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Swelling, melting point reduction and solubility of PEG 1500 in supercritical CO_2

Irene Pasquali, Lidia Comi, Francesca Pucciarelli, Ruggero Bettini*

Department of Pharmacy, University of Parma, Viale G. P. Usberti 27/A, 43100 Parma, Italy

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Abstract

The knowledge of the solubility of PEG 1500 as well as the swelling and melting point variation in supercritical CO_2 in a relatively high-pressure range is a necessary prerequisite to set-up pharmaceutical processes dealing with the polymer in the molten state.

Experiments carried out in a pressurized view cell indicated that the PEG 1500 progressively decreases its melting point and increases its volume as a consequence of the absorption of the CO_2. The melting point depression was pronounced (from 46 to 28 °C) up to 8.7 MPa. Thereafter a constant value was attained. Analogously, under CO_2 the polymer increased its volume (about 34%) until 10 MPa; after this pressure, the polymer volume no longer increased.

PEG 1500 showed solubility in SC-CO_2 at 35 and 55 °C in the 10–40 MPa range in the order of 10^{-6} mole fraction. An empirical model based on solubility parameters was used to fit the experimental data and to predict the maximum concentration achievable by the polymer in the dense gas, as well as to quantify the polymer concentration at low pressures where the experimental determination may be extremely difficult.

Keywords: Supercritical CO_2; PEG 1500; Solubility; Melting point depression; Polymer swelling; Heuristic model

1. Introduction

The use of supercritical (SC) carbon dioxide to process various biodegradable/biocompatible polymers for pharmaceutical and medical applications has attracted a great interest in the last two decades (Yeo and Kiran, 2005; Reverchon et al., 2003; Lyons et al., 2007). The high-versatility, the flexibility in offering alternative processing approaches, the possibility to avoid or minimize the use of organic solvents and the opportunity to tune the solvent properties of the SC-CO_2 by varying its density, namely by changing temperature and pressure (Pasquali et al., 2006), should be mentioned as major advantages in the use of SC-CO_2 technologies.

A number of SC-fluid based techniques where the SC-CO_2 acts as solvent, antisolvent or plasticizer have been used to obtain drug delivery systems (Duarte et al., 2007; Moneghini et al., 2001; Li et al., 2007). The main drawback in using the SC-CO_2 as a solvent is represented by the poor solubility of most pharmaceutical products in the dense gas. The CO_2 is a non-polar molecule with low molecular weight, scarcely able to dissolve molecules with more or less pronounced polar characteristics (such as weak bases or acids), and hydrophilic polymers.

Alternatively, the CO_2 can be used as an antisolvent to precipitate drugs and polymers from an organic solvent solution (Kikic et al., 2006).

On the other hand, CO_2 is also able to plasticize many polymers owing to its capability to solubilize into the polymer. In fact, the gas sorption is not a merely physical phenomenon, but it implies also specific chemical interactions (Kazarian et al., 1996). These last in turn may cause an increase of chain mobility resulting in a decrease either of the glass transition temperature, in the case of amorphous polymers, or of melting point, in the case of crystalline polymers. Both in the rubbery or in the liquid state the polymer can incorporate drugs giving rise to a molecular dispersion that can be extruded or sprayed at lower pressure to obtain drug loaded microparticles. Furthermore, the CO_2 may induce in the polymer other physical changes such as swelling (Guadagno and Kazarian, 2004), foaming, crystallization and viscosity or density reduction (Kazarian, 2000; Funami et al., 2007). Being a gas at standard conditions the CO_2

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* Corresponding author. Tel.: +390521905089; fax: +390521905006.
E-mail address: bettini@unipr.it (R. Bettini).

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may be easily removed from the final product at the end of the process.

The knowledge of the phase behavior of CO_2/polymer binary system is a necessary prerequisite, in order to properly design and develop a SC-CO_2-based processes such as the production of drug loaded microparticles or monolithic matrices (Lyons et al., 2007; Costa et al., 2007). In this respect, the solubility of the polymer in SC-CO_2 and the study of the behavior of the polymer in the presence of CO_2 (swelling, foaming, melting point, etc.) are the most important issues that should be addressed.

Among the hydrophilic polymers widely used in pharmaceutical and cosmetic formulations, polyethylene glycols (PEGs) play a major role due to their biocompatibility and non-toxicity (Fruijtier-Pölloth, 2005; Kibbe, 2000).

