UNIVERSITI PUTRA MALAYSIA

FLOWABILITY OF SELECTED MALAYSIAN HERBAL POWDERS AND THEIR FORMULATIONS

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CHRISTOPHER JOSEPH ETTI

September, 2015

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This thesis presents a study on flowability of selected Malaysia herbal powders and their formulation. *Orthosiphon stamineus, Eurycoma longifolia jack, Labisia pumila and Andographis paniculata* powders and a freeze dried extracts of *Labisia pumila* which all have a wide industrial and human applications were used. This study evaluates flowability of the selected herbal powders based on conventional methods of flow measurements (like bulk and tapped densities, Carr index, Hausner ratio and angle of repose), with technological advanced, innovative methods of characterization of powder flow such as cohesion determination, shear cell for effective angle of internal friction and wall friction angle and the use of very recently automated powder flow analyzer (powder rheometer). Powders material properties like particle size, moisture content, tap, bulk and true densities were determined and their influence on flowability properties were evaluated. The effects of anti-caking agents (flow aids) on the powders using the powder flow analyzer were also described. The herbal powders were also formulated with sugar and creamer into herbal powder beverages mix and their flowability was also investigated. *Labisia pumila* powder was compressed into tablets using a stainless steel cylindrical uniaxial die of a 13-mm- diameter with compaction pressures ranging from 7 to 25 MPa. Two feed weights, 0.5 and 1.0g were used to form tablets and four compression models were used to describe and understand compressibility characteristics of the herbal powders. The strength of the tablets increased with increase in compaction pressure. Powders with smaller particle sizes gave more problems to flowability. *Labisia pumila extracts* with highest particle size range was freest with the least cohesion index, least angle of wall friction, least effective angle of internal friction as well as least angle of repose. The mean caking strength of powders reduced by the addition of 1% Silicon dioxide and potato starch respectively. The flowability properties of all the formulated mix was greatly improved based on enhancement of material properties. Toxicological studies of the formulated beverage mix on healthy female wistar rats showed the mix to

be safe after the acute oral toxicity and sub-chronic studies was carried out for 28 days. In conclusion, this study enhances the understanding of powder flowability which can improve the development and formulation of herbal powder beverage mix.

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysis sebagai memenuhi keperluan untuk ijazah Doktor Falsafah

KEUPAYAAN ALIRAN DAN FORMULASI SERBUK HERBA MALAYSIA TERPILIH

Oleh

CHRISTOPHER JOSEPH ETTI

September, 2015

Pengerusi: Profesor Madya Yus Aniza Yusof, PhD

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Tesis ini membentangkan kajian keupayaan aliran serbuk herba Malaysia yang terpilih serta rumusan mereka. Serbuk *Orthosiphon stamineus, Eurycoma longifolia jack, Labisia Pumilia* dan *Andographis paniculata* dan ekstrak kering beku daripada Labisia Pumilia yang mempunyai aplikasi yang luas oleh manusia dan industri telah digunakan. Kajian ini menilai keupayaan aliran serbuk herba terpilih berdasarkan kaedah konvensional pengukuran aliran (seperti kepadatan pukal dan mampat, indeks Carr, nisbah Hausner dan sudut berbaring). Dengan kaedah teknologi yang maju, pencirian inovatif aliran serbuk seperti penentuan perpaduan, ricih sudut geseran dan dinding dalaman yang berkesan dan juga penggunaan analisis aliran serbuk automatik. Sifat-sifat bahan serbuk seperti saiz zarah, kandungan lembapan, paip, pukal dan kepadatan sebenar ditentukan dan pengaruh mereka terhadap sifat-sifat keupayaan aliran telah dinilai. Kesan ejen anti-menyelaputi keatas serbuk juga diterangkan menggunakan analisis aliran serbuk. Serbuk herba tersebut juga telah dirumus dengan gula dan krimer ke dalam minuman campuran serbuk herba dan keupayaan aliran mereka juga diselidik. Serbuk *Labisia Pumilia* telah dimampatkan ke dalam bentuk menggunakan keluli tahan karat satu arah 13-mm-diameter dengan tekanan pemadatan antara 7 hingga 25 MPa. Dua nilai suapan, 0.5 dan 1.0g telah digunakan untuk membentuk dan empat model mampatan telah digunakan untuk menggambarkan dan memahami ciri-ciri ketermampatan serbuk herba tersebut. Kekuatan pil meningkat dengan pertambahan tekanan pemadatan. Serbuk dengan saiz zarah yang lebih kecil memberi lebih banyak masalah kepada keupayaan aliran. Ekstrak *Labisia Pumilia* dengan saiz zarah yang tertinggi mempunyai indeks perpaduan rendah, indeks sudut geseran dinding rendah, sudut geseran dalaman rendah serta sudut berbaring rendah. Purata kekuatan menyelaputi serbuk berkurang masing-masing dengan penambahan 1% silikon dioksida dan kanji kentang. Sifat keupayaan aliran semua rumusan campuran bertambah baik disebabkan oleh sifat-sifat bahan yang lebih baik. Kajian formulasi minuman campuran terhadap tikus sihat wistar betina menunjukkan rumusan campuran adalah selamat selepas kajian ketoksikan oral dan sub-kronik telah dijalankan selama 28 hari. Kesimpulannya, kajian ini meningkatkan pemahaman tentang

