RAMAN SPECTROSCOPY AS TOOL FOR THE CONTROL OF BATCH ANTISOLVENT PROCESS

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Crystallization induced by supercritical carbon dioxide as non-solvent is gaining importance, but pressurized vessels actually hinder in-situ monitoring of crystallization course. This paper explores for the first time the potentialities of Raman spectroscopy as a tool to determine the composition of the liquid CO_2-solvent mixture as CO_2 is introduced into the vessel and to monitor the desupersaturation profile of the solution as crystallization proceeds.

INTRODUCTION

Spectroscopic techniques [1-3] have gained in popularity during the last years, specially in the pharmaceutical field of crystallization where there is a need for on-line process monitoring and control. Examples from literature refer usually to crystallizations performed at atmospheric pressure, most of them being induced by cooling and only few by antisolvent addition. Crystallization induced by supercritical CO_2 as non-solvent is gaining importance, but pressurized vessels actually hinder in-situ monitoring of the crystallization course. One work recently reports the use of the UV-vis spectroscopy to investigate the precipitation kinetics of a biodegradable polymer by compressed CO_2 [4]. The method is based on the measurement of the slurry turbidity generated by the polymer precipitation, and on the correlation of absorbances with the second moment of a simulated particle-size distribution.

The results were however obtained at small scale (high-pressure cell of 8-mL, 3 mL of the initial liquor) that might be detrimental for industrial perspectives.

The objective of our current work is to develop spectroscopy to monitor crystallization induced by CO_2, at scale and conditions suitable for industrial perspectives. Raman spectroscopy was proposed due to its ability to monitor the individual concentration of each component involved in the crystallization process, i.e. the solute, the solvent and CO_2, through the selection of specific wavenumbers and spectra calibration. Griseofulvin was chosen as a model solute due to previous investigations on its precipitation by CO_2 [5] and on phase equilibria as well [6]. These investigations have highlighted the antisolvent effect of CO_2 when added to an acetone liquor, based on the decrease of the equilibrium concentration of griseofulvin with the enrichment of the mixture in CO_2.

1. MATERIALS AND METHODS

Materials : Carbon dioxide was purchased from Air Liquide (99.5% purity). Acetone (RP, 99.8% purity) and griseofulvin (minimum 95% purity) were provided by Sigma Aldrich.

Apparatus: Experiments were carried out in a high-pressure, optically accessible vessel, that operated in a batch mode. Additional details of set-up and procedure can be found elsewhere [5]. The crystallizer is a vessel of 0.491 L equipped with three sapphire windows and with an electric motorized stirrer. The stirring was settled at 500 rpm. The CO_2, cooled by a chiller, was delivered through the impeller by a high pressure pump. Pressure and temperature of the vessel were measured with an accuracy of 0.1 MPa and 1°C, respectively.

Procedure : Experiments were carried out at 40°C by adding CO_2 to 100 mL of an acetone solution of griseofulvin at ~24 mg/mL. The procedure consisted in a pressurization step where CO_2 was first introduced by opening a metering valve up to a vessel pressure equal to the reservoir pressure, before activating the pump for an introduction up to 10 MPa. The CO_2 introduction feed was of 0.12 MPa/min. The system was maintained at the final pressure and upon agitation when desired. The subsequent solution discharge was operated by regulating the exit flow and compensating by a feed of fresh CO_2. A flow of pure CO_2 was further maintained to dry the crystals. Depressurization was finally performed by venting CO_2 by the exit line. Crystals were collected on filter and on stirrer for subsequent analysis. Raman spectra were collected over the whole procedure excepted during the depressurization step, thus at each pressure increment of 0.5 MPa, or, in case of steady conditions, every ~ 4 min.

Raman Instrumentation: Crystallization was monitored with a DILOR spectrometer equipped with a CCD camera detector. The range of wavenumbers selected for the study was $750 - 1770$ cm^{-1}, since this region contained accessible griseofulvin, acetone and CO_2 vibrational bands. Raman measurements were performed through a probe head equipped with interferential and notch filters, and connected to the laser and the spectrometer by two optical fibers of 100 μm core and 5 m long. The probe, working in the back-scattered mode, was directly positioned in front of one sapphire window of the vessel. Each spectrum was a sum of ten accumulations collected over 10 s each (for a total spectra acquisition time of 100 s). Data were collected using the Dilor Spectramax program, and processed using an home-made code run with Grams^{TM} software.

