OPTIMIZATION AND KINETICS OF GREEN PRESSURIZED-LIQUID EXTRACTION FOR ANDROGRAPHOLIDE FROM *ANDROGRAPHIS PANICULATA*

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This work is dedicated to Allah (SWT).

Knowledge is lost if it is not shared!
(Ibnu Khaldun, Rahimahu Allah)

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ABSTRACT

This research was focused on green solid-liquid extraction (SLE), one of the most crucial stages for the upstream phytochemical processing because the extracted product would affect the quality of finished product. The influence of process variables for green SLE of andrographolide from *Andrographis paniculata* (AP) was investigated through exploratory experimentation using a 2^3 complete factorial experimental design, and a rotatable central composite design (RCCD). The main and interaction effects of the solid-liquid ratio (1/50 – 5/50 mg/L), average particle size (0.175 – 1.200 mm), time (5 – 25 minutes), and temperature (80 – 120 °C) were examined. The process was studied under isothermal condition at 80°C, and other temperatures; 100 °C and 120 °C in a pressurized liquid extractor using water as the greenest solvent. The multiple objectives for the green SLE of andrographolide from AP were simultaneously optimized using the RCCD technique coupled with desirability and penalty functions based on the concepts of extraction yield, and new developed techniques for extraction selectivity of andrographolide. The extraction kinetics was found to follow the second-order rate law. As the particle size decreases and solid-liquid ratio increases, the observed specific extraction rate constant, k_{obs}, and the initial rate of solid-liquid extraction of andrographolide, r_{B0} significantly increase. It was found at 80 °C that k_{obs} increased to nearly twofold from 0.000653 to 0.00128 $Lmg^{-1}min^{-1}$ for the solid-liquid ratio of 1:10 g/mL when particle size was decreased from 1.200 to 0.175 mm. Besides, it increased to more than fivefold, 0.00344 $Lmg^{-1}min^{-1}$ and virtually fourfold, 0.00496 $Lmg^{-1}min^{-1}$ for particle sizes of 1.200 and 0.175 mm, respectively when the solid-liquid ratio was increased to 1:50 g/mL. k_{obs} increased for a solid-liquid ratio of 1:10 g/mL to more than 143 times, 1.10 X 10^{-1} $Lmg^{-1}min^{-1}$ and nearly 221 times, 7.22 X 10^{-1} $Lmg^{-1}min^{-1}$ for a solid-liquid ratio of 1:50 g/mL when temperature was raised from 80 °C to 100 °C, and 120 °C. Hence, k_{obs}, and the activation energy, E_a significantly increased with a decrease in particle size and an increase in solid-liquid ratio and temperature.

