Case Studies in Thermal Engineering 41 (2023) 102621

Contents lists available at ScienceDirect

Case Studies in Thermal Engineering

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

# Experimental measurement and thermodynamic modeling of Chlorothiazide solubility in supercritical carbon dioxide

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ARTICLE INFO

*Keywords:*
Pharmaceutics
Chlorothiazide
Thermodynamics
Supercritical carbon dioxide
Solubility
Equation of state

ABSTRACT

Chlorothiazide, with the brand name *Diuril*, is used as a diuretic as well as an antihypertensive drug. This medicine with very slight solubility in water and low permeability is categorized in the class IV of Biopharmaceutical Classification System (BCS) and possess low bioavailability. Therefore, enhancement of the drug solubility would be of great importance to reduce its dosage and consequently side effects. Decrement of Chlorothiazide particles size to micro/nano scale using a supercritical carbon dioxide ($scCO_2$)-based method can be an efficient approach to enhance its bioavailability and therapeutic efficiency. To select and design a proper supercritical micronization/nanonization method, solubility of Chlorothiazide in $scCO_2$ should be determined which is conducted in this work by gravimetric method. In this study, solubility of Chlorothiazide in $scCO_2$ was obtained at various operating conditions (308–338K and 130–290 bar). It was found between $0.417 \times 10^{-5}$ to $1.012 \times 10^{-5}$ mol $mol^{-1}$ (mole fraction) for Chlorothiazide. Moreover, the obtained values were correlated through five empirical models (Chrastil, Mendez-Santiago and Teja (MST), Kumar- Johnston (K-J), Bartle, and Garlapati-Madras), as well as SRK and PR equations of state. All of the mentioned models have shown satisfactory correlation accuracy for the drug solubility. Meanwhile, the K-J model with the minimum *AARD%* value of 3.15 and the PR-EoS with the mean *AARD%* value of 6.51 have the highest precision to fit the experimental data. Also, the extrapolative ability of the mentioned empirical models to predict the Chlorothiazide solubility outside the considered range of operating conditions was investigated.

## 1. Introduction

Development of drugs with high solubility and bioavailability is one of the key challenges in pharmaceutical area, since the majority of newly discovered drugs are of poor water solubility. Chlorothiazide, the synonym name of 6-Chloro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide, is one of the most widely used thiazide diuretics (water pill). It is used in the form of tablet or oral

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https://doi.org/10.1016/j.csite.2022.102621
Received 7 October 2022; Received in revised form 16 November 2022; Accepted 1 December 2022
Available online 5 December 2022

suspension to treat edema (excess fluid trapped in the body's tissues) caused by kidney disease, severe liver illness, and congestive heart failure, or treatment with hormonal or steroid drugs. This drug with very low solubility in water (0.27 mg/ml at 30 °C) and low intestinal permeability is categorized in the class IV of Biopharmaceutical Classification System (BCS) [1], and has low bioavailability [2,3].

In general, low aqueous solubility and poor permeability are the main reasons of low bioavailability, high dosage, and severe side effects of poorly water-soluble drugs. Therefore, the development of new techniques to enhance the solubility of medicines in the aqueous medium of the human body is one of the attractive research areas of pharmaceutical companies. Among the proposed methods for solubility enhancement, reducing the particles size of an active pharmaceutical ingredient (API) has been introduced as the most efficient one. This method is also considered sometimes as the top-down approach if the size of the drug particles is reduced using some mechanical techniques such as milling. Also as shown by the Ostwald–Freundlich [4] and Noyes-Whitney [5] relationships, reducing the particles scale of a material down to micro/nano size increases their surface area and thus enhances their solubility and dissolution rate. Significant effect of micronization/nanonization of various APIs on enhancement their solubility and dissolution rate are well documented [6–9]. Diverse methods such as solvent evaporation, jet milling, spray drying, and recrystallization have been suggested to produce fine particles of different materials. However, some operational characteristics of these methods, such as the high operating pressure/temperature leading to mechanical/thermal decomposition of the API, and the need for large amounts of toxic solvents can hinder their widespread utilization in the pharmaceutical industries for preparation of sub-micron size drug particles [10–12].

During the last few decades, producing fine pharmaceutical particles (micro/nano) through a supercritical process has received much attention. Among the available supercritical fluids, supercritical $CO_2$ ($scCO_2$) is the most popular solvent, owing to its availability, low price, FDA approval to use it as a clean solvent, and its other unique specifications. So far, various supercritical processes with different operational roles of $scCO_2$ have been proposed to produce fine pharmaceutical particles [13]. Solubility of the desired API in $scCO_2$ is a determinative parameter in these processes, so that $scCO_2$ can be used as a solvent for compounds with high solubility, and as an anti-solvent for substances with poor solubility. Therefore, determining the solubility of various APIs in $scCO_2$ at different conditions is of great importance in order to be able to design and operate the process for a drug candidate [13]. Experimental measurement of compounds solubility in $scCO_2$ is so valuable, but it is a time consuming, complex, and costly task which needs to be replaced with alternative approaches such as computational techniques. So, different theoretical methods have been proposed and developed to predict the SC solubility data of drugs [13,14]. The fugacity coefficient models based on different equations of state, activity coefficient models, empirical models, intelligent methods, and molecular dynamics simulations are some of the most popular models applied for theoretical analysis of various compounds solubility in $scCO_2$. It is worth noting that, the appropriate model to predict and correlate the supercritical solubility data of a compound should be specified through comparison of the laboratory data with the data computed through the desired model, and its anticipating is impossible.

