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Phase equilibria of the binary systems of fenofibrate and dense gases (carbon dioxide, propane, trifluoromethane)

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ABSTRACT

The purpose of this work was to investigate phase equilibria, namely equilibrium solubility and melting point depression of fenofibrate in several dense gases (carbon dioxide, propane, trifluoromethane). The equilibrium solubility of fenofibrate in sub- and supercritical gases was measured using a static-analytical method at temperatures of 303.15 K, 323.15 K and 338.15 K in the pressure range from 0.10 MPa up to 35 MPa. In general, the solubility of fenofibrate in gas rich phase increases with increasing pressure at a constant temperature. The highest solubility of fenofibrate was observed in the presence of propane at all investigated temperatures. In addition, an empirical correlation based on Gordillo model was employed to estimate the experimental data. For determining the melting point of fenofibrate under pressured gas, a modified capillary method was applied in the pressure range from 0.10 MPa to 41 MPa. A melting point depression with a temperature minimum in the *p,T* - projection of the SLG line has been noticed for all of the investigated systems.

1. Introduction

Poorly soluble drugs represent an important challenge in all stages of pharmaceutical development, from the initial *in vitro* studies of pharmacological activity to the development of a stable dosage form. The number of low soluble compounds has tremendously increased due to the arrival of combinatorial chemistry and high throughput screening. In particular, around 40% of the marketed oral drugs for immediate release (e. g. fenofibrate) are identified as nearly insoluble in water (<100 μg/mL). Furthermore, approximately 70% of newly synthesized drug candidates show low aqueous solubility and are often discarded in the early stages of development [1].

Pharmaceutical ingredients of this type may potentially lead to low dissolution rate in biological fluids, particularly when delivered via the oral route of administration [2]. Slow dissolution process is reflecting in poor drug bioavailability, as well as in a high rate of side effects due to a high-dose administration in order to attain the desired therapeutic effect [3]. This leads to less favorable clinical outcomes. Thus, the knowledge on the solubility of a pure pharmaceutical substance is one of the most basic and important information in pre-formulation studies of pharmaceutical ingredients.

Fenofibrate is a fibrate lipid regulating agent used for the treatment of hypertriglyceridemia and hypercholesterolemia. It reduces high plasma concentration of triglycerides and cholesterol to a normal level. Fenofibrate a BCS (The Biopharmaceutical Classification System) class II drug is characterized by a good permeability but a low oral bioavailability due to the poor solubility in an aqueous environment [4].

Modification of the delivery system presents a promising solution to improve dissolution behavior of such poorly soluble drugs. A number of various physical and chemical modifications, plus miscellaneous methods have been reported in the literature. These techniques are particle size reduction, crystal- [2] and pH modification [2], amorphization, cyclodextrin complexation [5], self-emulsification [6], solid dispersion [7], etc.

The solubility of a certain solute in water may be highly related to its polarity. This relationship is used in practice to alter the solubility of a drug in a pharmaceutical solution [8]. As fenofibrate has a hydrophobic character (log P = 5.24), its solubility is supposed to be enhanceed in a presence of a nonpolar solvent. Propane (C_3H_8), which can be used as a supercritical fluid (SCF) may represent a

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suitable media for processing of fenofibrate. In addition, compressed propane in comparison to SCF CO_2 requires the application of lower pressures [9].

Trifluoromethane (R23) has been involved into the present study as an SCF used for comparison purposes. Due to the low critical point of R23 (299.05 K and 4.86 MPa), SCF processes can be performed at nearly-ambient temperatures, thus preventing the thermal degradation of the solute. It has a benign impact on the environment and is affordable at modest costs. Hojjati et al. [10] reported that simvastatin, also a BCS II drug as fenofibrate, is poorly soluble in SC CO_2 in the temperature range from 308 K to 348 K and in the pressure range from 12.16 MPa to 35.46 MPa; on the contrary, Fattahi et al. [11] showed that using trifluoromethane as a supercritical fluid in RESS process resulted in production of simvastatin nanoparticles (optimum operating conditions of 10 MPa at 323.15 K, and the spray distance of 7 cm) and dissolution rate enhancement. Although trifluoromethane possesses a significant dipole moment, it seems to be a good solvent simvastatin. It forms a hydrogen bond with the simvastatin ester group [12].

Current work represents experimentally determined data of equilibrium solubility for the system of fenofibrate and different dense gases, particularly CO_2, C_3H_8, and R23 at temperatures 303.15 K, 323.15 K and 338.15 K and in the pressure range from 0.1 MPa to 35 MPa. The phase equilibria experiments were carried out in a high-pressure optical cell using the static analytical method. The obtained experimental solubility data were further correlated using empirical model proposed by Gordillo et al. [16]. In addition, a modified capillary method was applied to measure melting point depression of fenofibrate under atmosfere of CO_2, C_3H_8, R23 in the pressure range from 0.1 MPa to 41 MPa.