ABSTRAK

Kajian ini memberi tumpuan kepada pengekstrakan pepejal-cecair (SLE) menggunakan teknologi hijau, salah satu peringkat yang paling penting untuk pemprosesan fitokimia kerana produk yang diekstrak akan memberi kesan kepada kualiti produk siap. Pengaruh pembolehubah proses untuk SLE hijau daripada andrographolide dari *Andrographis paniculata* (AP) telah disiasat melalui ujian penerokaan menggunakan 2^3 reka bentuk uji kaji faktorial lengkap dan reka bentuk komposit pusat berputar (RCCD). Kesan-kesan utama dan interaksi nisbah pepejal-cecair (1/50 – 5/50 mg/L), saiz zarah purata (0.175 – 1.200 mm), masa (5 – 25 minit), dan suhu (80 – 120 °C) telah dikaji. Proses ini dikaji di bawah keadaan isoterma pada 80 °C, dan suhu yang lain; 100 °C dan 120 °C dalam pemerah cecair bertekanan menggunakan air sebagai pelarut pilihan. Pelbagai objektif bagi SLE hijau andrograpolida dari AP serentak dioptimumkan menggunakan teknik RCCD ditambah pula dengan keinginan dan fungsi penalti berdasarkan konsep hasil pengeluaran, dan teknik-teknik maju baru untuk pemilihan pengekstrakan andrograpolida. Kinetik pengekstrakan didapati mengikuti hukum kadar peringkat-kedua. Oleh kerana penurunan saiz zarah dan nisbah pepejal-cecair meningkat, diperhatikan kadar perahan tertentu yang berterusan, k_{obs} dan kadar awal pengekstrakan pepejal-cecair andrograpolida, r_{B0} telah meningkat dengan ketara. Diperhatikan pada 80 °C, k_{obs} meningkat kepada hampir dua kali ganda 0.000653-0.0128 $Lmg^{-1}min^{-1}$ untuk nisbah pepejal-cecair 1/10 (g/mL) apabila saiz zarah telah berkurangan daripada 1,200 kepada 0.175 mm. Selain itu, ia meningkat kepada lebih daripada lima kali ganda, 0.00344 $Lmg^{-1}min^{-1}$ dan hampir empat kali ganda, 0.00496 $Lmg^{-1}min^{-1}$, masing-masing untuk saiz zarah 1.200 dan 0.175 mm, apabila nisbah pepejal-cecair telah meningkat kepada 1:50 (g/mL). k_{obs} meningkat untuk nisbah pepejal-cecair 1:10 g / mL kepada lebih daripada 143 kali, 1.10×10^{-1} $Lmg^{-1}min^{-1}$ dan hampir 221 kali, 7.22×10^{-1} $Lmg^{-1}min^{-1}$ untuk pepejal yang nisbah cecair 1/50 (g/mL) apabila suhu dinaikkan daripada 80 °C hingga 100 °C dan 120 °C. Oleh itu, k_{obs}, dan tenaga pengaktifan, E_a telah menunjukkan peningkatan yang ketara dengan penurunan dalam saiz zarah dan peningkatan dalam nisbah pepejal-cecair dan suhu.

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LIST OF SYMBOLS/ABBREVIATIONS

r_{B0}	—	Initial rate of extraction for andrographolide, mg L^{-1}min
A_{AASM}	—	Actual amount of solid material disappeared in extraction
β_i	—	Coefficient for linear
β_{ii},	—	Coefficient for quadratic
$\hat{S}_D$	—	Overall selectivity of desired product extract
$\hat{S}_{D/U}$	—	Overall selectivity of desired product extract with respect to undesired product extracts (other phytochemical compounds)
$\hat{S}_U$	—	Overall selectivity of undesired product extracts (other phytochemical compounds)
$D_{overall}$	—	Overall desirability objective function
E_a	—	Activation energy (J mol^{-1})
L_i	—	Lower specification limit
S_D	—	Instantaneous selectivity of desired product extract
$S_{D/U}$	—	Instantaneous selectivity of desired product extract with respect to undesired product extracts (other phytochemical compounds)
S_U	—	Instantaneous selectivity of desired product extracts (other phytochemical compounds)
T_i	—	Target or goal of the optimization

U_i	—	Upper specification limit
d_i	—	Desirability function
w_i	—	Weight for emphasis
x_i, & x_j	—	Coded independent process variables
y_i	—	*i*th response for the process
β_0	—	Constant
β_{ij}	—	Coefficient for second order interaction effects
A	—	Frequency factor or pre-exponential factor
A_D	—	Amount of desired phytochemical product extract
A_D	—	Amount of desired extract (andrographolide or whole extracts)
ANOVA	—	Analysis of variance
AP	—	*Andrographis paniculata*
A_s	—	Total liquid-solid interfacial area at any time t
ASE	—	Accelerated Solvent Extraction
ASE 100®	—	Accelerated Solvent Extraction 100® commercialized by Dionex
A_{SM}	—	Amount of solid material *(Andrographis paniculata)*
A_U	—	Amount of undesired phytochemical product extract (s)
b	—	Thickness of liquid film across which mass transfer takes place
C_{Be}	—	Equilibrium concentration of andrographolide in the liquid

