Z = 1 \quad \rightarrow \quad \frac{\partial x_b}{\partial Z} = 0 \tag{3.64}$$

The following equations were derived by rearranging Equation 3.53-3.64.

$$\frac{\partial x_b}{\partial \theta} + a\frac{\partial x_b}{\partial Z} = \frac{a}{Pe}\frac{\partial^2 x_b}{\partial Z^2} - 3Bi\frac{(1-\varepsilon)}{\varepsilon}\frac{(x_b - 1)}{(1 - Bi(1 - 1/\xi_c))} \tag{3.65}$$

$$\frac{\partial \xi_c}{\partial \theta} = \frac{Bi(1 - x_b)}{\varepsilon_p Bi(x_p - 1) + (1-\varepsilon_p) b \xi_c (\xi_c + Bi(1 - \xi_c))} \tag{3.66}$$

The cumulative fraction of solute extracted up to dimensionless time θ is given by:

$$\text{yield} = \frac{ab\varepsilon}{1-\varepsilon}\int_0^\theta x_b \, d\theta \tag{3.67}$$

where C_{sat} is estimated from equations of state combined with the solid – vapour phase equilibrium relationship. To begin with the solution procedure, Equation 3.65-3.66 are discretised and solved simultaneously by the method of lines using Gproms software. Then, extraction curve is described as yield versus time.

3.2.2 Model Parameters

The proposed model involves five parameters: mixture density (ρ_m), mixture viscosity (μ_m), film mass transfer coefficient (k_f), axial dispersion coefficient in the fluid phase (D_L), the binary diffusion coefficient (D_{AB}), and the effective pore diffusivity in the particles (D_e). These parameters are evaluated using existing correlations and available data.

3.2.2.1 Mixture Density

In order to estimate the density for the carbon dioxide plus cosolvent (ρ_m) system, it is assumed that the cosolvent behaves as an incompressible liquid. LKP and PR-EOSs are used to obtain the density of nonpolar and polar cosolvent (CS), respectively. The molar fractions of carbon dioxide and cosolvent (y_{CO_2} and y_{CS}) are required. Then, the mixture density can be determined using:

$$\rho_m = y_{CO_2} \cdot \rho_{CO_2} + y_{cs} \cdot \rho_{cs} \tag{3.68}$$

3.2.2.2 Mixture Viscosity

Jossi et al. developed the viscosity equation of pure substances at high pressures in both the gaseous and liquid states (Jossi, Stiel and Thodos, 1962). It was found that the following fourth degree polynomial was necessary to define accurately the analytical relationship over the entire range of reduced densities:

$$\begin{aligned}\left[(\mu-\mu^{*})\xi+10^{-4}\right]^{1/4} &= 0.10230+0.023364\rho_r+0.058533\rho_r^2-0.040758\rho_r^3 \\ &\quad +0.0093324\rho_r^4\end{aligned} \tag{3.69}$$

Alternate analytical expressions for limited regions of reduced densities were developed which are less complex in application than Equation 3.69 in two ranges of ρ_r.

For densities in the range $0.3 \leq \rho_r \leq 2.0$:

$$(\mu-\mu^{*})\xi = \left[23.12e^{1.079\rho_r} - 25\right]\times 10^{-5} \tag{3.70}$$

Similarly for $\rho_r < 0.3$ the following expression can be employed:

$$(\mu - \mu^*)\xi = 11.0 \times 10^{-5}\left[e^{1.584\rho_r} - 1\right] \quad (3.70)$$

$$\xi = \frac{T_c^{1/6}}{M^{1/2} P_c^{2/3}} \quad (3.71)$$

where μ and μ^* are the viscosity at the desired condition and viscosity at 0.1 to 5 atm) (unit: centipoises). ρ, ρ_c, and ρ_r are the density at desired condition, critical density, and critical reduced density (ρ/ρ_c) (kg/m^3), respectively. ξ is a viscosity parameter. In order to determine μ^*, it is specified in two cases: nonpolar and polar gases. For nonpolar gases the following relationships result:

For $T_r \leq 1.50$, $$\mu^*\xi = 34.0 \times 10^{-5} T_r^{0.94} \quad (3.72)$$

For $T_r > 1.50$, $$\mu^*\xi = 17.78 \times 10^{-5}\left[4.58T_r - 1.67\right]^{5/8} \quad (3.73)$$

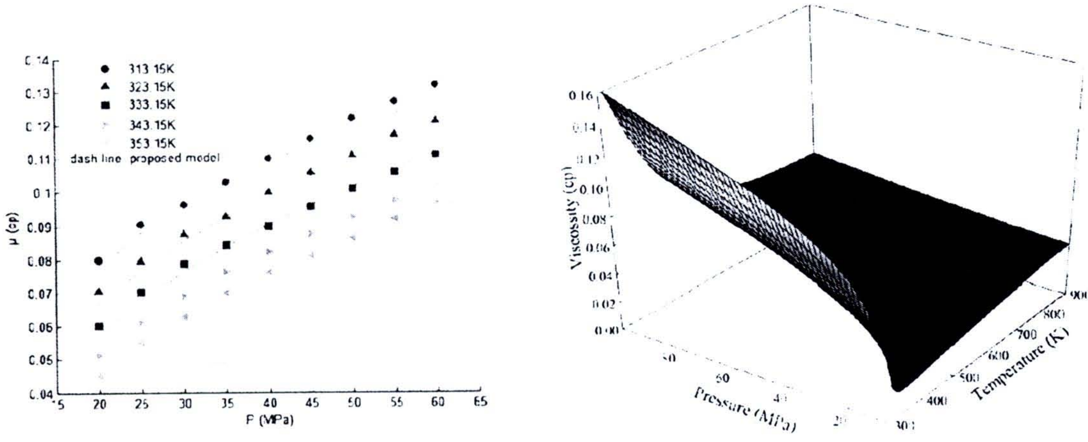
For polar gases the viscosity parameter $\mu^*\xi$ was found to depend on both T_r and Z_c. (Z_c is the compressibility factor at the critical point, $Z_c = P_c V_c / RT_c$). This dependence can be expressed as follows for polar substances which exhibit hydrogen bonding:

$$(\mu^*\xi) Z_c^{5/4} = \left[7.55T_r - 0.55\right] \times 10^{-5} \quad (3.74)$$

Similarly, for polar gases which do not exhibit hydrogen bonding:

$$(\mu^*\xi) Z_c^{2/3} = \left[1.90T_r - 0.29\right]^{4/5} \times 10^{-4} \quad (3.75)$$

Finally, Figure 3.6 (a) and (b) show the overall behaviour of experimental viscosity under various critical conditions. This figure indicates that the viscosity value is a strong function of pressure at low temperature. However, viscosity is a weak function of pressure at high temperature. The maximum value of viscosity is obtained at low temperature and high-pressure region, and the minimum viscosity is obtained at low temperature and low pressure.



(a) (b)

Figure 3.6 Results of the viscosity using Heidaryan et al. correlation in comparison with Pensado et al. data (a) (Pensado et al., 2008) and Variation of CO_2 viscosity with temperature and pressure calculated from Heidaryan et al. correlation (b) (Heidaryan et al., 2011).

3.2.2.3 Film Mass Transfer Coefficient

The resistance to mass transfer of solute from the surface of a particle in a packed bed of particles to the fluid phase is normally described in terms of an external film mass transfer coefficient. Mass transfer of solute from the particle surface takes place by diffusion and/or natural convection. The concentration of the solute in the fluid at the particle surface is C_p. (When the particle consists only of soluble material the concentration at the particle surface is assumed to be the equilibrium concentration). The solute concentration in the film of fluid immediately adjacent to the particle decreases with distance normal to the surface until the bulk or average concentration in the fluid (C_b) is reached. If it is assumed that the mass transfer coefficient is not a function of concentration or bed co-ordinates, the local mass transfer coefficient becomes the average mass transfer coefficient, k_f (or the film mass transfer coefficient). In practice the coefficient is usually predicted from correlation's using dimensionless numbers, which have been developed from mass transfer studies using gases and liquids at near ambient conditions. These correlations are in general of the form:

$$Sh = f(Re, Sc, Gr, \varepsilon_b) \qquad (3.76)$$

where, $Sh = \frac{d_p k_f}{D_{AB}}$, $Re = \frac{d_p v_f \rho_m}{\mu_m}$, and $Sc = \frac{\mu_m}{\rho_m D_{AB}}$. v_f is the interstitial velocity of $SCCO_2$ through the process vessel (m/s).

