Determination of Changes in Flow Property of Different Mixtures of Powder Excipients with the Varying Amounts of Powder Lubricants

Sumaiya Ahmed Bhasha

ID # 2010-1-70-023

Department of Pharmacy

East West University

Research Supervisor: Md. Anisur Rahman, Senior Lecturer

A thesis report, submitted to the Department of Pharmacy, East West University, in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation, entitled “Determination of changes in flow property of different mixtures of powder excipients with the varying amounts of powder lubricants” is an authentic and genuine thesis project carried out by me under the guidance of Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University, Dhaka.

_____

Sumaiya Ahmed Bhasha

ID # 2010-1-70-023

Department of Pharmacy

East West University

ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation entitled “Determination of changes in flow property of different mixtures of powder excipients with the varying amounts of powder lubricants” is a genuine research work carried out by Sumaiya Ahmed Bhasha, under the supervision of Md. Anisur Rahman (Senior Lecturer, Department of Pharmacy, East West University, Dhaka). I further certify that no part of the thesis has been submitted for any other degree and all the resources of the information in thus connection are duly acknowledged.

_____

Prof. Dr. Chowdhury Faiz Hossain

Chairperson and Ex Dean

Department of Pharmacy

East West University

CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled “Determination of changes in flow property of different mixtures of powder excipients with the varying amounts of powder lubricants”, submitted to the Department of Pharmacy, East West University, Dhaka, in partial fulfillment of the requirements for the Degree of Bachelor of Pharmacy, was carried out by Sumaiya Ahmed Bhasha, ID # 2010-1-70-023 under my supervision and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree/Diploma.

Md. Anisur Rahman

Senior Lecturer

Department of Pharmacy

East West University

Acknowledgment

First, all praise and glory to almighty Allah for all His generosities granted to me and I genuinely accept that only with His support and help this achievement has become possible for me.

The success and final outcome of this project also required a lot of guidance and the assistance from many people and I am extremely fortunate to have got this all along completion of my project work. Whatever I have done is only due to such guidance and assistance and I would not forget to thank them.

I respect and thank Md. Anisur Rahman, for giving me an opportunity to do the project and providing all support and guidance which made me complete the project on time. I am extremely grateful to him for providing such a nice support and guidance though he had busy schedule managing the academic affairs.

It is also my great pleasure and privilege to acknowledge my deepest regards and gratitude to Prof. Dr. Chowdhury Faiz Hossain, Chairperson and Dr. Shamsun Nahar Khan, Associate Professor of the Dept. of Pharay, East Wet University,for their kind words during my troubling moments, and of course for constant inspiration and whole hearted cooperation.

I would not forget to remember my friends Mynul Islam Mufti and Mahjabin Haque for their endless cooperation and whole hearted inspiration throughout the period of the research work.

I owe my profound gratitude to our laboratory officers for their kind support till the completion of our project work by providing all the necessary information for developing a good system.

I am thankful to and fortunate enough to get constant encouragement, support and guidance from all teachers of Department of Pharmacy which helped me in successfully completing this project work. Also, I would like to extend our sincere regards to all the non-teaching staff of our department for their timely support.

Sumaiya Ahmed Bhasha

This Research Paper is Dedicated

To

My Beloved Parents

LIST OF CONTENTS

CHAPTER THREE: MATERIALS AND METHODS

CHAPTER FOUR: RESULTS

CHAPTER FIVE: DISCUSSION

CHAPTER SIX: CONCLUSION

CHAPTER SEVEN: REFERENCE

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

A thorough understanding of the nature of pharmaceutical excipient is required before handling of these inactive ingredients during both small (laboratory) and bulk (commercial) scale production of dosage forms. The flow characteristic of powder excipients is directly related to both the physical properties of the material itself, as well as the specific processing conditions in the handling system. Flow property of powder excipients can be easily measured by checking few parameters and hereafter followed by a calculation. In this thesis work, values determined by Carr's index, Hausner's ratio, and angle of repose have been considered to represent the flow characteristic of powders, and the numerical data have been put into a linear graph. All of the studies presented in this thesis were performed without aiding the flow of powder externally, like shaking or pressurization. This experiment work for the thesis project has shown the improvement in flow characteristic while using lubricants in a drug formulation, as lubricants are supposed to enhance the rate of flow. Besides the numerical data, I have also presented the graphs along with the regression values, and equation about the represented data, thinking that it will be further beneficial for manufacturing new products or modifying the existing one.

Keywords: Flow property, Excipients, Direct Compressible Tablets, Carr's Index, Hausner's Ratio, Angle of Repose, Lubricants.

Chapter One

INTRODUCTION

1.1 INTRODUCTION

In our pharmaceutical industries, apart from active ingredients, inactive excipients also play a major role in formulation development. Pharmaceutical excipients are substances other than the pharmacologically active drug or prodrug which are included in the manufacturing process or are contained in a finished pharmaceutical product dosage form. The topic of the thesis is to find out the values of some physical characteristic of excipient, whether it is individually or along with others, which directly indicates the flow characteristic of the powder in a distinct way.

The objective of this dissertation is to identify the nature of flow of a particular formulation prepared only by various powdered excipients with different amount of lubricating agents. This experiment may turn out of great importance as there are many drug formulations in which powdered excipients are used, for example, in case of powder for suspension, tablets, capsule, even in semisolid preparations (gel, cream, ointment etc) and suppositories to some extent. Surprisingly, soluble powdered excipients are also used in liquid preparations, like syrup and solutions. In this study, I considered such excipients which are popularly known to be used in direct compaction tablets. In my study I have chosen to compare the flow properties of a group of excipients while adding different types and amount of lubricants with it. The main purpose of this research work is to determine, whether lubricants change the flow property of a group of excipients or not. If they really change, to what extent the changes occur and the changes result in good or bad impact for the whole formulation. In this study, we have most importantly considered the formulations of direct compressible tablets to be discussed and assessed about, as they contain minimal amount of excipients and their way of manufacturing is quite easier than other, like dry or wet granulation tablets.

1.2 POWDER FLOW

1.2.1 Definition: A simple definition of powder flowability is the ability of a powder to flow. By this definition, flowability is sometimes thought of as a one-dimensional characteristic of a powder, whereby powders can be ranked on a sliding scale from “free-

flowing" to "non-flowing". The inability to achieve reliable powder flow during manufacturing process of solid dosage forms of any drug can have a significant adverse effect on the total process, whether from manufacture to the release of a product to market. Production costs can be significantly higher than anticipated due to interference required on the part of operators, low yield or unplanned process redesign.

1.2.2 Importance of learning accurate flow property

Measuring flow rate of powders is by far one of the most important parameter to check while preparing a solid dosage form, for example, tablets, capsules, and to some extent it is also important in liquid preparations. A thorough understanding of a bulk material's flow properties and its flow characteristics are crucial for identifying the cause of poor flow, powder flooding or rate limitations, segregation, or product non-uniformity. Powder flow behavior can affect manufacturing efficiency and can directly affect product quality variables, such as dose uniformity. The critical attributes such as cohesivity index, caking strength, and flow stability are determined by examining the excipients.

It is really important for a pharmaceutical manufacturer to check about the flow property of the formulation for any solid dosage form preparation. The same powder may flow well in one hopper but poorly in another; likewise, a given hopper may handle one powder well but cause another powder to hang-up. It is required to have knowledge of the flowability of any single powder or a bulk because it helps in designing powder handling equipment such as hoppers that no flow problems (flow impediments, segregation, or any irregular flow, etc.) will occur. Few methods of assessing powder flow can be time consuming. However, the benefits of accurately exemplifying powder flow measurement can far be more important than this venture of time.

- *Developing new product/ dosage form*

A team from product development can assess new excipients, active drugs and formulations, predicting their behavior prior to inauguration of large-scale production. They can also check how new powders (excipients) interact with existing ingredients. This speeds up development time and which minimizes errors during final production;

and this strategy is really beneficial when active ingredients or any inactive materials are extremely valuable and may have only been produced in undersized quantities.

- *Quality improvement*

Predictable powder flow enables constituent selection, manufacturing procedures and equipment to be optimized. This in turn maximizes speed of production, reduces the risk of stoppages and improves blend quality, filling procedures and end product quality.

- *Cost-savings of existing product*

The substitution of expensive constituents with lower cost powders is a smart approach because the cost of existing product should be driven down. Although these substitutes may be produced to the same specification as the original substance, they may not essentially store, convey and process as effortlessly. Discovering this after production has started would incur downtime and additional cost. Final product quality may also be negotiated. (Young, 2013)

1.2.3 Factors Affecting Powder Flow Properties

Powders are probably the least predictable of all materials in relation to flowability because of the large number of factors that can change their rheological properties. Flow Properties of powders depend upon- Collective forces acting on individual particles, particle variables environmental conditions, particle size distribution, shape, cohesivity, surface texture, surface coating, particle interaction, electrostatic charge, hardness, stiffness, strength, compaction condition, humidity etc. (Slideshare, 2013)

1.3 PARAMETERS CHECKED DURING THIS EXPERIMENT

Flowability of powders is multi-dimensional and in fact it depends on many powder characteristics. This is really important to know, no particular test could ever quantify flow property of powder. In fact, flowability is not an intrinsic material property at all. Flowability is the results of a combination of material physical properties that affect flow and it also vary accordingly the equipments used for handling, storing, and processing the material. Equal consideration must be given to both the material characteristics and the equipment. There are few physical parameters commonly checked while determining flow property, which have also been carried out in this experiment,

and they are- Carr's index, Hausner's ratio and another important parameter named Angle of repose. Flow characteristic can also be measured by checking the powder flow through an orifice, or by shear cell method. As both these methods were not conducted in this dissertation, so let us not discuss about those.

1.3.1 Carr's Compressibility Index and Hausner Ratio

According to Wikipedia, the Carr's index or Carr's Compressibility Index is an indication of the compressibility of a powder. It is named after the pharmacologist Charles Jelleff Carr (1910–2005). In recent years the compressibility index and the closely related Hausner ratio have become the simple, fast, and popular methods of predicting powder flow characteristics. The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content, and cohesiveness of materials because all of these can influence the observed compressibility index.

The compressibility index and the Hausner ratio are determined by measuring both the bulk volume and the tapped volume of a powder. These two parameters can also be determined by measuring bulk density and true density of a particular amount of any powder.

In accordance with United States Pharmacopeia, although there are some variations in the method of determining the Carr's index and Hausner ratio, the basic procedure is to measure the unsettled bulk volume and the final tapped volume of the powder after tapping the material until no further volume changes occur. The compressibility index and the Hausner ratio are calculated as follows:

$$\boldsymbol{Carr's\ Compressibility\ Index} = 100 \times \left(\frac{Bulk\ volume\ -\ Tapped\ volume}{Bulk\ volume}\right)$$

$$\boldsymbol{Hausner's Ratio} = \left(\frac{Bulk\ volume}{Tapped\ volume}\right)$$

Alternatively, the Carr's index and Hausner ratio may be calculated using measured values for bulk density and tapped density of a powder as follows:

$$\boldsymbol{Carr's\ Compressibility\ Index} = 100 \times \left(\frac{True\ density - \ Bulk\ density}{True\ density}\right)$$

$$\boldsymbol{Hausner's Ratio} = \left(\frac{True\ density}{Bulk\ density}\right)$$

Both the Hausner ratio and the Carr index are sometimes criticized, despite their relationships to flowability being established empirically, as not having a strong theoretical basis. Use of these measures persists, however, because the equipment required to perform the analysis is relatively cheap and the technique is easy to learn.

In a variation of these methods, the rate of consolidation is sometimes measured rather than, or in addition to, the change in volume that occurs on tapping. For the compressibility index and the Hausner ratio, the generally accepted scale of flowability is given in the following table:

Table 1.1: Scale of Nature of flow in Carr' Index and Hausner's Ratio Values

Carr's Index (%)	Flow Character	Hausner Ratio
≤10	Excellent	1.00–1.11
11–15	Good	1.12–1.18
16–20	Fair	1.19–1.25
21–25	Passable	1.26–1.34
26–31	Poor	1.35–1.45
32–37	Very poor	1.46–1.59
>38	Very, very poor	>1.60

1.3.1.1 Experimental Considerations for the Carr's index and Hausner ratio:

Carr's index and Hausner ratio are not intrinsic properties of the powder; i.e., they depend on the methodology used. In the existing literature, there are discussions of the following important considerations affecting the determination of the unsettled bulk volume, the final tapped volume, the bulk density, and the true density:

- ✓ The diameter of the cylinder used
- ✓ The number of times the powder is tapped to achieve the tapped density

- ✓ The mass of material used in the test
- ✓ Rotation of the sample during tapping

1.3.2 Angle of Repose

The angle of repose has been used in several branches of science to characterize the flow properties of solids. Angle of repose is a characteristic related to interparticulate friction or resistance to movement between particles. Angle of repose test results is reported to be very dependent upon the method used. Experimental difficulties arise as a result of segregation of material and consolidation or aeration of the powder as the cone is formed. Despite its difficulties, the method continues to be used in the pharmaceutical industry, and a number of examples demonstrating its value in predicting manufacturing problems appear in the literature.

The angle of repose is the constant, three-dimensional angle (relative to the horizontal base) assumed by a cone-like pile of material formed by any of several different methods.

1.3.2.1 Angle of Repose General Scale of Flowability

Although there is some variation in the qualitative description of powder flow using the angle of repose, much of the pharmaceutical literature appears to be consistent with the classification shown in the following table. There are examples of formulations with an angle of repose in the range of 40^0 to 50^0, even those are satisfactorily accepted by the manufactures. But when the angle of repose exceeds 50^0, the flow is rarely acceptable for manufacturing purposes, and here comes the implication of our study, that is to add such ingredients which help to decrease the value of angle of repose, and result in improved flow property.

Table 1.2: Flow Properties and Corresponding (Angles of Repose)

Flow Property	*Angle of Repose (degrees)*
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55

Very poor	56–65
Very, very poor	>66

1.3.2.2 Experimental Considerations for Angle of Repose

Angle of repose is not an intrinsic property of the powder; i.e., it is very much dependent upon the method used to form the cone of powder. The following important considerations are raised in the existing literature:

- The peak of the cone of powder can be distorted by the impact of powder from above. By carefully building the powder cone, the distortion caused by impact can be minimized.
- The nature of the base upon which the powder cone is formed influences the angle of repose. It is recommended that the powder cone be formed on a "common base," which can be achieved by forming the cone of powder on a layer of powder. This can be done by using a base of fixed diameter with a protruding outer edge to retain a layer of powder upon which the cone is formed.

1.4 DIRECT COMPRESSIBLE TABLETS

This thesis paper is certainly about the formulations and excipients used in direct compressible tablets. Direct compression (DC) is by far the simplest means of manufacturing of a pharmaceutical tablet. It requires only that the active ingredient is properly blended with appropriate excipients before compression. Apart from simplicity of formulation and manufacture, the key advantages of direct compression include reduced capital, labour and energy costs for manufacture and the avoidance of water for granulation for water sensitive drug substances.

1.4.1 Applications of direct compression

The most apparent factor in determining whether direct compression is applicable to a certain drug substance is dose. Three key factors for successful tableting are flow and compactability of the compression mix, and drug content uniformity in the mix and the final tablets. All of these factors are likely to be affected by drug dose.

According to a previous study, let us consider low dose is taken to mean 10 mg or below, medium dose is taken to mean 10 mg to 50 mg and high dose is taken to mean above 50 mg.

For low dose drugs, flow and compaction of the compression mix are largely conferred by the excipients and the primary concern is likely to be achievement of good content uniformity in the blend and in the tablets. For medium dose drugs flow of the compression mix may become a critical factor, and for high dose drugs the flow and compaction are highly dependent on the properties of the drug substance.

Table 1.3: Some factors determining the applicability of direct compression tableting

Description	**Low Dose**	**Medium Dose**	**High Dose**
Drug Dose	< 10 mg	10-50 mg	> 50 mg
% of a 250mg tablet	< 4%	4– 20%	> 20%
Content Uniformity	Primary concern	Not likely to prove a problem	Minimal concern
Flow	Largely taken care of by excipients	Milled drugs may interfere with flow	Highly dependent on the drug properties
Compaction	Largely taken care of by excipients	Unlikely to be a major issue	Highly dependent on the drug properties

1.5 PHARMACEUTICAL EXCIPIENTS

All solid oral dosage products consist of an “active” ingredient or drug. It is rare to find a solid oral dosage product consisting of drug alone. To produce a final product that is not only practical and convenient to handle but also facilitates patient compliance, the drug substance needs to be processed with other excipients. These drug excipients serve many roles in the formulation.

1.5.1 Definition:

Excipients are defined as any pharmacologically inactive substance that has been appropriately evaluated for safety and is included in the formulation which is used as a carrier of active ingredient during and after the process of manufacturing. Excipients also protect, support or enhance stability, bioavailability, or patient acceptability to the drug and also assist in product identification, or enhance any other attribute of the overall safety and effectiveness of the drug delivery system during storage or use.

1.5.2 Functions of excipients:

Excipients are used in almost each directly compressed tablet preparation due to its many functions which can not be neglected in any way. Most importantly, excipients add bulk to a minimum amount of active ingredient and result in a distinct size and weight of an individual tablet. On the other hand, excipients are also used to control the release of tablet where it is used and make it bioavailable to a certain part of our body where the drug is meant to release and exert its effect. They may also be important for keeping the drug from being released too early in the assimilation process in places where it could damage tender tissue and create gastric irritation or stomach upset. Others help the drug to disintegrate into particles small enough to reach the blood stream more quickly and still others protect the product's stability so it will be at maximum effectiveness at time of use. In addition, some excipients are used to aid the identification of a drug product. Last, but not the least, some excipients are used simply to make the product taste and look better. This improves patient compliance, especially in children. (Drug Topic, 2008)

1.5.3 Categories of excipients:

There are many types and categories of excipients used in pharmaceutical dosage formulations, whether in case of liquid, solid or semisolid preparations. As this thesis paper is all about the excipients used in case of solid dosage forms, especially about the excipients those are commonly used within the formulations of a directly compressible tablet, we will categorize the excipients in a particular manner that will largely filled by powder excipients. Direct compression formulations can be developed with minimal numbers of excipients. In a conventional direct compressible tablet, the excipients used in the formula may be categorized as follows:

- ✓ Diluents/fillers
- ✓ Binders
- ✓ Disintegrants
- ✓ Lubricants
- ✓ Glidants
- ✓ Miscellaneous

1.5.3.1 Diluents: Diluents or fillers are used to increase the bulk content of the dosage form, and it is really important for a direct compressible tablet, because each tablet contains a very minor amount of active ingredients and diluents add bulk to it. For example if the active ingredient is just 5 mg, is such a case a tablet of just 5 mg is very difficult to manufacture and handle too, thus the bulk content is increased by addition of inactive excipient. Round tablets of weight 120mg to 700mg and for oval tablets 800mg are easy to handle.

Examples: lactose, lactose anhydrous, lactose spray dried, directly compressible starch, hydrolyzed starch, MCC, other cellulose derivatives, dibasic calcium phosphate dihydrate, mannitol, sorbitol, sucrose, calcium sulfate dehydrate, dextrose.

Diluents can be either dehydrated (containing certain amount of bound water that reduces hygroscopic nature of the formulation) or without water (used in case of those formula containing an active drug sensitive to water). Spray dried lactose, microcrystalline cellulose, starch, and sometimes anhydrous calcium phosphate are used as diluents in direct compressible tablet manufacturing.

1.5.3.1.1 Reasons for using Diluents:

- ➢ Inert substance designed to make up the required bulk of tablet when the drug dosage itself is inadequate to produce its bulk.
- ➢ To provide better tablet properties such as:
  - ✓ Improved cohesion (maintain proper shape of tablet)
  - ✓ To permit use of direct compression manufacturing
  - ✓ To promotes flow
  - ✓ To adjust weight of tablet as per die capacity. (Apu, 2010)

1.5.3.1.2 Influence of diluents on bioavailability

- Although diluents are normally thought of as inert ingredients, they can significantly affect the biopharmaceutical, chemical and physical properties of tablet.The calcium salts interfering with the absorption of tetracycline from the gastrointestinal tract. They make half the bioavailability of standard product.
- Antiepileptic drug sodium phenytoin will form poorly absorbable calcium-phenytoin complex, when calcium sulphate dihydrate used as diluent in the formulation. But using of lactose as diluent improves bioavailability of the antiepileptic drug significantly.

1.5.3.1.3 Influence of diluents on incompatibility

➢ Sometimes diluents cause discoloration of tablet. In case of amine drugs, lactose used as dilent along with metal stearate (Magnesium stearate) used as lubricant, cause discoloration of tbalets with time.

1.5.3.2 Binders

Binders are mostly used in case of wet granulating tablets during the process of granulation, but the powdered form of certain binders are also used in the formulation of direct compressible tablets, and they are termed as ‘dry binders’. Binders hold the ingredients in a tablet together. Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets.

There are few common binders used in both granulating and directly compressed tablet, they are:

➢ Saccharides and their derivatives:

✓ Disaccharides: sucrose, lactose;

✓ Polysaccharides and their derivatives: starches, cellulose or modified cellulose such as microcrystalline cellulose and cellulose ethers such as hydroxypropyl cellulose (HPC);

✓ Sugar alcohols such as xylitol, sorbitol or maltitol;

➢ Protein: Gelatin

- Synthetic polymers: polyvinylpyrrolidone (PVP), polyethylene glycol (PEG).

According to Wikipedia, binders are actually classified according to their application:

- Solution binders are dissolved in a solvent (for example water or alcohol can be used in wet granulation processes). Examples include gelatin, cellulose, cellulose derivatives, polyvinylpyrrolidone, starch, sucrose and polyethylene glycol (PEG).
- Dry binders are added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula. Examples include cellulose, methyl cellulose, polyvinylpyrrolidone (PVP) and polyethylene glycol.