keupayaan aliran serbuk yang boleh meningkatkan pembangunan dan pembentukan serbuk campuran minuman herba.

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

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a	Kawakita and Lüdde's constant represent as porosity of powder
a_e	Empty aluminium cup in crude fat calculation
a_l	Weight of an aluminium cup with sample in crude fat calculation
A_c	Walker's intercept
A_{10}	Parameter related to the compact densification by particle deformation in Panelli-Filho model
b	Kawakita and Lüdde's constant; represent as easiness in volume reduction to occur
B	Heckel's intercept
B_{10}	Parameter related to powder density at the onset of compression in Panelli-Filho model
Carr I.	Carr Index
C_r	Relative volume reduction
C_h	Cohesion (kPa)
CI	Cohesive index
d_d	Tablet diameter (m)
d_m	Mean diameter of the constituent particles (m) in mass flow rate
D	Orifice diameter (m) in mass flow rate
D_i	A measure of packed initial relative density of formulations
D_{av}	Average particle diameter (cm) in angle of repose
E_b	The initial porosity in tapped density
F_t	Tensile force (N)
g	Weight of crucible together with the ash after the furnace in ash content calculation
h	Weight of empty crucible in calculation of ash content
HR	Hausner Ratio
K	Heckel's slope

L	Overall length of the profile under examination (m) in surface roughness test
M	Moisture content in % dry basis
n	Shape factor based on specific surface in angle of repose
P	Compaction pressure
P_k	Pressure required to reduce half of the volume of the powder bed in Kawakita and Lüdde model
P_y	Yield pressure
R_a	Arithmetic average surface roughness or average deviation (μm)
S_g	Specific gravity
t	Tablet thickness (m)
T	Tensile stress (MPa)
V	Volume of powder at compaction pressure P (m^3)
V_b	Volume of the powder obtained from tarred graduated cylinder without tapping (m^3)
V_m	Mass flow rate (kg/s)
V_o	Initial volume (m^3)
V_x	Relative volume (m^3)
V_{ta}	Volume of the powder bed after 500 taps (m^3)
V_1	Volume of acid used in the titration
V_2	Corresponding amount of acid for the blank titration
W	Walker's constants and describes the compressibility coefficient
w_t	Weight of powder (kg)
W_s	Weight of sample (g)
$Z(x)$	Profile ordinates of the roughness profile in surface roughness tests
σ_t	Tablet tensile strength
ρ_a	Apparent density
ρ_b	Bulk density (kg m^{-3})
ρ_t	True density

ρ_{rel}	Relative density
ρ_{tap}	Tapped density of the powders
σ_o	Yield strength
$\propto$, φ	Are empirical coefficients
$\emptyset_r$	Angle of repose (degrees)
δ	Effective angle of internal friction
μ	Wall friction coefficient
$\emptyset_w$	Angle wall friction
τ	Shear stress at the wall
σ	Normal stress at the wall (MPa)
τ_f	Failure shear stress (MPa)
j	Shear index (dimensionless)

CHAPTER 1

INTRODUCTION

1.0 Introduction

This Chapter introduces the study background, herbs and their trends, herbal products, herbal powders used and their benefits are also presented. Followed by the problem statements, objectives, scope and relevance of the study and thesis outline.