Among the different proposed models, the empirical models and the cubic equations of state (EoS) (especially, Soave-Redlich-Kwong (SRK-EoS) [15] and Peng-Robinson (PR-EoS) [16]) are the most common ones. Numerous reports have indicated different forms of empirical models based on the relationships between pressure, temperature, $scCO_2$ density, and the solute solubility. These are simple models which have shown acceptable results for correlating the supercritical solubility of different substances. The equations of state-based models are more complex than the empirical models, because they need the physicochemical properties of the solute which are not known for all the materials. However, dependency of these models to laboratory data is lower than the empirical models.

According to our literature review, no study is conducted to obtain the supercritical solubility of Chlorothiazide in supercritical $CO_2$. In this research, for the first time it has been experimentally measured at different conditions (temperature of 308–338 K and pressure of 130–290 bar). Moreover, resultant data was correlated through five popular empirical models (Chrastil [17], Kumar-Johnston (K-J) [18], Bartle [19], Garlapati- Madras [20], and Mendez-Santiago and Teja (MST) [21]), as well as SRK-EoS and PR-EoS based models. Also, the accuracy of these models to fit the supercritical solubility data of Chlorothiazide was analyzed and discussed.

## 2. Materials and methods

### 2.1. Materials

Chlorothiazide (CAS number of 58-94-6) was bought from the Sigma-Aldrich company. It is a white, or practically white crystalline powder with the empirical formula of $C_7H_6ClN_3O_4S_2$ and the molecular weight of 295.73. Fig. 1 shows the chemical structure of Chlorothiazide, retrieved from the https://webbook.nist.gov. High purity carbon dioxide gas (99.98%) was supplied from a local company, and used as the solvent in the processing and measuring the amount of drug solubility. These substances were utilized with no additional treatment.

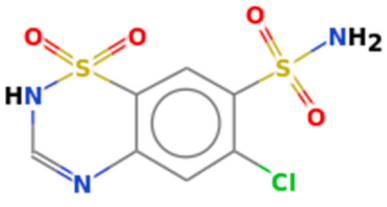


**Fig. 1.** Chlorothiazide structure.

### 2.2. Experimental method of measuring solubility of Chlorothiazide

We designed and used a simple process for measuring the solubility of Chlorothiazide in the supercritical solvent. As shown in Fig. 2, the laboratory setup used to determine the Chlorothiazide solubility in $scCO_2$ is composed of (1) $CO_2$ cylinder, (2) filter, (3) needle valve, (4) chiller unit, (5) HPLC pump (6) oven, (7) heating coil, (8) equilibrium column, (9) back pressure regulator (10) sampler, and (11) UV-Vis Spectrophotometer. To perform the solubility measurements, the experimental setup design was followed by the methods described in resources such as the method reported by Abourehab et al. to measure the solubility of Febuxostat [13] and Alendronate [14] in the $scCO_2$. Also, to evaluate the reliability of the experimental setup used to measure the supercritical solubility of Chlorothiazide, solubility of Aspirin in $scCO_2$ was measured with this setup and the results were compared with the data reported by Huang et al. [22,23]. and Behjati Rad et al. [24], as shown in Fig. 3.

To separate possible impurities of the $CO_2$ gas, it is first passed through the filter as indicated in Fig. 2. Then, it is injected into the chiller at a temperature of approximately $-25\ ^{\circ}C$ and converts to liquid $CO_2$ to be later used as the dense solvent in the process. The pressure of this flow is elevated up to the desired pressure, with a precision of $\pm 1$ bar, using an HPLC pump. Obtained high pressure liquid $CO_2$ is heated to the considered temperature, with a precision of $\pm 0.1$ K, by flowing through the heating coil. Next, it is injected into the equilibrium column which is placed in an oven to maintain the desired operating temperature. For each experimental run, 4 gr of Chlorothiazide powder was loaded in this column. The liquid $CO_2$ is placed in contact with Chlorothiazide powder for about 150 min to achieve the equilibrium state. After reducing the pressure, the obtained saturated solution of Chlorothiazide in $CO_2$ was collected in the sampler containing methanol. Chlorothiazide concentration ($C_{Chlorothiazide}$) of this solution is calculated using UV-Vis spectrophotometer at the wavelength of 270 nm. The mean solubility value at the desired pressure and temperature, in terms of equilibrium Chlorothiazide mole fraction was computed as the following [13,25]:

$$y = \frac{\frac{C_{Chlorothiazide} \times V_s}{M_{Chlorothiazide}}}{\underbrace{\frac{C_{Chlorothiazide} \times V_s}{M_{Chlorothiazide}}}_{n_{Chlorothiazide}} + \underbrace{\frac{\rho_{CO_2} \times V_L}{M_{CO_2}}}_{n_{CO_2}}} = \frac{C_{Chlorothiazide} \times V_s \times M_{CO_2}}{C_{Chlorothiazide} \times V_s \times M_{CO_2} + \rho_{CO_2} \times V_L \times M_{Chlorothiazide}} \tag{1}$$

where, $M_{Chlorothiazide}$, $M_{CO2}$, $V_s$ $(m^3)$, and $V_L$ $(m^3)$ are the molecular weight of the Chlorothiazide (295.73 g $mol^{-1}$), the molecular weight of $CO_2$ (44 g $mol^{-1}$), the volume of the sampler, and the volume of the sampling loop, respectively. Also, $\rho_{CO2}$ $(kg.m^{-3})$ is the $CO_2$ density at the desired operating condition, extracted from the NIST chemistry webbook. Also, equilibrium solubility of Chlorothiazide in $scCO_2$ ($S$ (kg.$m^{-3}$)) can be obtained as follows [14,25]:

$$S = \frac{C_{Chlorothiazide} \times V_s}{V_L} \tag{2}$$

### 2.3. Thermodynamic analysis

#### 2.3.1. Empirical models

These models which were first presented in 1978 [26], have been formulated based on a linear relationship between the logarithm of the solute solubility and density of the supercritical solvent (*e.g.* $scCO_2$) or its logarithm. Therefore, supercritical solvent density, operating pressure and temperature, and solute solubility are the only information required to correlate the experimental solubility through these models. Accordingly, they are the simplest models presented to correlate the supercritical solubility data, which have been satisfactorily used to correlate the solubility data of various drugs [27–33], pigments and dyes [34–36], and other compounds [37,38].

