

MICRONIZATION OF CALCIUM SALTS USING SUB AND SUPERCRITICAL CARBON DIOXIDE: EQUILIBRIUM MEASUREMENTS AND THERMODYNAMIC MODELING

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Abstract. Calcium salts with particle sizes in the range of micron and submicron are useful for the manufacture of calcium reinforced beverages such as water, juices and milk. These particles can be produced by using compressed carbon dioxide (sub or supercritical) to increase the aqueous solubility of the calcium salt followed by a rapid expansion of the saturated solution through a nozzle. This process has several advantages over conventional processes such as milling. In this work, the aqueous solubility of calcium citrate and calcium carbonate in the presence of compressed carbon dioxide was measured at pressures between 7 and 138 bar, and temperatures between 15 and 45 °C, by using a high pressure visual cell connected to a UV-VIS spectrophotometer. Experimental measurements of pH in the compressed water-salt-CO₂ mixtures were made. A thermodynamic model to predict the pH based on dissociation reactions, CO₂ mass balances and charge balances was developed. The model has a maximum deviation of 4% for calcium carbonate and 6% for calcium citrate. Limiting values of the equilibrium constants were determined for predicting the complete solubility of calcium salts at constant temperature, pressure and salt concentration. These results help to understand and thus to potentially manipulate the solubility, an important step in the process for producing micron-size particles of calcium salts.

Keywords: Calcium salt, micronization, carbon dioxide, calcium citrate, calcium carbonate.

1. Introduction

The world demand for liquid food products reinforced with calcium is rapidly growing as a result of an increasing consumer perception on the need for calcium intake to prevent calcium-related pathologies such as osteoporosis. Of the calcium salts commercially available, citrate provides the greatest calcium bioavailability, although calcium carbonate is also available for this purpose. Because the aqueous solubilities of calcium salts are small (0.012 g/L at 20°C for calcium carbonate and 0.85 at 15 °C for calcium citrate [1]), these products are provided in solid form [2], and thus, for manufacturing calcium reinforced beverages, small particle sizes (5 to 10 µm) are required to prevent the perception of grittiness during consumption and the settlement of solids during the shelf life of the product.

We have been studying the micronization of calcium salts by expanding aqueous solutions saturated with sub and supercritical carbon dioxide [3,4,5]. This process has several advantages: (1) It is easy to implement, (2) it requires a low energy consumption, (3) it provides sterile conditions and (4) it reduces the particle size while exerting control over the size distribution. For making practical such a process, knowledge regarding the aqueous solubility of calcium salts in the presence of compressed CO₂ is important. In a previous work [4] we reported on our preliminary experiments for determining the regions of pressure and temperature where solubility of calcium citrate and calcium carbonate in water saturated with sub and supercritical carbon

dioxide can be obtained. In this work we measured the aqueous solubilities of calcium citrate and carbonate in the presence of compressed CO₂. In addition, we measured the pH for these systems at high pressure and developed a thermodynamic model that helps to explain our observations.

2. Fundamentals

The process we have been studying has two steps: (1) dissolve the calcium salt present in an aqueous suspension by using compressed carbon dioxide, and (2) then expand the saturated solution through a nozzle. To illustrate, Figure 1 shows the solubility of calcium citrate in water at different pH values. Notice that solubility increases at lower pH, especially at pH below 4.5. This behaviour is common for several calcium salts, carbonate included. A decrease in the pH can be easily obtained by using compressed carbon dioxide. Figure 2 shows the pH of water in equilibrium with supercritical CO₂ [6]. At moderate pressures carbon dioxide has a low solubility in water (0.036 %mol), while at supercritical conditions (up to 74 atm) the solubility increases up to 2 %mol [7], resulting in acid conditions with pH values below 3.0 [6,7,8]. This is a result of the formation of carbonic acid according to the reaction:



Figure 1 indicates that the aqueous solubility of calcium citrate increases also with decreasing temperature. This temperature dependence is referred as “inverse solubility”, and indicates that large dissolution can be obtained at high pressures and low temperatures. As a result, both the supercritical and subcritical regions have to be explored for searching appropriate processing conditions.

