UNIVERSITI PUTRA MALAYSIA

MECHANICAL CHARACTERISTICS OF TABLETTED BINARY AND TERTIARY PHARMACEUTICAL EXCIPIENT MIXTURES

ZAHRAA ABDULHUSSEIN MOUSA AL-IBRAHEEMI

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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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DEDICATION

To my ever-encouraging mother

To my father's soul who never go away

To my altruistic and beloved husband (Ali)

To my lovely brothers (Ali and Ahmed)

To my Angel, lovely son (Shubbar)

To every striving person who is constantly who is constantly improving aspects of life…

To those who are compassionate towards achieving perfection…

To the consistent pursuers of knowledge aiming for positive change..

A special contribution to my home country Iraq and to Malaysia;

With lots of gratitude*…*

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

MECHANICAL CHARACTERISTICS OF TABLETTED BINARY AND TERTIARY PHARMACEUTICAL EXCIPIENT MIXTURES

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March 2014

Chairman: Mohd Shamsul Anuar, PhD

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Various excipients are used in the pharmaceutical tablet industries to present desirable properties in the final product. All excipients should have suitable flowability to produce homogenous distribution at the point of mixing. In addition, the excipients have to be hydrophilic as a disintegrant, have proper compactibility as a binder, and confer acceptable taste results as a diluent. In fact, there is no one type of excipient that has all these characteristics. Therefore, the focus point of this research is to formulate the desirable tablets consisting of different types of excipient mixtures to achieve tablets that meet requirements of recommended tablet formulation.

In this study, the components of compacted tablets by direct compression consist of Microcrystalline Cellulose as a plastic material (binder), Sodium Starch Glycolate as an elastic material (super disintegrant), and alpha Lactose monohydrate as a brittle material (filler). The physical and flow properties of the excipients used have been investigated. The uniaxial compaction process was conducted by using a universal testing instrument.

The tablets were compacted under pressure ranging from 75 to 375 MPa. A 13 mm diameter cylindrical die was used to investigate the compression characteristics of the single binary and tertiary mixtures with 1.0 ± 0.01 g of powder. The loading and unloading stages of the compaction process for the tablets were evaluated based upon the energies derived from the force-displacement data obtained for the tablets with different mass ratios compacted at 150 MPa. The effect of increasing the compression pressure from 75 to 375 MPa on the volume-pressure measurements for single, binary with different mass ratios and tertiary tabletted mixtures was investigated. The tabletted mixture characteristics and recommended tablet formulations were evaluated by using elastic relaxation, indirect tensile strength, friability, and disintegration tests.

The strong influence of the physical powder characteristics on the flow properties of the powders used was observed. The plastic material (MCC) shows a dominant property over the elastic (SSG) and brittle (LAC) materials in terms of their tensile strength and their behaviour during compaction events. Applying a high pressure produces tablets with a low elastic relaxation, higher tensile strength, low friability percentage and a long disintegration time. Increasing the MCC and decreasing LAC and SSG percentages lead to an increase in tensile strength, disintegration time, and decreases the friability percentage. According to the recommended formulation of the tablets, tertiary formulation can be considered as the best formulation. One of the more significant findings to emerge from this study is that the use of mixtures of the direct compression excipients has proven to be significantly more appropriate for use compared to the individual components.

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

SIFAT MEKANIKAL TABLET CAMPURAN FARMASEUTIKAL EKSIPIEN BINARI DAN TERTIARI

Oleh

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Terdapat pelbagai jenis eksipien yang digunakan dalam industri tablet farmaseutikal bagi memperolehi ciri-ciri yang dikehendaki dalam produk akhir. Semua eksipien harus mempunyai daya alir yang optimum untuk menghasilkan campuran yang homogen ketika proses pencampuran. Tambahan pula, eksipien perlu bersifat hidrofilik sebagai penyahintegran, mempunyai daya pemadatan yang sesuai sebagai pengikat dan memperlihatkan rasa yang boleh diterima sebagai pencair. Hakikatnya, tiada eksipien yang mempunyai semua ciri-ciri tersebut. Oleh itu, fokus penyelidikan ini adalah untuk memperkenalkan rumusan tablet ideal yang dibentuk daripada pelbagai jenis campuran eksipien dan mampu memenuhi syarat-syarat formulasi tablet yang disarankan.

