UNIVERSITI PUTRA MALAYSIA

EFFECTS OF FORMULATION COMPOSITION ON HARDNESS AND FRIABILITY OF OKARA TABLET USING DIFFERENT CHEMOMETRIC METHODS

NUR IZZATI MOHAMAD ZEN

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By

NUR IZZATI MOHAMAD ZEN

Thesis Submitted to the School of Graduated Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for Degree of Master of Science

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Abstract of the thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of requirement for the degree of Master of Science

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June 2016

Chairman : Siti Salwa Abd. Gani, PhD
Institute : Halal Products Research Institute

The usage of soy is keep on increasing year by year. It increases the problem of financial crisis and environmental pollution due to large amount of waste produced every year. Therefore, the nutrients of soy residue called Okara were studied and developed to become a beneficial waste. The used Okara was dried using a freeze dryer at -105°C to avoid from microbial growth which may cause contamination. The results of proximate analysis show that, the dried Okara contain about 21.78±1.06% of protein, 3.43±0.22% of fats, 15.82±0.79% of fiber, 3.53±0.12% of ash and 10.87±0.55% of moisture. The total phenolic content (antioxidant) in Okara is 0.86±0.39 GAE mg/100g of Okara. The major aim of this study is to investigate the effect of ingredient towards the tablet physical properties. The Okara tablets were produced using the direct compression method. Four inputs were studied; the percentage of Okara (A), maltodextrin (B), guar gum (C) and microcrystalline cellulose (D) toward the tablets' hardness and friability using three statistical software methods; D-optimal mixture design, artificial neural network (ANN), and wavelet neural network (WNN). For comparison study of D-optimal mixture design, ANN and WNN, data sets from mixture design were adopted for predicting the hardness and friability of tablet based on optimal composition ingredient which are 30.608% of A, 15.000% of B, 5.764% of C, and 46.628% of D. Based on RMSE, R^2, and AAD values, ANN has shown the topology of GA which gave the best performance in both hardness and friability studies. The best architecture of hardness response is GA-4-12-1 with importance of variables; 24.79% of A, 27.45% of B, 22.37% of C, and 25.39% of D. On the other hand, the best architecture of friability response is GA-4-1-1 with importance of variables; 10.59% of A, 2.73% of B, 18.49% of C, and 68.49% of D. The order of overall prediction ability for hardness response is ANN-GA>MD>WNN-GA, while for friability response is ANN-GA>WNN-GA>MD. Finally for safety procedure, heavy metal tests and microbiological tests were carried out. The results show satisfactory level for both heavy metals and microbes. Thus, the Okara tablet formulation was successfully optimized using different chemometric method and excellent for nutraceutical industry.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

KESAN KOMPOSISI FORMULASI TABLET OKARA TERHADAP KEKERASAN DAN KERAPUHAN MENGGUNAKAN KAEDAH KIMOMETRIK YANG BERBEZA

Oleh

NUR IZZATI MOHAMAD ZEN

Jun 2016

Pengerusi : Siti Salwa Abd. Gani, PhD
Institut : Institut Penyelidikan Produk Halal