In this research, the most widely used empirical models, with 3 fitting parameters, are utilized to correlate the supercritical solubility data of Chlorothiazide. These include the Garlapati-Madras, Chrastil, and Kumar- Johnston (K-J) models, which relate the Chlorothiazide solubility to $scCO_2$ density and temperature, as well as the models presented by Mendez-Santiago and Teja (MST) and Bartle who, in addition to $scCO_2$ density and temperature effects, also considered the pressure impression on the supercritical solubility

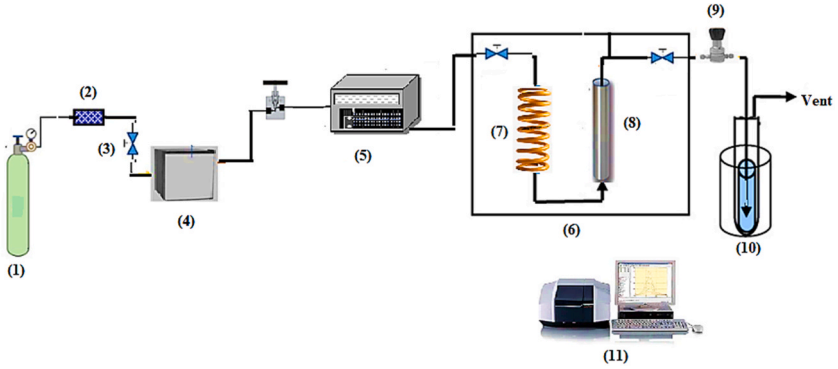


**Fig. 2.** Laboratory setup for supercritical solubility measurement of Chlorothiazide.

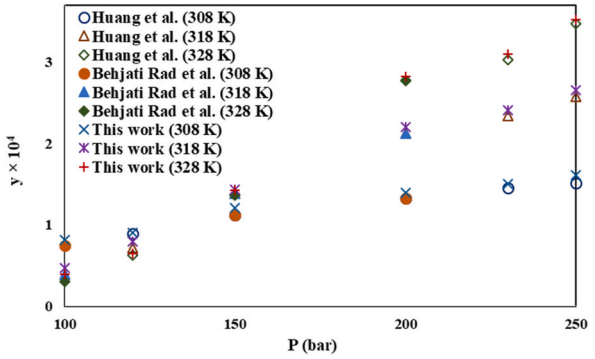


**Fig. 3.** The solubility of Aspirin in $scCO_2$ measured using the developed method in this study and comparison with previously reported methods.

of Chlorothiazide. The formula of these models is shown in Table 1. In these relationships, *y*, *ρ*, *T,* and *P* denote the Chlorothiazide solubility (mole.mole$^{-1}$), $scCO_2$ density (kg.m$^{-3}$) which is obtained from the NIST chemistry web-book, temperature (K), and pressure (bar). The parameters of $P_{ref}$ and $\rho_{ref}$ in the Bartle model are the reference pressure and the reference $scCO_2$ density, 1 bar and 700 kg m$^{-3}$, respectively. The optimum value of the fitting parameters *($a_0$, $a_1$, and $a_2$)* should be obtained through the curve fitting methods.

### 2.3.2. Equations of state-based models

The necessary condition to reach the equilibrium solubility state between two phases, the solvent ($scCO_2$, phase 1) and the solute (Chlorothiazide, phase 2), is equality of pressure and temperature, as well as the fugacity of the solute in both phases [13,14]. Assuming that the solute is pure and incompressible, and its molar volume doesn't depend on pressure, and also assuming that $scCO_2$ is insoluble in the solute, the equilibrium solubility at the temperature of *T* (*K*) and pressure of *P* (*MPa*) can be obtained by the following relationship [39]:

$$y_2 = \frac{P_2^{sub}}{P}\frac{\varphi_2^{sat,s}(T)}{\varphi_2(T,P,y)}\exp\left[\frac{\nu_2^s\left(P-P_2^{sub}\right)}{RT}\right] \tag{3}$$

Due to the low sublimation pressure of Chlorothiazide, its saturation fugacity coefficient $\varphi_2^{sat,s}(T)$ can be considered one. Also, the fugacity coefficient of Chlorothiazide in $scCO_2$, $\varphi_2(T,P,y)$, can be obtained through the following relationship, using an equation of state [39]:

$$RT\ ln\ \varphi_i = -RT\ ln\frac{PV}{RT} + \int_V^\infty\left[\left(\frac{\partial P}{\partial n_i}\right)_{T,V,n_j\neq n_i} - \frac{RT}{V}\right]dV \tag{4}$$

where, *R* ($Jmol^{-1}K^{-1}$), $n_i$, and *V* are the ideal gas constant, number of species *i* moles, and the $scCO_2$ volume. Here, PR-EoS and SRK-EoS, with the mathematical relations shown in Table 2, are selected for calculation of $\varphi_2(T,P,y)$. Furthermore, Van der Waals (vdW) mixing rule [40] is chosen to obtain the *a* and *b* parameters of the Chlorothiazide - $scCO_2$ mixture:

$$a_m = \sum_j y_i y_j \sqrt{a_i a_j}\left(1-k_{ij}\right) \tag{5}$$

$$b_m = \sum_j y_i y_j \frac{\left(b_i+b_j\right)}{2}\left(1-l_{ij}\right) \tag{6}$$

In these relations, $l_{ij}$ and $k_{ij}$ are the interaction parameters of the *i* and *j* species, which their optimum values were calculated by minimizing the difference between the calculated values and the experimental data, through the PSO method of MATLAB software.