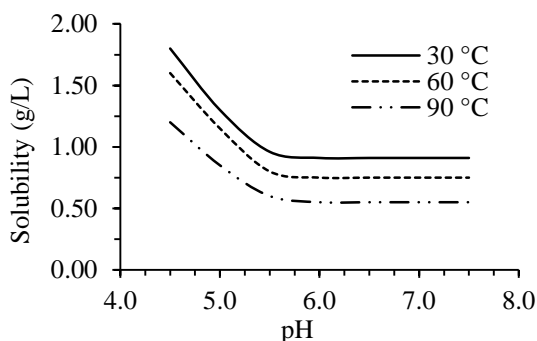


Figure 1. Solubility of calcium citrate in water [9].

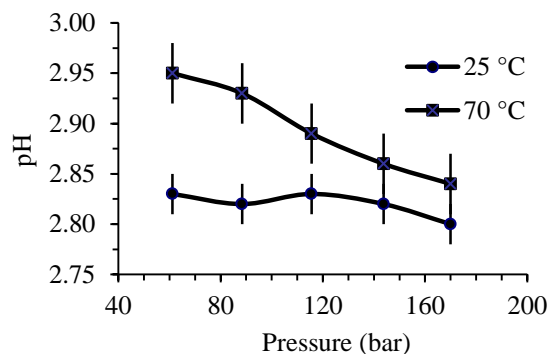


Figure 2. pH variation of water in equilibrium with SC CO₂[6].

The second step in the process is the precipitation that takes place once the saturated solution is expanded through a nozzle. During such a rapid expansion, the carbon dioxide is liberated and the solution becomes supersaturated with the calcium salt, which precipitates. Because the expansion occurs very fast, there is no time for the crystals to grow and this results in a precipitate with a small particle size. Except for the fact that the solution is saturated with the calcium salt and carbon dioxide, this step of the process is not different in essence from several other micronization processes discussed in the literature [10,11,12], which have been used to produce micro and nanoparticles for a wide range of materials [13].

3. Materials and methods

3.1 Materials

USP-grade calcium citrate was kindly provided by Sucromiles (Cali, Colombia). USP-grade calcium carbonate was obtained from a local supplier. Both of them were stored in a dry environment. CO₂ (purity 99.9%) was obtained from Oxígenos de Colombia S.A (Cali, Colombia). All these material were used as received.

3.2 Experimental apparatus and procedure

Figure 3 shows the experimental apparatus that was used for determining the solubility of the calcium salts, and for the pH measurements. This apparatus was designed for pressures up to 4000 psi and was built in our laboratory [5]. It is conformed by a 10 cm³, magnetically stirred, high-pressure visual cell. The cell has four windows and a port for loading compressed CO₂. Each window has a lens made of borosilicate that was polished to guarantee optical purity and planarity. The cell is located inside an isolated copper block whose temperature can be controlled between 10 and 85 °C to a ±0.3 °C by using a PID controller (Pacific supercool, model SDC-45-D) connected to a K-thermocouple as measuring element, and to a thermoelectric heater/cooler (i.e., a Peltier), which is in thermal contact with the copper block, as final control element. The temperature inside the cell was measured with a K thermocouple connected to a digital thermometer (Fluke, model 52-II). The thermocouples were calibrated using a NIST-traceable RTD secondary standard. A Williams-Milton Roy pneumatic pump (Williams-Milton Roy, model CP250V225, rated for pressures up to 7000 psi) and a high-pressure cylinder (HIP, model 62-2-10) were used for delivering CO₂ and for finely setting the operating pressure, respectively. Pressures were measured with a Bourdon-type pressure gauge (Ashcroft, model AISI 403, 0 to 7500 psi), and are precise to ±5.0 psi.

