OPTIMIZATION AND CORRELATION OF *PIPER BETLE* LEAVES EXTRACTION USING SUPERCRITICAL CARBON DIOXIDE

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DEDICATION

This thesis is specially dedicated to my parents Arsad Bin Abu Hassan and Almarhummah Nopipah Binti Abdul Rahman, parent-in-law, Baba Bin Yaacob and Sarbiah Binti Omar, husband, Syarizal Iqbal Bin Baba, children, Nur Hana and Syah Imran, siblings, Hilmi, Nur Adibah, Norlin, Mohd Fairus, Hizami, Salmah, Hibri, Siti Nadhirah, Nur Fiqin, Muhammad Akmal and Almarhum Haziq bin Arsad and to all who supported me through their love, prayer and work.

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ABSTRACT

Piper betle leaves, which contains a high level of eugenol, is abundantly grown and distributed in many Asian countries. Eugenol is an important principal phytochemical found in betel leaves. Interestingly, structure of eugenol consists of polar bond and non-polar bond which indicates that eugenol is a slightly polar compound. However, because the extraction solvent, carbon dioxide (CO_2), is non-polar in nature, making it superior in extracting non-polar compounds, a modification to the supercritical fluid extraction (SFE) processing parameter is required to make it universal to the extraction of mild to highly polar compounds. An experimental investigation was conducted to explore the oil extracted and concentration of Eugenol by manipulating the supercritical carbon dioxide (SC-CO_2) process parameters which were pressure of 10 MPa to 30 MPa, temperature of 40 ^oC to 70 ^oC and flow rate of 4 mL/min to 8 mL/min, at constant mean particle size of 302.5 μm with extraction time of 210 minutes. The optimum condition and the most influential SC-CO_2 process conditions were investigated using the response surface methodology. Two established solubility models, including the Chrastil and the Del Valle and Aguilera were applied to describe the solubility behaviour. Furthermore, the mathematical model formulation and validation were employed for describing the mass transfer phenomena of *Piper betle* leaves oil. However, a reliable model that involves quantitative analysis of fluid flow phenomena is needed to explore the relationship between flow rate, temperature and pressure concurrently. Two models, namely Hot ball model and Lee BC model were used to obtaine diffusion coefficient and overall mass transfer coefficient data. Mass transfer correlation of *Piper Betle* leaves oil was also established to describe the behaviour of mass transfer of solute in SC-CO_2 process condition with relation to the fluid flow. The maximum extraction yield (361 mg) and eugenol concentration (102.5 mg/g extract) were obtained at 10.16 MPa, 40.12°C and 8 mL/min, respectively. It was proven that interaction term between flow rate and pressure was the significant factors required to achieve high yield extract, whereas the interaction term between flow rate and temperature gave the significant impact to obtain high eugenol. In solubility study, the Chrastil model offered the best fitting to correlate the solubility data of *Piper betle* leaves extract with the lowest percentage of average absolute relative deviation (%AARD) of 5.72% at the highest CO_2 flow rate. The coefficient values of k at flow rate of 4, 6 and 8 mL/min were 0.17, 0.26 and 0.75, respectively. It is hence believed that the solvation power of SC-CO_2 was higher at high flow rate to increase the solubility of *Piper betle* extract. Furthermore, the diffusivity was obtained in the range of 0.3101×10^{-13} to 1.1240×10^{-13} m^2/s. The overall mass transfer coefficient obtained was from 5.3535×10^{-8} to 23.5560×10^{-8} m/min. The mass transfer correlation model based on the dimensionless number of Reynolds, Sherwood and Schmidt was successfully established with the correlation of determination (r^2) of 0.9987. The model equation established was $Sh = 0.0051ReSc^{1/3}$. The overall mass transfer coefficient was found to be strongly correlated between the observed and predicted data with r^2 of more than 0.9 at the significant level of 0.05. The results of this study revealed that that the flow rate plays an important role along with pressure and temperature in supercritical fluid extraction process.