1.5.3.3 Disintegrants

Disintegrant are basically added to the formulation as it breaks the dosage form inside our body into very smaller particles when it comes in contact with the body fluids. These smaller fragments of dosage forms have greater surface area which will increase the dissolution of the drug. Direct compressed tablets mainly require a super disintegrants that can effectively disintegrate a tablet when used at low concentrations (typically 2% to 6% by weight). The selection of the appropriate disintegrant will depend partly on the drug substance and the selection of the filler-binders. Tablets containing a proportion of microcrystalline cellulose tend to be readily disintegrated by all super disintegrants, whereas tablets containing a high proportion of dibasic calcium phosphate may require the extra disintegrating power of, say, croscarmellose sodium, especially after storage at accelerated stability conditions.

Croscarmellose sodium, sodium starch glycolate, polyvinyl pyrrolidone and crospovidone are the most commonly used super disintegrants.

1.5.3.4 Lubricants

Lubricants prevent sticking of the tablets to the tablet punches during the compression phase of the tablet manufacturing process. When lubricants are added to a powder mass, they form a coat around individual particles which remains more or less intact during compression. Lubricants are mostly hydrophobic. The presence of lubricant coating may cause an increase in the disintegration time and a decrease in drug dissolution rate. The

choice of a lubricant may depend upon the type of tablet being manufactured, dissolution, flow characteristics and requirements of the formulation in terms of hardness, friability and compatibility.

Any stearates, like magnesium, calcium, zinc, or sodium stearates, Sodium stearyl fumerate, boric acid, sodium lauryl sulfate, stearic acid etc can be used as lubricant within direct compressible tablets.

1.5.3.5 Glidants

Direct compression filler binders have been developed to exhibit sufficient flow for direct compression, and a glidant will only be needed when the drug is present in sufficient concentration to interfere with flow. Glidants improve the flow of powder into the tableting machines for compaction. They act to minimize the tendency of a granulation to separate or segregate due to excessive vibration. High speed tablet machine require smooth even flow of material to die cavities (tablet mold). The uniformity of tablet weights directly depends on how uniformly the die cavity is filled.

Talc is an ideal glidant to be used in this dosage form. Concentration of starch is common up to 10%, but should be limited otherwise it will worsen the flow of material. Besides colloidal silicon dioxide added at a typical level of 0.1% to 0.2% will improve the flow characteristics of a compression mix.

1.5.3.6 Miscellaneous

Above from the above mentioned principal ingredients following excipients also improve the dosage form characters they are stabilizers, colouring agents, surfactants, flavorants etc.

- *Stabilisers:* These are typically used, if necessary, to minimise pH dependent hydrolysis or oxidation depending on the requirement of the drug substance. To promote intimate contact of the drug with the stabiliser it is generally recommended to include the stabiliser in finely divided form at the premix stage.
- *Colourants:* Colouranats are added to the formulation in order to increase the patent compliance or for identification of the formulation. Usually the colurants are added in the form of insoluble powder or in the form as liquid in the granulation liquid.

To obtain evenness of colouration in directly compressed formulations the use of insoluble pigments (aluminium lakes and iron oxides) is preferred. Inclusion at the premix stage can minimise “speckling” in the finished tablets. Alternatively the tablets can of course be film coated.

- *Surfactants:* Wetting agents such as sodium lauryl sulphate may be included, especially if the drug substance is hydrophobic.
- *Flavorants:* These are incorporated into the formulation to improve the flavor or give a pleasant taste to the formulation. Flavoring agents are mostly restricted to the formulations in which are intended to be released in the mouth or chewable tablets. They are usually added in along with the granules.

1.6 AN OVERVIEW OF THIS THESIS

For this thesis paper, I have chosen to test the effect of different ratio of an individual lubricant in a particular hypothesized formulation of a direct compressible tablet. Due to certain inconveniences and lack of expertise, use of active ingredient was totally overlooked. All the experiment was done without active drugs, upon the powder excipients only; those are commonly used in case of direct compressible tablets production. Now let us know about this targeted excipient, and the probable changes in the existing tablet formulations those are followed by addition or removal of a lubricant, and also the changes of its amount in the formula.

1.6.1 Definition- Lubricants:

Lubricants are agents added in small quantities to tablet and capsule formulations to improve certain processing characteristics. Lack of lubricant can lead to problems like capping, scratch on the sides of the tablet, fragmentation of the tablet, shape out etc. It is not a liquid or oil, but a light, fine powder. Typically, lubricants account for a small percentage of the formula’s content, and many of them may be used as less as 0.25 percent of a formulation.

1.6.2 Functions of Lubricants:

According to the Wikipedia, There are three main roles identified with lubricants as follows:

1. **True Lubricant Role:** To decrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punch dies.
2. **Anti-adherent Role:** Prevent sticking to the punch faces or in the case of encapsulation, lubricants prevent sticking to the machine dosators, tamping pins, etc.
3. **Glidant role:** Enhance product flow by reducing inter particulate friction.

Lubricants also have some other functional properties apart from the above three, though they are somehow interconnected with each other.

- Lubricants are supposed to help in the reduction of friction:
  - ✓ Between particles during compression and
  - ✓ Between the walls of tablet and the walls of the cavity in which tablet was formed
- Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine.

1.6.3 Criteria of an Ideal Lubricant:

- An ideal lubricant should reduce friction at small quantity.
- It should be inert, non-toxic and water soluble, colorless, odorless,
- It must be capable of reducing wear on rubbing surfaces. To perform this function the lubricant must provide film that will prevent solid to solid contact, and is easily sheared.
- A lubricant must have low shear strength
- It must be able to form a "double layer" over the surface covered,
- It should be unaffected by process variables,
- Lubricants must not possess minimal adverse effects on the finished dosage forms. (Formulation, 2013)

1.6.4 Disadvantages of lubricants:

The lubricants are believed to form a coat around each granule and this effect also gets extended to the tablet surface. The lubricants may show some inherent drawbacks:

- ✓ Lessen tensile strength (may interfere with the particle – particle bonding)
- ✓ Extension of disintegration and dissolution time (waterproofing properties)

Since primarily lubricants are required to act at the tooling or material interface, lubricants should be incorporated in the final mixing step, and concentration should be limited for producing maximum flow rate. (Apu, 2010)

1.6.5 Effect of variation in parameters of Lubricants in a formulation:

For a lubricant the time of addition, concentration in which it is to be added and the combination are the important parameters.

- ➢ *Concentration:* as most of the lubricants are hydrophobic in nature thus the an increased concentration of lubricant would lead to problems like poor wettability, and dissolution and disintegration problem this they are added in the concentration less than 1%.
- ➢ *Time of mixing:* it is important as over mixing may lead to reduction in tablet dissolution and disintegration.
- ➢ *Combination:* if the lubricant is mixed with the disintegrant it will lead to formation of a film of lubricant on the tablet surface which will reduce the disintegration.

Determining the concentration of lubricants use and mixing time are critical. If concentrations are too low, or distribution and mixing times are inadequate, problems can occur, such as- punch filming, picking, sticking, capping, and binding in the die cavity.

Traditionally, over-lubrication has been associated with over mixing in the blender, but new evidence suggests that other parts of the manufacturing process may contribute to the overall effect. This study confirms that the force feeder of the rotary tablet press may play an important role in the over-lubrication effect. (Tablet Manufacturing, 2013)

If concentrations are too high, or distribution and mixing times are too great, other problems can occur, such as-

- Decrease in tablet hardness
- Inability to compress into tablets
- Increase in tablet disintegration times
- Decrease in rate of dissolution. (Carter, 2006)

1.6.6 Types of Lubricants: Lubricants can be majorly of two types-

1.6.6.1 Insoluble or Hydrophobic lubricants: These are added to the formulation at the end before the compression of the tablet. They are the most widely used lubricants in use today are of the hydrophobic category. Hydrophobic lubricants are generally good lubricants and are usually effective at relatively low concentrations. Many also have both anti- adherent and glidant properties. For these reasons, hydrophobic lubricants are used much more frequently than hydrophilic compounds.examples include: magnesium stearate, calcium stearate, zinc stearate, stearic acid, glyceryl behnate, glyceryl palmito stearate.

1.6.6.2 Soluble or Hydrophillic lubricants: These are added to overcome the defects caused by the insoluble lubricants. These are generally poor lubricants, with no glidant, or anti-adherent properties. Examples include: polyethylene gycol, poly oxyethylene stearate, lauryl sulphate salt.

1.7 SHORT NOTES ON THE EXCIPIENTS USED IN THE EXPERIMENT

In this research, I have used few excipients which belong to the categories of binders, diluents, tablet disintegrants, glidants, and most importantly lubricants. Here are the notes written about those excipients briefly.

1.7.1 Calcium Phosphate, Dibasic Anhydrous ($CaHPO_4$): Anhydrous calcium hydrogen phosphate or dibasic calcium phosphate is commonly used in pharmaceutical industries as tablet and capsule diluents or filler. It is white, odorless, tasteless powder or crystalline solid with molecular weight of 136.06. It is used particularly as a source of calcium in nutritional supplement and also used in pharmaceutical products because of its compaction properties and good flow properties of the coarse- grade material. Two

particle- size grades of anhydrous dibasic calcium phosphate are used in the pharmaceutical industries:

- **Milled material** is typically used in wet-granulated and roller compacted formulations.
- **Unmilled or Coarse-grade** material is used in direct compression tablet.

Anhydrous dibasic calcium phosphate is nonhygroscopic and stable at room temperature. It does not hydrate to form the dehydrate calcium phosphate. It is used in the quantity as other common tablet, capsule diluents.

1.7.2 Magnesium Stearate: In United States Pharmacopia, magnesium stearate is described as a compound of magnesium with a mixture of solid organic acid that consists chiefly of variable proportions of Mg stearate and Mg palmitate ($C_{32}H_{62}MgO_4$). It has structural formula of $[CH_3(CH_2)_{16}COO]_2Mg$ with molecular weight of 591.34. It is popularly used in tablet or capsule formulations as lubricant at concentrations between 0.25% and 6.0%. Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin. Mg stearate is stable and should be stored in a well-closed container in a cool, dry place. There is one significant adverse effect of this lubricant that it is highly hydrophobic and may retard the dissolution of a drug from the solid dosage form, therefore the lowest possible concentration is used in such formulations.

1.7.3 Zinc Stearate: According to United States Pharmacopia, zinc stearate is a compound of zinc with a mixture of solid organic acids obtained from fats and consists chiefly of variable proportions of zinc stearate and zinc palmitate. It contains the equivalent of 12.5%- 14.0% of zinc oxide (ZnO). It is used as tablet and capsule lubricant and also as thickening and opacifying agent in pharmaceutical creams widely. Zn stearate occurs as a fine, white, bulky, hydrophobic powder, free from grittiness and with a faint characteristic odor. Though zinc stearate is stable compound, it is readily decomposed by dilute acids and highly hydrophobic. Due to adversed effect, it is now normally replaced

by other lubricants. However, following inhalation, it has been associated with fatal pneumonitis, especially in infants.

1.7.4 Talc: Talc or talcum is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4OH_4$. It may contain small, variable amounts of aluminium silicate and iron. It is s very fine, white to grayish white, odorless, impalpable, crystalline powder, free from grittiness. Talc has many uses in solid dosage form manufacturing, like as- anticaking agents, glidant, diluent and lubricant. Talc is now commonly used for another reason, that it is now used as a dissolution retardant in some controlled released products. As a glidant or lubricant, talc is used in the range between 1.0 and 10.0%, whereas it is used as tablet and capsule diluents in the range between 5.0 and 30.0%. Talc is a stable material and may be sterilized by heating at 160^0 C for not less than 1 hour.

1.7.5 Starch: Starch is a compound of large molecular weight (approximately 50000-160000) with a empirical formula of $(C_6H_{10}O_5)_n$, where n = 300- 1000. Starch is used as glidant, lubricant, binder, diluents in case of pharmaceutical formulations, primarily in oral- solid dosage forms. It is used as a tablet binder in the amount of 5-25% w/w and 3-15% w/w as tablet disintegrants in common dosage form preparations. Starch has an odorless and tasteless, fine, white colored powder comprising very small spherical or ovoid granules whose size and shape are characteristic for each botanical varieties, eg. rice, corn, tapioca, potato etc.

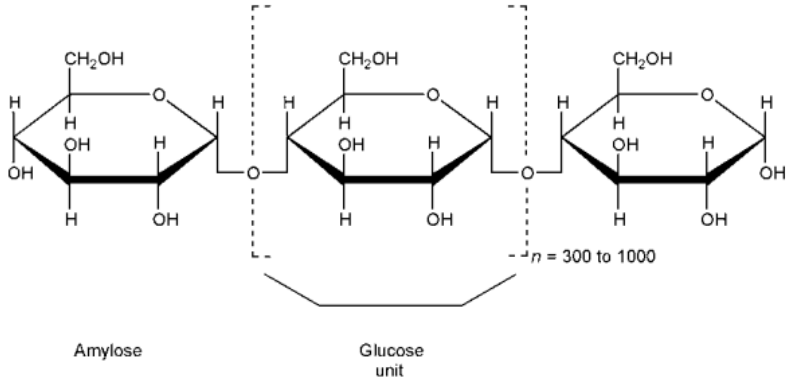

Figure 1.1: Structure of Starch

1.7.6 Polyvinyl pyrrolidone: This excipient is also commonly known as povidone, PVP or 1-vinyl-2-pyrrolidinone polymer. It has large molecular weight of about 2500-3000000 with an empirical formula $(C_6H_9NO)_n$. Although povidone is used in a various pharmaceutical formulations, it is primarily used in solid dosage forms, as disintegrants (upto 5%) and tablet binder. Povidone solution is also used as coating agents. It is found as a fine, white to creamy white, odorless or almost odorless, hygroscopic powders. Nowadays povidone and is related product crosspovidone are combined in a particular excipients combination which serves a constant criteria with particular amounts of these powders along with other excipients.

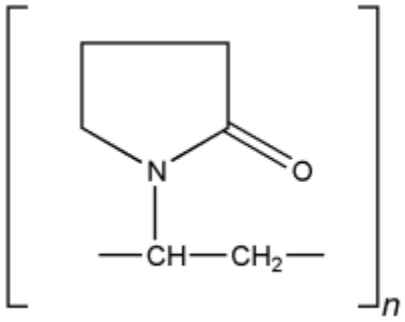

Figure 1.2: Structure of Polyvinyl Pyrrolidone

1.7.7 Sodium Lauryl Sulfate: United States pharmacopeia describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly (not less than 85%) of sodium lauryl sulfate. It is comprised of white or cream to pale yellow-colored crystals. Flakes, powders having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances. Molecular weight of sodium lauryl sulfate is 288.38 with an empirical formula of $C_{12}H_{25}NaO_4S$. Though it has many functional categories (eg. anionic surfactant, detergent, emulsifying agent), sodium lauryl sulfate is used as lubricant in solid dosage formulations very popularly. It is very much stable under normal environmental conditions but it may be moderately toxic to certain group of people being allergic to it, and that is why it is used along with other lubricants in case of tablet or capsule.

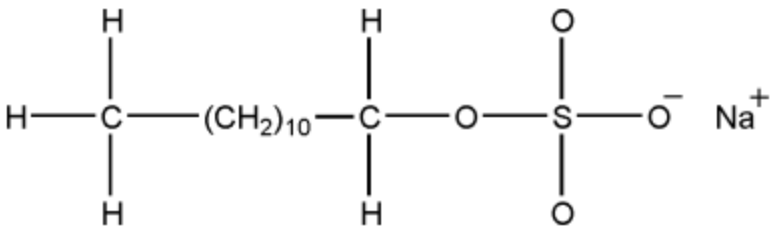

Figure 1.3: Structure of Sodium lauryl Sulphate

1.7.8 Lactose: Lactose or lactose monohydrate is a commonly used tablet or capsule filler or diluents as well as binder with a molecular weight of 360.31. In the solid state, lactose appears as various isomeric forms, depending on the crystallization and drying technique/ conditions. Among all the forms α- lactose monohydrate is widely used in case of direct compressible tablets. The USPNF 23 describes lactose monohydrate as natural disaccharide, obtained from milk and it may be modified as to its physical characteristics, and may contain various proportions of amorphous lactose. Lactose occurs as white to off white crystalline particles or powders, which is odorless and slightly sweet-tasting. α – lactose is approximately 20% as sweet as sucrose, while β-lactose is 40% as sweet. Lactose is commonly used as diluents in dry powder inhalers also.

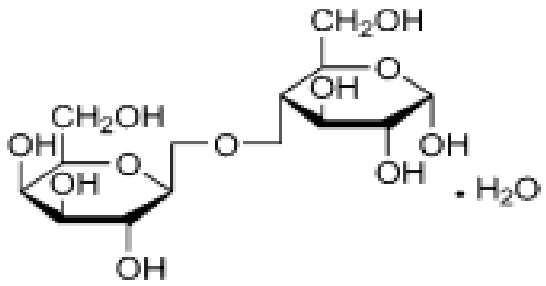

Figure 1.4: Structure of α-lactose monohydrate

1.7.9 Boric Acid: In its solid form, boric acid is a weak acidic white crystalline powder that is soluble in water (about 27% by weight in boiling water and about 6% at room temperature), soft, ductile, stable, free flowing and easily handled. Two of the most

important characteristics of boric acid for use as a lubricant are that it is readily available and environmentally safe. Examining its physical characteristics, boric acid is the common term for orthoboric (or boracic) acid H_3BO_3 (molecular weight 61.83), which is a hydrate of boric oxide B2O3. As boric acid is incompatible with water, it is generally used in case of directly compressible tablets only for lubrication.

Chapter Two

Literature Review

In the whole world, around 80% of drug dosage forms is covered by solid dosage forms, like tablet, capsules etc. Powder flow characteristic is one of the most important parameter to be checked in case of these dosage preparations. Flowability of the formulations for the dosage forms, including both active pharmaceutical ingredients and powder excipients, is usually tested while the ingredients' flow by the research team. After their approval for certain ingredients, flow property is further tested commercially by the team within a pharmaceutical to be assured of whether this formulation is appropriate for bulk scale preparation or not. This flow characteristic determination of pharmaceutical ingredients has been continuing for many decades, and the researcher finally reached to a conclusion about using any ingredient, or benefits or problems of few ingredients together. Some of the studies are overviewed in the following of this review.

In earlier time, Gold and Palermo (1965) described the instrumentation for measuring the sign and magnitude of static charges produced by particles flowing through a tablet hopper. They took acetaminophen in crystalline form, which had a higher negative hopper flow static charge than granulation prepared from the powder. At the end of the study, they concluded that other tablet excipient, such as diluents (eg dicalcium phosphate dihydrate, mannitol, spray-dried lactose) and lubricants like magnesium stearate and talc declined the hopper flow static charge of active drug, acetaminophen. They also showed that particle size and water concentration influence the magnitude of the hopper flow static charge.

In the last of the following year, again Gold, with his another research team studied the affect of different parameters of glidants on its flow rate and angle of repose. Glidants is often selected by subjective methods like measurement of the angle of repose. They compared the both results; one is by using the glidants practically in tablet preparation and thus checking its flowability, and other result was achieved by identifying their angle of repose. They took some widely used glidants for their study, like fumed silicon dioxide, starch, magnesium stearate, and talc, in combination with selected materials. Many of the more commonly used glidants actually decreased the flow rate. Glidants, which lowered the angle of repose of the tablet formula did not necessarily enhance the

flow rate and noticeable changes in flow rate were not always visible by angle of repose measurement. Finally they concluded the study by showing that, a comparison between the angle of repose of a particular glidant and the flow rate of it using with various common raw materials indicated that the angle of repose was not a consistent method for assessing the flow of these materials. (Gold, et al., 1966)

In the year 1979, Bolhuis and his researcher team studied on the flow and lubrication properties of a high dosage range drug, acetylsalicylic acid with different particle size distributions, which was formulated with directly compressible excipients and compressed into tablets. They investigated the weight variation, drug content, crushing strength, friability, disintegration time, dissolution rate of the drug and stability after storage for eight weeks at 20^0C and 50% or 85% relative humidity of 500 mg acetylsalicylic acid. Their result showed that knowledge of the properties and interactions of drug, directly compressible excipients and other tablet vehicles makes possible the formulation and compression of different particle size acetylsalicylic acid powders into good quality tablets. (Bolhuis, Lerk, Moes, 1979)

In the year 1982, a study was performed showing the effect of particle size on the compression mechanism and tensile strength of prepared tablets. They took some excipients for their study to check the effect of its particle size, like Sta-Rx 1500, spray-dried lactose and Avicel PH-101. In the experiment they found that declining the particle size of spray-dried lactose and Sta-Rx 1500 resulted in stronger compaction. On the other hand, particle size variation of Avicel PH-101 did not showed any impact on tablet tensile strength. Their study was concluded by identifying a statement that angle of repose and Hausner ratio measurements indicated a connection between the internal forces of friction and cohesion of the different sized powders and the tensile strength of compacts formed from them. (Mckenna and Mccafferty, 1982)

In midth of 1994, Torrado and Augsburger (1994) examine possible protective effect of different excipients on the tableting of theophylline granules coated with Eudragit RS by using drug release data as an indirect method. They developed an order of least damage

to the coating that was: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. These results were in good conformity with the yield values of these materials. It seemed that the tablet matrix had a lower yield pressure than the pellet, or pellet coating, such that the energy of compaction was absorbed by the matrix, and that the matrix was preferentially deformed. Under our experimental conditions, and even at very low compressional pressure there is always damage of the coating membranes. Nevertheless, it is possible to achieve a formulation to ensure minimum damage to this coating by appropriate selection of the excipients. The result of their study was that, a combination of the following excipients with low yield pressure values is proposed as a suitable excipient mixture for coated particles: microcrystalline cellulose 50%, PEG 3350 25% and crospovidone 25%.