As a part of a research project aiming at preparing a new microparticulate drug delivery system, the goal of the present work was to study the solubility of PEG 1500 in SC-CO_2 in a relatively high-pressure range as well as the swelling and the melting point variation of the polymer in SC-CO_2.

As far as the PEGs/CO_2 phase behavior is concerned, only few and inconsistent data are available in the literature (Gourgouillon et al., 1998; Wiesmet et al., 2000; Lopes et al., 2000; Daneshvar and Gulari, 1989) especially for PEG with molar mass of 1500 Da (Weidner et al., 1997; Daneshvar et al., 1990). In many of these works the mutual polyethyleneglycol/CO_2 solubility measurements were carried out by sampling, assuming attainment of equilibrium. However, some authors have underscored the inherent problematic nature of such procedure, especially taking into account the need of validating the evenness of the specimen and its capability to represent the whole system (Kazarian, 2000).

The accurate quantification of the CO_2 concentration in the polymer and of the polymer in the SC-CO_2 still represents a challenging issue. In particular, the measurement of the solubility of the solid polymer in the pressurized gas is still quite difficult because of the very low concentration attained by macromolecules in SC-CO_2, in particular at low pressure.

In the present work the solubility of the PEG 1500 in CO_2 at low pressure was calculated by fitting the experimental data (obtained at higher pressure) with a heuristic model based on solubility parameters according to the approach proposed by Giddings and co-workers (Czubryt et al., 1970).

2. Experimental

2.1. Measurement of the density of PEG 1500 and CO_2

The density values of the PEG (1500 Da molecular mass, A.C.E.F., Fiorenzuola, Italy) were calculated at 35 and 55 °C at atmospheric pressure. The value at 35 °C was measured by means of a helium pyknometer (Multivolume Pycnometer 1305, Micromeritics, USA) as to 1.28 g/mL. PEG 1500 melts at ambient pressure between 44 and 48 °C (Kibbe, 2000), therefore, its density at 55 °C was measured by means of calibrated (2 mL) glass pyknometer for liquid; the measured value resulted 1.11 g/mL.

The density values of CO_2 at given pressures and temperatures were calculated by means of the Refprop software (NIST, MD, USA) (http://www.nist.gov/data/ 151 nist23.htm).

2.2. High-pressure view cell

A high-pressure view cell (SITEC-Sieber Engineering AG, Zurich, Switzerland) (internal volume 74 mL) was used to visualize the behavior of the PEG 1500 in the presence of CO_2 (99.99% grade, Sapio, Piacenza, Italy) at fixed temperature and pressure. The cell is equipped with two sapphire windows (diameter 18 mm) facing to each other. The temperature was imposed by a heating jacket within ± 1 K (SITEC-Sieber Engineering AG, Zurich, Switzerland) and the pressure by a high-pressure pump (Teledyne ISCO 260D, Nebraska, USA) with a ± 0.5% pressure gauge monitoring (series D pump controller, Teleodyne ISCO).

2.2.1. Melting point under SC-CO_2

The measurement of the melting points of the PEG 1500 and PEG 4000 (4000 Da molecular mass, A.C.E.F., Fiorenzuola, Italy) under pressure was based on a modified capillary method. The polymer (nearly 1 g) was introduced in a glass cylinder and placed in the high-pressure view cell. Vacuum was created inside the cell (membrane pump KNF, Italy), then, the pressurized CO_2 was introduced and heated.

The melting of the polymer was observed through the sapphire windows and registered with a photo camera (Finepix S602 Zoom, Fujifilm).

For each analysis the temperature value was fixed while the pressure was increased until the polymer melting onset (appearance of the first liquid drop). Each experiment was replicated at least twice.

2.2.2. Polymer swelling under SC-CO_2

PEG 1500 (1.28 g) was placed in a calibrated glass cylinder (2 mL) and introduced inside the high-pressure view cell. After vacuum application, the pressurized CO_2 was introduced into the cell and heated at the desired temperature. The polymer was kept in contact with the CO_2 until the attainment of the equilibrium (typically 24 h). Pictures of the polymer-containing cylinder were recorded at fixed time until a constant volume was reached.

The obtained images were analyzed by means of Image J software (NIH, Bethesda, USA) (http://rsb.info.nih.gov/IJ/) to quantify the polymer volume increase.

Measurements were carried out at least in triplicate at 35 and 55 °C in the 3–25 MPa pressure range.