ABSTRAK

Daun sirih yang mengandungi kandungan eugenol yang tinggi banyak ditanam dan tumbuh meluas di negara Asia. Eugenol adalah fitokimia utama yang terdapat dalam daun sirih. Menariknya, struktur eugenol terdiri daripada ikatan polar dan ikatan bukan polar yang menjadikannya sebagai sebatian separa polar. Namun, di sebabkan karbon dioksida (CO_2) yang digunakan sebagai pelarut pengekstrakan adalah bersifat tidak polar, yang mana menjadikannya lebih unggul dalam mengekstrak sebatian bukan polar, maka pengubahsuaian pada parameter pemprosesan pengekstrakan bendalir lampau genting di perlukan untuk menjadikannya sesuai dalam mengekstrak sebatian separa polar sehingga sangat polar. Penyelidikan eksperimental telah dijalankan untuk meneroka hasil minyak yang diekstrak dan kepekatan Eugenol dengan memanipulasi parameter proses pengekstrakan karbon dioksida lampau genting (SC-CO_2) pada tekanan, suhu dan kadar aliran masing- masing di antara 10 MPa sehingga 30 MPa, 40 ^{o}C sehingga 70 ^{o}C dan 4 mL/min sehingga 8 mL/min, pada ukuran garispusat 302.5 μm dengan masa pengekstrakan selama 210 minit. Keadaan yang optimum dan parameter yang paling mempengaruhi proses SC-CO_2 dikaji dengan menggunakan kaedah gerak balas permukaan. Dua model kelarutan yang mantap, termasuk model Chrastil dan Del Valle dan Aguilera digunakan untuk menggambarkan kelarutan. Seterusnya, formulasi dan pengesahan model matematik digunakan untuk menerangkan fenomena pemindahan jisim minyak daun sirih. Walau bagaimanapun, model yang melibatkan analisis kuantitatif fenomena aliran bendalir diperlukan untuk meneroka hubungan antara kadar aliran, suhu dan tekanan secara bersama. Dua model, iaitu model ‘Hot Ball’ dan ‘Lee BC’ digunakan untuk memperoleh pekali resapan dan data pekali pemindahan jisim keseluruhan. Model korelasi pemindahan jisim minyak daun sirih juga dihasilkan untuk menggambarkan tingkah laku pemindahan zat terlarut dalam proses SC-CO_2 berkaitan dengan aliran bendalir. Hasil pengekstrakan maksimum (361 mg) dan kepekatan eugenol (102.5 mg/g ekstrak) masing-masing diperoleh pada 10.16 MPa, 40.12 °C dan 8 mL/min. Dalam kajian kelarutan, model Chrastil memberikan data yang paling sesuai untuk menghubungkan data kelarutan ekstrak daun sirih dengan peratusan sisihan relatif mutlak terendah (% AARD) iaitu 5.72% pada kadar aliran CO_2 tertinggi. Nilai pekali k pada kadar aliran 4, 6 dan 8 mL/min ialah masing-masing 0.17, 0.26 dan 0.75. Oleh itu, didapati bahawa daya pelarutan SC-CO_2 lebih tinggi pada kadar aliran tinggi untuk meningkatkan kelarutan ekstrak sirih. Selanjutnya, daya resapan diperolehi adalah di antara 0.3101×10^{-13} hingga 1.1240×10^{-13} m^2/s. Pekali pemindahan jisim keseluruhan yang diperoleh adalah dalam lingkungan antara 5.3535×10^{-8} hingga 23.5560×10^{-8} m/min. Model korelasi pemindahan jisim berdasarkan nombor tak berdimensi seperti Reynolds, Sherwood dan Schmidt berjaya dihasilkan dengan korelasi penentuan (r^2) 0.9987. Persamaan model yang di hasilkan ialah $Sh=0.0051ReSc^{1/3}$. Pekali pemindahan jisim keseluruhan didapati sangat berkorelasi dengan data yang diperhatikan dan diramalkan dengan r^2 lebih daripada 0.9 pada tahap signifikan 0.05. Hasil kajian ini menunjukkan bahawa kadar aliran memainkan peranan penting bersama dengan tekanan dan suhu dalam proses pengekstrakan bendalir lampau genting.