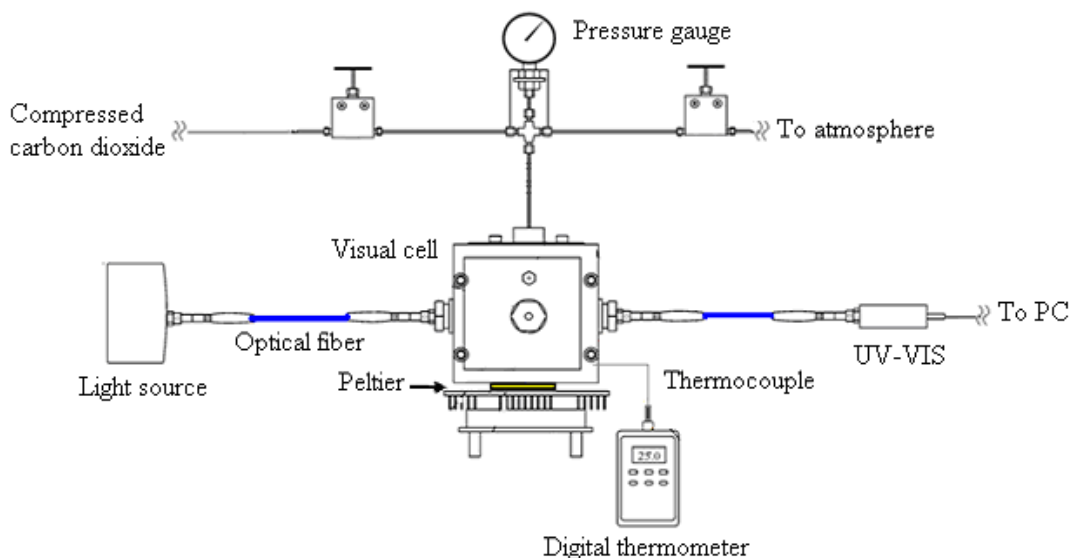


Figure 3. Experimental apparatus.

A UV-VIS spectrophotometer (USB 4000, Ocean optics) was used to continuously monitor the presence of solid particles during the equilibration time by registering the spectral changes of the solution. The UV-VIS was connected to the visual cell by using an optical fiber probe (QP600-2SR, Ocean Optics) and the signal was sent to a personal computer. *Spectra Suite* software was used to collect the spectra obtained during the experiments.

In a solubility experiment, 9 mL of water and 3 drops of a blue bromophenol solution (0.04% w/v) were loaded into a glass vial that was located inside the high pressure cell, and were magnetically stirred. After obtaining a constant desired value of temperature, stirring was stopped and a reference absorbance at 580 nm was registered. A known amount of the calcium salt was then added and the system was stirred again. Then, carbon dioxide was pumped until a desired pressure was reached. After 1 h the stirring was stopped and a new value of the absorbance was registered. Complete solubility of the salt was observed when the difference between this absorbance and that of the reference was a minimum. Usually such a minimum was suddenly reached when reading absorbance at increasing pressures.

For determining the pH of calcium salt solutions at high pressures, first a calibration curve of pH with absorbance was obtained by using a set of 12 buffer solutions which cover the range of pH between 2.5 and 6.5. The buffer solutions were prepared with potassium-hydrogen-phthalate, chlorhydric acid and sodium

hydroxide. Three drops of the blue bromophenol solution were added to 9 mL of each buffer and the absorbances at 440 and 580 nm were determined. We used the ratio between these two absorbances to correlate the pH of the buffer solutions, as described by Toews [6]. We observed that the ratio of absorbances measured at each pH did not change when CO₂ at high pressures was added. With the described calibration curve, experimental values of pH for the calcium salt-water-CO₂ system at high pressures were then determined.

4. A thermodynamic model

A thermodynamic model to represent the measured equilibrium and to predict the pH of the saturated solutions was developed. For each salt the model is conformed by the equilibrium equations for the dissociation reactions, the mass balance and the charge balance. The set of equations must be solved to determine the activities of species *i* and to calculate the solution pH based on hydrogen ion activities.