The Grashof number (*Gr*) is only significant under condition of free and natural condition. In case of forced convection, *Gr* can be negligible. The prediction of k_f at near-critical conditions requires an accurate value of the diffusion coefficient in the film surrounding the particle. In case of a binary mixture the binary diffusion coefficient, D_{AB} at the same temperature and pressure as k_f, is used. A number of dimensionless correlation's have been published in the literature covering wide ranges of *Re*, *Sc* and *Sh*. Only some three will be mentioned here: the Wakao and Funazkri (1978), Tan et al. (1988), and Mongkholkhajornsilp et al. (2005) correlations. These are given by Equations 3.77-3.79, respectively. These correlations were developed for conventional process and they have been used successfully for supercritical extraction by various researchers in the past (Goto and Hirose, 1993; Puiggené, Larrayoz and Recasens, 1997; Shi et al., 2007).

The Wakao and Funazkri correlation is given by (Wakao and Funazkri, 1978)

$$Sh = 0.38 Re^{0.83} Sc^{0.33} \qquad \text{when} \quad 0.5 < Sc < 10,000;\ 3 < \mathrm{Re} < 3000 \qquad (3.77)$$

The Tan et al. correlation is given by (Tan, Liang and Liou, 1988)

$$Sh = 0.38 Re^{0.83} Sc^{0.33} \qquad \text{when} \quad 2 < Sc < 40;\ 2 < \mathrm{Re} < 40 \qquad (3.78)$$

The Mongkholkhajornsilp et al. correlation is given by (Mongkholkhajornsilp et al., 2005).

$$Sh = 0.135 Re^{0.5} Sc^{0.33} \qquad \text{when} \quad 6 < Sc < 25;\ 0.1689 < \mathrm{Re} < 1.2918 \qquad (3.79)$$

3.2.2.4 Axial Dispersion Coefficient

With regards to the assumption, dissolved solute in the SCF diffuses along the bed (dispersion coefficient) as a result of axial concentration gradients. The axial dispersion coefficient (D_L) is a measure of back-mixing in the packed bed during fluid flow. The dispersion coefficient may take any value from zero to infinity ($D_L = 0 \rightarrow \infty$), where zero represents no back-mixing within the extraction vessel or plug flow and infinity represents perfect mixing (Del Valle and De La Fuente, 2006). It is desirable to avoid axial dispersion of the solute along the bed in order to maintain the driving forces for extraction at their maximum level (Del Valle and De La Fuente, 2006). Axial dispersion may be avoided and hence neglected in the modelling by: maintaining a larger interstitial solvent velocity in the bed; by using sintered metal plates to cause ≥ 1 MPa of pressure loss in the solvent at the inlet; to avoid gradients in solvent viscosity due to radial gradients in temperature by operating at near ambient temperatures and/or using smaller diameter extraction vessels; and by maintaining a small enough particle diameter to extractor diameter ratio ($d_p/D < 0.1$) to diminish the radial variations in bed porosity (Brunner, 1994). Dispersion coefficients are generally expressed in the Peclet number (Pe) which is correlated as a function of the Reynolds number (Re) and the Schmidt number (Sc).

$$Pe = f(Re, Sc) \text{ with } Pe = \frac{Lv_f}{D_L} \tag{3.80}$$

where L is bed length (m). In this work, D_L was approximated by correlations chosen (Tan and Liou, 1989; Catchpole, Bernig and King, 1996; Funazukuri, Kong and Kagei, 1998) as illustrated in Figure 3.7. There were two cases to select an appropriate correlation such as $\varepsilon_b Re Sc$ and particle size values.

