EXTRACTION OF SINENSETIN, ISOSINENSETIN AND ROSMARINIC ACID FROM *ORTHOSIPHON STAMINEUS* LEAVES USING ETHANOL ASSISTED SUPERCRITICAL CARBON DIOXIDE

AHMAD HAZIM BIN ABDUL AZIZ

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Faculty of Engineering
Universiti Teknologi Malaysia

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ABSTRACT

Sinensetin, isosinensetin and rosmarinic acid are potent bioactive compounds for human health benefits that can be extracted from *Orthosiphon stamineus* (*O. stamineus*) leaves. Supercritical carbon dioxide (SC-CO_2) extraction which has emerged as the preferable green solvent for natural products has been employed in the present study. The most important factor for designing SC-CO_2 extraction process is to obtain the solubility data. The solubility of extract yield in SC-CO_2 extraction has been widely reported, however, the extract yield consists of a mixture of interacting solutes which could affect the solubility. Thus, the solubility data of the solutes from *O. stamineus* leaves were determined in this study. The chemical parameters of temperature and pressure in the range of 40 - 80 °C and 10 - 30 MPa, respectively were investigated. Meanwhile, insignificant mechanical parameters of mean particle size (400 µm), total flow rate (5 mL/min), ethanol (5% v/v) and extraction time (4 hours) were kept constant. The concentration of solutes increased as temperature increased while the dual effect of pressure was observed. The solute vapor pressure prevailed over solvent power. The optimum SC-CO_2 condition was obtained at 10 MPa and 80 °C with a high concentration of sinensetin, isosinensetin and rosmarinic acid of 440.3, 392.9 and 752.0 mg/kg sample, respectively by using response surface methodology with central composite design. Due to interaction of solutes, the solubility of sinensetin, isosinensetin and rosmarinic acid were varied from 0.617 - 17.179, 0.446 - 10.119 and 0.066 - 8.729 mg/kg solvent, respectively. Investigation on the effect of chemical parameters on the solute's solubility showed similar behaviour as the solute's concentration. However, rosmarinic acid with the highest concentration has the lowest solubility in SC-CO_2. The presence of hydrogen bond acceptor and donor sites on the rosmarinic acid's structure causes strong solute-solute interaction which contributes to the shortest intermolecular distance of 1.669 Å. On the other hand, the solubility of sinensetin was significantly higher than its isomer (isosinensetin) due to difference in melting point and dipole moment. Sinensetin has a lower melting point and dipole moment of 452.15 K and 3.36 D, respectively compared to isosinensetin with 479.15 K and 4.9 D. Thus, isosinensetin has stronger interaction between its molecules with the intermolecular distance of 2.395 Å compared to sinensetin with 2.454 Å. Then, the solubility data were correlated using two semi-empirical models namely Chrastil and del Valle-Aguilera. The obtained results revealed that both models were successfully correlated the experimental solubility data with low value of average absolute relative deviation percent in the range of 3.04% to 5.24%. Sinensetin (0.337) has the lowest value of coefficient of interaction, k followed by isosinensetin (0.676) and rosmarinic acid (1.012). These values indicates that sinensetin has the weakest solute-solute interaction but strong solute-solvent interaction which led to highest solubility in SC-CO_2. Negative value of k was obtained due to negative effect of pressure on the solute solubility. Besides, the enthalpy of vaporization and solvation of solutes were obtained from the correlation models which vary from 4.19 to 13.38 kJ/mol and -1.59 to -0.41 kJ/mol, respectively. Hence, the present study has provided various data on sinensetin, isosinensetin and rosmarinic acid extracted from *O. stamineus* leaves in SC-CO_2 which can be applied for further research.

