The Journal of Supercritical Fluids 140 (2018) 91–100

Contents lists available at ScienceDirect

The Journal of Supercritical Fluids

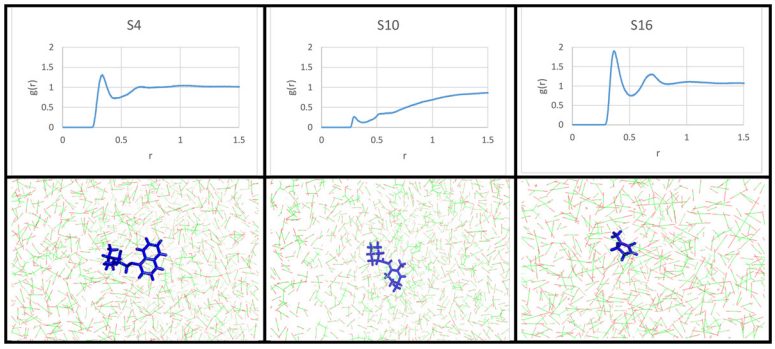
journal homepage: www.elsevier.com/locate/supflu

Study of the effects of methanol, ethanol and propanol alcohols as Co-solvents on the interaction of methimazole, propranolol and phenazopyridine with carbon dioxide in supercritical conditions by molecular dynamics

Seyedeh Zeinab Hosseini, Mohammad Reza Bozorgmehr*, Mahbubeh Masrurnia*, Safar Ali Beyramabadi

Department of Chemistry, Mashhad Branch, Islamic Azad University, Mashhad, Iran

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Molecular dynamics
Co-solvent effects
Supercritical carbon dioxide
Phenazopyridine

ABSTRACT

Using the molecular dynamics simulation, the effect of methanol, ethanol and propanol solvents on the interaction of CO_2 with methimazole, propranolol and phenazopyridine was studied under subcritical and supercritical conditions. The density of studied systems was calculated at different temperatures and pressures and relative error values were obtained. The results show good agreement with experimental data. The results revealed that methanol altered the aggregation of CO_2 around phenazopyridine in supercritical conditions and increased aggregation, while for methimazole and propranolol, propanol cosolvent was more effective than other two alcohols on the aggregation of CO_2 around the drug. Also, the aggregation of solvents around phenazopyridine occurs more than two other drugs. The analysis of weak interactions was performed based on Local Orbital Localization and it was determined that hydrogen interactions and steric effects of the drug ring and cage structures of CO_2 play a greater role than the Van der Waals interaction.

1. Introduction

Supercritical fluid extraction has been widely used in the pharmaceutical industry [1,2]. The supercritical fluid extraction process is very common with the use of the supercritical carbon dioxide solvent. Carbon dioxide, as an supercritical fluid, has the advantages of:

* Corresponding authors.
E-mail addresses: bozorgmehr@mshdiau.ac.ir (M.R. Bozorgmehr), masrour@mashdiau.ac.ir (M. Masrurnia).

https://doi.org/10.1016/j.supflu.2018.06.005
Received 15 January 2018; Received in revised form 7 June 2018; Accepted 7 June 2018

medium critical pressure, low critical temperature, low toxicity and reaction, high purity with low cost, extraction of heat unstable compounds, ideal extractor for non-polar species, a good reasonable extractor for relatively polar species which can allow direct entry into the atmosphere, lack of chemical change in the absence of light and air.

Supercritical fluid extraction procedure has been used in the separation and extraction of drugs in several fields. For instance, to prepare the sample for direct separation of the drug from the plasma [3], reverse extraction of polar drugs from creams and ointments [4], emulsification of vitamin [5], extraction of drugs from natural sources, water and serum [6], extraction of medicinal plants [7], and simultaneously extracting and measuring drugs [8], or studying the extraction of drugs by the computational method of the equation of state and G^{ex} model [9], or investigating the extraction of drugs with the neural network [10] can be mentioned. The drugs that have been studied under this method are steroidal drugs such as medroxy progesterone, cyproterone acetate [11], testosterone drugs, nortestosterone, methyl testosterone [12] using SFE and using supercritical fluid CO_2 was extracted and analyzed by GC and HPLC methods, which achieved a mean extraction of 97 to 98%. Yadollah Yamini et al focused on enhancing the solubility of megestrole acetate [13] based on extraction with CO_2 supercritical fluid, Fatemeh Rezaei et al., investigated Levonorgestrol [13,14], megestrol [14] in the real blood sample and have been able to measure up to 0.2 mg kg^{-1}. Marcel Kohler et al studied drugs such as artemisinin [15,16] and artemisinic acid [15] with the SFE-SFC-FID method and were able to extract and measure the drug for 20 min. Mohammad Hojjati et al. [17] have been able to extract anticholesterol drugs such as simvastatin, lovastatin, atrovastatin, rosuvastatin and flovastatin up to 8.8% with increasing drug solubility. Other drugs have also been studied [13,18–21]. Excessive carbon dioxide extraction and solubility of methimazole, propranolol and phenazopyridine have also been reported [22–24].

