Nanopowder Production through the RESS Process

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Abstract

In this paper, the mathematical modeling of Ibuprofen Nanopowder production through the Rapid Expansion of Supercritical Solutions (RESS) is studied. In this process, a supercritical solution is expanded through a fine capillary, where high supersaturation leads to the formation of nano-particles. Redlich-Kwong, and Peng-Robinson equations of state along with refined mixing rules formulated by T.Y. Kwak and G.A. Mansoori are used to model this process. Results obtained using traditional van der Waals mixing rules are used to test the accuracy of the model.

Introduction:

Many drugs including Ibuprofen are organic molecules, which are highly insoluble in water solutions such as the blood. In order, for the cells in the body to absorb the drug, it must first be dissolved in the blood. However, dissolution rate is a function of the surface area of the drug particles and their solubility in the blood. By reducing the particle size of the drug, the surface area is increased which in turn results in greater dissolution. This increases the bioavailability (the percentage of the drug absorbed compared to the initial dosage) of the drug. Furthermore, the deep alveoli region of the lungs that contain many blood vessels have only a diameter of 5 µm, and therefore drugs that are to target this region of the body will require sizes in the nano range [1].

Overview of the RESS process

In the RESS process, a gaseous solvent is pressurized and heated until it reaches the supercritical region. Once in this stage, the solute, which will eventually be turned into nanopowders, is dissolved in the supercritical solvent. Next, the supercritical solution is expanded through a small capillary or nozzle, where a fast phase change from the supercritical state to the gas state results in high supersaturation due to loss in solvating power. The high supersaturation and homogeneous conditions attained due to the rapid expansion along the
capillary initiate the rapid nucleation of small particles with narrow particle size distributions [1].

Figure 1, shows the schematics of a typical apparatus used in the RESS process. The solvent that is normally used is gaseous CO₂. In general, the CO₂ (A) first passes through a column with molecular sieve (B) where it is purified. Next, it passes through a cooling device where it is turned into liquid CO₂ (C). A pump (D) is then used to send the liquid to a thermostated extractor (E) where the solute is dissolved in the CO₂. The solution is subsequently heated (F) and then cooled (G) in order to adjust its temperature. Next, the solution is heated (F) once more in order to bring it to the supercritical region and is then rapidly expanded through the capillary nozzle (H). Finally, the solution enters the expansion chamber (I) where most of the nucleation takes place [2].

![Figure 1. Common apparatus used in the RESS process [2]](image)

**Solvent Selection**

In the RESS process, a solute is dissolved in a supercritical solvent (sc-solvent), and it is the solute that is eventually turned into the nanopowders. There are different types of materials available for use as the sc-solvent in the RESS process. Table 1, lists some of the common solvents and their critical properties [3].
The sc-solvent that is used in the modeling described in this paper is supercritical CO$_2$. Below its critical conditions most solids are not soluble in CO$_2$. However, once the CO$_2$ is in the supercritical region it can dissolve many solids. There are many advantages for using CO$_2$ as the sc-solvent in the RESS process. CO$_2$ is very abundant on earth, is non-flammable, and is currently the second least expensive solvent. Furthermore, CO$_2$’s non-toxicity makes it an even more attractive agent for the production of ibuprofen nanopowders due to a less concern for drug contamination. On the other hand, supercritical water, which also possesses many of the aforementioned properties, is not preferable for use in this process because it would take a lot of energy to bring water and confine it in the supercritical phase. Additionally, when water is used, coagulation and condensation will lead to the formation of larger particles [7,8].

**Notion behind Supercritical fluids (SCF)**

A substance that is in a region above its critical temperature, critical pressure, and critical density is said to be a supercritical fluid (SCF). Figure 2, shows a Pressure versus Temperature phase diagram, where the supercritical phase is located in the top right hand part of the plot. In the supercritical state, the substance possesses properties similar to both gas and liquid properties. Table 2, compares some of carbon dioxide’s physical properties in the supercritical phase to those in the liquid and gas phase. As is clear from the data in the table, supercritical fluids have both solubilities and densities similar to

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**Table 1.**

Critical Properties of some common RESS solvents

<table>
<thead>
<tr>
<th>Solvent</th>
<th>T$_c$(K)</th>
<th>P$_c$(MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbon Dioxide</td>
<td>304.2</td>
<td>7.38</td>
</tr>
<tr>
<td>Triflouro-methane</td>
<td>299.0</td>
<td>4.80</td>
</tr>
<tr>
<td>Propane</td>
<td>369.8</td>
<td>4.24</td>
</tr>
<tr>
<td>Water</td>
<td>647.2</td>
<td>22.12</td>
</tr>
</tbody>
</table>
those of liquids, but yet they have viscosities similar to gases [9].