ABSTRAK

Sinensetin, isosinensetin dan asid rosmarinik adalah sebatian bioaktif yang penting untuk manfaat kesihatan manusia yang dapat diekstrak dari daun *Orthosiphon stamineus* (*O. stamineus*). Bendalir lampau genting karbon dioksida (SC-CO_2) yang telah muncul sebagai pelarut hijau yang paling disukai untuk produk semula jadi telah digunakan dalam kajian ini. Faktor yang paling penting untuk mereka bentuk proses pengekstrakan SC-CO_2 adalah mendapatkan data kebolehlarutan. Kebolehlarutan hasil ekstrak dalam pengekstrakan SC-CO_2 telah dilaporkan secara meluas, namun hasil ekstrak terdiri daripada campuran bahan larut berinteraksi yang dapat mempengaruhi kebolehlarutan. Oleh itu, data kebolehlarutan bahan larut dari daun *O. stamineus* ditemukan dalam kajian ini. Parameter kimia iaitu suhu dan tekanan masing-masing dalam julat 40 - 80 °C dan 10 - 30 MPa, telah diselidiki. Sementara itu, parameter mekanikal yang tidak ketara dari purata ukuran zarah (400 µm), jumlah kadar alir (5 mL/min), etanol (5% v/v) dan masa pengekstrakan (4 jam) dijadikan malar. Kepekatan bahan larut meningkat apabila suhu meningkat sementara kesan berganda bagi tekanan telah ditunjukkan. Tekanan wap bahan larut mengatasi kuasa pelarut. Keadaan optimum SC-CO_2 telah diperoleh pada 10 MPa dan 80 °C dengan kepekatan yang tinggi bagi sinensetin, isosinensetin dan asid rosmarinik sekitar 440.3, 392.9 dan 752.0 mg/kg sampel, masing-masing dengan menggunakan kaedah sambutan permukaan dengan reka bentuk komposit berpusat. Kerana interaksi bahan larut, kebolehlarutan sinensetin, isosinensetin dan asid rosmarinik masing-masing berbeza dari 0.617 - 17.179, 0.446 - 10.119 dan 0.066 - 8.729 mg/kg pelarut. Kesan parameter kimia terhadap kebolehlarutan bahan larut menunjukkan tingkah balas yang sama dengan kepekatan bahan larut. Walau bagaimanapun, asid rosmarinik dengan kepekatan tertinggi mempunyai kebolehlarutan terendah dalam SC-CO_2. Kehadiran bahagian penerima dan penderma ikatan hidrogen pada struktur asid rosmarinik menyebabkan interaksi bahan larut menjadi kuat serta menyumbang kepada jarak antara molekul yang terdekat iaitu 1.669 Å. Sebaliknya, kebolehlarutan sinensetin jauh lebih tinggi daripada isomernya (isosinensetin) kerana perbezaan pada takat lebur dan momen dwikutub. Sinensetin mempunyai takat lebur dan momen dwikutub yang lebih rendah masing-masing pada 452.15 K dan 3.36 D, berbanding dengan isosinensetin pada 479.15 K dan 4.9 D. Oleh itu, isosinensetin mempunyai interaksi yang lebih kuat antara molekulnya dengan jarak antara molekulnya pada nilai 2.395 Å berbanding dengan sinensetin pada 2.454 Å. Kemudian, data kebolehlarutan dihubungkan dengan menggunakan dua model separa empirikal iaitu Chrastil dan del Valle-Aguilera. Hasil yang diperoleh menunjukkan bahawa kedua-dua model berjaya mengaitkan dengan data kebolehlarutan eksperimen dengan purata sisihan relatif mutlak yang rendah dalam julat 3.04% hingga 5.24%. Sinensetin (0.337) mempunyai pekali interaksi, *k* terendah diikuti oleh isosinensetin (0.676) dan asid rosmarinik (1.012). Nilai-nilai ini menunjukkan bahawa sinensetin mempunyai interaksi bahan larut paling lemah tetapi interaksi bahan larut-pelarut sangat kuat sehingga menyebabkan kebolehlarutan sinensetin tertinggi dalam SC-CO_2. Nilai negatif bagi *k* diperolehi kerana pengaruh tekanan negatif terhadap kebolehlarutan bahan larut. Selain itu, entalpi pengewapan dan pensolvatan bahan larut diperoleh dari model korelasi masing-masing bervariasi dari 4.19 hingga 13.38 kJ/mol dan -1.59 hingga -0.41 kJ/mol. Oleh itu, kajian ini telah memberikan pelbagai data mengenai sinensetin, isosinensetin dan asid rosmarinik yang diekstrak dari daun *O. stamineus* dalam pengekstrakan SC-CO_2 dan data ini dapat digunakan untuk penyelidikan lebih lanjut pada masa akan datang.

