UNIVERSITI PUTRA MALAYSIA

COMPACTION CHARACTERISTICS OF FICUS DELTOIDEA JACK EXTRACT POWDER

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COMPACTION CHARACTERISTICS OF *FICUS DELTOIDEA* JACK EXTRACT POWDER

By

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

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia
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COMPACTION CHARACTERISTICS OF *FICUS DELTOIDEA* JACK EXTRACT POWDER

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June 2012

Chairman : Assoc. Prof. Yus Aniza Yusof, PhD
Faculty : Engineering

In Malaysia, *Ficus deltoidea* is locally known as Mas Cotek and is traditionally used to treat cardiovascular diseases, diabetes, and as an aphrodisiac specifically to increase male virility. The main objective of this thesis is to investigate the compressibility and compactability of *Ficus deltoidea* extract powders for tableting processes. Avicel and Acdisol powders are used as excipients. Both of these powders are essentially easily soluble and disintegrate in water. The physical, material and flow properties of the powders have been investigated as it is essential to understand the compression and compaction mechanisms. The *Ficus deltoidea* extract powder has a particle size of less than 40 µm and was compressed into a tablet by using a 13-mm-cylindrical uniaxial die. Applied pressures between 7.53 to 73.84 MPa were adopted using a universal testing machine. To further investigate the properties, the friability and modified dissolution tests were carried out. This was aimed to provide a convenient soluble form for consumers who have difficulties in swallowing tablets and chewing difficulties, whereby the tablet can dissolve easily in water and can be drunk directly. From the tests, tablets composed of Acdisol had a faster dissolve time in the modified dissolution time test compared to Avicel. Based on these stud-

ies, a few recommended tablet conditions have been classified from the best conditions of compression and compaction characteristic tablet. The best formulation for the tablets was a combination of 50 % and 70 % of Avicel and Acdisol with *Ficus deltoidea* extract powder respectively at a pressure of 73.84 MPa. As a safety measure before consumption, these three main material powders were chosen for a toxicity test, utilizing an *in vitro* technique for testing cancer toxicity on human cells. Thus, this study provides information concerning the extent of the application of compression and compaction characteristics for product development of *Ficus deltoidea* extract as a safe and healthy supplement.

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

SIFAT KEMAMPATAN DAN KEPADATAN SERBUK EKSTRAK *FICUS DELTOIDEA* JACK

Oleh

FAIQA SHAZEAA BINTI MOHD SALLEH

Jun 2012

Pengerusi : Prof. Madya Yus Aniza Yusof, PhD

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Di Malaysia, *Ficus deltoidea* lebih dikenali sebagai 'Mas Cotek' dan secara tradisional ianya digunakan untuk merawat penyakit seperti kardiovaskular, kencing manis, afrodisiak, dan khususnya untuk meningkatkan kesejahteraan lelaki. Objektif utama tesis ini adalah untuk menyiasat kebolehmampatan serbuk ekstrak *Ficus deltoidea* dalam proses pembentukan tablet. Serbuk Avicel dan Acdisol telah digunakan sebagai eksipien, dimana pada dasarnya kedua-dua serbuk ini mudah hancur dan larut di dalam air. Sifat bahan dan aliran serbuk yang telah disiasat adalah penting untuk memahami mekanisme pemampatan dan pemadatan. Serbuk ekstrak *Ficus deltoidea* yang bersaiz zarah kurang daripada 40 μm telah dimampatkan pada tablet dengan menggunakan acuan keluli yang berbentuk satu arah silinder berdiameter 13-mm. Tekanan yang dikenakan adalah antara 7.53 dan 73.84 MPa dengan menggunakan mesin pemeriksa pemampat universal. Hubungan antara ketumpatan, daya ejeksi dan kekuatan tegangan dengan tekanan telah dikenal pasti bagi menyiasat kesan mampatan dan pemadatan pada serbuk ekstrak *Ficus deltoidea* dan eksipien yang berbeza komposisi. Siasatan ke atas sifat tablet diteruskan, apabi-

