KINETIC PROPERTIES ON SUPERCRITICAL CARBON DIOXIDE EXTRACTION OF CHARANTIN FROM *MOMORDICA CHARANTIA* L. WITH CO-EXTRACTANT

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A thesis submitted in fulfilment of the
requirements for the award of the degree of
Doctor of Philosophy

School of Chemical and Energy Engineering
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OCTOBER 2019

To my beloved family and friends

ACKNOWLEDGEMENT

"In the Name of Allah, the Most Merciful and the Most Gracious"
Without His guidance and permission, the completion of this thesis is impossible.

I wish to express my gratitude towards my supervisor, Assoc. Prof. Dr. Mohd Azizi Che Yunus and co-supervisor, Dr. Ana Najwa Mustapa for their guidance in completing my study. I am also very thankful to the Centre of Lipids Engineering & Applied Research (CLEAR) staff, Mrs Noor Sabariah Mahat and Mrs Zuhaili Idham for helping me with the equipment in the lab and other matter regarding my study in UTM. Not to forget the Post-Doctoral staff, Dr. Lee Nian Yian and Dr. Helen Kong as well as other postgraduate students, Salsabila, Diyana, Husnina, Faadila, Hazim, Syahmi and Nicky for their helpful hands, constructive comments and ideas regarding my research.

I also would like to extend my sincere gratitude to the people who help me with the mathematical modeling section, Dr. Hasmida Mohd Nasir and Dr. Izni Atikah Abd Hamid. In addition, I would like to thank my siblings, close friends as well as other people who have been helping me throughout this journey with or without their knowledge.

Lastly, my utmost greatest gratitude goes to my beloved parents, Hajah Zauyah Haji Awang and Haji Aris Haji Tongah who supported me through thick and thin, emotionally and financially. Without them, I would be a nobody. Thank you and I love you both so much.

ABSTRACT

Charantin is a bioactive compound in bitter gourd (*Momordica charantia*) fruit that has been claimed to be able to lower blood glucose level in type 2 diabetes mellitus patient. Its unique dual polarity compound and larger molecular weight makes it difficult to be extracted using conventional extraction method such as Soxhlet and water extraction. The aim of this study is to extract charantin from *Momordica charantia* using supercritical carbon dioxide (SC-CO_2) in the presence of absolute ethanol as co-extractant (1:3 w/v feed-to-solvent ratio). As mean particle size influences the extraction yield, its effects were investigated in the range of 0.2-0.7 mm and validated using the extraction curve model. The optimum extraction pressure and temperature ranging from 10-30 MPa and 45-65 ^{o}C respectively were determined using response surface methodology with 3-level factorial while the effect of SC-CO_2 operating conditions and kinetic properties on the extraction yield were validated using the kinetic models of Barton, Crank, simplified linear driving force (SLDF) and Sovová. Results demonstrated that the extraction efficiency of charantin was found to be 13.25 x 10^{-3} mg ch/g CO_2 with the highest concentration of charantin of 112.56 mg/100 g dry weight at optimum condition of 0.3 mm particle size, 30 MPa pressure, 65 ^{o}C temperature and 5 mL/min flowrate. The highest extraction yield of 42.4 mg/g gave the highest diffusion coefficient (D_e) value of 16.49 x 10^{-12} m^2/s, with percentage deviation error of 4.48% at 30 MPa and 55 ^{o}C using the Crank model. Additionally, the mass transfer coefficient in the fluid phase (k_f) was 4.28 x 10^{-6} m/s and overall mass transfer coefficient (k_p) was 4.87 x 10^{-7} m/s obtained by SLDF model with experimental solubility (y_s) of 2.8 g/kg CO_2. The SC-CO_2 extraction with co-extractant has been demonstrated to be a promising technique to extract the highly valued charantin compound producing a novel product for nutraceutical and pharmaceutical industries.