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LIST OF ABBREVIATIONS

SFE	-	Supercritical Fluid Extraction
CO_2	-	Carbon Dioxide
SC-CO_2	-	Supercritical Carbon Dioxide
RSM	-	Response Surface Methodology
HPLC	-	High-Performance Liquid Chromatography
%AARD	-	Percentage of Average Absolute Relative Deviation
CER	-	Constant Extraction Rate
GRAS	-	Generally Recognized as Safe
LLE	-	Liquid-Liquid Extraction
FER	-	Falling Extraction Rate
SDE	-	Simultaneous Distillation Solvent Extraction
GC/MS	-	Gas Chromatography/Mass Spectrometry
w/w	-	Weight by weight
v/v	-	Volume by volume
HB	-	Hot Ball
LBC	-	Lee B.C
MTC	-	Mass Transfer Correlation
N_{Sc}	-	Schmidt number
N_{Re}	-	Reynolds number
N_{Sh}	-	Sherwood number
ANOVA	-	Analysis of Variance
SSR	-	Sum of Square Regression
SSE	-	Sum of Square Error
SST	-	Sum of Square Total
mAU	-	milli-Absorbance Units
FDA	-	Food and Drug Administration

LIST OF SYMBOLS

^{o}C	-	Degree Celcius
MPa	-	Mega Pascal
R^2	-	High coefficient of determination
T_c	-	Critical temperature
P_c	-	Critical pressure
g	-	Gram
mL/min	-	Mili litre per minit
D_e	-	Diffusion coefficient
ρ	-	Density
µm	-	Micrometer
%	-	Percentage
M_c	-	Moisture content
W_{oil}	-	Weight of extracted oil
T	-	Temperature
P	-	Pressure
f	-	Flow rate
K	-	Overall mass transfer coefficient
A_p	-	Specific surface area
m	-	Metre
mg	-	Milligram
t	-	time
C	-	Concentration
kg	-	kilogram
s	-	Second
V	-	Velocity
D	-	Diffusivity
h	-	Length or diameter of column
Sh	-	Sherwood
Re	-	Reynolds
Sc	-	Schmidt

v	-	Volume
Y_{exp}	-	Solubility data from experimental
Y_{calc}	-	Solubility data from model
dp	-	Particle size
η	-	Viscosity of solvent
Bi	-	Biot number
ΔH_{solv}	-	Heat of salvation
ΔH_{vap}	-	Heat of vaporization
k	-	Equilibrium constant
r, R	-	Radius of particle
$C_{10}H_{12}O_2$	-	2-methoxy-4-(prop-2-en-1-yl) phenol
cm	-	Centimeter
mmHg	-	millimetre of mercury
Wt%	-	Weight percent
nm	-	Nanometre

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

Medicinal plants play a golden role by providing for use as cosmetic substances, source of food, and ancient medicines. Undoubtedly, these plants should be employed in the discovery of a more natural, sustainable, and affordable source of medication in the primary health care system due to the wide diversity of bioactive compounds (Jamshidi-Kia, Lorigooini and Amini-Khoei, 2018). *Piper* species are estimated to contained 4,000 species (Nakatani *et al*., 1986), among the estimated of 250,000-500,000 plant species (Mahesh and Satish, 2008) and the most distributed in the world is *Piper Betle Linn.* (Family: *Piperaceae*). The *Piper betle* plant is a perennial dioecious and semi-woody climber with glossy and heart-shaped leaves flourishes in warm and humid environments and can grow up to one meter in length (Bajpai *et al.,* 2010). The leaves are recognized as "Green Gold" due to its colour and it is widely used in Malaysia, Thailand, India, Sri Lanka, Taiwan and others southeast Asian countries (Devjani and Barkha, 2011) especially in the improvement of oral health (Ali *et al*., 2010).