la ujian kerapuhan dan ubahsuaian kelarutan telah dijalankan. Ini adalah untuk menyediakan satu penyelesaian yang mudah untuk pengguna yang mempunyai kesukaran untuk menelan tablet dan masalah mengunyah, di mana tablet boleh larut dengan mudah di dalam air dan boleh terus diminum. Dari ujian yang telah dijalankan, tablet yang terdiri daripada Acdisol mempunyai masa yang lebih cepat untuk larut dalam air berbanding Avicel. Berdasarkan kajian ini, beberapa tablet telah disyorkan, apabila mematuhi syarat yang diklasifikasikan mempunyai keadaan terbaik dari tepi mampatan dan ciri-ciri pemadatan tablet. Tablet gabungan 50% dan 70% Avicel dan Acdisol dengan serbuk ekstrak *Ficus deltoidea* masing-masing pada tekanan daripada 73.84 MPa telah dipilih. Sebagai langkah-langkah keselamatan sebelum penggunaan, tiga serbuk bahan utama dipilih untuk ujian ketoksikan dengan menggunakan teknik in vitro pada ujian ketoksikan pada sel kanser manusia. Dengan demikian, penyelidikan ini menyediakan siasatan sejauh mana permohonan mampatan dan ciri-ciri pemadatan untuk pembangunan produk ekstrak *Ficus deltoidea* sebagai makanan tambahan yang lebih selamat dan sihat.

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I certify that an Examination Committee has met on 14th June 2012 conduct the final examination of Faiqa Shazeaa binti Mohd Salleh on her degree thesis entitled " Compaction Characteristics Of *Ficus Deltoidea* Extract Powder " in accordance with Universiti Pertanian Malaysia (Higher Degree) Act 1980 and Universiti Pertanian Malaysia (Higher Degree) Regulations 1981. The Committee recommends that the student be awarded the (Name of relevant degree).

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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 the Supervisory Committee were as follows:

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DECLARATION

I declare that the thesis is my original work except for quotations and citations which have been duly acknowledged. I also declare that it has not been previously, and is not concurrently, submitted for any other degree at Universiti Putra Malaysia or at any other institution.

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FAIQA SHAZEAA MOHD. SALLEH

Date: 14 June 2012

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Acd	Acdisol/Croscarmellose Sodium
Avi	Avicel pH101
ANOVA	Analysis of variance
ASTM	American Society for Testing and Materials
ATCC	American Type Culture Collection
Ave	Average
BSI	British Standards Institute
CaOV3	Ovarian carcinoma cell line
CI	Carr Index
FD	*Ficus deltoidea*
FRIM	Forest Research Institute of Malaysia
HL60	Leukemic cells
HR	Hausner Ratio
HT29	Human colon cancer cell line
IChemE	Institution of Chemical Engineers
MAKNA	'Majlis Kanser Nasional'
MARDI	Malaysian Planting Research Institute
MCC	Microcrystalline cellulose
MCF-7	Estrogen receptor alpha positive breast cancer cells
MDA	Estrogen receptor alpha negative breast cancer cells
MCS	Major consolidation stress
PVP	Polyvinyl pyrolidone
SEM	Scanning electron microscope
SD	Standard deviation
SE	Standard error
UM	University Malaya
UYS	Unconfined yield strength
WHO	World Health Organization
vs	Versus
AOR	Angle of repose [^{o}]
ff	Flow factor

IC_{50}	50 % inhibition of the viability of all the experimental human cancer cells
m	Weight of powder [kg @ g]
P	Applied pressure [MPa]
ρ_b	Bulk density [kgm^{-3}]
ρ_{rel}/D	Relative density [kgm^{-3}]
ρ_{tr}	True density [kgm^{-3}]
ρ_t	Tap density [kgm^{-3}]
R^2	Correlation coefficient
T	Tensile strength [MPa]
t	Tablet thickness [m]
V	Volume after compression [m^{-3}]
V_t	Volume of tapped powder [m^{-3}]
V_b / V_o	Initial volume of the powder bed [m^{-3}]
w	Weight of tablet [kg @ g]
ϕ_w	Angle of Wall Friction [^{o}]
τ	Average shear stress [kPa]
σ	Normal stress [kPa]
δ	Effective angle of internal friction [^{o}]