Table 1 shows the dissociation reactions involved in the dissolution of the calcium salts considered in this study. For each reaction, the equilibrium constant is expressed in terms of activities as:

$$K = \prod a_i^{v_i} \quad (2)$$

where *K* is the equilibrium constant, *a_i* is the activity of species *i*, and *v_i* is the stoichiometric coefficient of *i* in the reaction. The activities are most commonly expressed in terms of activity coefficients, thus:

$$K = \prod (\gamma_i x_i)^{v_i} \quad (3)$$

where *x_i* is the molar concentration of *i*, and *γ_i* is the activity coefficient of *i*.

Table 1. Dissociation reactions involved in the dissolution of the calcium salts considered in this study.

Reactions	Equilibrium constants	Reaction numbers
<u>Water – CO₂</u>		
$H_2O \leftrightarrow H^+ + OH^-$	K_w	(4)
$H_2O + CO_2 \leftrightarrow H_2CO_3$	K_1	(5)
$H_2CO_3 \leftrightarrow H^+ + HCO_3^-$	K_2	(6)
$HCO_3^- \leftrightarrow H^+ + CO_3^{2-}$	K_3	(7)
<u>Calcium carbonate dissociation</u>		
$CaCO_{3(s)} \leftrightarrow Ca^{2+} + CO_3^{2-}$	K_4	(8)
$CaCO_{3(s)} + H^+ \leftrightarrow Ca^{2+} + HCO_3^-$	K_5	(9)
<u>Calcium citrate dissociation</u>		
<i>(For brevity, Ca₃(C₆O₇H₅)_{2(s)} = Ca₃Cit_{2(s)})</i>		
$Ca_3Cit_{2(s)} \leftrightarrow Ca^{2+} + 2Ca(Cit)^-$	K_6	(10)
$Ca(Cit)^- \leftrightarrow Ca^{2+} + Cit^{3-}$	K_7	(11)
$Ca^{2+} + Cit^{3-} + 2H^+ \leftrightarrow CaH_2Cit^+$	K_8	(12)
$Ca^{2+} + Cit^{3-} + H^+ \leftrightarrow CaHCit$	K_9	(13)

By expressing Equation 3 for the chemical reactions 4 to 13 we obtain:

$$\underbrace{Water - CO_2 - Calcium carbonate}_{(\gamma_{H^+} \gamma_{OH^-}) x_{H^+} x_{OH^-} - K_w = 0} \quad (14)$$

$$(\gamma_{CO_2}) x_{CO_2} - (\gamma_{H_2CO_3}) x_{H_2CO_3} K_1 = 0 \quad (15)$$

$$(\gamma_{H^+} \gamma_{HCO_3^-}) x_{H^+} x_{HCO_3^-} - (\gamma_{H_2CO_3}) x_{H_2CO_3} K_2 = 0 \quad (16)$$

$$(\gamma_{H^+} \gamma_{CO_3^{2-}}) x_{H^+} x_{CO_3^{2-}} - (\gamma_{HCO_3^-}) x_{HCO_3^-} K_3 = 0 \quad (17)$$

$$(\gamma_{Ca^{2+}}\gamma_{CO_3^{2-}})x_{Ca^{2+}}x_{CO_3^{2-}} - K_4 = 0 \quad (18)$$

$$(\gamma_{Ca^{2+}}\gamma_{HCO_3^-})x_{Ca^{2+}}x_{HCO_3^-} - (\gamma_{H^+})x_{H^+}K_5 = 0 \quad (19)$$

The mass balance equation for CO₂ is:

$$x_{H_2CO_3} + x_{CO_2} + x_{HCO_3^-} + x_{CO_3^{2-}} - S_{CO_2} = 0 \quad (20)$$

where S_{CO₂} is the solubility of CO₂ in water in mol/L.