Dalam kajian ini, komponen-komponen tablet yang telah dipadatkan secara pemampatan langsung termasuk Mikrokristal Sellulosa sebagai bahan plastik (pengikat), Natrium Kanji Glycolate sebagai bahan elastik (penyahintegran super) dan alfa Monohidrat Laktosa sebagai bahan rapuh (pengisi). Sifat-sifat fizikal dan daya alir

eksipien yang diguna telah dikaji. Proses pemampatan ekapaksi telah dilakukan dengan menggunakan sebuah alat penguji universal. Tablet tersebut telah dipadatkan dengan tekanan dari 75 hingga 375 MPa. Kelulitahan karat berbentuk silinder dengan diameter berukuran 13mm telah digunakan untuk menyiasat sifat pemampatan campuran binari dan tertier dalam bentuk serbuk dalam kuantiti 1.0 ± 0.01 g. Peringkat pembebanan dan penyahbebanan proses pemadatan tablet dikajiselidik berdasarkan kepadatenaga yang diperoleh daripada data daya-anjakan bagi tablet berlainan nisbah jisim yang dipadatkan dengan tekanan 150MPa. Turut dikaji ialah kesan peningkatan tekanan pemampatan daripada 75 hingga 375 MPa terhadap ukuran isipadu-tekanan untuk campuran tablet secara tunggal, binary dengan pelbagai nisbah jisim dan juga tertier. Pencirian campuran tablet itu telah dilakukan melalui ujian pelonggaran kenyal, kekuatan tegangan tidak langsung, kerapuhan dan penyahintegran.

Pengaruh kuat sifat fizikal serbuk pada kebolehaliran serbuk telah diperhatikan dalam penyelidikan ini. Bahan plastik (MCC) mempamerkan sifat dominan berbanding bahan elastik (SSG) dan bahan rapuh (LAC) dari segi daya tegangan dan pencirian ketika proses pemadatan. Pengaplikasian tekanan tinggi menghasilkan tablet yang mempunyai pelonggaran kenyal yang rendah, daya tegangan yang lebih tinggi, peratusan kerapuhan yang rendah dan tempoh perpecahan yang panjang. Peningkatan peratusan (MCC) dan pengurangan peratusan LAC dan SSG dapat meningkatkan daya tegangan, tempoh perpecahan dan mengurangkan peratusan kerapuhan. Berdasarkan formulasi tablet yang disarankan, formulasi tertier adalah formulasi terbaik. Satu penemuan yang paling penting daripada penyelidikan ini ialah campuran eksipien secara pemampatan langsung lebih sesuai digunakan berbanding dengan komponen-komponen secara individu.

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

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Declaration by Members of Supervisory Committee

This is to confirm that:

- The research conducted and the writing of this thesis was under our supervision
- Supervision responsibilities as stated in the Universisti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

API	Active Pharmaceutical Ingredient
D50	Mean Particle Size Diameter
CI	Carr Index
C	Cohesion Strength [KPa], is the cohesion of the powder, and is obtained from the intercept of the yield locus on the shear stress axis.
DC	Direct Compression
EE	Elastic Energy
E%	percentage of the elastic relaxation`
E	Tablet porosity
EYL	Effective Yield Locus, Straight line passing through the origin of the σ- τ plane and tangential to the steady state or largest Mohr circle , corresponding to steady state flow conditions of a bulk solid of given bulk density
FF	Flow Function, a plot of *UYS* and *MCS* and it represents the ratio of *UYS/ MCS*
ff_c	Flow Index or Flow Factor, the ratio of *MCS* to the *UYS* at defined normal load. it is obtained from the inverse of the slope of the flow function line
GI	Animal gastrointestinal
HR	Hausner Ratio
h	The Height of the Powder [m]
LAC	α - Lactose Monohydrate
m	Mass of powder [kg]
MCC	Microcrystalline Cellulose
MCS	Major consolidation stress, is the value obtained with the right hand side intercept of this second Mohr circle (which is tangential to the end point of the yield locus) and with the normal stress axis
P	Tensile force [N]
PE	Plastic energy