Data analysis: Provided that a calibration was performed, the absolute concentration of a specie can be calculated from the area of a spectral peak [7]. A calibration curve for griseofulvin in acetone was constructed from the Raman spectra of six binary solutions ranging from 2.69 to 26.12 mg/mL. The spectral peaks selected to quantify griseofulvin and acetone were centered at Raman shifts of 1620 cm^{-1} and 795 cm^{-1} respectively. As the griseofulvin peak was partly overlapped by the Raman lines of acetone, the spectrum of pure acetone was extracted from the mixture spectra prior to integrating the solute peak. Moreover, to account for incidental changes over time of the Raman parameters which could affect the absolute magnitude of signals, the griseofulvin peak intensity (I_{gri}) was ratioed to the acetone peak intensity (I_{ace}). The CO_2 concentrations were quantified from the area of the peak centered at 1283 cm^{-1}. Raman spectra of pure CO_2 at five pressures and 40°C were used to construct the calibration curve.

2. MONITORING LIQUID VOLUME AND COMPOSITION

The Raman probe was positioned at the vessel bottom, allowing thus to monitor the liquid phase behavior. As said before, the integrated intensity is proportional to the specie density. Assuming that there is no loss of acetone during the pressurization step (no leaks out of the vessel, or negligeable transfer into the vapor-phase) the variation of the acetone peak intensity at time t, I_t, reflects the variation of the liquid phase volume, according to the general expression of $I_t \propto n / V_t$. With reference to the initial volume of the solution V_0 introduced into the vessel and its corresponding integrated signal I_0, it comes:

$$V_t = V_0 \times (I_0/I_t) \tag{1}$$

or :

$$(V_t - V_0)/V_0 = (I_0/I_t) - 1 \tag{2}$$

The relationship shows that the expansion of the solution during the addition of CO_2 could be monitored via the ratioed acetone signal. **Figure 1** presents the evolution of $(V_t - V_0)/V_0$ versus pressure, together with a plot of expansion coefficient measured elsewhere [8].
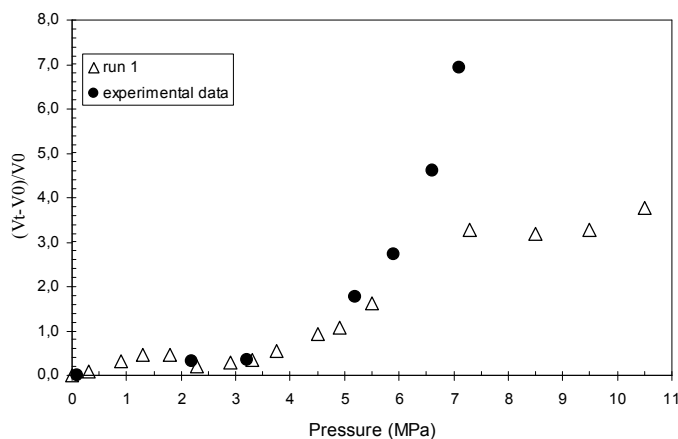

Figure 1. Volumetric expansion of acetone estimated from Raman signal, during a crystallization experiment performed at CO_2 introduction rate of 0.12 MPa/min and 40°C (open symbols) and experimental values reported in [8] (black symbols).

The Run 1 curve shows a smooth increase as the pressure increases to 3.5 MPa, then increases significantly up to the attainment of a plateau, that can be averaged to the expansion value of 3.4, or to a final value at 10.5 MPa of 3.8. These values express the limitation of the expansion by the vessel dimensions, since the corresponding expansion volume and the vessel volume were in the same range of order. The comparison with data obtained previously is satisfactory, considering that the former data were obtained at equilibrium conditions, whereas the estimates were obtained in crystallization conditions, i.e. at a CO_2 introduction feed of 0.12 MPa/min.