Schmidt and Rubensdörfer (1994) observed the tableting properties of Ludipress, and assessed and compared to the physical blend of these base materials present in Ludipress and to other binders or fillers including Cellactose and Avicel PH 200 and Cellactose. They determined the data in order to assess flowability, bulk and tapped density, Hausner ratio, angle of repose as well as particle size distribution. Scanning electron microscopy (SEM) was used to examine morphology and constitution of particle, and differential scanning calorimetry (DSC) for detecting differences between lactose based products. Several Ludipress samples showed a good batch-to-batch uniformity and flow characteristics compared to the physical blend and other excipients investigated. Tableting parameters, like crushing strength, friability and disintegration time were tested. The tableting parameters tested were crushing strength, friability and disintegration time. The ability to form rational compacts was similar for Ludipress, Cellactose and Avicel PH 200, on the other hand tablets made from the physical blend resulted significantly softer. The disintegration times of Avicel PH 200 compacts were nearly constant and were also the shortest in the compaction load range examined.

In following year Amidon with Houghton (1995) showed the effect of moisture on the mechanical and powder flow properties of microcrystalline cellulose (MCC). Mechanical properties of MCC were determined on different range of moisture (0 to 12.2%) and few

other parameters were also checked, such as, compaction, hardness study, compressibility index and also shear cell index. They found significant changes in the results as the moisture level of the excipient was increasing. The permanent deformation pressure and tensile strength of compacts were monitored to be relatively independent of moisture content below about 5% moisture and then decrease as the moisture content increased further. Above 5% of moisture level the flow rates of MCC were getting poorer as the moisture level increased, and it was identified by the value achieved from Compressibility index and using shear cell method. The data of mechanical property are consistent with the hypothesis they made that water acts as a plasticizer and influences the mechanical properties of microcrystalline cellulose. At moisture levels above about 5%, the material exhibits significant changes consistent with a transition from the glassy state to the rubbery state.

Taylor and his fellow researchers tested the flow properties of typial tablet and capsule formulation excipients, active compounds, and representative formulation blends with current and novel flow measurement techniques. This test was conducted to identify a reliable bench test to quantify powder flow as a screening method in early tablet and capsule formulation development. Test methods used were vibrating spatula, angle of repose, compressibility index, critical orifice, and avalanching analysis. Results of powder flow from each method were compiled in a database, sorted, and compared. An experimental composite index was established and powder flow was ranked accordingly formulator experience. Principal components analyses of the angle of repose, percent compressibility, and critical orifice of the powder materials were also performed. Scientists found that the first principal component accounted for 72.8% of data variability; scores associated with this principal component score can serve as an index of flowability. Data generated from vibrating spatula and avalanching methods were not reproducible with formulator experience and cited vendor references for flow. The researchers concluded that improvements of test instruments and further studies are necessary for better assessment of these approaches. (Taylor et al. 2000)

Again in later 2000, two researchers Podczeck and Newton (2000) studied granulated powdered cellulose in terms of powder bulk properties and capsule filling performance. They conducted the study on a tamp-filling machine with and without adding of different concentration of magnesium stearate. As magnesium stearate is widely used as a lubricating agent, in their research, they found Carr's compressibility index to be reached at its minimum value 0.4%. This suggested a development of powder flow in comparison to any unlubricated material. While conducting shear cell measurement and using a powder rheometer, they found that the addition of 0.2% Mg stearate and more impairs powder flow and does not lessen interparticulate friction. They finally observed and concluded that increase in concentration of Mg stearate caused both plug density and fill weight to go through a minimum at a lubricant concentration of 0.4%. The most favorable concentration of lubricant in terms of ease of machine function, which was recognized from tamping pressure measurements, was found to be 0.8% Mg stearate, which was not an optimal concentration for the powder bulk properties.

In the year 2001, Hancock and his team (Hancock, et al., 2001) examined two recently developed matrix forming polymers; those are cross-linked high-amylose starch and poly acrylic acid. The operating parameters were powder flow and compact mechanical properties. The scientists also matched up to the properties with two previously established matrix-forming polymers such as hydroxypropyl methylcellulose (HPMC) and hydroxypropyl cellulose (HPC). The research showed that, the four materials were different in particle morphology, size distribution and tapped density. The materials also exhibited different powder flow, compact ductility, compact elasticity and compact tensile strength. The researchers concluded that, these excipients can be suggested for formulating solid dosage forms after considering their physical properties and performance.

In the year 2001, Gabaude and his research team studied on four characterisation techniques, such as packing and rearrangement under pressure methods or shear cell measurement methods, used to assess powder flow properties. They used mercury porosimetry and two compressibility methods and analyzed the reduction of the powder

bed volume under low pressures. They determined flow functions, deduced from shear cell measurements using a Johanson Indicizer Tester. Their examination of the reduction of the powder bed volume leads to new parameters such as the packing coefficient and the volume of mercury interrupted. They found that packing coefficient appears to be a reliable approximation of powder flow properties. They found that it is actually well correlated with shear cell measurements and it is more accurate than classical flowability tests recommended by the European Pharmacopoeia. Finally they concluded that this method is able to give very early in the development, a quite accurate estimation of powder flow properties of new drug substances and this may be very helpful for an early determination of the optimum particle granulometry or for a rapid development of a feasible industrial process. (Gabaude, et al., 2001)

In the March of 2002, an Indian scientist, Vijay Kumar along with two others conducted a study with UICEL that is actually a new cellulose-based tabletting excipient. This has been developed by treating cellulose powder with an aqueous solution of NaOH (conc. ≥5N) and subsequently precipitating it with ethyl alcohol. UICEL is similar in structure to Avicel® PH-102, a commercial direct compression excipient commonly referred to as microcrystalline cellulose (MCC). Compared to Avicel® PH-102, UICEL shows higher true density, bulk density, tap density, Carr's index and Hausner ratio values. The mean deformation pressure (P_y) values calculated from the linear portion of the Heckel plots for UICEL and Avicel® PH-102 were about 104 and 87 MPa, respectively, suggesting that UICEL is less pliable than Avicel® PH-102. The hardness values of UICEL tablets increased nearly linearly with increasing compression pressures. Avicel® PH-102 formed stronger tablets in comparison to that made up of UICEL. Irrespective of the compression pressure used, all UICEL tablets disintegrated within 15 s, whereas Avicel® PH-102 tablets of comparable strengths remained intact for over 12 h. The whole study concluded that UICEL can be used as a direct compression excipient, especially in the design and development of fast-disintegrating tablets. (Kumar, Reus-Medina, Yang, 2002)

Pharmaceutical excipients may have a great effect on flow properties that affects tablet production. Nagel and Peck (2003) conducted a study to evaluate whether formulations containing theophylline anhydrous would have better properties allowing them to be easily tableted, functional parameters affecting powder flow were examined. The Carr's flowability indices were used for this study purpose. They invented formulations including theophylline anhydrous as the active ingredient, hydrous lactose and dicalcium phosphate dihydrate as diluents, polyvinylpyrrolidone as a binder, and fumed silica as a flow promoter. They discussed about effects of each ingredient that affects powder flow from hopper in their journal.

In the midth of the year 2003, Mullarney and his fellow researchers (Mullarney et al., 2003) investigated the flow characteristic and compact mechanical properties of sucrose and other three highly intense sweeteners those were widely used in chewable tablets. The physical, flow, and mechanical properties of four common pharmaceutical sweeteners, like Sucrose, saccharin sodium, acesulfame potassium (Sunett®) and aspartame were measured to assess their relative manufacturability in solid dosage formulation. Those were examined to determine significant differences in particle shape, size distribution, and true density, which are related to its flowability. Cohesivity and compact mechanical properties, like ductility, elasticity, and tensile strength were measured and found to be visibly different. Among these sweeteners, sucrose and Sunett® showed excellent relative to over 100 widely used pharmaceutical excipients evaluated in the scientists' laboratory. Saccharin sodium and aspartame showed poor powder flow and superior compact strength relative to sucrose and acesulfame. These data suggest that careful selection of an appropriate sweetener is warranted in obtaining desirable process and tableting strength, particularly if sweetener loading is high.

Again at the end of that year, Zhang and his fellow researchers came out with another analysis. They investigated the basic physico-chemical property and binding functionality of commonly used commercial direct compression binders/fillers through their study. The compressibility of these materials was also analyzed using compression parameters derived from various sources, like Heckel, Kawakita, and Cooper-Eaton equations. They

evaluated five classes of excipients, including microcrystalline cellulose (MCC), starch, lactose, dicalcium phosphate (DCP), and sugar. In general, the starch category exhibited the highest moisture content followed by MCC, DCP, lactose, and finally sugars; DCP displayed the highest density, followed by sugar, lactose, starch, and MCC; the material particle size is highly processing dependent. The data also exhibited that MCC had moderate flowability, excellent compressibility, and extremely good compact hardness; with some exceptions among starch, lactose, and sugar. This research additionally confirmed the binding mechanism that had been well documented: MCC performs as binder because of its plastic deformation under pressure; fragmentation is the predominant mechanism in the case of lactose and DCP; starch and sugar perform by both mechanisms. (Zhang, Law, Chakrabarti, 2003)

In the following year, Jonat with his research group evaluated and compared the flow characteristic of glidant properties of compacted hydrophilic and hydrophobic colloidal silicon dioxides with respect to mixing time and mixer type using microcrystalline cellulose, starch and α-lactose-monohydrate as model excipients. Angle of repose measurements and a novel dynamic conveyor belt method showed differences in the flow enhancement between the colloidal silicon dioxide types. An influence of mixing conditions on flowability was also observed for hydrophilic colloidal silicon dioxide. The influence of size and distribution of the colloidal silicon dioxide particles on the surface of the excipient, mixing time, mixer type are explained in detail. In addition, moisture studies showed that colloidal silicon dioxide protects the excipients against a flowability decline caused by humidity. (Jonat et al., 2004)

Again in 2004, Thalberg and two other researchers compared flow characteristic of powders for inhalation. A series of placebo powders for inhalation was illustrated regarding bulk density and powder flowability using different techniques. The powders were prepared by mixing a pharmaceutical carrier grade of lactose with different fractions of intermediate sized and micronized lactose. A modified Hausner Ratio was attained by measurement of the bulkand the true densities. Other tests done were the angle of repose, the avalanching behaviour using the AeroFlow, and the yield strength using the Uniaxial

tester. Furthermore, the relation between ordered mixture composition and flowability was examined. The modified Hausner Ratio differentiates well between the investigated powders and seems to have the widest measuring range. It was also found that the poured and compressed bulk densities provide information about the packing of the particles in the powders. A good correlation was obtained between the modified Hausner Ratio and the angle of repose. Regarding the powder composition, addition of micronized particles has a strong influence on the flowability of ordered mixtures, while intermediate sized particles have little impact on the powder flow. (Thalberg, Lindholm, Axelsson, 2004)

In that year, an experiment was done to determine the effect of powder properties and its storage condition on the flowability of milk powders with different fat contents (Fitzpatrick et al., 2004). Consistent reliable flow of milk powders out of hoppers is very important in their handling and processing. Shear cell methods were applied in this work to measure and compare the flow characteristics of a commercial skim-milk powder (SMP), a whole milk powder (WMP) and a 73% high fat milk powder (HFP), and to examine how storage temperature and exposure to moisture in air affected the flowability of these milk powders. This technique was also used to investigate how powder particle size and free-fat content affected the flowability of a number of milk powders produced at pilot-scale. WMP and HFP were cohesive powders while SMP was easy flow, but SMP showed greater wall friction on the stainless steel material tested. Decreasing particle size from 240 to 59 μm produced a major increase in cohesion of 26% fat milk powders.

Again in the year 2004, a pioneer research team (Bhattachar et al., 2004) introduced the world a statement that in the development of dosage form, the flow properties of pharmaceutical excipients in solid oral dosage forms is a fundamental phenomenon. In this case, the vibratory feeder method was considered as the flow measurement technique to measure flow properties of common excipients in solid oral dosage forms. In this experiment, seventeen different powders were evaluated with the instrument to measure the flow properties and the result was stated as the powder flow index (PFI). On the other hand, the powder flow was evaluated with another commonly used avalanche instrument

and similarly the data was included in mean time to avalanche (MTA) as mean time. The results obtained from the two different instrumental methods (PFI and MTA) having different algorithms, were compared with nonparametric statistical assessment of the data and proved as a reliable document. Afterwards, vibratory feeder method was recommended for measuring powder flow.

In the following year, Kim and his research team examined on the surface composition of four industrial spray-dried dairy powders, skim milk powder, whole milk powder, cream powder and whey protein concentrate by electron spectroscopy for chemical analysis (ESCA). They also studied its influence on powder flow characteristic. At the end of the study they found that skim milk powder flows well compared to the other powders. This is perhaps because the surface is made of lactose and protein with a small amount of fat, whereas the high surface fat composition inhibits the flow of whole milk, cream and whey protein powders. They noticed poor flowability of the powders with high surface fat coverage was drastically improved by removal of fat present on the surface through a brief wash with petroleum ether. Finally they concluded that even though there are several parameters including particle size, which influence the flowability of powders, the flowability of powders is powerfully influenced by the surface composition of powders, chiefly for fat-containing powders. (Kim, Chen, Pearce, 2005)

In the year 2007, another study was conducted on flow property of co-processed particles of microcrystalline cellulose (MCC) and mannitol. Both the excipients were fabricated by spray drying process to be used as a direct compression excipient in fast dissolving tablet formulation. The composite particles were examined for their powder and compression properties. The scientists observed that an increase in the MCC proportion imparted greater compressibility to the composite particles, but the flowability of these mixtures was decreased. Although MCC and mannitol have been widely used in the formulation of fast dissolving tablets, the non-wetting property of the hard compact central core may delay the disintegration time. Optimizing the ratio of mannitol and MCC in 1.25:1, the scientists found to have optimized powder and compressibility characteristics with fast

disintegrating property (<15 s). It was concluded that a higher rate of powder flow can indirectly influence the rate of disintegration. (Jacob et al., 2007)

Another study was performed by Faqih and his research fellows in the following year (Faqih et al., 2007). They evaluated flow in a rotating drum and flow in bench scale hoppers. They studied flow properties of 13 cohesive granular materials in the gravitational displacement Rheometer (GDR). They compared it to flow in hoppers of varying angle and discharge diameter at fixed temperature and moisture conditions. They found that GDR was an effective and convenient tool for examining flow properties of pharmaceutical materials, both pure and mixtures. A flow Index acquired from GDR measurements is directly correlated to the flow through hoppers, providing a predictive method for hopper design and a convenient experimental test for screening materials and determining their suitability for specific hopper systems.

In the year 2008, Hou and his co-researcher Sun studied the effects of particle size, morphology, particle density, and surface silicification, on powder flow properties using a ring shear tester. They studied eleven powders from three series of microcrystalline cellulose (MCC) (a) Avicel, regular MCC, elongated particles, (b)Prosolv, silicified MCC, elongated particles, and (c) Celphere, spherical MCC. They identified that smaller particles always led to poorer powder flow properties. They found that mechanism of the detrimental effect of particle size reduction on flow properties and that was the larger powder specific surface area. They stated that flow properties of Celphere were significantly enhanced than Avicel of comparable particles size. They finally suggested that spherical morphology promoted better powder flow properties. They identified that flow properties of powders different in densities but similar in particle size, shape, as well as they found similar surface properties.

Again in that year, Freely and his team studied the surface thermodynamic properties of two nominally equivalent batches of salbutamol sulphate by employing Inverse gas chromatography (IGC). They studied the surface energetic changes induced on micronisation. They used powder flow avalanching analyser to probe the relationship between powder flow and the surface energetic properties. Their results demonstrated the

potential of these techniques to detect and quantify differences in powder samples, before and after micronisation. They also indicated that surface energy differences detected by IGC can be related to important secondary processing properties such as powder flow. (Freely et al., 2008)

Sarraguca and his fellow researchers (Sarraguca et al., 2010) studied the flow properties of pharmaceutical excipientss using near infrared spectroscopy. They illustrated that physical properties of pharmaceutical powders are of topmost significance in the pharmaceutical industry. They examined the critical significant properties of flowability using processes like blending, tablet compression, capsule filling and transportation using angle of repose, Carr's index and Hausner ratio. They used near infrared spectroscopy because it is fast and low-cost analytical technique to determine the parameters of flow properties of pharmaceutical powders based on active ingredient paracetamol. The spectra were recorded on a Fourier-transform near infrared spectrometer in which the parameters were the angle of repose, true and tapped density. The comparison was made between near infrared based properties and reference methods results. The result showed that the physical properties affect the flowability of pharmaceutical powders. The correlation between the reference method values and the near infrared spectrum was carried out and both the results were compared. They concluded the study showing that prediction errors varied between 2.51% for the tapped density, 3.18% for the bulk density and 2.35% for the angle of repose.

Recently a study was performed investigating the effect of particle size on compaction behavior of two forms of ranitidine hydrochloride (form I and II). These studies were performed using three particle size ranges, which are 450–600 (a), 300–400 (b), and 150–180 (c) μm] of both the forms by using a fully instrumented rotary tableting machine. Tabletability of the studied size fractions followed the order; Form I-B > Form I-A > > Form II-C > Form II-B > Form II-A at all the compaction pressures. They found that in both the polymorphs, decrease in particle size improved the tabletability. They identified that Form I showed greater tabletability over form II at a given compaction pressure and sized fraction and decrease in particle size increased the compressibility and plastic

deformation of both the forms. They found improved tabletability of smaller sized particles was attributed to their increased compressibility. Though, IA and IB, despite poor compressibility and deformation, showed increased tabletability over IIA, IIB, and IIC by virtue of their greater compactibility. They performed Microtensile testing which revealed higher nominal fracture strength of form I particles over form II, thus, supporting greater compactibility of form I. They finally concluded that though particle size exhibited a trend on tabletability of individual forms, better compactibility of form I over form II has an overwhelming impact on tabletability. (Khomane, Bansa, 2013)

Chapter Three

MATERIALS AND METHODS

3.1 MATERIALS

3.1.1 Excipients Collection:

For the research purpose different classes of excipients were collected from the different labs of Pharmacy Dept. of East West University.

3.1.2 Excipients:

The list of excipients those were used during this research is given below with their individual source (supplier name):

Table 3.1: List of excipients through this research work

SL no.	Name of Excipients	Source (Supplier Name)
1.	Boric Acid	MERK, Germany
2.	Calcium Phosphate	MERK, Germany
3.	Lactose	MERK, Germany
4.	Magnesium Stearate	MERK, Germany
5.	Polyvinyl pyrrolidine	MERK, Germany
6.	Sodium Lauryl Sulphate	MERK, Germany
7.	Starch	MERK, Germany
8.	Talc	MERK, Germany
9.	Zinc Stearate	MERK, Gerrmany

3.1.3 Equipments and Instruments:

Table 3.2: List of instruments through this research work

Serial No.	Equipments	Source (Supplier Name)	Origin
1.	Weight Balance	SHIMADZU	Japan
2.	Mixture Machine	Locally Produced	Bangladesh

3.1.4 Images of Instruments:

Some images of important instruments those were used in different times during this research work.

Figure 3.1: Mixture Machine

Figure 3.2: Electronic Balance

3.1.5 Apparatus:

Some apparatus are listed in the following table those were used through the research work.

Table 3.3: List of apparatus used throughout this research work

Serial No.	Apparatus
1.	Beakers (100 mL)
2.	Test tubes, with stand
3.	Aluminum Foil Paper
4.	Cling Wrap (Transparent Plastic Paper)
5.	Mortar & Pastels
6.	Spatula
7..	Funnel (glass), Stand
8.	Measuring Cylinder (25ml, 50ml, 100ml)
9.	Conical Flask (50 ml)
10.	White Paper
11.	Desiccant (Silica Gel Beads)
12.	Black Marker, Pencil
13.	Ruler

3.2 METHODS

3.2.1 Preparation of Fomulation sets of excipients:

Two sets of formulas have been prepared by using varying amounts and types of excipients, and flow property of these two formulas were determined by adding lubricants. This has been purposely done to check whether the variation (percentage) of lubricants in a particular formula somehow affects the existing formula, or not. If they affect, do the changes particularly follow any tract, or rule? The formulation sets of excipients were made up of relying upon books and online journal that have mentioned about the excipients and in what amount they are used in a solid dosage form, especially in case of direct compressible tablets serving a definite phenomenon, that is whether they are used as diluents, or binder, or disintegrants. Both of my formulas contained all the group of excipients, generally used in a direct compressible tablet except the Lubricants!

Table 3.4: Amounts of excipients in both formulas with justification

Formula	Excipients used	Justification	Amounts in the formula (%)
Formula: One	**Calcium Phosphate**	Diluent	**40%**
	Lactose	Diluent	**10%**
	Starch	Binder	**30%**
	Polyvinyl Pyrrolidone	Disintegrants	**4%**
	Talc	Binder +Glidants	**6%**
Formula: Two	**Calcium Phosphate**	Diluent	**20%**
	Lactose	Diluent	**30%**
	Starch	Binder	**20%**
	Polyvinyl Pyrrolidone	Disintegrant	**6%**
	Sodium Lauryl Sulfate	Glidant	**4%**
	Talc	Binder + Diluent	**20%**

3.2.1.1 Procedure:

I have weighed all the ingredients in electronic analytical balance in the amount mentioned above, and mixed that with help of a clean and dry mixer machine. The machine was run for about one minute. After mixing, the powders were brought out from the machine and kept in a beaker (100 ml). The beaker was previously washed, dried and most importantly, I poured some silica gel beads, around 5 gms into the beaker and kept it over night by making it air tight. This was done for the most obvious reason so the beads can adsorb the moisture already present in the beaker, and no more moisture could enter the beaker anyhow.

Then the mixture was put into the beaker and again covered by plastic wrap to make it air tight, and further covered by aluminum foil to avoid penetration of light of heat exchange. I weighed particular amount of this formula and continued my study that is to evaluate the difference in flow while adding lubricants.

3.2.1.2 Formula One

I have prepared 20gm of this mixture to test its flow property in various ratios with an individual lubricant of varying ratio. For the preparation of 20 grams of the formula mixture, I have had to take each of the ingredients in the following calculated amount.

