CHEMICAL ENGINEERING TRANSACTIONS, Volume 11, 2007
Edited by Sauro Pierucci
 ISBN 978-88-95608-00-6

The Ketoprofen Partition between Supercritical CO_2 and Poly-vinyl-pyrrolidone for Drug Delivery Systems Preparation

M. Banchero, L.Manna, A.Ferri, S.Sicardi
Dipartimento di Scienze dei Materiali e Ingegneria Chimica - Politecnico di Torino
Corso Duca degli Abruzzi 24, 10129 Torino

The aim of the work is to perform the impregnation of a biocompatible polymer (poly-vinyl-pyrrolidone) with an anti-inflammatory drug (ketoprofen) with a supercritical solvent (CO_2) to produce drug delivery systems.
The partition of the drug between the supercritical and the polymer phases has been experimentally studied at different working conditions. The results showed the feasability of the process leading to a high drug uptake ($60\%_{w/w}$) at not too severe working conditions (220 bar, 50 °C). The influence of the working conditions on the drug partition was also studied and the drug solubility data in the CO_2 were successfully regressed with some density-based literature correlations.

1. Introduction

Drug delivery systems are pharmaceutical devices able to control the amount of a drug in the human body. They are often obtained by coupling crystalline drugs with a biocompatible polymer, such as polyethylene glycol, hydroxy-propyl-methyl-cellulose, poly-vinyl-pyrrolidone, etc. Crystalline drugs, in fact, often have very low solubility and dissolution rate in aqueous solutions. This problem can be overcome when the drug is dispersed in a polymeric carrier (Serajuddin, 1999).
Many traditional techniques are used in literature for drug dispersion preparation such as melt extrusion (Forster et al., 2001), under vacuum solvent evaporation (Tantishaiyakul et al., 1999) and spray-drying (Takeuchi et al., 1998). Unfortunately, all these techniques have some drawbacks: for example, melt extrusion is not suitable for thermo-sensible drugs, while solvent evaporation and spray-drying techniques require the final product to be purified from the least traces of residual potentially toxic solvents. For this reason the use of a supercritical fluid can be considered an interesting alternative for the preparation of drug dispersions (Kazarian, 2004, p. 343). In particular, CO_2 has been found to be the most suitable solvent thanks to its swelling and plasticization action towards many polymers, which results in high concentrations of the organic solutes in the polymeric phase, even at low temperatures, despite their relatively low solubility in the supercritical one. It is, then, much easier to remove from the final product when the process is complete and, even though a small amount of CO_2 remains trapped inside the polymeric matrix, it poses no danger to the patient (Kikic, 2000).
The aim of the present work is to perform the impregnation of a biocompatible crosslinked poly-vinyl-pyrrolidone (PVP) with ketoprofen, an anti-inflammatory drug widely used in pharmaceutics, in the presence of supercritical CO_2. This work is a preliminary study mainly focused on the experimental investigation of the equilibrium partition of the drug between the polymeric phase and the supercritical solvent by varying the working conditions of the impregnation process (40-60 °C; 100-220 bar).

As far as the ketoprofen solubility in the CO_2 is concerned, the experimental measures have also been fitted with some correlations existing in literature.

2. Experimental Set-up

Pure carbon dioxide (99.998%) was purchased from SIAD S.p.A., while ketoprofen (>98%), crosslinked PVP and spectrophotometric grade methanol were supplied by Sigma-Aldrich.

Experiments were conducted in the experimental apparatus shown in Fig. 1. For this purpose, the saturation vessel, E1, contains a large amount of drug mixed with glass beads while the impregnation vessel, E2, is filled with the PVP powder, mixed with the beads as well.

The apparatus can be conducted in two modes: a continuous and a batch one. When the apparatus works in continuous mode (Fig. 1.a), a supercritical CO_2 stream flows through the saturation vessel (E1) while the impregnation one (E2) is by-passed. The system is pressurized through pump P1, while pump P2 provides the flow rate control through vessel E1. A CO_2 stream by-passes the main circuit line to dilute the saturated solution in order to avoid the clogging of the expansion valve in the discharge section (Ferri et al., 2004). The CO_2 stream is then depressurized through restrictor R and sent to a methanol trap, T. The drug solubility in the supercritical solvent was evaluated measuring the ketoprofen collected in the trap (UV spectroscopy analysis) and the CO_2 flowed through E1 (with a mass flow meter not shown in the figure).