Given that it is a cheap and readily accessible plant, various parts of the *Piper betle* plant are used in traditional medicine for treatment of several conditions such as constipation, conjunctivitis, itches, rheumatism and abrasions (Choudhary et al., 2002; Valentao *et al.*, 2010). It has been suggested that the main compound that contributed to its medicinal properties was Eugenol (Dubey and Tripathi, 1987; Beuchat *et al.*,1989; Cowan, 1999; Rodiah *et al.,* 2020). Eugenol is a phenylpropene, an allyl chain-substituted guaiacol and a member of the phenylpropanoids class of chemical compounds with colourless to pale yellow oily liquid. This fairly soluble in water and organic solvents which can categorized as a slightly polar compound. Eugenol is considered as versatile molecule used as an ingredient in various products including pharmaceutical, food industry, fragrance, flavour, cosmetics. To date, the food industry is moving towards the application of eugenol in food preservation owing to its antimicrobial properties. The rise in foodborne diseases worldwide also have been driving the demand for eugenol to be used as ingredients effective preservation strategy. Thus, an effective extraction process for eugenol production is important in ensuring that this compound is feasible to its clinical or pharmaceutical application.

Separation procedures are critical in the processing of biomaterials. Because the density of supercritical fluid is closer to that of liquids and its viscosity is low, equivalent to that of gases, it exhibits ideal transport qualities that boosted its adaptability as a solvent for liquid extraction procedures. As a result, supercritical fluid extraction (SFE) technology has been used to improve high-quality products and reduce the amount of solvent required, where the supercritical fluid's high density contributes to a high diffusivity equivalent to that of liquids, resulting in faster solute particle dissolution in solvent. Thermally labile, lipophilic, non-volatile biological products are frequently required to be maintained and processed at room temperature. Thus, this study focuses on supercritical carbon dioxide (SC-CO_2) as the extracting solvent because it has a near ambient critical temperature (31.1 °C), making it a particularly appealing medium for the extraction of biological materials. The key features of SC-CO_2 extraction are its ability in manipulating the dissolving power of CO_2 towards targeted compounds by using appropriate parameters condition. SC-CO_2 extraction also offers the major advantage in term of producing high purity and high selectivity extracts. These have made supercritical fluid technology a primary alternative for the extraction and fractionation of active ingredients compared to traditional solvent extraction such as steam distillation, water extraction, evaporation and spray drying methods that was not sufficient to achieve the exact separation between the desired and the undesired compounds (Mohd, 2007).

SC-CO_2 however has limitation to this study compound of interest since it is more suitable for extraction non-polar compounds. In generally, in order to extract mild polar to polar compound from leaves using SC-CO_2 extraction process, additional co-solvent is needed to enhance the extraction rate (Sato *et al.,* 2019; Uquiche *et al.,* 2019; Kumoro *et al.,* 2019; Moura *et al.,* 2012). Although several studies have shown the potential of chemical parameters for example pressure, temperature and modifier concentration in SC-CO_2 extraction as an efficient tool to alternate the chemical properties of SC-CO_2 however studies on the effect of mechanical parameters such as fluid flow rate, sample particle size, extraction time and extractor diameter to length ratio in SC-CO_2 extraction are currently limited. This study therefore focuses on the both chemical and mechanical parameters of SC-CO_2 extraction that can be manipulated so that mild polar compound such as eugenol can be extracted. This is also due to the critical requirement in many countries which have restricted the use of organic solvents such as ethanol, methanol and hexane due to their safety, health and environmental related issues.

SC-CO_2 extraction is favoured due to its high selectivity, high efficiency, and short extraction time. Thus, factors influencing the SC-CO_2 extraction process can be adjusted for a dual purpose to improve the extraction efficiency and/or selectivity. Pressure and temperature are predominant during the SC-CO_2 extraction process design and make them influential on both equilibrium and kinetics as well as to control the density and solvating power of CO_2 (Pascaline *et al.*, 2020). In addition, the flowrate of CO_2 can reduce the external mass transfer resistances, which normally occurs during constant extraction rate (CER). CER is characterized as the extraction of solute on the surface of the sample matrix. It is controlled by the mass transfer dependence to flow rate of CO_2. Previous studies have showed that the effect of flow rate of CO_2 did not significantly enhance the extraction rate or yields (Zaouali *et al.*, 2010). However, the effect of flowrate of CO_2 has been noted in several research works related to the extraction of oil in leaves; in which an increment of the oil's quality correlated to solvents flow rate are evidenced (Svetlana *et al.*, 2011). Currently, the understanding of solvent flowrate effects to supercritical carbon dioxide mechanism process are still limited. Therefore, mathematical models are used as a tool to investigate the mechanism of supercritical CO_2 extraction process and its conditions that will be beneficial in understanding the scientific and fundamental of the process.