Table 3.5: Calculation of excipients in 20gms of *Formula- One*

Ingredients	Calculations	Amount in 20gm
Calcium Phosphate	40% of 20gm, or, $\frac{40 \times 20}{100}$	8.0 gm
Lactose	10% of 20gm, or, $\frac{10 \times 20}{100}$	2.0 gm
Starch	30% of 20gm, or, $\frac{30 \times 20}{100}$	6.0 gm
Polyvinyl Pyrrolidone	4% of 20gm, or, $\frac{4 \times 20}{100}$	0.8 gm
Talc	16% of 20gm, or, $\frac{16 \times 20}{100}$	3.2 gm

I had to assess the flow characteristic of the above formula five times with varying amount of five different lubricants used in direct compressed tablet. So it was better for me to prepare the formula in 5 times greater amounts for convenience of the whole experiment, that is, I had to prepare total 100gms of *Formula: One*, which contained-

Table 3.6: Amount (gm) of excipients in 100gm of *Formula- One*

Excipients	Amount in 100gms
Calcium Phosphate	40 gm
Lactose	10gm
Starch	30 gm
Polyvinyl Pyrrolidone	4 gm
Talc	16gm

3.2.1.3 Formula Two

I have also prepared 20gm of another mixture to test its flow characteristics in different amounts again. Here I also took lubricants that will indicate the variation in flow as I did with the above formula. Each individual lubricant was taken in various. For the preparation of 20 grams of the next formula mixture, I have taken each of the ingredients in the following calculated amount.

Table 3.7: Calculation of excipients in 20gms of *Formula- Two*

Ingredients	Calculations	Amount in 20gm
Calcium Phosphate	20% of 20gm, or, $\frac{20 \text{ X } 20}{100}$	4.0 gm
Lactose	30% of 20gm, or, $\frac{30 \text{ X } 20}{100}$	6.0 gm
Starch	20% of 20gm, or, $\frac{20 \text{ X } 20}{100}$	4.0 gm
Polyvinyl Pyrrolidone	6% of 20gm, or, $\frac{6 \text{ X } 20}{100}$	1.2 gm

Sodium Lauryl Sulfate	4% of 20gm, or, $\frac{4 \text{ X} 20}{100}$	0.8 gm
Talc	20% of 20gm, or, $\frac{20 \text{ X} 20}{100}$	4.0 gm

The flow characteristic of the above formula was even assessed for five times with varying amount of five different lubricants commonly used in direct compressed tablet. So for the convenience of my overall study, it was a better option for me to prepare the formula in 5 times greater amounts, that is, I had to prepare total 100gms of *Formula: Two*, which contained-

Table 3.8: Amount (gm) of excipients in 100gm of *Formula- Two*

Excipients	Amount in 100gms
Calcium Phosphate	20 gm
Lactose	30gm
Starch	20 gm
Polyvinyl Pyrrolidone	6 gm
Sodium Lauryl Sulfate	4 gm
Talc	30 gm

3.2.2 Combination of *Formulas* and Lubricants in different Ratio

The prepared formula was further mixed in an amount with the lubricant to conduct the ultimate study that is the assessment of flow characteristics of the combination. Here I have made 10 different combinations of formula and lubricants which differed from each other whether by the amounts of the excipients present in the formula, or by the lubricant itself. Each combination was again divided into four sets of ratio (in percentage) within the fomula and the individual lubricant.

3.2.2.1 Procedure:

I have weighed the formula from the previously made formula bulk according to each of the following combinations and taken the powder into a clean and dry test tube. The required amount was lubricant was also added with its respective formulations and the test tube was made air tight and seal. The ingredients were again mixed by shaking it properly. Each combination was shaken for around 1 minute to assure proper mixing. The test tubes and other apparatuses were labeled properly and after preparing a particular combination, the next procedures were followed, which are to measure the values for carr's index, Hausner's ratio, and angle of repose.

3.2.2.2 Combination 1: [F_1 : Boric Acid]

Formulation One was examined in different ratios with Boric acid, that is also a lubricant and some physical parameters were checked which are significant in describing flow property of a powder mixture, like as- Carr's index, Hausner's ratio and Angle of Repose. To conduct this study, I have prepared four sets of ratios in following manner-

Table 3.9: Amounts of Excipients in Combination 1

Ratio	Formula One (F_1) : Boric Acid (%)	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_1 : 0.1 gm boric acid
Ratio 2	96 : 4	4.8 gm F_1 : 0.2 gm boric acid
Ratio 3	94 : 6	4.7 gm F_1 : 0.3 gm boric acid
Ratio 4	92 : 8	4.6 gm F_1 : 0.4 gm boric acid

3.2.2.3 Combination 2: [F_1 : Talc]

Formulation One was examined in different ratios with talc (lubricant) and few physical parameters were checked which are significant in describing flow property of a powder mixture, like as- Carr's index, Hausner's ratio and Angle of Repose. Talc is generally used as lubricant in the range of 2- 12%. So I have prepared four sets of ratios in following manner-

Table 3.10: Amounts of Excipients in Combination 2

Ratio	Formula 1 : Talc (%)	Amount in 5 gm
Ratio 1	97: 3	4.85 gm F_1 : 0.15 gm Talc
Ratio 2	94 : 6	4.7 gm F_1 : 0.3 gm Talc
Ratio 3	91 : 9	4.55 gm F_1 : 0.45 gm Talc
Ratio 4	88 : 12	4.4 gm F_1 : 0.6 gm Talc

3.2.2.4 Combination 3: [F_1 : Sodium Lauryl Sulfate]

Though sodium lauryl sulfate has other functional categories in pharmaceutical and cosmetic preparations, it is always proved to be an ideal lubricant if used in exact amount. Formulatio-Two was examined in different ratios with this lubricant, and physical parameters were checked which are significant in describing flow property of a powder mixture, like as- Carr's index, Hausner's ratio and Angle of repose. To conduct this study, I have prepared four sets of ratios in following manner-

Table 3.11: Amounts of Excipients in Combination 3

Ratio	Formula One (F_1) : Na lauryl sulfate	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_1 : 0.1 gm Na lauryl sulfate
Ratio 2	96 : 4	4.8 gm F_1 : 0.2 gm Na lauryl sulfate
Ratio 3	94 : 6	4.7 gm F_1 : 0.3 gm Na lauryl sulfate
Ratio 4	92 : 8	4.6 gm F_1 : 0.4 gm Na lauryl sulfate

3.2.2.5 Combination 4: [F_1 : Zinc Stearate]

Zinc stearate is also a common lubricant though it is nowadays replaced by other lubricants. Formulation-One was examined in different ratios with this lubricant in my dissertation, and the physical parameters checked during the experiment were Carr's index, Hausner's ratio and Angle of repose. Each of them is really significant in describing flowability of a powder mixture. To conduct this study, I have prepared four sets of ratios in following manner-

Table 3.12: Amounts of Excipients in Combination 4

Ratio	Formula One (F_1) : Zn Stearate (%)	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_1 : 0.1 gm Zn Stearate
Ratio 2	96 : 4	4.8 gm F_1 : 0.2 gm Zn Stearate
Ratio 3	94 : 6	4.7 gm F_1 : 0.3 gm Zn Stearate
Ratio 4	92 : 8	4.6 gm F_1 : 0.4 gm Zn Stearate

3.2.2.6 Combination 5: [F_1 : Magnesium Stearate]

Formula-One was examined in different ratios with magnesium stearate and assessment of few physical parameters, significant in describing flow property of a powder mixture were carried out to reach to a final conclusion about the flowability of the mixture, such as- Carr's index, Hausner's ratio and Angle of Repose. I have prepared four sets of ratios in following manner-

Table 3.13: Amounts of Excipients in Combination 5

Ratio	Formula One (F_1) : Mg Stearate	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_1 : 0.1 gm Mg Stearate
Ratio 2	96 : 4	4.8 gm F_1 : 0.2 gm Mg Stearate
Ratio 3	94 : 6	4.7 gm F_1 : 0.3 gm Mg Stearate
Ratio 4	92 : 8	4.6 gm F_1 : 0.4 gm Mg Stearate

3.2.2.7 Combination 6: [Formula 2 (F_2): Boric Acid]

Formulation Two is examined in different ratios with Boric acid, that is also a lubricant and some physical parameters were checked which are significant in describing flow property of a powder mixture, like as- Carr's index, Hausner's ratio and Angle of Repose. To conduct this study, I have prepared four sets of ratios in following manner-

Table 3.14: Amounts of Excipients in Combination 6

Ratio	Formula Two (F_2) : Boric Acid (%)	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_2 : 0.1 gm boric acid
Ratio 2	96 : 4	4.8 gm F_2 : 0.2 gm boric acid
Ratio 3	94 : 6	4.7 gm F_2 : 0.3 gm boric acid
Ratio 4	92 : 8	4.6 gm F_2 : 0.4 gm boric acid

3.2.2.8 Combination 7: [F_2 : Talc]

Formulation Two is examined in different ratios with talc (lubricant) and few physical parameters were checked which are significant in describing flow property of a powder mixture, like as- Carr's index, Hausner's ratio and Angle of Repose. Talc is generally used as lubricant in the range of 2- 12%. So I have prepared four sets of ratios in following manner-

Table 3.15: Amounts of Excipients in Combination 7

Ratio	Formula 2 : Talc	Amount in 5 gm
Ratio 1	97: 3	4.85 gm F2 : 0.15 gm Talc
Ratio 2	94 : 6	4.7 gm F2 : 0.3 gm Talc
Ratio 3	91 : 9	4.55 gm F2 : 0.45 gm Talc
Ratio 4	88 : 12	4.4 gm F2 : 0.6 gm Talc

3.2.2.9 Combination 8: [F_2 : Sodium Lauryl Sulfate]

Though sodium lauryl sulfate has other functional categories in pharmaceutical and cosmetic preparations, it is always proved to be an ideal lubricant if used in exact amount. Formulatio-Two was examined in different ratios with this lubricant, and physical parameters were checked which are significant in describing flow property of a powder mixture, like as- Carr's index, Hausner's ratio and Angle of repose. To conduct this study, I have prepared four sets of ratios in following manner-

Table 3.16: Amounts of Excipients in Combination 8

Ratio	Formula Two (F_2) : Na lauryl sulfate (%)	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_2 : 0.1 gm Na lauryl sulfate
Ratio 2	96 : 4	4.8 gm F_2 : 0.2 gm Na lauryl sulfate
Ratio 3	94 : 6	4.7 gm F_2 : 0.3 gm Na lauryl sulfate
Ratio 4	92 : 8	4.6 gm F_2 : 0.4 gm Na lauryl sulfate

3.2.2.10 Combination 9: [F_2 : Zinc Stearate]

Zinc stearate is a common lubricant though it is nowadays replaced by other lubricants. Formulation-Two was examined in different ratios with this lubricant in my dissertation, and the physical parameters checked during the experiment were Carr's index, Hausner's ratio and Angle of repose. Each of them is really significant in describing flowability of a powder mixture. To conduct this study, I have prepared four sets of ratios in following manner-

Table 3.17: Amounts of Excipients in Combination 9

Ratio	Formula Two (F_2) : Zn Stearate (%)	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_2 : 0.1 gm Zn Stearate
Ratio 2	96 : 4	4.8 gm F_2 : 0.2 gm Zn Stearate
Ratio 3	94 : 6	4.7 gm F_2 : 0.3 gm Zn Stearate
Ratio 4	92 : 8	4.6 gm F_2 : 0.4 gm Zn Stearate

3.2.2.11 Combination 10: [F_2 : Magnesium Stearate]

Formula-Two was examined in different ratios with magnesium stearate and assessment of few physical parameters, significant in describing flow property of a powder mixture were carried out to reach to a final conclusion about the flowability of the mixture, such as- Carr's index, Hausner's ratio and Angle of Repose. I have prepared four sets of ratios in following manner-

Table 3.18: Amounts of Excipients in Combination 10

Ratio	Formula Two (F_2) : Mg Stearate (%)	Amount in 5 gm
Ratio 1	98 : 2	4.9 gm F_2 : 0.1 gm Mg Stearate
Ratio 2	96 : 4	4.8 gm F_2 : 0.2 gm Mg Stearate
Ratio 3	94 : 6	4.7 gm F_2 : 0.3 gm Mg Stearate
Ratio 4	92 : 8	4.6 gm F_2 : 0.4 gm Mg Stearate

3.2.3 Carr's index and Hausner's ratio:

To identify the value of Carr's compressibility index and Hausner's ratio of pharmaceutical excipients, I had to find out the values of bulk and tapped volume of the powders and put those values to the following equation-

$$\boldsymbol{Carr's\ Compressibility\ Index} = 100 \times \left(\frac{Bulk\ volume\ -\ Tapped\ volume}{Bulk\ volume}\right)$$

$$\boldsymbol{Hausner's Ratio} = \left(\frac{Bulk\ volume}{Tapped\ volume}\right)$$

There is another most acceptable way of calculating Carr's index and Hausner's ratio, and that way requires the identification of bulk and true densities of the powder excipients. Due to lack of facilities and expertise, it was really inconvenient for me to assess the densities of the excipients. So I had followed the above equation to get the values of Carr's index and Hausner's ratio. Nevertheless, the other equations for identifying the parameters are the following-

$$\boldsymbol{Carr's\ Compressibility\ Index} = 100 \times \left(\frac{True\ density - \ Bulk\ density}{True\ density}\right)$$

$$\boldsymbol{Hausner's Ratio} = \left(\frac{True\ density}{Bulk\ density}\right)$$

3.2.3.1 Bulk Volume measurement:

✓ To measure bulk volume of the individual or a group of excipients, first of all I weighed particular amount for the experiment on an electric weighing machine.

✓ I have taken 3gms while measuring bulk volume of an individual excipient, whereas 5gms of mixture of excipients (including lubricant) was weighed each time for measuring their bulk voumes.

✓ This certain amount of powder was poured into a 25ml or 25cm^3 measuring cylinder, using a glass funnel without any aid or shaking it up. The measuring cylinder should be ofcourse clean and dry, and also made free of excess moisture by the help of silica beads for some time.

✓ Then the cylinder was slightly tapped for maximum two to three times to set all the powders in a vertical level.

✓ Then the volume that is occupied by the powder excipient has been identified.

✓ The same process was run for three times with the same weighed excipient, and the values were averaged to justify the exact value.

3.2.3.2 Tapped Volume measurement:

The tapped volume is a decreased bulk volume attained after tapping a container containing the powder sample. The tapped volume of powders can be measured followed by the bulk volume measurement with that distinct amount of the powder. The tapped volume is obtained by manually or mechanically tapping a graduated measuring cylinder or vessel containing the powder sample. After observing the powder bulk mass, the measuring cylinder or vessel is tapped, and volume reading is taken after tapping.

✓ Due to lack of equipment facility, I had to perform this test of measuring tapped volume manually.

✓ I tapped the measuring cylinder for 40-50 times per 30 seconds, and after that checked the volume of the particular amount of excipients.

✓ The process was performed for three times without any product loss and the values of tapped volume were averaged to justify the exact result.

3.2.4 Angle of repose Measurements:

The angle of repose was formed on a fixed base with a retaining tip to retain a layer of powder on the base. The base should be free of vibration. Vary the height of the funnel to carefully build up a symmetrical cone of powder. The angle of repose is determined by measuring the height of the cone of powder and calculating the angle of repose, α, from the following equation:

$$\tan \alpha = \left(\frac{height}{0.5\ diameter}\right)$$

$$\boldsymbol{Angle\ of\ repose, \alpha} = tan^{-1}\left(\frac{height}{0.5\ diameter}\right)$$

Procedure to measure and calculate the angle of repose:

1. At first certain amount of powder, whether individual excipient (3gm) or excipient mixture, including lubricant (5gm) was weighed by an electric weighing machine.
2. A dry, glass funnel was hanged with help of a rod stand, and the opening portion of the funnel was not so far from the base where a white paper was laid.
3. The excipient(s) was poured through the funnel slowly and let the mixture to form a pile upon the white paper. This will result in a pile with a relatively circular base, making measurement easier.
4. Using the ruler, the height (h) of the pile of excipients mixture was measured from the peak to the ground. The ruler was kept standing next to the pile so that it can be read easily.

5. A round mark was made around the edge of the pile in at the paper. After removing the powder from the paper, the diameter of the circle was measured with a ruler, and it was halved to identify the radius.
6. The whole process was performed thrice for getting the most accurate value of angle of repose of the powder, and the height and diameter/ radius were averaged to identify a single value.
7. These averaged values were further put in the equation and angle of repose was calculated in each case.

Chapter Four

RESULTS

4.1 RESULTS

Flow property of each single excipients was tried to identify by checking the following physical parameters, that is- Carr's index, Hausner's ratio and angle of repose. All the values of individual excipients those have undergone the physical parameters testing are tabled below:

4.1.1 Calculation of Carr's index and Hausner ratio of individual excipients: To calculate Carr's index and Hausner's ratio, at first measurement bulk volume and tapped volume of the certain amount of powders was carried out. Each time, the tests were carried out thrice, and most acceptable value was identified that was put during final calculations. Here the values are-

Table 4.1: Values of individual excipients for determining Carr's index and Hausner's ratio

Excipients Name	Bulk volume, cm^3	Acceptable Bulk vol., V_b	Tapped volume, cm^3	Acceptable Tapped vol., V_t
Lactose	10.0	10.0	6.5	6.5
	9.5		7.0	
	9.5		7.0	
Starch	8.5	8.5	5.5	5.5
	8.5		6.0	
	8.0		5.0	
Calcium Phosphate	10.0	10.5	7.0	7.0
	10.0		7.0	
	10.5		7.5	
Polyvinyl pyrrolidone	13.5	13.5	10.0	10.0
	13.0		10.0	
	13.5		10.5	

Excipients Name	Bulk volume, cm^3	Acceptable Bulk vol., V_b	Tapped volume, cm^3	Acceptable Tapped vol., V_t
Magnesium Stearate	52.5	52.5	40.0	40.0
	52.5		40.0	
	52.0		40.5	
Zinc Stearate	50.5	50.5	38.5	38.5
	50.5		39.0	
	49.5		39.0	
Sodium Lauryl Sulfate	17.0	17.0	14.0	14.0
	16.5		14.0	
	17.0		14.5	
Talc	4.5	4.75	3.0	3.0
	4.5		3.0	
	4.75		3.0	
Boric Acid	5.0	5.0	3.5	3.5
	4.5		3.5	
	4.5		3.5	

4.1.2 Calculation of angle of repose of individual excipients: To calculate the value of angle of repose in case of each individual excipient, height and radius of the pile that formed on the surface after pouring the powder on it, are required. This experiment was also done thrice with the same excipient, and the values were averaged to get the exact value to be put on the equation to get the exact value of angle of repose. Here the values are-

Table 4.2: Values of individual excipients for determining angle of repose

Excipients Name	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm
Lactose	2.1	1.97	4.6	2.3	2.25
	1.8		4.4	2.2	
	2.0		4.5	2.25	
Starch	2.6	2.47	5.0	2.5	2.47
	2.3		5.0	2.5	
	2.5		4.8	2.4	
Calcium Phosphate	2.6	2.53	4.8	2.4	2.38
	2.5		4.6	2.3	
	2.5		4.9	2.45	
Polyvinyl pyrrolidone	2.1	2.13	5.8	2.9	2.88
	2.2		5.6	2.8	
	2.1		5.9	2.95	
Magnesium Stearate	2.0	2.03	5.2	2.6	2.67
	2.1		5.4	2.7	
	2.0		5.4	2.7	
Zinc Stearate	1.8	1.7	5.6	2.8	2.77
	1.7		5.6	2.8	
	1.6		5.4	2.7	
Sodium Lauryl Sulfate	2.8	2.9	6.0	3.0	2.98
	3.0		6.0	3.0	
	2.9		5.9	2.95	
Talc	2.2	2.03	3.8	1.9	1.88
	1.9		3.7	1.85	
	2.0		3.8	1.9	

Boric Acid	1.5	1.4	3.9	1.95	1.93
	1.6		3.8	1.9	
	1.4		3.9	1.95	

4.1.3 Determining Carr's index Hausner Ratio, and angle of repose of individual excipients: Finally the values of Carr's index, Hausner's ratio and angle of repose were calculated with help of the most acceptable bulk and tapped volume, and averaged height and radius of the piles formed with the powder excipients. These values are put into the formula of calculating the parameters and it resulted in the following-

Table 4.3: Determination of Carr's index, Hausner ratio, and angle of repose of individual excipients

Excipients Name	**Carr's Index, $\frac{100\ (Vb-Vt)}{Vb}$**	**Hausner Ratio, $\frac{Vb}{Vt}$**	**Angle of Repose, $\tan^{-1}(h/r)^{0}$**
Lactose	35.0	1.54	41.204
Starch	35.29	1.55	45.0
Calcium Phosphate	33.33	1.50	46.75
Polyvinyl pyrrolidone	25.92	1.35	36.486
Magnesium Stearate	22.8	1.28	37.246
Zinc Stearate	23.76	1.31	31.54
Sodium Lauryl Sulfate	17.6	1.21	44.22
Talc	36.84	1.58	47.197
Boric Acid	30.0	1.43	35.956

4.1.4 Excipients in Formula 1 (F_1)

The following excipients were selected to form F1 for this research work. Tables containing excipients with their percentage in total mixture (F1) are given below:

Table 4.4: Amount (%) of excipients in *Formula- One*

Ingredients	Amount in %
Calcium Phosphate	40%
Lactose	10%
Starch	30%
Polyvinyl Pyrrolidine	4%
Talc	16%

