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Solubility of fluvoxamine maleate in supercritical carbon dioxide

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ABSTRACT

During the past decades, processing and engineering the drug particle using new proposed methods have gained an increasing attention. Among the different methods, using supercritical fluids technology is one of the most desired one. In this way, measuring and knowing the solubility of pharmaceuticals in supercritical fluids are one of the most critical parameters must be systematically categorized as a function of pressures and temperatures. Regarding this fact, solubility of fluvoxamine maleate in supercritical carbon dioxide in wide ranges of temperature (308–338 K) and pressure (200–400 bar) was measured using a static method coupled with gravimetric method which is in the range of 1.23×10^{-5} to 4.45×10^{-4} based on the mole fraction. Finally, the solubility data are modeled using four different semi-empirical density-based correlations namely Mendez Santiago-Teja (MST), Bartle et al., Chrastil and Kumar and Johnston (KJ) models. The obtained results reveal that amongst the utilized correlations, Chrastil model leads to the most accurate results compared with the other examined correlations with average absolute relative deviation percent (AARD%) of 10.8%. Besides, the solubility data are modeled using Peng–Robinson equation of state which no satisfactory results are obtained since the AARD% for all of the examined isotherms are in the range of 58.01–67.04%.

1. Introduction

In the past two decades, the researchers are seeking for clean technologies that both reduce pollution or wastes and save energy while the quality of the products get better. One of the most concentered areas for new clean and efficient methods is pharmaceutical engineering and drug delivery industries. Among the different possible and potential processes, supercritical based technologies are the most examined one introduces satisfactory results [1–7].

One of the most important areas of using supercritical-based technologies in pharmaceutical industries is particle engineering which means production of controlled-size particles concomitant with high purity level reduces the risk of remaining solvent residue in the final products.

In all of the possible applications of supercritical-based technologies especially particle engineering is knowing the accurate and reliable equilibrium solubility of the pharmaceutical in the supercritical fluids as a function of temperature and pressure even at the absence or presence of co-solvent.

In the light of this vital requirement, many researchers have measured the solubility of different compounds in the supercritical fluids especially carbon dioxide ($SC–CO_2$) at the presence or absence of co-solvent extensively. The solubility of compounds in supercritical fluids is highly necessary to establish the technical and economic feasibility of any supercritical fluid-based process [8–16].

Among the different possible solvents, carbon dioxide is extensively used as the solvent due to its unique features including mild critical pressure and temperature, non-toxicity, inflammability, cost effective and its availability make it a good candidate for supercritical-based processes. Among these advantages, mild critical pressure and temperature are the most important since most of the pharmaceutical are not able to tolerate harsh condition of the temperature while carbon dioxide critical temperature is about 31.1 °C.

On the other hand, although experimental measurement is the most reliable method to obtain the required equilibrium solubility data for designing the processes, it is very costly, time consuming, tedious and even impossible in some cases, to measure the solubility of substances in supercritical carbon dioxide. Respect to this shortcomings, similar to the other fields of sciences, modeling approach and using predictive tools to find the solubility of substances are highly investigated and many several models are proposed including equation of state (EoS) [16–23] and semi-empirical correlations [24–29].

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Among these predictive methods, semi-empirical density-based correlations are recently gaining increasing attention since using these methods need no knowledge of critical properties and sublimation pressure of substances which are usually unavailable for complex compounds and must be estimated using group contribution methods or other methods introduces unreliability into the prediction results.

Semi-empirical correlations utilize several fitting parameters correlate the solubility of compounds only to operational pressure and temperature and density of supercritical fluid. In other words, there is no concern about the uncertainty of the used parameters since it is possible to measure temperature, pressure and density of supercritical fluids with high level of accuracy. According to these advantages, application of these correlations has been increases during the past decades compared to EoS's.

Considering all of these facts and requirements previously discussed, the solubility of fluvoxamine maleate is measured in the current investigation as a function of temperatures (308–338 K) and pressures (200–400 bar). Based on the best knowledge of the authors, there is no reported measured solubility data for fluvoxamine maleate in SC–CO_2 in the literature.