2.3. PEG 1500 solubility in SC-CO_2

The solubility of PEG 1500 in supercritical CO_2 was assayed by means of a laboratory scale extractor (Spe-ed SFE, Applied Separation, Allentown, PA, USA) operating under dynamic conditions at low CO_2 flux (about 4.5×10^{-3} mol/min) according to the validated method described by Stassi et al. (2000) and modified by Bettini et al. (2001) (Fig. 1).

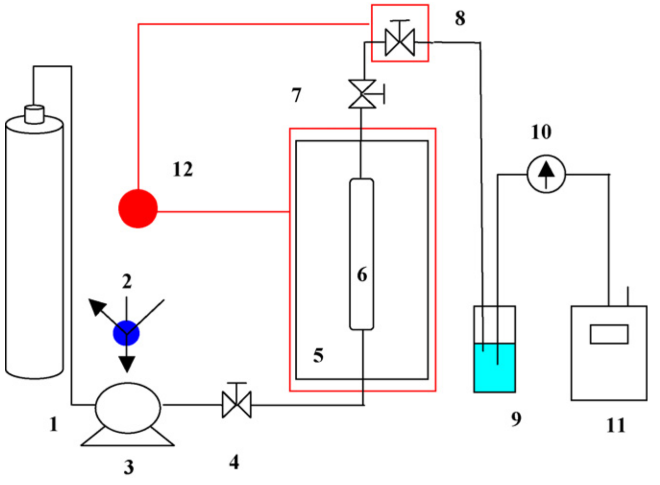

Fig. 1. Schematic representation of the apparatus used for the measurement of PEG 1500 solubility in SC-CO_2: (1) CO_2 reservoir; (2) chiller; (3) pump; (4) inlet valve; (5) thermostatic chamber; (6) saturation column; (7) outlet valve, (8) micrometric valve; (9) collecting flask; (10) flow-meter; (11) gas-meter and (12) temperature controller.

A stainless steel column with internal volume of 1.2 mL was loaded with 200 mg of polymer and placed in a thermostatic chamber at 35 or 55 °C. The CO_2 was introduced into the column and pressurized with a membrane pump to the desired pressure in the 10–40 MPa range. The CO_2 flow rate was tuned by a micrometric valve.

In a typical isothermal solubility determination, the CO_2 flowed through the polymer to remove the air, then, the pressure inside the column was raised up to the desired value holding the outlet valve closed. After reaching the pressure value, the outlet valve was opened and the CO_2 passed through the column. The run was stopped when about 0.9 moles of CO_2 had flowed through the column.

The PEG 1500 dissolved in CO_2 was collected in 25 mL distilled water after gas expansion. To avoid the risk of missing portion of the solute, at the end of each measurement, the micrometric valve and the connection tubing were repeatedly washed with the portion of distilled water. The amount of polymer dissolved in CO_2 was quantified by HPLC (see below). Each measurement was performed at least in triplicate.

The average uncertainty for the solubility experiments was calculated from the contribution of error for each parameter (e.g., pressure, temperature, etc.) applying the rules of the independent variables; the obtained figure resulted above 3.5%.

2.3.1. *HPLC analysis*

A HPLC equipped with Refractive Index detector (RID 10A, Shimadzu, Tokyo, Japan) was used to quantify the PEG 1500. The analyses were carried out using a size-exclusion column OHpak, SB-802.5 HQ (Shodex, Tokyo, Japan), and distilled water as mobile phase at flow of 1 mL min^{-1}. Injected volume was 100 μL and the PEG 1500 retention time was 7.6 min. PEG 1500 was quantified by comparing the sample signal with that of a standard solution of the polymer.

The HPLC method was validated for linearity ($R^2 = 1$), accuracy (98%), precision (R.S.D. < 1.6%), limit of detection (3.8 μg mL^{-1}) and quantification (12.7 μg mL^{-1}). Moreover the number of theoretical plates (2038) and tailing factor (1.05) were also calculated.

3. Results

3.1. *Melting point under SC-CO_2*

Fig. 2 reports PEG 1500 and PEG 4000 melting points as a function of the CO_2 applied pressure.

In the 0.1–0.2 MPa pressure range, the melting point (T_m) of PEG 1500 slightly increased (1 °C), while from 0.2 to 8.7 MPa a decrease was observed. Then, no further change was noticed up to 15 MPa.

As already stated by Shieh and Yang (2005) the first observed phenomenon was probably due to the crystallinity of the polymer, and it might be attributed to an increase in the crystal thickness during CO_2 exposure (Lian et al., 2006).