CHAPTER 1

INTRODUCTION

1.0 Introduction

In this chapter the background of the main sample, *Ficus deltoidea*, is introduced. It explains the benefits of the herb for traditional and modern consumption. It also describes the current applications of *Ficus deltoidea* in the nutraceutical industry in Malaysia. Then, it explains the summarization of the development of the study, which includes the flowability and processing steps in producing a soluble tablet form by a compaction mechanism from a powder form. Lastly, the objectives of the research are presented at the end of this chapter.

1.1 *Ficus deltoidea*

1.1.1 Background of *Ficus deltoidea*

Malaysia is listed as the 12th nation with the greatest biodiversity in the world and ranks fourth in Asia with over 3000 species of medicinal plant, while only about 50 herbal plants are used commercially and even less are being researched scientifically for their medicinal properties in nutraceutical products (Joy *et al.*, 1998). The term "nutraceutical" is a combination from nutrition and pharmaceutical, which is defined as food products that provide medical and health benefits including the prevention or treatment of disease (Brower, 1998). Due to their promising and highly commercial potential, the herbs in Malaysia are studied to further develop their scientific uses in terms of pharmaceutical dosage, such as in liquid, capsule, pill or tablet form due to their health-giving properties and nutritional benefits. Examples of popular herbs in Malaysia which are easily identifiable herbal plants are Tongkat Ali (*Eurycoma longifolia*), Kacip fatimah (*Labisia pumila*), Hempedu bumi (*Andrographis*

paniculata), Misai kucing (*Orthosiphon stamineus*) and Mas cotek (*Ficus deltoidea*).

This study focuses on Mas cotek, otherwise known by its scientific name *Ficus deltoidea*, manufactured as pharmaceutical herbal products in a cylindrical tablet form. In Malaysia, this medicinal plant is locally known as Mas cotek or *serapat angin, telinga beruk, sempit-sempit, agoluran* and a few other names. In Africa it is known as 'Kangkalibang' and in other western countries it is well known as Mistletoe fig or Mistletoe rubber plant (Bailey *et al.*, 1976). It is a valuable herbal plant that grows wild in the tropical forests of Malaysia and has become an international favourite for the medicinal and healthy values that it contains. As a herbal tree, almost all of the parts of the *Ficus deltoidea* plant including the roots, bark, stems, leaves and fruits are believed to have medicinal properties, which are beneficial for health purposes.

Ficus deltoidea is an evergreen shrub or small tree, which is usually bushy and sometimes epiphytic in the wild (Starr *et al.*, 2003). It is from the family of Moraceae and is normally found in several countries in Southeast Asia, including Malaysia (Mat-Salleh *et al.*, 2002). It is acknowledged that the *Ficus deltoidea* has male and female species with different shapes of leaves corresponding to its habitat. The upper leaf surface of Mas cotek is smooth while the other side of the leaf is wavy and has fine orange lines. The colour of the leaf on the upper surface is vegetable green whereas the lower surface is orange-green with black spots in between the veins. The main difference that can be seen between the male and female species of Mas cotek is the shape of the leaf, as the male leaf is small, slim and has a tapered shape (**Figure 1.1b**.), whereas the female species has bigger,

wider and rounder shapes (**Figure 1.1a.**). Moreover, there are red spots on the lower part of the male species leaf, while there are black spots and a clearer look compared to the male on the lower part of the female species leaf. This humble tree may reach up to two or three meters tall.