		extracts at saturation with insoluble solids, mg/L
C_{Bt}	—	Concentration of andrographolide in the liquid extracts (in the bulk liquid) at any time, t (min), mg/L
CFED	—	Complete factorial experimental design
D_{Aeff}	—	Average effective diffusivity of the solute A at any time t
DCM	—	Dichloromethane
DMSO	—	Dimethyl sulfoxide
DoE	—	Design of experiment
ECER	—	East Coast Economic Region
ES	—	Extraction selectivity
EY	—	Extraction yield
f	—	functional relationship between the response, y_i and the input process variables $(x_1 + x_2 + x_3 \ldots . x_k)$
GMP	—	Good manufacturing practice
GNI	—	Gross national income
HPLC	—	High-performance liquid chromatography
k_L	—	Liquid-solid interphase mass transfer coefficient at any time t
k_{obs}	—	Observed 1st or 2nd -order specific extraction rate constant, min^{-1} and $Lmg^{-1}min^{-1}$ respectively

M_{Bt}	—	Mass of solute, B transferred from the solid to the liquid phase at time, t
mM	—	Millimole
n	—	n^{th} order of extraction, *n*-number of variables
PLE	—	Pressurized liquid extractor
R	—	Universal gas constant (8.314 J mol^{-1} K^{-1})
RCCD	—	Rotatable central composite design
r_D	—	rate of formation of desired extract
r_{DPCs}	—	rate of dissolution of phytochemical compounds
r_{DSM}	—	rate of disappearance of solid material
RS	—	Reaction selectivity
RSM	—	Response surface methodology
r_U	—	rate of formation of undesired extract(s)
SFE	—	supercritical fluid extraction
SLE	—	Solid-liquid extraction
t	—	Extraction time, min
T	—	Temperature (°C, K)
THM	—	Thai Herbal Medicine
Y	—	Instantaneous yield of desired product extract
$\hat{Y}$	—	Overall yield of desired product extract

y_1, AOA, C_t	—	Amount of andrographolide, Rate of andrographolide extracted
y_2, OYE	—	Overall yield of extracts
y_3, OYA	—	Overall yield of andrographolide
y_4, OSA	—	Overall selectivity of andrographolide
y_5, OSPCC	—	Overall selectivity of other phytochemical compounds (Undesired products of extraction and reaction)
y_6, OSA/ OPCC	—	Overall selectivity of andrographolide (desired extract) with respect to other phytochemical compounds (Undesired products of extraction and reaction)
ε	—	Statistical error

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CHAPTER 1

INTRODUCTION

1.1 Background

In present days, there has been an increasing demand for specialty phytochemical compounds for herbal medicinal products, cosmeceuticals, nutraceuticals, functional food products, and other related products. This trend is somewhat due to consumer preference for products containing phytochemical ingredients, which are generally perceived as milder, safer and healthier than their synthetic equivalents (Harjo *et al.*, 2004). For thousands of years, medicinal plants have formed the basis of traditional medicine systems and more recently, are the good sources of the lead compounds for modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates and chemical entities for synthetic drugs, especially against numerous diseases (Isah, 2009). The global market of herbal and natural products is estimated at US$117 billion (Patel, 2015). According to the World Bank and WHO reports on trade in medicinal plants, botanical drug products and raw materials are growing at an annual growth rate between 5 to 15% (Kumari *et al.*, 2011, Augustin and Sanguansri, 2015). Recently, Kumari *et al*.,(2011) reported the increase in the international pharmaceutical market between 2004 and 2008 from US$550 billion to around US$900 billion; where the

global herbal medicines stand over US$62 billion annually with potential growth and have been projected to reach US$ 5 trillion by 2050 (Liu, 2011, Yadav *et al.*, 2014, Rajani and Kanaki, 2008). In China, the annual herbal drugs' production is valued about US$48 billion with export of US$3.6 billion, while in India, the worth of botanicals-related trade is around US$10 billion per annum with yearly export of US$1.1 billion (Kumari *et al.*, 2011). In Malaysia, the herbal industry is approximately calculated to grow at the rate of 15 % annually, with the market increase in value from RM 7 billion in 2010 to about a RM29 billion by 2020 (Othman *et al.*, 2015). The herbal plantation project of the East Coast Economic Region (ECER) has been estimated to create 2,500 new jobs and 530 entrepreneurial opportunities, and generate a gross national income (GNI) of US$ 1 billion or about a RM3 billion by 2020 (Yakcop, 2011). The total contribution of GNI from the herbal industry will be around US$ 11 billion by 2020 (Aziz *et al.*, 2011).

