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Effect of Solvents on the Optimal Thermodynamic Conditions of Ternary System (CO_2, Alcohol, Ampicillin) in GAS Process

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ABSTRACT

The gas antisolvent (GAS) process has been employed for the pharmaceutical micronization. Ampicillin was dissolved in an organic solvent and carbon dioxide as an antisolvent was injected into the solution, consequently, some volume expansion and sharp reduction in liquid solvent power were shown. The particles in GAS process are not seen in any operating conditions. The thermodynamic modeling of GAS can evaluate the operating conditions. In this project, the effect of solvents on the optimal thermodynamic conditions of the binary system (CO_2, solvent) and ternary system (CO_2, solvent, ampicillin) were investigated. The relative change in the molar volume in different solvents (ethanol, 1-propanol, 1-butanol, and 1-pentanol) was studied for the determination of the optimum operating conditions. The combination of the Peng-Robinson EOS and Vidal and Michelsen mixing rule (LCVM) was selected to determine the optimum operating condition of the GAS process. The effect of solvents on the minimum pressure was investigated. The calculated Pmin was 70, 70.86, 72.2 and 73.4 bar for ethanol, 1-propanol, 1-butanol, and 1-pantanol at, 308.15 K respectively. According to modeling results, when the molecular weight of the solvent was increased, the value of P_{min} was increased.

1. Introduction

In recent years, the application of supercritical fluids (SCFs) for the pharmaceutical micronization has attracted much interest. The solubility of micronized particles increases meanwhile the dosage of them decreases [1-6]. In the GAS process, a solute is dissolved in an organic solvent. This solution is loaded into the cell. Carbon dioxide is injected into the solution and dissolved in solvent. Each solvent has a special power to dissolve, so the solvent power of the organic solvent is decreased. Therefore, the dissolved solute is precipitated via new particle size distribution [5].

Many pharmaceuticals are micronized by the GAS process. Dittanet et al. [7] synthesized the composites of mefenamic acid (MEF) and polyvinylpyrrolidone via the GAS process. The production of ketoconazole-4-aminobenzoic acid cocrystals via the gas antisolvent method was

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investigated [8]. Tandya et al. [9] studied the micronization of the gastroesistant insulin via the gas antisolvent.

In the GAS process, the precipitation of particles occurs in special operating conditions. Therefore, the thermodynamic modeling is important in the GAS process before the GAS experiments. Operating conditions such as the minimum pressure at each temperature are determined via the thermodynamic modeling. In recent years, several modeling investigations have been conducted on the thermodynamic conditions of the GAS process. Shariati and Peters [10] modeled the phase equilibrium of the ternary system containing (carbon dioxide, 1-propanol, salicylic acid). De la Fuente et al. [11] studied the ternary systems of (CO_2, 1-propanol, salicylic acid), (CO_2, acetone, benzoic acid) and (ethane, acetone, benzoic acid).

The thermodynamic modeling of the (sclareol, ethyl lactate, carbon dioxide) for the GAS process was studied [12]. Erriguible et al. [13] developed the mathematical modeling of the GAS process for the cocrystal formation of naproxen and nicotinamide. Esfandiari and Ghoreishi [14] determined the optimal thermodynamic conditions of a ternary system (carbon dioxide, DMSO, ampicillin). They applied the Peng-Robinson EOS and LCVM Mixing rule to model the phase equilibrium. Pahlavanzade et al. [15] investigated the phase behavior of the ternary systems of (carbon dioxide- toluene-naphthalene) and (carbon dioxide, ethanol, acridine) at various temperatures in the range of 298.15-318.15 K and the pressure up to 8.9 MPa.

The aim of that study was to model the phase equilibrium of ampicillin with different solvents such as ethanol, 1-propanol, 1-butanol, and 1-pentanol. The PR-EOS was used for the thermodynamic modeling. The optimal conditions were investigated for each solvent. Then optimal conditions were compared with each other.