The charge balance equation is:

$$x_{H^+} + 2x_{Ca^{2+}} - x_{OH^-} - x_{HCO_3^-} - 2x_{CO_3^{2-}} = 0 \quad (21)$$

Water – CO₂ - Calcium citrate

$$(\gamma_{Ca^{2+}}\gamma_{Ca(Cit)^-})x_{Ca^{2+}}x_{Ca(Cit)^-} - K_6 = 0 \quad (22)$$

$$(\gamma_{Ca^{2+}}\gamma_{Cit^{3-}})x_{Ca^{2+}}x_{Cit^{3-}} - (\gamma_{Ca(Cit)^-})x_{Ca(Cit)^-}K_7 = 0 \quad (23)$$

$$(\gamma_{Ca^{2+}}\gamma_{Cit^{3-}}\gamma_{H^+})x_{Ca^{2+}}x_{Cit^{3-}}x_{H^+} - (\gamma_{CaH_2Cit^+})x_{CaH_2Cit^+}K_8 = 0 \quad (24)$$

$$(\gamma_{Ca^{2+}}\gamma_{Cit^{3-}}\gamma_{H^+})x_{Ca^{2+}}x_{Cit^{3-}}x_{H^+} - (\gamma_{CaHCit})x_{CaHCit}K_9 = 0 \quad (25)$$

The charge balance for this system is given by:

$$x_{H^+} + 2x_{Ca^{2+}} + x_{CaH_2Cit^+} - x_{OH^-} - x_{HCO_3^-} - 2x_{CO_3^{2-}} - 3x_{Cit^{3-}} - x_{CaCit^-} = 0 \quad (26)$$

The solubility of CO₂ in water as a function of pressure was estimated by using a correlation of the experimental data by Wiebbe and Gaddy [14,15]. Changes in activity coefficients and equilibrium constants due to temperature and pressure were estimated with the method by Helgesen and Kirkham [16,17]. Once activity coefficients and equilibrium constants were estimated, the system of equations was solved by using a MATLAB [18] code. The model allows one to obtain the ionic concentrations and the equilibrium constants at each pressure and temperature. The pH of the system was then calculated by the equation:

$$pH = -\log(a_{H^+}) = -\log(x_{H^+}) - \log(\gamma_{H^+}) \quad (27)$$

where a_{H^+} is the activity of hydrogen ions (mol/L), x_{H^+} is the molar concentration of hydrogen ions (mol/L), and γ_{H^+} is the activity coefficient of hydrogen ions.

5. Results and discussion

Table 2 shows temperatures and pressures for complete solubility of calcium salts. Concentrations of calcium carbonate as high as 2.2 g/L can be dissolved at 15 °C and 37.4 bar. This is 200 times the solubility of this salt at 20 °C and atmospheric pressure (0.012 g/L). In contrast, for calcium citrate, a maximum solubility of 1.6 g/L was observed at different conditions. For example at 44.7 °C and 65.3 bar or 22.5 °C and 35.3 bar, citrate is completely dissolved. This concentration is twice the one observed at 15 °C and atmospheric pressure. Curiously, at 30 °C citrate does not dissolve completely at any of the pressures we tried (up to 136 bar).

Table 3 shows the pH of water-CO₂-calcium salt mixtures at different pressures and temperatures. As expected, the higher the pressure the lower the pH for both calcium salts. Notice that the maximum deviation between the experimental and calculated data was 3.9% for calcium carbonate while for citrate was 6.4%. As we previously mentioned, increasing pressure results in acid conditions due to the formation of carbonic acid. In the case of citrate, pH decreases from 3.77 to 3.53 when pressure increases from 67.3 to 94.5 bar at 1.1 g/L and 45 °C. The same behavior is observed for calcium carbonate, *i.e.*, pH decreases from 4.55 to 3.89 when pressure increases from 36.7 to 103.6 bar at 1.6 g/L and 30 °C. Notice that for calcium citrate, there is not a

significant effect of the concentration on the pH. For instance, at 30 °C and 67.4 bar, increasing concentration from 1.1 to 1.3 g/L, the pH changes just from 3.81 to 3.87. The same effect on pH was observed at 45 °C and 94.5 bar (3.59 vs 3.53). Those results are intriguing especially if we consider the dissociation reactions 12 and 13, which suggest that increasing the citrate concentration should produce the formation of calcium-complexes that consume hydrogen ions affecting the pH of the solution; as a result, we observed a change in the pH that was least significant than the one we expected.