After 0.2 MPa, the PEG 1500 melting point decreased, and the extent of the melting point depression was directly related to the amount of absorbed CO_2, which, in turn, depended on the applied pressure.

For comparison purpose, the melting point depression as a function of pressure was determined for PEG 4000 as well. The behavior of the higher molecular mass polymer paralleled that of PEG 1500: after a slight T_m initial increase, a linear decrease of the melting point was observed up to 6.5 MPa, than T_m leveled off. This indicates that the capability of the CO_2 to reduce the polymer melting point, and therefore, to act as a plasticizer, is independent of the polymer molar mass. The shift between the two curves presented in Fig. 2 depends only on the different initial T_m value.

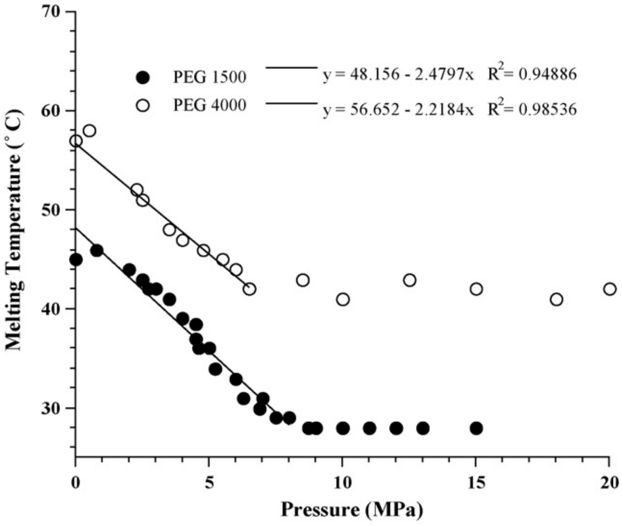

Fig. 2. Melting temperature of the PEG 1500 and PEG 4000 in the presence of CO_2 at different pressure values, along with the equations of the linear regressions of the experimental data in the 0.1–8 and 0.1–6.5 MPa range for PEG 1500 and PEG 4000, respectively.

The reported data are in good agreement with those from the literature (Weidner et al., 1997), and are accordingly interpreted in terms of solubility effect, namely as melting point depression of a pure component due to the incorporation of a diluent in a melt (Lian et al., 2006). These authors found that many polymers exhibit, at low pressure, CO_2-induced melting point decrease linearly dependent on pressure, followed by an approximately constant region at higher pressure. By using numerous experimental data (also from literature) they developed a method based on the Clapeyron equation for two components, three-phase equilibrium, for predicting the lowest melting temperature for crystalline polymer in the presence of CO_2. These authors demonstrated that, at low pressure, the simplified form of Clapeyron equation indicates that the melting temperature decreases linearly with pressure. Linear regression was applied to experimental data at low pressure (linear region) in order to determine the slope, dT_m/dP. The melting point variations between the experimental and theoretic data were compared. The obtained melting point variation of PEG 1500, dT_m/dP, was 2.62 and 2.41 for the experimental (Weidner et al., 1997) and the theoretical data, respectively, quite in agreement with the $dT_m/dP = 2.48$ found in the present work. As far as the PEG 4000 is concerned the theoretical, literature (Weidner et al., 1997) and this work figures for dT_m/dP were 2.1, 2.03 and 2.22, respectively.

3.2. Polymer swelling under SC-CO_2

The absorption of the dense gas into the polymer was also associated to the swelling, in fact the CO_2 solubilizes into the PEG 1500 increasing its volume.

In Fig. 3, the volume equilibrium degree of swelling % reported as a function of CO_2 pressure at 35 and 55 °C can be observed.

At fixed pressure the volume equilibrium degree of swelling, *Q*, was calculated as:

$$Q = \frac{V_f - V_i}{V_i} \times 100 \tag{1}$$

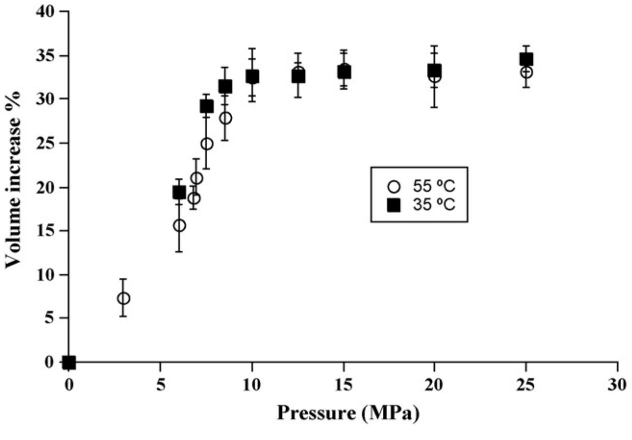

Fig. 3. Percentage of swelling (v/v) of the PEG 1500 as a function of CO_2 pressure at 35 and 55 °C in the 3–25 MPa pressure range. The bars represent the standard deviation ($n = 3$).