ABSTRAK

Karantin adalah sebatian bioaktif dalam buah peria katak (*Momordica charantia*) yang dikatakan dapat menurunkan tahap glukosa darah pada pesakit kencing manis jenis 2. Sebatian dua kekutubannya yang unik dan berat molekulnya yang besar menyebabkan ia susah disari menggunakan kaedah penyarian lazim seperti Soxhlet dan penyarian air. Tujuan kajian ini adalah untuk menyari karantin daripada *Momordica charantia* menggunakan bendalir lampau genting karbon dioksida (SC-CO_2) dengan kehadiran etanol tulen sebagai penyari bersama (1:3 w/v nisbah suapan-kepada-pelarut). Oleh kerana purata saiz zarah mempengaruhi hasil penyarian, kesannya disiasat dalam julat 0.2-0.7 mm dan disahkan menggunakan model lengkung penyarian. Tekanan dan suhu penyarian optimum daripada julat 10-30 MPa dan 45-65 ^oC masing-masing ditentukan menggunakan kaedah tindak balas permukaan dengan faktorial tahap-3, sementara kesan keadaan operasi SC-CO_2 dan sifat kinetik pada hasil penyarian adalah disahkan menggunakan model kinetik iaitu Barton, Crank, daya pacuan linear dipermudahkan (SLDF) dan Sovová. Keputusan menunjukkan bahawa kecekapan penyarian karantin didapati sebagai 13.25 x 10^{-3} mg ch/g CO_2 dengan kepekatan karantin tertinggi sebanyak 112.56 mg/100 g berat kering pada keadaan optimum saiz zarah 0.3 mm, tekanan 30 MPa, suhu 65 ^oC dan kadar alir 5 mL/min. Hasil penyarian tertinggi iaitu 42.4 mg/g memberikan nilai pekali resapan (D_e) tertinggi pada 16.49 x 10^{-12} m^2/s dengan peratus ralat sisihan 4.48 % pada tekanan 30 MPa dan suhu 55 ^oC menggunakan model Crank. Sebagai tambahan, pekali pemindahan jisim dalam fasa bendalir (k_f) adalah 4.28 x 10^{-6} m/s dan keseluruhan pekali pemindahan jisim (k_p) adalah 4.87 x 10^{-7} m/s menggunakan model SLDF, dengan kebolehlarutan ujikaji (y_s) 2.8 g/kg CO_2. Penyarian SC-CO_2 dengan penyari bersama menunjukkan teknik yang berpotensi untuk menyari sebatian karantin yang sangat berharga dalam penghasilan produk novel untuk industri nutraseutikal dan farmaseutikal.

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LIST OF ABBREVIATIONS

3D	-	three-dimensional
AARD	-	absolute average relative deviation
ANOVA	-	analysis of variance
AOAC	-	Association of Analytical Chemists
CER	-	constant extraction rate
CFCs	-	Chlorofluorocarbons
CO_2	-	carbon dioxide
DCM	-	dichloromethane
DM	-	diabetes mellitus
DME	-	dimethyl ether
DW	-	Dry weight
EFSA	-	European Food Safety Authority
EtAc	-	ethyl acetate
FDA	-	Food and Drug Administration
FER	-	falling extraction rate
FFA	-	free fatty acid
GI	-	Glycemic index
HPLC	-	high performance liquid chromatography
JNK	-	phospho-c-Jun N-terminal kinase
LDF	-	linear driving force
LER	-	low extraction rate
MeOH	-	methanol
MOH	-	Ministry of Health
NA	-	not available
NCD	-	non-communicable disease
NF-κB	-	nuclear factor-κB
O_2	-	oxygen
PLE	-	pressurized liquid extraction
PPARα	-	liver peroxisome proliferator activated receptors
PPARɣ	-	adipose peroxisome proliferator activated receptors

RSM	-	response surface methodology
$SC\text{-}CO_2$	-	supercritical carbon dioxide
SCF	-	supercritical fluid
SFE	-	supercritical fluid extraction
SLDF	-	Simplified linear driving force
STZ	-	streptozotocin
T1DM	-	type 1 diabetes mellitus
T2DM	-	type 2 diabetes mellitus
US EPA	-	United States Environmental Protection Agency

