SOLUBILITY OF FLURBIPROFEN AND TIMOLOL MALEATE IN DENSE CARBON DIOXIDE

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Equilibrium solubilities in supercritical carbon dioxide of bioactive compounds flurbiprofen and timolol maleate were measured by a static analytical method from 10 up to 26 MPa at 313K. Solubility data were correlated using Chrastil's empirical density-based model. The effect of adding ethanol, as a cosolvent, was also investigated, at 313 K and 19 MPa for timolol maleate, and at 313 K and 20 MPa for flurbiprofen. For both compounds, solubility is enhanced with an increasing amount of cosolvent added.

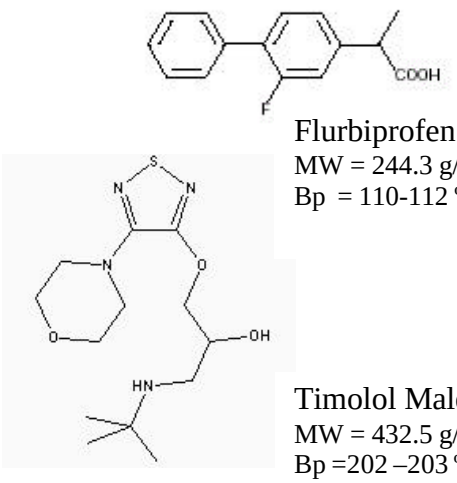
INTRODUCTION

This work is part of a research project designed for the study, development, preparation and characterization of controlled drug release systems for ophthalmic applications, namely for glaucoma and several other corneal pathologies treatment.

Recently, in several applications for pharmaceutical purposes, there is an increasing need to replace conventional solvents by supercritical fluids[1],[2], specially by supercritical carbon dioxide, due to its non-toxic properties and to the low operation temperatures involved in supercritical processes, which do not degrade thermally labile substances. Furthermore, compressed carbon dioxide has excellent plasticizing properties and can swell most bio-compatible polymeric matrixes, thus promoting drug impregnation processes[1]. The knowledge of drug solubility in compressed carbon dioxide is essential for the development and optimization of these supercritical fluid processes.

Flurbiprofen is a well known and used non-steroidal anti-inflammatory agent. It is used to prevent pupil constriction and to reduce pain and inflammation in the eyes[3].

Timolol Maleate is a beta-adrenergic receptor blocking agent and it is used for the treatment of glaucoma in order to reduce the elevated intraocular pressure which is characteristic of this eye disease[4].



Flurbiprofen
MW = 244.3 g/mol
Bp = 110-112 ºC

Timolol Maleate
MW = 432.5 g/mol
Bp =202 –203 ºC

Figure 1: Structural formula of Flurbiprofen and Timolol maleate

In this work, equilibrium solubilities in supercritical carbon dioxide of these bioactive compounds, flurbiprofen and timolol maleate, were measured by a static analytical method from 10 up to 26 MPa at 313K. The effect of adding ethanol, as a cosolvent, was also investigated at 313 K and 19 MPa for timolol maleate, and at 313 K and 20 MPa for flurbiprofen. Solubility data were correlated using Chrastil's empirical density-based model.

MATERIALS AND METHODS

Materials

Flurbiprofen, CAS [5104-49-4], (97% purity), and timolol maleate, CAS [26921-17-5], (98% purity), were purchased from Sigma-Aldrich. Dichloromethane, CAS [75-09-2], (99.95% purity), was purchased from Fluka. Ethanol, CAS [64-17-5], (99,8% purity), was purchased from Riedel-de Häen. Carbon dioxide, (99.998 mol%) was supplied by Air Liquide. All chemicals were used without further purification.

Solubility Measurements

The solubility of the above referred pharmaceutical solids was measured using a static analytic high-pressure apparatus schematically, presented in Figure 2.