To use these models, critical pressure *($P_c$)*, acentric factor *($\omega$)*, critical temperature *($T_c$)*, boiling point *($T_b$)*, molar volume ($v$), and

**Table 1**
Empirical thermodynamic models of this study.

| Model | Formula |
|---|---|
| Chrastil | $ln\,y = a_0 + a_1\,ln(\rho) + \frac{a_2}{T}$ |
| Bartle | $ln\frac{y.P}{P_{ref}} = a_0 + a_1(\rho - \rho_{ref}) + \frac{a_2}{T}$ |
| Mendez-Santiago and Teja (MST) | $T\,ln(y.P) = a_0 + a_1\rho + a_2 T$ |
| Garlapati-Madras | $ln\,y = a_0 + \frac{a_1}{T} + a_2\,ln(\rho.T)$ |
| Kumar-Johnston (K-J) | $ln\,y = a_0 + a_1\rho + \frac{a_2}{T}$ |

**Table 2**
Mathematical formula of the PR-EoS and SRK-EoS.

| Model | Formula | $a(T)$ | $b$ |
|---|---|---|---|
| PR-EoS | $P = \frac{RT}{\nu - b} - \frac{a(T)}{\nu(\nu+b)+b(\nu-b)}$ | $a(T) = \frac{0.45724R^2T_c^{\,2}}{P_c} \times \alpha(T_{r,\omega})$<br>$\alpha(T_{r,\omega}) = [1 + k(1 - T_r^{0.5})]^2$<br>$k = 0.37464 + 1.54226\omega - 0.26992\omega^2$ | $b = \frac{0.0778RT_c}{P_c}$ |
| SRK-EoS | $P = \frac{RT}{\nu - b} - \frac{a(T)}{\nu(\nu+b)}$ | $a(T) = \frac{0.42747R^2T_c^2}{P_c} \times \alpha(T_{r,\omega})$<br>$\alpha(T_{r,\omega}) = [1 + m(1 - T_r^{0.5})]^2$<br>$m = 0.480 + 1.574\omega - 0.176\omega^2$ | $b = \frac{0.08664RT_c}{P_c}$ |

the sublimation pressure ($P^{sub}$) of the Chlorothiazide must be known. These unknown properties can be computed through the appropriate group contribution methods [13,14]. In this study, the Marrero and Gani method [41] has been applied for estimation of $T_b$, $T_c$, and $P_c$. The molecular groups considered to calculate these properties include; two aCH, two aC fused with non-aromatic subring, one aC-Cl, one aC-$SO_2$, one NH(cyclic), one $SO_2$ (cyclic), one $NH_2$, one CH (cyclic), and one N (cyclic) from the first-order group. The Immirzi method [42], and the Constantinou-Gani method [43] have been applied for calculation of $\nu$ and ω, respectively. Also, $P^{sub}$ has been computed using the Ambrose - Walton method [44], as the following:

$$P^{sub} = P_c \, exp\left[\frac{-5.97616\tau + 1.29874\tau^{1.5} - 0.60394\tau^{2.5} - 1.06841\tau^5}{T_r} + \omega\left(\frac{-5.03365\tau + 1.11505\tau^{1.5} - 5.41217\tau^{2.5} - 7.46628\tau^5}{T_r}\right) + \omega^2\left(\frac{-0.64771\tau + 2.41539\tau^{1.5} - 4.26979\tau^{2.5} + 3.25259\tau^5}{T_r}\right)\right] \quad (7)$$

Here, $T_r$ is the reduced temperature $\left(\frac{T}{T_c}\right)$, and $\tau = 1 - T_r$.

The acceptable accuracy of the mentioned group contribution methods for determining the unknown physicochemical properties of the complex molecules has been previously confirmed [14,39,45]. The computed properties of Chlorothiazide are presented in Table 3.

## 3. Results and discussion

### 3.1. Chlorothiazide solubility in $scCO_2$

Solubility of Chlorothiazide in $scCO_2$ was determined at different operating pressures (130–290 bar) and temperatures (308–338 K), through the procedure described in section 2.2. After three times repetition each experiment, the average solubility values were calculated in terms of $S\ (kg.m^{-3})$ and $y\ (mole.mole^{-1})$ with a relative standard deviation less than 4%, as shown in Table 4. Pressure and temperature were determined with the standard uncertainties of $u(P) = 1$ bar and $u(T) = 0.1$ K, respectively. Also, the $scCO_2$ density was specified with a relative uncertainty of $u_r(\rho) = 0.002$ kg $m^{-3}$.

The variations of Chlorothiazide solubility with temperature and pressure are depicted in Fig. 4. Clearly, a direct relationship between the pressure and the solubility is observed, such that pressure enhancement at a fixed temperature leads to solubility increment. This can be due to reducing the intermolecular distance between the $CO_2$ molecules and increasing its density, which results to increasing the $CO_2$ - Chlorothiazide intermolecular interactions [14] and enhancing the $scCO_2$ solvation power, as reported by other researchers, too [13,46].