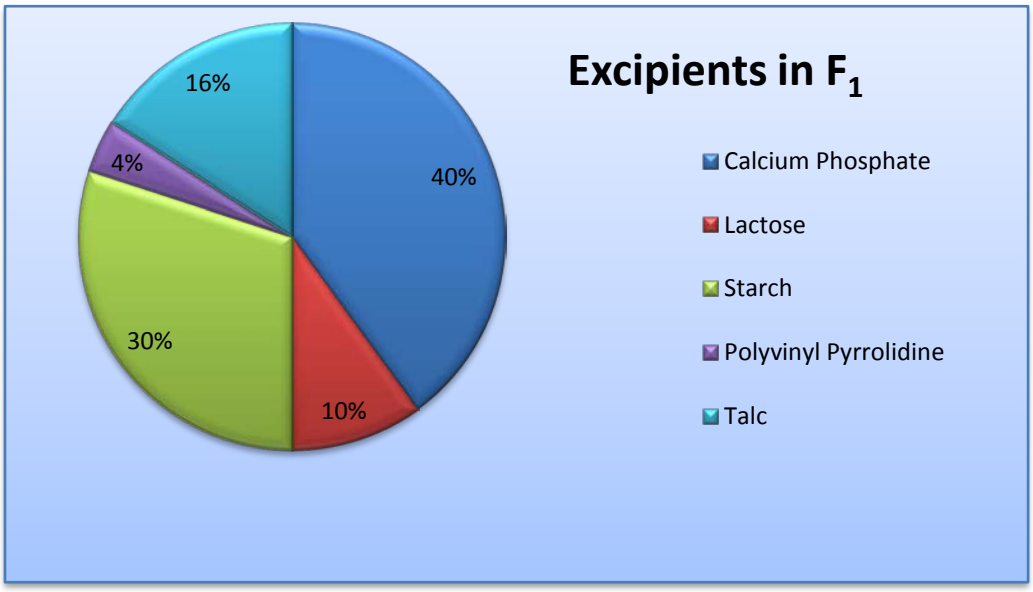

Figure 4.1: Pie- chart showing the amount of excipients in *Formula- One* (F_1)

4.1.4.1 Combination 1: [F_1 : Boric Acid]

4.1.4.1.1 Values of Carr's Index and Hausner Ratio of Combination 1

Table 4.5: Determination of Carr's index and Hausner's ratio of Combination 1

Ratio	Bulk volume, cm^3	Acceptable Bulk volume, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	8.5	8.75	**6.25**	6.25	**28.57**	**1.40**
	8.5		6.5			
	8.75		6.5			
Ratio 2	**9.0**	9.0	7.0	6.5	**27.78**	**1.38**
	8.75		6.75			
	8.75		**6.5**			
Ratio 3	**9.0**	9.0	7.0	6.75	**25.0**	**1.33**
	9.0		**6.75**			
	8.5		**6.75**			
Ratio 4	9.0	9.25	7.25	7.0	**24.32**	**1.32**
	9.25		**7.0**			
	9.0		7.25			

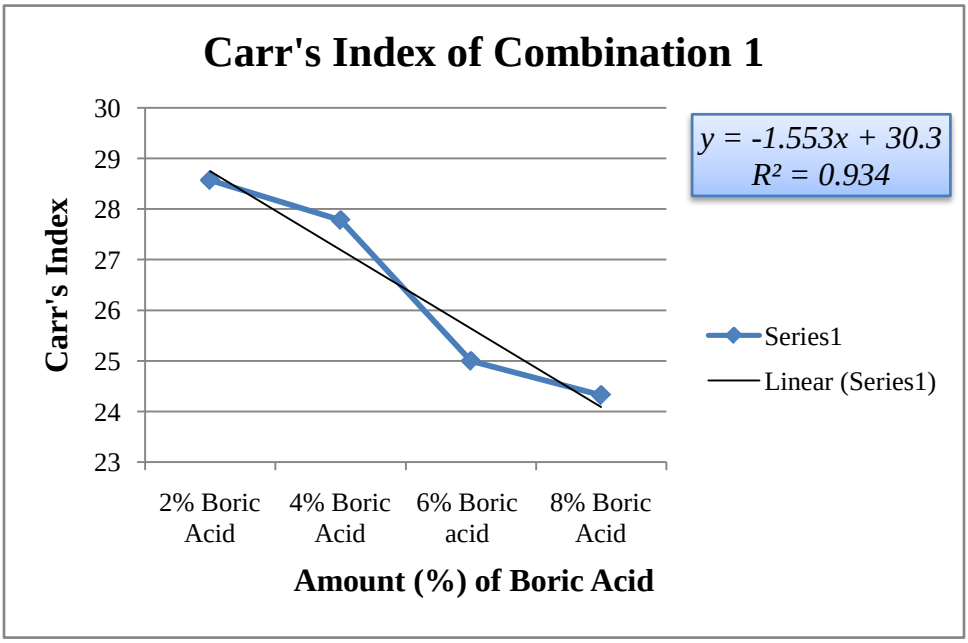

Figure 4.2: A plot showing Carr's indexes of Boric Acid in Combination 1

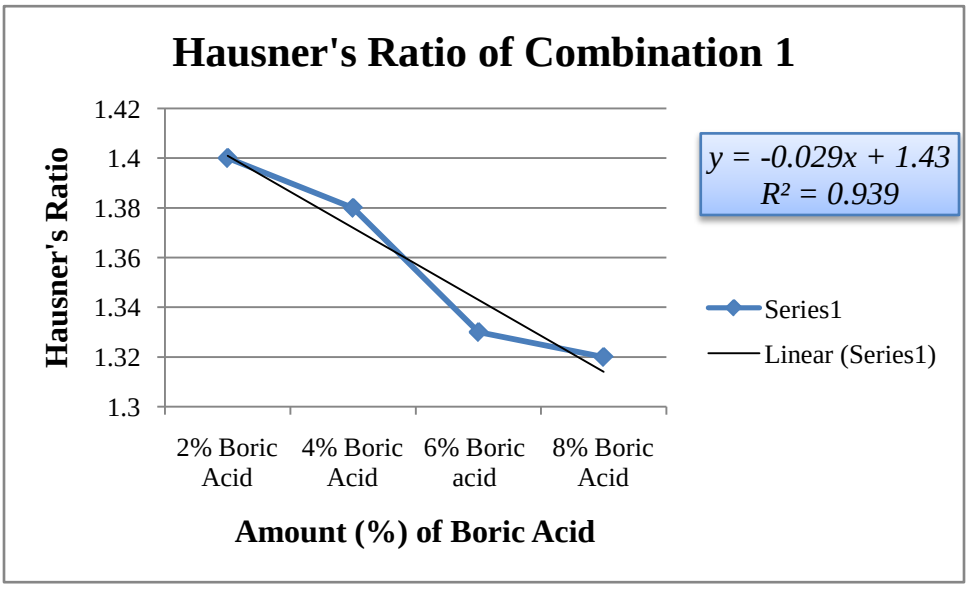

Figure 4.3: A plot showing Hausner's ratios of Boric Acid in Combination 1

4.1.4.1.2 Values of Angle of Repose of Combination1

Table 4.6: Determination of Angle of repose of Combination 1

Ratio	Height of the pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^0$
Ratio 1	1.6	1.7	5.2	2.6	2.55	**33.7**
	1.6		5.3	2.65		
	1.9		4.8	2.4		
Ratio 2	1.8	1.5	4.8	2.4	2.35	**32.55**
	1.4		4.8	2.4		
	1.3		4.5	2.25		
Ratio 3	1.6	1.7	5.4	2.7	2.75	**31.72**
	1.7		5.4	2.7		
	1.8		5.7	2.85		
Ratio 4	1.4	1.5	5.3	2.65	2.6	**29.98**
	1.4		5.1	2.55		
	1.7		5.2	2.6		

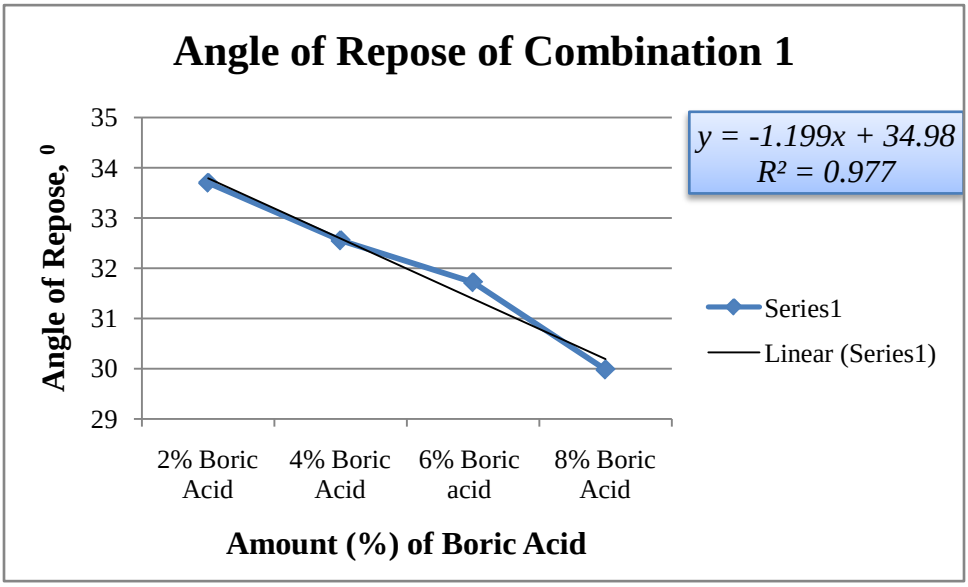

Figure 4.4: A plot showing Angles of repose of Boric Acid in Combination 1

4.1.4.2 Combination 2: [F_1 : Talc]

4.1.4.2.1 Values of Carr's Index and Hausner Ratio of Combination2

Table 4.7: Determination of Carr's index and Hausner's ratio of Combination 2

Ratio	Bulk volume, cm^3	Acceptable Bulk volume, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	8.25	8.5	6.5	6.25	**26.47**	**1.36**
	8.25		**6.25**			
	8.5		6.5			
Ratio 2	8.5	8.75	6.75	6.5	**25.71**	**1.34**
	8.5		7.0			
	8.75		**6.5**			
Ratio 3	**8.75**	8.75	7.0	6.75	**22.86**	**1.3**
	8.75		**6.75**			
	8.5		**6.75**			
Ratio 4	**9.0**	9.0	7.25	7.0	**22.22**	**1.28**
	8.75		**7.0**			
	8.5		**7.0**			

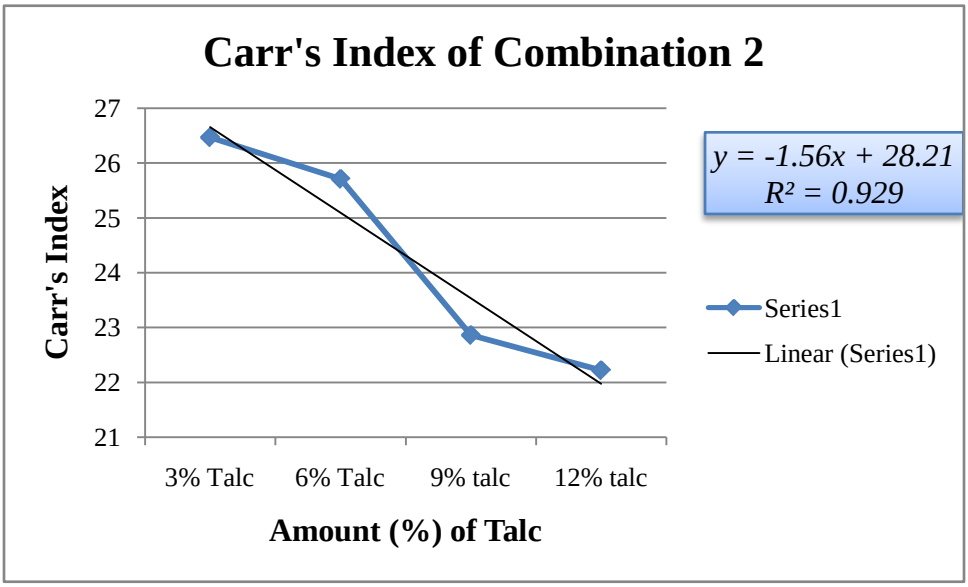

Figure 4.5: A plot showing Carr's indexes of Talc in Combination 2

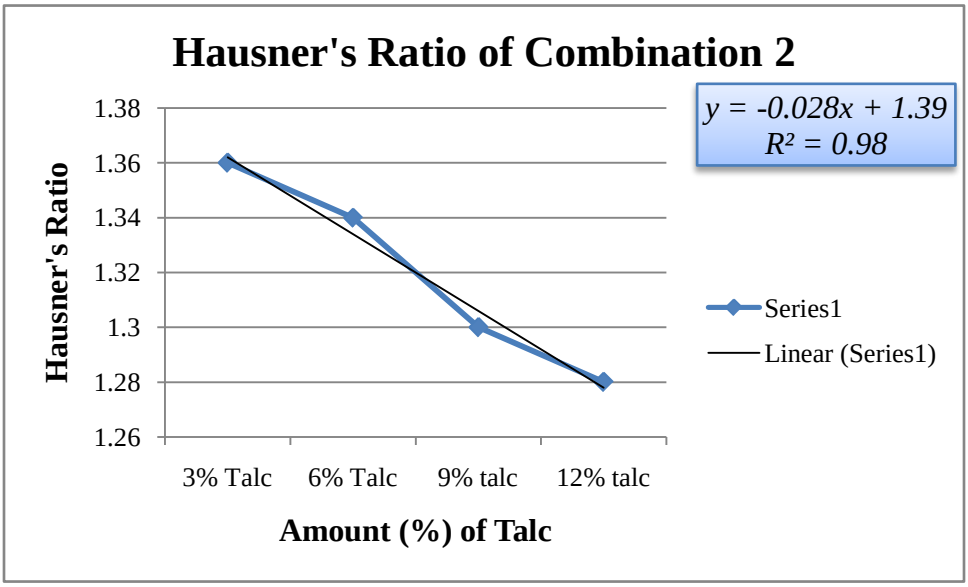

Figure 4.6: A plot showing Hausner's ratio of Talc in Combination 2

4.1.4.2.2 Values of Angle of Repose of Combination 2

Table 4.8: Determination of Angle of repose of Combination 2

Ratio	Height of the pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^{0}$
Ratio 1	1.6	1.8	4.5	2.25	2.15	**39.94**
	2.0		4.2	2.1		
	1.8		4.2	2.1		
Ratio 2	1.6	1.7	4.3	2.15	2.15	**38.33**
	1.9		4.4	2.2		
	1.6		4.2	2.1		
Ratio 3	1.8	1.8	4.3	2.15	2.1	**36.87**
	1.9		4.0	2.0		
	1.7		4.3	2.15		
Ratio 4	1.4	1.6	4.7	2.35	2.3	**34.82**
	1.5		4.7	2.35		
	1.9		4.4	2.2		

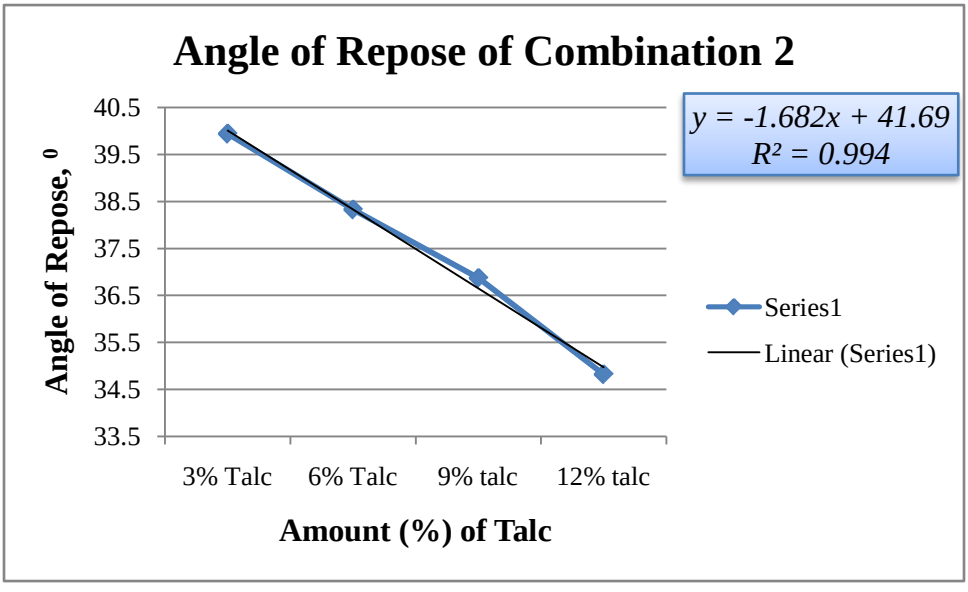

Figure 4.7: A plot showing Angles of reposes of Talc in Combination 2

4.1.4.3 Combination 3: [F_1 : Sodium Lauryl Sulfate]

4.1.4.3.1 Values of Carr's Index and Hausner Ratio of Combination 3

Table: 4.9: Determination of Carr's index and Hausner's ratio of Combination 3

Ratio	Bulk volume, cm^3	Acceptable Bulk volume, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	**9.0**	9.0	**7.5**	7.5	**16.67**	**1.2**
	8.5		7.75			
	8.75		**7.5**			
Ratio 2	8.75	9.0	8.25	8.0	**11.11**	**1.125**
	9.0		**8.0**			
	9.0		**8.0**			
Ratio 3	**9.5**	9.5	9.0	8.5	**10.52**	**1.11**
	9.25		**8.5**			
	9.0		8.75			
Ratio 4	**10.5**	10.5	10	9.5	**9.52**	**1.10**
	10		**9.5**			
	10.25		9.75			

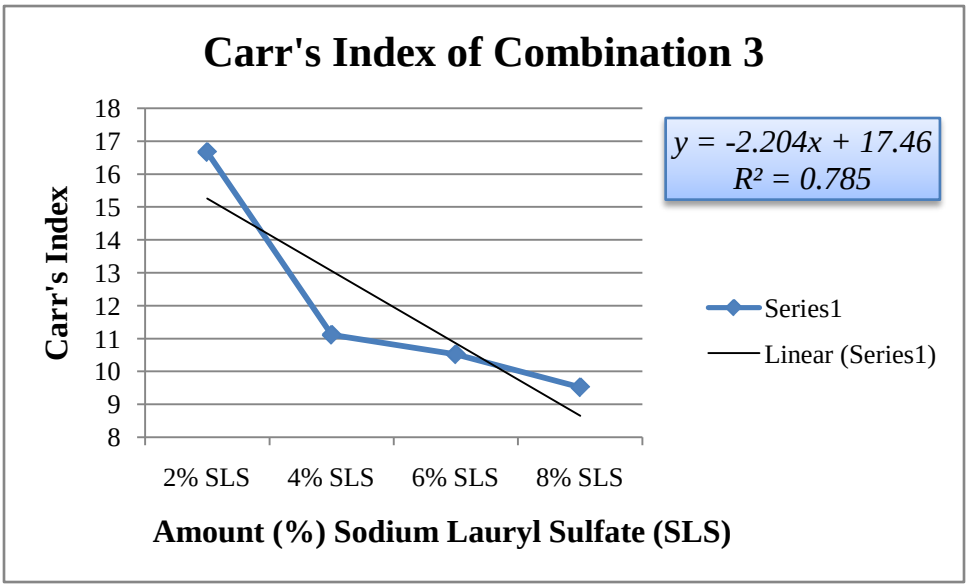

Figure 4.8: A plot showing Carr's indexes of Na Lauryl Sulfate in Combination 3

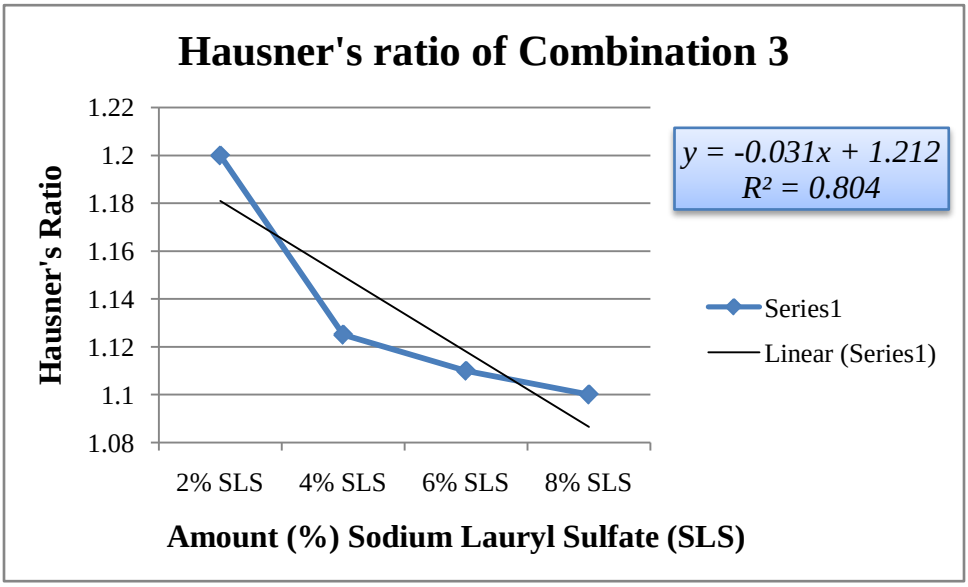

Figure 4.9: A plot showing Hausner's ratios of Na Lauryl Sulfate in Combination 3

4.1.4.3.2 Values of Angle of Repose of Combination 3

Table 4.10: Determination of Angle of repose of Combination 3

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^{0}$
Ratio 1	1.6	1.4	4.6	2.3	2.25	**31.89**
	1.4		4.6	2.3		
	1.2		4.3	2.15		
Ratio 2	1.6	1.5	4.8	2.4	2.5	**30.96**
	1.3		5.1	2.55		
	1.6		5.1	2.55		
Ratio 3	1.6	1.6	5.2	2.6	2.7	**30.65**
	1.6		5.6	2.8		
	1.6		5.4	2.7		
Ratio 4	1.5	1.4	5.2	2.6	2.55	**28.76**
	1.4		4.9	2.45		
	1.3		5.2	2.6		