![Figure 2. Pressure versus Temperature phase diagram](image)

**Table 2.**
Carbon Dioxide properties for different states [9]

<table>
<thead>
<tr>
<th></th>
<th>Gas P=0.1MPa T=15~30°C</th>
<th>Supercritical fluid Tc , Pc</th>
<th>Supercritical fluid Tc , 4Pc</th>
<th>Liquid P=0.1MPa T=15~30°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Density (g / cm²)</td>
<td>0.0006 ~0.002</td>
<td>0.2~0.5</td>
<td>0.4~0.9</td>
<td>0.6~1.6</td>
</tr>
<tr>
<td>Viscosity (μ Pa·s)</td>
<td>10~30</td>
<td>10~30</td>
<td>30~90</td>
<td>200~3000</td>
</tr>
<tr>
<td>Diffusion coefficient (cm²/sec)</td>
<td>0.1~0.4</td>
<td>0.7×10⁻³</td>
<td>0.2×10⁻³</td>
<td>(0.2~2) ×10⁻⁵</td>
</tr>
</tbody>
</table>

Because of its high density in the supercritical phase, a substance can have greater solvating ability. This is because the high solvent density leads to smaller distances between the solvent-solvent and solute-solvent molecules, which in turn allows for a greater and stronger intermolecular attraction between the solute and solvent particles. Another aspect of supercritical solvents such as CO₂, is their ability to lower the melting point of the solute that they interact with. This is because the high-pressured CO₂ forces its way into the solid crystal lattice, which in turn causes a greater separation between solute-solute particles. As a result, the solute comes into contact with the solvent particles where it is
then dissolved. Because of this, the overall melting point of the solute is decreased [5,7].

**Mathematical modeling of the capillary**

Because supersaturation is the driving force behind nucleation and the formation of nanopowders, the supersaturation equation (1), can be used to find the radius of the nanoparticles that are formed in the RESS process under different conditions. The supersaturation is calculated using the equation [7]:

\[
S = \left[ \frac{y_E(T_E, P_E) \phi(T, P, y_E)}{y'(T, P) \phi(T, P, y')} \right]
\]

(1)

Where \(y_E\) is solute mole fraction of the mixture, which is a function of the extraction temperature, \(T_E\), and extraction pressure, \(P_E\). The fugacity equation at the extraction conditions is given by \(\phi(T, P, y_E)\), and \(y'(T, P)\) is the equilibrium mole fraction at T and P along the capillary. The general equation for solute mole fraction is given by [7]:

\[
P_{\text{sat}}(T) \exp\left[ \frac{v_{\text{solid}}(P - P_{\text{sat}}(T))}{RT} \right]
\]

\[
y_2 = \frac{y_{\text{sat}}(T) \exp\left[ \frac{v_{\text{solid}}(P - P_{\text{sat}}(T))}{RT} \right]}{\phi_2 P}
\]

(2)

Where, \(P_{\text{sat}}(T)\) is the solid saturated vapor pressure at temperature T, R is the universal gas constant, P is the operating pressure, \(v_{\text{solid}}\) is the solid molar volume and \(\phi_2\) is the vapor fugacity of the solute. The general fugacity equation, using the Redlich-Kwong equations of state, is given by [7]:

\[
\ln \phi = \ln \left( \frac{v}{v-b} \right) + \left( \frac{2 \sum y_j b_j - b}{v-b} \right) - \ln z + \left( \frac{2 \sum y_j b_j - b}{b^3 RT^{1.5}} \right) \ln \left( \frac{v+b}{v} \right) - \frac{b}{v+b} \left( \alpha \left( \frac{\sum y_i a_i^3 b_i^1}{b^2} \right) \right) - \frac{2 \alpha \left( \sum y_j b_j^3 \right)}{b RT^3} \ln \left( \frac{v+b}{v} \right)
\]

(3)