Unlike the pressure, analysis of the influence of temperature on the Chlorothiazide solubility is not straightforward. As seen in Fig. 4, at pressures lower than 170 bar, the solubility at higher temperatures is less than its value at lower temperatures ($y_{338} \prec y_{328} \prec y_{318} \prec y_{308}$). At the pressure of 170 bar, the solubility at all the desired temperatures are almost the same ($y_{308} \simeq y_{318} \simeq y_{328} \simeq y_{338} \simeq 0.6 \times 10^{-5}\ mole.mole^{-1}$), and at pressures higher than that, increasing the temperature leads to solubility enhancement ($y_{338} \succ y_{328} \succ y_{318} \succ y_{308}$). Accordingly, the pressure of 170 bar is a crossover point of the Chlorothiazide-$scCO_2$ system in the solubility curve. This phenomenon can be explained according to reverse impact of temperature on the solute vapor pressure and the $scCO_2$ density which is a criterion of its solvation power. Increasing the temperature reduces the $scCO_2$ density and the solute

**Table 3**
The calculated properties of Chlorothiazide through the group contribution methods.

| Component | $T_b$ (K) | $T_c$ (K) | $P_c$ (bar) | ω | $v_s$ ($cm^3.mole^{-1}$) | T (K) | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | 308 | 318 | 328 | 338 |
| | | | | | | $P^{sub} \times 10^5$ (Pa) | | | |
| Chlorothiazide | 677.70 | 933.24 | 45.85 | 0.62 | 369.20 | 2.30 | 8.64 | 29.33 | 91.12 |

**Table 4**
Solubility of Chlorothiazide in $scCO_2$ at different operational conditions.

| T (K) | P (bar) | ρ (kg.m$^{-3}$) | y × 10$^5$ (mole.mole$^{-1}$) | Expanded uncertainty × 10$^5$ | S × 10$^2$ (kg m$^{-3}$) |
|---|---|---|---|---|---|
| 308 | 130 | 786.89 | 0.488 ± 0.014 | 0.031 | 2.581 |
| | 170 | 838.96 | 0.597 ± 0.021 | 0.037 | 3.366 |
| | 210 | 874.40 | 0.661 ± 0.009 | 0.017 | 3.885 |
| | 250 | 901.87 | 0.741 ± 0.018 | 0.026 | 4.492 |
| | 290 | 924.56 | 0.761 ± 0.024 | 0.033 | 4.729 |
| 318 | 130 | 695.25 | 0.466 ± 0.008 | 0.021 | 2.178 |
| | 170 | 776.53 | 0.628 ± 0.020 | 0.034 | 3.278 |
| | 210 | 823.71 | 0.721 ± 0.022 | 0.032 | 3.992 |
| | 250 | 857.82 | 0.79 ± 0.015 | 0.021 | 4.555 |
| | 290 | 884.91 | 0.818 ± 0.018 | 0.024 | 4.865 |
| 328 | 130 | 573.33 | 0.48 ± 0.011 | 0.026 | 1.850 |
| | 170 | 704.97 | 0.62 ± 0.015 | 0.026 | 2.938 |
| | 210 | 768.74 | 0.795 ± 0.021 | 0.028 | 4.108 |
| | 250 | 811.37 | 0.847 ± 0.026 | 0.032 | 4.619 |
| | 290 | 843.77 | 0.919 ± 0.025 | 0.029 | 5.212 |
| 338 | 130 | 449.02 | 0.417 ± 0.011 | 0.029 | 1.258 |
| | 170 | 625.09 | 0.641 ± 0.024 | 0.039 | 2.693 |
| | 210 | 709.69 | 0.851 ± 0.024 | 0.030 | 4.059 |
| | 250 | 762.69 | 0.911 ± 0.017 | 0.021 | 4.670 |
| | 290 | 801.33 | 1.012 ± 0.038 | 0.039 | 5.451 |

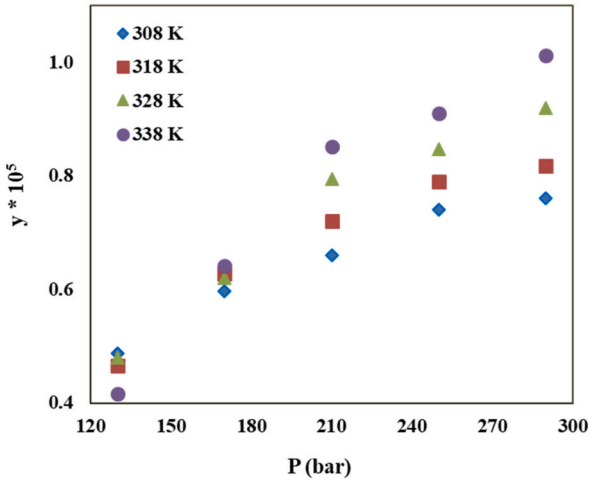


**Fig. 4.** Measured solubility of Chlorothiazide vs. the pressure and temperature.

solubility, while increases the solute vapor pressure and its solubility. This trend has been reported previously [47–49].

### 3.2. Theoretical study of Chlorothiazide solubility in $scCO_2$

As described, the obtained Chlorothiazide solubility data are correlated via two groups of theoretical models: empirical models and cubic EoS-based models. The accuracy of these models to fit the laboratory data is evaluated based on their average absolute relative deviation *(AARD%)* and adjusted correlation coefficient ($R_{adj}$) values. These statistical parameters were computed as the following [50]:

$$AARD\% = \frac{1}{N}\sum_{i=1}^{n}\left|\frac{y_{i,cal} - y_{i,\exp}}{y_{i,\exp}}\right| \times 100\% \tag{8}$$

$$R_{adj} = \sqrt{\left|\frac{1 - \frac{SS_E}{SS_T}}{R^2} - \frac{Q\left(1 - \left(1 - \frac{SS_E}{SS_T}\right)^2\right)}{N - Q - 1}\right|} \tag{9}$$

In the above relationships, $y_{i,cal}$, $y_{i,exp}$, $N$, and $Q$ denote the solubility value calculated through the desired model, the experimental solubility value, number of data points, and number of independent variables, respectively. Also, error sum of squares and total sum of

squares are shown by the *SSE* and *SST* abbreviations, respectively.

### 3.2.1. Empirical models

As explained, conventional empirical models proposed by Chrastil, Kumar- Johnston (K-J), Bartle, Garlapati-Madras, and Mendez-Santiago and Teja (MST) were used to correlate the Chlorothiazide solubility data. The optimum value of the fitting parameters ($a_0$, $a_1$, and $a_2$), as well as the *AARD%* and $R_{adj}$ values of each model were presented in Table 5.