The mathematical modelling for supercritical can be formulated by application of differential equation principle and dimensionless analysis. The process developing mathematical modelling equation is very complex because according to Alonso *et al.*

(2002), in spite of complexity of differential equation, some assumption must be made because most of the equation attempt to analyse data only during steady state conditions. Consequently, since supercritical fluid extraction phenomena is in unsteady state, the result obtained will affect the simulation of conditions since the solution are approximated in the steady state. For this reason, there will be limitation to the quantitative analysis of SC-CO_2 fluid flow phenomenon. Therefore, the mathematical modelling correlated to the fluid flow phenomena is needed so that better understanding on the parameters that may affect SC-CO_2 fluid flow can be anticipated.

In addition, it is also essential to understand the relationship of average transfer rates (mass, heat, momentum) and applied forces that are used to drive the transport such as concentration difference, temperature difference and velocity difference. In SFE, this type of mathematical modelling can be developed by using dimensionless analysis which are known to be powerful tool in establishing a correlation of relating dimensionless numbers to the mass transfer like Sherwood number, Schmidt number and Reynolds number.

The Reynolds number is defined as the ratio of convective transport of momentum due to the fluid velocity and diffusive transport caused by momentum diffusivity. Meanwhile, the Schmidt number is the dimensionless combination of the diffusivity, viscosity and density while the dimensionless group for mass transfer is the Sherwood number. Empirical correlations for forced convection of heat and mass transfer usually relate the dimensionless fluxes that represent by Sherwood number, Reynolds number that related to ratio of convection and momentum diffusion and Schmidt number that represent ratio of momentum and mass diffusion. Therefore, dimensionless analysis is another approach to formulate mass transfer correlation coefficient data for SC-CO_2 fluid flow phenomena. This analysis involved formulating dimensionless numbers that describe the behaviour or phenomena of SC-CO_2 fluid flow Problem Background.

1.2 Problem Statement

Eugenol was identified as the principal compound that contributed to its anti-microbial property. The demand for nit-picking requirements for industrial commercialization appealing to any food materials to be labelled as “generally recognized as safe” (GRAS) as the food industry is moving towards the application of eugenol in food preservation. Thus, an effective extraction process for eugenol is crucial in employing to the industries application. SC-CO_2 extraction is one of the best techniques for extracting bioactive compounds, and it represents a sustainable alternative to traditional extraction systems due to its significant benefits, such as higher selectivity, diffusivity, and ecology. However, CO_2 is non-polar in nature, which make it an outstanding green solvent to extract non-polar compounds but not for polar compounds and mild polar compounds. Eugenol is categorized as a slightly polar compound and CO_2 solvent was able to extract both, the polar and non-polar compounds at the higher SC-CO_2 extraction conditions or with the additional of organic solvent. To prevent the used of organic solvent, the additional of flow rate as a parameter could significantly enhance the yield and quality of extract by improving the polarity of CO_2.

The feasibility of the SC-CO_2 extraction method may be determined by utilising well-known models to estimate the solubility behaviour and mass transfer mechanism of the interesting solute. However, the quantitative analysis of fluid flow phenomena has limitations because most differential equation models ignore the behaviour of the mass transfer of solute in SC-CO_2 in connection to the fluid flow. Therefore, a credible model is required to assist the application of supercritical fluid in natural product extraction in terms of scaling up and process design. In order to solve this issue, several objectives have been identified.

1.3 Objectives

The objectives of this study were:

(a) To determine the effect and the optimum SC-CO_2 extraction conditions on the *Piper betle* leave oil yield and its eugenol concentration.

(b) To investigate the solubility of *Piper betle* leaves oil in CO_2 fitted in the solubility based mathematical equations.

(c) To correlate the mass transfer coefficient using dimensionless analysis approach.