1 The equations listed in this section are taken from “Mathematical Modeling of the RESS Process for Pharmaceuticals with the Redlich-Kwong EOS and modified van der Waals Mixing Rules.” Written by P. Q. Fisher. For a more detailed explanation of these equations please look there.
Where Redlich-Kwong equations of state along with Kwak and Mansoori’s modified van der Waals mixing rules were used to calculate the different constants that appear in the above equation. These constants are given by the following equations [7]:

\[
a_i = 1.2828RT_c^{1.5}v_c = 0.42748R^2 \frac{T_c^{5/2}}{P_c}
\]

\[
b_i = 0.26v_c = 0.08664R^2 \frac{T_c}{P_c}
\]

\[
a = \frac{\left(\sum_{i=1}^{\infty} \sum_{j=1}^{\infty} y_i y_j a_{ij}^{7/6} b_{ij}^{1/3}\right)^{1.5}}{\left(\sum_{i=1}^{\infty} \sum_{j=1}^{\infty} y_i y_j b_{ij}\right)^{1/2}}
\]

\[
b = \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} y_i y_j b_{ij}
\]

\[
a_{ij} = \sqrt{a_i a_j} (1 - k_{ij})
\]

\[
b_{ij} = \left[\frac{b_i^{7/6} + b_j^{7/6}}{2}\right]^{3/2} (1 - I_{ij})
\]

\[
\alpha = \sum_{i=1}^{\infty} \sum_{j=1}^{\infty} y_i y_j a_{ij}^{2/3} b_{ij}^{1/3}
\]

(4)

The following equations were used to find \(v\), the volume:

\[
z^3 - z^2 + [A - B - B^2]z - AB = 0
\]

\[
A = \frac{aP}{R^2 T_c^{5/2}}
\]

\[
B = \frac{bP}{RT}
\]

\[
z = \frac{PV}{RT} = \frac{v}{v - b} - \frac{a}{RT^{1.5} (v + b)}
\]

(5)

Where \(z\) is the compressibility factor.

The fugacity equation using Peng-Robinson equations of state, along with Kwak and Mansoori’s modified van der Waals mixing rules takes on the following form:
\[
\ln \phi_j = \left( \frac{2 \sum x_j b_j - b}{b} \right) (z-1) - \ln(z-B) - \frac{A}{2\sqrt{2}B} \left( 2 \sum x_j a_j + 2RT \sum x_j d_j - 2\sqrt{RT} \right) \left( \frac{a \sum x_j d_j + d \sum x_j a_j}{\sqrt{a_d}} \right)
\]

\[
\left( \frac{2 \sum x_j b_j - b}{b} \right) \ln z + \left( \frac{1 + \sqrt{2}}{B} \right) z - \left( \frac{1 - \sqrt{2}}{B} \right) = 0
\]

(6)

The properties of Ibuprofen used in this model are those that are estimated by group contribution using the Lydersen method. This information is provided in Table 3.

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**Table 3.**

Ibuprofen properties using the Lydersen method [7]

<table>
<thead>
<tr>
<th>Tc [K]</th>
<th>749.7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pc[bar]</td>
<td>23.0</td>
</tr>
<tr>
<td>Kij</td>
<td>0.085</td>
</tr>
</tbody>
</table>

Finally, the equation that is used to find the radius, \( r^* \), of the nanopowders is given by [7]:

\[
r^* = \frac{2\sigma v_s}{kT \ln S}
\]

(7)

Where, Boltzmann’s constant, \( k = 1.38 \times 10^{-23} \text{ [J K}^{-1}\text{]} \), and the surface tension of solid, \( \sigma = 0.02 \text{ [N m}^{-1}\text{]} \).

**Simulation**

A program was written in Matlab© to find the solute fugacity in vapor phase, \( \phi_j \), and the mole fraction, \( y_2 \). This program is listed in Appendix A. The program prompts the user for a temperature, pressure, and an initial guess for \( y_2 \), and it then calculates the actual \( y_2 \) for the given temperature and pressure.
using the equations which were discussed previously. To test the program, experimental values from Table 4 were used. These experimental values are Solubility data for Ibuprofen and Carbon Dioxide, which are taken from “Micronization by Rapid Expansion of Supercritical Solutions to Enhance Dissolution Rates of Poorly Water Soluble Pharmaceuticals,” written by M. Charoenchaitrakool, F. Dehgahani, and N.R. Foster [4]. However, the results that were obtained using the Matlab program did not agree with the experimental results.

To find the source of the problem, a second program was written using just the Peng-Robinson equation for fugacity. This code appears in Appendix B. Next, the solubility was calculated at different pressures while keeping the temperature constant at 35º C. This information was then used to generate a Solubility versus Pressure plot. Figure 3, shows a plot that was obtained experimentally by Charoenchaitrakool. Figure 4, shows the plot that was obtained using the Matlab code that appears in Appendix B.