2. Modeling

The liquid phase volume expansion was proposed as the criteria to determine the optimum conditions of the GAS process. This parameter is expressed as follows [11, 14]:

$$\frac{\Delta v}{v} = \frac{v(T,P) - v_0(T,P_0)}{v_0(T,P_0)} \tag{1}$$

In Eq. (1), $v, \frac{\Delta v}{v}$, T, P, P_0 are the molar volume, the relative change in the molar volume, temperature, pressure and the reference pressure respectively. The equality of fugacity, pressure, and temperature is applied to compute the phase equilibrium of the GAS process. The fugacity of each component, including CO_2, the solvent and ampicillin are set equal in all equilibrium phases. This equality can be written as follows [14]:

$$\frac{\widehat{\varphi_1}^{L}}{\widehat{\varphi_1}^{V}} x_1 - y_1 = 0 \tag{2}$$

$$\frac{\widehat{\varphi_2}^{L}}{\widehat{\varphi_2}^{V}} x_2 - y_2 = 0 \tag{3}$$

$$\frac{\widehat{\varphi_3}^{L}}{\widehat{\varphi_3}^{V}} x_3 - y_3 = 0 \tag{4}$$

If the solid phase is considered as a pure solid in a solid-liquid equilibrium, the following expression can be used [14]:

$$\frac{\varphi_3{}^{S}}{\widehat{\varphi_3}^{L}} - x_3 = 0 \tag{5}$$

Moreover, the sum of mole fractions in liquid and vapor phase is unity [16]. The PR-EOS with a linear combination of Vidal and Michelsen mixing rules (LCVM) was used for modeling liquid and vapor phases [17]:

$$P = \frac{RT}{v-b} - \frac{a(T)}{v(v+b)+b(v-b)} \quad (6)$$

in which

$$a_i(T) = 0 \cdot 45724\left(\frac{R^2(T_{ci})^2}{P_{ci}}\right)[1 + (0 \cdot 37464 + 1 \cdot 54226\omega_i - 0 \cdot 26992\omega_i{}^2)\left(1 - \sqrt{\frac{T}{T_{ci}}}\right)]^2 \quad (7)$$

$$b_i = 0 \cdot 0778\frac{RT_{ci}}{P_{ci}} \quad (8)$$

The LCVM mixing rule is written as follows:

$$\alpha = \left(\frac{\lambda}{A_V} + \frac{1-\lambda}{A_M}\right)\frac{G^E}{RT} + \frac{1-\lambda}{A_M}\sum x_i \ln\left(\frac{b}{b_i}\right) + \sum x_i\bar{\alpha}_i \quad (9)$$

$$\alpha = \frac{a}{bRT} \quad (10)$$

$$\bar{\alpha}_i = \left[\frac{\delta n\alpha}{\delta n_i}\right]_{T\,P\,n_j\neq i} = \left(\frac{\lambda}{A_V} + \frac{1-\lambda}{A_M}\right)\ln\gamma_i + \frac{1-\lambda}{A_M}\left(\ln\frac{b}{b_i} + \frac{b_i}{b} - 1\right) + \alpha_i \quad (11)$$

$$\bar{\alpha}_i = \frac{a_i}{b_iRT} \quad (12)$$

In Eq. (9), $A_M = -0.52$; $A_V = -0.623$, and $\lambda = 0.36$. G^E is the excess Gibbs energy. γ_i is the activity coefficient of the component i computed based on the UNIFAC model [12, 18]. The fugacity coefficient of each component in the liquid and vapor mixture is calculated as follows [12]:

$$\hat{\varphi}_i = \exp\left[\frac{b_i}{b}(z-1) - \ln(z-b) - \frac{\bar{\alpha}_i}{2\sqrt{2}}\ln\left(\frac{z+2.414\,B}{z-0.414B}\right)\right] \quad (13)$$

The PR-EOS is not suitable to predict the behavior of the solid phase. Therefore, the following equation has been used to calculate the fugacity of the solid phase [11].

$$\ln\varphi_3^S = \ln\varphi_3^L + \frac{\Delta H_{tp}}{R}\left(\frac{1}{T_{tp}} - \frac{1}{T}\right) + \frac{v_{tp}}{RT}(P - P_{tp}) \quad (14)$$

A group contribution method was used for the calculation of physical properties of ampicillin [19]. The two-phase and three-phase calculations were followed based on the algorithms in the previous investigation [14].