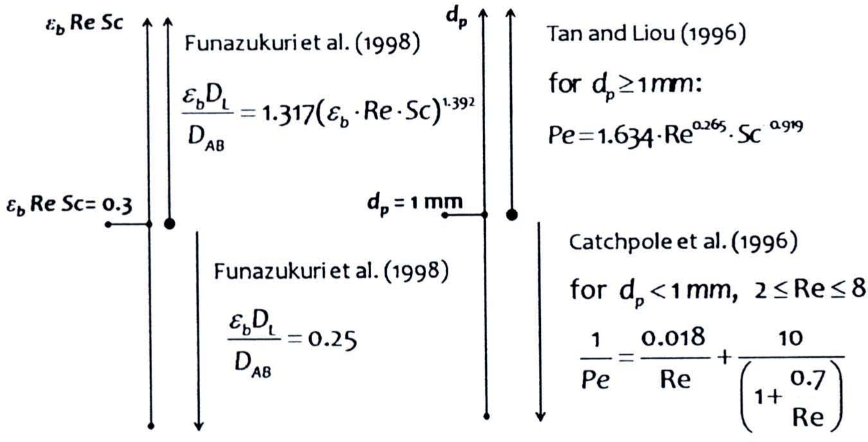


Figure 3.7 Axial dispersion coefficient correlations used in this work.

3.2.2.5 Effective Diffusivity Coefficient

The effective diffusivity coefficient (D_e) describes the influence of the porous network on the diffusion inside the particle. It depends on the form of the pore size (ε_p which is particle porosity) and the pore structure. This may consist, for example of monodisperse pores, bidisperse (macro and micro) pores or there may be a random distribution of pore size. The effective diffusivity coefficient also depends on the molecular diffusivity (free diffusivity) of the solute in supercritical solvent or binary diffusion coefficient (D_{AB}). The correlation of Wakao and Smith (1962) was chosen to calculate D_e (Wakao and Smith, 1962).

$$D_e = \varepsilon_p^2 D_{AB} \tag{3.81}$$

The macroporous and microporous solid particle characterization allows knowing the values of the particle porosity (ε_p). Both The effective diffusivity coefficient and the binary diffusion coefficient are a function of temperature and pressure. The binary diffusion coefficient is estimated using a recently published correlation proposed by He et al. (He, 1997).

$$D_{AB} = (V_{C,A}^{k} - 23)\sqrt{\frac{T}{M_B}}10^{-10}\left[0.61614 + 3.0902\exp\left(\frac{-0.87756\sqrt{M_A V_{C,A}}}{P_{C,A}}\right)\right] \tag{3.82}$$

where $k = 1$ for $\rho_r \geq 1.2$ and $k = 1 + (\rho_r - 1.2)/\sqrt{M_A}$ for $\rho_r < 1.2$. A and B are solute and solvent properties, respectively. $P_{C,A}$ is the critical pressure of solute A (bar), $V_{C,A}$ is the critical volume of solute A (cm^3/mol); M_A and M_B are the molecular weight of solute and solvent, respectively.

3.2.3 Sensitivity Analysis

Sensitivity Analysis (SA) is the study of how the variation (uncertainty) in the output of a mathematical model can be apportioned to different source. In the identification of physic-mathematical model we cannot determine the exact values of the parameters but only their mean values and variances. This causes the uncertainty of parameters. A measure about the significance of the model results in order to understand the level of confidence characterise them is necessary. Therefore, SA plays an important role in the development of any practical engineering model. It can help to reveal the sources and mechanisms of variability that provide the key to understanding system uncertainty. The effects of parameter variations on a model's result is to vary selected input parameters, rerun the code, and record the corresponding changes in the results (i.e. responses) calculated by the code. Then, uncertainty is a measure of the 'goodness' of a result; without such a measure. The model parameters responsible for the largest relative changes in the responses are then classified to be the most important. The results can be used to strengthen the knowledge base by guiding subsequent research in order to increase the confidence in the model and its predictions. SA can also be used to calibrate simulation models for closer agreement with experimental results (Fiori, Calcagno and Costa, 2007). Our proposed model for cosolvent-modified supercritical fluid extraction involves intensive parameter determination method. We have applied sensitivity analysis to find out how much error is introduced by parametric errors. In this work, parameters and their variance are supposed to be known as described above. Different kinds of uncertainty in mathematical models are taken into account.