As can be seen, all of the models have an acceptable *AARD%* and $R_{adj}$ values, which confirms their ability to correlate the Chlorothiazide solubility laboratory data in the supercritical $CO_2$ as the solvent. Meanwhile, the K-J model, with the minimum *AARD%* value of 3.15, and MST model with the maximum *AARD%* value of 11.20, possess the highest and the lowest correlation precision, respectively. Moreover, $R_{adj}$ value for all of the mentioned models was found to be almost ~0.98, which means that approximately 98% of the data calculated through the models can match the laboratory data with high accuracy. The comparison between the calculated solubility values through the mentioned models and the laboratory solubility data was illustrated in Fig. 5. In this figure, the computed and laboratory values were shown by line and dot, respectively.

Capability of calculating the total enthalpy ($\Delta H_t$) and vaporization enthalpy ($\Delta H_{vap}$) of the binary supercritical mixtures, such as Chlorothiazide-sc$CO_2$, is one of the important benefits of the empirical models. They can be computed through the $a_2$ fitting parameters of the Chrastil and Bartle models, respectively. So, $\Delta H_t$ and $\Delta H_{vap}$ of the Chlorothiazide-sc$CO_2$ mixture were determined through the following relationships:

$$\Delta H_t = -a_{2,Chrastil}.R = 17.34\ kJ.mol^{-1} \tag{10}$$

$$\Delta H_{vap} = -a_{2,Bartle}.R = 21.50\ kJ.mol^{-1} \tag{11}$$

Using the Hess's law, the solvation enthalpy ($\Delta H_{sol}$) of this mixture can also be computed as follows:

$$\Delta H_{sol} = \Delta H_t - \Delta H_{vap} = -4.16\ kJ.mol^{-1} \tag{12}$$

The extrapolative ability is another interesting feature of the empirical models used in the current study. Therefore, they can be used to extrapolate data out of the considered values of the pressure (130–290 bar) and temperature (308–338 K) of this study. This capability can be investigated by plotting the linear graphs of the experimental data and fitting a line over them at different temperatures of 308, 318, 328, and 338 K, as shown in Fig. 6.

Moreover, self-consistency analysis was conducted for MST model, as a representative model, to further investigate the extrapolation ability of the empirical models (Fig. 7). As is evident, all the solubility values of various temperatures are placed on a line with an approximate angle of 45°, which indicates passing the self-consistency test [27,31].

### 3.2.2. Equations of state-based models

As previously described, the fugacity coefficient of Chlorothiazide in sc$CO_2$, which is needed to estimate its solubility through Eq. (3), was calculated using PR-EoS and SRK-EoS. These are the most popular EoSs, used to correlate the solubility of various materials, especially pharmaceutical substances [29,33,51].

The compatibility between the laboratory and the computed values of Chlorothiazide solubility in sc$CO_2$ through the PR-EoS and SRK-EoS was shown in Fig. 8. Also, the optimum values of the binary interaction parameters ($k_{12}$ and $l_{12}$), and the statistical parameters (*AARD%* and $R_{adj}$) of these models were listed in Table 6. It is seen that the model of PR indicates better performance in terms of fitting accuracy.

Fig. 9 shows the binary interaction parameters ($k_{12}$ and $l_{12}$) of PR-EoS and SRK-EoS versus the temperature. As is evident, they are decreasing linear functions with respect to temperature, whose slopes and intercepts are determined by the regression method. This decreasing trend versus the temperature has already been reported, too [25,52].

## 4. Conclusion

The manufacture of micro or nano size particles of pharmaceutical substances has been introduced as an efficient approach to enhance their bioavailability and therapeutic efficiency. Among the proposed micronization/nanonization pharmaceutical techniques, supercritical carbon dioxide (sc$CO_2$)-based methods are recognized as green and safe methods with unique advantages. However, the solubility of the desired medicinal compound is an essential parameter for selecting and designing a suitable supercritical process.

Chlorothiazide is a common thiazide diuretic which is orally used to treat edema caused by kidney disease, severe liver illness, and

**Table 5**
Fitting and statistical parameters of the Chlorothiazide-sc$CO_2$ mixture, obtained for the empirical models used in this study.

| Model | Fitting parameters | | | Statistical parameters | |
|---|---|---|---|---|---|
| | $a_0$ | $a_1$ | $a_2$ | *AARD (%)* | $R_{adj}$ |
| Chrastil | −4.94 | 1.76 | −2085.36 | 4.80 | 0.976 |
| Kumar and Johnston (K-J) | −7.21 | 2.49 | −2128.58 | 3.15 | 0.986 |
| Bartle | 7.98 | −4208.67 | −2585.63 | 7.80 | 0.985 |
| Mendez-Santiago and Teja (MST) | −6284.18 | 2045.91 | 7.96 | 11.20 | 0.979 |
| Garlapati- Madras | −16.91 | −1507.68 | 1.76 | 4.80 | 0.973 |

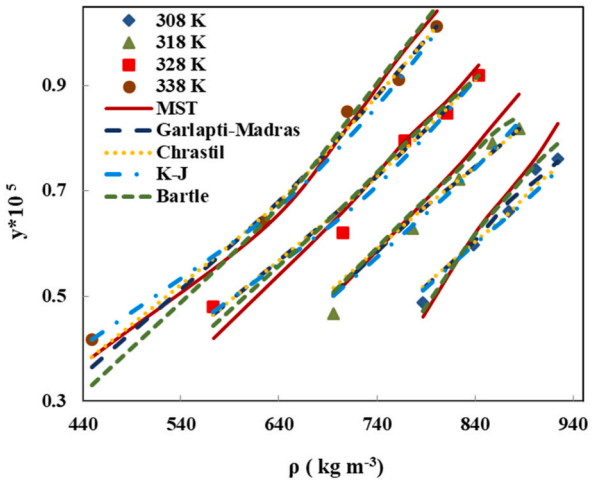


**Fig. 5.** Comparison of the calculated and laboratory values of Chlorothiazide solubility in $scCO_2$, at different conditions.