The composition of the liquid phase in CO_2 can be also estimated from the Raman signals. The mole number of CO_2, $\mathcal{N}_{CO2,}$ is expressed as :

$$\mathcal{N}_{CO2} = C_{CO2} \ (mol/L) \ x \ V_t \tag{3}$$

CO_2 concentrations were quantified using the integrated intensity of the peak at 1283 cm^{-1}, whereas the liquid phase volume was estimated from the acetone peak as described previously. The plot of calculated CO_2 molar fractions and pressure versus time is reported in **Figure 2**.
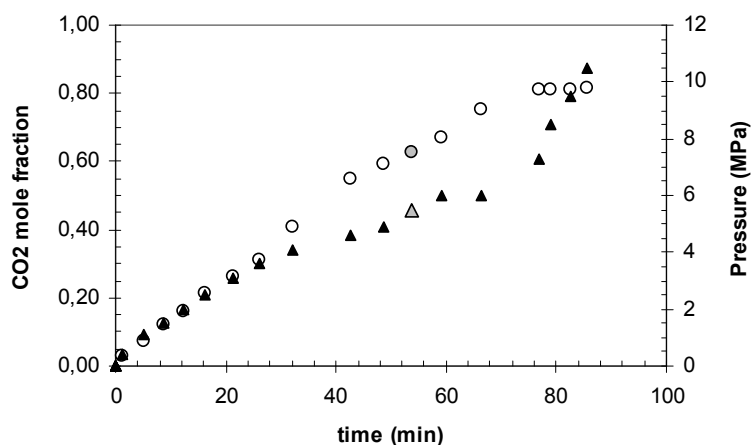

Figure 2. Estimation of the CO_2 content in the liquid phase (open symbols) and the corresponding pressure (dark symbols) during the crystallization performed at CO_2 introduction rate of 0.12 MPa/min and 40°C.

Although the CO_2 molar fraction closely parallels the pressure curves, there is a significant rupture after 7 MPa, since the composition of the liquid phase remains almost constant and close to 0.8, despite a significant increase of pressure. From 7 to 10 MPa, only 0.2 mole of CO_2 was introduced in the vessel, whereas 4.8 mol of CO_2 were introduced between 4 and 7 MPa. This has a direct influence upon crystallization behavior, as illustrated later on.

The question raised by this spectroscopic determination of CO_2 content is how does the measured composition fit the vapor-liquid equilibrium data. In **Figure 3**, both data are presented, in a plot of pressure versus composition. The figure shows that, up to a pressure of 4 MPa, the Raman calculations tend to underestimate the CO_2 content in the liquid phase, since our data (open symbols) are shifted towards lower values than those provided by the vapor-liquid equilibria of the CO_2-acetone system. For molar fractions higher than 0.5, our estimations are rather close to the phase equilibria data reported in literature.
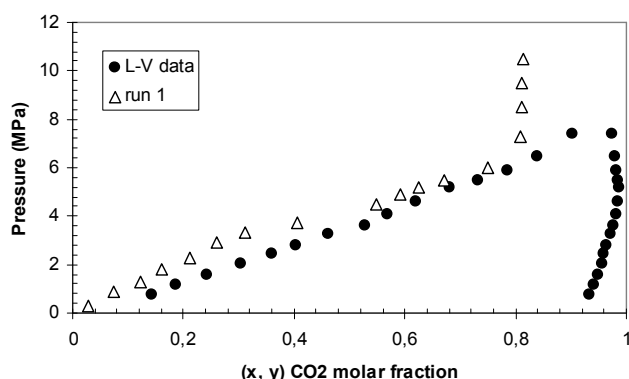
Figure 3. Raman-estimated CO_2 content (open symbols) plot in a equilibrium L-V data (dark symbols, [9]). Raman-estimates were obtained during a crystallization performed at CO_2 feed rate of 0.12 MPa/min and a final pressure of 10 MPa.

Our estimates obviously do not correspond to a situation of equilibrium, that is again, not surprising since data were obtained during a continuous introduction of CO_2 in the vessel. When time is giving to the system to settle without fresh feed of CO_2 (conditions not illustrated in the figure), the composition of the phase shifts gradually toward higher values and finally matches perfectly well with the equilibrium composition. Moreover, the Raman curve behavior (deviation from L-V data at pressure below 4 MPa and better fit at higher pressure) could be explained by the evolution of the introduction point of CO_2 during the feed course. Due to the position of the turbine and to the initial volume of the solution, the CO_2 was first introduced into the upper gaseous phase. Upon subsequent expansion of the liquid phase, the turbine dipped into the solution at pressure above 4.1 MPa. CO_2 was then directly introduced into the liquid phase, that accelerated the obtaining of an equilibrium situation.