1.1 Background of Powder Flowability

Different materials have different mode of behaviour with respect to flowability. For example, the flow of water when poured from a bottle is different from that of a gel like liquid from the same bottle in terms of the overall time it takes for the bottle to be completely emptied. The situation is also similar when it comes to solid particles in form of powders. Different powders have different particle sizes and shapes distribution, different weights, different chemical composition as well as different moisture contents and all these disparities also influence their flow behaviour (Schwedes and Schulze, 1990). Powder flowability behaviour study is very important because failure to understand may result in flow problems which can be expensive for the industries to offer solution. Prescott and Barnum (2000) reported that the final product quality of solid dosage form in the pharmaceuticals depends upon powder flow during manufacturing and flow complications like arching and rathole formation, may develop in the equipment that are used in handling fine powders. Muzzio *et al*. (2001) stressed the significance of powder technology processes in the production of pharmaceutical products like tablets and capsules. According to Larhrib *et al*. (2003) report, needle-shaped powders have the ability to adversely influence drug delivery from dry powder inhalers, likely because of the inferior flowability properties of the powders. Thalberg *et al.* (2004) proposed the importance of adjusting and controlling the flowability behaviour of fine powders in processing and formulation to enhance successful product development for inhalation. Fitzpatrick *et al*. (2004) also stated that powder properties can influence powder behavior in the course of storage and handling operation as flowability problems are frequently connected to the flowability pattern in the vessel. Prescott and Barnum (2000) showed powder flowability to be a collective effect of the impact of material properties and the equipment used to handle, store or process the material. Powders that indicate flow difficulties may be classified as poorly flowing or non-flowing. Such difficulties in flowability are common especially, that of cohesive powders with particle size range below 100μm. A number of reasons are responsible for this difficult behaviour, e.g. cohesive bridges formation and mechanical blocking of discharge openings by clumps or agglomerates. Thus, the flowability enhancement of such powders is a vital concern in research and product engineering. The flowability behaviour of cohesive powders is a function of powder physical or product characteristics and environmental conditions.

Many industrial operations make use of their raw materials in the powder forms and the outcome of the final products may as well be in the powder form. These industrial operations can be grouped into powder production, powder storage, powder transportation and powder processing. The need to understand powder flow is very essential during mixing, packaging, and transportation because various powder materials possess various characteristics. In general, powder flowability is about movement of the powder. The movement can be categorized in two classes according to Fitzpatrick *et al.* (2007) as packed and fluidized movement. Packed movement is a situation where particles of powders are not being suspended in a fluid and the powder particles are in close contact with each other and there is significant friction with cohesion forces resisting flow. Fluidized or suspended movement is a situation whereby particles are fully suspended in a fluid, for example, in fluid beds and dilute phase pneumatic transport. Handling and processing methods like flow from silos and hoppers, mixing, transportation, compression and packaging operations depends to a very large extent on powder flow properties (Knowlton *et al*., 1994; Peleg, 1978). One major problem associated with the powder flow in the industries is how to obtain consistent and steady flow out of feeders and hoppers without unnecessary spillage and dust generation.

1.2 Herbs and their Trends

Historically, herbs have been utilized as a source of food, medicinal and beauty enhancer as well as for fragrance. The use of herbs for medicinal purposes started from the era of Greek civilization in the West to the Arabic, Chinese and Indian civilization in the East (Aziz *et al.*, 2005). There is a rising trend of people leaving synthetic drugs to herbal cures. Some of the reasons for the shift from synthetic drugs to herbal cures involve a preference for a wellness oriented self-administered healthcare, the occurrence of chronic sickness that cannot be treated with conventional drugs and high pace of life which prompts higher stress and reduce free time (Pilzer, 2001). The global herbal supplement and remedies market is forecasted to value at USD 93.15 billion by 2015 and USD 107 billion by the year 2017, this forecast is impelled by rising aging population and increase in consumer awareness of general health and wellbeing (Stoia and Oancea, 2013). Historically, as reported by Kaefer and Milner (2008), herbs and spices have been significantly utilised traditionally due to their flavour enhancement properties and their medicinal values. The recent estimated market worth of herbal products used for traditional and complementary medicine is known to be between USD 40 to 100 billion with an average growth rate ranging from 15 to 20% each year (Aziz et al., 2004). Malaysia is a significant global player in the herbal medicine industry especially for its rich biological and cultural heritage as well as its unique trade links (Arif, 2002). Malaysia ranks 12th amongst the nations in the world in terms of bio-diversity and ranks 4th in Asia with more than 15,000 flowering plants and over 3,000 species of medicinal plants (Adenan, 2003). Out of the 3,000 enlisted medicinal plants species, it is only about 50 species that are being utilised and even less are being explored scientifically for their therapeutic behaviours, and still out of this 50, many have yet to be catalogued comprehensively through ethno botanical research (Adenan, 2003; Aziz and Sarmidi, 2003). Hence, Malaysian government are very supportive of

the development of its herbal industry. Malaysia has a rich tradition of herbal products which are mainly used for food, health and beauty. In 1997, Malaysians exhausted over RM 4.55 billion of herbal products (Aziz et al., 2005). The large market is due to the nutritive and medicinal properties of the herbs to enhance the general well-being such as improving blood circulation and reducing sugar level.