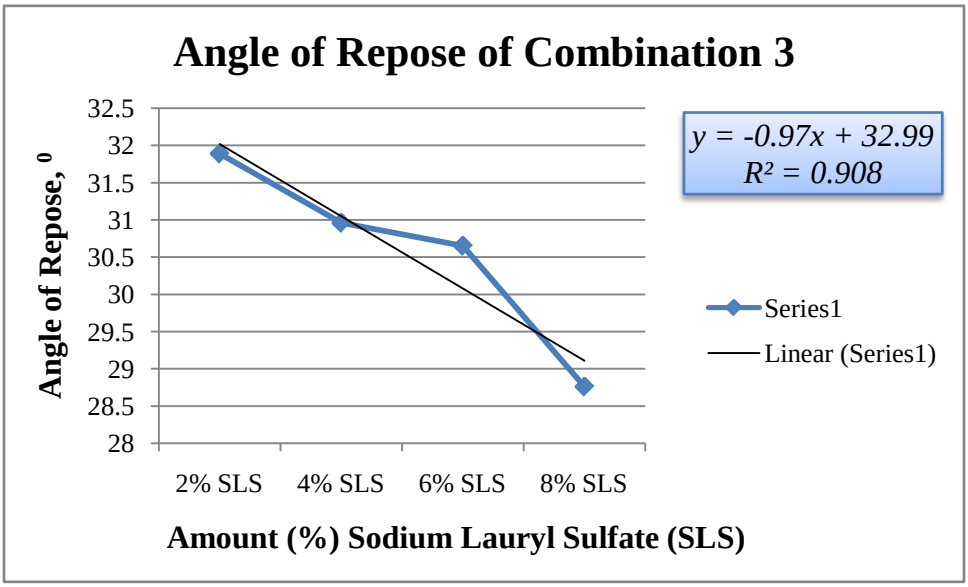

Figure 4.10: A plot showing angles of reposes of Na Lauryl Sulfate in Combination 3

4.1.4.4 Combination 4: [F_1 : Zinc Stearate]

4.1.4.4.1 Values of Carr's Index and Hausner's Ratio of Combination 4

Table 4.11: Determination of Carr's index and Hausner's ratio of Combination 4

Ratio	Bulk volume, cm^3	Acceptable Bulk volume, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	**10.0**	10.0	7.0	6.5	**35.0**	**1.54**
	9.5		**6.5**			
	9.75		6.75			
Ratio 2	9.75	10.0	7.0	6.75	**32.5**	**1.48**
	9.75		7.0			
	10.0		**6.75**			
Ratio 3	**10.0**	10.0	7.25	7.0	**30.0**	**1.42**
	10.0		**7.0**			
	9.75		7.25			
Ratio 4	**10.0**	10.0	7.5	7.25	**27.5**	**1.37**
	10.0		7.5			
	10.0		**7.25**			

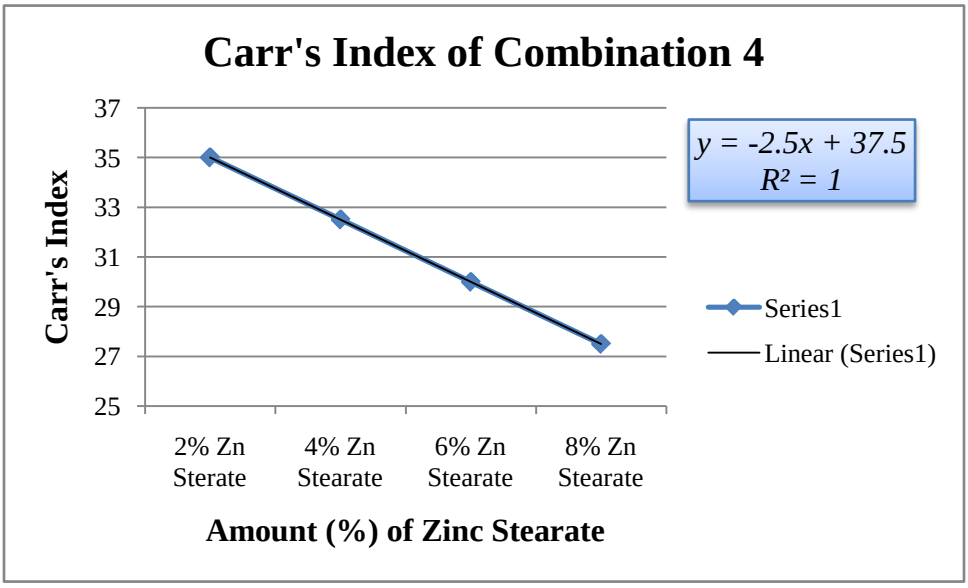

Figure 4.11: A plot showing Carr's indexes of Zn Stearate in Combination 4

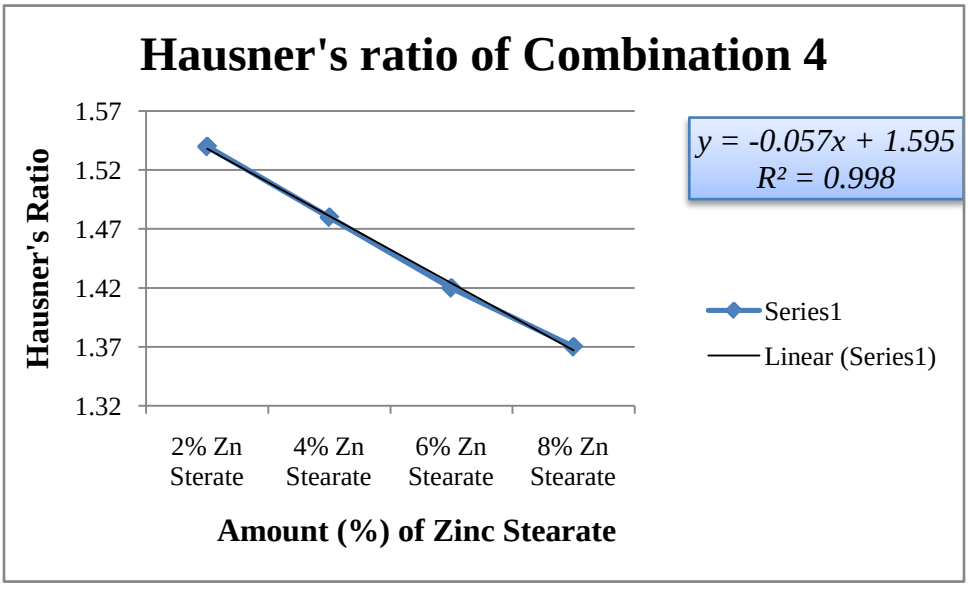

Figure 4.12: A plot showing Hausner's ratios of Zn Stearate in Combinaton 4

4.1.4.4.2Values of Angle of Repose of Combination 4

Table 4.12: Determination of Angle of repose of Combination 4

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^{0}$
Ratio 1	2.1	2.2	5.1	2.55	2.6	**40.23**
	2.3		5.4	2.7		
	2.2		5.1	2.55		
Ratio 2	1.8	1.9	5.1	2.55	2.5	**37.23**
	1.8		4.9	2.45		
	2.1		5.0	2.5		
Ratio 3	1.7	1.6	4.7	2.35	2.45	**33.15**
	1.5		4.8	2.4		
	1.6		5.2	2.6		
Ratio 4	1.1	1.3	4.9	2.45	2.4	**28.44**
	1.4		4.6	2.3		
	1.4		4.9	2.45		

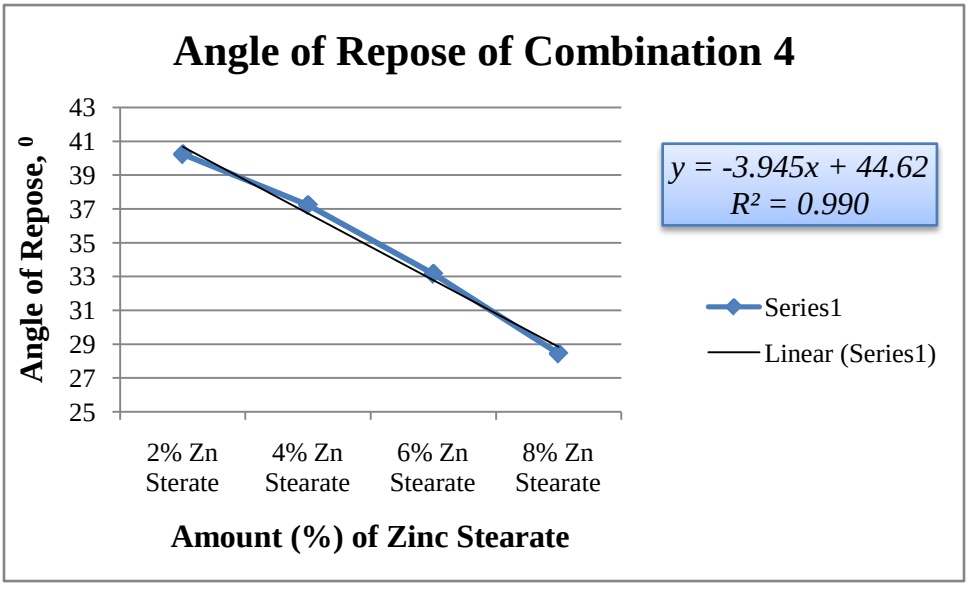

Figure 4.12: A plot showing angles of repose Zn Stearate in Combination 4

4.1.4.5 Combination 5: [F_1 : Magnesium Stearate]

4.1.4.5.1 Values of Carr's Index and Hausner's Ratio of Combination 5

Table 4.13: Determination of Carr's index and Hausner's ratio of Combination 5

Ratio	Bulk volume, cm^3	Acceptable Bulk volume, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	10	10.3	**7.5**	7.5	**27.18**	**1.37**
	10.25		7.75			
	10.3		7.75			
Ratio 2	10	9.5	**7.0**	7.0	**26.32**	**1.35**
	9.75		**7.0**			
	9.5		7.25			
Ratio 3	**10**	10.0	7.75	7.5	**25.0**	**1.33**
	9.75		**7.5**			
	10		8.0			
Ratio 4	**10**	10.0	7.75	7.6	**24.0**	**1.316**
	10		7.75			
	10		**7.6**			

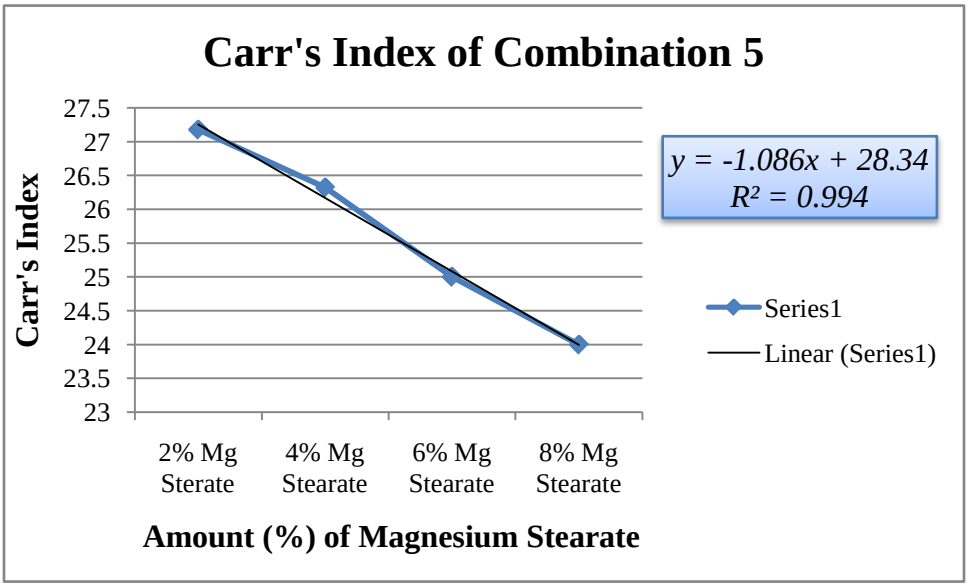

Figure 4.13: A plot showing Carr's indexes of Mg Stearate in Combination 5

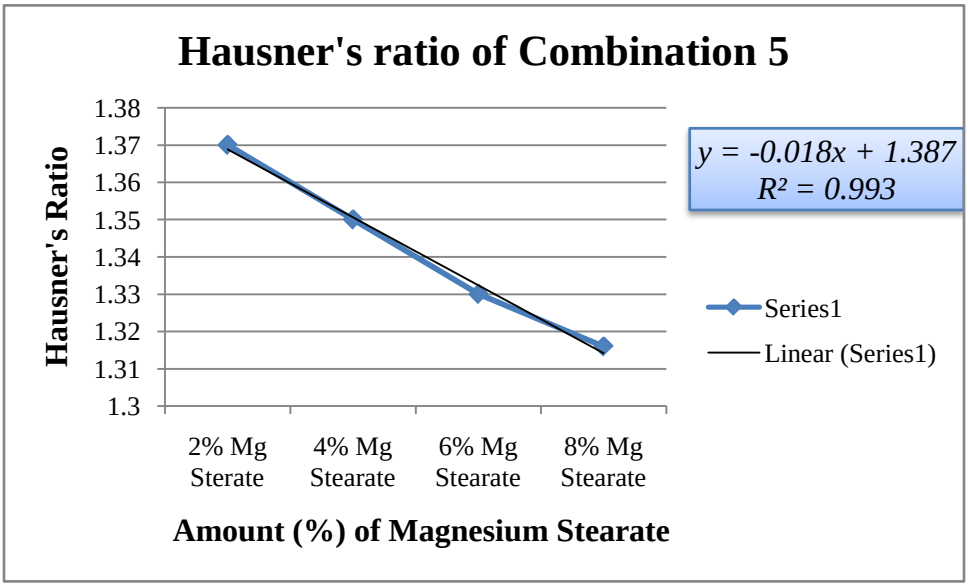

Figure 4.14: A plot showing Hausner's ratios of Mg Stearate in Combination 5

4.1.4.5.2 Values of Angle of Repose of Combination 5

Table 4.14: Determination of Angle of repose of Combination 5

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^{0}$
Ratio 1	1.5	1.4	4.8	2.4	2.4	**30.26**
	1.4		4.7	2.35		
	1.3		4.9	2.45		
Ratio 2	1.2	1.3	5.1	2.55	2.5	**27.47**
	1.2		5.1	2.55		
	1.5		4.8	2.4		
Ratio 3	1.5	1.4	5.6	2.8	2.85	**26.16**
	1.6		5.8	2.9		
	1.1		5.7	2.85		
Ratio 4	1.7	1.5	6.3	3.15	3.2	**25.11**
	1.4		6.3	3.15		
	1.4		6.6	3.3		

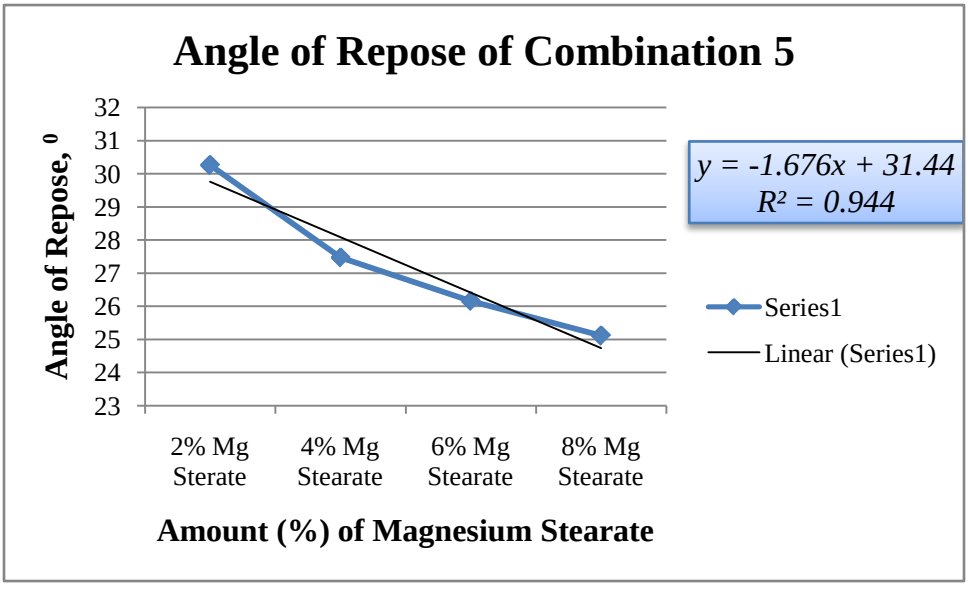

Figure 4.15: A plot showing angles of reposes of Mg Stearate in Combination 5

4.1.5 Excipients in *Formula-Two* (F_2)

The following excipients were selected to form F_2 for this research work. Tables containing excipients with their percentage in total mixture (F_2) are given below:

Table 4.15: Amounts (%) of excipients in *Formula-Two*

Ingredients	Amount in %
Calcium Phosphate	20%
Lactose	30%
Starch	20%
Polyvinyl Pyrrolidine	6%
Sodium Lauryl Sulfate	4%
Talc	20%

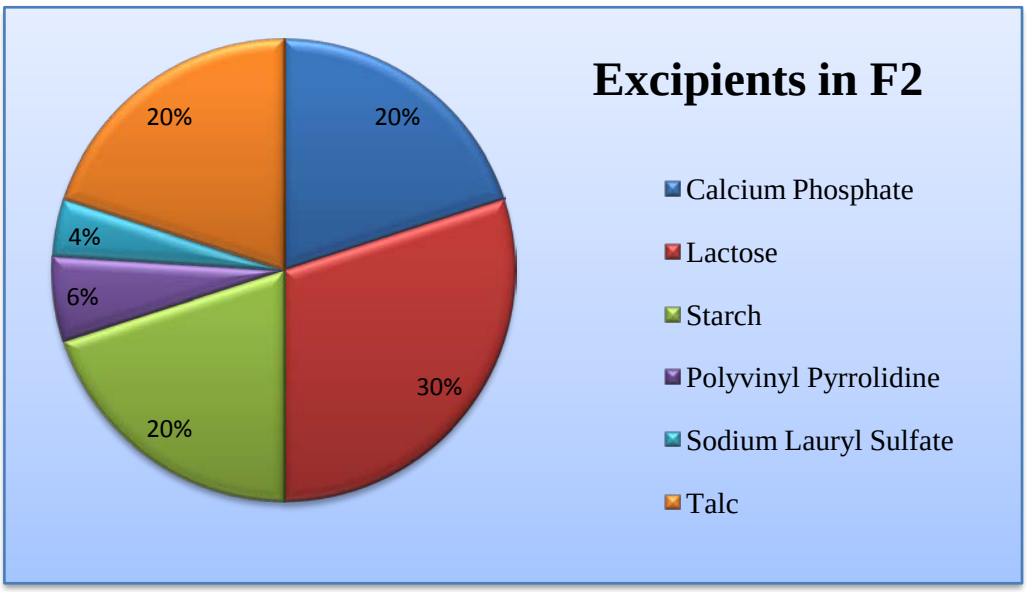

Figure 4.16: A Pie- chart showing the amount of excipients in *Formula- Two* (F_2)

4.1.5.1 Combination 6: [F_2 : Boric Acid]

4.1.5.1.1 Values of Carr's Index and Hausner Ratio of Combination 6

Table 4.16: Determination of Carr's index and Hausner's ratio of Combination 6

Ratio	**Bulk volume, cm^3**	**Acceptable Bulk volime, V_b**	**Tapped volume, cm^3**	**Acceptable Tapped volume, V_t**	**Carr's Index, $\frac{100(V_b - V_t)}{V_b}$**	**Hausner Ratio, $\frac{V_b}{V_t}$**
Ratio 1	9.0	9.0	**6.5**	6.5	**27.78**	**1.38**
	8.75		6.75			
	9.0		6.75			
Ratio 2	9.25	9.5	7.25	7.0	**26.32**	**1.36**
	9.25		**7.0**			
	9.5		7.25			
Ratio 3	9.5	9.5	7.5	7.25	**23.68**	**1.31**
	9.25		7.5			
	9.5		**7.25**			
Ratio 4	9.5	9.5	7.5	7.5	**21.05**	**1.26**
	9.0		7.75			
	9.5		7.75			

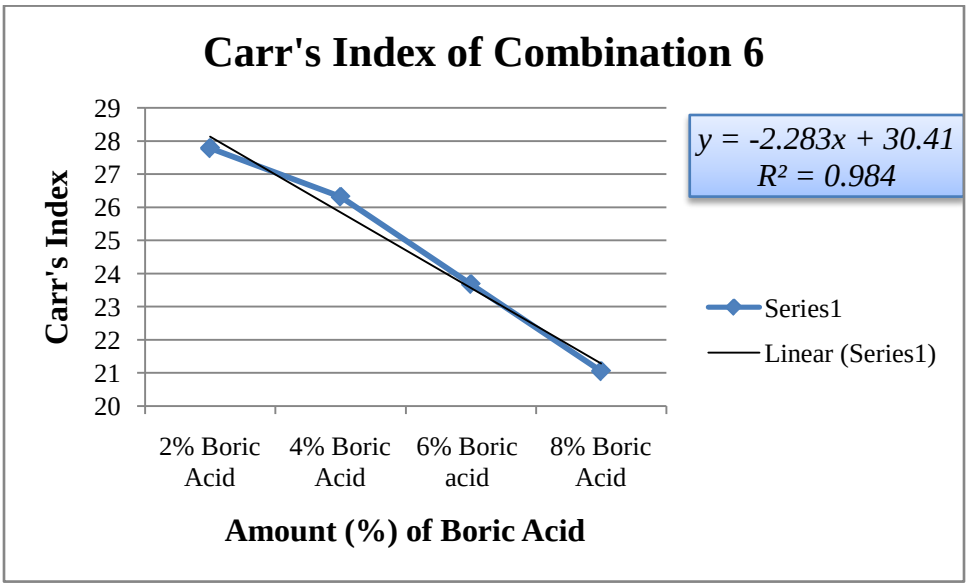

Figure 4.17: A plot showing Carr's indexes of Boric Acid in Combination 6

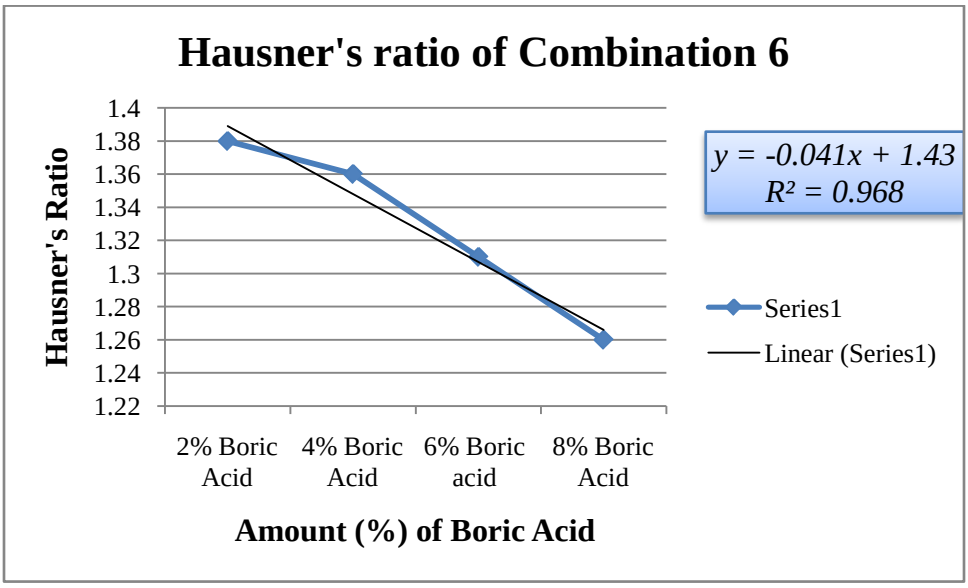

Figure 4.18: A plot showing Hausner's ratios of Boric Acid in Combination 6

4.1.5.1.2 Values of Angle of Repose of Combination 6

Table 4.17: Determination of Angle of repose of Combination 6

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^0$
Ratio 1	1.7	1.8	5.5	2.85	2.75	**33.21**
	1.7		5.4	2.8		
	2.0		5.2	2.6		
Ratio 2	1.7	1.7	5.2	2.6	2.65	**32.68**
	1.8		5.2	2.6		
	1.6		5.5	2.75		
Ratio 3	1.4	1.6	5.1	2.55	2.6	**31.61**
	1.4		5.3	2.65		
	1.8		5.2	2.6		
Ratio 4	1.7	1.6	5.9	2.85	2.75	**30.19**
	1.5		5.4	2.7		
	1.6		5.4	2.7		