As a result of the growing demand and interest in specialty phytochemical products, however, there are numerous challenges of meeting the requirements of high quality, safety, and efficacy of these high value products. The quality of a phytochemical product depends upon the quality of the raw herb itself and how the active ingredients are extracted from the raw herb. The selection of the appropriate extraction process, as well as the establishment of optimum operating conditions, and the characterization of the process at the early stage of process development is crucial in producing standardized extract for the safe and successful profitable business enterprise. The rate of extraction can vary from a value approaching infinity to essentially zero depending on the nature of extraction and extraction conditions. Most extraction processes take place at rates between these two boundaries, and for a successful rational design of an extractor, the engineer must employ the use of kinetic data to determine exact sizes of extraction equipment. It is very important to know how the extraction rate changes with process variables; the most influential operating variables are temperature, particle size of the raw herb, solid-liquid ratio and degree of agitation of the extraction mixture. This research focused on the kinetics of optimized green solid-liquid extraction of andrographolide from *Andrographis paniculata*.

Solid-liquid extraction (SLE) process is considered to be the heart of specialty phytochemical processing because once its jeopardized the whole industry will be affected (Isah, 2009, Das *et al.*, 2013). It is the process of leaching out soluble components from multi-component solid mixture by contacting the solid with suitable solvent that selectively dissolves some but not all components in the solid (Isah, 2009). Green SLE is an approach to the processing techniques of extraction through the utilization of harmless solvents that eliminate or reduce generation of products and byproducts that are hazardous to human health and the environment. This is similar to the definition of green extraction given by Chemat *et al.* (2012), and the general definition of green chemistry proposed by Anastas (1999). Kinetics of green SLE is the study of rate and mechanism by which soluble components of solid material are dissolved in the green solvent. The rate is the mass of a product produced or solid material disappeared in liquid solvent per unit time. The mechanism is the sequence of individual phytochemical or chemical events whose overall result produces the observed extraction.

Andrographis paniculata,(AP) is one of the most popular herbs widely used in Eastern Asia, South-Central Asia and South-East Asia for anti-cancer, anti-inflammatory, anti-diabetic, anti-hypertensive, anti-venom, hepatoprotective, cholestatic, anti-thrombotic, anti-retroviral, anti-microbial, anti-pyretic, anti-malarial, anti-oxidant, immunomodulatory, cardioprotective effects, treatment of appetite loss, skin condition eruption and scabies (Aziz, 2003, Subramanian *et al.*, 2012, Valdiani *et al.*, 2012). Andrographis is a genus within the Acanthaceae family consisting of about 40 species several members of which have a reputation in traditional medicine (Rao *et al.*, 2004). The major medicinally active constituent of AP was found to be andrographolide diterpenoid lactone (Gorter, 1911, Chakravarti and Chakravarti, 1951), with molecular weight, 350.45 g/mol, and molecular formula, $C_{20}H_{30}O_5$. The cost of purified andrographolide and its derivatives could be around US$100,000/kg reported by chemical suppliers(UNDP, 2002, Valdiani *et al.*, 2012).

1.2 Research Problem Statement

Although a lot of studies have been reported related to pharmacological and bioactivity properties of AP, very little is known and published with respect to green SLE of andrographolide from AP using water as solvent. However, green SLE is generally characterized with lower rates and poor performances due to some constraints of the process, its complex nature, and impacts of process variables. Besides, the extraction cycle time for the production of andrographolide water extract is very long. To date, no study has comprehensively and completely examined the kinetics of green SLE for andrographolide from AP. In view of the current challenges, potential size of the specialty phytochemical products' markets and growing demand for andrographolide water extracts from AP coupled with the challenges of meeting the requirements of high quality, safety, and efficacy, this research seeks for the safe, economic, and effective green extraction process of andrographolide; optimization of the key process variables; and developing the kinetics of SLE of andrographolide from AP.