LIST OF SYMBOLS

α	-	hydrogen bond donor
β	-	hydrogen bond acceptor
β_{ij}	-	coefficients of the interaction parameters
ε	-	porosity of solid sample
ϵ	-	residual associated to the experiments
ξ_c	-	changes in radius of unextracted core
π^*	-	dipolarity/polarizability
η_{Total}	-	total extraction yield
$\eta_{TotalSterol}$	-	total sterol extraction yield
ρ	-	fluid density (kg/m^3)
ρ_{CO_2}	-	fluid density of CO_2 (kg/m.s)
ρ_{mix}	-	mixture of fluid density (g/cm^3)
ρ_s	-	solid density (g/cm^3)
μ	-	fluid viscosity (kg/m.s)
μ_{CO_2}	-	fluid viscosity of CO_2 (kg/m.s)
μ_{mix}	-	mixture of fluid viscosity (kg/m.s)
a	-	specific surface area per unit volume of extraction bed (m^{-1})
b	-	constant
Bi	-	Biot number
C	-	concentration charantin (mg/mL)
C_{fo}	-	saturation concentration of solute
C_{rs}	-	concentration of extract left in the solid sample
$Conc_{ch}$	-	concentration of charantin (mg/g extract)
D	-	diffusivity (m^2/s)
D_e	-	diffusion coefficient (m^2/s)
d_p	-	diameter particle of solid sample (m)
e	-	Ratio of mass of oil recovered
e_{lim}	-	*e* value for infinite extraction time depend on the extracted material
Ext_{ch}	-	extraction efficiency (mg/g CO_2)

f	-	purity of charantin standard
k	-	mass transfer coefficient (m/s)
K	-	rate constant
k_f	-	mass transfer coefficient in the fluid phase
$k_f a$	-	volumetric convective coefficients in the fluid phase
k_p	-	overall mass transfer coefficient
k_s	-	mass transfer coefficient in the solid phase
$k_s a$	-	volumetric mass transfer coefficients in the solid cell
K_w	-	ionization constant
$m(t)$	-	extraction yield at time, t (g)
m_0	-	mass of glass dish (g)
m_1	-	mass of glass dish with sample before drying (g)
m_2	-	mass of glass dish with sample after drying (g)
M_t	-	total amount of solute diffused from sphere at time,t (g)
M_∞	-	total amount of solute (g)
$\dot{m}_{mix}$	-	mixture of fluid mass flow rate (g/min)
n	-	integer
N	-	solid mass on an extract-free basis (g)
N	-	total number of observations
N_e	-	total number of experimental data
P_c	-	Critical pressure
Q_{ch}	-	quantity of charantin (mg/g sample)
$\overline{q}_i$	-	average solute concentration in the particle
q_i^*	-	solute concentration in equilibrium with the fluid phase
r	-	diffusion path/particle radius (m)
Re	-	Reynolds number
S	-	surface area (m^2)
Sc	-	Schmidt number
Sh	-	Sherwood number
t	-	extraction time (s)
T_c	-	Critical temperature
t_{CER}	-	time for constant extraction rate (min)
t_{FER}	-	time taken for falling extraction rate (min)

v	-	interstitial fluid velocity (m/s)
V	-	volume of extract (mL)
V	-	volume (m^3)
W	-	dimensionless adjustable model parameters
$w_{extract, 105}$	-	weight of extract *Momordica charantia* at 105 min (g)
$w_{t,i}$	-	weight of dried *Momordica charantia* sample (g)
$W_{CO2, 105}$	-	weight of CO_2 at 105 min (g)
x_o	-	mass fraction of total solute content (g/g)
X_1	-	Pressure
X_2	-	Temperature
X_{EtOH}	-	ethanol content
X_i	-	variables
x_b	-	Concentration of easily accessible at the broken cell
x_i	-	Concentration of less accessible solute in the intact cell
x_k	-	mass fraction of inaccessible solute (g/g)
x_p	-	mass fraction of easily accessible solute (g/g)
X_p	-	pressure
Y	-	response
$\bar{Y}$	-	average value of all observations
y	-	overall extraction yield (g)
y_0	-	maximum extraction yield (g)
Y_1	-	Extract Yield
Y_2	-	Extraction Efficiency
Y_3	-	Solubility
$y_{calculated}$	-	extract yield obtained from model equations at *i* condition.
y_e	-	yield in weight fraction or percent
$y_{experimental}$	-	extract yield obtained from experiment at *i* condition.
Y_i	-	i^{th} observation
Y_s	-	solubility (g/g)
y_∞	-	Yield after infinite extraction time
$\hat{Y}_i$	-	predicted response
Z	-	dimensionless adjustable model parameters
Z_w	-	dimensionless adjustable model parameters

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CHAPTER 1

INTRODUCTION

1.1 Background of Study

The growing pandemic of Diabetes Mellitus (DM) is considered as an enormous public concern with 90% of the world population was diagnosed with Type 2 DM (T2DM) and roughly 1.6 million of deaths are directly attributed to diabetes each year (WHO, 2018). According to World Health Organization (WHO), there will be an increment of approximately 300 million diabetes patients globally by the year of 2025 (Wang *et al.*, 2014). In Malaysia, 99.3% of total registered patients were diagnosed with T2DM and 58.4% of the patients are women in the age of 45 to 54 years old (Feisul and Azmi, 2013).