R	radius of the graduated cylinder [m]
SEM	Scanning electron microscope
SSG	Sodium Starch Glycolate
T_{max}	Tablet height measured 24 hours after ejection
T_{min}	minimum height of the tablet [mm]
UYS	Unconfined yield strength [KPa], is the value obtained with the higher point of intersection of the small Mohr circle (which is drawn passing through the origin and tangential to the extrapolated yield locus) and with the normal stress axis
V_0	Untapped Apparent Volume Of The Powder [m^3]
V_{tap}	Tapped Volume of the Powder [m^3]
WHO	World Health Organization
YL	Yield Locus, the plot of shear stress versus normal stress at failure.
ρ_{bulk}	Bulk density [kgm^{-3}]
ρ_{tap}	Tapped density [kgm^{-3}]
ρ_{true}	True density [kgm^{-3}]
ϕ_{wall}	Angle of wall friction [º], is the arctan of the ratio of the wall shear stress to the wall normal stress
T	Shear stress [KPa], is the stress which is applied parallel or tangential to a face of a material. It determined by dividing the shear force to cross sectional area of the cell
σ	Normal stress [KPa], is the stress acting normally to the considered plane. It determined by dividing the normal force to cross sectional area of the cell
σ_t	Tensile strength [MPa]
δ_e	Effective angle of internal friction [º], is the angle between the effective yield locus (*EYL*) and x-axis

CHAPTER 1

INTRODUCTION

1.1 Introduction

This chapter provides an introduction and a brief review of the processing steps in the compaction of pharmaceutical tablets and the advantages of tablets including a summary of the properties of powder and the importance of measuring tablet characteristics. Lastly, a discussion of the knowledge gap and the objectives and scope of this study are given.

1.2 General View of the Background of the Processing Steps in Compaction and Pharmaceutical Tablets

Tablets are the most popular and common dosage form for administering drugs via an oral route, occupying two thirds of the global market (Pitt et al., 2007).

Powder compaction which is used in tablet manufacturing, is a process commonly utilized in various industrial fields, for example the ceramic and powder metallurgy industries, the detergent industry and chemical engineering, food industry, and in the pharmaceutical industry. The latter will form the focus in this study as millions of tablets are produced every day by the compaction technique.

The employment of the compaction technique for pharmaceuticals is primarily due to the many advantages of tablets as a final product in comparison with other dosage forms, such as:

- Physical and chemical stability
- Acceptable accuracy, shelf life of dosage and ease of controlling active ingredient (API) release
- For users, tablets are convenient as they are easy to administer and are portable
- Coatings or sweeteners can be used to cover up any unpleasant taste
- On the industrial side, tablets can be mass-produced with high production rates (Wu et al., 2005).

The processing of tableting can in general be divided into four distinct stages:

(1) die filling, where the powder is delivered into the die cavity under gravity (2) loading, this stage includes a compression stage where the powder is compressed inside a die by upper and lower punches (3) unloading, where the applied pressure or stress is removed, and finally (4) ejection, where the tablet is removed from the die (Pitt et al., 2007).This is summarised in **Figure 1.1.**

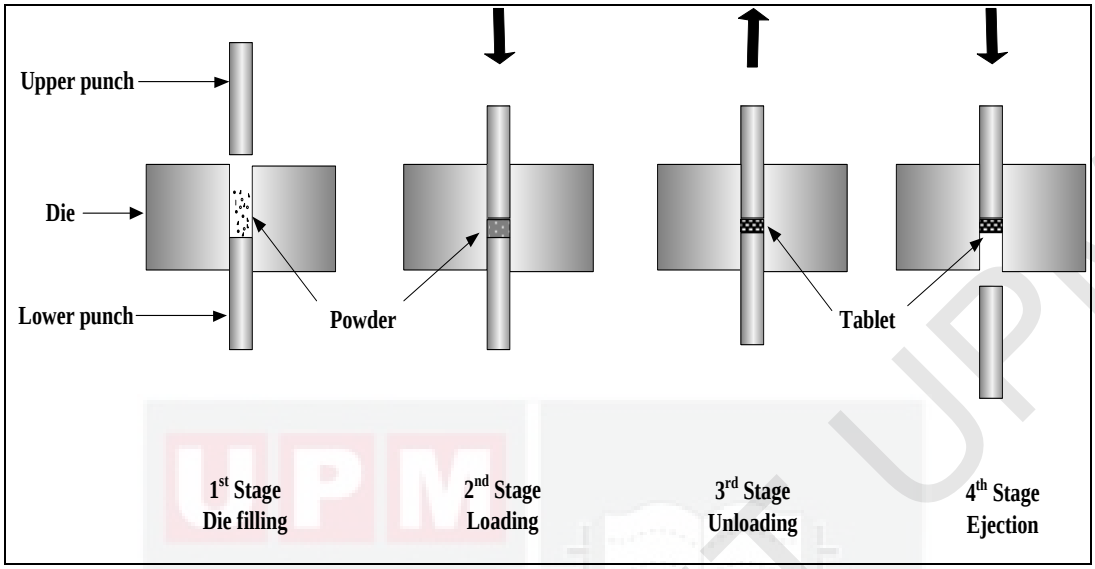

Figure 1.1.A typical laboratory-scale compaction process (compaction cycle)