The PVP impregnation process can be performed when the apparatus is run in batch mode (Fig.1.b). Pump P2 recirculates the CO_2 continuously through E1 and E2 while the line to restrictor R is isolated from the rest of the apparatus. The mass flow rate was set at about 0.3 g/min. The drug concentration in the stream leaving E2 was periodically monitored, switching from batch to continuous mode (without by-passing E2), to ensure

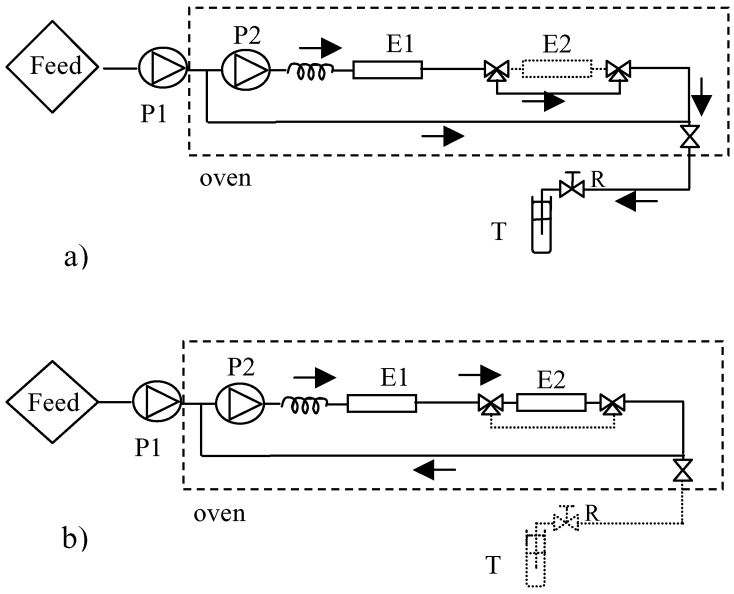

Fig. 1. Experimental apparatus. (a) Continuous operation mode for solubility tests. (b) Batch operation mode for impregnation tests.

that equilibrium conditions are reached. The impregnation run was stopped when the drug concentration reached its solubility value: a period of approximately 45 hours was always required.
At the end of the impregnation run, the impregnated polymer was sieved to separate it from the beads and methanol was employed to extract the drug: the ketoprofen concentration in the polymer can be obtained from the spectroscopic analysis of the solution in the UV range.

3. Results And Discussion

The evaluation of the drug partition between the supercritical and the polymeric phases requires the measurement of both the drug solubility in CO_2 and its equilibrium uptake in the PVP.

3.1 Drug solubility in the CO_2

Experimental results of ketoprofen solubility in CO_2 at different working conditions are shown in Table 1. Solubility data are reported both in terms of solute molar (y) and mass (ω) fraction, the latter for a better comparison with the drug uptake in the polymer. Experimental solvent densities at the different working conditions are also reported in Table 1. The obtained results are in satisfactory agreement with those measured by Macnaughton et al. (1996) and show the behaviour typical of all solutes in a supercritical fluid: drug solubility increases when the fluid density or the working temperature are increased.
The experimental values were also fitted with some density-based correlations existing in literature. Differently from more complex thermodynamic models, such as the Peng-Robinson equation of state, density-based approaches are much simpler to use in data correlation. They only need readily available indipendent variables (temperature, pressure, solvent density) without requiring any solute physical properties, such as critical pressure, acentric factors, sublimation pressures. Such properties are generally not experimentally available in literature and must be obtained through estimation

Table 1. Ketoprofen solubility in supercritical CO_2.

T(°C)	P (bar)	ρ (kg/m^3)	y·10^6	ω·10^6
40	100	667	8.94	51.6
	130	744	23.3	135
	160	833	46.9	271
	190	873	63.5	367
	220	900	103	595
50	115	579	9.70	56.1
	130	668	19.5	113
	160	757	42.3	244
	190	810	81.8	473
	220	847	140	812
60	116	422	7.80	45.0
	130	534	13.6	78.8
	160	669	33.9	196
	190	747	97.6	564
	220	789	166	959

Table 2. Density-based equations used to correlate drug solubility data.