1.3 Research Hypothesis

Water is considered to be the most likely greenest solvent on earth based on its unique qualities and tunable properties. The rate limiting step for the green SLE of andrographolide from AP is considered to be controlled by the rate of andrographolide dissolution with water.

1.4 Objective of the Research

The main objectives include the following:

i. To develop a novel technique for the complete process analysis of SLE of phytochemical compound(s);

ii. To investigate the feasibility of green SLE of andrographolide from AP using water as green solvent;

iii. To optimize the most influential process variables for green SLE of andrographolidee from AP based on the concepts of extraction yield and extraction selectivity of andrographolide;

iv. To determine the kinetics of green SLE of andrographolide from AP.

1.5 Scope of the Research

In order to achieve the above set objectives, the scope of the research is limited to the use of only water as the greenest solvent for:

i. Analyzing the process of SLE completely based on the reality of multiple SLEs of phytochemical compounds from plant materials, and developing novel techniques for the process analysis based on the concept of extraction selectivity;

ii. Examining the effects of process variables, namely solid-liquid ratio, particle size, and time at constant temperature on green SLE for andrographolide from AP using water as solvent in a pressurized liquid extractor (PLE). Quantifying the concentration of andrographolide from all experiments using high-performance liquid chromatography (HPLC) coupled with photodiode array (PDA) detector;

iii. Optimizing the most influential process variables, namely solid-liquid ratio, particle size, time, and temperature on green SLE for andrographolide from AP through DoE based on the concepts of extraction yield and extraction selectivity of andrographolide with respect to other phytochemical compounds;

iv. Determining the kinetic parameters of green SLE of andrographolide through empirical modelling of the observed experimental data with the most suitable extraction rate laws. Examining the effects of particle size and solid-liquid ratio on concentration dependent terms of the extraction rate law under isothermal condition. Investigating the temperature effects on the extraction kinetics, and establishing the extraction kinetics around the optimum process variables.

1.6 Significance of the Work

The quality, purity, efficacy, and safety of specialty phytochemical products solely depend on how the phytochemical compound(s) are extracted from raw herbs. Proper selection of solvent is one of the master keys to successful and safe extraction of phytochemical ingredients. Some of the volatile organic solvents have been very efficient in extracting phytochemical compounds from the raw herbs but are not completely safe for the product and process, and have been hazardous to the human health, and deleterious to the environment. The importance of replacing these hazardous processes with harmless green processes cannot be overemphasized. This research focused on searching green process for the safe, economic and effective extraction of phytochemical compounds from AP, studying the individual and combined effects of process variables such as temperature, solid-liquid ratio, particle size of the solids on the rate of solid-liquid extraction, optimizing the key process variables based on the concepts of extraction yields and selectivity of andrographolide with respect to other water soluble phytochemical compounds from AP, and characterizing the process through empirical modeling of green SLE kinetics. The results will be of great importance in completely understanding and

fully developing the extraction process of phytochemical compounds from AP and exact sizing of extraction equipment. Hence, it is anticipated to improve significantly the profitability of specialty phytochemical processing and turn the industry into a more lucrative, prosperous, and above all a greener industry.

1.7 Organization of the Thesis

This study comprised of five chapters. Chapter 1 presents the introductory background of the study. It also highlights the growing demands and market potentials for specialty phytochemical compounds, and problems associated with the specialty phytochemical processing. In addition, the chapter outlines the aim, main objectives and scope of the research, significance of the study, the expected contributions to the industry, and organization of the thesis. Chapter 2 gives the reviews of relevant researches to the study area. Important concepts of SLE, and green SLE, process optimization, and development of extraction kinetics. Chapter 3 presents the adopted research methodology techniques, the research materials, tools and equipment used in the investigation. Chapter 4 presents the outcome of exploration, examination, investigation and development, and discusses the results obtained, and give their inferences. Finally, Chapter 5 gives the summary for the findings, concluding remarks based on the set objectives of the research and recommendations for further studies.