The behaviour of the powder within these four stages all establishes or characterize the properties of the final product. Thus, understanding the mechanical behaviour of powders at every stage is crucial and has attracted much attention over the past 50 years. In this current study the compaction process (loading and unloading stages) will be specifically focused on due to its effect on the tablet properties being greater than the other factors.

Wu and his colleagues in their article divided the compaction process into two phases regarding the movement direction of the upper punch: compression and decompression (Wu et al., 2005). During the compression phase, when the upper punch moves towards the bottom punch, the powder bed experiences intensive densification and the particles of powder compress together to form aggregates with considerable cohesive strength because of van der Waals forces, the formation of solid bridges and mechanical interlocking (Alderborn, 2007). As the distance between the upper and lower punches

continues to decrease, the packing density of the powder bed and the compression pressure increases dramatically. Decompression occurs when the upper punch starts to move in the opposite direction to the lower punch. During this stage, the compression pressure decreases quickly since the distance between the upper and lower punches increases, and some of the elastic strain that emerged within the compression phase will recover. This is accompanied by an increase in the powder bed volume and then a decrease in the relative density.

A successful production process can minimize the defects of the tablets produced as a final product, and this requires an understanding of not only the process stages but also the essential characteristics of the powders. These characteristics include both physical and flow properties to predict how formulations will behave during all stages starting from tablet processing, packing, transportation, marketing, storage, and finally, handling of the product by the end user (Furll and Hoffmann, 2013).

In the pharmaceutical industry the uniformity of powder flow is one of the most significant considerations in the solid dosage industry (Sarraguca et al., 2012). Improper powder feeding from storage hoppers into die-presses can result in an inconsistent quality of product and may cause health impacts and economic consequences. Therefore, an investigation into the flow properties in addition to the properties affecting the powder flow such as moisture content, particle size and morphology and also the powder density is crucial. The importance of these properties also comes from processing equipment and parameters can be opted depending on the behaviour of the materials under specific stress conditions. Hence, it is possible to obtain a better understanding of why particular materials are prone to problems and defects during compaction (Jain, 1999). Finally, the optimum tablet production, as a whole, to produce

desirable products is a complex process as it is required to evaluate the final product after production. In other words, producing desirable products usually requires subjecting the final product to a number of tests to see the impact of the previously mentioned factors on the final product, namely, process parameters and powder properties. Based on all the above-mentioned aspects, the elucidation of the factors that lead to integrated tablet production is a challenging task, which has to be based on an improved understanding of the powder properties, powder behaviour during the compaction process, in addition to studying the tabletted powders specifications after ejection. Therefore the structure of the current research objectives is based on these basics as will be described in **Section 1.4.**

1.3 Knowledge Gap and Research Significance

There is not much information in the previous literature regarding the effect of physical properties on the flowability of pharmaceutical powders. There are several studies on coal and food powders, and various other powders, but limited studies that deal with pharmaceutical excipients. Precisely, currently there are few published papers on the flowability of the chosen materials in this study (Microcrystalline Cellulose (MCC), α - Lactose Monohydrate, and Sodium Starch Glycolate (SSG) in particular). There is also a necessity for a proper understanding of which properties of the three powders used affects flowability the most. On the other hand, there is controversy over the effect of the physical properties on the flow properties of fine powders in general. The effect of fine powder content such as the composition of ordered mixtures on tablet specifications is another area that is not well understood.