Traditional medicine had been included as one of the primary health care mediums in most countries (Payyappallimana, 2010) while herbal products in Malaysia are an essential component in the medicine system at approximately RM4.6 billion with 15 to 20% annual projected growth rate (Khatun *et al.*, 2011). *Momordica charantia* from *Cucurbitaceae* family, also locally known as bitter gourd had been consider as a useful dietary adjunct for diabetes in the early years (Marles and Farnsworth, 1995). During the early studies on the ability of *Momordica charantia* extract, charantin, polypeptide-*p* (p-insulin) and alkaloids are proven to be compounds responsible in reducing the gl se level in blood (Habicht *et al.*, 2011; Raman and Lau, 1996). Their synergistic effect resulted in reducing blood glucose level and improving insulin efficiency (Khanna *et al.*, 1981; Lo *et al.*, 2014; Wang *et al.*, 2014). In addition, charantin is said to be the dominant compound in lowering the blood glucose level which is equivalent to the effect of insulin in the body (Pitipanapong *et al.*, 2007).

Charantin is a steroidal glucoside compound with a unique combination molecule of sterol head and glucoside tail. It is a mixture of *β*-sitosterol glucoside and stigmasterol glucoside in which both are commonly known as an anti-diabetic agent (Alarcon *et al.*, 2005; Fadzelly *et al.*, 2006). The sterol head of charantin is a non-polar molecule that can dissolve in non-polar solvent whereas the glucoside tail is a polar molecule that can dissolve in polar solvents (Pitipanapong *et al.*, 2007).

Saad and Ali (2011) verified that the highest amount of charantin of 55.27mg/100 g Dry Weight (DW) was extracted as water was added into a 50% v/v ethanol solution for 60 h using the maceration method. Meanwhile, the lowest amount was extracted as only water was used as a solvent. This is because water in ambient condition is a highly polar solvent that prefers dissolving polar compound only. Likewise, Pitipanapong *et al.* (2007) also have the same opinion that a mixture of water-ethanol solvent in a ratio of 1:1 using pressurized liquid extraction (PLE), could increase the highest recovery of charantin compound which is 12.1 mg/ 100 g DW within 40 min.

Therefore, the selection of solvent used to extract charantin could be a challenging task as it needs a mixture of solvents and effective extraction method to extract both non-polar head and polar tail simultaneously. Most of the previous researchers extracted this valuable compound using conventional methods such as distillation, Soxhlet and maceration methods; with water and methanol as the common solvent (Shih *et al.*, 2008; Wang *et al.*, 2014; Xu *et al.*, 2015).

The conventional extraction process is an outdated process which consumes large amount of organic solvent, requires longer extraction time and downstream process to remove the toxic solvent. Besides, it produces less concentrate extract with small amount of valuable compound compared to modern extraction method such as the supercritical fluids (Lepojević *et al.*, 2017; Hadzri *et al.*, 2014; Hsieh *et al.*, 2012).

For instance, a study done by Fuangchan *et al.* (2011) showed that about 2000 mg/day of dried *Momordica charantia* can reduce the fructosamine level in T2DM patient, but the effect is still lower than the effect of being fed by 1000 mg/day of metformin (prescribed medicine for T2DM patient). This is due to the purity of extract from dried *Momordica charantia* used that has small trace of the active compound compared to modern medicine performance. Hence, an effective extraction method for concentrated extract should be simple, fast, eco-friendly which could be easily upscaled for industrial purposes (Syahariza *et al.*, 2017).

Supercritical fluid extraction (SFE) has been known widely as a fast and eco-friendly extraction technology to extract natural product. Carbon dioxide (CO_2) is a common fluid used in SFE mainly because it is inexpensive, nontoxic, non-flammable, inert, naturally abundant and has a relatively low critical temperature (31.1^{o}C) and pressure (72.8 atm) (McHugh and Krukonis, 1986).