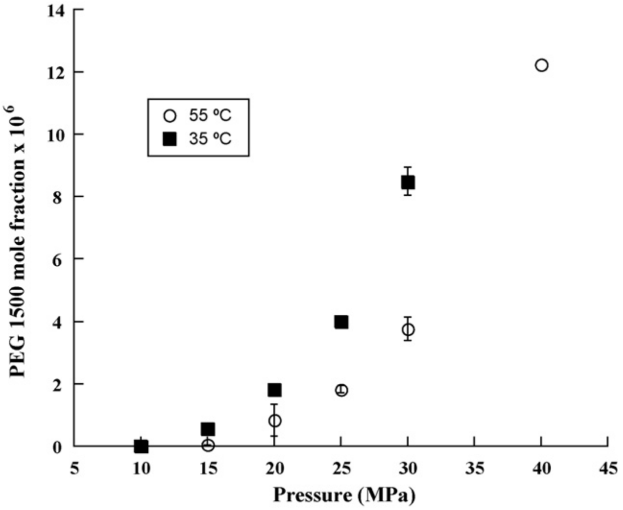

Fig. 4. Mole fraction of PEG 1500 dissolved in SC-CO_2 versus pressure at two different temperatures. The bars represent the standard deviation ($n = 5$).

where, V_f and V_i are the polymer volume after and before exposure to CO_2, respectively.

PEG 1500 swelled with pressure up to 10 MPa, thereafter the polymer volume remained practically constant. The maximum *Q* value was 34.6 and 33.2% (v/v) at 35 and 55 °C, respectively. As far as the effect of the temperature is concerned, up to 10 MPa swelling at 55 °C was lower than that at 35 °C, while the two curves overlapped above said pressure.

3.3. Solubility of PEG 1500 in CO_2

In Fig. 4, the solubility of PEG 1500 in CO_2 at 35 and 55 °C and in the 10–40 MPa pressure range is reported as mole fraction versus pressure.

PEG 1500 shows a low solubility in SC-CO_2. The solubility increased with pressure, while it decreased with temperature likely due to the CO_2 density change. It can be observed that the measured solubility values are rather low, although not negligible, due to the fact that the CO_2 is a small molecule with a weak dipolar moment, thus, it cannot easily dissolve large hydrophilic molecule such as PEG 1500. The obtained figures were in the order of 10^{-6} mole fraction, namely one order of magnitude lower than those reported by Daneshvar et al. (1990) for PEG 1000 at 50 °C.

Experimental data were correlated with the heuristic model proposed by Giddings and co-workers (Czubryt et al., 1970). These authors demonstrated that the solubility of stearic acid, PEG 1000, and PEG 4000 in a very high-pressure range (27–190 MPa) can be expressed as a function of the CO_2 solubility parameter and fitted by means of a second degree equation:

$$\log X = a\delta^2 + b\delta + C \tag{2}$$

where *X* is the solute mole fraction, *a* and *b* are coefficients, *C* is a constant and *δ* is the solubility parameter of the CO_2 at a given pressure and temperature.

In a previous paper, Giddings and collaborators (Giddings et al., 1968) reported that the solvent power of a gas depends in part on its state relative to its critical condition. The influence of the state, which depends on pressure and temperature was defined as *state effect*. Besides a *chemical effect*, unique to each chemical species depending on its polarity, acid–base properties, and hydrogen bonding tendency have to be considered. Solvent power differences among liquids depend only on the *chemical effect*, which is expressed by the square root of the ratio between cohesive energy and molar volume. Once a dense gas is employed as a solvent reduced density is the principal variable of the *state effect*, which reflects average distances and interactions between molecules.