3. Results and discussion

3.1. Binary mixtures

The miscibility of antisolvents and solvents is important in the GAS process. Therefore, the phase equilibrium behavior of (CO_2, Solvent) was studied. The volume expansion of the liquid phase and P-xy diagram were investigated at different temperatures. Ethanol, 1-propanol, 1-butanol and 1-pentanol were selected as solvents. The temperature was in the range of 308.15-316.15 K. At each operating temperature, the minimum of the operation pressure was determined by plotting the relative changes of the molar volumes in terms of pressure. In each figure, a minimum was observed. After this minimum, a sharp increase in the relative change of the molar volume was also seen. The operating pressures must be above the minimum pressure.

The relative change of the molar volume of the binary system (CO_2, 1-butanol) as a function of temperature and pressure is shown in Figure 1. As indicated in this figure, the value of minimum pressure (P_{min}) depended on temperature. P_{min} increased with temperature. The value of P_{min} was 69.2, 76.8 and 81.5 bar at 308.15, 313.15 and 316.15 K, respectively. Su et al. [20] studied the carbon dioxide-ethanol binary system. The relative change in the molar volume versus pressure at 308 K by using the VTPR- EOS was investigated. The minimum pressure was 71 bar [20].

Figure 2 shows the relative change of the molar volumes of the (CO_2, 1-butanol) binary

system in terms of the mole fraction of CO_2 at 313.15 K. Similar to Figure 1, a minimum was detected in Figure 2. The trend of changes in Figure 2 can be explained based on the concept of the liquid molar volume of a solution which can be defined as follows [21]:

$$v = x_1\overline{v_1} + x_2\overline{v_2} \tag{15}$$

Based on Eq. (15):

$$\left(\frac{\partial v}{\partial x_1}\right)_{P,T} = (\overline{v_1} - \overline{v_2}) \tag{16}$$

Until $\overline{v_1} > \overline{v_2}$, the molar volume of the liquid phase (v) decreased when the dissolution of carbon dioxide increased. If $\overline{v_1} = \overline{v_2}$, a minimum was observed and no changes in the molar volume of the liquid phase existed. After that point, the molar volume of the liquid phase increased. The mole fraction of carbon dioxide was 0.85 for the binary system of (CO_2, 1-butanol) at 313.15 K. Also, the following equation could be written:

$$\frac{dv}{dx_1} = \left(\frac{\partial v}{\partial P}\right)_{T\,x_1}\frac{dP}{dx_1} + \left(\frac{\partial v}{\partial x_1}\right)_{T\,P} \tag{17}$$

The first term of Eq. (17), $\left(\frac{\partial v}{\partial P}\right)_{T\,x_1}\frac{dP}{dx_1}$, was very small, so it could be neglected and the second term, $\left(\frac{\partial v}{\partial x_1}\right)_{T\,P}$,was initially negative and later positive. Therefore, the trends of Figure 1 and 2 were the same [21].

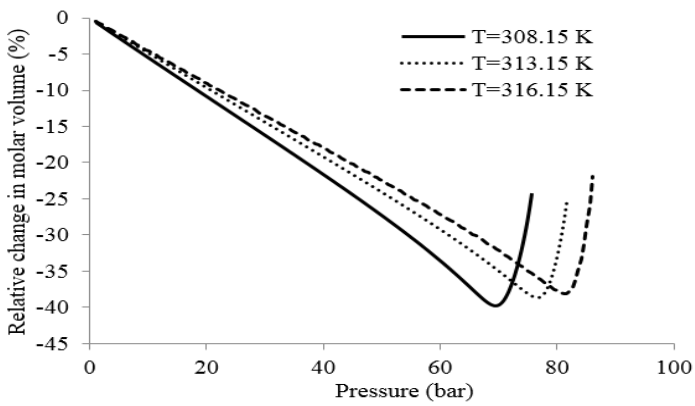

Figure 1. Relative expansion of the liquid phase as a function of pressure for (CO_2, 1-butanol) at different temperatures.