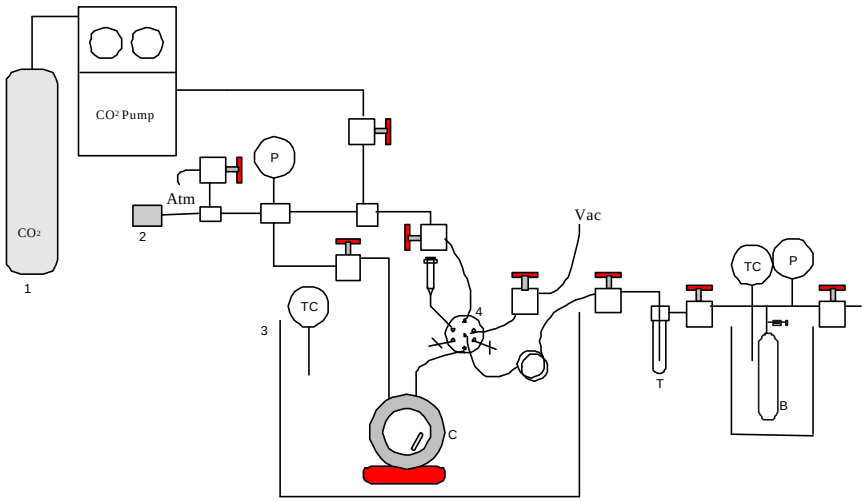


Figure 2: High pressure apparatus for solubility measurements: (1) CO_2 compressor; (2) rupture disk; (3) thermostatic water bath; (4) six port sampling HPLC-valve; (PT) pressure transducer; (TC) temperature controller; (C) equilibrium cell with sapphire windows; (T) glass trap; (B) expansion calibrated cylinder.

A stainless steel equilibrium visual cell, with an internal volume of approximately 30 cm^3, is immersed in a thermostatic water-bath, heated by means of a controller that maintained temperature within ± 0,1ºC. The cell is initially loaded with the solid and a magnetic internal stirrer. Carbon dioxide is pumped into the cell using a pneumatic compressor until the desired pressure is attained. The pressure inside the cell is measured

with a pressure transducer (*SETRA*, model 204, 0-5000 psi), calibrated between 0 and 3000 psi.

At fixed temperature, equilibrium is reached in approximately 30 minutes. After that, a sample is taken through a six-port sampling valve (HPLC). Solid samples are collected by quick depressurisation and expansion into a small glass trap. During sampling, gas is expanded into calibrated volumes. The amount of CO_2, in each sample, is calculated from the pressure increase at working temperature. Pressure, after the expansion, is measured with a pressure transducer (*SETRA*, model 204, 0-30 psi). The same procedure is followed when cosolvent (ethanol, chosen due to its low toxicity) is added into the cell. In order to ensure that all solute is recovered in the trap, some cleaning solvent (2-3 ml of dichloromethane or ethanol, for flurbiprofen or timolol maleate, respectively) is injected through the sample loops and expansion lines. Finally, pressure lines are cleaned with fresh CO_2, smoothly pressurized.

Analytical Method

The collected solid samples are dissolved and diluted in a convenient organic solvent, namely dichloromethane or ethanol. In order to determine the amounts of flurbiprofen and timolol maleate, the resulting solutions are analyzed by UV spectrophotometry in a UV-VIS (Cary 3E – *Varian*). Both compounds absorb in the region of ultraviolet, with a maximum absorbance at 247 and 298nm, respectively. Calibration was obtained via use of standard samples between $1.0x10^{-5}$ and $1.5x10^{-4}$ M.

RESULTS AND DISCUSSION

Design of clean techniques for processing pharmaceutical compounds using $scCO_2$ is strongly dependent on the solubility behavior of the low-volatile substances in the supercritical solvent.

Solubility of flurbiprofen, at 313 K, is expressed in terms of mass of solute per volume of carbon dioxide as a function of pressure and solvent density, as presented in Fig.3. At the referred temperature, pressure effect on the solute solubility follows the expected trend; i.e., the solvent capacity increases with pressure at constant temperature.