In addition, CO_2 solvent has been generally recognized as safe by Food and Drug Administration (FDA) and European Food Safety Authority (EFSA) (Herrero *et al.*, 2010). Above and beyond, greater mass transfer property such as diffusivity consequently gives faster extraction in a short time and the absence of surface tension increases the rapid penetration of supercritical CO_2 (SC-CO_2) inside solid particle thus enhances the extraction efficiency (Rakesh and Ramesh, 2012).

The nature of SC-CO_2 is a non-polar solvent which favors and excellent for extraction of non-polar compound similar to hexane (Larry, 1996). On the other hand, the key compound of *Momordica charantia* extract which is charantin is a unique compound with a combination of non-polar sterol head and polar glucoside tail (Pitipanapong *et al.*, 2007). Therefore, a mixture of non-polar and polar solvents is required to maximize the extraction of charantin compound.

In normal practice, a mixture of solvent could be created in SFE process via personal pump of a polar co-solvent such as ethanol (Salleh *et al.*, 2010). The co-solvent is mixed with SC-CO_2 solvent prior to the extraction process to modify its properties by increasing the solvent power of SC-CO_2 in extracting polar compound (Smith *et al.*, 2013). However, in many cases, co-solvent cannot be use due to limitation of equipment as it needs personal pump to operate and dissolve in SC-CO_2 before entering the extraction vessel. As an alternative, co-extractant can be introduced to facilitate the extraction of polar compound and unique compound such as charantin. Co-extractant is a substance that is directly applied on the solid particle prior to the extraction process in order to improve solute transport properties and enhances the extraction yield (Smith *et al.*, 2013). In this study, absolute ethanol is used as a co-extractant for the extraction of charantin compound using SC-CO_2 at different operating parameters. It is an innovation towards the current SC-CO_2 technology by modifying the *Momordica charantia* solid dried particle structure prior to the extraction process (Durante *et al.*, 2014b).

The use of SC-CO_2 with the addition of co-solvent/co-extractant in the extraction process has already been explored in industries such as in advanced materials of ceramic nanoparticles using SC-CO_2 with methanol (Hanhwa Chemical Co., South Korea) (Smith *et al.*, 2013), extraction of oakwood oil, water soluble hazelnut oil, water soluble sesame oil, water soluble sunflower oil and water soluble peanut oil using SC-CO_2 with ethanol (Evonik Industries AG, Germany) (Michael, 2018). At the same time, there are continuous researches on the extraction of SC-CO_2 with co-solvent/co-extractant consist of extraction of lycopene, β-carotene, and other bioactive compound from natural plants (Espinosa-Pardo *et al.*, 2017; Kehili *et al.*, 2017; Ruslan *et al.*, 2018a; Hatami *et al.*, 2019)

Mathematical model is important in the extraction using SC-CO_2 as it can optimize the variables via statistical model and estimate the extraction process using the extraction curve model (Song *et al.*, 2017). A statistical model could be in the form of design of experiment (DoE) or response surface methodology (RSM). DoE is a statistical model to minimize the number of experiments needed and operating cost whereas, RSM is a complete statistical model which includes experimental design and analysis, to determine how the response is affected by a set of quantitative variables in a specified region (Melo *et al.*, 2014).

Meanwhile, extraction curve model could be categorized into a simple empirical model, a heat transfer analogy kinetic model and a complex differential mass balance kinetic model. Most importantly, these models could represent an extraction curve and predict the kinetic properties such as diffusion coefficient (D_e) and mass transfer coefficient (k). Additionally, the operating time needed to complete the extraction could be determined from the predicted curve.

Crank and Sovová models are among the kinetic models commonly used for describing the extraction curves and determining the k and D_e value in SC-CO_2 extraction method (Huang *et al.*, 2011; Nasir *et al.*, 2017; Favareto *et al.*, 2017). Sovová *et al.* (1994) developed a kinetic model to investigate the effect of particle size, CO_2 flow rate and its direction for extraction of vegetable oil using SC-CO_2. The model confirms that larger particle size resulted in the lowest k value. Beside k value, D_e value is also important in the determination of mass transfer in SC-CO_2 process (López-Padilla *et al.*, 2016).