2. Experimental

2.1. Materials

White crystalline fenofibrate (Cat. No. PHR1246, ≥99.9%) with a mean particle size of 7 μm was purchased from Xi'an Health Biochemical Technology Co., Ltd, China and was used without further purification. Carbon dioxide (CO_2, 99.995%) was supplied by Messer, Slovenia. Propane (C_3H_8, 99.95%) and trifluoromethane (R23, 99.98%) were provided by Linde, Slovenia.

2.2. Equipment and methods

The modified capillary method has been used to determine the melting point of fenofibrate in carbon dioxide, propane, trifluoromethane. A static analytical method using the high-pressure optical cell was applied to determine the equilibrium solubility of the drug in dense gas and for the visual observation of the system behavior during the entire experiment. Experimentally determined results of the investigated binary system were compared with literature data. As an empirical approach to predict the solubility of the investigated systems Gordillo model was performed.

2.2.1. Determination of melting point in dense gases

Melting point depression for fenofibrate in dense gases were determined with the modified capillary method, which is in detail described in previous work [13]. A high-pressure optical cell with a volume of 74 mL was used (SITEC – Sieber Engineering AG, Zurich, Switzerland). The apparatus can operate at maximum pressure 100 MPa and temperature 723 K. The cell is made of stainless steel and equipped with two sapphire windows for observing the phase transitions of the substance during the measurements. The apparatus has three additional openings for introducing and emptying the gas, and to insert a thermocouple. The thermocouple was calibrated using pure fenofibrate with a known melting point ($T_m = 355.15$ K), which was determined with differential scanning calorimetry (TGA/DSC 1, Mettler Toledo, USA) with a heating rate of 5 K/min. An open glass capillary ($r = 0.4870$ mm) was compact prefilled with a small amount of substance (approx. 9 mg), then attached to the thermocouple and vertically inserted into the cell. Dense gas was introduced via a high-pressure pump (NWA PM-101). The cell was thermostated by a heating jacket (to ± 0.5 K) and the pressure was measured with an electronic pressure gauge (WIKA, Germany, to ± 0.1%). The phase transitions of fenofibrate in dense gases were visually observed and the upward strategy (pressure/temperature increase) was applied. Pressure and temperature were noted when the first droplet of melt was formed inside the system and when the substance completely liquified. Sample was all the time presented in the capilary and did not dissolved in the gas. At least three repeats were performed for each melting point. A maximum deviation of ±0.5 K was attained among the three repeated measurements.

2.2.2. Determination of equilibrium solubility

For the measurements of the equilibrium solubilities of fenofibrate in dense gases, a static-analytical method was used. A detailed description of the experimental procedure and measuring system can be found in literature [14,15]. Briefly, approximately 2 g of substance was placed into a 64 mL high-pressure view cell (NWA, Germany), which is designed for pressure up to 75 MPa and temperature up to 473 K. The system behavior inside the apparatus is possible to observe through a front sapphire window. The cell was thermostated by two stainless steel heater (Firefor, USA) and gas was charged into the cell by a high-pressure pump (NWA PM-101). To reduce the time required for equilibration during the measurements, mixing of the content has been performed. The equilibrium state was reached after 5 h (experimentally determined) and samples of gas-rich phase were taken through the sampling valve into a glass trap, where the sample was solubilized in approximately 5 mL of methanol (J. T. Baker, Netherlands, Ultra Gradient HPLC Grade). Pressure drop of 1.5 MPa was allowed during the sampling. Since the quantity of the sample was inadequate compared to the volume of the cell, further experiments could have been done.

The quantitative determination of the solute in methanol was carried out by UV spectrometry at 287 nm (accurate to ± 0.001) [16], while the volume of the released gas was measured by a volumetric method with a measuring cylinder and later on recalculated on the mass basis.

Each solubility data point represents the average of at least two measurements and the standard deviation of the solubilities was within 3%.

2.2.2.1. Correlation of solubility data. Experimentally obtained data of solid equilibrium were further correlated with the empirical model developed by Gordillo [17]. The parameters were calculated with MATLAB R2017a software using Curve Fitting Toolbox. The six-parameter (a_i) equation, which associates the solubility of the solute y (in mole fraction) with temperature T (K) and pressure p (MPa), is defined as follows:

$$\ln(y) = a_0 + a_1\, p + a_2\, p^2 + a_3\, p\, T + a_4\, T + a_5\, T^2 \quad (1)$$

The derogation of calculated data from experimentally obtained results was determined by calculating the average absolute relative deviation (AARD):