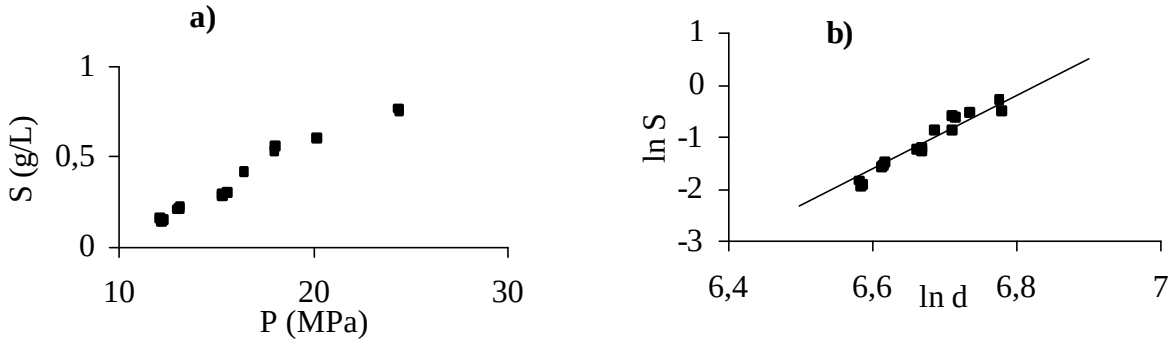


Figure 3: a) Solubility of flurbiprofen in CO_2, as a function of pressure, at 313 K. b) Logarithmic relationship between solubility of flurbiprofen and density of supercritical CO_2, at 313 K. Line represents the regression fit using Chrastil equation.

Experimental solubility data for flurbiprofen were correlated using the semi-empirical method proposed by Chrastil[5]. This method is based on the hypothesis that each solute molecule associates with *k* molecules of supercritical solvent, to form a solvato-complex, which is in equilibrium with the system. The relationship between solubility and density proposed by Chrastil can be expressed as:

$$S = \rho^k \exp(a/T + b),$$

where *S* is the solubility (g/L) of flurbiprofen in $scCO_2$, ρ is the density (g/L) of pure CO_2, at the experimental absolute temperature, *T*, and pressure, *P*. As referred, *k* expresses an average equilibrium association number, which is a characteristic constant for a given gas and solute.The *a* parameter is dependent on the solute's enthalpies of solvation and vaporization, $a = \Delta H/R$, (where ΔH is the sum of enthalpies of vaporization and solvation). The *b* parameter is dependent on the molecular weight of solvent and solute. The average absolute relative deviation of the fitted Chrastil equation, from experimental data, was calculated to be 10%.

Temperature is also an important and more complex factor affecting the solubility since it influences solute vapor pressure, solvent density and the intermolecular interactions in the fluid phase. Temperature effect on the solubility of flurbiprofen was studied at 18 MPa.

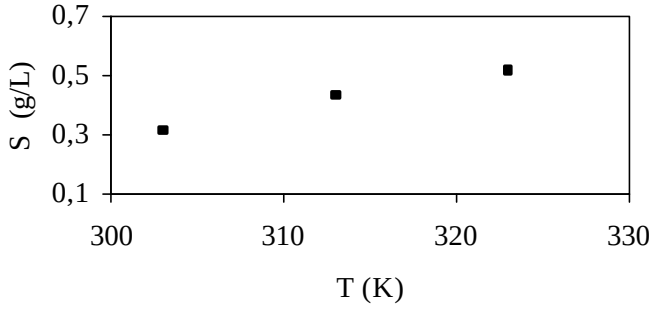


Figure 4- Effect of temperature on the solubility of flurbiprofen at 18 MPa.

Figure 4 shows that the solvent capacity increases with temperature at constant pressure. This means that, at these working conditions, the effect of temperature on the solute vapor pressure overlays the effect on the solvent density.

Solubility of timolol maleate in pure carbon dioxide, at 313 K, from 10 up to 20 MPa, was too low to be determined with this experimental method. This fact was expected if one take into account the molecular structure of this drug. The presence of many functional groups in the molecule makes the solubilization more difficult than for flurbiprofen[6]. Therefore, we add ethanol to pure CO_2, as a cosolvent, in order to enhance the solubility of timolol maleate (and also flurbiprofen).