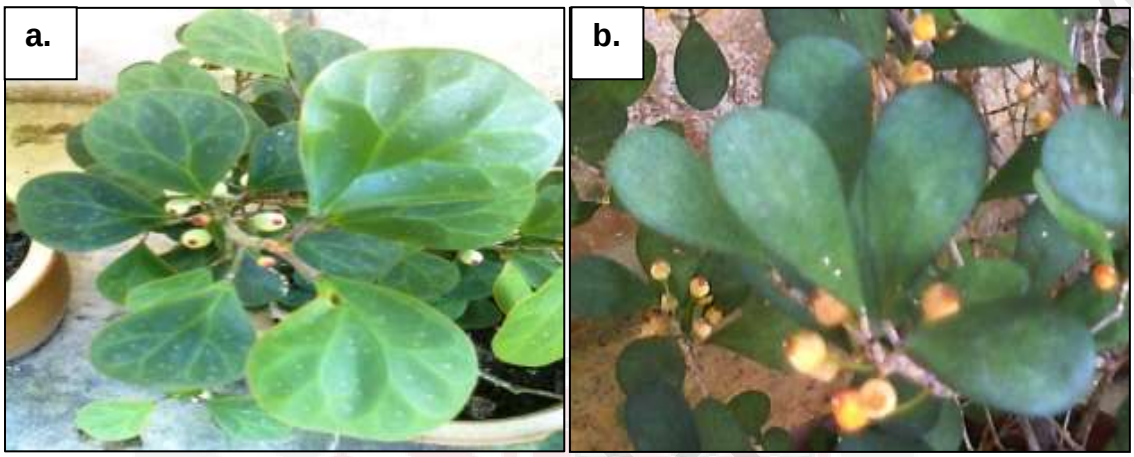

Figure 1.1: *Ficus deltoidea* leaves; a. female leaves and b. male leaves

1.1.2 Benefits of *Ficus deltoidea*

There are many studies which have proven or shown that *Ficus deltoidea* has medicinal properties that can complement the human body. In Malaysia, different parts of the *Ficus deltoidea* plant are traditionally used to treat various types of ailments or diseases due to the many active components it contains. Research results by two local institutions in Malaysia, the University Malaya (UM) and the Malaysian Planting Research Institute (FRIM) shows that Mas cotek possesses five active components which are required by the human body, namely flavanoids, tannins, triterpenoids, proanthocyanins and phenols (Anon, 2010). Other researchers in Forest Research Institute of Malaysia (FRIM) have proved that the *ficus* species contain compounds such as flavonoids, steroids and triterpenoids, alkaloids, α-tocopherol and its derivatives (Zunoliza *et al.*, 2009).

Each part of the *Ficus deltoidea* possesses various medicinal values or health benefits, for example contracting the vagina after delivery, delaying menopause, decreasing blood pressure, reducing lipids and cholesterols, possibly reducing the risk of cancer and reducing sugar levels in the blood (Sharipah *et al.*, 2009). Accordingly, the parts of *Ficus deltoidea* that are believed to have medicinal properties are the leaves, roots, and fruits (Adam *et al.*, 2007). Traditionally, the leaves are used for treating and preventing diarrhoea, pneumonia, diabetes, high blood pressure, heart problems, gout and skin diseases (Fasihuddin *et al.*, 1991; Zunoliza *et al.*, 2009). The study found a high total amount of polyphenols, flavonoids and tannins in the leaf extracts, which are associated with good antioxidant activity and hypoglycaemic properties (Zunoliza *et al.*, 2009). These may be used to prevent oxidative stress, as associated with diseases such as cancer, neurodegenerative and cardiovascular diseases. Other parts of the *Ficus deltoidea* plant, such as the fruits are chewed to relieve toothache, colds and headaches (Mahmood *et al.*, 2010). As for the roots and leaves, these are applied externally to sores, wounds and around joints for the relief of rheumatism and are traditionally consumed as a herbal drink for women after childbirth to help strengthen up the uterus as applied by the Malaysian people (Sulaiman *et al.*, 2008). These are also mixed to be used to relieve fever and headache (Mat-Salleh *et al.*, 2002).