There are numerous key stages in the manufacturing of herbal product; which are herbal crop planting, herbal product manufacturing and marketing, pre-processing which involve herbs size reduction through chopping and grinding for proper processing, and good storage methodologies which guarantee the maintenance of active phytochemicals before processing. New methods of producing extracts from herbs are highly necessary in order to develop or produce herbal resources of greater yield, minor operating costs and faster production rate. Marketing of herbal products can be done in a variety of forms such as capsules, tablets, tea bags, extracts and essential oils. The major issue in the production of herbal products and medicine is standardization. Standardization process involves the production of herbal resources like extracts or phytochemicals with guaranteed products potency and stability in active compound content level. Thus, high level of knowledge and skills in phytochemical analysis and process technology are necessary to ensure the required quality assurance.

The following are some common herbal products outlined below according to Aziz *et al*. (2005):

(a) Phytochemicals: This originated from Greek word "phyto" which means plant. It denotes all naturally occurring chemicals present in plants. Plants are major sources of many modern pharmaceutical (drugs). Approximately one quarter of most drugs contain plant extracts or active components acquired from plant substances.

(b) Cosmeticals: It is a combination of cosmetic and pharmaceutical and it describes ingredients that are made up of cosmetics that are bioactive in nature and also exert effects on people like anti-wrinkles creams, baldness treatments, moisturizers and sun screens.

(c) Nutraceutical: May be referred to as any substance that is considered to be food or part of a food that give therapeutic and health benefits, which may also include prevention and treatment of disease. Within the confines of the above broad definition, neutraceuticals can be nutrients that are isolated, dietary supplements, processed foods, herbal resources or genetically engineered "designed foods".

(d) Oleoresin: These are pure extracts of a spice or herb which is made up of concentrated natural liquid flavourings made of both volatile and non-volatile flavour compounds.

(e) Essential oils: These are plant volatile parts that are principally responsible for its distinctive aroma. It can be applied to enhance health via its effects on the body.

1.3 Problems Statement

The flow properties of these tropical herbal powders, such as *A. paniculata, E .longifolia, O. stamineus* and *L. pumila* are significant in handling and processing operations (Peleg 1978; Knowlton *et al*., 1994; De-silver 2000; Ortega-Rivas 2003). Powders normally flow under the influence of applied stress, this condition dictate the behaviour of powders in the die of a tablet compression machine (Sinka *et al*., 2004). In other words, without flowability there will be no compression (Li *et al*., 2004). There are no reported works on the compression properties of *L. pumila* powder yet as they have been reported on the other three tropical herbs, *A. paniculata, E. longifolia, O. stamineus* (Yusof *et al*., 2011; Mohd Salleh *et al*., 2014). Generally, flowability problems in hoppers and silos are common place challenges for engineers and process operatives (Purutyan *et al*., 1998; Johason, 2002; McGee, 2004). Powder discharge failure out of bins, hoppers, silos and unpredictable flow in feeders, dosing machines and packing machines normally cause undesirable interruptions in the production process, which may at times lead to complete plant shut down so as to correct the restrictions and stoppages. It can also lead to disparities in mixing process, pack weight, sensory and performance properties of powder products. Information on powder flowability is insufficient and would be useful in investigations on proper handling, processing operations, powder storage and transportation, and to enhance the product quality and shelf life. More than 50% of all materials used in all industries are estimated at some stage, to be in powder form. Measuring of powder and granule flow objectively can:

- Enable all customers to avoid extensive costs and time wastage involved in unloading powders that will be stocked in storage containers without proper flow.
- Enable the achievement of the best product formulation with properties that suit the requirements
- Ensure improvement in the quality and consistency of the product
- Enable the saving of costs by optimizing storage, packing, handling and transportation.