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LIST OF ABBREVIATIONS

CO_2	-	Carbon dioxide
O. stamineus	-	*Orthosiphon stamineus*
ANOVA	-	Analysis of variance
HPLC	-	High-performance liquid chromatography
RSM	-	Response surface methodology
CCD	-	Central composite design
SC-CO_2	-	Supercritical carbon dioxide
SFE	-	Supercritical fluid extraction
SCF	-	Supercritical fluid
AARD	-	Average absolute relative deviation
PMF	-	Polymethoxylated flavone
NKEA	-	National key economic area
GRAS	-	Generally regarded as safe
WHO	-	World Health Organization
TP	-	Triple point
UNEP	-	United Nations Environment Programme
CP	-	Critical point
n.a	-	Not available

LIST OF SYMBOLS

S	-	Solubility
ρ_{CO_2}	-	Density of carbon dioxide
$\rho_{modifier}$	-	Density of modifier
ρ_{mix}	-	Density of carbon dioxide and modifier mixture
μ	-	Dipole moment
T	-	Temperature
P	-	Pressure
T_c	-	Critical temperature
P_c	-	Critical pressure
ΔH_t	-	Total heat of reaction
ΔH_v	-	Heat of vaporization
ΔH_s	-	Heat of solvation
R	-	Gas constant (8.314 J mol^{-1} K^{-1})
k	-	Coefficient of interaction
D	-	Debye
Å	-	Angstrom
a, b and c	-	Adjustable parameter for correlation model

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Malaysia is one of the 12 mega-diverse countries identified by the United Nations Environment Programme (UNEP) as harboring the majority of the earth's species, which may have immense benefits for future generations (Nasir et al., 2015). More than 15,000 flowering plant species grow in Malaysia, and over 3,000 species have been identified as possible medicinal plants (Muhammad et al., 2011). Natural products have been used as a source of cosmetics, food, and traditional medicines. In recent years, herbal medicine has been gaining more acceptance and attention around the world, and the World Health Organization (WHO) estimates that 80% of the world's population uses herbal medicine. Herbal medicine is a common element in the practice of ayurvedic, homeopathy, and traditional oriented medicine system by using plants for healing purpose. In addition, a variety of herbal products are increasingly available at the Malaysian local market, and many of these herbal products are sold as over the counter medicine.

Plants are the most abundant natural entity on which folklore relies heavily on their pharmacological benefit. Therefore, numerous studies on the plant herbs have been studied extensively, such as *Eurycoma longifolia*, *Labisia pumila*, *Andrographis paniculata*, *Swietenia macrophylla,* and others. The other well-known herb in Malaysia is *Orthosiphon stamineus* (*O. stamineus*), which is used in the present study. *O. stamineus* is a perennial plant that contains a lot of medicinal benefits to humans, belongs to the family of Lamiaceae, also known as misai kucing. *O. stamineus* is natively grown in Southeast Asia, such as Malaysia, Indonesia, Thailand, Myanmar, and others where the leaves of *O. stamineus* are used as herbal tea, commonly known as Java tea.

The notion that *O. stamineus* is widely used for various diseases and disorders such as kidney stones, edema, gout, rheumatism, diabetes, high blood pressure, arthritis, detoxification, and others. Since the 1930s, the research on *O. stamineus* has been conducted extensively to meet its scientific evidence in various aspects. The aspects of phytochemical, pharmacological, toxicological, and clinical based on traditional approaches have been studied. It is approved that, the *O. stamineus* leaves extracts to have anti-inflammatory, antioxidant, antibacterial, antiangiogenetic, diuretic, hepatoprotective, and cytotoxic properties (Lee et al., 2015; Himani et al., 2013; Mohamed et al., 2012; Cicero et al., 2012; Han and Hussin, 2007; Olah et al., 2003). Plant-derived products have a wide variety of secondary metabolites. Adnyana et al., (2013) were found that about 116 secondary metabolites from *O. stamineus* leaves and have been isolated and classified as terpenoids, saponins, flavonoids, polyphenols, phenolic acids, and others. Flavonoids and phenolic acids are the main functional compound obtained in *O. stamineus* about 0.4 to 0.5% and 0.5 to 1.0%, respectively (Ghedira and Goetz, 2015). Hence, sinensetin and isosinensetin which are flavonoids and rosmarinic acid is a phenolic acid are the main interest compounds extracted from *O. stamineus* in this study.