Penggunaan soya meningkat dari tahun ke tahun. Ia meningkatkan masalah krisis kewangan yang disebabkan oleh sumber kacang soya yang terhad dan juga menyebabkan pencemaran alam sekitar kerana jumlah besar sisa yang dihasilkan. Oleh itu, nutrien sisa soya yang dikenali sebagai Okara telah dikaji dan dikembangkan untuk menjadikannya satu sisa berfaedah. Okara yang digunakan telah dikeringkan dengan menggunakan pengering-bekuan pada suhu -105°C untuk mengelakkan daripada pertumbuhan mikroorgamisma yang boleh menyebabkan pencemaran. Keputusan bagi analisis proksimat menunjukkan bahawa, Okara kering mengandungi kira-kira 21.78±1.06% protein, 3.43±0.22% lemak, 15.82±0.79% serat, 3.53±0.12% abu dan 10.87±0.55% kelembapan. Jumlah kandungan antioksida fenolik adalah 0.86±0.39 mg GAE /100g Okara. Tujuan utama kajian ini adalah untuk mengkaji kesan bahan ke arah sifat-sifat fizikal tablet. Tablet Okara telah dihasilkan menggunakan kaedah mampatan langsung. Empat input dikaji; peratusan Okara (A), maltodekstrin (B), gam guar (C) dan mikrokristalin selulosa (D) terhadap kekerasan dan kerapuhan tablet dengan menggunakan tiga kaedah perisian statistik; reka bentuk campuran D-optimum, rangkaian neural tiruan (ANN), dan rangkaian neural ombak (WNN). Untuk kajian perbandingan antara reka bentuk campuran D-optimum, ANN dan WNN, set data dari reka bentuk campuran telah diterima pakai untuk meramalkan kekerasan dan kerapuhan tablet berdasarkan komposisi bahan yang optimum iaitu 30.608% daripada A, 15.000% daripada B, 5.764% daripada C, dan 46.628% daripada D. Berdasarkan nilai-nilai RMSE, R^2, dan AAD, ANN telah menunjukkan topologi GA yang memberikan persembahan rangkaian yang terbaik dalam kedua-dua kajian kekerasan dan kerapuhan. Seni bina terbaik tindak balas kekerasan adalah GA-4-12-1 dengan kepentingan pembolehubah; 24.79% daripada A, 27.45% daripada B, 22.37% daripada C, dan 25.39% daripada D. Sebaliknya, seni bina terbaik sambutan kerapuhan adalah 4-1-1 dengan GA-kepentingan pembolehubah; 10.59% daripada A, 2.73% daripada B, 18.49% daripada C, dan 68.49% daripada D. Urutan keupayaan ramalan keseluruhan bagi tindak balas kekerasan adalah ANN-GA>MD>WNN-GA, manakala bagi tindak balas kerapuhan adalah ANN- GA>WNN-GA>MD. Akhir sekali bagi prosedur keselamatan, ujian logam berat dan ujian mikrobiologi telah dilakukan. Hasil kajian menunjukkan tahap yang memuaskan bagi kedua-dua logam berat dan mikroba. Oleh

itu, formulasi tablet Okara telah berjaya dioptimumkan menggunakan kaedah kimometrik yang berbeza dan sangat bagus untuk industri nutraseutikal.

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I certify that a Thesis Examination Committee has met on 20th of June 2016 to conduct the final examination of Nur Izzati Mohamad Zen on her thesis entitled "Effects of Formulation Composition on Hardness and Friability of Okara Tablet using Different Chemometric Methods" in accordance with the Universities and University Colleges Act 1971 and the Constitution of the Universiti Putra Malaysia [P.U.(A) 106] 15 March 1998. The Committee recommends that the student be awarded the Master of Science.

Members of the Thesis Examination Committee were as follows:

Nor Fadzillah binti Mohd Mokhtar, PhD
Senior Lecturer
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Mohamad Zaki b Abd Rahman, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Internal Examiner)

Salina Mat Radzi, PhD
Associate Professor
Faculty of Science and Technology
Universiti Sains Islam Malaysia
(External Examiner)

ZULKARNAIN ZAINAL, PhD
Professor and Deputy Dean
School of Graduate Studies
Universiti Putra Malaysia

Date: 26 July 2016

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of Supervisory Committee were as follows:

Siti Salwa Abd. Gani, PhD
Associate Professor
Faculty of Science
Universiti Putra Malaysia
(Chairman)

Rosnah Shamsudin, PhD
Associate Professor
Faculty of Engineering
Universiti Putra Malaysia
(Member)

Uswatun Hasanah Zaidan, PhD
Senior Lecturer
Faculty of Biotechnology and Biomolecular Sciences
Universiti Putra Malaysia
(Member)

_____

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Declaration by graduate student

I hereby confirm that:

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This is to confirm that:

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Name of Chairman of Supervisory Committee:	Prof. Madya Dr. Siti Salwa bt. Abd. Gani	Name of Member of Supervisory Committee:	Prof. Madya Dr. Rosnah bt. Shamsudin

Signature:	_____
Name of Member of Supervisory Committee:	Dr. Uswatun Hasanah bt. Zaidan