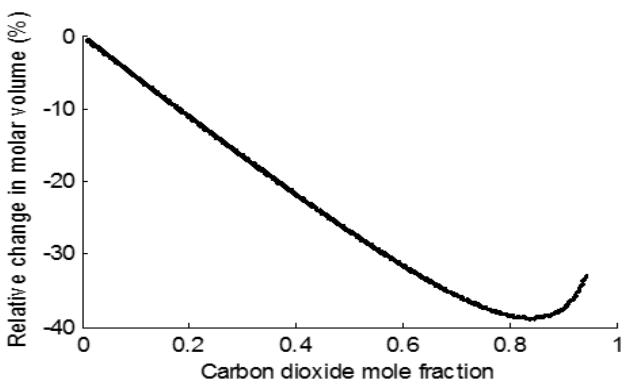

Figure 2. Relative change of the molar volume in terms of the mole fraction of CO_2 in the liquid phase for the (CO_2, 1-butanol) binary system at 313.15 K.

Figure 3 shows the vapor-liquid equilibrium of the (CO_2, 1-butanol) binary system at 313.15 K. The miscibility of 1-butanol and carbon dioxide was studied via this Figure. A similar trend was observed in the results of carbon dioxide-methanol and carbon dioxide-DMC by Pinera et al. [22]. Esfandiari and Ghoreishi indicated the same behavior for the (CO_2, DMSO) binary system [14].

The relative expansion of the liquid phase versus pressure and the carbon dioxide mole fraction for other solvents (ethanol, 1-propanol, and 1-pentanol) was studied. The results of that modeling at the temperatures of 313.15 and 316.15 K were collected in Table 1 and 2 respectively.

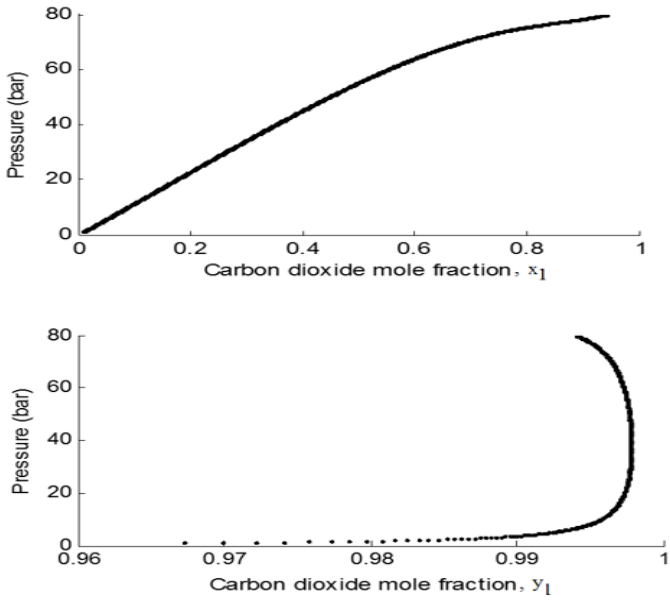

Figure 3. Vapor-liquid equilibrium of the (CO_2, 1-butanol) binary system at 313.15 K.

Table 1
Result of the modeling binary system of (CO_2, solvent) via different solvents at 313.15 K.

Solvent	MW	P_{min} (bar)	x_{CO2} at P_{min}	$\frac{\Delta v}{v}$
ethanol	46.06	69.6	0.67	-17
1-propanol	60.09	60	0.79	-29
1-butanol	74.12	76.8	0.85	-38.5
1-pentanol	88.15	79	0.88	-46.5

3.2. Ternary mixtures

The phase equilibrium of the (CO_2, solvent, ampicillin) ternary system was also studied. Figure 4 shows the ampicillin mole fraction in the ternary system of (CO_2, 1-butanol, ampicillin) at 313.15 K. As indicated in Figure 4, when pressure was increased the solubility of ampicillin in the liquid phase was increased. This trend continued up to 73.2 bar. When pressure was increased from 73.2 bar to 80.5 bar, a sharp decrease in the ampicillin solubility was indicated. The minimum solubility of ampicillin in the liquid phase was detected at the pressures higher than 80.5 bar. In fact, almost all ampicillin was precipitated in the liquid phase.

Table 2
Result of the modeling binary system of (CO_2, solvent) via different solvents at 316.15 K.