Moreover, the plant is used traditionally to treat cardiovascular diseases and diabetes (Hakiman *et al.*, 2009). Further, *Ficus deltoidea* also can be used as an aphrodisiac, specifically to increase male virility (Hakiman *et al.*, 2009). Lastly, *Ficus deltoidea* is also believed to be beneficial for the female reproductive system, as it improves blood circulation and helps with rejuvenation. As a result of all these studies, the

Ficus deltoidea plant can be used by both sexes, compared to *Eurycoma longifolia* which can only be used for males as to increase virility while *Labisia pumila* is used only by females to facilitate childbirth plus as a post-partum medication. Thus, this herb may become a huge and beneficial economic product for Malaysia as it can be exported internationally in standardized pharmaceutical dosage forms.

1.1.3 *Ficus deltoidea* in the Nutraceutical Industry

Recently, there has been great interest in herbal supplements among patients, but *Ficus deltoidea* products are still relatively new in the nutraceutical industry and market compared to other herbs such as Tongkat Ali and Misai kucing. According to Farhana *et al.* (2010) there are several types of Mas cotek (*Ficus deltoidea)* products being produced by Malaysian companies such as tea, coffee, capsules, and massage oil. Their study also indicated that the number of Mas cotek manufacturers has increased through the years up to the present, due to the demand for *Ficus deltoidea* products increasing from 2004 to 2007 (Farhana *et al.*, 2010). Thus it can be proved that there exists a strong positive relation between the availability of medicinal plants or herbs and human health. As all the studies cited above indicate the potential for the plant as usable or beneficial in manufacturing health products, thus research on the standardization of herbal products into pharmaceutical dosages in tablet form and its efficiency in fighting human cancer cells becomes a challenge due to a lack of knowledge as the plant has not been fully studied.

1.2 Review of Overall Processing Steps

1.2.1 The Flow and Tableting Process

Powder flow is defined as the movement of a bulk of powder particles in among other particles or along a container wall surface. The knowledge of powder behaviour can be used for equipment and performance prediction while the flow characteristics can be of great importance in handling and processing operations of the bulk material, as the ease of using the powder in tableting may depend on them. Hence, the shear testing of bulk solids by using the Jenike shear tester is extensively applied in the recent studies of the behaviour of pharmaceutical and food powder materials.

Next, the powder compaction process of the solid particles into compact dosage form involve the application of mechanical force with sufficient strength, as used in a wide range of industries, such as in the production of food, powder metallurgy and pharmaceutical tablets. The process is fast, economic and lends itself to high-volume production, for which the production rate depends on the complexity of the powder to become compact. This can be shown where recently the modern pharmaceutical presses produce hundreds of thousands of tablets per hour. Mostly, pharmaceutical tablets also have good long term storage stability, good tolerance to temperature and humidity and ease of use for the patients (Han *et al.*, 2008).

In this study tablets were made by using a direct compaction method, whereby a 13-mm-uniaxial die was adopted. The direct compaction method was used because of its lower cost, lower power consumption, less mechanical procedures and it is the

fastest method. The compaction process is composed of following steps (Pitt et al., 2007):

i. delivery of powder to the die,
ii. die fill,
iii. compaction of powder,
iv. ejection, and lastly,
v. post-compaction operations.

1.2.2 Characteristics of Powders and Tablets

The characteristics of the powders used and the tablets after compaction are very important in this study to select the best recommended and standardized tablet for manufacturing with the best characteristics and condition. A pharmaceutical dosage form, or tablet, is mostly composed of multiple components which comprise of an active drug ingredient (main sample; *Ficus deltoidea* extract so as to exert a pharmacological action) and inactive ingredients (excipients). The design of such excipients is quite complicated based on the range of formulations and a choice of compaction. As a result, the excipients affect the characteristics of the tablet, such as its mechanical strength. Two different fillers or excipients are blended uniformly with the *Ficus deltoidea* extract to produce a flat face tablet form with good characteristics.