Fluvoxamine maleate (Luvox) is an antidepressant which functions as a selective serotonin reuptake inhibitor. Fluvoxamine is used for the treatment of major depressive disorder, obsessive compulsive disorder, and anxiety disorders such as panic disorder and post-traumatic stress disorder. In addition, fluvoxamine CR (controlled release) is approved to treat social anxiety disorder. The FDA has added a Black box warning for this drug in reference to increase risks of suicidal thinking and behavior in young adults and children. A study from the Institute for Safe Medication Practices identified reports of violence from those taking fluvoxamine as being 8.4 times higher than expected given the of overall reports for that drug. In addition, several number of side effects have been reported for this drug which makes it application dangerous in some extend.

According to these information, it seems that it is applicable to produce controlled-size particles of this medication to reduce its potential risks of usage by reducing the necessary dosage. So, as a preliminary stage, it is necessary to measure the solubility of fluvoxamine maleate in different pressures and temperatures to further see if it is possible to manipulate its particle size or morphology of fluvoxamine maleate using supercritical fluid-based technologies.

Finally, the measured solubility data were correlated using four density based correlations namely Bartle et al. [21], Chrastil [26], Kumar and Johnston (KJ) [25], and Mendez Santiago-Teja (MST) [12] and Peng–Robinson EoS as the one of the most important equations utilized for modeling of the solubility data.

2. Experimental

2.1. Materials

Fluvoxamine maleate (see Table 1) with minimum purity of 98.8% was supplied from Damavand Darou Mgf., Co, Iran and further purified by passing SC–CO_2 at 308.15 K and 40 MPa through it for two hours. Additionally, carbon dioxide with minimum purity of 99.8% was supplied from Abughadareh Industrial Gas Company (Shiraz, Iran). Before and after each experiment, the model drug powder was heated up to 318 K in an oven (Behdad, Iran) overnight to ensure no presence of carbon dioxide in samples.

2.2. Experimental procedure

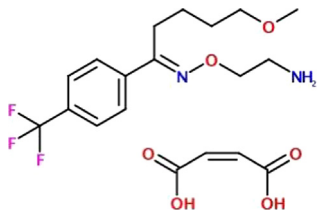
In this investigation, a home-made apparatus rated for pressure and temperature up to 60 MPa and 673 K, respectively, is used. This apparatus is equipped with a sapphire window giving the operator the capability of monitoring inside of the equilibrium cell for possible phase transitions. Upon the capability of this apparatus, the solubility of fluvoxamine maleate is measured using a static method coupled with a gravimetric method [29–36] (see Fig. 1).

A brief description of solubility measurement of using this apparatus is as follows; at the beginning, CO_2 was entered into the upper section of a piston cylinder type displacer. A low friction floating piston inside the cylinder prevents mixing the driving fluid with driven fluid in this case is carbon dioxide. The driving fluid was pressurized by a water-driven oil-free reciprocating manual pump (Haskel Pump, Burbank, USA). The pressure of the displacer was monitored using a pressure gauge (45 MPa) with precision of 0.1 MPa (DEWIT).

After increasing the pressure of the CO_2 entered into the displacer to a desired pressure it then passed into the homemade piston-cylinder type variable volume cell. The pressure of the equilibrium cell was monitored by a pressure transmitter (0–40 MPa, WIKA type, Germany) with precision of 0.01 MPa. The point worth-mentioning is that the pressure of the system was maintained constant within ±0.5% of the desired value throughout the experiment by continuous monitoring. Besides, a PT-100 resistance thermometer with a precision of 1 K was used to monitor the temperature of the system and a PID controlling method was used to keep the temperature of the equilibrium cell at a desired set point.

It must be mentioned that, before any action, for each experiment, 1 g of pure fluvoxamine maleate powder was compacted, (with no additives) in a compactor instrument (Compactor, T555228, Mellat Mashin Sazi Company, Iran) under

Table 1
Physiochemical properties of the fluvoxamine maleate and carbon dioxide.

Name	CAS number	Supplier	Purity	Chemical formula	Molar mass (g/mol)	Chemical structure
Fluvoxamine maleate	61718-82-9	Damavand Darou Mgf., Co, Iran	98.8%[a]	$C_{15}H_{21}F_3N_2O_2{\cdot}C_4H_4O_4$	434.41	
Carbon dioxide	124-38-9	Abughadareh Industrial Gas Company, Iran	99.8%[b]	CO_2	44.01	–

[a] based on weight fraction.
[b] based on mole fraction.