In contrast, note that for calcium carbonate the salt concentration affects the pH. For instance, at 36 bar and 30 °C, increasing the concentration from 1.1 to 1.6 g/L, changes the pH from 4.39 to 4.55. Reactions 8 and 9 indicate that formation of bicarbonate ion takes place; because formation of this ion consumes the hydrogen ion, it increases the pH.

In addition to the pH, it is important to consider the values of equilibrium constants to know the direction in which each dissociation reaction takes place. Table 4 shows the thermodynamic equilibrium constants for water-CO₂-calcium citrate mixtures at different temperatures, pressures and salt concentrations. Recall that K₆ and K₇ are the equilibrium constants for reactions 10 and 11 (see Table 1), which represent the dissociation of calcium citrate and the dissociation of the calcium-complex, respectively. The values of K₆ are very low (about 1x10⁻¹⁰) which indicates that the equilibrium tends to the left side of the reaction.

Table 2. Temperatures and pressures for complete solubility of calcium salts

Calcium carbonate			Calcium citrate		
Concentration (g/L)	Temperature (°C)	Pressure (psig)	Concentration (g/L)	Temperature (°C)	Pressure (psig)
1.1	15.0	260	1.1	14.8	210
1.1	22.5	350	1.1	22.5	490
1.1	45.2	850	1.4	14.8	710
1.6	22.5	400	1.1	44.6	820
1.6	30.0	530	1.6	44.7	960
1.6	45.8	900	1.35	30.3	950
2.2	15.0	550	1.6	22.5	520
2.2	45.0	1100	1.6	30.0	-----

Table 3. pH of water-CO₂-calcium salt mixtures at different pressures and temperatures

Calcium salt	Concentration, g/L	Temperature, °C	Pressure, bar	pH		
				Experimental	Calculated	Absolute error, %
Carbonate	1.1	29.8	38.1	4.57	4.39	3.9
	1.3	29.8	36.7	4.57	4.47	2.2
	1.6	29.9	36.7	4.60	4.55	1.1
	1.6	30.0	103.4	---	3.89	
	1.1	44.9	63.9	4.28	4.20	1.9
	1.6	45.0	71.4	4.34	4.29	1.2
	2.2	45.0	81.6	---	4.34	
Citrate	1.1	29.6	63.2	3.65	3.76	2.4
	1.1	45.0	67.3	3.60	3.77	4.5
	1.3	30.0	67.4	3.65	3.87 ^a	5.7
	1.1	30.0	67.4	--	3.81 ^a	
	1.3	44.8	94.5	3.82	3.59 ^b	6.4
	1.1	45.0	94.5	--	3.53 ^b	

Table 4. Thermodynamic equilibrium constants of water- CO₂-calcium citrate mixtures at different temperatures, pressures and concentrations.

Concentration g/L	Temperature °C	Pressure bar	-log(K ₆)	-log(K ₇)
1.1	29.6	63.2	9.66	3.37
1.1	45.0	67.3	9.66	3.37
1.1	45.0	94.5	9.67	3.37
1.3	30.0	67.4	9.45	3.31
1.3	44.8	94.5	9.46	3.32
1.6	30.0	94.5	<u>9.20</u>	<u>3.25</u>
2.2	30.0	67.4	<u>8.81</u>	<u>3.16</u>
1.6	44.8	94.5	<u>9.19</u>	<u>3.23</u>
1.6	15.0	47.6	<u>9.19</u>	<u>3.25</u>

Table 5. Thermodynamic equilibrium constants of water-CO₂-calcium carbonate mixtures at different temperatures, pressures and concentrations.