Numerous researches carried out on these selected herbs so far are limited to their chemical, therapeutic and medicinal properties with very little report on the powder compression of the herbs, *A. paniculata, E. longifolia* and *O. stamineus* (Yusof *et al*., 2011; Mohd Salleh *et al*., 2014). This study will enhance knowledge on compression properties of *Labisia pumila* powder which have not been reported on before, and flowability of all these tropical herbs, *Andrographis paniculata, Eurycoma longifolia*, *Orthosiphon stamineus* and *Labisia pumila* powders used.

Many powders and ingredients mixes are rendered complex because they contain many dissimilar components, and hence, it is difficult to predict their flow behaviour. And during handling process, storage period, processing and distribution to the final consumers, the powders may very much experience a variety of temperatures and humidity changes which may change the handling behaviour and appearance of the

powders. This is principally important especially if powders are transported to hotter, more humid climates, where a mix may cake solidly or liquefy from absorbing water. The consumer usually does not expect lumping, caking or difficulty in discharging the powder from its container. The flowability characteristics of tropical herbal powder extracts are neither well documented nor understood. The aim of this work was to investigate the flowability properties of *A. paniculata, E. longifolia, O. stamineus* and *L. pumila* powders. To also investigate the compressional properties of *L. pumila* powder which could also be said to be flowability under applied load and compare its result with the published compression results of *A. paniculata, E. longifolia* and *O. stamineus* powders. These herbal powders were also formulated into herbal powder beverage mix and their physical, flowability and proximate properties were analysed. The effect of anticaking agents on the flowability of both the herbal powders and the formulated herbal powder beverage mix was also carried out. The herbal powders formulated beverages mix were subjected to toxicological evaluations on mature healthy female wistar rats to ensure the safety of the beverages.

1.4 Scope and Relevance

This study evaluates flowability of the selected herbal powders based on conventional methods of flow measurements (like bulk and tapped densities, Carr index, Hausner ratio and angle of repose), With technological advanced, innovative methods of characterization of powder flow such as cohesion determination, shear cell for effective angle of internal friction and wall friction angle and the use of very recently automated powder flow analyzer (powder rheometer). The brief flow chart for this study is shown in Figure 1.1. Powders material properties like particle size, moisture content, tap, bulk and true densities were determined and their influence on flowability properties were evaluated. This study will help to give information on the flowability of *L. pumila* powder under applied load (compression) and compare the results with already reported work on compression properties of *E. longifolia jack, A. paniculata* and *O. stamineus* (Yusof *et al*., 2011). This information will enhance research on proper handling, processing operations, powder storage, transportation and enhancement of product quality and shelf life of these herbal powders which are highly beneficial due to their medicinal and therapeutic properties. The effects of anticaking agents (flow aids) on the powders using the powder flow analyzer are also investigated. The mean caking strength of powders are also studied using 1% of Silicon dioxide and potato starch anticaking agents respectively. The various powders were also mixed with nondairy creamer and sugar to form herbal powder beverage mix. The nutritional and material properties of the formulated beverage mix of herbal powders with creamer and sugar are also determined and flow properties investigated using both conventional flow measurements and powder flow analyzer to know if the flow of the formulated beverage mix was improved or not.