1.4 Scope of Research

The scopes of this research according to the objectives were:

a1) Conditioning the raw material process involving *Piper betle* leaves preparation and constant parameters such as moisture content, extraction time and particle size was studied to obtain the optimum value.

a2) Extraction of *Piper betle* leaves was performed using supercritical CO_2 extraction at pressures (10 - 30 MPa), temperatures (40 - 80°C) and flow rate of CO_2 (4 - 8 mL/min).

a3) Identification and quantification of eugenol concentration using High Performance Liquid Chromatography (HPLC) by overlaying the peak area obtained with the eugenol standard.

a4) The most significant process parameters (pressure, temperature and CO_2 flow rate) studied were determined using Response Surface Methodology (RSM).

b1) Determination of experimental solubility data from the slope at the fitted point in graph plotting experimental data of mass of oil extracted against the mass of CO_2 used using excel.

b2) The description of solubility model constants value (a, b, c and k) at different operating condition using two density-based solubility equations were Chrastil and del Valle-Aguilera equations.

c1) Determination of diffusion coefficient using hot ball model and overall mass transfer coefficient using Lee BC model for extraction of *Piper betle* leaves.

c2) The mass transfer correlation of *Piper betle* leaves extract was established from general correlation expression with respect to dimensionless numbers namely Sherwood, Schmidt and Reynolds.

c3) The best of mass transfer correlation data was evaluated based on the percentage of average absolute relative deviation (%AARD), Pearson correlation and high coefficient of determination (R^2).

1.5 Research Contribution

The main aim of this study was to better understand the conceptual of Supercritical CO_2 extraction on *Piper Betle* leaves and to distinguish the importance of its essential operating parameters in order to efficiencies the process and its entails on the oil yield and eugenol concentration. With that, the extraction of slightly polar compound such as eugenol using solely CO_2 solvent shows that the parameters involved can enhance the solvating power of CO_2 without using modifier.

From its application point of view, governing by the needs to enhance the extraction efficiency, the comprehensive design of Supercritical CO_2 extraction process and its fundamental of mechanism in the process to access high quality and quantity of valuable compounds in *Piper Betle* leaves. This will be useful in scaling up of industrial SFE processes. The establishment of mass transfer correlation model which relates to Sherwood, Schmidt and Reynolds number under the influence of supercritical conditions for extracting *Piper betle* leaves can therefore broaden the understanding of the behaviour or effect of extract yield, the properties of fluid flow and the problem that may limit the transport and separation process.

1.6 Limitation of study

The limitation of this study is the operating pressure and flowrate of the SC-CO_2 equipment since it has to be set at 30MPa (maximum) and flow rate of 8 mL/min to maintain the condition of the SC-CO_2 equipment and the pumps used, while the temperature was 80 ^oC. Although, the boiling point of eugenol is 255 °C, the eugenol can be damaged at temperatures more than 90 °C (Maheshwari, 2016). This is due to the thermo labile effect of eugenol. Furthermore, the minimum mean particle size was restricted to 302.5 µm to prevent the sample from forming a concrete lump that will eventually block the flow of solvents in the extraction cell (Ruslan *et al.*, 2015).

1.7 Thesis Outline

This is divided into five chapters. Chapter 1 begins with the introduction to the research project which covers brief introduction to supercritical fluid extraction, eugenol as the bioactive compound of *Piper betle* leaves and mathematical models in this study. This chapter also includes the problem statements that motivates this research, the objectives, scopes and significance of this study.

Chapter 2 presents an overview of the pharmacology properties of the *Piper betle* leaves. This chapter also describes the fundamental theory of supercritical fluid extraction, chemical and physical properties. It also presents the selection of extraction conditions and solvents, as well as reviews on previous research studies related to the topic of the study. The response surface methodology (RSM) and modelling of SC-CO_2 extraction are also reviewed in this chapter.

Chapter 3 is describing the detailed methodology used to achieve the research objectives. The experimental work for the extraction process, compound analysis and biological analysis are mentioned as a guideline for this research. The design of experiments is also presented in this chapter.

Chapter 4 is discussed in two different parts. The first part presented the findings through experimental work including the effects of operating conditions on the extracted yield and eugenol concentration. The mathematical models of solubility behaviour are discussed in the latter part.

Finally, Chapter 5 highlights the conclusions and recommendations of the work. The conclusions are made based on the results and discussion in Chapter 4. Few recommendations on the guidance and improvement for future work related to the modified SC-CO_2 extraction and *Piper betle* leaves are also addressed in this chapter.

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