Sinensetin is a rare polymethoxyflavones (PMF) with 5 methoxy groups with carbonyl group being attached to their basic benzo-c-pyrone or flavone. Isosinensetin is an isomer-type PMF of sinensetin, which has a similar molecular weight with a different location of a methoxy group from C6 to C8 in the flavone backbone. On the other hand, rosmarinic acid is a highly valued natural phenolic ester of caffeic acid and 3,4-dihydroxyphenyllactic acid with 4 hydroxyl groups in its structure. These three interest compounds were reported to have high beneficial to human health. Sinensetin was reported to have antidiabetic activity, antiangiogenesis, and diuretic activity (Ameer et al., 2012). Meanwhile, isosinensetin has more potent antiproliferative activity compared to sinensetin (Du and Chen, 2010). Rosmarinic acid is an excellent source of antioxidant activity (Gonçalves et al., 2019).

Traditionally, for processing herbs involves boiling them in water for hours so that most of the ingredients are extracted. While, another similar method consists of the use of conventional organic solvents where the most commonly used organic solvents are ethanol, ether, chloroform, and methanol (Martinez, 2008). The extract consists typically of various compounds, including some undesired substances that dissolve with the desired products. Therefore, further purification steps are necessary to remove the coextracted impurities. In addition, high boiling or extraction temperatures often lead to the degradation of heat-sensitive compounds.

Moreover, traces of toxic solvents are hardly removed from the extracts, which directly influences the quality of the products. Furthermore, the extraction method is not notoriously inefficient were having a low concentration of the bioactive compound relative to the high energy input but expensive due to the treatment of large amounts of organic waste. Therefore, alternative extraction techniques with better selectivity and efficiency are highly desirable to extract the interest compounds (Goyeneche et al., 2018).

The emergence of green chemistry for extraction processes occurred in the 1990s intending to reduce energy consumption and replace the conventional solvents many extraction methods were introduced. High-pressure technology like supercritical fluid extraction (SFE) is a relatively new tool that is growing interest in an alternative technological process. SFE could minimize the environmental impact such as reduced energy consumption, less toxic residues, better quality, and safety of final products (Che Yunus, 2007). SFE of solids and liquids from natural materials is one of the most widely studied in recent years. The unique solvent properties of the SFE process where the operating condition above critical temperature and pressure. Fortunately, the most common solvent used is carbon dioxide (CO_2), known as supercritical carbon dioxide (SC-CO_2). SC-CO_2 has a critical temperature close to ambient conditions of 31.1 ˚C that ideal method for thermolabile compound extraction and mild critical pressure of 7.38 MPa. SC-CO_2 has been successfully used as a green solvent to recover high-value-added compounds from natural plants. CO_2 is considered a non-toxic solvent, and the extract can be used with no further purification steps required.

Besides, the CO_2 molecule has no net dipole moment, $\mu=0$, it is nonpolar and serves as an ideal solvent for natural molecules that are nonpolar. However, it has a quadrupole moment, which it can also dissolve polar molecules but at relatively high pressure. Meanwhile, the interest compounds of sinensetin, isosinensetin, and rosmarinic acid are polar. Therefore, a modification on SC-CO_2 must be done to avoid the extraction process occurred at high pressure. SC-CO_2 is made by adding a small volume of modifiers to increase the polarity of CO_2 and enhanced the solubility of interest compounds (Brachet et al., 2000; Sharif et al., 2015; Chai et al., 2020).

The modifiers that have been studied in the SC-CO_2 process are ethanol, acetonitrile, acetone, methanol, and water. Methanol is the most popular used among the other modifier due to its miscible with CO_2. However, ethanol is a better choice for the extraction of natural products because of its lower toxicity. Generally, about 1 to 15% of modifiers were used in the SC-CO_2 process (Pereira and Meireles, 2010). On the other hand, the modifier could distort and swell the plant matrices as a consequence, favouring the penetration of CO_2 into the plant matrices for extracting the solute or interest compounds (Casas et al., 2007).