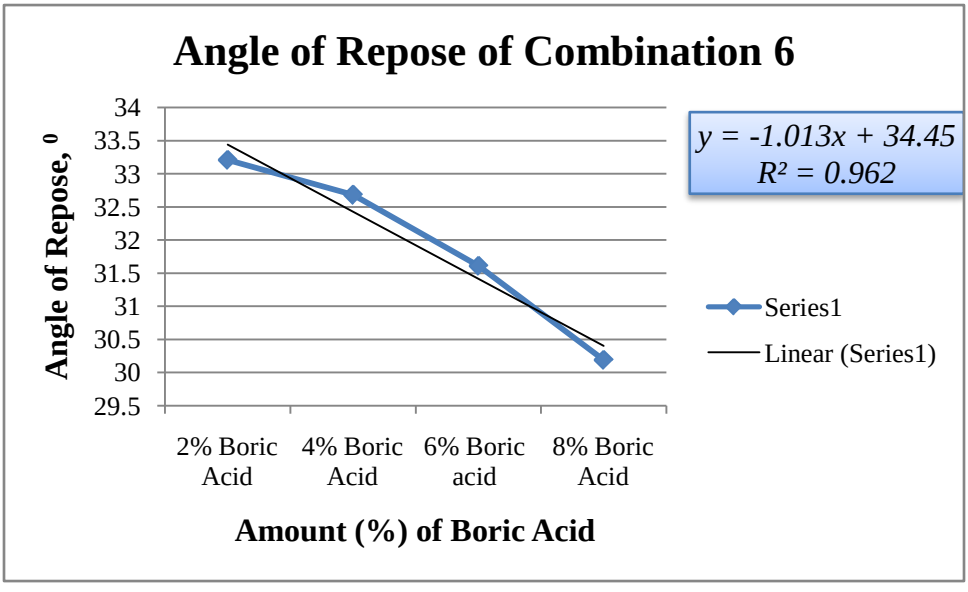

Figure 4.19: A plot showing Angles of repose of Boric Acid in Combination 6

4.1.5.2 Combination 7: [F_2 : Talc]

4.1.5.2.1 Values of Carr's Index and Hausner's Ratio of Combination 7

Table 4.18: Determination of Carr's index and Hausner's ratio of Combination 7

Ratio	**Bulk volume , cm^3**	**Acceptable Bulk volime, V_b**	**Tapped volume, cm^3**	**Acceptable Tapped volume, V_t**	**Carr's Index, $\frac{100(V_b - V_t)}{V_b}$**	**Hausner Ratio, $\frac{V_b}{V_t}$**
Ratio 1	**8.75**	8.75	7.25	7.0	**20.0**	**1.25**
	8.5		7.25			
	8.5		**7.0**			
Ratio 2	**9.0**	9.0	7.5	7.4	**17.78**	**1.22**
	9.0		**7.4**			
	8.75		7.75			
Ratio 3	8.75	9.0	7.75	7.5	**16.67**	**1.20**
	9.0		**7.5**			
	8.75		7.75			
Ratio 4	**9.25**	9.25	8.0	7.75	**16.21**	**1.19**
	9.0		8.0			
	9.0		**7.75**			

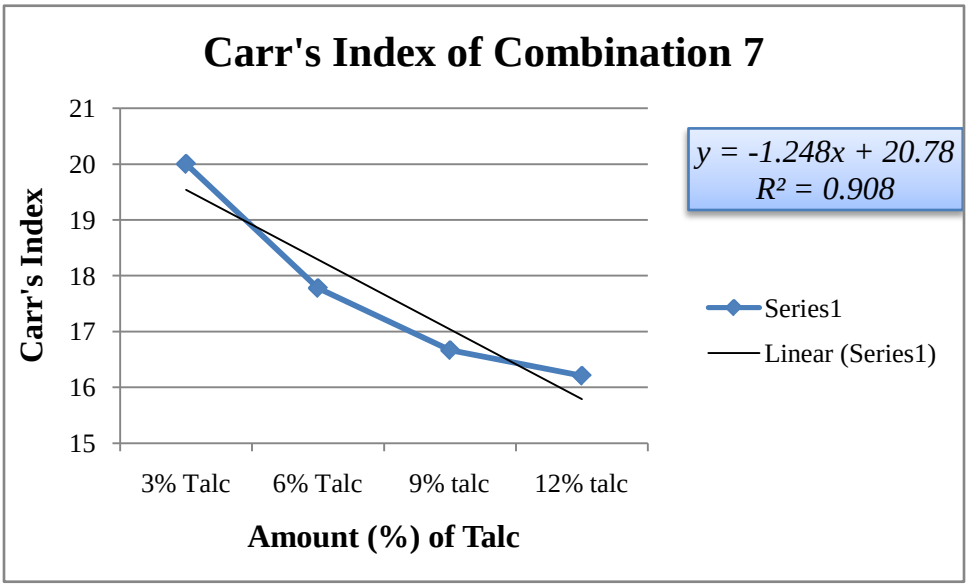

Figure 4.20: A plot showing Carr's indexes of Talc in Combination 7

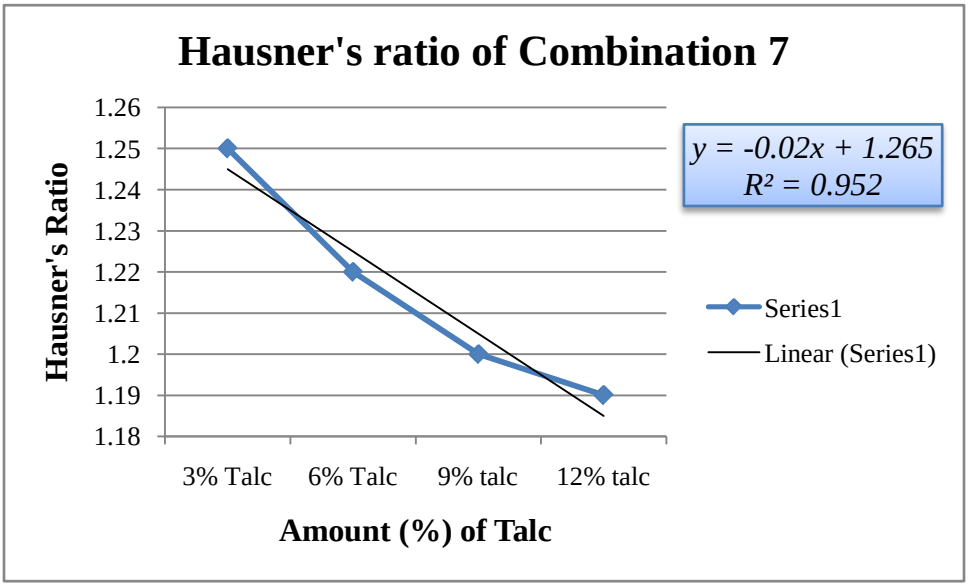

Figure 4.21: Aplot showing Hausner's ratios of Talc in Combination 7

4.1.5.2.2 Values of Angle of Repose of Combination 7

Table 4.19: Determination of Angle of repose of Combination 7

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^0$
Ratio 1	1.7	1.8	4.5	2.25	2.3	**38.05**
	1.9		4.5	2.25		
	1.8		4.8	2.4		
Ratio 2	1.6	1.8	4.8	2.4	2.4	**36.87**
	1.9		4.6	2.3		
	1.9		5.0	2.5		
Ratio 3	1.6	1.7	5.1	2.55	2.4	**35.31**
	1.6		4.7	2.35		
	1.9		4.6	2.3		
Ratio 4	1.5	1.6	4.6	2.3	2.3	**34.82**
	1.7		4.6	2.3		
	1.6		4.6	2.3		

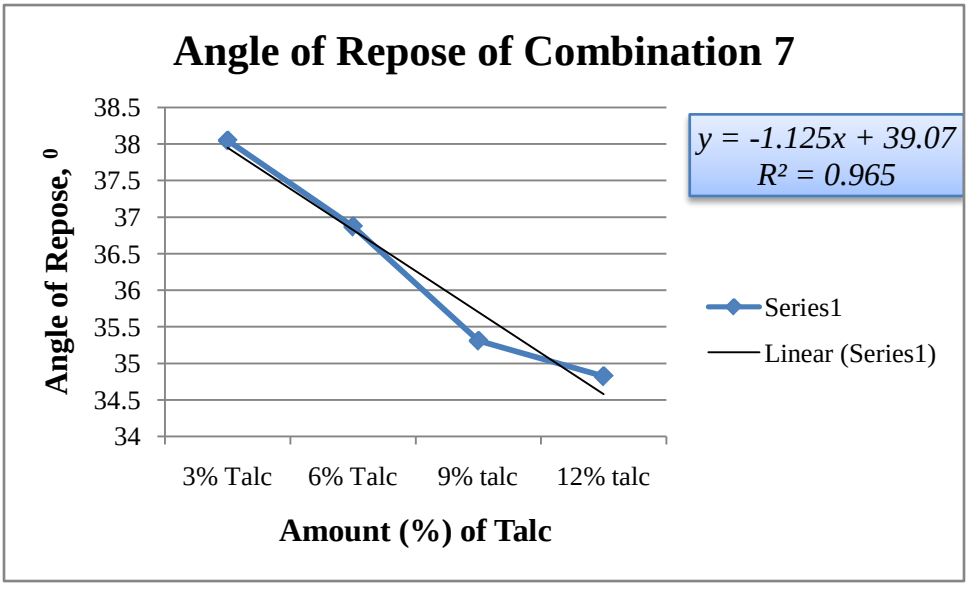

Figure 4.22: A plot showing Angles of repose of Talc in Combination 7

4.1.5.3 Combination 8: [F_2 : Sodium Lauryl Sulfate]

4.1.5.3.1 Values of Carr's Index and Hausner Ratio of Combination 8

Table 4.20: Determination of Carr's index and Hausner's ratio of Combination 8

Ratio	Bulk volume, cm^3	Acceptable Bulk volume, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	**10.0**	10.0	**7.0**	7.0	**30.0**	**1.43**
	9.5		7.25			
	9.75		**7.0**			
Ratio 2	**10.0**	10.0	7.5	7.0	**30.0**	**1.43**
	9.75		7.25			
	9.75		**7.0**			
Ratio 3	**10.0**	10.0	7.5	7.25	**27.5**	**1.38**
	10.0		7.5			
	9.75		**7.25**			
Ratio 4	10.0	10.25	8.0	7.75	**24.4**	**1.32**
	10.25		**7.75**			
	10.0		**7.75**			

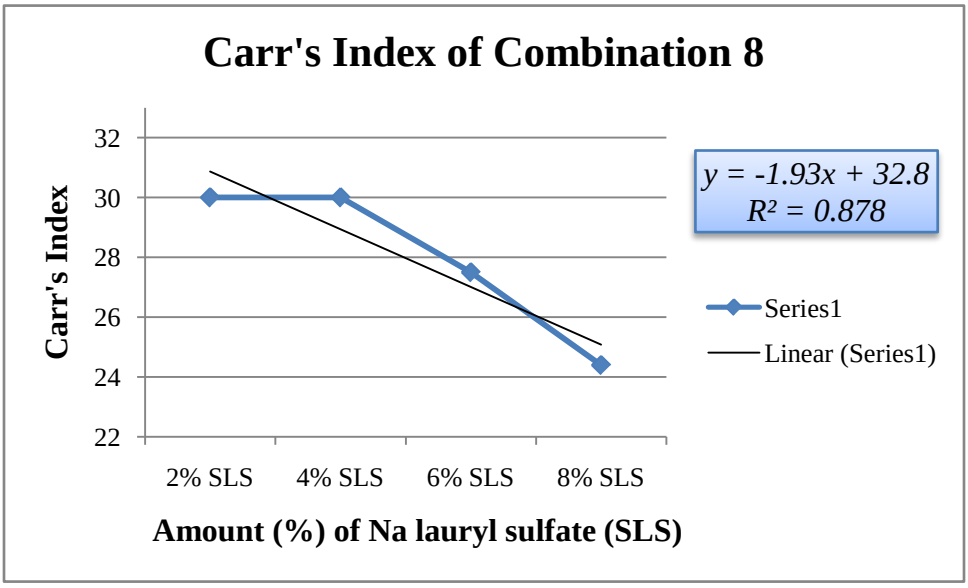

Figure 4.23: A plot showing Carr's indexes of Na Lauryl Sulfate in Combination 8

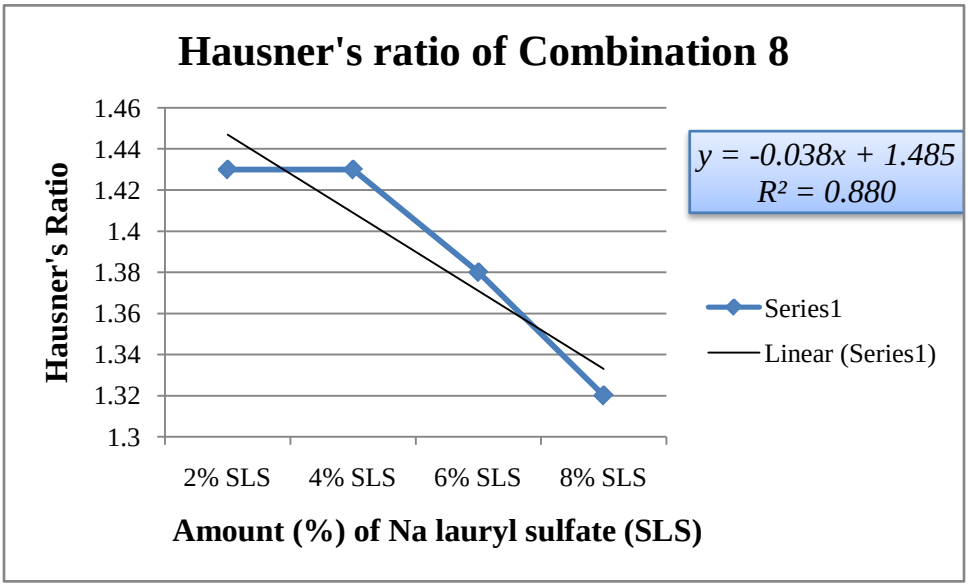

Figure 4.24: A plot showing Hausner's ratios of Na Lauryl Sulfate in Combination 8

4.1.5.3.2 Values of Angle of Repose of Combination 8

Table 4.21: Determination of Angle of Repose of Combination 8

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^0$
Ratio 1	1.5	1.6	5.2	2.6	2.5	**32.62**
	1.8		4.8	2.4		
	1.5		5.0	2.5		
Ratio 2	1.7	1.7	5.6	2.8	2.75	**31.72**
	1.9		5.3	2.65		
	1.5		5.6	2.8		
Ratio 3	1.5	1.6	5.3	2.65	2.7	**30.65**
	1.7		5.6	2.8		
	1.6		5.3	2.65		
Ratio 4	1.5	1.5	5.4	2.7	2.7	**29.05**
	1.5		5.2	2.6		
	1.5		5.6	2.8		

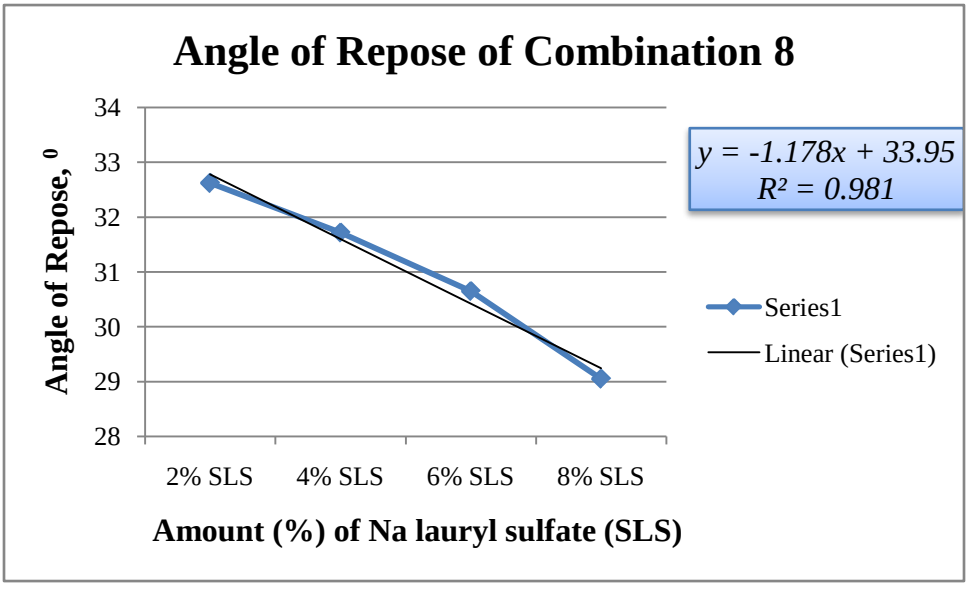

Figure 4.25: A plot showing angles of repose of Na Lauryl Sulfate in Combination 8

4.1.5.4 Combination 9: [F_2 : Zinc Stearate]

4.1.5.4.1 Values of Carr's Index and Hausner Ratio of Combination 9

Table 4.22: Determination of Carr's index and Hausner's ratio of Combination 9

Ratio	Bulk volume, cm^3	Acceptable Bulk volime, V_b	Tapped volume, cm^3	Acceptable Tapped volume, V_t	Carr's Index, $\frac{100(V_b - V_t)}{V_b}$	Hausner Ratio, $\frac{V_b}{V_t}$
Ratio 1	9.25	9.5	**7.0**	7.0	**26.31**	**1.36**
	9.5		**7.0**			
	9.25		**7.0**			
Ratio 2	9.5	9.75	7.25	7.0	**25.64**	**1.34**
	9.5		**7.0**			
	9.75		**7.0**			
Ratio 3	**10.0**	10.0	8.0	7.75	**22.5**	**1.29**
	9.5		**7.75**			
	9.75		**7.75**			
Ratio 4	10.25	10.5	**8.25**	8.25	**21.42**	**1.27**
	10.5		8.5			
	10.5		8.5			