Crank (1975) developed a model to determine the D_e value specially for a solid particle which has limited extractable solute (Huang *et al.*, 2012). The D_e value varies from subcritical to supercritical regions depending on the chemical potential of solute that influences the diffusion flux (Medina, 2012). The use of D_e value in Schmidt and Sherwood numbers is important in describing the mass transfer phenomena in the extractor vessel (Funazukuri, 2018). Therefore, it is important to consider the D_e value for the design and efficiency of the SFE process (Liong *et al.*, 1991).

At the same time, the application of RSM in this study was employed to optimize the operating pressure and temperature in the extraction process. As a matter of fact, the scale-up of SC-CO_2 extraction unit for industrial purposes requires information such as mass transfer kinetics, the equilibrium and optimum operating conditions which could be retrieved from the mathematical model and experimental data.

To date, no reports on the extraction of charantin, a unique compound with dual polarity from Malaysia's genus *Momordica charantia* (flesh + seed), using SC-CO_2 with ethanol as co-extractant is available in the literature. Besides, the valuable data from kinetic properties using kinetic models and optimization by RSM, could be fruitful towards developing new products in nutraceuticals and pharmaceuticals industries for the treatment of T2DM.

1.2 Problem Statement

The stumbling block in this study is the extraction of charantin from *Momordica charantia* fruit which is quite challenging due to its unique chemical structure with dual polarity. The sterol head tends to dissolve in a non-polar solvent which could be fulfilled by n-hexane or SC-CO_2 solvent. Meanwhile, its glucoside tail needs a polar solvent such as methanol or ethanol to dissolve as it is a polar molecule with bulk structure. Hence, the needs for suitable mixed solvents are crucial.

The mixture of organic solvent such as n-hexane and methanol could enhance the extraction of charantin but then, the mixture of both solvents is hazardous and toxic towards human and environment. Thus, the mixture of SC-CO_2 and ethanol could be used to extract charantin as both solvents are non-toxic and environmentally friendly. In fact, with only small amount of ethanol as co-solvent, it can tune the polarity of SC-CO_2 (main solvent in SFE) and enhance the extraction of polar molecule such as glucoside tail in the charantin compound.

However, another issue in this study is the use of ethanol as a co-solvent as it needs a personal pump to operate. Due to the limitation of this study, which is the use of personal pump for co-solvent, the solution is to use ethanol as co-extractant rather than as co-solvent. As mentioned previously in the background of study, a co-extractant is a substance directly mixed with a solid particle. Hence, ethanol as co-extractant is directly mixed and thus swells the solid particle prior to the extraction process, to ensure SC-CO_2 (main solvent in SFE) could diffuse easily and extract both charantin compound (sterol and glucoside molecules). The truth is the polarity of SC-CO_2 instantly tunes as ethanol is co-extracted by SC-CO_2 thus enhance its solvent power to extract polar and large molecules. In conclusion, this eco-friendly extraction method which is SC-CO_2 with the addition of ethanol as co-extractant, could be fruitful in the extraction of charantin compound from *Momordica charantia* for nutraceutical and pharmaceutical industries.

1.3 Objectives of Research

The aim of this study is to extract charantin, a dual-polarity compound of *Momordica charantia* using SC-CO_2 with absolute ethanol as co-extractant. In order to achieve this aim, the following objectives are identified;

i. To investigate the effects of different operating parameters on *Momordica charantia* extract yield and concentration of charantin using SC-CO_2 extraction with co-extractant.
ii. To optimize the operating pressure and temperature in SC-CO_2 extraction with co-extractant on *Momordica charantia* extract yield and charantin extraction efficiency using response surface methodology (RSM).
iii. To validate operating parameters influencing the extraction process in terms of diffusion coefficient, D_e and mass transfer coefficient, k, by extraction curve model.

1.4 Scopes and Limitations of Study

A research study conducted must have its scopes and limitations in order to achieve all the objectives stated. Therefore, the scopes and limitations of this research study are:

i. Preliminary studies were performed to obtain constant parameters prior to dynamic extraction using SC-CO_2. The parameters are consist of moisture content (<10% wet basis) (Shi *et al.*, 2010), mean particle sizes (0.2, 0.3, 0.5 and 0.7 mm) (Sun and Temelli, 2006; Ekinci and Gürü, 2014), carbon dioxide flow rate (3, 4, 5, 6 and 8 mL/min) (Ruslan *et al.*, 2015; Aziz *et al.*, 2016), extraction time (120 min) (Park *et al.*, 2007a) and addition of ethanol as a co-extractant (1:3 feed-to-solvent ratio) (Woźniak *et al.*, 2017). The range of parameters was chosen based on the previous literature. For instance, excessive higher moisture content can lead to poor extraction oil yield and undermine the specialty of SC-CO_2. Meanwhile, a fine particle of less than 0.2 mm and higher feed-to-solvent ratio could create inlet clogging on the SC-CO_2 flow line. On the other hand, a flow rate of higher than 8 mL/min could reduce the solubility of solute in the SC-CO_2 solvent whereas longer extraction time would be less sustainable.