In the additional stage of the study, a cytotoxicity test is undertaken on selected human cancer cells for each main sample; *Ficus deltoidea* extract, Avicel and Acdisol. The measurement of cytotoxicity plays a central role in attempts to find

new anti-cancer drugs in addition to elucidating their mechanism of action as well as basic checking that the sample is safe, nontoxic and harmless to humans.

1.3 Research Problems and Significances of Study

Shown by other studies that production of products, such as tea, coffee, capsules and massage oils are increased through the years (Farhana *et al.*, 2010), thus there are still low number of scientific work has been conducted to investigate the physical properties of *Ficus deltoidea*, which may give benefits to its handling in manfacturing. Still, there is lack of empirical knowledge and fundamental understanding the relative contribution of mechanical properties of *Ficus deltoidea* water extract powder; such as flowabilities and tableting of the this herb to neutraceutical industries. In addition, as all the studies cited above indicate the potential for the plant as usable or beneficial to our health. It include with low knowledge approach of its toxicity to human cells, also its potential to cure cancer illnes in human. Thus, the significance of the study are shown below, as we focuses the objectives of the study:

1. Improve knowledge in handling and processing operation of Malaysian herb (*Ficus deltoidea* extract powder)
2. Improve the quality of die compaction tablet production particularly its mechanical properties.
3. Increased knowledge of the functionality of a binder.
4. Develop knowledge of medicinal properties of Ficus Deltoidea extract powder as better herb supplement.

1.4 Research Objectives

The overall objectives of this research are:

1. To obtain the physical, mechanical and flow properties of *Ficus deltoidea* extract powder.
2. To investigate the compaction characteristics of *Ficus deltoidea* with the addition of a binder.
3. To determine the cytotoxicity test of *Ficus deltoidea* extract powder.

1.5 Outline of the Thesis

Chapter 1 is an introductory chapter which briefly reviews one of the famous herbs in Malaysia, namely *Ficus deltoidea*. The background of the herb and its advantages for consumers are explained. The expectations for this new drug may brighten and diversify the nutraceutical industry and its potential as a commercial plant. The reviews of the overall processing steps that clarify the scope of the study are also presented. Lastly, the overall objectives are described.

In **Chapter 2,** the theoretical background and literature review are given for the background theory and the analysis involved in this study. The background theory discusses the raw ingredients including the binders, the powder properties and the mechanical properties of the tablets. The analysis covers the tableting process, the mechanical behaviour and lastly, the cytotoxicity test.

Following on in **Chapter 3**, the physical properties are discussed especially the flowability properties of the powders used. This is in order to compare and optimize the understanding of the powders that may allow for a better choice of

recommended tablet formulation between *Ficus deltoidea* and the binders. It also benefits the handling and tableting in subsequent steps of the experiments or in industry. Hence, in order to compare and optimize the powders with regard to flowability, a Jenike shear tester was used to measure the flow properties of the powder particles: the effective angle of internal friction, flow function and the angle of wall friction.

Next, **Chapter 4** examines the effect of feed powder quantity and the effect of binder compositions on compaction with different formulations of *Ficus deltoidea* tablets. Hence, in this study, the Ficus deltoidea extract powders with different compositions of binder are compressed by uniaxial die compaction method at pressures ranging between 7.53 and 73.84 MPa using Universal Testing Machine (Instron 5566).Thus, the aim of the chapter is to determine the best-recommendation for formulations of tablets by comparing the tablet characteristics.

The cytotoxicity test for the powders is reviewed in **Chapter 5**, especially the traditional herb *Ficus deltoidea* due to its various medicinal properties that can well complement the human body. Therefore, the investigation includes the cytotoxicity test by utilizing the *in vitro* technique for testing toxicity on human cancer cells for the product development of *Ficus deltoidea* extract as a safe and healthy supplement for consumers.

Lastly, **Chapter 6** presents a summary of the overall work of this research. In addition, recommendations or suggestions for future work are also presented in this final chapter.

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