Several parameters were investigated in SC-CO_2 extraction, which categorized as chemical and mechanical factors. Chemical factors were affected by temperature and pressure, while mechanical factors were affected by particle size, flow rate, modifier, and extraction time. Solubility is an indispensable parameter for the successful design of SC-CO_2 techniques. The solute solubility in SC-CO_2 mostly affected by two competing chemical parameters of vapour pressure, which is temperature dependence and density, which is pressure dependence. In addition, solute solubility data at various temperatures and pressures is tedious and time-consuming. Thus, correlations by using mathematical models of the solute solubility can be used to predict the solute solubility at any conditions of SC-CO_2.

Equation of State (EOS) like Soave-Redlich-Kwong and Peng-Robinson have been widely used to calculate and correlate the solubility of solutes in supercritical carbon dioxide (SC-CO_2). However, the EOS required solute properties data such as critical properties, acentric factor, molar volumes and vapour pressure, which are

limited sources of this information. In addition, large deviations between experimental and calculated solubilities were obtained from EOS due to an error in sublimation pressure about 15.3 to 35.1% of error (González et al., 2001). Hence, semi-empirical models are well known for their simplicity; there is no need to use physicochemical properties of solute. The first semi-empirical density-based model for solubility correlation in SC-CO_2 was proposed by Chrastil (Chrastil, 1982), and some modification has been done by del Valle and Aguilera (del Valle and Aguilera, 1988).

In addition, the solubility of global yield in SC-CO_2 has been reported widely; however, the solubility can be affected by molecular interactions between solutes where the extract yield consists of a mixture of interacting solutes. Thus, the solubility of extract yield does not express the solute solubility. These are due to the molecular interactions are attractive or repulsive forces between molecules which involve solute-solute interactions and solute-solvent interactions. The solute-solute interactions are the intermolecular attractions between solute molecules, which related to the properties of a solute such as molecular weight, dipole moment, melting point, and functional compound. Meanwhile, the solute-solvent interactions are intermolecular attractions between solute and solvent molecules, which explained as solubility. The interactions that may involve in the molecular interactions are Van der Waals forces, dipole-dipole interactions, induced-dipole interactions, London dispersion forces, and hydrogen bonding. Therefore, the proposed models can predict an intermolecular interaction in SC-CO_2 based on the coefficient of interaction, k value where the competing effect of the solvent to dissolve the solute can be determined.

1.2 Problem Statement

SC-CO_2 extraction is known as environment-friendly and generally regarded as a safe solvent by the Food Drug Administration (FDA) to extract natural product. However, there are various parameters to be considered in SC-CO_2 extraction which can be categorized as chemical (temperature and pressure) and mechanical factors (mean particle size, modifier ratio, flow rate, extraction time). The temperature and pressure are the most importance parameters in SC-CO_2 extraction where by

manipulation of temperature and pressure the properties of SC-CO_2 changes and cause the increase or decrease the extraction efficiency. To date, most of the researchers combine the chemical and mechanical factors in SC-CO_2 extraction of natural products however, it turns out that the mechanical factors gave insignificant effect toward the extraction efficiency.

In SC-CO_2 extraction of natural products, the solubility data is a crucial parameter needs to be determined so that the overall extraction behaviour can be explained. To date, most of the researchers' study on the solubility of the extract yield from natural plants. However, the solubility of extract yield does not represent the solute solubility due to the mixture of interacting solutes that strongly affect the solubility. Besides, the recent solubility data of solute in SC-CO_2 were reported on the pure component based on the cloud point calculation where the most preferrable method on the calculation of the solubility is determine its constant extraction rate phase or dynamic method. To date, there is no study was reported on the solubility of solutes extracted from the natural plant by dynamic method.

In addition, the solubility data in SC-CO_2 extraction is strongly affected by manipulation of the chemical parameters. However, the effect of intermolecular interaction on the solubility is less focused by the other researchers. Determination of solute solubility at various operating conditions is time-consuming; thus, a mathematical model of Chrastil and del Valle-Aguilera can be applied. The models can be used to predict the solute solubility as well as the interactions that occurred in the process by referring to the coefficient of interaction, k. In addition, the thermodynamic data of solutes on the enthalpy of solvation and vaporization in SC-CO_2 can be calculated from the correlation models.