**Figure 3.**
Solubility versus Pressure plot for experimental results
In comparing the two plots, it is clear that both plots have similar shape and inflection points. However, the results obtained for solubility are off by a factor of a hundred (at most of the pressure points) when compared to the experimental values. After trying different equations of state and different methods of programming them, it seems that the problem is due to the fugacity equation that is used. However, we were not able to resolve this problem during the course of the research.

Conclusion

Nanopowders have many industrial uses. The RESS process is one way of producing these nanopowders. It is important to be able to theoretically calculate the radius of the nanopowders that are produced. The program that appears in appendix A, is supposed to calculate the solubility at the given pressure and temperature, which can then be easily used to calculate the radius using equation 7. However, the results that were produced by the program are not in agreement with some of the experimental results. We were unable to find out why this happens, although after checking all equations used, it seems that they are all mathematically and fundamentally correct. In future works, results obtained from Redlich-Kwong and Peng-Robinson equations of state using
traditional mixing rules will be compared to those with modified Kwak and Mansoori’s mixing rules.
Appendix A

The following is a code that is written in Matlab, to calculate the solubility at a given temperature, pressure and initial guess, using Redlich-Kwong EOS and modified van der Waals Mixing rules.

```matlab
T=input(' enter the temperature: ')';
P=input(' enter the pressure: ')';
y2=input(' enter the initial guess for y: ')';

Pc1=7.38;  %CO2
Pc2=2.3;   %Ibuprofen
Tc1=304.2;
Tc2=749.7;
R=8.314*10^-6;
K12=8.5*10^(-2);
Psat=4.95*10^-8;
Vs=1.821*10^-4;

a1=0.42748*(R^2)*((Tc1^(2.5))/(Pc1));
a2=0.42748*(R^2)*((Tc2^(2.5))/(Pc2));
b1=0.08664*R*(Tc1/Pc1);
b2=0.08664*R*(Tc2/Pc2);

a12=((a1*a2)^0.5)*(1-K12);
b12=(((b1^(1/3))+(b2^(1/3)))/2)^3;

y0=1;
count=0;

while (abs(y2-y0)>1e-4)
    count=count+1;
y0=y2;

    avap=(((1-y2)^2)*(a1^(2/3))*(b1^(1/3))+2*(1-y2)*y2*(a12^(2/3))*(b12^(1/3))+(y2^2)*(a2^(2/3))*(b2^(1/3)))^(3/2))/(((1-y2)^2)*b1+2*(1-y2)*y2*b12+(y2^2)*b2)
    bvap=((1-y2)^2)*b1+2*y2*(1-y2)*b12+(y2^2)*b2
    coef=[1 -1 ((avap*P)/((R^2)*(T^2.5)))-((bvap*P)/(R*T))-(((bvap*P)/(R*T))^2) (-avap*bvap*P^2))/((R^3)*(T^3.5))]
    zvap=roots(coef)

    %code to find real root
    z=-inf;
    for i=1:3
        conv=isreal(zvap(i));
        %picks the biggest real root
        if conv==1 & zvap(i)>z
            z=zvap(i);
        end
    end
```

\begin{align*}
V &= (z \cdot R \cdot T) / P; \\
xpr1 &= \log((V / (V - bvap))) ; \\
xpr2 &= (2 \cdot ((1 - y2) \cdot b12 + y2 \cdot b2) - bvap) / (V - bvap) - \log(navv) ; \\
xpr3 &= avap \cdot ((2 \cdot ((1 - y2) \cdot b12 + y2 \cdot b2) - bvap) / ((bvap^2) \cdot R \cdot (T^{1.5})) ; \\
xpr4 &= \log(((V + bvap) / V)) ; \\
xpr5 &= (bvap / (V + bvap)) ; \\
xpr6 &= (((1 - y2) \cdot a1^2) \cdot (a1^2) \cdot (b1^2) \cdot (1 / 3)) + (2 \cdot y2 \cdot (1 - y2) \cdot (a12^2) \cdot (b12^2) \cdot (1 / 3)) + ((y2^2) \cdot (a2^2) \cdot (b2^2) \cdot (1 / 3))) ; \\
xpr7 &= (((1 - y2) \cdot a1^2) \cdot (a12^2) \cdot (b12^2) \cdot (1 / 3)) + (y2 \cdot (a2^2) \cdot (b2^2) \cdot (1 / 3)) / (bvap^0.5) ; \\
xpr8 &= ((xpr6^2) \cdot (1 - y2) \cdot b12 + y2 \cdot b2) / ((bvap^2.5) \cdot R \cdot (T^{1.5}) ) .
\end{align*}

\begin{align*}
\Phi2 &= \exp(xpr1 + xpr2 + (xpr3 \cdot xpr4 \cdot xpr5) - (3 \cdot (xpr6^0.5) \cdot xpr7) - (xpr8 \cdot xpr4)) ; \\
y2 &= (Psat \cdot \exp((Vs \cdot (P - Psat)) / (R \cdot T)) / (\Phi2 \cdot P)) ; \\
\end{align*}