Thus, the solubility parameter of a compressed gas can be calculated by the equation (Giddings et al., 1968):

$$\delta = 1.25\,\mathrm{Pc}^{1/2}\left[\frac{\rho \mathrm{r}}{\rho \mathrm{r(liq)}}\right] \tag{3}$$

where Pc is the critical pressure in atmospheres and the ρr is the reduced density expressed as:

$$\rho \mathrm{r} = \frac{\rho \mathrm{a}}{\rho \mathrm{c}} \tag{4}$$

here, ρa is the CO_2 density at the given pressure and temperature and ρc is the critical density (for CO_2 = 0.458 g/mL). The parameter ρr(liq) is the reduced density of the liquid that, for CO_2 is 2.66 g/mL. Here the *state effect* can be identified with the second term of the right end side of Eq. (3), [ρr/ρr(liq)], while the first term, 1.25 $\mathrm{Pc}^{1/2}$, is associated with the *chemical effect*.

The density values at given pressures and temperatures, calculated using the Refprop software are reported in Table 1 along with the relevant solubility parameter calculated with Eq. (3).

The solubility parameter of PEG 1500 was calculated with the method of group contributions according to Hildebrand and Scott (1950) as 11.07 $\sqrt{\mathrm{cal/cm^3}}$. The difference between the solubility parameters of SC-CO_2 and the polymer justifies the observed low solubility of PEG 1500 at the studied temperatures and pressures. In fact, the solubilization of a solute in a solvent is favored when the solubility parameters of both solvent and polymer are equal (Hildebrand and Scott, 1950).

Table 1
Density values and solubility parameters at different temperatures and pressures

Temperature (°C)	Pressure (MPa)	Density (g/cm^3)	δ ($\sqrt{\mathrm{cal/cm^3}}$)
35	7.5	0.27	2.38
35	8.5	0.61	5.38
35	10	0.71	6.21
35	15	0.81	7.10
35	20	0.86	7.54
35	25	0.90	7.84
35	30	0.93	8.12
55	7.5	0.18	1.59
55	8.5	0.23	1.98
55	10	0.32	2.83
55	15	0.65	5.69
55	20	0.75	6.57
55	25	0.81	7.06
55	30	0.85	7.45
55	40	0.91	7.89

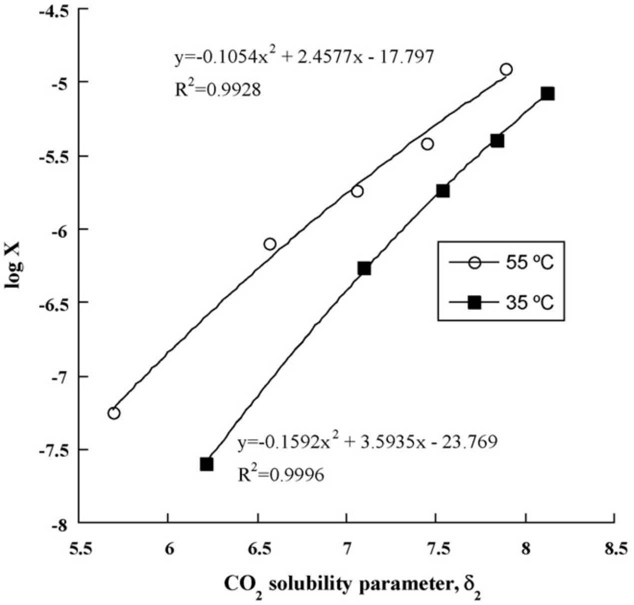

Fig. 5. Logarithm of PEG 1500 mole fraction in SC-CO_2 versus the solubility parameter of the solvent.

The values of the logarithm of the dissolved polymer mole fraction were plotted versus the relevant δ values (see Table 1) for the two studied isotherms (Fig. 5). The obtained data were fitted to a second-degree polynomial equation in order to obtain the *a* and *b* coefficients and the constant *C* of Eq. (2) (R^2 = 0.993 and 0.999 at 55 and 35 °C, respectively).

From the data reported in Fig. 5 it can be noticed that at lower δ values, namely at lower density, for the same solubility parameter (corresponding the same density) the solubility of PEG 1500 at 55 °C is higher than that at 35 °C. This difference decreases with δ increase since, not surprisingly, the two curves tend to a common maximum value that was calculated as $-b/2a$. At this point the solubility parameter were 11.66 $\sqrt{\mathrm{cal/cm^3}}$ at 55 °C and 11.29 $\sqrt{\mathrm{cal/cm^3}}$ at 35 °C. Indeed these figures are very close to that of δ calculated for PEG 1500 (11.07 $\sqrt{\mathrm{cal/cm^3}}$).