ii. Optimization of *Momordica charantia* yield (mg/g sample) and charantin extraction efficiency (mg charantin/g CO_2) were performed by response surface methodology (RSM) analysis with two different parameters, temperature (45, 55, 65 ^oC) and pressure (10, 20, 30 MPa) using 3-Level Factorial.

iii. Determination of charantin extraction efficiency via analysis using High Performance Liquid Chromatography (HPLC).

iv. Development of extraction curve model, Barton and Crank models on experimental data is performed in order to determine the diffusion coefficient, D_e. The accuracy of the coefficient was evaluated using the absolute average relative deviation (AARD) method.

v. Mass transfer coefficient, k is calculated using kinetic model of simplified linear driving force (SLDF) model and Sovová model. The accuracy of the coefficient was evaluated using the AARD method.

1.5 Significance of Study

This study would expand the current technology of supercritical fluid and increase the database of supercritical fluid extraction. The application of SC-CO_2 with the addition of absolute ethanol as co-extractant, will increase the extraction of charantin compound with its unique dual-polarity from *Momordica charantia*. This method could solve the use of tremendous amount of hazardous organic solvent and the limitation of co-solvent. Additionally, it will enhance the innovation of current SC-CO_2 extraction process by exploring the use of co-extractant instead of co-solvent.

Moreover, the effect of operating parameters on diffusion coefficient, D_e and mass transfer coefficient, k values are the first investigated for extraction of *Momordica charantia* fruit with addition of absolute ethanol as a co-extractant. These values are important in chemical scale up of extraction process especially when considering the design of extraction vessel.

In conclusion, this study is very important as it will be an eye opener in the selection of solvent and extraction method for the extraction of natural plants. In fact, this study should raise public awareness on the increasing number of T2DM patients in Malaysia. In addition, the industries such as nutraceutical and pharmaceutical could gain new knowledge on the extraction method and hopefully to implement it in order to develop new products to improve the current treatment of T2DM.

1.6 Thesis Outline

Chapter 1 is consisting of brief introduction of the research containing the background of study, problem statement, objectives of the study, scope and limitation of the study, and the significance of the study as well as thesis outline.

Chapter 2 provides an in-depth discussion on the studies which have been performed by previous researchers and related to this study such as the structure and characteristics of charantin as the interest compound in this study and the unique dual polarity compound in *Momordica charantia*. Furthermore, the conventional extraction method and SC-CO_2 extraction method is explained in detail along with the factors affecting the extractability in SC-CO_2. Then, the optimization of operating conditions is discussed in order to achieve high amount of *Momordica charantia* extract yield and extraction efficiency of charantin using RSM. Moreover, this chapter also includes the mathematical extraction curve model for *Momordica charantia* extract yield for determination of diffusion coefficient (D_e) and mass transfer coefficient (k) values.

In chapter 3, the methodology of sample preparation, determination of constant parameters in SC-CO_2 extraction, the procedure of SC-CO_2 extraction technique and analysis of compounds using HPLC are presented. Optimization of *Momordica charantia* extract yield and extraction efficiency of charantin using RSM, mathematical model and statistical analysis are also included in this chapter.

Results of experimental work and effects of operating conditions of SC-CO_2 which are mean particle size, addition of co-extractant, extraction time, fluid flow rate, pressure and temperature as well as Soxhlet extraction outcome values are discussed in Chapter 4. The optimizations of *Momordica charantia* extract yield and extraction efficiency of charantin using RSM are also presented. The tailored extraction curve models are also reported and its operating parameters effects on D_e and k value are discussed.

Finally, chapter 5 concludes the findings of this study and summarizes the research outcome. Few recommendations are presented in this chapter for future works related to this study.

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