\text{end}

display(y2);
Appendix B

The following is a code that is written in Matlab, to calculate the solubility at a given temperature, pressure and initial guess, using Peng-Robinson equation for fugacity.

```matlab
T=308.15;
Pressure=[8 8.5 9 10 11 12 13 14 15 16 17 18 20 21 22]*10;
guess=[0.053 0.543 0.995 1.35 1.81 2.13 2.5 2.43 2.68 3.23 3.82 3.78 4.23 4.23 4.41];
graphy=[];

Pc1=73.8;   %CO2
Pc2=23;   %Ibuprofen
Tc1=304.2;
Tc2=749.7;
R=8.314*10^-5;
K12=8.5*10^(-2);
Psat=4.95*10^-7;
Vs=1.821*10^-4;
W1=0.225;
W2=0.819;
K1=0.37464+1.54226*W1-0.2699*(W1^2);
K2=0.37464+1.54226*W2-0.2699*(W2^2);

AL1=(1+K1*(1-((T/Tc1)^0.5)))^2;
AL2=(1+K2*(1-((T/Tc2)^0.5)))^2;
a1=(0.45724*(R^2)*(Tc1^2)*AL1)/(Pc1);
a2=(0.45724*(R^2)*(Tc2^2)*AL2)/(Pc2);

b1=(0.07780*R*Tc1)/Pc1;
b2=(0.07780*R*Tc2)/Pc2;
a12=((a1*a2)^0.5)*(1-K12);
b12=(b1+b2)/2;

for runs=1:15
P=Pressure(runs);
y2=guess(runs)*10^-3;

y0=1;
count=0;
```

```matlab
while (abs(y2-y0)>1e-4)
    count=count+1;
    y0=y2;

    avap=((1-y2)^2)*a1+2*(1-y2)*y2*a12+(y2^2)*a2;
    bvap=((1-y2)^2)*b1+2*y2*(1-y2)*b12+(y2^2)*b2;
    coef=[1 -(1-(bvap)/(R*T)) ((avap*P)/((R^2)*(T^2)))- 3*(((bvap*P)/(R*T))^2)-2*((bvap*P)/(R*T)) - ((avap*bvap*(P^2))/((R^3)*(T^3)))-((bvap*P)/(R*T))^2)-((bvap*P)/(R*T))^3];
    zvap=roots(coef);

    % code to find real root
    z=-inf;
    for i=1:3
        consv=isreal(zvap(i));
        if consv==1 & zvap(i)>z
            z=zvap(i);
        end
    end
    V=(z*R*T)/P;

    xpr1=(b2*(z-1))/bvap;
    xpr2=log(z-((bvap*P)/(R*T)));
    xpr3=avap/(2*(2^0.5)*bvap*R*T);
    %xpr4=((2*(1-y2)*a12+y2*a2)/avap)-(b2/bvap);
    xpr4=(2*a12)/avap-(b2/bvap);
    xpr5=(bvap*P)/(R*T);
    xpr6=log((z+(1+(2^0.5))*xpr5)/(z+(1-(2^0.5))*xpr5));
    Phi2=exp(xpr1-xpr2-(xpr3*xpr4*xpr6));
    y2=(Psat*exp((Vs*(P-Psat))/(R*T)))/(Phi2*P);
end
graphy(runs)=y2;
end
plot(Pressure,graphy)
xlabel('Pressure (bar)');
ylabel('Solubility (mole fraction)');
```
Acknowledgments:

I would like to thank Professor G.A. Mansoori for his helpful suggestions and contributions in developing our mathematical model of the RESS process. I would also like to thank Paul Fisher who has spent countless hours in developing the actual model that I have worked with, and I am exceedingly grateful for his patients in helping me learn many of the concepts involved in this research project. Finally, I am grateful for the generous support of the National Science Foundation, and the Faculty at UIC, who made this work possible.
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