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LIST OF ABBREVIATIONS

AAD	Absolute Average Deviation
AAS	Atomic absorption spectrophotometry
ANN	Artificial Neural Networks
ANOVA	Analysis of Variance
BBP	Batch Back Propagation
BGLB	Brilliant green lactose bile
BP	Baird Parker
BSA	Bismuth sulfite agar
CAB	Cellulose acetate butyrate
CAP	Cellulose acetate phtalate
cfu	Colony-forming units
Chol	Cholesterol
CMCNa	Sodium carboxymethyl cellulose
CV	Coefficient Variation
df	Degree of freedom
EC	Ethyl cellulose
FDA	Food and Drug Administration
GA	Genetic Algorithm
HCl	Hydrochloric acid
HEA	Hektoen enteric agar
H_2SO_4	Sulphuric acid
HPMC	Hydroxypropyl methyl cellulose
HNO_3	Nitric acid
IBP	Incremental Back Propagation
LDL	Low-density lipoprotein
L-EMB	Levine eosin methylene blue
L-HPC	Low-substituted hydroproxyl cellulose
LM	Levenberg Marquardt
LST	Lauryl sulphate tryptose
MCC	Microcrystalline cellulose
MLF	Multilayer feedforward
MLP	Multilayer Perceptron
MPN	Most probable number
MS	Mean square
MSE	Error mean square
MSR	Regression mean square
NaOH	Sodium hydroxide
NFE	Nitrogen-free extract
ODT	Orally disintegrating tablet
PC	Phosphatidyl choline
PCA	Plate count agar
PEG	Polyethylene glycol
PLS	Partial Least Squares
PRESS	Prediction Error Sum of Squares
PUFA	Polyunsaturated fatty acids
PVP	Polyvinyl pyrrolidone
QP	Quick Propagation

QSAP	Quantitative structure-analysis relationship
R^2	Correlation of determination
RMSE	Root Mean Square Error
RSM	Response Surface Methodology
SD	Standard Deviation
SS	Sum of squares
SSE	Error sum of squares
SSR	Regression sum of squares
SST	Total sum of squares
TDF	Total dietary fiber
TPC	Total plate count
WNN	Wavelet Neural Network
XLD	Xylose lysine deoxycholate
Y&M	Yeast and mold

CHAPTER 1

INTRODUCTION

1.1 Research background

Obesity is a disease where amount of fat exceeds in human body (James and Linton, 2008). Obesity is measured by body mass index (BMI). A person which have BMI higher than 30.0 is classified as obese person (Gumbiner, 2001). Obesity is strongly related with other chronic diseases like cardiovascular diseases and diabetes (Whitney and Rolfes, 2008). One of the method that can manage and prevent obesity problem is by consuming fiber-rich foods because high fiber food intake provide satiety (Eckel, 2003).

Okara is one of the low-cost nutritious fiber-riched in soybean, so it may treat weight loss (Li *et al.*, 2012). Okara is the by-product of the production of soybean milk and tofu. The major component of Okara is fiber, about 50% which composed of cellulose, hemicellulose, and lignin. Okara also contain about 25% of protein, 10% of oil, and low amount of starch and simple carbohydrates (Li *et al.*, 2012). It was also reported by Bowles and Demiate (2006) and Jackson *et al.* (2001) that 1/3 of total isoflavones was remained in Okara (Grizotto and Aguirre, 2011). Isoflavones has many advantages in health, like act as antioxidant and prevent chronic diseases like cancer, heart disease (Bowles and Demiate, 2006), obesity and diabetes. Thus, Okara will be very effective as dietary supplement. Okara in formulation of dietary supplement only requires one process which no heat applied. Hence, its nutritional value remained in the formulation. Furthermore, people nowadays are very busy with their work and forgot to take their meals daily. Highly nutrient Okara dietary supplement with will be very good in substitute meals or provide satiety for living a healthy lifestyle.

There are many forms of dietary supplements, for examples, tablets, capsules, liquids, powders, and gels. Dietary supplements are different from drugs; and they are non-potent drugs. Food and Drug Administration (FDA) defined a dietary supplement as an alternative food containing essential nutrients like vitamins, minerals and proteins. Subsequently, Nutrition Labeling and Education Act of 1990 added "herb or nutritional substances" to the definition (Oomah, 2000; Hoffmann and Manning, 2014). In the pharmaceutical industry, tablets are the most acceptable form for consumers in comparison with other oral dosage forms (Wen and Park, 2011). Tablet oral dosage has many advantages such as its ease of handling, chemically and physically stability, and being portable. Furthermore, this type of dosage form ensures accuracy and consistency of dosages (Gad, 2008). There are many examination can be done in order to maintain the physical qualities of the tablets, for examples hardness test, percentage friability test, disintegration test and dissolution test (Seitz and Flessland, 1965).