3. MONITORING CRYSTALLIZATION OF GRISEOFULVIN

The monitoring of crystallization course during run 1 is illustrated in **Figure 4**, as a plot of the I_{gri}/I_{ace} ratio versus pressure.
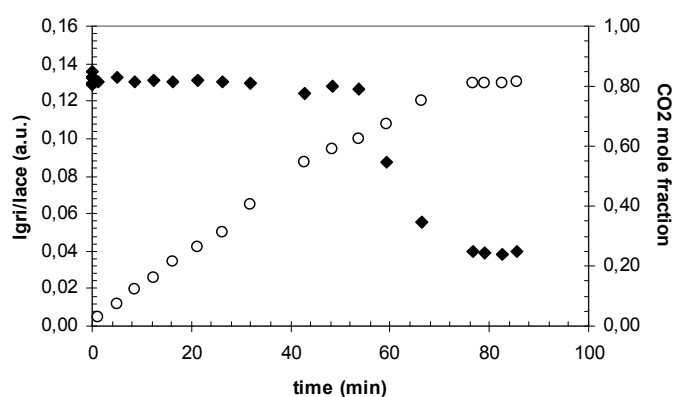

Figure 4. Evolution of the griseofulvin signal expressed as $I_{gri}/I_{acetone}$ during the introduction of CO_2 at a rate of 0.12 MPa/min to a final pressure of 10 MPa. (dark symbols) and plot of the corresponding CO_2 mole fraction in the liquid phase (open symbols)

The curve shows three different periods that reflect the events that the solution undergoes. During the first additions of CO_2, the I_{gri}/I_{ace} ratio remains constant. Both the solute and the solvent undergo the same effect, that is a dilution caused by the mixing of the solution with CO_2. As more CO_2 is added, crystallization begins. The solution is depleted in the

griseofulvin amount that turns into solid particles, and consequently, the ratio decreases. Finally, an almost constant value is recovered as the pressure is further increased to 10 MPa. The sharp decrease of the I_{gri}/I_{ace} ratio signs the precipitation onset. In case of run #1 conditions, the onset occurred at a pressure of 5.0 MPa, corresponding to a mole fraction of CO_2 in the 0.61 range, as calculated from Eq. 3. Since carbon dioxide addition continues after this first burst of nucleation, two phenomena compete for the depletion of the solution in solute, new bursts of nucleation upon continuous CO_2 feed and growth of the early nuclei. These two phenomena are not discernable by the I_{gri}/I_{ace} monitoring and upon these experimental conditions. After a pressure of 7.4 MPa, the I_{gri}/I_{ace} ratio stabilizes at a value of 0.039, meaning that there is no further significant nucleation nor growth. The absence of new nucleation events after 7.4 MPa is understandable, since there is only a slight increase of the CO_2 content in the solution, so no new occurrence of conditions for supersaturation. The pressure of 7.4 MPa corresponds to a CO_2 mole fraction of 0.81. The calculation of the griseofulvin concentration in such solution gives a value of 2.5×10^{-4} mol/mol, that is in the same range of order than the solubility value determined by phase equilibria [6]. Thus, the plateau is an experimental evidence that the system has regained an equilibrium status in terms of crystallization behavior after 7.4 MPa.

CONCLUSION

These first results validate the use of Raman spectroscopy to detect the precipitation onset and to monitor the crystallization course of a component during the addition of CO_2 to a liquor solution. The spectroscopy enabled also the analysis of the phase behaviour involved during the CO_2 feed and the monitoring of the solvent removal during the washing and drying of produced crystals (that were not outlined here). Other results obtained in various conditions of crystallization are still under analysis, but they already do confirm the potentialities of the technique for on-line monitoring and process control, besides providing an experimental evidence of the foreboded scenario of a CO_2-induced crystallization.

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