Chrastil et al. (1982)	$\ln y = a + b\ln\rho + \frac{c}{T}$
Kumar and Johnston (1988)	$\ln y = a + b\rho + \frac{c}{T}$
Bartle et al. (1991)[a]	$\ln\frac{yP}{P_{ref}} = a + b\left(\rho - \rho_{ref}\right) + \frac{c}{T}$
Mendez-Santiago and Teja (1999)	$T\ln yP = a + b\rho + cT$

[a] P_{ref} is a reference pressure of 1 bar, ρ_{ref} is a reference density of 700 kg/m^3

Table 3. Correlated results for drug drug solubility in supercritical CO_2.

Density-based equation	a	b	c	AA%D
Chrastil	-32.93	7.00	-7548	14.22
Kumar and Johnston	6.79	$9.81\cdot10^{-3}$	-7798	11.23
Bartle	25.3	$1.25\cdot10^{-2}$	-9955	14.16
Mendez-Santiago and Teja	-12888	3.99	25.7	13.99

methods which often introduce strong uncertainties in the themodynamic model. On the other hand, density-based correlations only need three or more parameters that are simply obtained through experimental data fitting.

Among the different density-based approaches existing in literature, those shown in Table 2 were chosen. They are some of the most used ones and were also employed to compare data correlation in a recent paper (Huang et al., 2005). All equations in Table 2 need the same number of parameters (simply denoted as a, b, c even though they have a different physical meaning for each equation), which were calculated minimizing the absolute average percent deviation (AA%D):

$$AA\%D = \frac{100}{N}\sum_i \left|\frac{y_i^{\exp} - y_i^{calc}}{y_i^{\exp}}\right| \qquad (1)$$

where N is the number of experimental points; $y_i^{\exp}$ and y_i^{calc} are the experimental and calculated solubility values.

The values of the fitting parameters and the AA%D for each correlation are reported in Table 3. All approaches succeed in correlating the experimental results since AA%D values are always much lower than the mean values (20-28%) found in literature over 600 solubility data points (Huang et al., 2005). This confirms the possibility of using some density-based equation for solubility prediction, in particular the Kumar and Johnston approach, which shows the lowest AA%D.

3.2 Drug uptake in the PVP

The results of the impregnation tests are reported in Fig. 2, which shows the equilibrium mass uptake of the drug in the polymeric phase at different working conditions. The drug partition was found to be much more favourable to the polymer than to the

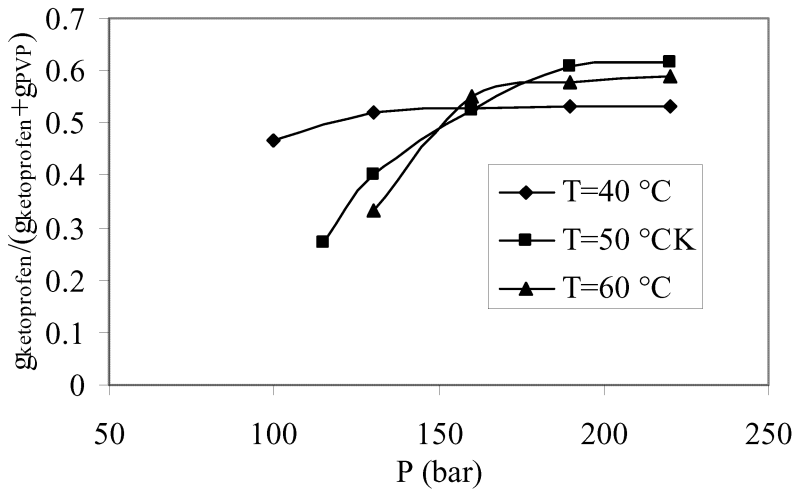

Fig. 2. Ketoprofen equilibrium uptake in the PVP.

supercritical phase. Ketoprofen mass fractions of $5 \cdot 10^{-5}$-$1 \cdot 10^{-3}$ in CO_2 (Table1) are, in fact, sufficient to obtain a 25-60% $_{w/w}$ drug uptake in the polymer. This confirms the high affinity between the drug and the polymer. Supercritical CO_2, then, can be definetly employed as a proper solvent for this particular impregnation process.