Concentration g/L	Temperature °C	Pressure bar	-log(K ₄)	-log(K ₅)
1.1	29.8	38.1	10.39	0.24
1.1	44.9	63.9	10.45	0.50
1.3	29.8	36.7	10.19	0.04
1.6	29.9	36.7	9.96	-0.19
1.6	45.0	71.4	9.98	0.07
2.2	45.0	81.6	9.64	-0.22
2.4	15.0	36.7	<u>9.54</u>	-0.74
2.5	45.0	67.3	<u>9.44</u>	-0.48
3.0	15.0	47.3	<u>9.32</u>	-0.91

For the second dissociation reaction (Reaction 11) the equilibrium constant is around 1×10^{-4} , which means that this last reaction takes place more easily than the former. However, as the value of the constants are smaller than 1, the presence of calcium-complexes dominate over the presence of Ca^{2+} and Cit^{3-} ions in solution.

The logarithms of the equilibrium constants are larger than 9.3 for K₆ and 3.3 for K₇ for those operating conditions at which complete solubility was experimentally observed. In contrast, we obtained smaller values in experiments where complete dissolution of the salt was not observed. For example, we found that at 2.2 g/L and 30 °C it was not possible to completely dissolve that concentration of calcium citrate. At these conditions the logarithm values of K₆ and K₇ are 8.81 and 3.16 respectively. In Table 4 other conditions at which it was not possible to obtain a complete dissolution of the salt are shown as underlined data. A small logarithmic value of a constant indicates that the reaction tends to the right. In the case of citrate this means more dissociation of calcium-complexes that decreases the solubility of calcium citrate [19], and it might explain the unexpected insolubility of citrate at 1.6 g/L and 30 °C.

As it is known, temperature, pressure and salt concentration affect the equilibrium constant. However, notice in Table 4 that the effect of the operating conditions on the equilibrium constants is not significant. For example, at 45 °C and 1.1 g/L, increasing pressure from 67.4 to 94.5 bar does not change the value of the equilibrium constants K₆ and K₇. On the other hand, there is a significant effect of concentration on the equilibrium constant. For instance, at 45 °C and 94.5 bar, increasing the citrate concentration from 1.1 to 1.6 g/L causes a change of the logarithm of the equilibrium constant K₆ from 9.67 to 9.19.

Table 5 shows the thermodynamic equilibrium constants for water-CO₂-calcium carbonate mixtures at different temperatures, pressures and salt concentrations. In the case of carbonate K₄ and K₅ are the equilibrium constants for reactions 8 and 9, which represent the dissociation of solid calcium carbonate and the formation of the bicarbonate ion, respectively. The value of the equilibrium constant for the dissociation of calcium carbonate is fairly low (around 1×10^{-10}). This indicates that the reaction takes place towards the left side. A comparison of this value with the one obtained for the second dissociation reaction (Reaction 9) indicates that the formation of the bicarbonate ion occurs easier than the dissociation of calcium carbonate to

Ca^{2+} and CO_3^{2-} . This fact probably explains the unexpected larger pH of the solutions shown in Table 3. As in the case of citrate, a value of 9.60 in $\log K_4$ represents the limiting value that marks the region of insolubility.

6. Conclusions

Expansion of solutions saturated with calcium salts and carbon dioxide is a simple way to produce calcium salts with a reduced particle size, which are important for producing calcium reinforced foods and beverages. A thermodynamic model to predict pH and dissociation equilibrium constants was developed. To validate the model, experimental pH measurements were made by using an UV-Vis spectrophotometer. Results indicate that the model has a maximum deviation of 4% with respect to the experimental pH for calcium carbonate, and 6% for calcium citrate. As expected, lower values of pH were obtained at higher pressures due to the formation of carbonic acid. However, in the case of carbonate, the formation of bicarbonate ions explains the unexpected larger values of pH that were observed. Limiting values of the equilibrium constants were determined for predicting the complete solubility of calcium salts at constant temperature, pressure and salt concentration. In the case of citrate, values below 9.3 for $\log K_6$ and 3.3 for $\log K_7$ mark a region of incomplete dissolution of this salt. In the case of carbonate, such a region is marked by a value of $\log K_4$ below 9.6. These results help to understand and thus to potentially manipulate the solubility for producing micron-size particles of calcium salts.