More recent literature has provided little discussion concerning the use of binary component excipients in direct compression tableting process (DC) (Liu et al., 2013). In addition, there is no one who offers considerable findings regarding the use of tertiary mixtures of the chosen materials by using the DC technique. Thus, one of the significance of this study is to evaluate tablets compacted by using binary and tertiary excipient mixtures used that cover the requirements for satisfactory tablet production. In addition, this study will present how these excipients are influenced by each other and by the process parameters during tableting and after ejection. Moreover, most studies related to SSG tableting have only been carried out by using wet granulation (Patel et al., 2011). In contrast with previous studies, another significant of the current study is using SSG in a single formulation and mixtures including SSG by DC. Industrially, there is a need to formulate the tablets covering a wide range of medical needs in order to improve the patient compliance as antacid, stroke, and heart attack medicines in term of all the medicines for these cases have to dissolve fast. On the other hand by adding disintegrants as SSG, the tablets will be brittle and break easily so it need to be improved by adding binders as MCC. Furthermore, as these tablet dissolve fast in the mouth according to the medical case requirements, so it have to has good mouth feeling by adding diluent as LAC. Hence, in term of patients and markets requirements there is a need to form tablets satisfy the patient compliance and have acceptable taste from one side and these tablets have to still intact till reach to the end user from the other side.

As a result, this study proposed to enhance the understanding of the criteria and parameters that lead to improving the quality of pharmaceutical tablets. This can be considered in terms of how the tablets can be made by mix different types of excipients with certain manufacturing parameters to stay intact starting from manufacturing

through packing, transportation, storage stages, and finally supply to the end user and the same time can be used efficiently, properly, and comfortably by patients

1.4 Research Objectives

The selected gaps in the knowledge prescribed above supports the following four objectives of this study:

1- To study the relationship between physical and flow properties of the powders used (MCC, LSC, and SSG).

2- To determine the effect of the changing the tablet mixture compositions (single and binary) mixtures compacted under the same compression pressure on force – displacement measurements, volume-applied pressure and tablet tensile strength with respect to changing the compression pressure and mixture compositions.

3- To formulate the desirable tablets covering a wide range of medical and markets needs by subjecting compacted tablet to the basic tests to evaluate under which conditions and by using any components the recommended formulation can be achieved.

1.5 Outline of Thesis

Chapter 1 introduces the thesis, gives an outline of the processing steps for the compaction of tablets, describes the knowledge gap, research objectives, and explains the outline and scope of the thesis.

In *Chapter 2* the related technical background and the literature review are presented in this chapter. The background theory discusses the raw ingredients used in this study in addition to the physical and flow properties in the relevant literature. A background

review is given that is relevant to understanding the mechanics and fundamentals of the compression and compaction of powder particles, analysis, and tests involved in this study.

Following in *Chapter 3*, the physical and flow properties of the powders and a better understanding of the relationship between these properties is discussed. Physical properties such as particle size, shape, moisture content and density for different powders of varying shapes and sizes are characterized using different techniques. Furthermore, the flowability of the test powders using different techniques such as the measurement of shear strength, measurement of angle of repose, and measurement of powder compressibility using the Hausner ratio and the Carr index are covered and discussed in this chapter.

Next in *Chapter 4,* the effect of feed powder quantities or mass ratios on the tablet force-displacement measurements as total work, plastic and elastic energies and total displacement are examined. This is in addition to an investigation into the tensile strength of these tablets which are formed at an ultimate compression stress of 150 MPa and using deformation behaviour materials in a single form and binary mixtures.

Following by *Chapter5* which presents the effect of change of the applied pressure by applying high pressures in the tableting process on the essential properties of single component, and mixtures with different mass ratios in terms of volume-applied pressure profile measurements. The applied pressures in this part start from 75 to 375 MPa. The properties of the tablets of single, binary and tertiary mixtures are determined by essential tests for checking the tablet characteristics and quality such as elastic relaxation, Brazilian, friability, and disintegration time tests. By doing these tests the

recommended tablet formulation assesses. In this thesis, chapter 3 to 5 is similar to journal layout as it has its own methodology, results, and discussion.

Lastly, *Chapter 6* which includes the conclusion and summary of the thesis, followed by the discussion of the key contributions of the proposed work. There are several directions for future research which are also suggested for further investigation.