In agreement with the Hildebrand and Scott theory (Hildebrand and Scott, 1950) as well as with the model proposed by Giddings and co-workers (Czubryt et al., 1970) the maximum of the curves in Fig. 5 represents the highest concentration that can be achieved by PEG 1500 in the dense gas. The solubility of the polymer at this point was calculated from Eq. (2) and resulted 3.23×10^{-4} and 3.39×10^{-4} mole fraction at 35 and 55 °C, respectively.

On the other hand, Eq. (2) can be used also for predicting the solubility of the PEG 1500 in dense CO_2 at those densities (namely temperatures and pressures) at which the solubility is too low to be determined experimentally. In Table 2, the solubility data calculated at 7.5 and 8.5 MPa for the two studied temperatures are reported.

It can be noticed that the solubility of PEG 1500 at 55 °C at both pressures is practically negligible, while at 35 °C higher values were obtained. In particular, the solubility value calculated at 8.5 MPa is comparable to that measured at 10 MPa at the same temperature (2.52×10^{-8} mole fraction).

Table 2
Mole fraction of PEG 1500 in carbon dioxide, X_G, and solubility parameter at 35 and 55 °C and 7.5 and 8.5 MPa

T (°C)	P (MPa)	δ	X_G
35	7.5	2.38	2.85×10^{-13}
35	8.5	5.33	2.04×10^{-8}
55	7.5	1.59	3.48×10^{-19}
55	8.5	1.98	5.27×10^{-18}

4. Conclusions

The observation of the behavior of the PEG 1500 under pressurized CO_2 by means of a high-pressure view cell evidenced two phenomena stemming from the absorption of the CO_2 into the polymer: the reduction of the melting point and the polymer swelling. Both phenomena were proportional to pressure until a value around 9–10 MPa; thereafter the pressure no longer affected the polymer melting point and volume.

PEG 1500 shows solubility in SC-CO_2 in the order of 10^{-6} mole fraction in the pressure interval 10–40 MPa. Isothermal solubility increases with pressure, while at fixed pressure it decreases with temperature, likely due to CO_2 density changes. At the same density, temperature exhibits a positive effect on PEG 1500 solubilization in the SC gas.

The heuristic model proposed by Giddings and co-workers proved to be a useful and simple tool to predict the maximum concentration achievable by the polymer in the dense gas at a given temperature, as well as to quantify the polymer concentration at low pressures where its experimental determination can be extremely difficult.

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References

Bettini, R., Bonassi, L., Castoro, V., Rossi, A., Zema, L., Gazzaniga, A., Giordano, F., 2001. Solubility and conversion of carbamazepine polymorphs in supercritical carbon dioxide. Eur. J. Pharm. Sci. 13, 281–286.

Costa, M.S., Duarte, A.R., Cardoso, M.M., Duarte, C.M., 2007. Supercritical antisolvent precipitation of PHBV microparticles. Int. J. Pharm. 328, 72–77.

Czubryt, J.J., Myers, M.N., Giddings, J.C., 1970. Solubility in dense carbon dioxide gas in the range 270–1900 atmospheres. J. Phys. Chem. 74, 4260–4266.

Daneshvar, M., Gulari, E., 1989. Supercritical fluid science and technology. In: ACS Symposium Series 406. America Chemical Society, Washington, DC, pp. 72–85.

Daneshvar, M., Kim, S., Gulari, E., 1990. High-pressure phase equilibria of poly(ethylene glycol)-carbon dioxide systems. J. Phys. Chem. 94, 2124–2128.

Duarte, A.R.C., Simplicio, A.L., Vega-González, A., Subra-Paternault, P., Coimbra, P., Gil, M.H., De Sousa, H.C., Duarte, C.M.M., 2007. Supercritical fluid impregnation of a biocompatible polymer for ophthalmic drug delivery. J. Supercrit. Fluids 42, 373–377.

Fruijtier-Pölloth, C., 2005. Safety assessment on polyethylene glycols (PEGs) and their derivates as used in cosmetic products. Toxicology 214, 1–38.

Funami, E., Taki, K., Ohishima, M., 2007. Density measurement of polymer/CO_2 single-phase solution at high temperature and pressure using a gravimetric method. J. Appl. Polym. Sci. 105, 3060–3068.

Giddings, J.C., Myers, M.N., Mclaren, L., Keller, R.A., 1968. High pressure gas chromatography of non-volatile species, compressed gas is used to cause migration of intractable solutes. Science 162, 67–73.