Due to its low toxicity, ethanol is one of the few organic solvents that are considered suitable for contact with products for human consumption and use. The cosolvent effect on the solubility of these drugs in supercritical carbon dioxide was studied, at 313 K, at 19 MPa (for timolol maleate) and at 20 MPa (for flurbiprofen). Different ethanol concentrations, 10, 15 and 20 mol%, were investigated. Results obtained are illustrated in Figure 5, in which we plot the solubility of flurbiprofen and

timolol maleate in the supercritical phase (g/L) as a function of ethanol concentration (mol%). It can be seen that solubility of flurbiprofen in CO_2+ethanol is around one order of magnitude higher than the solubility of timolol maleate in the same solvent, at the experimental conditions investigated.

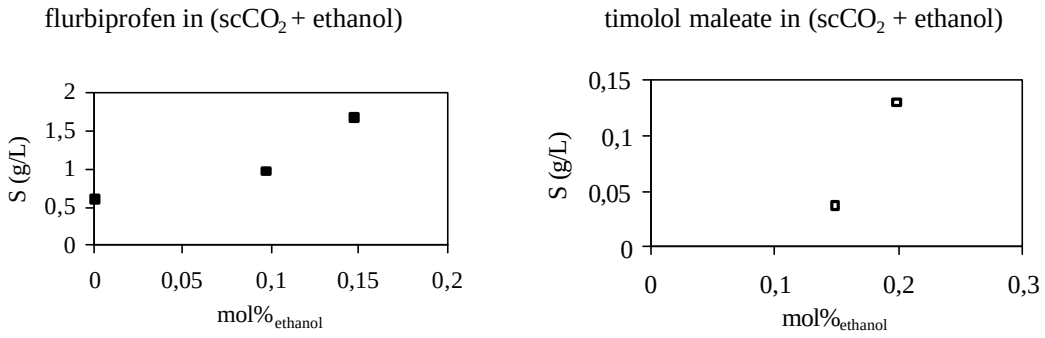


Figure 5: Ethanol Cosolvent effect on the solubility of flurbiprofen (■), at 20 MPa and 313K, and timolol maleate (□), at 19 MPa and 313 K, in $scCO_2$.

CONCLUSIONS

Equilibrium solubilities of flurbiprofen and timolol maleate, in supercritical CO_2, were measured by a static analytical method in the pressure range from 10 to 26 MPa at 313 K.

Measured flurbiprofen equilibrium solubility data, at 313 K, expressed in terms of mass of solute per volume of CO_2, varies from 0 to 1 g/L, and, as expected, increases with pressure increase, at constant temperature (313 K). At constant pressure, 18 MPa, flurbiprofen solubility also increases with increasing temperature. Experimental solubility data were correlated using the semi-empirical method proposed by Chrastil and the average absolute relative deviation of fitted Chrastil equation was calculated to be 10%.

Timolol maleate solubility, at 313 K, and from 10 up to 20 MPa, was too small to be determined experimentally with the adopted method.

Ethanol, as a cosolvent, was added in order to increase the solubility of these two pharmaceutical compounds. Solid solubility enhancement was determined for three different ethanol concentrations (10, 15 and 20 mol%), at 313 K, at 20 MPa and at 19 MPa, for flurbiprofen and timolol maleate, respectively. For both compounds, solubility is enhanced as the amount of cosolvent increases. The effect of the addition of cosolvent is more pronounced for timolol maleate than for flurbiprofen. In the case of timolol maleate, solubility triplicates when the concentration of ethanol rises just 5%.

These can be very promising preliminary results, for both drugs, in order to develop and prepare controlled drug delivery systems by the means of supercritical processes.

ACKNOWLEDGEMENTS

Ana Rita C. Duarte is grateful for financial support from SFRH/BD/10780/2002 grant.

This work was financially supported by FCT-MCES and FEDER, Portugal, under contract POCTI/FCB/38213/2001.

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