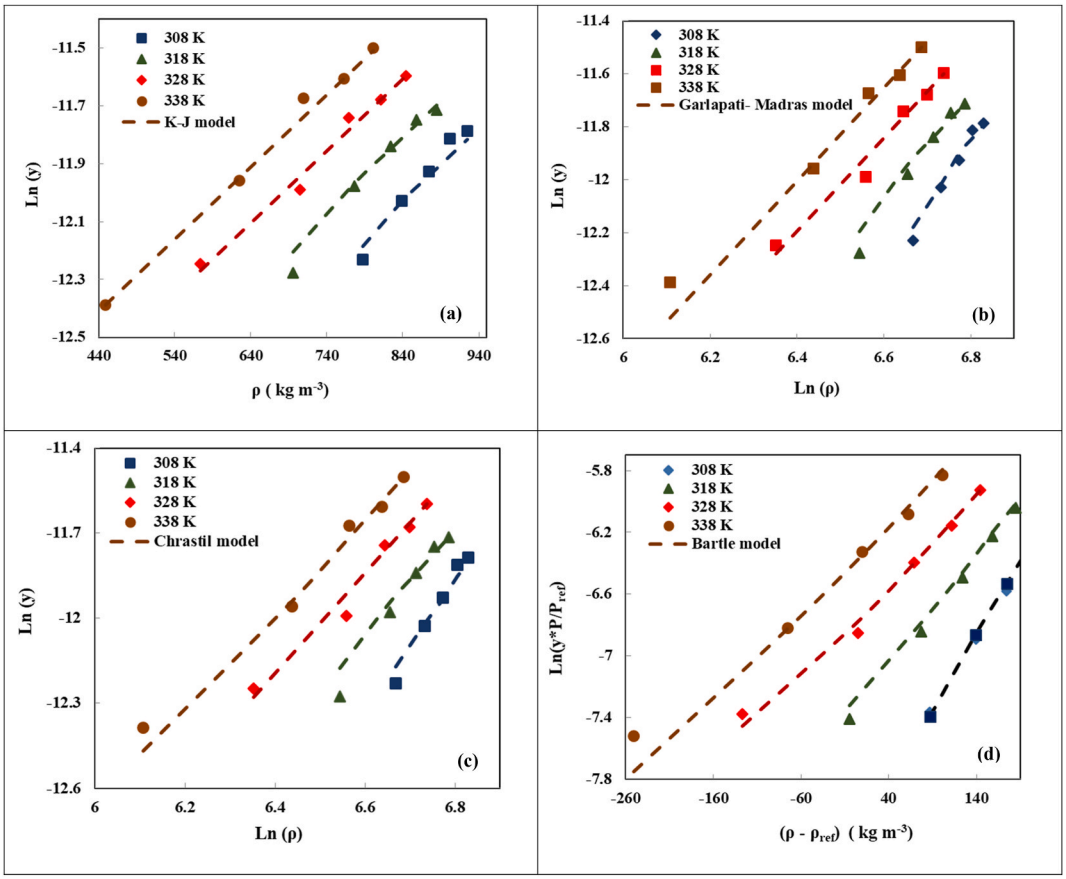


**Fig. 6.** Correlated Chlorothiazide solubility in $scCO_2$ at different temperatures using (a) K-J model, (b) Garlapati - Madras model, (c) Chrastil model, and (d) Bartle model.

congestive heart failure, or treatment with hormonal or steroid drugs. This medicine with very low solubility in water and low permeability is categorized in the class IV of Biopharmaceutical Classification System (BCS), and possess low bioavailability. In the current research, solubility of this medicine in $scCO_2$ was obtained in the range of $0.417 \times 10^{-5}$ to $1.012 \times 10^{-5}$ mol $mol^{-1}$, at 308–338 K and 130–290 bar. Moreover, obtained experimental values were correlated through traditional empirical models, proposed by Chrastil, Kumar- Johnston (K-J), Bartle, Garlapati-Madras, and Mendez-Santiago and Teja (MST), and two cubic equations of state