Tablets are mixtures of active ingredients and other excipients. Mixtures mean the sum of all the ingredients is 100% (Eriksson, 2008). There are many types of excipient with their own function in dosage formulation; diluents or fillers, binders, lubricants, glidants, antiadherents, disintegrants, colorants, and flavor or sweeteners. In order to optimize the mechanical strength of tablet, the excipients used for tablet formulation become the factor variables. From the previous study, it shown that maltodextrin is a good binder for a tablet, which is to provide cohesiveness within the tablet (Elnaggar et

al., 2010). Microcrystalline cellulose was used as the tablets' filler to improve the flowability during compression (Gad, 2008). The disintegrant used was guar gum. Guar gum is a very good disintegrant due to its high water solubility (Shirwaikar *et al.*, 2008). Silicon dioxide also used as the excipient but only as constant due to its function in reducing the friction in tablet formulation. The mixture design statistical method is the most suitable method used in optimizing the tablet production process. The mixture design method is usually used in mixture formulation (Brereton, 2003). For example (Eq. 1.1 and 1.2), in three components of formulation,

$$0 < x_i < 1 \quad 1.1$$

$$x_1 + x_2 + x_3 = 1 \quad 1.2$$

where i= 1, 2, 3 and x is the factor variables. There are many types of mixture design: simplex-lattice design, simplex-centroid design, axial design, and D-optimal design. In this study, computed-generated D-optimal mixture design was used. D-optimal design is constructed to minimize the overall variance of the predicted regression coefficient by maximize the value of determinant of the information matrix (Esbensen *et al.*, 2002). The advantages of D-optimal design, the experimental region is not simplex but it is irregular (Valko, 2000). As compared with other design, D-optimal has smaller number of runs, thus needs low cost of experimentation. Furthermore, combined mixture and process variables can be used in the same experimental design (Eriksson, 2008).

In this present work, Okara and other excipients used in tablet production were optimized using D-optimal mixture design in order to meet the physical properties of the tablet in term of hardness and friability. Then, the results were further validated using artificial neural network (ANN) and wavelet neural network (WNN) software. ANN and WNN are not similar to other standard statistical analysis, because the method is biologically brain-based. Furthermore, ANN and WNN is able to specify the optimum weight in the analysis through the learning process of a training set using various kinds of algorithms.

1.2 Problem statement

The influx of soybean waste or Okara became a worldwide problem. This problem is contributing to financial crisis. Furthermore, the increasing Okara production from soybean processing are causing environment contamination (O'Toole, 1999). So, the use of Okara in industry can provide a solution to these problems. Okara as dietary supplement is a very great idea because of its nutritional value. However, the use of Okara as excipient toward the mechanical strength as tablet have not tested yet. Moreover, according to statistic of obesity problem from 2006 to 2011 in Malaysia increases about 1.1% which is from 14.0% to 15.1% (Cheng, 2013). Furthermore, the dietary supplement in solid-dosage form is the best choice for consumer, because dietary supplement in powder form sometimes makes people nausea due to its milky taste. In addition, dietary supplement in solid-dosage form provide accurate content dosage because of its compacted texture.

1.3 Objectives

The main objective of the present investigation was to develop and optimize the formulation composition of Okara tablet on hardness and friability responses using

different chemometric methods. Therefore, the research was carried out according to the following specific objectives:

i. To evaluate the proximate composition of Okara
ii. To optimize the formulation composition of Okara tablet using D-optimal mixture design.
iii. To develop statistical algorithm approaches in optimizing the formulation composition of Okara tablet using neural networks.
iv. To evaluate the safety of Okara tablet using detection of microorganisms and heavy metals.

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BIODATA OF STUDENT

Nur Izzati binti Mohamad Zen was born in Johor (1991). She acquired her early primary study at Sekolah Kebangsaan Simpang Renggam, Johor, followed by secondary school at Sekolah Menengah Sains Kota Tinggi (2004-2008). After that, she completed her matriculation programme at Kolej Matrikulasi Negeri Sembilan. In 2010, she continued her study at Universiti Putra Malaysia, majoring in Biochemistry and graduated with a B. Sc. (H) in 2013. Thereafter, she enrolled M. Sc. programme at Halal Products Research Institute, Universiti Putra Malaysia to pursue her M. Sc. in the field of Halal Products Development.

PUBLICATION

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