Solvent	MW	P_{min} (bar)	$\frac{\Delta v}{v}$
ethanol	46.06	74.5	-16.6
1-propanol	60.09	78	-28
1-butanol	74.12	81.5	-37.9
1-pentanol	88.15	84.2	-45.9

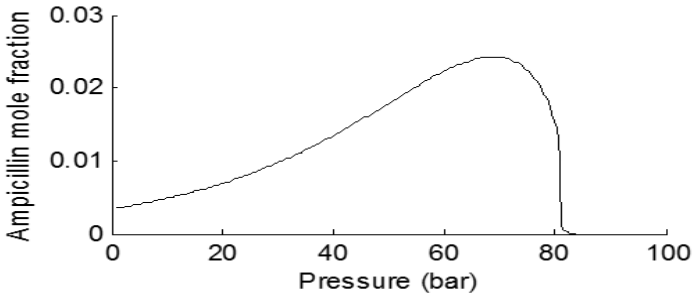

Figure 4. Calculated ampicillin solubility in the liquid phase expanded via the supercritical carbon dioxide in the ternary system of (CO_2, 1-butanol, ampicillin) at 313.15 K.

The mixtures of antisolvent-solvent-solute indicated different behaviors [23-25]. The solubility of griseofuluin in the (CO_2, acetone, griseofulvin) ternary system was studied. The experimental data showed that the solubility of griseofulvin was decreased when the concentration of CO_2 was increased in the liquid phase [26]. A similar trend of results for the solubility of acetaminophen in the (CO_2, ethanol, acetaminophen) ternary system at 315 K, solubility of naproxen in (CO_2, ethanol, naproxen) and (CO_2, acetone, naproxen) ternary systems at 298 K was indicated [27].

Gioannis et al. [26] studied the solubility of griseofulvin in the ternary system of (CO_2, ethanol, griseofulvin) at 312.15 and 326.15 K. Experimental data indicated that the solubility of griseofulvin increased when carbon dioxide was injected to the initial solution, then reached a maximum and then decreased [27]. Sclaroel has shown the same behavior in the (carbon dioxide, ethyl lactate, sclaroel) ternary system [12].

Figure 5 describes the relative expansion of the molar volume as a function of pressure for the (CO_2, 1-butanol, ampicillin) ternary system at different temperatures of 308.15, 313.15 and 316.15 K. The value of the minimum pressure was 71.9, 80.5 and 87.5 bar at 308.15, 313.15 and 316.15 K, respectively. The comparison of Figure 4 and 5 shows that the minimum pressure in two figures had the same value. This means that, when the relative expansion reached the maximum value at the minimum pressure of 80.5 bar, almost all ampicillin was precipitated. The calculated P_{min} was 69.2, 76.8 and 81.5 bar for the (CO_2, 1-butanol) binary system at 308.15, 313.15 and 316.15 K, respectively. Based on the calculated P_{min} for binary and ternary systems, at a fixed temperature, the values of P_{min} in ternary systems were higher than the ones in binary systems. Therefore, the calculation of the optimum operation condition for the ternary

system was important.

The relative expansion of the molar volume with temperature and pressure for the ternary system of (CO_2, ethanol, ampicillin) was studied. The calculated P_{min} for the ternary system was 70, 72.9, and 78.8 bar at 308.15, 310.15, and 313.15 K respectively. In the binary system, the value of the minimum pressure was 62.7 and 69.6 bar at 308.15 and 313.15 K. As demonstrated, in the P_{min} binary and ternary systems at a fixed temperature, the value of P_{min} in the binary system was less than that of in the ternary system. The solubility of ampicillin in the liquid phase was investigated at 313.15 K. A slight increase in the ampicillin solubility in the liquid phase was observed up to 62 bar. A sharp decrease of the ampicillin solubility was indicated from 70.7 to 78.8 bar. All ampicillin was precipitated at above 78.8 bar because a minimum amount of ampicillin was detected in the liquid phase.

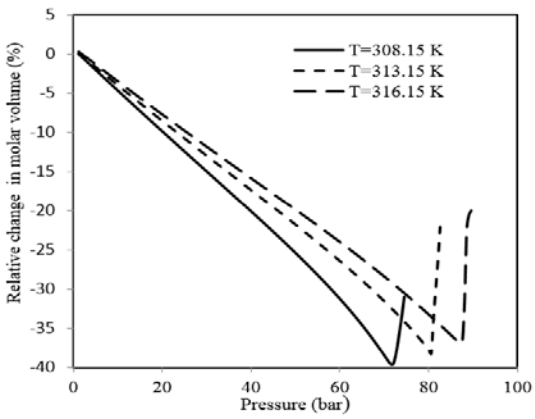

Figure 5. Relative expansion of the liquid phase as a function of pressure for the ternary system of (CO_2, 1-butanol, ampicillin) at different temperatures.