Fig. 2 also allows to examine the influence of the working conditions on the drug uptake. While the drug uptake simply increases with pressure until an asymptotic value is reached, the effect of temperature was found to be much more complex. A possible explanation may be connected with the different role of temperature towards the drug solubility in the fluid and the CO_2 uptake in the PVP.

Kikic et al. (1999) measured the CO_2 uptake in a crosslinked PVP and found that above 60 bar the CO_2 amount in the polymer does not change with pressure. On the other hand, the CO_2 uptake in the polymer decreases when temperature increases from 308.3 K to 334.7 K. A temperature increase, then, would obstacle the drug uptake, since the solvent is the solute conveyor inside the polymer. This behaviour is confirmed by data in Fig. 2, only for pressures below 170 bar.

The drug uptake in the polymer also strongly depends on the drug solubility in the supercritical solvent. The influence of temperature on the drug solubility in CO_2 depends on the pressure range, for the well known “cross-over” behaviour. For pressures below the cross-over point (approximately equal to 170 bar, for the present case) solubility decreases when temperature increases, the opposite occuring above the cross over point (Table 1). For this reason, when pressure is under the cross over point (170 bar) both the drug solubility in the solvent and the CO_2 uptake in the polymer diminish with temperature; the result is that the drug uptake diminishes with temperature. On the other hand, when pressure is increased above 170 bar, the drug solubility increases with temperature while the CO_2 uptake keeps the same behaviour as before: the two phenomena are now in competition and the effect of a temperature change on the drug uptake is not any more monotonous.

4. Conclusion

The impregnation of a crosslinked PVP with ketoprofen in a supercritical medium has been succesfully performed. Equilibrium concentration of the drug between the two phases were obtained at different working conditions. The results proved that the drug partition is much more favourable to the polymer and a high equilibrium uptake (up to 60% $_{w/w}$) can be obtained at not too severe working conditions (50 °C, 220 bar).
The influence of the working conditions on the drug partition was also studied. As far as the ketoprofen solubility in the CO_2 is concerned, it shows the behaviour typical of all solutes in a supercritical fluid. The experimental values were also successfully fitted with some correlations existing in literature.
The drug uptake in the polymer was found to increase with pressure until an asymptotic value is reached. The effect of temperature is much more complex, since at high pressures, the drug uptake is not monotonous with a temperature change.

5. Acknowledgement

The athors are grateful for the financial support from the Italian Ministry of Scientific Research (PRIN 2005).

6. References

Bartle, K.D., A.A. Clifford, S.A. Jafar, G.F. Shilstone, 1991, J. Phys. Chem. Ref. Data 20, 713.
Chrastil, J., 1982, J. Phys. Chem. 86, 3016.
Ferri, A., M. Banchero, L. Manna, S. Sicardi, 2004, J.Supercrit. Fluids 30, 41.
Forster, A., J. Hempenstall, T. Rades, 2001, Internet J. Vib. Spectro. 5, 6 (www.ijvs.com).
Huang, Z., Y. Guo, G. Sun, Y.C. Chew, S. Kawi, 2005, Fluid Phase Equilibr. 236, 136.
Kazarian, S.G., 2004, Supercritical Fluid Technology for Drug Product Development: Supercritical fluid impregnation of polymer for drug delivery, Eds., M. Dekker, P. York, New York.
Kikic, I., 2000, Proceedings of the 5th International Symposium on Supercritical Fluids, Atlanta, USA.
Kikic, I., M. Lora, A. Cortesi, P. Sist, 1999, Fluid Phase Equilibr. 155-160, 913.
Kumar, S.K., K.P. Johnston, 1988, J. Supercrit. Fluids 1, 15.
Macnaughton, S.J., I. Kikic, N.R., Foster., P. Alessi, A. Cortesi, I. Colombo, 1996, J. Chem. Eng. Data 41, 1083.
Mendez-Santiago, J., A.S. Teja, 1999, Fluid Phase Equilibr. 158, 501.
Serajuddin, A.T.M., 1999, J.Pharm.Sci. 88, 1058.
Takeuchi, H., T. Yasuji, T. Hino, H. Yamamoto, Y. Kawashima, 1998, Int. J. Pharm. 174, 91.
Tantishaiyakul, V., N. Kaewnopparat, S. Ingkatawornwong, 1999, Int. J. Pharm. 181, 143.