Mathematical models representing real phenomena contain two kinds of uncertainties:

- ***Model uncertainty (theoretical deviation):*** due to a non-extract physico-mathematical description of the system, for instance an overestimation.
- ***Parametric uncertainty***: resulting from errors in the experimental data utilized to estimate the model parameters and the adopted estimation procedure.

3.2.3.1 Sensitivity Analysis Formulation

The analysis of the effects of uncertainties is performed referring to the time τ at which the outlet concentration of extracted compounds reach the same time of a reference value (Fiori, Calcagno and Costa, 2007). The definition of sensitivity of the time of process τ with respect to a generic parameter p is:

$$s(p)=\frac{d\left[\tau(p)\right]}{dp}\cdot\frac{p}{\tau(p)} \tag{3.83}$$

A local sensitivity analysis is performed at mean values of the parameters, determined during the parameter estimation, i.e. for the values used in the modelling of this particular existing system, which matched the model results and the data of the experimental data. It is called the reference values and the corresponding sensitivity as $s(p_r)$ is defined. Therefore, $\tau(p_r) = \tau_r$ is the reference length of the system process.

The simplified method for the evaluation of the range of uncertainty of the output of the model induced by the uncertainty of the parameters consists of a combination of sensitivity with the uncertainty of each parameter. Therefore, the order of the percentage uncertainty must be considered.

$$i(p) = \frac{\Delta p}{p_r} \tag{3.84}$$

where Δp is the confidence interval of the parameter. The effective quantity for our study is the product:

$$e(p_r) = i(p_r) \cdot s(p_r) \tag{3.85}$$

From above equation, it is related to the Taylor series of $\tau(p)$: the sensitivity is connected to the first derivative of τ with respect to p, the uncertainty to the increment of p. The product $e(p_r)\cdot\tau_r$ can be obtained as following:

$$e(p_r) \cdot \tau_r = \left(\frac{d\tau}{dp}\right)_{p_r} \Delta p \tag{3.86}$$

If we consider the first term of the Taylor series of the function $\tau(p)$ at the point (p_r, τ_r) when the increment of the independent variable p equals its confidence interval Δp, the following result could be obtained:

$$\tau \approx \tau_r + \left(\frac{d\tau}{dp}\right)_{p_r} \cdot \Delta p = \tau_r \left(1 + e(p_r)\right) \tag{3.87}$$

$$e(p_r) = \frac{\Delta\tau_r}{\tau_r} \tag{3.88}$$

where *e(p$_r$)* is the percentage uncertainty on τ. As the first term of the Taylor series is a linear approximation of a non-linear function, *e(p$_r$)* is a useful, though simple, approximation of a non-linear and statistical dependence of the percentage uncertainty of τ to the percentage uncertainty of p.

3.2.3.2 Model Parameters

A sensitivity analysis of the model will be performed involving the following parameters:

- Operative conditions: solvent mass flow rate
- Physical properties of the supercritical fluids: mixture density and viscosity.
- Transport parameters: axial dispersion coefficients, effective diffusivities, and external mass transfer coefficients (the latter depending on the viscosity and molecular diffusivity of the solute in the supercritical solvent).
- Phase equilibrium relationship: solute solubility in the supercritical solvent.

The effects of the parameter variation on predictions (in particular on the time of the process, but also on solvent consumption) are examined through a local sensitivity analysis taken at the mean values of the parameters (i.e. the values coming from the parameter estimation from experimental data, or the values calculated by known theoretical correlations). Then, in order to correctly identify those parameters mainly affecting predictions, the local sensitivity of each parameter is weighted with its own uncertainty. The combined effect of sensitivity and uncertainty is of major interest in our analysis. A parameter, which the system is very sensitive to could be very well known and the effects on design uncertainty could result negligible; on the contrary, even if the sensitivity is not so large, combining it with a large parameter uncertainty could lead to a significant effect on model predictions.