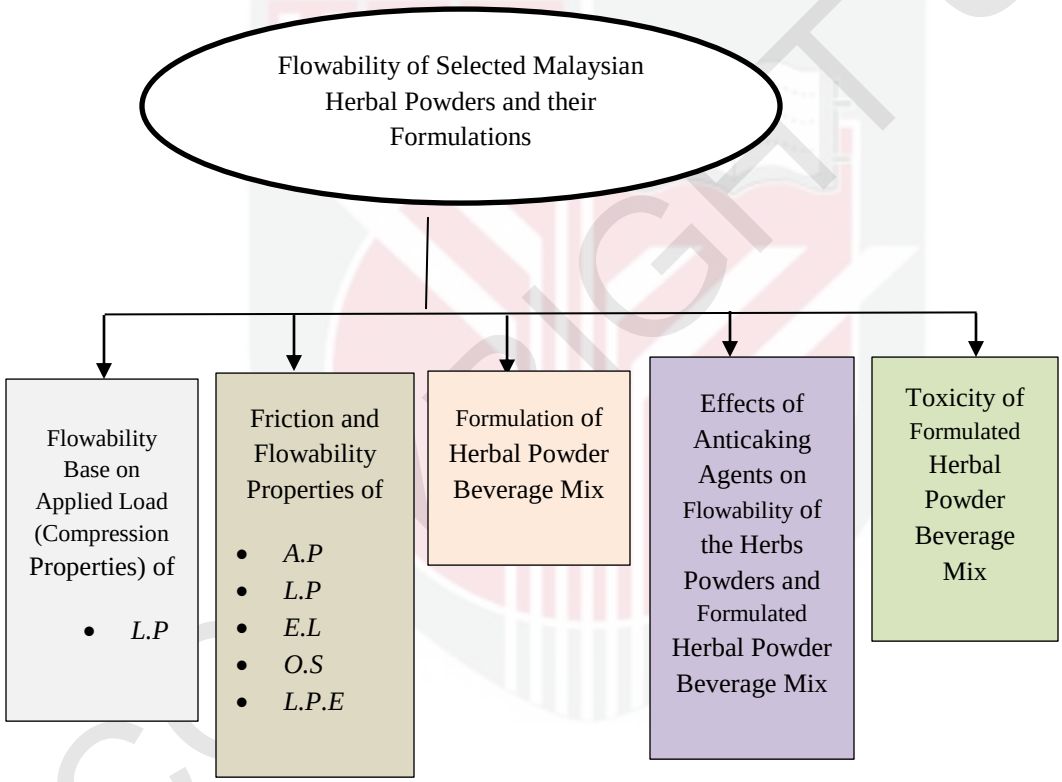
Toxicological studies on the formulated beverage mix using female wistar rats for acute oral toxicity (AOT) and sub-chronic toxicity studies were carried out for 28 days. The hematological, biochemical and histological profiles of the female wistar rats were

analyzed to know if the formulated beverage mix are toxic to ascertain the safety of the beverage products.

1.5 Research Gaps

Amongst the research gaps are:

1. The flowability properties of these powders were yet to be carried out
2. The compression properties of *L. pumila* powder which is flowability under applied load is yet to be carried out
3. The flowability characterization of the formulated herbal powder beverage mix which was a mixture of herbal powders with nondairy creamer and sugar to solve the flowability problems posed by the powder itself was also a novelty in this work.



Note:
L.P is *Labisia pumila* powder, *A.P* is *Andrographis paniculata* powder, *E.L* is *Eurycoma longifolia* powder, *O.S* is *Orthosiphon stamineus* powder, *L.P.E* is *Labisia pumila* extracts

Figure 1.1 Flow Chart for this Study

1.6 Objectives of the Study

The objectives of this study which is based on the brief study flow charts (see Figure 1.1) are as follows:

1. To investigate the compression properties of *L. pumila* powder being flowability under applied load, in comparison with already reported result on compression properties of *A. paniculata, E. longifolia* and *O. stamineus* powders.

2. To investigate the frictional and flowability properties of *L. pumila, A. paniculata, E. longifolia* and *O. stamineus* powders and *L. pumila* extracts.

3. To formulate herbal powder beverages mix by mixing the powders with non-dairy creamer and sugar.

4. To investigate the effects of anticaking agents and formulation on the flowability of the herbal powders and also carry out the toxicity of the formulated herbal powder beverages mix to ascertain their safety.

1.7 Outline of the Thesis

The introductory chapter gives the theoretical background of the study. The herbal powders review and global trends in herbal products are also presented. The reason behind the conduct of this research, scope, relevance and objectives of the study are further presented in this chapter.

Chapter 2 starts by presenting a review on previous studies in the background of *Labisia pumila, Orthosiphon stamineus, Eurycoma longifolia* and *Andrographis paniculata* powders and their therapeutic functions. Tableting methods especially uniaxial die compaction which is also a direct compression method mostly relevant in industry today and models describing the powder compression are also presented. Friction parameters like effective angle of internal friction, wall friction angle, angle of repose and cohesion are useful indices to understand powder flowability as their review are also presented. Safety of the herbal powders are considered as their toxicity requirement are also reviewed.

Chapter 3 defines the procedural techniques adopted in conducting this research. The description of material properties analysis is presented as well. This chapter is concluded with the safety procedure of the herbal powder formulated beverage mix.

Chapter 4 expresses on how the quantities of feed powders affect compression. Force transmissibility, surface roughness characteristics, density, strength analysis of tablets and verification of compressibility behaviour by four classical models are also presented. Friction, flowability and anticaking properties of the herbal powders are analysed. The subjection of the formulated herbal powders beverage mix through haematological, biochemical and histological evaluations are used to determine and ensure their safety.

A short summary of the research findings are given in Chapter 5. Future work recommendations are presented in this concluding chapter.

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