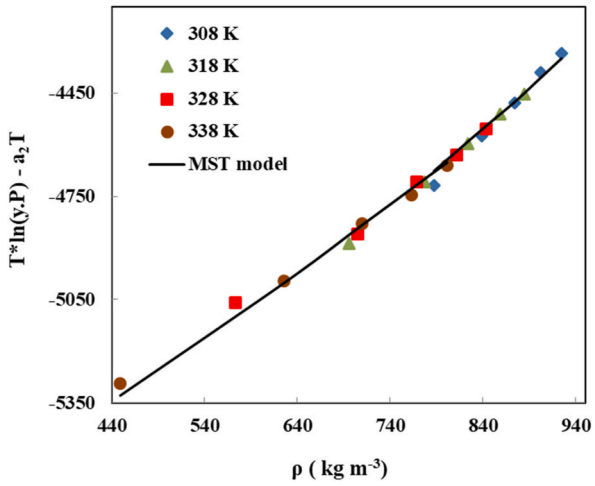


**Fig. 7.** Self-consistency curve of Chlorothiazide solubility in $scCO_2$ at different conditions, using MST model.

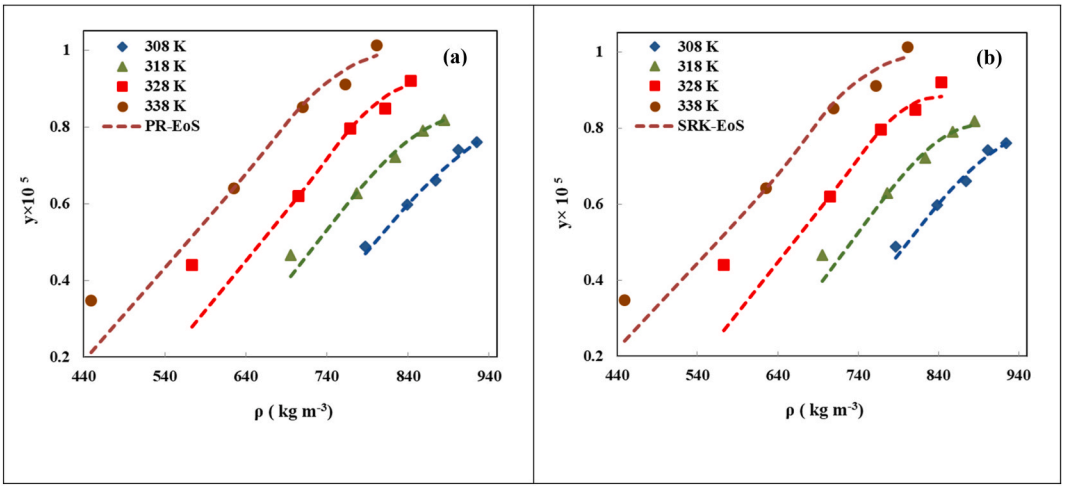


**Fig. 8.** Comparison between the laboratory (dots) and the computed solubility values (line), using (a) PR-EoS, and (b) SRK-EoS, at various temperatures.

**Table 6**
Correlation results of Chlorothiazide solubility in $scCO_2$, using PR-EoS and SRK-EoS.

| Model | Parameter | 308 K | 318 K | 328 K | 338 K |
|---|---|---|---|---|---|
| PR- EoS | $k_{12}$ | −0.290 | −0.560 | −0.740 | −0.837 |
| | $l_{12}$ | 0.859 | 0.530 | 0.366 | 0.237 |
| | ***AARD %*** | 1.56 | 2.78 | 9.26 | 12.45 |
| | $R_{adj}$ | 0.999 | 0.999 | 0.990 | 0.988 |
| SRK- EoS | $k_{12}$ | −0.126 | −0.448 | −0.590 | −0.890 |
| | $l_{12}$ | 0.991 | 0.902 | 0.720 | 0.259 |
| | ***AARD %*** | 2.11 | 3.63 | 10.10 | 13.90 |
| | $R_{adj}$ | 0.998 | 0.995 | 0.960 | 0.950 |

(PR-EoS and SRK-EoS) thermodynamic models.

All the mentioned models could satisfactorily correlate the supercritical solubility of Chlorothiazide. Meanwhile, the K-J model with the minimum *AARD%* value of 3.15 and the PR-EoS with the average *AARD%* value of 6.51 show the highest precision to fit the laboratory data. Additional to correlation capability, the extrapolation ability of the empirical models to predict the Chlorothiazide solubility in $scCO_2$ outside the considered range of pressure and temperature was also examined. Moreover, the total enthalpy ($\Delta H_t$), vaporization enthalpy ($\Delta H_{vap}$), and the solvation enthalpy ($\Delta H_{sol}$) of the Chlorothiazide - $scCO_2$ mixture were computed using the employed models.

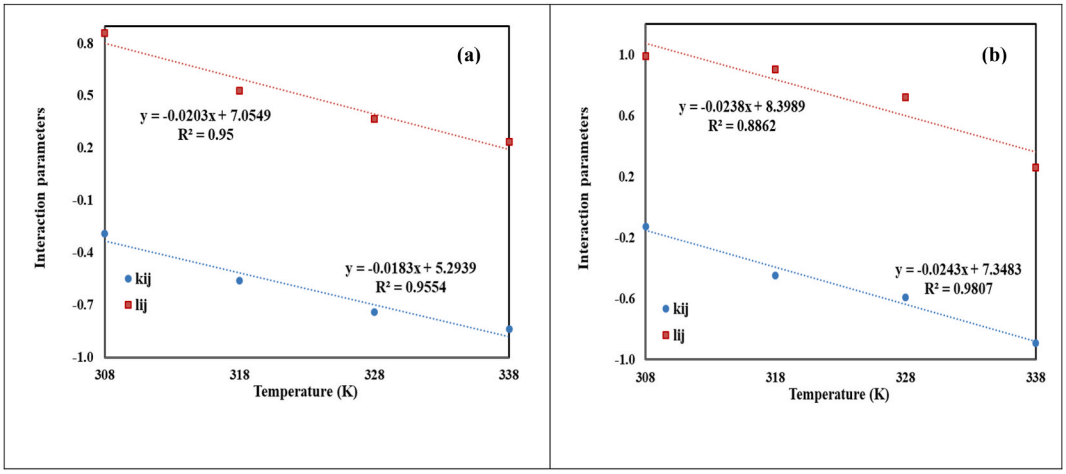


**Fig. 9.** Decreasing linear functions of $l_{ij}$ and $k_{ij}$ versus the temperature, for (a) PR-EoS and (b) SRK-EoS.

## Authors statement

**Mohammed Majrashi**: Conceptualization, Writing – original draft, Validation, Formal analysis.
**Ahmed Salah Al-Shati**: Data curation, Investigation, Writing – original draft.
**Maria Grishina**: Resources, Formal analysis, Conceptualization, Software.
**Shaheen M. Sarkar**: Formal analysis, Writing – Review & Editing, Investigation.
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**Saeed Shirazian**: Supervision, Formal analysis, Funding acquisition, Conceptualization.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Data availability

All data are within the published paper.

## Acknowledgements

This work was supported by Ministry of Science and Higher Education of Russia (grant FENU-2020-0019).
This research was carried out with financial support of Al-Mustaqbal University College (grant number MUS-E-0122).

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