The solubility data of sinensetin, isosinensetin, and rosmarinic acid in SC-CO_2 extraction is still scarce. Sinensetin, isosinensetin and rosmarinic acid are main and potent bioactive compounds can be obtained from *O. stamineus*. The compounds have been proved that gives a lot of health benefit to the human being. In addition, *O. stamineus* is widely available in Southeast Asia especially Malaysia and has been listed in National Key Economic Area (NKEA) development program to produce a high

value of a product from local herbs where it is an opportunity to market our local herbs products to the world. The possibilities of the product sources of *O. stamineus* leaves extract are tablets, capsules, tea sachets, and others. Thus, the green extraction process such as SC-CO_2 extraction is necessary to produce a high quality of products.

1.3 Research Objectives

Based on the preceding challenge and issues, this study is centred on the following objectives:

(a) To determine the effect of the ethanol assisted SC-CO_2 conditions on the concentration of sinensetin, isosinensetin and rosmarinic acid from *O. stamineus* leaves

(b) To optimize the ethanol assisted SC-CO_2 conditions on the concentration of sinensetin, isosinensetin and rosmarinic acid using response surface methodology

(c) To evaluate and correlate the solubility of sinensetin, isosinensetin, and rosmarinic acid in ethanol assisted SC-CO_2 using semi-empirical density-based models

(d) To investigate the effect of solute molecular properties on the solubility of sinensetin, isosinensetin and rosmarinic acid based on the intermolecular interaction of solute-solute and solute-solvent interactions

1.4 Research Scope

The scopes of this research are:

i. Preliminary of mechanical parameters were studied on mean particle size, modifier ratio, flow rate and extraction time. Thus, the determination of ideal mechanical parameters was conducted at various mean particle size from 400 to 650 µm, modifier composition from 0 to 10 v/v%, the flow rate from 3 to 5 mL/min and extraction time was fixed at 4 hours extraction

ii. Chemical parameters of temperature and pressure were investigated on the extraction of sinensetin, isosinensetin and rosmarinic acid from *O. stamineus* leaves using SC-CO_2 extraction. The extraction was performed in the range of 40 to 80 °C and 10 to 30 MPa for temperature and pressure, respectively

iii. Identification and quantification of sinensetin, isosinensetin and rosmarinic acid extracted from *O. stamineus* leaves by using high-performance liquid chromatography (HPLC)

iv. Optimization of the extraction conditions for the sinensetin, isosinensetin and rosmarinic acid concentration using Design Expert software 11 with face-centered central composite design

v. The solubility of the sinensetin, isosinensetin and rosmarinic acid was calculated by a dynamic method. Meanwhile, the correlation of solutes solubility was performed by the semi-empirical model of Chrastil and del Valle-Aguilera model

vi. The solutes molecular properties of sinensetin, isosinensetin and rosmarinic acid were predicted using the group contribution method by ICAS software and computational chemistry methods by Gaussian 09 software

vii. The effect of intermolecular interactions on solubility was determined as a function of solute properties like melting point, molecular weight, dipole moment and functional compound

viii. Coefficient of interaction, k from the correlation models was established to predict the intermolecular interactions either solute-solute interaction or solute-solvent interaction in the process

ix. The enthalpy of vaporization (ΔH_v) and solvation (ΔH_s) were calculated from the coefficient parameter of a from the correlation models.

1.5 Significance of Research

The main contribution of this study is the solubility data of flavones which is sinensetin and isosinensetin, and phenolic acid which is rosmarinic acid from *O. stamineus* in ethanol assisted SC-CO_2 extraction. To obtain the solubility data, several contributions has been achieved. First, the best extraction conditions of ethanol assisted SC-CO_2 was obtained at a maximum concentration of sinensetin, isosinensetin and rosmarinic acid from *O. stamineus* leaves. The SC-CO_2 extraction with ethanol assisted was enhanced the concentration of sinensetin, isosinensetin and rosmarinic acid from *O. stamineus* leaves compared with conventional extraction method is considered as a new finding since there is no available articles were reported. In addition, the chemical parameters of SC-CO_2 extraction showed a significance effect on the extraction of sinensetin, isosinensetin and rosmarinic acid from *O. stamineus* leaves.