A summary of the scope of this thesis is illustrated in **Figure 1.2**. In this figure the direction of the flow of the proposed schemes is indicated by the bold lines, whereas the dotted lines indicate related research areas which are beyond the scope of this thesis. As stated in **Figure 1.2**, the experimental work in this study starts with measuring the physical and flow properties of the excipients used which have been investigated so as to obtain a more comprehensive understanding of the compression and compaction behaviours which will be conducted in the second stage. The second stage of the experimental work as it is clear in the mentioned figure, including tableting the excipient powders used "filler, binder, and disintegrants" in an individual and mixtures state. Final stage, to ensure achieving adequate tablet properties and to avoid damage of the final product (tablets) during transportation, storage and ending with handling by the end user, the recommended tablet formulation by conducting the basic test was evaluated.

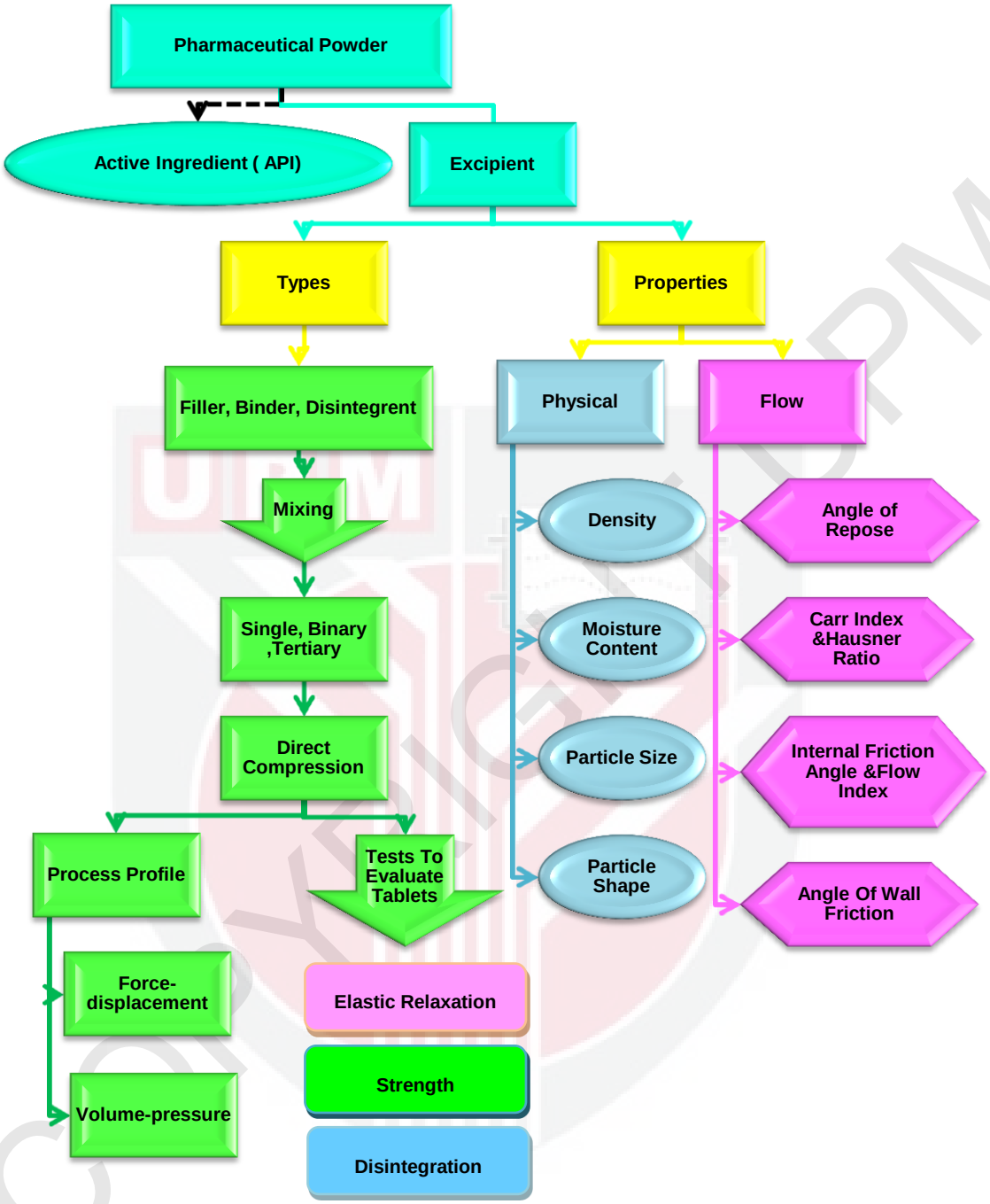

Figure 1.2: Thesis scope

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