The calculated P_{min} for the (CO_2, 1-propanol, ampicillin) ternary system was 70.8, 80 and 87.4 bar at 308.15, 313.15 and 316.15 K respectively. The solubility of ampicillin in the liquid phase for the expanded solution by carbon dioxide reached a minimum at the pressure of 80 bar at 313 K. This pressure was shown in the relative change of the molar volume.

Similarly, the calculated P_{min} for the (CO_2, 1-pentanol, ampicillin) ternary system was 73, 81.8 and 88.1 bar at 308.15, 313.15 and 316.15 K respectively. The minimum pressures of the (CO_2, solvent, ampicillin) ternary system with different solvents are listed in Table 3.

Table 3
Influence of different solvents on the operational conditions of the ternary system of (CO_2, solvent, ampicillin) at 313.15 K.

Solvent	MW	P_{min} (bar)
ethanol	46.06	78.8
1-propanol	60.09	80
1-butanol	74.12	80.5
1-pentanol	88.15	81.8

Figure 6 shows the changes of the molar volume with the pressure for the (CO_2, solvent, ampicillin) ternary system at 308.15 K. The calculated P_{min} was 70, 70.86, 72.2 and 73.4 bar for ethanol, 1-propanol, 1-butanol, and 1-pantanol at, 308.15 K respectively. According to these results, when the molecular weight of the solvent was increased, the value of P_{min} was increased.

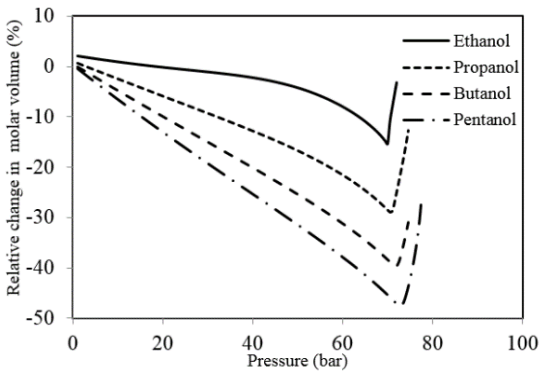

Figure 6. Relative expansion of the liquid phase as a function of pressure for the (CO_2, solvent, ampicillin) ternary system at 308.15 K.

4. Conclusions

The phase equilibrium of binary system (CO_2, solvent) and ternary system (CO_2, solvent, ampicillin) with different solvents were studied. The ethanol, 1-propanol, 1-butanol, and 1-pantanol were selected as solvents. The combination of the Peng-Robinson EOS and Vidal and Michelsen mixing rule (LCVM) was selected to determine the optimum operating condition of the GAS process. The optimal operational conditions of each system were determined by the relative volume expansion of the liquid phase. Those optimal conditions were the same as conditions that were indicated from the mole fraction of ampicillin as a function of pressure. The minimum value of pressure increased with temperature. The values of P_{min} in binary systems were less than those of in ternary systems. When the molecular weight of the solvent increased, the value of P_{min} increased.

Nomenclature

a	parameter in the PR-EOS [J m^3/mol^2].
b	parameter in the PR-EOS [m^3/mol].
G^E	excess Gibbs energy [J/mol].
H	heat of fusion [J/mol].
P	pressure [Pa].
R	universal gas constant, R= 8.31 [J/mol K].
T	temperature [K].
v_α	molar volume of the α phase [m^3/mol].
x_i	mole fraction of component i in liquid phase.
y_i	mole fraction of component i in vapor phase.
z	compressibility factor.
Greek letters	
Δ	property change.
φ	fugacity coefficient.
ω	acentric factor.
α	correction factor of attractive parameter.
γ_i	activity coefficient.
Superscripts and subscripts	
0	reference condition.
i	species i.
1	antisolvent.
2	solvent.
3	solute.
c	critical.
tp	triple point.
L	liquid.
V	vapor.
S	solid.
α	phase.

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