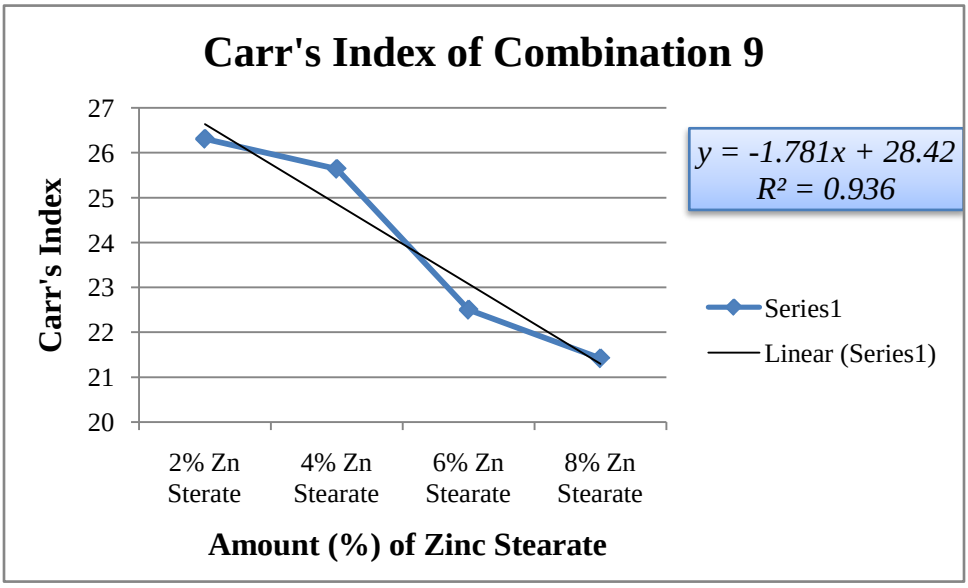

Figure 4.26: A plot showing Carr's indexes of Zn Stearate in Combination 9

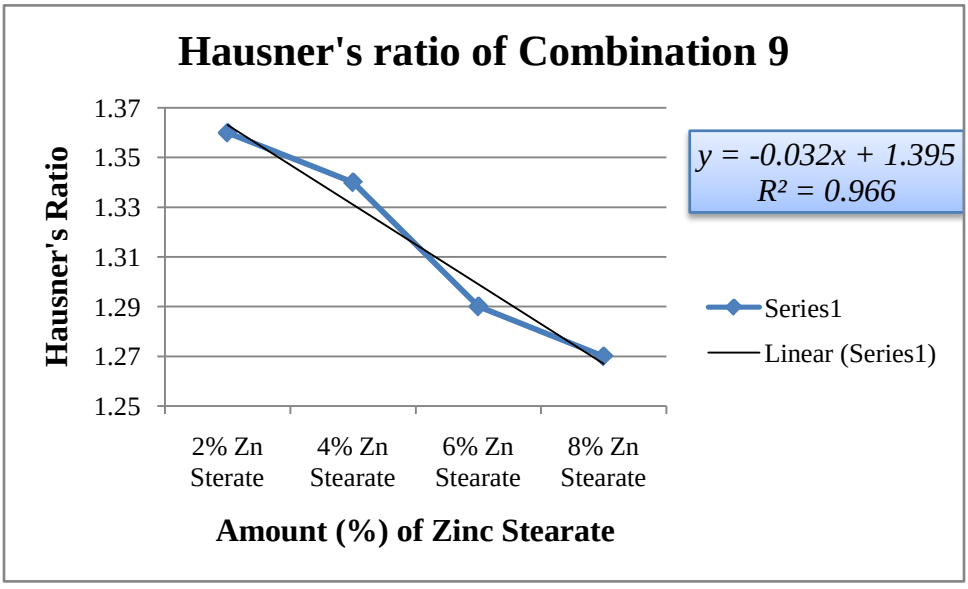

Figure 4.27: A plot showing Hausner's ratios of Zn Stearate in Combination 9

4.1.5.4.2 Values of Angle of Repose of Combination 9

Table 4.23: Determination of Angle of repose of Combination 9

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^0$
Ratio 1	1.5	1.4	4.9	2.45	2.4	**30.25**
	1.5		4.9	2.45		
	1.2		4.6	2.3		
Ratio 2	1.4	1.4	5.3	2.65	2.6	**28.30**
	1.4		5.1	2.55		
	1.4		5.2	2.6		
Ratio 3	1.5	1.3	5.3	2.65	2.6	**26.57**
	1.4		5.3	2.65		
	1.0		5.0	2.5		
Ratio 4	1.4	1.3	5.7	2.85	2.8	**24.9**
	1.1		5.4	2.7		
	1.4		5.7	2.85		

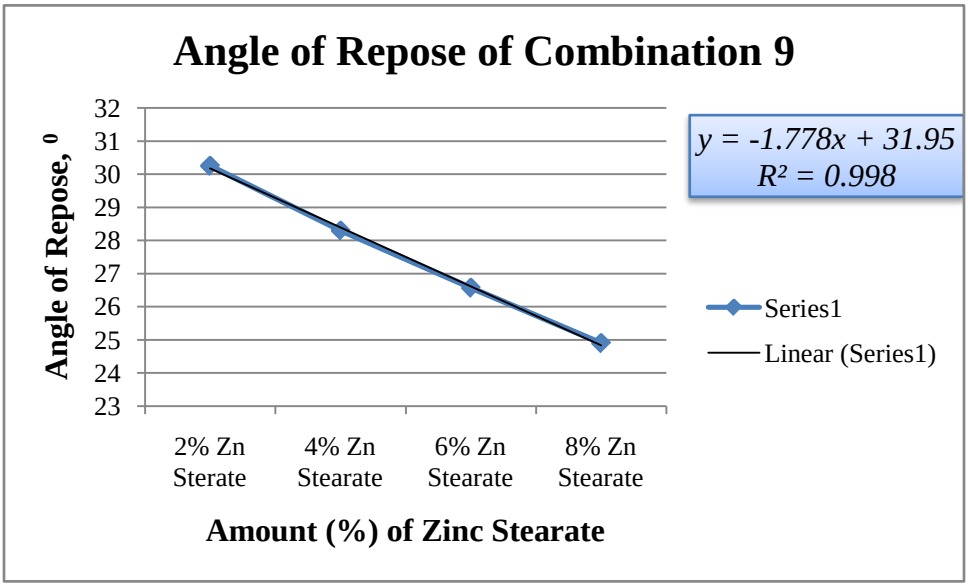

Figure 4.28: A plot showing Angles of repose of Zn Stearate in Combination 9

4.1.5.5 Combination 10: [F_2 : Magnesium Stearate]

4.1.5.5.1 Values of Carr's Index and Hausner Ratio of Combination 10

Table 4.24: Determination of Carr's index and Hausner's ratio of Combination 10

Ratio	**Bulk volume , cm^3**	**Acceptable Bulk volume, V_b**	**Tapped volume, cm^3**	**Acceptable Tapped volume, V_t**	**Carr's Index, $\frac{100(V_b - V_t)}{V_b}$**	**Hausner Ratio, $\frac{V_b}{V_t}$**
Ratio 1	**10.0**	10.0	7.25	7.0	**30.0**	**1.43**
	10.0		**7.0**			
	10.0		7.25			
Ratio 2	10.5	11.0	8.75	8.0	**27.27**	**1.375**
	11.0		8.25			
	10.75		**8.0**			
Ratio 3	**11.5**	11.5	**8.5**	8.5	**26.09**	**1.352**
	11.0		9.0			
	11.25		8.75			
Ratio 4	11.75	12.5	10.0	9.5	**24.0**	**1.31**
	12.5		9.75			
	12.0		**9.5**			

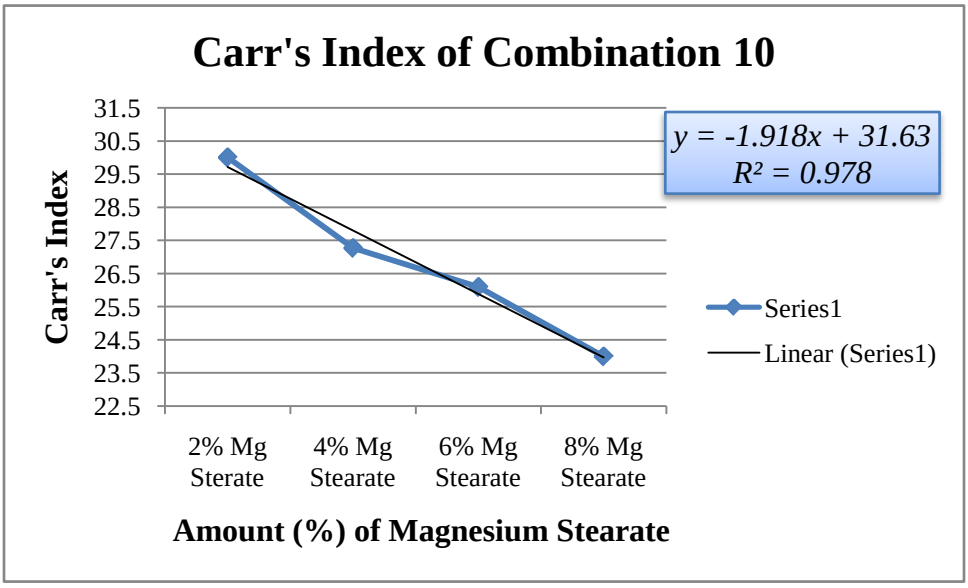

Figure 4.30: A plot showing Carr's Indexes of Mg Stearate in Combination 10

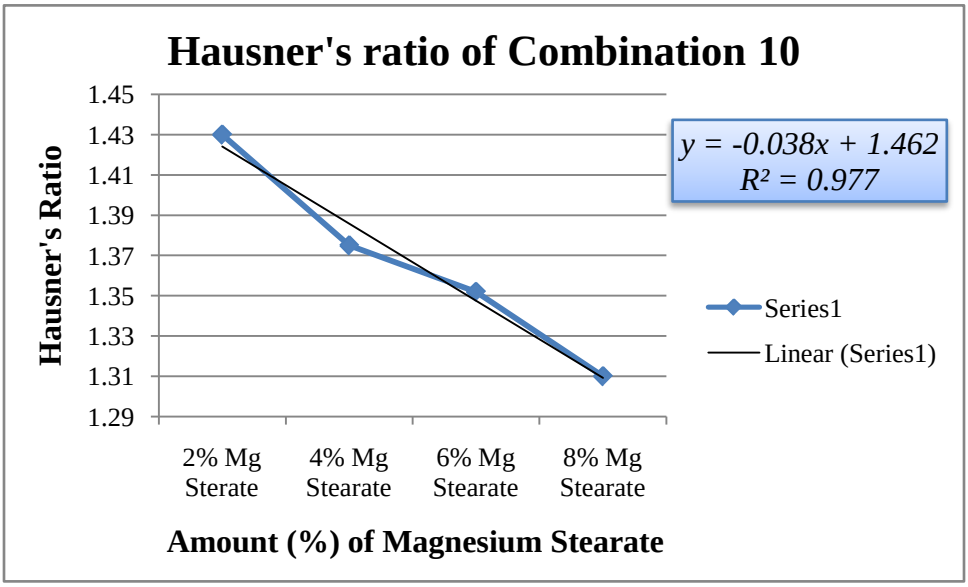

Figure 4.30: A plot showing Hausner's ratios of Mg Stearate in Combination 10

4.1.5.5.2 Values of Angle of Repose of Combination 10

Table 4.25: Determination of Angle of repose of Combination 10

Ratio	Height of pile, cm	Avg. height, h cm	Diameter of Pile, cm	Radius of pile, cm	Avg. Radius, r cm	Angle of Repose, $\tan^{-1}(h/r)^0$
Ratio 1	1.6	1.7	5.1	2.55	2.55	**33.69**
	1.8		5.2	2.6		
	1.7		5.0	2.5		
Ratio 2	1.5	1.6	4.9	2.45	2.5	**32.62**
	1.5		4.8	2.4		
	1.8		5.3	2.65		
Ratio 3	1.9	1.8	5.7	2.85	2.95	**31.39**
	1.6		5.9	2.95		
	1.9		6.1	3.05		
Ratio 4	1.7	1.7	6.1	3.05	3.0	**29.54**
	1.9		6.1	3.05		
	1.5		5.8	2.9		

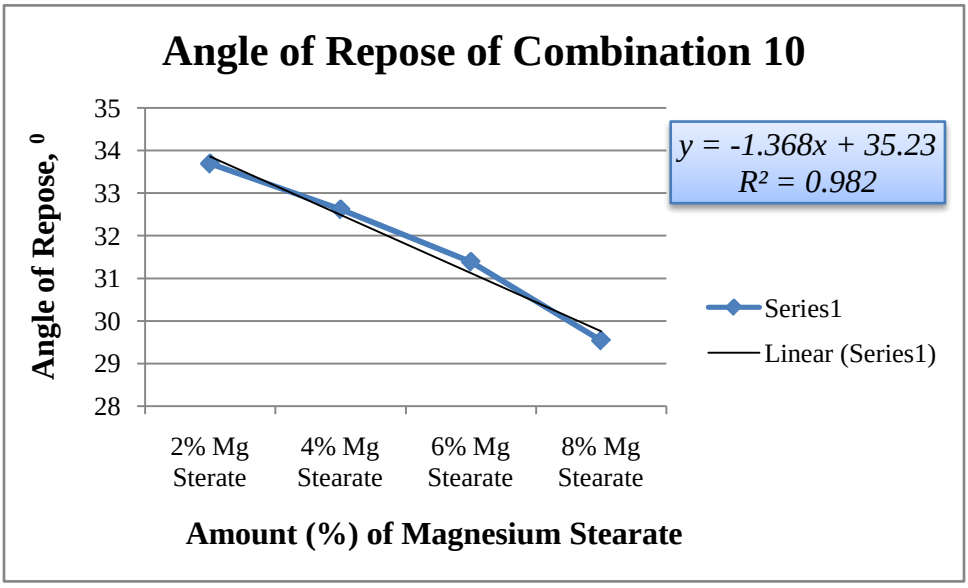

Figure 4.31: A plot showing Angles of repose of Mg Stearate in Combination 10

Chapter Five

DISCUSSION

5.1 DISCUSSION

In this dissertation, I have determined flow characteristic of individual powder excipients that were used throughout the research work, as well as of some groups of excipients, which were generally termed as 'Combination'. Each of the combinations contained a certain formula prepared by excipients and a lubricant. Lubricants were used in various amounts with the formulas to check its effect on the existing formula. For the most obvious property of lubricant, that, it accelerates powder flow, the existing formulas have performed better with the addition of increasing amount of lubricants. Almost each of the combinations have shown excellent results, others might have gone through any environmental imbalance, or human error, as all of this assessments was conducted manually and there was lack of expertise.

5.1.1 Carr's Index Determination:

The values of Carr's compressibility indexes of the ten different combinations have shown good results. In each combination, the Carr's index values have declined more or less with gradual increase of lubricant in the combination. According to United States Pharmacopeia, there is a chart that shows the nature of flow of powders of each distinct value of Carr's Index.

Table 5.1: Flow Characteristics of Powders with Varying Carr's Index Values

Carr's Index Values	Flow Characters
≤ 10	Excellent
11- 15	Good
16- 20	Fair
21- 25	Passable
26- 31	Poor
32- 37	Very poor
> 38	Very, very poor

The Carr's index values of all individual excipients have not performed that well unless they belong to the category of lubricants. The lubricants almost entered within the group of *passable* and *fair*, among them sodium lauryl sulfate have shown the best result.

Table 5.2: Nature of Powder flow of the Combinations Determined by Hausner's Ratio with Regression values denoted by the Graph

No.	Combinations	Ranges of Carr's Index with increasing Lubricant	Nature of Flow of Powders	Regression Values (R^2)	Best flowability with lubricants used in the amount of (%)
1.	[F_1: Boric Acid]	28.57- 24.32	Poor-Passable	0.934	8%
2.	[F_1 : Talc]	26.47- 22.22	Poor-Passable	0.929	8%
3.	[F_1 : Sodium Lauryl Sulfate]	16.67- 9.52	Fair-Excellent	0.785	8%
4.	[F_1 : Zinc Stearate]	35.0- 27.5	Very Poor-Poor	1.0	8%
5.	[F_1 : Magnesium Stearate]	27.18- 24.0	Poor-Passable	0.994	8%
6.	[F_2 : Boric Acid]	27.78- 21.05	Poor-Passable	0.984	8%
7.	[F_2 : Talc]	20.0- 16.21	Fair	0.908	8%
8.	[F_2 : Sodium Lauryl Sulfate]	30.0- 24.4	Poor-Passable	0.878	8%
9.	[F_2 : Zinc	26.31- 21.42	Poor-	0.936	8%

	Stearate]		Passable		
10.	[F_2 : Magnesium Stearate]	30.0- 24.0	Poor- Passable	0.978	8%

Most of the combinations are to be in the range of 'Poor- Passable', though this is not that much appreciated. If the interference of moisture, or human errors could be overcome, we assure that the values of Carr's indexes of the combinations would be far better.

5.1.2 Hausner's Ratio Determination:

The values of Carr's index and Hausner's ratio are nearly similar, as the way of determining these parameters are quite same. The fact that makes these parameters distinguished from each other is the equation that is used to get the values. United State Pharmacopeia has also given a chart showing the nature of powders against the values of Hausner's ratio determined by their recommended procedure.

Table 5.3: Flow Characteristics of Powders with Varying Hausner's Ratio Values

Hausner's Ratio Values	Flow Characters
1.00 -1.11	Excellent
1.12- 1.18	Good
1.19- 1.25	Fair
1.26- 1.34	Passable
1.35-1.45	Poor
1.46- 1.59	Very poor
> 1.60	Very, very poor

In case of individual excipients, again sodium lauryl sulfate have shown good value even in case of Hausner's ratio determination. In each combination, these values of Hausner's ratio have also declined more or less with increasing amount of lubricant used in the combination.

Table 5.4: Nature of Powder flow of the Combinations Determined by Hausner's Ratio with Regression values denoted by the Graph

No.	Combinations	Ranges of Hausner's Ratio with increasing Lubricant	Nature of Flow of Powders	Regression Values (R^2)	Best flowability with lubricants used in the amount of (%)
1.	[F_1: Boric Acid]	1.40- 1.32	Poor-Passable	0.939	8%
2.	[F_1 : Talc]	1.36- 1.28	Poor-Passable	0.980	8%
3.	[F_1 : Sodium Lauryl Sulfate]	1.20- 1.10	Fair-Excellent	0.804	8%
4.	[F_1 : Zinc Stearate]	1.54- 1.37	Very Poor-Poor	0.998	8%
5.	[F_1 : Magnesium Stearate]	1.37- 1.316	Poor-Passable	0.993	8%
6.	[F_2 : Boric Acid]	1.38- 1.26	Poor-Passable	0.968	8%
7.	[F_2 : Talc]	1.25- 1.19	Fair	0.952	8%
8.	[F_2 : Sodium Lauryl Sulfate]	1.43- 1.32	Poor-Passable	0.880	8%
9.	[F_2 : Zinc Stearate]	1.36- 1.27	Poor-Passable	0.966	8%
10.	[F_2 : Magnesium Stearate]	1.43- 1.31	Poor-Passable	0.977	8%

5.1.3 Angle of Repose Determination:

Angle of repose is determined by the totally different process than that of Carr's index and Hausner's ratio. I have determined the angle that is produced on the plane by pouring powders on it retaining its tip. There is also a chart defining the characters of flow for certain value of angles of repose declared by the United State Pharmacopeia.

Table 5.5: Flow Characteristics of Powders with Varying Angle of Repose

Flow Property	Angle of Repose (degrees)
Excellent	25–30
Good	31–35
Fair—aid not needed	36–40
Passable—may hang up	41–45
Poor—must agitate, vibrate	46–55
Very poor	56–65
Very, very poor	>66

Angles of repose were determined in cases of individual excipients used in this thesis project, and most of them showed a good result. The results have become better when angle of repose was assessed in cases of the combinations of powder excipients along with lubricants. Most of them showed that powder flow have become Good to Excellent in nature with the addition of lubricant.

Table 5.6: Nature of Powder flow of the Combinations Determined by Angle of Repose with Regression values denoted by the linear Graphs

No.	Combinations	Ranges of angle of repose with increasing Lubricant	Nature of Flow of Powders	Regression Values (R^2)	Best flowability with lubricants used in the amount of (%)
1.	[F_1: Boric Acid]	33.7^0-29.98^0	Good-Excellent	0.977	8%
2.	[F_1 : Talc]	39.94^0-34.82	Fair- Good	0.994	8%
3.	[F_1 : Sodium Lauryl Sulfate]	31.89^0-28.76^0	Good-Excellent	0.908	8%
4.	[F_1 : Zinc Stearate]	40.23^0-28.44^0	Fair-Excellent	0.990	8%
5.	[F_1 : Magnesium Stearate]	30.26^0-25.11^0	Good-Excellent	0.944	8%
6.	[F_2 : Boric Acid]	33.21^0-30.19^0	Good-Excellent	0.962	8%
7.	[F_2 : Talc]	38.05^0-34.82^0	Fair- Good	0.965	8%
8.	[F_2 : Sodium Lauryl Sulfate]	32.62^0-29.05^0	Good-Excellent	0.981	8%
9.	[F_2 : Zinc Stearate]	30.25^0-24.9^0	Good-Excellent	0.998	8%
10.	[F_2 : Magnesium Stearate]	33.69^0-29.54^0	Good-Excellent	0.982	8%

This table shows that each of the combination denotes quite good changes in flow characteristics by gradual decrease of the angles of the cones with addition of lubricants. Each of the also possesses a good regression value, and the best angle (small) is shown while the lubricant is used in its maximum amount that is declared in the beginning of the research paper.

According to the above tables, we can come to the conclusion that, the natures of the powders are quite different which are represented by the values of Carr's index- Hausner ratio and angle of repose. Carr's index- Hausner's ratio values show a combination to be in the range of 'Poor- Passable', while angle of repose values denote the same combination to be in the range of 'Good- Excellent'. This may happen due to the presence of moisture within the glass apparatus, like conical flask, or measuring cylinders used to determine the values for Carr's index- Hausner's ratio, or lack of expertise and rate of tapping for getting *Tapped volume*.

We have seen that, more we use lubricants the flow property gets much better. But there is a certain limit to the use each and every ingredient, so happen with the lubricants. If we use excess ingredients, the formulation will become sticky, and it will rather hamper the flow. Again excess use of few lubricants is injurious to health, for example, sodium lauryl sulfate may produce foam both *in vivo* and *in vitro*, as it is commonly used as surfactant. Again large amount of magnesium stearate in solid dosage forms will retard the dissolution as it is highly hydrophobic in nature. Zinc state is also hydrophobic and it may also cause fatal pneumonitis, especially in infants, so nowadays it is replaced.

After putting each determined values of the parameters achieved by the assessment, a linear graph is prepared, from which we have had the regression value, along with an equation that will help to identify-

- ✓ The amount of Lubricants if we want a partical value of the parameters like, Carr's index, Hausner's ratio, as well as angle of repose; and
- ✓ The values of physical parameters and the nature of powder flow, if we use a definite amount of Lubricants.

Chapter Six

CONCLUSION

6.1 CONCLUSION

This thesis paper has come to an end with a conclusion that increased amount of lubricant results in improved flow property of pharmaceutical excipients, though this large amount of excipient does not bring a positive effect all time and it leaves an impact on the final dosage forms, affecting its robustness, dissolution and ultimately on the shelf life of the dosage form itself. I have introduced linear graphs, along with regression value and an equation that represent the changes of the flow characteristic of the existing *formula* with addition of lubricants to it. These equations and regression values will be of great importance in further modifications to the existing *formulas*, or in case of new formula development with the same lubricant. In case of further research work with the same formula and lubricant the amount can easily be modified with help of the equation.

Chapter Six

REFERENCE