Gourgouillon, D., Avelino, H.M.N.T., Fareleira, J.M.N.A., Nunes Da Ponte, M., 1998. Simultaneous viscosity and density measurement of supercritical CO_2-saturated PEG 400. J. Supercrit. Fluids 13, 177–185.

Guadagno, T., Kazarian, S.G., 2004. High-pressure CO_2-expanded solvents: simultaneous measurement of CO_2 sorption and swelling of liquid polymers with in situ near-IR spectroscopy. J. Phys. Chem. B 108, 13995–13999.

Hildebrand, J.H., Scott, R.L., 1950. The solubility of monelectrolytes, New York, Reynolds.

Kazarian, S.G., 2000. Polymer processing with supercritical fluids. Polym. Sci. Ser. C 42, 78–101.

Kazarian, S.G., Vincent, M.F., Bright, F.V., Liotta, C.L., Eckert, C.A., 1996. Specific interaction of carbon dioxide with polymers. J. Am. Chem. Soc. 118, 1729–1736.

Kibbe, A.H., 2000. Handbook of Pharmaceutical Excipients. Pharm. Press, London.

Kikic, I., Alessi, P., Eva, F., Moneghini, M., Perissuti, B., 2006. Supercritical antisolvent precipitation of atenolol: the influence of the organic solvent and of the processing approach. J. Supercrit. Fluids 38, 434–441.

Li, Z., Jiang, J., Liu, X., Zhao, S., Xia, Y., Tang, H., 2007. Preparation of erythromycin microparticles by supercritical fluid expansion depressurization. J. Supercrit. Fluids 41, 285–292.

Lian, Z., Epstein, S.A., Blenk, C.W., Shine, A.D., 2006. Carbon dioxide-induced melting point depression of biodegradable semicrystalline polymers. J. Supercrit. Fluids 39, 107–117.

Lopes, J.A., Gourgouillon, D., Pereira, P.J., Ramos, A.M., Nunes Da Ponte, M., 2000. On the effect of polymer fractionation on phase equilibrium in CO_2 + poly(ethylene glycol)s systems. J. Supercrit. Fluids 16, 261–267.

Lyons, J.G., Hallinan, M., Kennedy, J.E., Devine, D.M., Geever, L.M., Blackie, P., Higginbotham, C.L., 2007. Preparation of monolithic matrices for oral drug delivery using a supercritical fluid assisted hot melt extrusion process. Int. J. Pharm. 329, 62–71.

Moneghini, M., Kikic, I., Voinovich, D., Perissutti, B., Filipović-Grčić, J., 2001. Processing of carbamazepine-PEG 4000 solid dispersions with supercritical carbon dioxide: preparation, characterisation, and in vitro dissolution. Int. J. Pharm. 222, 129–138.

Pasquali, I., Bettini, R., Giordano, F., 2006. Solid-state chemistry and particle engineering with supercritical fluids in pharmaceutics. Eur. J. Pharm. Sci. 27, 299–310.

Reverchon, E., Volpe, M.C., Caputo, G., 2003. Supercritical fluid processing of polymers: composite particles and porous materials elaboration. Curr. Opin. Solid State Mater. Sci. 7, 391–397.

Shieh, Y.-T., Yang, H.-S., 2005. Morphological changes of polycaprolactone with high-pressure CO_2 treatment. J. Supercrit. Fluids 33, 183–192.

Stassi, A., Bettini, R., Gazzaniga, A., Giordano, F., Schiraldi, A., 2000. Assessment of solubility of ketoprofen and vanilic acid in supercritical CO_2 under dynamic conditions. J. Chem. Eng. Data 45, 161–165.

Weidner, E., Wiesmet, V., Knez, Z., Skerget, M., 1997. Phase equilibrium (solid–liquid-gas) in polyethylenglicol-carbon dioxide systems. J. Supercrit. Fluids 10, 139–147.

Wiesmet, V., Weidner, E., Behme, S., Sadowski, G., Arlt, W., 2000. Measurement and modelling of high-pressure phase equilibria in the systems polyethyleneglycol (PEG)-propane, PEG-nitrogen and PEG-carbon dioxide. J. Supercrit. Fluids 17, 1–12.

Yeo, S.-D., Kiran, E., 2005. Formation of polymers particles with supercritical fluids: a review. J. Supercrit. Fluids 34, 287–308.