Next, the competing effect between sinensetin, isosinensetin and rosmarinic acid in SC-CO_2 extraction can be observed by variations of solubility data at different extraction conditions. In addition, there is another element that could affect the solute solubility in SC-CO_2 that has less attention by other researchers which is intermolecular interactions such as solute-solute and solute-solvent interaction. Besides, the semi-empirical models also play an important role in this study to correlate the solubility data of solute as well as to predict the interactions occur in the SC-CO_2 system by the coefficient of interaction, k. The models used also can provide the thermodynamic data of solute such as enthalpy of vaporization and solvation. Apart from that, the available data from the present study is useful in scaling up and economic evaluation of industrial SFE processes.

1.6 Limitation of Study

The limitation of this study could be highlighted based on the extraction process parameters. The targeted compounds in this study were sinensetin, isosinensetin, and rosmarinic acid are polar compounds. Meanwhile, CO_2 is a nonpolar but has large quadrupole moment which can interact with polar molecules but at very high pressure. Thus, the modification on the SC-CO_2 extraction by adding a small amount of modifier is required to avoid the extraction process occurred at very high pressure to extract the targeted compounds. Since the polarity of CO_2 has been enhanced, the maximum ethanol assisted SC-CO_2 conditions of 30 MPa is satisfied. In addition, CO_2 has a low latent heat of vaporization that led to less energy needed for the extraction process. Therefore, the maximum temperature of 80 °C is sufficient to extract the interest compounds even though their melting point is over 100 °C.

Besides, for the software used in this study were ICAS and Gaussian 09. The ICAS software is able to predict the properties of solute based on the group contribution method, thus the properties of sinensetin and isosinensetin are the same due to similar functional group on the structure. Meanwhile, the Gaussian 09 software is only able to optimize the interactions of two similar molecules. The latest version of the software is not available yet which could help to improve the data.

1.7 Thesis Outline

Overall, this thesis consists of 5 chapters. Chapter 1 began with an introduction to the research project. This chapter included the background of the research, problem statement, objective of the research, the scope of study, significant study and limitation of the research. A brief introduction of this research was explained on the *O. stamineus* and its interest compounds, SC-CO_2, solubility models and intermolecular interactions.

In Chapter 2, the literature review describes the fundamental theory and application used in this study. The chapter includes previous studies on the SC-CO_2 extraction process and the fundamental behind the process. In addition, it also provides an overview of the sample of *O. stamineus* leaves and interest compounds of sinensetin, isosinensetin and rosmarinic acid. Besides that, the chapter also describes an overview of response surface methodology (RSM). The molecular interactions were discussed in the chapter. The overview of Chrastil and del Valle-Aguilera also describes in the chapter.

Chapter 3 discusses in detail on the research methodology used for SC-CO_2 extraction of *O. stamineus*. The pre-treatment of the sample and the determination of constant mechanical parameters were discussed. In addition, the comparison of the method of extraction between SC-CO_2 and Soxhlet extraction was discussed. The solute properties were predicted using Gaussian 09 and ICAS software was explained in this chapter. The HPLC analysis was conducted to quantify the concentration of sinensetin, isosinensetin and rosmarinic. In addition, response surface methodology using central composite design was discussed in this chapter.

In Chapter 4, the results and discussion obtained from the process conducted in Chapter 3 are described briefly. The results from the pre-treatment process are presented first, followed by the comparison of the extraction method. Next, the effect of extraction condition on the concentration of interest compounds is discussed. Then, the optimization of the operating conditions on the concentration of interest compounds was presented with the best extraction conditions. The solubility of

sinensetin, isosinensetin and rosmarinic acid was illustrated and correlated with the semi-empirical model of Chrastil and del Valle-Aguilera. The effect of intermolecular interactions on the solubility of solutes also discussed. Lastly, the enthalpy of vaporization and solvation of the solutes was obtained from the correlation models.

The conclusion in Chapter 5 answers all the objectives stated in Chapter 1. Recommendations are also provided for future work and improvement.

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