However, due to the non-polar nature, the supercritical carbon dioxide solvent power is not enough, and to improve this weakness, an organic polar solvent or modifier can be used [25]. Most drugs are polar compounds, and given that carbon dioxide is not soluble due to its non-polar structure, it has limitation when exposed to drugs, in order to improve the solubility of carbon dioxide, supercritical is used with other solvents, which is called “Cosolvent”. The role of cosolvents is the change in the polarity of the solvent (by interaction with the matrix or interaction with the analyte). The effect of the cosolvent is associated with the increase in solubility due to the increase in solvent density or intermolecular interactions between the cosolvent and the solute. Also associated with the increase of the solvent is a particular intermolecular interaction which occurs between the cosolvent and one or more components of the mixed components which improves the selectivity in separation [26]. Increasing the amount of cosolvent increases the ability of supercritical carbon dioxide to solubility of polar compounds, drugs, lipids, and dyes. Methanol and ethanol, for example, and other compounds [27–30] are used as a cosolvent for the extraction of drugs. Jun-su Jin et al., studied the solubility of benzene sulfonamide in a carbon dioxide solvent, along with ethanol, ethylene glycol and ethyl acetate cosolvents [31]. Ran Ran Zhou et al., have used methanol, ethanol and acetone as cosolvents for the extraction of steroidal drugs [29]which improved the solubility of steroidal drugs by up to 75%. Haji Hosseini et al., achieved a 56-fold increase in the solubility of clozapine and approximately 8-fold in Lamotrigine drug [32]. Banchero et al., have studied the solubility of dyes in ethanol cosolvent and achieved the results of solubility which increased from 3.91 to 25.9 times of pure carbon dioxide solvent for different dyes [33]. In the study of Araus et al., the solubility of beta-carotene in a triple system (solute and supercritical carbon dioxide solvent and cosolvent) has been reported to be similar to the binary system (solute and supercritical carbon dioxide solvent) [34]. Araus also reported an increase in the amount of dissolution of capsanthin from 0.65 to 5.27 μmol using of triolein cosolvent [35]. Lucien et al., have reviewed the factors affecting increase solubility caused by cosolvent [36]. Also, the use of cosolvent can reduce the melting point of the analyte during extraction [37].

Hyo-Kwang Bae et al., have investigated experimentally and computationally the effect of cosolvent on solubility of dyes in a triple system [38]. Bitencourt et al., used a quadratic system (supercritical carbon dioxide solvent and mixture of two cosolvent) in order to solve ferulic acid to separate it from plants. The results obtained are probably due to the strong interactions between acid and alcohol molecules which is less than experimental results [39]. Yang et al., by using the SAFT equation, modeled the solubility of aromatic compounds in the supercritical carbon dioxide solvent and cosolvent system [40]. Huang et al., by using the Peng-Robinson equation, have studied the solubility of cholesterol and its steric compounds in a supercritical carbon dioxide solvent with or without cosolvent [41].

Molecular dynamics simulation is a technique that studied the behavior of the system by using Newton equations of motion and potential energy functions over a given time on a nuclear scale. Bozorgmehr has studied the behavior of sodium dodecyl sulfate in the presence of lysozyme using molecular dynamics simulation [42]. Bozorgmehr et al., have studied the molecular dynamics of all polyethylene polymer atoms in supercritical ethanol, supercritical water and supercritical methanol systems [43]. Housaindokht and Bozorgmehr, studied the structural behavior of *Candida antarctica* lipase B in water and supercritical carbon dioxide by molecular dynamics simulation [44]. Housaindokht and Bozorgmehr also examined the solubility of propranolol, phenazopyridine and methimazole in supercritical conditions and without cosolvent [23]. Sohrevardi et al., have studied the transport properties in a mixture of water, acetone and carbon dioxide using molecular dynamics simulation [45].

In this work, molecular dynamics simulation is carried out using Gromacs software to investigate the effects of cosolvent (methanol, ethanol and propanol) on the interaction of methimazole, propranolol and phenazopyridine with carbon dioxide supercritical solvent. For this purpose, a wide range of test conditions has been considered from subcritical conditions to supercritical conditions.

2. Calculation method

All simulations were performed using Gromacs software version 5.1.2 [46]. To simulate, the optimal structure of the compounds is required. The optimal structure of propranolol, phenazopyridine and methimazole drugs was obtained using the density functional theory with B3LYP level and basis set of 6-31 G. In order to control the optimum conditions, the number of virtual frequencies was obtained in quantum computation, which is the unit equivalent, which indicates that the structures are optimized. In the optimization calculations, the CHELPG model [47] was employed to calculate the partial charge of atoms in the drug molecule. The calculations were performed using GAMESS software [48] at this stage. Furthermore, to simulate, the force field is required. The force field CHARMM27 was used, which is the all-atom force field, because the parameters of this force field for drugs and carbon dioxide and alcohols do not exist in the Gromacs software by default. Charmm27 Force Field Parameters for the studied compounds were obtained from the SwissParam website [49]. Then the simulation boxes were designed and the drugs were placed in the center of the box. Dimensions of the designed simulation boxes are $7 \times 7 \times 7 nm^3$. At the end, the boxes were filled with carbon dioxide. The temperature and pressure control in the simulation boxes were done with V-rescale and Nose-Hover thermostats, respectively. Periodic boundary conditions have been applied to designed systems and the cut off applied is 1.4 nm. The specifications of the simulation boxes along with the number of molecules of each box are reported in Table 1.

In the next step, in order to remove the primary kinetic energy of the systems and eliminate undesirable contacts between system particles, the energy minimization was carried out using a steepest descent. Systems in the NPT and NVT ensembles were equilibrated and