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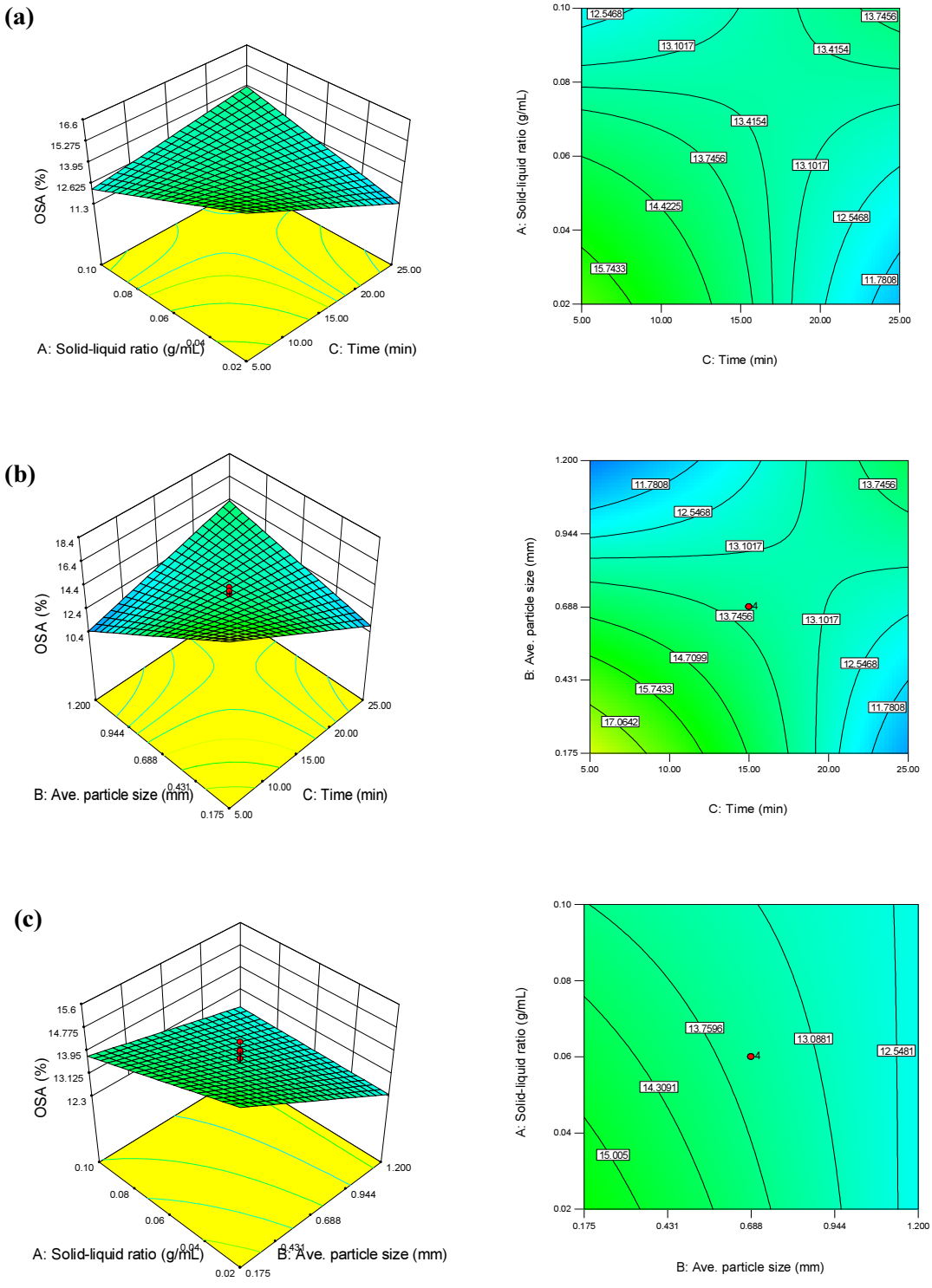

Figure 4.3 3D response surface and contour plots for OSA (%) as a function of (a) solid-liquid ratio and time at average particle size of 0.69 mm, (b) average particle size and time at S-L ratio of 3/50 (g/mL) and (c) solid-liquid ratio and average particle size at time of 15 min.

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