Acknowledgments

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References

- [1] R.H., Perry, D., Green, Perry's Chemical Engineers Handbook, 6th edition, Mc Graw Hill, New York, 1984
- [2] V., Boldyrev, T. P., Shakhtshneider, S. A., Chizhik, On the mechanism of solubilization of drugs in the presence of poorly soluble additives, *International Journal of Pharmaceutics* 295 (2005) 177-182
- [3] I., Paz, A study on micronization of calcium citrate. M.Sc. Thesis. Universidad del Valle, Cali, Colombia, 2007.
- [4] I., Mejía, G., Bolaños, Micronization of calcium salts by rapid expansion of solutions saturated with sub and supercritical carbon dioxide, Proceedings of 9th International Symposium on Supercritical Fluids, Arcachon, France, 2009
- [5] I., Mejía, Production of calcium citrate and calcium carbonate nano and microparticles by using sub and supercritical carbon dioxide. Ph.D. dissertation, Universidad del Valle, Cali, Colombia, 2012
- [6] K., Toews, R., Shroll, C., Wai, pH – defining equilibrium between water and supercritical CO₂. Influence on SFE of organics and metal chelates. *Anal. Chem.* 67 (1995) 4040 – 4043
- [7] K. J., Ziegler, J. P., Hanrahan, J., Glennon, J., Holmes, Producing 'pH Switches' in biphasic water/CO₂ systems, *J. of Supercrit. Fluids* 27 (2003) 109-117
- [8] R., Thiering, F., Dehghani, N., Foster, Current issues relating to anti-solvent micronization techniques and their extension to industrial scale, *J. of Supercrit. Fluids* 21 (2001) 159 – 177
- [9] G., Gerstner, Feasibility of calcium fortification in dairy and soft drinks Wellness Foods Europe – October/November, 2004. Available from www.junbunzlauer.com
- [10] N., Foster, F. R., Mammucari, F., Dehghani, A., Barrett, K., Bezanehtak, E., Coen, G., Combes, L., Meure, A., Ng, H.L., Regtop, A., Tandia, Processing pharmaceutical compound using dense gas technology, *Ind. Eng. Chem. Res.* 42 (2003) 6476 – 6493
- [11] M., Perrut, J.Y., Clavier, Supercritical fluid formulation: process choice and scale –up, *Ind. Eng. Chem. Res.* 42 (2003) 6375 – 6383
- [12] E., Reverchon, G., Caputo, I., De Marco, Role of phase behavior and atomization in the supercritical antisolvent precipitation, *Ind. Eng. Chem. Res.*, 42 (2003) 6406 - 6414
- [13] E., Reverchon, R., Adami, Nanomaterials and supercritical fluids, *J. of Supercritical Fluids*, 37 (2006) 1 - 22
- [14] R., Wiebe, V., Gaddy, The solubility of carbon dioxide in water at various temperatures from 12 to 40 °C and at pressures to 500 atmospheres. *Critical phenomena, J. Am. Chem. Soc.*, 62 (4) (1940) 815 -817
- [15] R., Wiebe, V., Gaddy, Vapor phase composition of carbon dioxide-water mixtures at various temperatures and at pressures to 700 atmospheres, *J. Am. Chem. Soc.*, 63 (2) (1941) 475-477

- [16] H.C., Helgeson, D.H., Kirkham, Theoretical prediction of the thermodynamic behavior of aqueous electrolytes at high pressures and temperatures: I. Summary of the thermodynamic/electrostatic properties of the solvent, *Am. J. of Science*, 274 (1974) 1089-1178
- [17] H.C., Helgeson, D.H., Kirkham, Theoretical prediction of the thermodynamic behavior of aqueous electrolytes at high pressures and temperatures: II. Debye-Hückel parameters for activity coefficients and relative partial molal properties, *Am. J. of Science*, 274 (1974) 1199-1261
- [18] The Mathworks, Inc., "MATLAB 7.0 Release 14." Natick, MA, USA., 2004
- [19] Ch., Pak, Enhanced solubility of preformed calcium citrate by adding citric acid, US patent 00655422, 2007